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The reaction of dialkyl acetylenedicarboxylates with 2-oxo-2-phenylacetaldehyde in the presence of primary amines: synthesis of alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives

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A 3-component domino reaction approach between a primary amine, a dialkyl acetylenedicarboxylate, and 2-oxo-2-phenylacetaldehyde that affords novel alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives is reported. The reaction sequence consists of an initial Michael addition of primary amines to dialkyl acetylenedicarboxylates, followed by an aldol-like reaction with 2-oxo-2-phenylacetaldehyde, and then γ-lactonization to afford the products. This cascade reaction sequence represents a rapid and unprecedented route to the described biologically interesting molecules.

Key Words: Dialkyl acetylenedicarboxylates, 2-oxo-2-phenylacetaldehyde, primary amines, furan, Michael addition

Introduction

Multicomponent reactions (MCRs) allow more than 2 simple and flexible building blocks to be combined in practical, timesaving 1-pot operations. Due to their valued features such as atom economy, inherent

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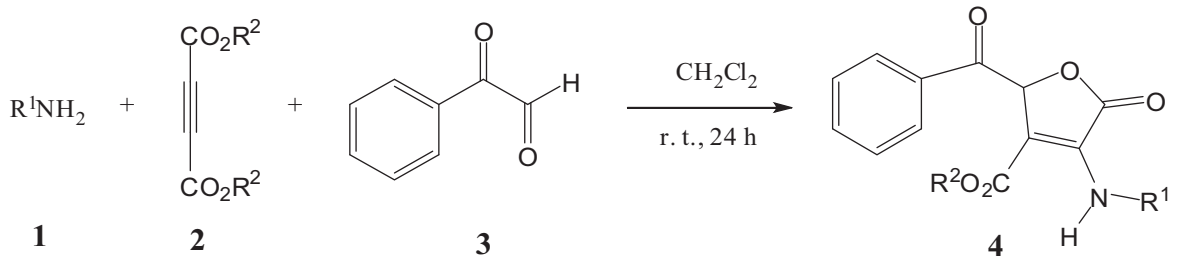
simple experimental procedures, and their 1-pot character, they are perfectly suited for automated synthesis.[1] Therefore, MCRs have attracted much attention because of their exceptional synthetic efficiency.[2–5] Since all the organic reagents employed are used and moved toward the target compound, purification of products resulting from MCRs is simple.[6,7] Isocyanide-based multicomponent reactions (abbreviated to IMCRs by Ugi and Dömling) have an advantageous position. The special features of IMCRs include unique synthetic potential, high atom economy, convergent nature, ease of implementation, and the generation of molecular diversity.[6–12]

For years, acetylenic esters have attracted the attention of organic chemists, mostly as Michael acceptors.[7,13,14] Recently, there has been increasing interest in the applications of acetylenic esters in multicomponent syntheses[1,7] especially for preparing stabilized phosphonium ylides.[15–17] Due to the atom economy, convergent character, and simplicity of 1-pot procedures, multicomponent condensation reactions have great potential in synthesis. The development of novel multicomponent condensation reactions is also receiving growing interest from industrial chemistry research groups, and represents a challenge for organic chemists.[1,7]

Furans, benzofurans, and their reduced forms are important core structures in many biologically active natural products. Moreover, they are useful building blocks in the total synthesis of natural products and pharmaceuticals.[18–21] Many naturally occurring furans have exhibited considerable biological activities, such as antitumor and cytotoxic properties[22,23] as well as antimicrobial,[24,25] antispasmodic,[26] and several other potentially useful activities.[27] In addition, furans are also present in commercially important products, such as agrochemical bioregulators, essential oils, cosmetics, dyes, photosensitizers, and flavoring and fragrance compounds.[27–29] As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[30,31] we sought to develop a convenient way to prepare alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives **4a-j**. Herein we report a hitherto unknown, 1-pot, 3-component reaction, which, starting from readily available 2-oxo-2-phenylacetaldehyde **3**, affords **4a-j** (Scheme 1).



