Kojic acid in organic synthesis

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Abstract: The reactions of kojic acid in organic synthesis are reviewed. The aim of this review is to cover the literature up to the end of 2014, showing the distribution of publications involving kojic acid chemistry in the synthesis of various pyrone containing compounds, pyridine and pyridone heterocycles, and also other organic compounds. First, introductory text about the preparation, biological, and industrial applications, and the chemical properties of kojic acid is given. Then its uses in organic synthesis are presented considering the reaction type.

Key words: Kojic acid, pyrone, pyridone, organic synthesis

1. Introduction
Kojic acid (KA), 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one, is produced from carbohydrate sources, especially glucose, through multistep enzymatic reactions.1 KA can be also produced by fungi during aerobic fermentation using various substrates such as sucrose, glucose, xylose, and arabinose.2,3 Industrially, KA was produced by Aspergillus species in aerobic fermentation. Saito discovered KA in the mycelia of Aspergillus oryzae grown on steamed rice in 1907 and then its structure was established in 1924 by Yabuta. In 1930, KA was obtained from D-glucose by chemical synthesis.4 Due to the importance of KA in industry, the production of KA is increasing and a considerable amount of research has been devoted to the biosynthesis of KA, and numerous publications have dealt with its chemical and biological properties. KA has a wide range of applications in the cosmetic, medicine, food, agriculture, and chemical industries. In the cosmetic industry, KA is a natural skin whitening agent5,6 that prevents ultraviolet radiation and inhibits tyrosinase activities,7,8 which cause pigmentation. In the medical field, KA has been reported as a potential antibacterial,9 antimicrobial,10 antileukemic,11 and antifungal12,13 agent. In the food industry, KA is used as an agent to prevent undesirable melanosis (blackening) of agricultural products such as vegetables, fruits, and crustaceans during storage.14 KA also exhibits the action of a polyphenol oxidase (PPO) enzyme when these products are exposed to oxygen.15 In the chemical industry, KA can be used as an analytical tool for the determination of cations, since the reaction of KA with a trace of Fe3+ ions can form a deep red complex.16 In addition, KA can be converted to comenic acid, which is an important intermediate for the preparation of maltol and its derivatives. Finally, KA is widely used in agriculture as a chelating agent and insecticide activator.17

KA, with the molecular formula C6H6O4, is a monocyclic pyrone consisting of a carbon ring with two double bonds (Figure) that can be found in the form of nearly odorless white crystals or pale yellow crystalline

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powder. The hydroxyl group at position C5 shows a weakly acidic characteristic. KA is a polyfunctional heterocycle, with several important reaction centers, incorporated in many types of reactions, involving addition, alkylation, acylation, oxidation, ring opening, and nucleophilic and electrophilic substitution reactions. Although there are some reviews about biological properties,\(^\text{18,19}\) and one old book chapter\(^\text{20}\) on very limited chemical properties of KA, to the best of our knowledge, there are no comprehensive reviews or book chapters on the reactions of KA in organic synthesis. Moreover, there is a growing number of published papers on the reactions of KA in organic synthesis. We have recently published two review articles on the synthesis of heterocyclic compounds,\(^\text{21,22}\) and in continuing our works on pyrone chemistry,\(^\text{23-25}\) we decided to write a review on the application of KA in organic chemistry. The aim of this review is to cover the literature up to the end of 2014, showing the distribution of publications involving all types of reactions of KA, such as synthesis of pyridine and pyridone derivatives, aldol, Mannich, Michael addition, multicomponent, diazo coupling, Claisen rearrangement, cycloaddition, cross-coupling, Wittig, and ring-opening reactions, and substitution at enolic OH and hydroxymethyl involving protections, and metal complexation.

![The structure of KA.](image)

**2. Reactions of kojic acid**

**2.1. Synthesis of pyridones and pyridines**

O’Malley et al.\(^\text{26}\) reported the synthesis of pyridine-2-carbaldehyde 2 starting from KA in four steps. Methylation of KA using Me\(_2\)SO\(_4\) in the presence of KOH and then heating with NH\(_4\)OH at 90 °C afforded pyridone 1. Pyridine-2-carbaldehyde 2 was prepared from the reaction of pyridone 1 with p-methoxybenzyl chloride (PMBCl) and then by oxidation with O-iodoxybenzoic acid (IBX) in DMSO. The obtained pyridine-2-carbaldehyde 2 was transformed into pterocellin A 3, which exhibited anticancer activity (Scheme 1).

![Scheme 1.](image)

5-Hydroxypipecolic acid 8, a natural substances found in *Rhapis/Iabellifannis* (Rhapisercelsa, Acacia-species), Rhodesian teak (Baikaeaphurijuga), and in the pericarp of edible dates (Phoenixdactyl/era), was synthesized from KA in a sequence of reactions as outlined in Scheme 2. Reaction of KA with Me\(_2\)SO\(_4\) and then with 22% aqueous NH\(_3\) at 90 °C for 2–3 h, followed by oxidation using HNO\(_3\) at room temperature for 3–4
days and then treatment of the obtained product with Na$_2$CO$_3$ in water for 2–3 h, gave 5-methoxy-4-pyridone-2-carboxylic acid 4 in 90% yield. By reaction of 4 with SOCl$_2$ under reflux conditions for 5 h continued by reduction with H$_2$ in the presence of Pd/C at room temperature, ethyl 5-methoxypyridine-2-carboxylate 5 was obtained quantitatively, which was converted to 6 and 7 by treatment with H$_2$/Pt in EtOH at 40–50 °C and HI under N$_2$ atmosphere at 135 °C for 3 h, respectively. 5-Hydroxypipelicolic acid 8 was obtained from 6 by treatment with HI under N$_2$ atmosphere at 130 °C for 2.5 h or from 7 through reduction with H$_2$/Pt at 40–50 °C. 27

Stangeland et al. 28 described the total synthesis of WS75624 B 14, which is a potent endothelin converting enzyme (ECE) inhibitor and potential antihypertensive agent. 29 This compound was synthesized from KA in ten steps. By protection of enolic OH with BnCl in the presence of NaOMe in MeOH (70% yield) and then oxidation of the hydroxymethyl group to carboxylic acid with Jones reagent in acetone (63% yield), followed by reaction with concentrated NH$_4$OH in a sealed flask at 90 °C, pyridone 9 was obtained quantitatively for the last step. Pyridine carboxylate 10 was obtained in 23% yield by methylation of both the carboxyl and phenolic OH with trimethylsilyldiazomethane (TMSCHN$_2$) in MeOH/toluene, followed by deprotecting of the benzyl ether moiety with Pd/C in MeOH. By treatment of compound 10 with acetaldehyde in the presence of t-BuOOH and FeSO$_4$, compound 11 was obtained in 97% yield, according Patt and Massa’s synthesis. 30 Compound 11 was converted to WS75624 B 14 in further steps through compounds 12 and 13 as outlined in Scheme 3. WS75624 A was also synthesized in a similar procedure.

Norton et al. 31,32 reported the synthesis of 5-hydroxy-2-pyridine-DL-alanine 17, a potent competitive antagonist of tyrosine in Leuconostoc desulfitriseum 8086 and a moderately active growth inhibitor of Escherichia coli 9723, and β-(5-hydroxy-2-pyridyl 1-oxide)-DL-alanine 20, analogues of tyrosine, through a sequence of reactions starting from KA. Reaction of KA with Me$_2$SO$_4$ in the presence of KOH solution and then treatment with concentrated NH$_4$OH in a stainless steel bomb at 90 °C for 2 h, followed by reaction with POCl$_3$ under reflux conditions, gave 4-chloro-2-chloromethyl-5-methoxypyridine 15. Diethyl 2-acetamido-2-(4-chloro-5-methoxy-2-pyridinemethyl) malonate 16 was obtained from the reaction of 15 with ethyl acetamide malonate
in the presence of Na/EtOH under reflux conditions for 24 h, which was converted to \( \text{17} \) in further steps as shown in Scheme 4. In addition, the pyridine \( N \)-oxide, \( \beta \)-(5-hydroxy-2-pyridyl 1-oxide)-DL-alanine \( \text{20} \), was synthesized by oxidation of \( \text{15} \) with \( \text{H}_2\text{O}_2 \) in glacial AcOH at 70 \( ^\circ \text{C} \) for 3 h, to afford 4-chloro-2-chloromethyl-5-methoxypyridine 1-oxide \( \text{18} \), which by treatment with ethyl acetamide malonate led to product \( \text{19} \) under reaction conditions similar to those mentioned above (Scheme 4).
Barfoot et al. synthesized pyridyl analogues of 2,3-dihydro-1,4-benzodioxin-6-carbaldehydes as a key intermediates for antibacterial medicinal chemistry. 2,3-Dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde 22a was prepared by treatment of KA with BnCl in the presence of NaOH in MeOH at reflux for 8 h and then reaction with NH₃ in EtOH under reflux conditions to give pyridone 21, followed by deprotection and cyclization with 1,2-dibromoethane in the presence of K₂CO₃ in DMF at 85 °C and oxidation using of MnO₂ in CH₂Cl₂ at room temperature for 3 days. Moreover, pyridines 22b-f were synthesized by a similar procedure (Scheme 5).

By reaction of Bn-protected KA with MeNH₂ in EtOH/water, followed by treatment with SOCl₂ in CH₂Cl₂, pyridinone 23a was obtained in good yield. Reaction of pyridinone 23a and amine 24 was carried out in DMF in the presence of Et₃N and the obtained product was deprotected using HCl and AcOH to give hydroxy pyridinone 25 in 73% yield (Scheme 6). The complexing ability of 25 with VO²⁺ and its biological activity were also investigated.³⁴

Li et al. reported the synthesis of hydroxypyrindinone and L-phenylalanine conjugates as potential tyrosinase inhibitors from KA. Firstly, protection of the OH group of KA with BnCl in MeOH/water at 70 °C for 6 h, followed by treatment with alkyl amines in EtOH/water in the presence of NaOH at reflux for 3 h, gave
pyridone 26 in 72%–85% yields. Coupling of the resulting pyridone 26 with Cbz-L-phenylalanine by ester bond formation in the presence of EDC and DMAP in DMF at room temperature led to 27, which after deprotection of the benzyl and Cbz groups in the presence of H2/Pd/C in EtOAc/water (1/1) at room temperature for 5 h converted to the desired product 28 in 88%–93% yields (Scheme 7).