4a: R^1=4-methoxybenzyl, R^2=CH_3; **4b**: R^1=2-methoxybenzyl, R^2=CH_3; **4c**: R^1=4-methoxybenzyl, R^2=CH_3CH_2; **4d**: R^1=4-methylbenzyl, R^2=CH_3; **4e**: R^1=4-methylbenzyl, R^2=CH_3CH_2; **4f**: R^1=benzyl, R^2=CH_3; **4g**: R^1=benzyl, R^2=CH_3CH_2; **4h**: R^1=4-fluorobenzyl, R^2=CH_3; **4i**: R^1=4-fluorobenzyl, R^2=CH_3CH_2; **4j**: R^1=propyl, R^2=CH_3

Scheme 1. Three-component synthesis of alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives **4** (see Experimental part).

Experimental

The starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The methods used to follow the reactions were TLC and NMR, which indicated

that there was no side product. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured ($CDCl_3$) with a BRUKER DRX-250 AVANCE spectrometer at 250.0 and 62.5 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Flash chromatography columns were prepared with Merck silica gel (F_{254}) powder.

General procedure for the preparation of compound 4a

To a magnetically stirred solution of 4-methoxybenzyl amine (1 mmol, 0.137g) was added dimethyl acetylenedicarboxylate (1 mmol, 0.142 g) in CH_2Cl_2 (7 mL). The mixture was stirred for 1 h. Then oxo-2-phenylacetaldehyde **3** (1 mmol, 0.134g) was added, and the mixture was stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel (F_{254}); petroleum ether–AcOEt (10:2). The solvent was removed under reduced pressure and the products were obtained. The characterization data of the compounds are given below.

Methyl 2-benzoyl-4-[(4-methoxybenzyl)amino]-5-oxo-2,5-dihydro-3-furancar- boxylate (4a)

Yellow oil, yield: 346 mg (91%). IR (KBr): 3350 (NH), 3000, 1770, 1700, 1670, 1600, 1475, 1150 cm^{-1}; ^{1}H-NMR δ 6.86-8.06 (m, 9H, arom), 6.32 (s, 1H, CH), 4.82-4.98 (m, 2H, CH_2), 3.60 and 3.80 (2s, 6H, $2OCH_3$), 2.17 (s, 1H, NH exchangeable by D_2O). ^{13}C-NMR δ 192.3, 169.1, 167.5 (3C=O), 159.1, 137.6, 130.4 (3C arom), 134.1, 129.3, 129.1, 129.0, 128.8 (9CH arom), 135.1, 114.2 (2C, alkene), 76.2 (CH), 55.3, 51.3 (2MeO), 46.0 (CH_2). Ms m/z (%) 381 (M^+, 14), 276 (19), 136 (29), 121 (89), 105 (100), 77 (53). Anal. Calcd. for $C_{21}H_{19}NO_6$ (381.38): C 66.13, H 5.02, N 3.67. Found: C 66.18, H 5.06, N 3.63.

Methyl 2-benzoyl-4-[(2-methoxybenzyl)amino]-5-oxo-2,5-dihydro-3-furancar- boxylate (4b)

Yellow oil, yield: 361 mg (95%). IR (KBr): 3400 (NH), 3050, 3000, 1770, 1700, 1670, 1600, 1475, 1120 cm^{-1}; ^{1}H-NMR δ 6.91-8.05 (m, 9H, arom), 6.27 (s, 1H, CH), 4.96-5.04 (m, 2H, CH_2), 3.59, 3.89 (2s, 6H, 2MeO), 2.19 (s, 1H, NH). ^{13}C-NMR δ 192.4, 169.1, 164.3, (3C=O), 157.7, 136.8, 129.6 (3C arom), 135.2, 110.4 (2C alkene), 134.1, 129.2, 129.1, 129.0, 128.8, 126.57, 120.6 (9CH arom), 76.2 (CH), 55.3, 51.2 (2MeO), 42.2 (CH_2). Ms m/z (%) 381 (M^+, 2), 105 (100), 135 (50), 121 (87), 77 (91). Anal. Calcd. for $C_{21}H_{19}NO_6$ (381.38): C 66.13, H 5.02, N 3.67. Found: C 66.17, H 4.99, N 3.70.

Ethyl 2-benzoyl-4-[(4-methoxybenzyl)amino]-5-oxo-2,5-dihydro-3-furancar- boxylate (4c)

Yellow oil, yield: 343 mg (87%). IR (KBr): 3300 (NH), 3100, 3000, 1750, 1700, 1670, 1600, 1475, 1465, 1375, 1100 cm^{-1}; ^{1}H-NMR δ 6.90-7.81 (m, 9H, arom), 6.35 (s, 1H, CH), 4.83-4.98 (m, 2H, CH_2), 4.03 (q, J = 7.25

Hz, 2H, CH_2 of Et), 3.67 (s, 3H, MeO), 2.17 (s, 1H, NH), 1.18 (t, J = 7.25 Hz, 3H, CH_3). ^{13}C-NMR δ 192.7, 169.0, 165.4 (3C=O), 159.1, 137.1, 130.4 (3C arom), 135.3, 114.2 (2C alkene), 134.2, 129.1, 129.0, 128.8, 128.7 (9CH arom), 75.8 (CH), 55.3, 60.4 ($2CH_2$), 13.8 (CH_3). Ms m/z (%) 395 (M^+, 6), 373 (33), 195 (39), 124 (84), 109 (100). Anal. Calcd. for $C_{22}H_{21}NO_6$ (395.41): C 66.83, H 5.35, N 3.54. Found: C 66.80, H 5.39, N 3.49.

Methyl 2-benzoyl-4-[(4-methylbenzyl)amino]-5-oxo-2,5-dihydro-3-furancarboxylate (4d)

Yellow oil, yield: 299 mg (82%). IR (KBr): 3450 (NH), 3050, 3000, 1735, 1700, 1600, 1475,1465, 1100 cm^{-1}; ^{1}H-NMR δ 7.60-8.05 (m, 9H, arom), 6.02 (s, 1H, CH), 4.09-4.16 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3), 2.17 (s, 1H, NH). ^{13}C-NMR δ 192.8, 169.2, 165.6 (3C=O), 136.8, 134.9, 132.2 (3C arom), 135.2, 116.3, (2C alkene), 129.6, 129.1, 128.8, 128.6, 128.3 (9CH arom), 71.4 (CH), 51.2 (MeO), 44.3 (CH_2), 21.1 (CH_3). Anal. Calcd. for $C_{21}H_{19}NO_5$ (365.38): C 69.03, H 5.24, N 3.83. Found: C 69.07, H 5.19, N 3.85.

Ethyl 2-benzoyl-4-[(4-methylbenzyl)amino]-5-oxo-2,5-dihydro-3-furancarboxylate (4e)

Yellow oil, yield: 288 mg (76%). IR (KBr): 3350 (NH), 3070, 3000, 1750, 1735, 1700, 1600, 1475, 1170 cm^{-1}; ^{1}H-NMR δ 6.80-8.21 (m, 9H, arom), 6.02 (s, 1H, CH), 3.42- 3.69 (m, 2H, CH_2), 4.10 (q, J=7.25, 2H, CH_2 of Et), 2.30 (s, 3H, CH_3), 2.19 (s, 1H, NH), 1.20 (t, J= 7.25, 3H, CH_3). ^{13}C-NMR δ 192.7, 170.1, 166.4 (3C=O), 135.2, 126.0, (C alkene), 135.1, 133.6, 129.5 (3C arom), 129.1, 128.8, 128.6, 128.5, 128.4 (9CH arom), 71.4 (CH), 53.3 (CH_2O), 47.8 (CH_2), 14.5, 21.0 ($2CH_3$). Anal. Calcd. for $C_{22}H_{21}NO_5$ (379.41): C 69.64, H 5.58, N 3.69. Found: C 69.60, H 5.61, N 3.64.