![Scheme 7. Chemoselective protection of enolic OH of KA with BnCl in the presence of NaOH in EtOH under reflux conditions for 24 h, followed by reaction with MeNH2 or c-PrNH2 in EtOH and then chlorination using neat SOCl2, afforded the intermediates 23a,b. Treatment of 23a,b with N-(7-chloro-4-quinolinyl)diaminoalkane 29 in the presence of Na2CO3 and Et3N in DMF under reflux conditions for 2–24 h, followed by deprotection with HCl at 74 °C gave aminochloroquinoline–pyridone hybrids 30 that exhibited β-hematin inhibition and antiplasmodial activity against drug resistant (K1) and sensitive (3D7) strains of plasmodium falciparum (Scheme 8).]

A series of 1,2,5-trisubstituted 4(1H)-pyridinone derivatives 32 were reported by Öztürk et al.37,38 through reaction of KA with amines in EtOH. Treatment of KA with SOCl2 and then reduction with Zn/HCl, followed by the protection of OH with BnCl afforded 4-pyrone derivative 31. Pyridinone derivatives 32, with
high analgesic and anti-inflammatory activities, were produced in 50%–72% yields by reaction of 31 with amines continued by deprotection with BBr$_3$ in DCM (Scheme 9).$^{39-41}$ Furthermore, synthesis of $N$-aryl-$\gamma$-pyridones starting from KA was reported.$^{42}$

Sakurai et al.$^{43}$ described the synthesis of pyridine-4-thiones 35 from KA in five steps. The OH group of KA at the C-5 position was protected by reaction with BnCl in the presence of NaOH, followed by treatment with alkyl iodides in the presence of NaH to give the O-alkylated products 33. Addition of amines to $O,O'$-disubstituted KAs and then debenzylation with 10% Pd/C as a catalyst under an H$_2$ atmosphere gave pyridinones 34. By treatment of the resulting 5-hydroxy-4(1H)-pyridinones 34 with P$_2$S$_5$ in the presence of hexamethyldisiloxane (HMDSO), the C=O bond was converted into C=S. Reaction of two equimolar amounts of 35 with ZnSO$_4$ afforded the corresponding zinc complexes, 36, which exhibited antidiabetic and antimetabolic syndrome effects in animals (Scheme 10).

The reaction of KA with hydrazine was investigated by Thomas et al. and 4-oxo-1,4-dihydropyridazine was obtained. As shown in Scheme 11, KA in reaction with hydrazine and then SOCl$_2$ was converted to dihydropyridazine 37 in 45% yield. Reduction of compound 37 with H$_2$ in the presence of Pd/C afforded product 40. Moreover, compound 37 in treatment with NaOMe in MeOH and then reduction with H$_2$/Pd/C gave dihydropyridazine 38, while the isomer 39 was not produced.$^{44-47}$
2.2. Aldol reaction

Maltol-derived ruthenium–cymene complex 42 with tumor inhibiting properties was reported by Kandioller et al.\textsuperscript{48} in 2009. As shown in Scheme 12, aldol product 41 was synthesized in three steps from KA. Reaction of KA with SOCl\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} at room temperature and then reduction with Zn/HCl in water at 75 °C, followed by treatment with formaldehyde under alkaline conditions gave aldol product 41 in 70% yield. The corresponding Ru\textsuperscript{II} complex 42 was obtained in good yields (81%) by reaction of 41 and bis[dichlorido(\(\eta^6\)-p-cyachyngtremungmene)ruthenium(II)] using NaOMe in MeOH for 5–18 h.

Poppy acid, 3-hydroxy-4-oxo-4\(\text{H}\)-pyran-2,6-dicarboxylic acid 43, was prepared in 30% yield by subjecting KA to formaldehyde in the presence of NaOH in MeOH/water mixture for 4 h, followed by oxidation with air in the presence of NaOH and Pd/C (Scheme 13).\textsuperscript{49}

Liu et al.\textsuperscript{50} synthesized 2-substituted- 3-hydroxypyridin-4-ones 45 starting from KA and evaluated the inhibitory activity of the corresponding iron-containing metalloenzyme. By reaction of KA with SOCl\textsubscript{2}, followed by reduction using Zn/HCl and then treatment with formaldehyde, aldol product was obtained, which was transformed into compound 44 by protection of enolic OH with BnBr, and CH\textsubscript{2}OH moiety with Me\textsubscript{2}SO\textsubscript{4}.  

\begin{align*}
\text{HO}_2\text{C} & \quad \text{MeO} \\
\text{OH} & \quad \text{O} \\
\text{HO}_2\text{C} & \quad \text{MeO}
\end{align*}

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Pyridinone 45 was obtained in 82\% yield when 44 was treated with MeNH₂, followed by deprotection using H₂ in the presence of Pd/C (Scheme 14).

[Diagram]

Scheme 14.

Treatment of a mixture of KA in absolute EtOH with paraformaldehyde in the presence of either KHCO₃ or anhydrous K₂CO₃ at room temperature afforded 3-hydroxy-2,6-bis(hydroxymethyl)-4\(H\)-pyran-4-one 46, which in the reaction with benzoyl chloride via the Schotten–Baumann method, yielded (5-hydroxy-4-oxo-4\(H\)-pyran-2,3,6-triy1tris(methylene) tribenzoate 47. When a mixture of KA with paraformaldehyde in absolute EtOH was heated at 75 °C in the presence of KHCO₃ for 17 h, 3-hydroxy-2,5,6-tris(hydroxymethyl)-4\(H\)-pyran-4-one 48 was produced (Scheme 15). 51 Hydroxyl methylation of KA was also reported. 52

[Diagram]

Scheme 15.

The synthesis of 2-(1-hydroxyalkyl)-3-hydroxypyridin-4-ones 50, as 4-hydroxypyridinium ions, was reported by Liu et al. 53 starting from KA in six steps. Compounds 49 were produced by treatment of KA with SOCl₂ and then Zn in acidic solution, followed by the aldol condensation with aliphatic aldehydes under alkaline aqueous conditions and then protection with benzaldehyde dimethylacetal in DMF in the presence of a catalytic amount of \(p\)-TSA. Treatment of 49 with primary amines and then deprotection with H₂ in the presence of Pd and HCl gave the desired product 50 in 73\%–87.5\% yields (Scheme 16).

[Diagram]

Scheme 16.
Kandioller et al.\textsuperscript{54} described the synthesis of Ru(II)-p-cymene complexes 53, which exhibit anticancer activity against human tumor cell lines. The precursor allomaltol 51 was prepared from KA by reaction with SOCl\textsubscript{2}, followed by reduction with Zn under acidic conditions. Then allomaltol 51 was treated with substituted benzaldehydes in the presence of NaOH in water to give aldol products 52 in 64%-91% yields. Complexes 53 were obtained in 54%-73% from the reaction of 52 with bis[dichloride(\(\eta^6\)-p-cymene)ruthenium(II)] in the presence of NaOMe in MeOH (Scheme 17). A similar aldol reaction of 51 with formaldehyde was also reported.\textsuperscript{55}

\[ \text{Scheme 17.} \]

Ochiai et al.\textsuperscript{56} synthesized polyurethane containing KA moiety 55 in the main chain and investigated the Fe(III)-complexation ability of the hydroxyl group of KA. The aldol product 54 was prepared in 35% yield by stirring KA with 2-ethylhexanal in the presence of Na\textsubscript{2}CO\textsubscript{3} in EtOH at 95 °C for 24 h. Polymerization of KA dimer 54 with disocyanates in the presence of catalyst in DMSO under heating at 70 °C and N\textsubscript{2} atmosphere for 24 h led to polymers 55a, b in 26%-71% yields. Ratios of the polymers 55a/55b are outlined in Scheme 18. Metal-complexation ability of the polyurethane-bearing KA structure was examined by mixing a DMSO solution of the polyurethane 55 and FeCl\textsubscript{3}. There are also other reports on the synthesis of KA dimers similar to 54 from aldol reaction of KA with various aldehydes.\textsuperscript{57,58}

Synthesis and radical polymerization of styrene derivative containing KA moieties 56 was reported by Tomita et al.\textsuperscript{59} p-Formyl styrene was reacted with 2 equiv. KA in the presence of Na\textsubscript{2}CO\textsubscript{3} in MeOH under N\textsubscript{2} atmosphere at reflux for 4 h and then protected with acetic anhydride in pyridine at room temperature to afford styrene derivative 56 in 90% yield. Radical copolymerization of 56 with styrene was conducted using AIBN under heating at 60 °C for 36 h, in which copolymer 57 was obtained in 83% yield. Deacetylation of copolymer 57 was carried out using Et\textsubscript{3}N in MeOH/THF at room temperature for 4 h, which underwent complexation with AlCl\textsubscript{3} in the presence of Et\textsubscript{3}N in 1,4-dioxan to 58 (Scheme 19). Other metal complexing polymers containing KA moiety were reported by Davies et al. in 1959.\textsuperscript{60}

In addition to common aldehydes, glyoxal was also investigated in the aldol reaction, in which a solution of KA and glyoxal in EtOH was stirred at room temperature overnight, and 1,2-bis-(2-hydroxymethyl-5-hydroxy-4-pyrene)-ethylene glycol 59 was obtained in good yield (Scheme 20).\textsuperscript{61}
Scheme 18.

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Scheme 19.
The aldol reaction of KA with aromatic and aliphatic aldehydes was performed using alumina as a base in dioxane/water (1/1) at room temperature for 24 h, and the desired products 60 were achieved in 83%-98% yields. Moreover, treatment of KA (1 mmol) with aldehydes (1.2 mmol) in the presence of DABCO under reaction conditions similar to those mentioned above, followed by treatment with indole (1.5 equiv.) in the presence of silica-H$_2$SO$_4$ as a catalyst in CH$_3$CN at 80 °C for 2 h, gave indol-KA conjugates 61 as active insulin mimics in 86%-98% yields. Nucleophilic substitution of aldol product 60a to 62 was performed with various substituted indoles and other nucleophiles under similar reaction condition (Scheme 21). Sadeghi et al. reported one-pot synthesis of 2-substituted aryl(indolyl)KA derivatives 61 from the reaction of KA with aromatic aldehydes and indole using FAU zeolite nanoparticles and kaolin/Ag nanocomposite as catalyst under solvent-free conditions. Furthermore, 2-substituted aryl(indolyl)KA derivatives 61 were obtained in good yields and high selectivity from the three-component reaction of aldehyde, indole, and KA in the presence of catalytic amounts of InCl$_3$ and $p$-TSA under solvent-free conditions.

One-pot three-component synthesis of pyrano[3,2-b]pyrazolo[4,3-c]pyridin-8(1$H$)-ones 64 was described by Safaei et al. by heating KA (1 mmol), 1,3-diphenyl-1$H$-pyrazol-5-amine 63 (1 mmol), and an aldehyde (1 mmol) in the presence of Zn(OTf)$_2$ at 120 °C under solvent-free conditions for 1 h, followed by treatment with H$_2$O$_2$ (30 mol%) in CH$_3$CN under reflux conditions for 30 min in 82%-96% yields (Scheme 22). The proposed reaction mechanism for the formation of 64 involves the condensation of 1$H$-pyrazol-5-amine 63 with the keto tautomer of KA, and then nucleophilic attack of enamine intermediate 65b to the aldehyde that
produced intermediate 66, which converted to compound 67 by intramolecular cyclization and dehydration. Finally, oxidative aromatization of intermediate 67 gave the corresponding product 64.

Scheme 22.

2.3. Mannich reaction

Aytemir et al. described the Mannich reaction of piperazine derivatives, formaldehyde, and KA in 2010, as outlined in Scheme 23. The reactions were carried out in MeOH at room temperature, and Mannich bases 68 were obtained in 50%–86% yields. Anticonvulsant activities of 68 were investigated and all compounds exhibited anticonvulsant activities. In another investigation, treatment of KA with 37% formalin and piperidine derivatives in similar reaction conditions afforded Mannich products 69 in 58%–96% yields (Scheme 23). Aytemir et al. also reported similar synthesis of other Mannich bases from KA.

Scheme 23.

Reaction of KA with methylamine, followed by treatment with formaldehyde (37% aqueous solution) and piperidine under reflux conditions in EtOH for 24 h under a Mannich reaction gave 3-hydroxy-6-hydroxymethyl-l-methyl-2-piperidinomethyl-4(lH)-pyridinone 70 in 47% yield (Scheme 24), which acts as a bidentate ligand with high affinity for metal ions in high oxidation state.

Scheme 24.
Mannich reactions between KA, cyclic secondary amines, and 35% formaldehyde solution were performed in MeOH under reflux conditions and Mannich adducts 71 were obtained in 25%–94% yields. Stirring the obtained Mannich adducts 71 (2 equiv.) and bis[dichlorido(η⁶-p-cymene)ruthenium(II)] in the presence of NaOMe in MeOH/CH₂Cl₂ at room temperature for 18 h afforded complexes 72 in 81%–98% yields (Scheme 25), which exhibited anticancer and antitumor activities.⁷⁵

![Scheme 25](image)

Furthermore, a Mannich-type reaction of KA derivatives, 7-piperazinylquinolones 73, and 37% formalin solution was carried out in MeOH at room temperature for 48–72 h to give Mannich bases 74 in 20%–90% yields (Scheme 26). The obtained Mannich adducts exhibited antibacterial activity.⁷⁶

![Scheme 26](image)

Treatment of KA with SOCl₂ continued by reduction with Zn/HCl gave allomaltol 51, which was reacted with cyclic secondary amines and formaldehyde in MeOH to produce Mannich adducts 75 in 73%–92% yields. The complexation properties of the obtained Mannich adducts 75 were investigated by subjecting
with \([\text{M(arene)}\text{Cl}_2]_2\) in the presence of NaOMe in MeOH for 15 min under argon atmosphere, which led to pyrone-based organometallic complexes 76 in 50%–73% yields (Scheme 27). Among the prepared complexes, Ru(II or III) complex exhibited moderate activity in CH1 cells.\(^{77}\)

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\text{Scheme 27.}
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Nurchi et al.\(^{78}\) described a Mannich-type reaction of KA, formaldehyde, and \(N, N\)-diethylethylenediamine by dropwise addition of a solution of \(N, N\)-diethylethylenediamine and aqueous formaldehyde (36%) (2.2 equiv.) in EtOH to a solution of KA (2 equiv.) in EtOH and stirring at room temperature for 5 h, leading to 6,6\(^{'-}\)[2-(diethylamino)ethylazanediyl]bis(methylene)bis[5-hydroxy-2-(hydroxymethyl)-4\(H\)-pyran-4-one] 77 as a potential therapeutic iron chelating agent in 67% yield (Scheme 28). A Mannich-type reaction of KA, formaldehyde, and other amines such as methyl amine, benzyl amine, and piperazine was reported by Toso et al. in 2013.\(^{79,80}\)

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\text{Scheme 28.}
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A Mannich-type reaction of KA with amino acids and formaldehyde was reported by O’Brien et al.;\(^{81}\) it is not as simple as the reaction with other types of amines because of variations in the structure and solubility characteristics of amino acids. The reaction of KA with several amino acids was carried out in the presence of 37% formaldehyde in water/EtOH. In the case of glycine, taurine, DL-leucine, and DL-isoleucine, both hydrogen atoms of amines were replaced, and bis-Mannich adducts 79 were produced, while only one hydrogen atom of amines can be replaced by KA in the case of sarcosine, DL-valine, DL-methionine, and L-proline to give Mannich-adducts 78 (Scheme 29). However, reactions with L-asparic acid, L-asparagine, L-glutamic acid, L-glutamine, DL-phenyl alanine, and DL-tyrosine did not occur. In addition, O’Brien et al.\(^{82}\) in 1960 showed that the reaction of KA with secondary amines such as dimethyl and diethyl amine, pyrrolidine, morpholine, piperidine, \(N\)-methylpiperazine, and 1,2,3,4-tetrahydroquinoline afforded a product similar to 78, but the reaction with lauryl and stearyl amines gave bis-Mannich adducts, similar to 79.
The multicomponent reaction of 1,4,7-triazacyclononane 80 and KA (3 equiv.) with excess amount of formaldehyde (30% aqueous solution) was carried out in EtOH under reflux conditions for 20 h, leading to 6,6′,6″-(1,4,7-triazonane-1,4,7-triy1)tris(methylene)tris[5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one] 81 in 54% yield, which underwent complexation with metal salts to produce complexes 82 in 35%–61% yields (Scheme 30).

The multicomponent Mannich-type reaction of KA, aryl amines, and 37% formalin in the presence of concentrated HCl was reported under heating conditions for 15 min. As shown in Scheme 31, reactions occurred at both C-3 and C-6 positions, leading to 83 in good yields.\(^{84}\)
5-(Benzyloxy)-4-oxo-4\textsubscript{H}-pyran-2-carbaldehyde (\textit{O}-protected comenic aldehyde) \(84\) was synthesized by protection of KA with benzyl bromide in the presence of NaOH, followed by oxidation with MnO\(_2\) in \(\text{CH}_2\text{Cl}_2\) at room temperature according to the literature\(^8\) and used in a three-component direct Mannich-type reaction with different anilines and cyclohexanone using \(\text{ZrOCl}_2\cdot\text{H}_2\text{O}\) as catalyst in EtOH at room temperature over 50 min to give Mannich adducts \(85\) in high yields with moderate stereoselectivity (Scheme 32).\(^8\)

2.4. Conjugate addition

By stirring crotonic acid with KA in the presence of NaHCO\(_3\) in absolute EtOH under reflux conditions for 20 h, conjugate addition occurred at the C-6 position of KA and gave 3-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4\textsubscript{H}-pyran-2-yl)butanoic acid \(86\). On the other hand, refluxing ethanolic solution of \(\beta\)-bromopropionic acid with KA in the presence of NaHCO\(_3\) for 5 h afforded 3-(3-hydroxy-6-(hydroxymethyl)-4-oxo-4\textsubscript{H}-pyran-2-yl)propanoic acid \(87\) via an alkylation reaction (Scheme 33).\(^8\)

Wang et al.\(^8\) developed an enantioselective Michael addition of a KA derivative to nitro olefins using bifunctional chiral thiourea–tertiary amine \(88\) as catalyst. Reactions were conducted by stirring a solution of KA derivative and nitro olefins in MeOH in the presence of \(88\) (0.1 equiv.) at \(-10\) °C for 4 days to obtain products \(89\) in 58\%–99\% yields and good enantioselectivities (Scheme 34). Moreover, Subba Reddy et al.\(^8\) reported a
similar approach using cinchonine-derived sugar thioureas in 2014, in which the corresponding Michael adducts exhibited promising cytotoxicity against various cancer cell lines.

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\text{Scheme 34.}
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Michael addition/hemiketalization reaction of KA derivatives and \((E)\)-ethyl-2-oxo-4-phenylbut-3-enoate 90 was catalyzed with 92 in DCM at 0 °C for 12 h, and products 91 were obtained in excellent yields, with high enantioselectivity, up to 95% ee (Scheme 35).\(^90\)

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\text{Scheme 35}
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Enantioselective reaction of KA derivatives with ynals 93 catalyzed by \(N\)-heterocyclic carbenes 95 was described by Kaeobamrung et al.\(^91\) Reactions were carried out using \(N\)-mesityl substituted precatalyst 95 in toluene at 40 °C, which led to unstable dihydropyranones that converted to products 94 in good yields and high enantioselectivity when stirred in MeOH for 6 h. The reaction did not occur without triazolium salt. As outlined in Scheme 36, the proposed reaction mechanism involves in situ generation of intermediate 97 by addition of NHC to aldehyde moiety, followed by a redox reaction and then protonation to give 98, which underwent 1,2- or 1,4-addition with KA to give intermediates 99 or 100, respectively; however, hemiacetal 99 transformed into 100 via Claisen rearrangement. Tautomerization with subsequent acetalization of compound 100 afforded 101, which gave pyrano-pyrane derivatives 96 by lactonization, along with removal of triazolium salt.\(^92\)–\(^95\) There is another similar report in the literature.\(^96\)
The four-component condensation reaction of aromatic aldehydes, alomaltol 51, Meldrum’s acid, and NH$_4$OAc (2 equiv.) was accomplished in ionic liquid [bmim]BF$_4$ at 60 °C, and 3-(3-hydroxy-6-methyl-4-oxo-4H-pyran-2-yl)-3-phenylpropanamides 103 were produced in 65%–92% yields (Scheme 37). 97

Synthesis of 2-hydroxymethylpyrano[3,2-b]pyran-4,6-dione 104 was achieved from the reaction of KA with maleic acid (1 equiv.) catalyzed by H$_2$SO$_4$ at 120–130 °C for 3 h in 69% yield (Scheme 38). The reaction occurred by conjugate addition of KA to maleic acid, followed by lactonization and decarboxylation. 98
2.5. Multicomponent reactions

An alumina-catalyzed three-component reaction of KA, aldehydes, and dimedone $105$ was conducted under solvent-free conditions at 100 °C, and 2-(hydroxymethyl)-7,7-dimethyl-10-phenyl-7,8-dihydropyrano[3,2-$b$]chromene-4,9(6$H,10H$)-diones $106$ were obtained in short time and high yields. The possible mechanism for this reaction involves a domino Knoevenagel-hetero-Diels–Alder reaction intermediate $107$ and then dehydration of in situ generated tricyclic hemiacetal intermediate $108$ (Scheme 39). With aliphatic aldehydes no reaction occurred.$^{99}$ A three-component reaction of KA, aldehyde, and 1,3-diones was also performed by InCl$_3$ and CAN$^{101}$ as catalyst under solvent-free conditions.