Methyl 2-benzoyl-4-(benzylamino)- 5-oxo-2,5 dihydro-3-furancarboxylate (4f)

Yellow oil, yield: 288 mg (79%). IR (KBr): 3450 (NH), 3050, 3000, 1750, 1700, 1600, 1475, 1150 cm^{-1}; ^{1}H-NMR δ 7.15-8.30 (m, 10H, arom), 6.09 (s, 1H, CH), 4.14-4.29 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 2.17 (s, 1H, NH). ^{13}C-NMR δ 191.9, 169.3, 166.0 (3C=O), 136.5, 132.5 (2C arom), 135.2, 126.0 (2C alkene), 130.3, 129.4, 129.3, 129.3, 126.9, 126.4 (10CH arom), 76.1(CH), 51.2 (MeO), 42.4 (CH_2). Anal. Calcd. for $C_{20}H_{17}NO_5$ (351.35): C 68.37, H 4.88, N 3.99. Found: C 68.32, H 4.84, N 4.02.

Ethyl 2-benzoyl-4-(benzylamino)-5-oxo-2,5 dihydro-3-furancarboxylate (4g)

Yellow oil, yield: 266 mg (73%). IR (KBr): 3450 (NH), 3050, 3100, 3000, 1750, 1700, 1600, 1475, 1170 cm^{-1}; ^{1}H-NMR δ 7.07-8.05 (m, 10H, arom), 6.00 (s, 1H, CH), 4.10 (q, J=7.12, 2H, CH_2 of Et), 3.44-3.73 (m, 2H, CH_2), 2.15 (s, 1H, NH), 1.10 (t, J=7.12 Hz, 3H, CH_3). ^{13}C-NMR δ 192.5, 168.5, 164.2 (3C=O), 136.9, 126.4, (2C alkene), 136.1, 134.3 (2C arom), 134.1, 129.6, 129.3, 129.1, 127.2, 126.1 (10CH arom), 76.1 (CH), 53.9 (CH_2O), 48.1 (CH_2), 13.5 (CH_3). Anal. Calcd. for $C_{21}H_{19}NO_5$ (365.38): C 69.03, H 5.24, N 3.83. Found: C 69.06, H 5.19, N 3.87.

Methyl-2-benzoyl-4-[(4-fluorobenzyl)amino]-5-oxo-2,5-dihydro-3-furancar- boxylate (4h)

Yellow oil, yield: 276 mg (75%). IR (KBr): 3400 (NH), 3070, 3000, 1770, 1750, 1700, 1600, 1475, 1150 cm^{-1}; ^{1}H-NMR δ 6.91-8.18 (m, 9H, arom), 5.94 (s, 1H, CH), 4.10-4.25 (m, 2H, CH_2), 3.41 (s, 3H, OCH_3), 2.11 (s, 1H, NH). ^{13}C-NMR δ 192.1, 170.0, 167.2 (3C=O), 162.8 (d, $^1J_{CF}$ = 212.2 Hz, C, arom), 143.2, 122.4 (2C alkene), 135.8, 133.6 (2C arom), 132.4, 130.2, 129.2 (5CH arom), 129.8 (d, $^3J_{CF}$ = 8.8 Hz, 2CH, arom), 115.3 (d, $^2J_{CF}$ = 21.4 Hz, 2CH, arom), 76.1 (CH), 50.4 (MeO), 47.4 (CH_2). Anal. Calcd. for $C_{20}H_{16}FNO_5$ (369.34): C 65.04, H 4.37, N 3.79. Found: C 65.01, H 4.32, N 3.84.

Ethyl 2-benzoyl-4-[(4-fluorobenzyl)amino]-5-oxo-2,5-dihydro-3-furancarboxylate (4i)