The three-component reaction of KA, malononitrile, and aromatic aldehydes was described by Banitaba in 2013. Reactions were carried out by ultrasound irradiation of a mixture of malononitrile, benzaldehyde (1 equiv.), and KA (1 equiv.) in water in an ultrasonic bath at 50 °C to produce 2-amino-4,8-dihydropyrano[3,2-$b$]pyran-3-carbonitrile derivatives $110$ in 35%–88% yields.$^{102}$ Moreover, Piao et al. reported the synthesis of amino-substituted 4$H,8$H-pyran[3,2-$b$]pyran-4-ones $110$ in high yields from the reaction of KA with substituted benzylidene malononitriles $109$, which exhibited nonpeptide human immunodeficiency virus (HIV) protease inhibitory activity. The reaction was carried out by treatment of KA with benzylidene malononitriles $109$ in the presence of piperidine in EtOH under reflux conditions for 10 min (Scheme 40).$^{103}$
Scheme 40.

Shestopalov et al.\textsuperscript{104} reported the synthesis of dihydropyrano[3,2-b]pyran-4-ones 110–112, analogues of human immunodeficiency virus (HIV) protease inhibitors, starting from KA. Reactions were performed by refluxing ethanolic solution of KA, malononitrile (1 equiv.), and p-trifluoromethylthiobenzaldehyde, N-methylpiperidin-4-one, and N-methylisatine (1 equiv.) in the presence of Et\textsubscript{3}N for 15 min, leading to 4,8-dihydropyrano[3,2-b]pyran-4-ones 110–112 in 97%, 83%, and 89% yields, respectively (Scheme 41). Moreover, a multicomponent reaction of KA, isatin, and malononitrile or ethyl cyanoacetate catalyzed with DABCO-functionalized mesoporous SBA-15 was reported by Azimi et al. in 2014.\textsuperscript{105}

\begin{equation}
\begin{array}{c}
\text{HO} \quad \text{OH} \\
\text{HO} \quad \text{OH}
\end{array}
\end{equation}

Tu et al.\textsuperscript{106} synthesized pyrano[2′,3′:5,6]pyrano[2,3-b]pyridines 114 via three-component bicyclization of KA, aldehydes, and 2-aminoprop-1-ene-1,1,3-tricarbonitrile 113. Reactions were carried out by heating a mixture of KA, aldehydes (1 equiv.), and 2-aminoprop-1-ene-1,1,3-tricarbonitrile 113 (1 equiv.) in EtOH in the presence of Et\textsubscript{3}N at 80 °C under microwave irradiation for 16 min, and corresponding pyrano[2′,3′:5,6]pyrano[2,3-b]pyridines 114 were obtained in 44%–84% yields (Scheme 42).
Treatment of KA (2 mmol) with acetylenic esters (2 mmol) and isoquinoline 115 (2 mmol) in THF afforded 1,2-dihydroisoquinoline derivatives 116 in 58%-80% yields that showed moderate to good antibacterial activity. In the case of dialkyl acetylenedicarboxylates, the reaction mixture was stirred at room temperature for 2 h, while with alkyl acetylenecarboxylates, reactions were carried out at 60 °C for 7–8 h. However, C-vinylated products of KA 117 were obtained from the reaction of KA with acetylenic esters and pyridine instead of isoquinoline under reaction conditions similar to those mentioned above (Scheme 43).\textsuperscript{107}

Regioselective vinylation of KA was performed using acetylenic esters in the presence of Ph\textsubscript{3}P or tert-butylisocyanide, in which C- or O-vinylated KA derivatives 119 or 120 were obtained. The reaction of KA with dialkyl acetylenedicarboxylates was carried out in the presence of Ph\textsubscript{3}P in THF at room temperature and C-alkylation 119 was achieved in a regioselective manner. However, the reaction of KA with alkyl propiolate in the presence of tert-butylisocyanide in THF at room temperature gave O-alkylated KA regioselectively. A possible reaction mechanism of C-vinylation of KA involves nucleophilic addition of Ph\textsubscript{3}P to the dialkyl acetylenedicarboxylates 121 and subsequent protonation by KA to give intermediate 122. The resulting enolate from KA attacked 122 via the C-atom to produce intermediate 123, which was converted to final C-vinylated product 119 in two steps by proton transferring, followed by removal of Ph\textsubscript{3}P intermediates 125. Moreover, nucleophilic addition of tert-butylisocyanide to the acetylenic ester 126 with subsequent protonation by KA yielded positively charged intermediate 127, which was attacked by the negative oxygen atom of KA enolate to generate intermediate 128, which was transformed into O-vinylated KA derivatives 120 by removing the tert-butylisocyanide molecule (Scheme 44).\textsuperscript{108}
Functionalized 4,8-dihydropyrano[3,2-b]-pyran-4-ones 129 were synthesized in 75%-80% yields from the three-component reaction of KA, alkyl isocyanides, and dialkyl acetylenedicarboxylates in THF at room temperature for 24 h. In the proposed reaction mechanism, nucleophilic addition of alkyl isocyanide to dialkyl acetylenedicarboxylate led to zwitterion 130, which underwent protonation by KA to give intermediate 131. Attack of the KA anion on 131 and then 1,3-proton transfer of 132 to 133 with subsequent cyclization gave dihydropyrano[3,2-b]-pyran-4-ones 129 (Scheme 45).

Shahrisa et al.\textsuperscript{110} described the Ugi four-component reaction of O-protected comenic aldehyde, isocyanides, carboxylic acids, and amines in the absence of any catalyst. Stirring a mixture of O-protected comenic aldehyde (0.5 mmol), amines (0.5 mmol), carboxylic acid (0.5 mmol), and isocyanide (0.6 mmol) in MeOH at room temperature for 2 h gave bis-carboxamide derivatives of KA 134 in 71%-88% yields (Scheme 46). The obtained Ugi products 134 showed considerable cytotoxic potential, especially in the HL-60 cell line. O-protected comenic aldehyde was obtained from KA by benzylaition of enolic OH, followed by oxidation of the hydroxymethyl moiety with active MnO\textsubscript{2}.\textsuperscript{111}
2.6. Diazo coupling

By treatment of KA (0.01 mol) with phenyl diazonium oxide hydrate (1 equiv.) in water in the presence of 5% NaOH at 0 °C, 4-oxo-3,3-dihydroxy-6-hydroxymethyl-2,3-dihydropyran-2-phenylhydrazone 135 was obtained in 75% yield. Refluxing of crude hydrazone 135 in EtOH in the presence of HCl for 15 min gave 3-hydroxy-6-(hydroxymethyl)-2-(phenyldiazenyl)-4H-pyran-4-one 136 in 54% yield (Scheme 47). In addition, 3-hydroxy-6-(hydroxymethyl)-2,5-bis(phenyldiazenyl)-4H-pyran-4-one 137 was obtained in 45% yield from the reaction of phenyldiazohydrate with KA using 5% NaOH in water.\(^{112}\)

Kuznetsov et al.\(^{113,114}\) prepared dibenzo-18-crown-6 derivatives having KA fragment 139, potential double ionophores, from the diazo-coupling reaction of diazonium salt 138 with KA in water. The mixture
of reaction was stirred for 3 h below 5 °C, and 4’-(6-azo-5-hydroxy-2-hydroxymethyl-γ-pyronyl)dibenzo-18-crown-6s 139 were obtained in 66%–74% yields (Scheme 48). Diazonium salts 138 were prepared from the reaction of corresponding amines with NaNO₂/HCl in water.¹¹⁵

![Scheme 48.](image)

6-Arylazo-substituted-5-hydroxy-2-hydroxymethyl-4-pyridones 141 were prepared from the reaction of 5-hydroxy-2-hydroxymethyl-4-pyridone 140, derived from the action of amines on KA, with aryldiazonium salts in the presence of NaOAc in water for 2 h, in 21%–83% yields (Scheme 49).¹¹⁶

![Scheme 49.](image)

2.7. Claisen rearrangement

Xiong et al.¹¹⁷ reported the preparation of (indolyl)KA 144 as antidiabetes agents. Protection of hydroxymethyl moiety of KA with THP followed by treatment with 142 in the presence of Cs₂CO₃ at room temperature for 12 h and then with Amberlyst 15 at room temperature for 3 h in MeOH gave 143 quantitatively for the last step. Claisen rearrangement of 143 in toluene at 190 °C for 30 min yielded (indolyl)KA 144 in 87% yield (Scheme 50). In another report, (indolyl)KA derivatives were obtained via Claisen rearrangement using of Zn(OTf)₂ as a catalyst under microwave irradiation.¹¹⁸
Furthermore, indol-substitute KA 147 was synthesized via Claisen rearrangement of 146, obtained in 70% yield from the Sonogashira reaction of 145 with O-idoaniline sulfonamide in the presence of PdCl$_2$(Ph$_3$P)$_2$/CuI as catalyst. Compound 145 was prepared by treatment of KA with propargyl bromide in the presence of K$_2$CO$_3$ and Bu$_4$NBr in acetone, in 99% yield. Claisen rearrangement of 146 was conducted by MW irradiation in toluene at 190°C for 30 min, in 85% yield. In the similar procedure, coupling of 145 with N-Bociodoaniline in the presence of PdCl$_2$(Ph$_3$P)$_2$/CuI and Et$_3$N produced 148 in 62% yield. Cyclization of 148 was performed by treatment with Bu$_4$NF in THF at room temperature for 1.5 h to afford (indolyl)methyl kojate 146 in 90% yield, which was converted to (indolyl)KA 147 when heated in toluene for 30 min as outlined in Scheme 51.

The synthesis of indole substituted pyridinone 150 was achieved from Sonogashira coupling and Claisen rearrangement of pyridinone 149 and N-Boc-protected o-idoaniline. Pyridinone 149 was synthesized in three steps starting from KA by protecting hydroxymethyl moiety of KA with THP and then reacting with propargyl bromide to give compound 145, followed by treatment with MeNH$_2$ under acidic conditions. The reaction of
with \( N \)-Bocidoaniline in the presence of \( \text{PdCl}_2(\text{Ph}_3\text{P})_2 \) and CuI as catalyst in \( \text{Et}_3\text{N} \) for 12 h, followed by treatment with \( \text{Bu}_4\text{NF} \) in THF at room temperature for 1.5 h, and then heating in toluene at 190 °C for 30 min gave indolyl KA derivatives 150 in good yield (Scheme 52).

**Scheme 52.**

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### 2.8. Cycloadditions

In 1991, Wender et al.\(^{119}\) synthesized the precursors of tiglianes, daphnanes, and ingenanes, as highly potent tumor promoters, via \([5 + 4]\) cycloaddition reaction starting from KA. The synthesis of pyrone 152 was achieved in 90% yield from the reaction of potassium kojate and bromide 151 in MeOH at 20 °C, followed by Claisen rearrangement in EtOH under reflux condition for 60 h. Compound 152 was converted to 153 in three steps, by reaction with MeOTf in \( \text{CH}_2\text{Cl}_2 \) and then by treatment with 2,2,6,6-tetramethylpiperidine (TMP) in \( \text{CH}_2\text{Cl}_2 \), followed by treatment with TBSCl in the presence of imidazole in DMF. Moreover, treatment of potassium kojate with bromide 154 and then reduction with Zn/Cu(OAc)\(_2\cdot\text{H}_2\text{O} \) in the presence of AgNO\(_3 \) in MeOH/H\(_2\text{O} \) at 20 °C, followed by the reaction with BuCl in the presence of Et\(_3\text{N} \) and DMAP in CH\(_2\text{Cl}_2 \) afforded diene 155 in 72% yield. Compound 155 was converted to 156 by refluxing in EtOH for 60 h (Claisen rearrangement). Finally 157a and 157b were produced via \([5 + 4]\) cycloaddition reaction by stirring 156 with MeOTf in CH\(_2\text{Cl}_2 \) at 40 °C for 11 h, followed by treatment with TMP in CH\(_2\text{Cl}_2 \) at 20 °C for 10 h (Scheme 53).

The reaction of KA with SOCl\(_2 \) in CHCl\(_3 \) at 60 °C and then reduction with H\(_2\)/Pd in the presence of NaOAc in MeOH at room temperature, followed by aldol condensation with formaldehyde using KOH in H\(_2\text{O} \) at room temperature, afforded compound 158 in 76% yield. In continuation, compound 158 was converted to compound 159 by treatment with SOBr\(_2 \) in the presence of Et\(_3\text{N} \) in CHCl\(_3 \) at room temperature and then allyl mercaptane in THF at room temperature. Compound 159 underwent protection using TBSCl in the presence of imidazole in CH\(_2\text{Cl}_2 \), and then regio- and stereoselective \([5 + 2]\) cycloaddition when heated in toluene at 170 °C, to give the corresponding cycloadduct, which was transformed into compound 160 in 50% yield, by reductive desulfurization using Raney Ni in THF at room temperature. Tetrahydrofuran 161 was obtained in 72% yield by desilylation of 160 with TBAF·3H\(_2\text{O} \) and then oxidative cleavage of the C—C bond with Pb(OAc)\(_4 \) in MeOH at room temperature (Scheme 54).\(^{120,121}\) There is another similar multistep approach for the construction of tetrahydrofuran starting from KA.\(^{122}\)
McBride et al.\textsuperscript{123,124} reported intramolecular cycloaddition of KA derivatives 164, by refluxing a mixture of 164 and NaI in \( \text{Ac}_2\text{O} \) and HOAc for 4.5 h, to give cycloadduct 165. Compounds 164 were prepared by acylation of 163 with KA derived acyl chloride 162 in the presence of NaI in THF. Acyl chloride 162 was obtained from conmenic acid in two steps, by protection of enolic OH with \( \text{Ac}_2\text{O} \) and then reaction with SOCl\(_2\) in benzene at reflux. Similarly, cycloaddition of alkyne 166 in xylene under reflux conditions for 20 h afforded the desired product 167 (Scheme 55). As shown in Scheme 56, compounds 169 and 171 were obtained by heating of KA derivatives 168 in xylene at 140 °C and refluxing of 170 in the presence of \( p \)-TSA and trimethylorthoformate in MeOH for 12 h, respectively.

Very recently, synthesis of functionalized cyclohepta[b]indoles 175 was reported by Mei et al.\textsuperscript{125} via [5+2] cycloaddition reactions. Firstly, treatment of chloromethyl derivative 172 with diethyl 2-[(1-methyl-1\( H \)-indol-3-yl)methyl]malonate 173 in the presence of NaH and TBAI in THF at 0 °C afforded indole KA derivatives 174 in 56%–82% yields. Then the intramolecular [5+2] cycloaddition reaction between methoxy
oxidopyrylium ylide, in situ generated by reaction of 174 with MeOTf in DCM at 40 °C for 12 h, and indole moiety was conducted by addition of CsF in a mixture of DCM/DMF at 25 °C for 7 h, to give functionalized cyclohepta[b]indoles 175 in 43%–85% yields (Scheme 57).

Scheme 55.

Volkmann et al.\textsuperscript{126} reported an ionic [4 + 2] cyclization of KA with acrylonitrile as outlined in Scheme 58. Intermediate 176 was obtained in situ and converted to 177 in the reaction with the second molecule of KA. Compound 177 transformed into compound 178 in acidic conditions.
2.9. Cross coupling reactions

Compounds 182 and 184, candidates for quinone replacement in demethylasterriquinone B1 185, ZL196 186a, and LD17 186b as insulin mimic with oral activity in mouse models of diabetes, were prepared via Stille coupling reaction of stannane 180 and 2-bromoKA derivative 179, as shown in Scheme 59. The reaction was performed using Pd(Ph$_3$P)$_4$ as catalyst in toluene at 90 °C and product 181 was obtained in 62% yield. Deprotection of O-silyl and N-Boc groups with excess fluoride ions in THF gave product 182 in 54% yield. In addition, deprotection of O-silyl groups and then selective protection of the enol 181 with PMB-Cl afforded 183 in 43% yield, which was converted to 184 in 41% yield, by treatment with methylamine, along with removal of the N-Boc group, followed by deprotection of the PMB group. 127

The total synthesis of lodopyridone 191, an inhibitor of human quinone reductase 2 (NQO2, QR2), was recently described by George et al. 128 starting from KA. 6-Bromo KA derivative 187 was prepared by adding a solution of bromine and NaH$_2$PO$_4$ in water to a solution of KA in H$_3$PO$_4$ at 0 °C and stirring for 72 h at 4 °C, in 45%–55% yield, which was converted to 187 in 55%, by protection with DHP in the presence of p-TSA in THF at room temperature and then with Me$_2$SO$_4$ in DMF at room temperature. Compound 187 was treated with 188 in the presence of bis(diphenylphosphino)ferrocene palladium dichloride in 1,4-dioxane/water at 80 °C to give 189 in 92% yield. Deprotection of compound 189 in methanolic HCl solution, followed by treatment with tert-butylidiphenylsiloxethanamine in the presence of NaCN and MnO$_2$ in EtOH at reflux, and then by treatment with MeNH$_2$ in THF/water at 4 °C gave pyridone 190 in 27% yield for three steps. Finally, lodopyridone 191 was obtained by the reaction of 190 with pyridinium tribromide in pyridine under
reflux conditions and then treatment with NaSMe in dioxane at 90 °C, followed by deprotection of TBDPS group by using hydrogen fluoride pyridine complex in pyridine at room temperature in 99% yield, for the last step (Scheme 60).

Tomoyukikamo et al.\textsuperscript{129} reported Heck and Suzuki reactions of the triflate derivative of KA 192 as outlined in Scheme 61. KA was converted to triflate 192 by protection of the hydroxymethyl group using TBSCI in the presence of imidazole in DMAP/DMF, and then treatment with Tf\textsubscript{2}O in pyridine. Triflate 192 transformed into stannane 193 in 91% yield by the reaction with Me\textsubscript{3}SnSnMe\textsubscript{3} in the presence of Pd(OAc)\textsubscript{2}, Ph\textsubscript{3}P, and LiCl in DMF at room temperature. The Suzuki reaction of triflate 192 with furyl-B(OH)\textsubscript{2} in the presence of PdCl\textsubscript{2}(dppe)\textsubscript{2} and K\textsubscript{2}CO\textsubscript{3} in dioxane at 60 °C and the Heck reaction of 192 with ethyl acrylate using Pd(OAc)\textsubscript{2}/PPh\textsubscript{3} and Et\textsubscript{3}N at 100 °C in DMF gave 195 and 194 in 62% and 73% yields, respectively. In addition, the Stille coupling of stannane 193 with iodobenzene in the presence of PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}/CuI in DMF at room temperature and β-bromo-methacrylate 198 using Pd(PPh\textsubscript{3})\textsubscript{4}/CuI in DMF at 0 °C yielded 196 and 197, in 74% and 72% yields, respectively.
Furthermore, \([\text{Pd(allyl)Cl}]_2\) catalyzed carbonylation of stannane 193 with \(\text{PhI}\) and \(\text{CO}\) in DMF at room temperature led to 5-benzoyl-4-pyrone 199 in 72% yield (Scheme 62).
Rapicone 203, with HIV integrase inhibitory, plant growth reduction, and antifungal activities, was synthesized from KA in several steps as shown in Scheme 63. The reaction of KA with SOCl₂ at room temperature and then reduction with Zn/HCl in water at 75 °C gave allomaltol in 50% yields over 2 steps, which was protected with Tf₂O in the presence of pyridine at 0 °C to room temperature to give 200 in 90% yield. Protected allomaltol 200 transformed into 201 in 81% yield by direct stannylation with hexamethylditin in the presence of LiCl and Pd(OAc)₂/X-Phos catalyst in DMF at room temperature. Carbonylative Stille cross-coupling of 201 with 202 using Pd(OAc)₂/X-Phos and CsF as additive in dioxane at 95 °C produced rapicone 203 in 50% yield.