Yellow oil, yield: 268 mg (70%). IR (KBr): 3450 (NH), 3050, 3000, 1750, 1700, 1600, 1475, 1200 cm^{-1}; ^{1}H-NMR δ 6.86-8.20 (m, 9H, arom), 5.97 (s, 1H, CH), 4.20 (q, J=7.0, 2H, CH_2 of Et), 3.40- 3.75 (m, 2H, CH_2), 2.10 (s, 1H, NH), 1.30 (t, J=7.0, 3H, CH_3). ^{13}C-NMR δ 192.8, 168.1, 165.8 (3C=O), 162.0 (d, $^1J_{CF}$ = 244.7 Hz, C, arom), 142.9, 123.3 (2C alkene), 136.2, 134.5 (2C arom), 132.05, 130.29, 129.1 (5CH arom), 129.9 (d, $^3J_{CF}$ = 8.1 Hz, 2CH, arom), 115.3 (d, $^2J_{CF}$ = 20.8 Hz, 2CH, arom), 76.1 (CH), 54.0 (MeO), 47.3 (CH_2), 11.0 (CH_3). Anal. Calcd. for $C_{21}H_{18}FNO_5$ (383.37): C 65.79, H 4.73, N 3.65. Found: C 65.84, H 4.70, N 3.69.

Methyl 2-benzoyl-5-oxo-4-(propylamino)-2,5 dihydro-3-furancarboxylate (4j)

Yellow oil, yield: 272 mg (90%). IR (KBr): 3350 (NH), 3050, 3000, 2970, 1770, 1700, 1650, 1475, 1120 cm^{-1}; ^{1}H-NMR δ 7.50-8.05 (m, 5H, arom), 6.30 (s, 1H, CH), 3.72 (t, J=7.0, 2H, CH_2), 3.61 (s, 3H, OCH_3), 2.11 (s, 1H, NH), 1.60-1.65 (m, 2H, CH_2), 0.90 (t, J=7.0, 3H, CH_3). ^{13}C-NMR δ 165.1, 168.5, 191.1 (3C=O), 134.8, 123.3 (2C alkene), 134.1 (C arom), 132.6, 129.1, 128.8 (5CH arom), 75.4 (CH), 53.4 (MeO), 24.3, 51.2 ($2CH_2$), 11.01(CH_3). EI ms: m/z: 303 (M^+, 25), 105 (100), 77 (66), 198 (50), 239 (39). Anal. Calcd. for $C_{16}H_{17}NO_5$ (303.31): C 63.36, H 5.65, N 4.62. Found: C 63.32, H 5.69, N 4.58.

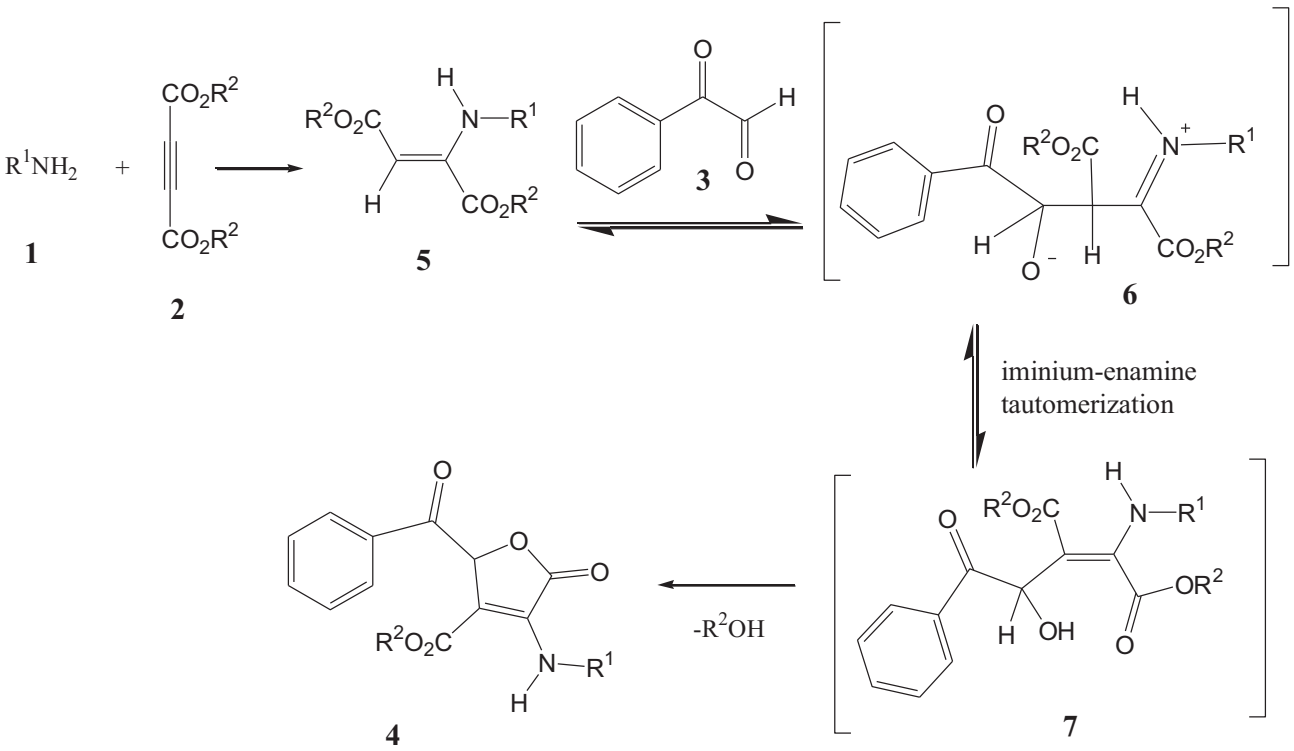
Results and discussion

We examined the reaction of the primary amines with dialkyl acetylenedicarboxylate in the presence of 2-oxo-2-phenylacetaldehyde in dry CH_2Cl_2 at room temperature (25 °C) and we obtained the corresponding alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives **4** in 70%-95% yields. ^{1}H and ^{13}CNMR spectra of the crude products clearly indicated the formation of alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate **4**.

The structures of the products were deduced from their IR, mass, ^{1}H-NMR, and ^{13}C-NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^{1}H-NMR spectrum of **4a** consisted of a singlet for NH (δ 2.17), exchangeable by D_2O, 2 singlets for OMe (δ 3.60 and 3.80), a multiplet at δ 4.82-4.98 ppm for CH_2 of the benzyl group, a singlet for CH (δ 6.32), and a multiplet at δ 6.86-8.06 ppm for H-aromatic. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 17 distinct resonances;

partial assignment of these resonances is given in the experimental section. The ^{1}H- and ^{13}C-NMR spectra of compounds **4b-j** were similar to those of **4a**, except for the aromatic moiety, which exhibited characteristic signals with appropriate chemical shifts.

A possible mechanism for the present reaction is shown in Scheme 2, which envisages a tandem sequence. On the basis of the well established chemistry of trivalent nitrogen nucleophiles, the successful nucleophilic attack by amines on a carbon atom is facilitated when the latter is conjugated with a carbonyl group, or when it is a part of an unsaturated bond otherwise activated. First, nucleophilic Michael addition of the primary amine **1** to the β-carbon of the electron-deficient alkyne **2** generates the aminobutendioate **5** as an electron-rich enaminone.[32] The aldehyde carbonyl group, such as 2-oxo-2-phenylacetaldehyde possesses outstanding electrophilic (electron-pair accepting) properties.[33] The polar reactions with carbanion-like (electron rich) species, such as enaminones give rise to nucleophilic addition reactions of carbonyl groups under exclusive C–C bond formation.[34] Subsequent nucleophilic aldol-like attack of aminobutendioate **5** to the aldehyde carbonyl group of the 2-oxo-2-phenylacetaldehyde **3** would yield iminium–oxoanion intermediate **6**, which can be tautomerized to dialkyl 2-(1-hydroxy-2-oxo-2-phenylethyl)-3-(alkylamino)-2-butenedioate **7**. γ-Lactonization of **7** would produce the alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives **4**



Scheme 2. Proposed mechanism for the formation of alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3- furan carboxylate derivatives **4a-j**.

Conclusions

The reported method offers a mild, simple, and efficient route for the preparation of alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives **4**. Its ease of work-up, high yields, and fairly mild reaction conditions make it a useful addition to modern synthetic methodologies. Other aspects of this process are under investigation.

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