2.10. Wittig reaction

Synthesis of funicone analogue 206, a compound with cytostatic and antiproliferative properties, was investigated by Manzo et al.¹³¹ in 2012. A solution of KA and SOCl₂ in CH₂Cl₂ was stirred at room temperature overnight to give chloro-KA in 88% yield, which was treated with Ph₃P in THF at 67 °C for 4 days, followed by treatment with acetaldehyde in CH₃CN in the presence of K₂CO₃ and dicyclohexyl-18-crown-6, leading to a Wittig product. By addition of Tf₂O to the reaction mixture, Wittig product 204 was obtained in 70% yield, which was transformed into product 205 in 81% yield when reacted with Pd(OAc)₂, hexamethylditin, Ph₃P, and LiCl in DMF at room temperature for 21 h. Stille carbonylative coupling between stannane derivative 205 and iodobenzo precursor 202 in CO atmosphere in the presence of allylpalladium(II) chloride dimer as catalyst in DMF at room temperature for 1 day resulted in the formation of deoxyfunicone 206 in 33% yield (Scheme 64).
Chen et al.\textsuperscript{132} reported the preparation of a class of KA derivatives \textbf{209}, which exhibit antiproliferative activity against Hella cells in chelated form with Cu(II). KA was converted to \textbf{207a} or \textbf{207b} in 92\% or 87\% yield by protection using PMBCl or BnBr in the presence of K$_2$CO$_3$ in DMF, respectively, followed by treatment with MsCl in the presence of Et$_3$N and then NaBr in DMF. Compounds \textbf{208a} and \textbf{208b} were obtained from the Arbuzov reaction of \textbf{207a} and \textbf{207b} with P(OEt)$_3$ in THF at reflux, followed by the Horner–Emmons reaction with benzaldehyde in the presence of NaH in THF in 58\% and 64\% yields, respectively. Deprotection of \textbf{208a} with BBr$_3$ in DCM at \(-40\ ^\circ\text{C}\) to room temperature and \textbf{208b} with TFA in DCM at room temperature afforded the final products \textbf{209a} and \textbf{209b} in 63\% and 55\% yields, respectively (Scheme 65).

The reaction of \textit{O}-protected KA with SOCl$_2$ at room temperature, followed by treatment with P(OMe)$_3$ gave phosphonate \textbf{210}. Reactions of \textbf{210} with ferrocene carboxaldehyde in the presence of EtOLi under Wittig–Horner conditions and then deprotection using BCl$_3$ at room temperature led to ferrocene-containing compound \textbf{211} in 70\% yield, which is sensitive to Fe$^{3+}$ (Scheme 66).\textsuperscript{133}

Lee et al.\textsuperscript{134} reported KA derivative \textbf{214}, possessing melanin synthesis and tyrosinase inhibitory activity, by joining two pyrone rings via Horner–Emmons reaction of phosphonate \textbf{212} with aldehyde \textbf{213} in the presence
of NaH in THF at room temperature for 1 h. Comenic aldehyde 213 was produced by protection of enolic OH with PMB-Cl in the presence of K$_2$CO$_3$ in DMF at 80 °C to 207b, followed by oxidation with MnO$_2$ in CHCl$_3$ under reflux conditions, and phosphonate 212 was obtained from protection of KA as above, followed by the reaction with MsCl in the presence of Et$_3$N in CH$_2$Cl$_2$ and NaBr in DMF and then with P(OMe)$_3$ in toluene (Scheme 67).

The Horner–Emmons reaction of aldehyde 213 was also performed with phosphonate 215 by NaH in THF, and methyl ester 216 was obtained in 81% yield. Hydrolysis of ester moiety with LiOH in aqueous THF followed by alkylation with alkyl iodides in the presence of K$_2$CO$_3$ as a base in DMSO and then deprotection of the PMB group using trifluoroacetic acid (TFA) in CH$_2$Cl$_2$ afforded products 217, as a tyrosinase inhibitor, in 15%−72% yields (Scheme 68). Aldehyde 213 was obtained by protection of KA with PMB-Cl continued by oxidation with MnO$_2$.

Ma et al. reported the synthesis of 2-aryl substituted pyrones 220 and 221 from KA. As shown in Scheme 69, benzoylation of KA followed by selective oxidation with sulfur trioxide pyridine complex in DMSO afforded 6-formyl-3-benzyloxypyran-4(1$H$)-one 84, which converted to products 219 in 32%−38% yield by Wittig reaction with phosphonium salt 218 in the presence of NaOH in CH$_2$Cl$_2$ at room temperature for 0.5 h. Deprotection of product 219 using BCl$_3$ in CH$_2$Cl$_2$ at room temperature for 5 h afforded products 220 in 67%−70% yields. Deprotection of 219 with catalytic hydrogenation using H$_2$/Pd/C for 5 h yielded product 221 in 32% yield.
2.11. Ring opening reactions

The chloromethyl derivative of KA was a versatile intermediate to yield benzothiazoles 225 and pyrido[1,2-a]benzimidazoles 227 in the reaction with thiourea and 2-aminopyridine 226, via ring opening of KA, respectively. The chloromethyl pyrone 222 was heated with thiourea derivatives in the presence of KOAc in EtOH at 110 °C overnight and benzothiazoles 225 were obtained in 74%–93% yields. The proposed mechanism for this conversion involves the nucleophilic substitution of Cl with thiourea through the S-atom to give intermediate 223, which underwent intramolecular conjugate addition of nitrogen to α-carbon of KA and thereby opening the pyrone ring, yielding the intermediate 224. Final benzothiazols 225 were obtained by the cyclodehydration of 224. The reaction of 222 with 2-aminopyridins 226 in EtOH at reflux for 24 h gave the pyrido[1,2-a]benzimidazoles 227a,b in 20% and 25% yields, respectively. Hydrolysis of 227a,b in concentrated HCl produced dihydroxyl compounds 227c,d in 17%–25% yields (Scheme 70).

By stirring equimolar amounts of 5-hydroxy-2-methoxycarbonyl-4-pyrone 228 and aromatic amines in AcOH or MeOH at 75–80 °C for 20–60 min, 3-arylamino-2,4-dihydroxy-4-methoxycarbonyl-2-cyclopenten-1-ones 230 were obtained in 42%–73% yields. Reactions proceeded by conjugate addition of amine to pyrone,
followed by ring opening to intermediate 229a, which underwent cyclization to 230. As shown in Scheme 71, 4-pyridone 231 was not formed. On the other hand, the reaction of methyl comenate 228 with 3.5 equiv. of 4-anisidine in HOAc/MeOH under reflux conditions for 2 h led to a mixture of pyrrole 232 and pyridone 233.\textsuperscript{138,139}

![Scheme 71.]

2.12. Reactions in enolic OH

5-[(3-Aminopropyl)phosphinooxy]-2-(hydroxymethyl)-4\textit{H}-pyran-4-one 235 was prepared in 98% yield from the reaction of KA with 2-chloro-[1,3,2]oxazaphosphinane 2-oxide 234 in the presence of Et\textsubscript{3}N as an organic base in CHCl\textsubscript{3}/EtOH at room temperature for 12 h, continued by hydrolysis in acidic conditions in aqueous MeOH (Scheme 72). The obtained kojyl-APPA 235 exhibited a tyrosinase inhibition effect (30%) in vivo, but not in vitro.\textsuperscript{140}

![Scheme 72.]

Reaction of KA with ethyl and benzyl \(\beta\)-diazoopropionates in the presence of KOH in MeOH at room temperature for 2 h produced ethyl \(\beta\)-(2-hydroxymethyl-4-pyrone-5-oxy)-propionate 236a and benzyl \(\beta\)-(2-hydroxypropyl-4-pyrone-5-oxy)-propionate 236b in 21% and 29.8% yields, respectively (Scheme 73).\textsuperscript{141}

![Scheme 73.]
O-Alkylation of enolic OH was conducted by stirring a mixture of KA and bromo butenolides 237 in the presence of anhydrous K$_2$CO$_3$ in dry DMF at room temperature for 18 h, and product 238, germination stimulants for seeds of parasitic weeds, was obtained in 36.6% yield (Scheme 74).\textsuperscript{142}

In 2012, Cho et al.\textsuperscript{143} reported cinnamate derivatives of KA 243 and 244 that act as depigmenting agents. Reaction of KA with 3,4-(methylenedioxy)cinnamoyl chloride 240 was performed in the presence of Et$_3$N (1.1 equiv.) in DMF at room temperature and compound 243 was obtained in 65% yield. Treatment of KA with 241 or 242 in the presence of Et$_3$N in DMF gave 243 in 65% yield. The reaction of KA with 3,4-(methylenedioxy)cinnamic acid 239a in the presence of EDC and DCC led to the formation of anhydride of cinnamic acid 245, whereas compound 244 was not obtained. Moreover, side product 246 was obtained besides product 244 when chloro KA was treated with potassium salt of 3,4-(methylenedioxy)cinnamic acid 239b in DMF at 110–120 °C (Scheme 75).
Stirring 3a-methoxyserrat-14-en-21b-ol 247a or 3b-methoxyserrat-14-en-21b-ol 247b linked to succinic acid with an equimolar amount of KA in the presence of EDC·HCl and 1-hydroxybenzotriazole (HOBT) in DMF at 60 °C for 1 h under N₂ atmosphere produced conjugates 248a or 248b in 17% or 40% yields, respectively. Conjugates 249a and 249b were also obtained in 30% and 19% yields, from 2 molecules of 247a and 247b linked to succinic acid with one molecule of KA under conditions similar to those mentioned for 248a and 248b (Scheme 76). Conjugates 248 and 249 act as anti-HIV agents.¹⁴⁴

![Scheme 76.](image)

Preparation of 2H-furo[2,3-c]pyran-2-one derivatives 253 and evaluation of their germination-promoting activity were reported by Flematti et al.¹⁴⁵ As shown in Scheme 77, butenolides 253 were obtained from KA in 7 steps. Treatment of 250 with P₂S₅ followed by the reaction with 2-chloropropionylchloride in the presence of Me₃N afforded ester 251 in 79% yield. Heating 251 in Ac₂O in the presence of Ph₃P and NaOAc under reflux conditions gave 253 in 50% yield along with 252 in 22% yield. Furthermore, by heating butenolides 253 in concentrated NH₄OH and aqueous methylamine solution, the expected pyridine 255 and N-methyl-pyridone 254 were obtained in 10% and 14% yields, respectively.

![Scheme 77.](image)
A series of 5-arylamino-4H-pyran-4-ones 258 were prepared using a palladium-catalyzed amination reaction with triflates 257 as key intermediates. Selective protection of the primary alcohol function of KA by 3,4-dihydro-2H-pyran in the presence of p-TSA as a catalyst in CH₂Cl₂ at room temperature and then protection of enolic OH with Tf₂O in pyridine at 0 °C to room temperature, followed by deprotection of THP moiety under acidic conditions in EtOH at 70 °C and oxidation with Jones reagent in acetone at 0 °C gave carboxylic acid 256 in 81% yield. The reaction of 256 with anilines in the presence of PDCP and Et₃N in CH₂Cl₂ at 0 °C to room temperature afforded carboxamides 257 in 37%–90% yields. 5-Arylamino-4H-pyran-4-ones 258 were obtained in 18%–72% yields from a Buchwald–Hartwig-type amination reaction of the triflates 257 with arylamines catalyzed with Pd₂dba₃, xantphos, and Cs₂CO₃ in toluene (Scheme 78). Moreover, 5-amido-3-hydroxy-4-pyrones and 2-amido-3-hydroxy-4-pyrones, and other 6-amido-3-hydroxy-4-pyrones as inhibitors of matrix metalloproteinases, were reported.

2.13. Reactions at hydroxymethyl moiety

Shahrisa et al. synthesized fused pyrimidone derivatives containing KA skeleton 260 and 261. The Baylis–Hillman reaction of comenic aldehyde 84, derived from KA, with methyl acrylate using DABCO in THF followed by the reaction with AcCl and pyridine in CH₂Cl₂ at room temperature produced 259 in 67% yield. Fused pyrimidines 260 and 261 were obtained in 76% and 74% yields from the reaction of 259 with 2-aminopyridine and 2-aminothiazole in water/MeOH at room temperature, respectively (Scheme 79).
$N,N$-Dimethylhydrazones 262 were obtained from the reaction of KA with MnO$_2$ in CH$_2$Cl$_2$, followed by the reaction with $N,N$-dimethylhydrazine in the presence of catalytic amount of $p$-TSA in toluene at reflux for 4 h. Stirring of hydrazones 262 with MCPBA in CH$_2$Cl$_2$ at -15 to 20 °C for 24 h gave nitriles 263 in 53%-69% yields (Scheme 80).\(^{151}\)

\[
\text{Scheme 80.}
\]

Chen et al.\(^{152}\) reported the preparation of a class of KA derivatives 266-268, which exhibit antiproliferative activity against Hela cells in chelated form with Cu(II). Bromides 207b and 207a were reacted with 8-hydroxyquinoline 264a and resorcinol 264b in the presence of K$_2$CO$_3$ in acetone and then underwent deprotection with TFA and BBr$_3$ in DCM to give 266 and 267 in 72% and 46% yields, respectively. Moreover, treatment of compound 207a with arylsulfonilpiperazine 265 in the presence of K$_2$CO$_3$ in DMF, followed by deprotection using BBr$_3$ in DCM, afforded product 268 in 86% yield (Scheme 81). In 2003, Kadokawa et al.\(^{153}\) synthesized two KA derivatives containing phenolic hydroxy groups, like 267. The reactions were carried out by treatment of chloro KA 222 with phenol derivatives in the presence of K$_2$CO$_3$ in DMF at room temperature, followed by subsequent deprotection, leading to corresponding products in 24.8% and 56.6% yields, respectively.

\[
\text{Scheme 81.}
\]
Benzoate esters of KA \(269\) were synthesized and their tyrosinase inhibitory activity and depigmenting activity were evaluated. Treatment of KA with thionyl chloride in DMF at room temperature, followed by reaction with potassium salts of benzoic acids in DMF at 110–120 °C, gave benzoate derivatives \(269\) in good yields.\(^{154,155}\) Furthermore, treatment of chloro KA with sodium benzoate and sodium salicylate gave (5-hydroxy-4-oxo-4\(H\)-pyran-2-yl)methyl benzoate \(269a\) and (5-hydroxy-4-oxo-4\(H\)-pyran-2-yl)methyl 2-hydroxybenzoate \(269b\) in 75\% and 80\% yields, respectively. [Bis-(5-hydroxy-4-oxo-4\(H\)-pyran-2-yl)methyl benzoatato] oxovanadium (BBOV) and bis[(5-hydroxy-4-oxo-4\(H\)-pyran-2-yl)methyl 2-hydroxybenzoatato] oxovanadium (BSOV) \(270\), as potent hypoglycemic and great potential antidiabetic agents, were obtained from the reaction of \(269\) with vanadyl sulfate by heating at 70 °C for 12 h, in 50\% and 65\% yields, respectively (Scheme 82).\(^{156,157}\)

\[
\text{Scheme 82.}
\]

Ahn et al.\(^{158}\) reported KA derivatives containing trolox moiety \(271a\) and \(271b\) that exhibited potent tyrosinase inhibitory activity and radical scavenging activity. Reaction of KA with SOCl\(_2\) in DMF at room temperature, followed by treatment with potassium salts of trolox in DMF at 110–120 °C, gave the corresponding ester \(271a\). In addition, \(272\) was obtained from the reaction of chloro KA with Me\(_2\)SO\(_4\) in the presence of K\(_2\)CO\(_3\) in acetone under reflux conditions, which transformed into \(271b\) under the same conditions for \(271a\) (Scheme 83).

\[
\text{Scheme 83.}
\]

Liu et al.\(^{159}\) prepared the water-soluble chitosan oligosaccharide (COS) derivative \(276\), by treatment of \(273\) with benzaldehyde in MeOH at 60 °C for 12 h to give \(274\) and then by treatment with chloro KA in DMSO in the presence of pyridine at room temperature for 6 h leading to \(275\), followed by deprotection with HCl at room temperature for 12 h (Scheme 84). The synthesized \(276\) showed more antibacterial activity than the chitosan oligosaccharide \(273\).
Atkinson et al.\textsuperscript{160} synthesized kojic amines \textsuperscript{278} that are skeletal muscle relaxants and partial agonists in chick spinal cord neurons. The reaction of KA derivative \textsuperscript{277} with NH\textsubscript{3} in MeOH/CHCl\textsubscript{3} afforded kojic amine \textsuperscript{278} in 40\% yield and dimer \textsuperscript{279} in 20\% yield. Dikojic amine \textsuperscript{279} was deprotected in the presence of HBr-HOAc to give compound \textsuperscript{280} in 80\% yield (Scheme 85). Moreover, kojic amine \textsuperscript{278} was obtained in 81\% yield from reaction of chloro KA with NaN\textsubscript{3} in DMF, followed by reduction with HBr-HOAc-phenol.

KA–chitosan conjugate \textsuperscript{281}, an interesting compound for some applications in the food, cosmetics, and pharmacy industries, was synthesized from treatment of KA with chitosan in two different approaches: (a) covalent binding of chloro KA to chitosan via free amino groups, and (b) complexation of KA with iron(III) bound to chitosan as nanoparticles of subcolloidal FeO(OH). In the first way, chloro KA was reacted with chitosan \textsuperscript{273} in DMSO or DMF at room temperature for 7 days to produce chit/koj \textsuperscript{281} in 7\%–27\% yields. In the second way KA was attached to polysaccharide via FeO(OH) nanoparticles. Chitosan–FeO(OH) composite \textsuperscript{282} was formed by the reaction of chitosan with FeCl\textsubscript{3}, and then KA was chelated to peripheral iron(III) cations of the FeO(OH) particles bounded to chitosan \textsuperscript{283} (Scheme 86).\textsuperscript{161} In addition, KA–polymer-based magnetic nanocomposites, such as KA–chitosan–iron oxide nanoparticles, and KA–polyethylene glycol–iron oxide nanoparticles, were synthesized in 2014 for medical applications.\textsuperscript{162}
Ghasemi et al.\textsuperscript{163} reported a series of imidazolium and benzimidazolium salts of KA derivatives \textsuperscript{284} and \textsuperscript{285}, which were used to synthesize functionalized \textit{N}-heterocyclic carbenes and ionic liquids. Treatment of chloromethyl KA derivatives with \textit{N}-methylimidazole in CH\textsubscript{3}CN at 25 °C for 24 h or \textit{N}-alkylbenzimidazoles in the presence of KI at 70 °C for 10 h afforded imidazolium salts \textsuperscript{284a} or benzimidazolium salts \textsuperscript{285} in 83\%-88\% or 68\%-90\% yields, respectively. In addition, anion exchange reactions of imidazolium salts \textsuperscript{284a} with AgBF\textsubscript{4} in water at room temperature led to salts \textsuperscript{284b} as new ionic liquids (Scheme 87).

Rho et al.\textsuperscript{164,165} synthesized derivatives of KA containing thioether \textsuperscript{286}, sulfoxide \textsuperscript{287}, and sulfone \textsuperscript{288} linkages and evaluated their tyrosinase inhibitory and anti-inflammatory activities. Treatment of KA with SOCl\textsubscript{2} in DMF at room temperature, followed by the reaction with potassium salts of thiols in DMF at room temperature, gave kojyl thioether derivatives \textsuperscript{286}. Sulfoxide derivatives \textsuperscript{287} were achieved from the reaction of kojyl thioether derivatives \textsuperscript{286} with MCPBA in CH\textsubscript{2}Cl\textsubscript{2} at room temperature. Furthermore, kojyl thioether derivatives \textsuperscript{286} were transformed into sulfones \textsuperscript{288} by oxidation with oxone in a MeOH/water mixture at room temperature (Scheme 88).
4-Oxo-6-[(pyrimidin-2-ylthio)methyl]-4H-pyran-3-yl 4-nitrobenzoate 289, as a functional antagonist of the apelin (APJ) receptor, was prepared from the reaction of KA with SOCl₂ continued by treatment with RSH in the presence of NaOMe in CH₃CN and then the reaction with an acid chloride in the presence of CS₂CO₃ in CH₃CN (Scheme 89).

Rho et al. demonstrated KA derivatives 290-292 having two molecules of KA connected by various linkages such as ester, amide, and thioether. Treatment of kojyl chloride with NaN₃ in DMF and then with HBr-HOAC in phenol continued by the reaction with succinyl chloride in the presence of Et₃N in THF at room temperature for 1 h afforded product 290 in 91% yield. Compound 291 was prepared in 83% yield by reaction of kojyl chloride with potassium salt of kojyl succinic acid in DMF at 110 °C for 4 h. As outlined in Scheme 90, stirring of kojyl chloride with dithiols in the presence of Et₃N in THF at room temperature for 10 h gave the desired products 292 in good yields. In another report, a tetradentate chelator for Fe(III), Al(III), Cu(II), and Zn(II) metal ions was prepared by the reaction of KA with succinimide in the presence of TsCl or MsCl. Hudecova et al. described azidometalkojates from KA and evaluated their biological activity.

Treatment of KA with caprylic acid (1.4 equiv.) for 12 h or caprylic acid (2.8 equiv.) for 36 h in DMAP/DCC/CH₂Cl₂ at room temperature afforded KA octanoates 293 or 294 in 76% or 83% yields, respectively. In addition, KA octanoates 295 and 296 were obtained from the reaction of KA with di-tert-butyl-dicarbonate, followed by treatment with caprylic acid and N-BOC-aminoundecanoic acid under reaction conditions similar to those above and then deprotection using TFA in CH₂Cl₂ in 60% and 35% yields, respectively (Scheme 91).
Raku et al.\textsuperscript{171} reported regioselective synthesis of KA esters \textbf{298} by \textit{Bacillus subtilis} protease as outlined in Scheme 92. By addition of \textit{B. subtilis} protease to a mixture of KA and vinyl ester \textbf{297} in DMF and stirring at 30 °C for 7 days, \textit{O}-vinyladaipoyl KA \textbf{298} was obtained in 25% yield. Other compounds \textbf{298} were obtained in a similar procedure from the reaction of KA with vinylhexanoate, vinyl octanoate, and vinyl decanoate in 25%, 27%, and 13% yields, respectively.
The solid-phase synthesis of KA-tripeptides 302, exhibiting tyrosinase inhibitory activities, was reported by Kim et al.172 starting from KA. Treatment of KA with carbonyl diimidazole (CDI) in THF at room temperature for 24 h afforded activated KA 299 in 70% yield. On the other hand, the tripeptides were assembled on 2-chlorotrityl chloride (CTC) resin 300 using solid-phase Fmoc chemistry. N-Fmoc-amino acid was quantitatively introduced to the resin using DIPEA in NMP and then the general procedure of benzotriazole-1-yloxy-tris(dimethylamino)-phosphoniumhexafluorophosphate (BOP)-mediated coupling method gave resin-bound tripeptides 301, which then reacted with activated KA 299. After the final cleavage, KA-tripeptides 302 were obtained in 49%–95% yields (Scheme 93). KA–tripeptide amide as a tyrosinase inhibitor was also synthesized in a similar procedure by Noh et al.173

Kwak et al.174 described the synthesis of KA–phenylalanine amide 304, which exhibited an excellent tyrosinase inhibitory activity, from KA. Treatment of KA with CDI in dry THF for 24 h gave KA 7-imidazolide 299 in 78% yield, which was transformed into 303 in several steps by reaction with 303 as outlined in Scheme 94. In addition, complexation of 304 with CuCl₂ and Zn(OAc)₂ was developed. In 2011, Kwak et al.175 synthesized KA–amino acid amides and their metal complexes, and investigated their tyrosinase inhibitor activity.

N-Kojic-amino acid 305 and N-kojic-amino acid-kojate 306 derivatives were prepared from KA. The reaction of KA with amino acids was carried out using N,N′-disuccinimidyl carbonate and 4-dimethylaminopyridine and Et₃N in a mixture of CH₂Cl₂/CH₃CN (1/1) at room temperature, and N-kojic-amino acid derivatives 305 were obtained in 11%–42% yields. By stirring N-kojic-amino acid derivatives 305 with KA in the presence
of EDC in CH₂Cl₂ at 0 °C for 2 h, N-kojic-amino acid-kojiate derivatives 306 were achieved in 9%-36% yields (Scheme 95). 176

![Scheme 94.](image)

2.14. Metal complexation

KA was used for the preparation of Mn, Zn, and Sn complexes 307. Complexation of KA with Mn(OAc)₂·4H₂O or Zn(OAc)₂·2H₂O in EtOH at room temperature and Sn(Ot-Bu)₂ in toluene gave 307a, 307b, and 307c in 50%, 82%, and 45% yields (Scheme 96), respectively, which exhibited potential radioprotective activity. 177, 178 Lord et al. 179 synthesized complexes of molybdenum involving KA moiety 308 that were effective in lowering blood glucose and free fatty acid levels. MoO₂(ka)₂ 308 was prepared in 36% yield from addition of aqueous solution of KA to a stirred suspension of molybdate in water.

![Scheme 96.](image)

Protection of the enolic OH-group of KA with BnCl followed by the reaction with CrO₃ and then refluxing in NMP gave O-protected 3-HP, which was deprotected by refluxing in 4 M HCl to give 309. Treatment of 309...
with VO or Zn afforded VO or Zn complexes that showed insulin-mimetic activity (Scheme 97).\textsuperscript{180,181} Other antidiabetic VO\textsuperscript{2+} complexes containing KA ligand were also described.\textsuperscript{182}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme97}
\end{center}

\textit{N}-substituted tris(6-hydroxymethyl-3-hydroxy-4-pyridonato) complexes of Al(III), Ga(III), and In(III) \textsuperscript{312} were synthesized in good yield. First, the metal pyrone complexes \textsuperscript{311} were formed in situ and then reacted with primary amines to give appropriate 3-hydroxy-4-pyridinone complexes \textsuperscript{312} in 21\%–63\% yields under pH 4–9 (Scheme 98).\textsuperscript{183} Moreover, other complexes of KA with various metal ions have been reported.\textsuperscript{60,184–195}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme98}
\end{center}

\subsection*{2.15. Miscellaneous reactions}

4-[2-(2,4-Dinitro-phenyl)hydrazono]-6-(hydroxymethyl)-4\textsubscript{H}-pyran-3-ol \textsuperscript{313} was obtained in 85\% yield, from heating a solution of 2,4-dinitrophenylhydrazine and KA in EtOH under reflux for 4 h (Scheme 99). \textsuperscript{313} is a new probe for water analysis that acts as a selective colorimetric probe for the determination of Cu\textsuperscript{2+} ions at trace level.\textsuperscript{196}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme99}
\end{center}

Bastidas et al.\textsuperscript{197} reported the oxidation of KA catalyzed by H\textsubscript{2}O\textsubscript{2} in the presence of horseradish peroxidase (HRP) and Mn(OAc)\textsubscript{2}, leading to 6,6′-bis[5-hydroxy-2-(hydroxymethyl)-4\textsubscript{H}-pyran-4-one] \textsuperscript{314} in low yield. Urzúa et al.\textsuperscript{198} also oxidized KA to \textsuperscript{314} by manganese peroxidase (MnP) from \textit{Ceriporiopsis subvermispora} in the absence of H\textsubscript{2}O\textsubscript{2} (Scheme 100).
Sibi et al.\textsuperscript{199} described the conversion of pyrones 315 to pyrans 317, a structural unit present in compounds with significant biological activity. Enantioselective radical additions to pyrones 315 were carried out in the presence of 30 mol\% of 316 as a catalyst and RI using \text{Bu}_3\text{SnH}, \text{Et}_3\text{B}, and \text{O}_2 in CH\textsubscript{2}Cl\textsubscript{2} at \(-78\) °C, and pyrans 317 were produced in 35\%–98\% yields, with excellent diastereoselectivity (99:1), and moderate ee (72\%–93\%). Compounds 319 were also obtained by the reaction of 315 with allyltin in the presence of 318 as a catalyst and \text{Et}_3\text{B} and \text{O}_2 in CH\textsubscript{2}Cl\textsubscript{2} at \(-78\) °C in 77\%–90\% yields (Scheme 101).

Other reactions of KA are also reported in the literature, such as acylation and benzoylation,\textsuperscript{200–205} cyanoethylation,\textsuperscript{206} esterification,\textsuperscript{207–216} methylation,\textsuperscript{217,218} mesylation of KA,\textsuperscript{219} bromination,\textsuperscript{220} thiocyanation,\textsuperscript{221} cyanidation,\textsuperscript{222} glucosylation of KA,\textsuperscript{223,224} reaction of KA with acrylonitrile and acrylic ester,\textsuperscript{225,226} diethyl malonate,\textsuperscript{227} s-butyl mercaptan,\textsuperscript{228} glucose pentaacetate,\textsuperscript{229} ethyl levulinate\textsuperscript{230} and nucleophilic substitution reactions,\textsuperscript{231} formation of KA diacetate,\textsuperscript{232} Betti reaction of KA,\textsuperscript{233} synthesis of selenocyanato derivatives of KA,\textsuperscript{234} oxidation of the side chain in KA,\textsuperscript{235} and Hoesch reaction of KA.\textsuperscript{236}
3. Conclusion

We have presented an overview of the use of kojic acid in organic synthesis. The organic transformations of kojic acid were presented in order of the type of reaction. Thanks to the poly-functionality of kojic acid with different reactivity, such as carbonyl group, enol moiety, primary alcohol functional group, diene, and also aromatic characters, kojic acid was incorporated in various types of reactions, including aldol, Mannich, diazo coupling, conjugate addition, Claisen, and cycloaddition reactions. The synthesis of pyridone and pyridine heterocycles is one of the most important reactions of kojic acid. Moreover, there are some reactions at primary alcoholic moiety, such as halogenation, and oxidation, followed by other transformations. Although the synthesis of variety types of compounds and complexes through different one- or multistep kojic acid reactions are presented, the future evolution of other methodologies promises the synthesis of new organic compounds that were previously thought to be inaccessible.

References

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