Synthesis of Novel Proponohydrazides and Their Hydrolysis Reactions

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4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)-2,3-furandione 1 reacted with N-aryl substituted phenyl-
hydrazones 3a-h via the p,p'-dimethoxydibenzoylketene intermediate 2 giving the proponohydrazide
derivatives 5a-h. In addition, compounds 5a-h were converted into corresponding pyrazolone deriva-
tives 7i,j by the reactions of hydrolysis in acidic solution. The structures of these new synthesized
compounds were determined by ¹³C NMR, ¹H NMR and IR spectroscopic data and elemental analysis.

Key Words: Furan-2,3-dione, Proponohydrazide, Hydrolysis, Pyrazolone.

Introduction

The reactions of the substituted 2,3-furandiones with various nucleophiles or dienophiles in different solvents
and at different temperatures have been studied recently¹⁻⁴. In a previous study, 4-(4-methoxybenzoyl)-
5-(4-methoxyphenyl)-2,3-furandione 1 was obtained from the cyclocondensation reaction that occurs be-
tween p,p'-dimethoxydibenzoylketene 2 and oxalychloride⁵⁻⁶. We have previously reported the synthesis
of some 1H-pyrazole-3-carboxylic acid and pyrazolo[3,4-d] pyridazinone compounds from the reaction of
4-benzoyl-5-phenyl-furan-2,3-dione and various phenylhydrazones in benzene solvent or without any solvent
in approximately 1 h⁷. In general, furan-2,3-diones are considered convenient and versatile synthons in het-
erocyclic synthesis. These compounds have been demonstrated to be a versatile, multifunctional, synthetic
building block for the construction of novel heterocyclic systems⁸. Different types of furan-2,3-diones have
been used successfully in the synthesis of various heterocycles for a long time⁹. Thermal decomposition of
the furan-2,3-diones leads to the formation of reactive α-oxoketenes (acylketenmes) as intermediates¹⁰⁻¹². In
general, α-oxoketenes include thermolysis and photolysis of 2-diazo-1,3-dicarbonyl compounds¹³,¹⁴, solution
thermolysis or photolysis of 1,3-dioxinones¹⁵,¹⁶ and thermolysis of furan-2,3-diones¹⁷, β-keto-esters¹⁸ and
acid chlorides¹⁹. These ketenes are currently of considerable interest, not only because of mechanistic

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and theoretical considerations\textsuperscript{20}–\textsuperscript{22}, but also because of their use as synthetic building blocks in organic synthesis\textsuperscript{23}–\textsuperscript{26}. Several acylketenes can be easily detected by low-temperature IR spectroscopy at 77 °K or in Ar matrix condition at 12 °K\textsuperscript{27}.

In recent years, many methods have been reported for the synthesis of various pyrazolone derivatives\textsuperscript{28}–\textsuperscript{31}. The reaction of furandiones with hydrazines can be given as a simple example of pyrazolone derivatives\textsuperscript{31}. Some of these compounds are known to show dyestuff and pigment substance properties and as well as biological activities\textsuperscript{28}–\textsuperscript{30}.

In this study, we synthesized proponohydrazide derivatives 5a-h from N-aryl substituted phenylhydrazones 3a-h and 2. Compound 2 is a product that cannot be isolated. In addition, 2 novel pyrazolone derivatives 7i,j were synthesized from the reactions of hydrolysis of compounds 5a-h in acidic solution.

**Experimental**

Solvents were dried by refluxing with appropriate drying agents (metallic sodium for ether, CaCl\textsubscript{2} or Na\textsubscript{2}SO\textsubscript{4} for benzene, toluene etc.) and distilled. Melting points were determined by the use of a Büchi melting point apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer Model 1108. The IR spectra were obtained as potassium bromide pellets using a Jasco Plus Model 460 FTIR spectrometer. The \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Varian XL-200 (200 MHz) and Varian XL-200 (50 MHz) spectrometers using tetramethylsilane as an internal standard. All experiments were followed by TLC using DC Alufolion kieselgel 60 F 254 Merck and with a Model Camag TLC lamp (254/366 nm).

**General method for the synthesis of compounds 5**

Compound 1 and the corresponding N-aryl substituted phenylhydrazones 3a-h were refluxed in xylene for 1-3 h. After the solvent was removed by evaporation, the oily residue was treated with dry ether and the crude product formed was recrystallized from an appropriate solvent to afford the desired compound.

2-(4-methoxybenzoyl)-N’-benzylidene-3-(4-methoxyphenyl)-3-oxo-N-phenyl-proponohydrazide (5a): Compound 5a was obtained from 1 (0.30 g, 0.88 mmol) and benzaldehyde phenylhydrazone 3a (0.17 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from n-butanol. The yield 0.29 g (65%); mp 211 °C. IR: 1654, 1657, 1660 cm\textsuperscript{−1} (C=O). \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 8.05-6.93\) (m, 20H, Ar-H, N=CH, keto-C-H). 3.86 ppm (s, 6H, CH\textsubscript{3}O). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 192.76\) (Ar-CO), 170.36 (N-C=O), 165.83-115.99 (Aromatic C), 65.57 (diketo, C-H), 57.53 ppm (CH\textsubscript{3}O).

Anal. Caled. For C\textsubscript{31}H\textsubscript{26}N\textsubscript{2}O\textsubscript{5}: C, 73.51; H, 5.13; N, 5.53. Found: C, 73.29; H, 5.29; N, 5.63.

2-(4-methoxybenzoyl)-N’-(2,4-dimethylphenyl)methylene-3-(4-methoxyphenyl)-3-oxo-N-phenyl-proponohydrazide (5b): Compound 5b was obtained from 1 (0.30 g, 0.88 mmol) and benzaldehyde-2,4-dimethylphenylhydrazone 3b (0.19 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from ethanol. The yield 0.19 g (40%); mp 205 °C. IR:1675, 1687 cm\textsuperscript{−1} (C=O). \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta = 8.05-6.93\) (m, 18H, Ar-H, N=CH, keto-CH). 3.86 ppm (s, 6H, CH\textsubscript{3}O), 3.13-2.37 ppm (s, 6H, CH\textsubscript{3}). \textsuperscript{13}C NMR (CDCl\textsubscript{3}): \(\delta = 192.78, 192.68\) (Ar-CO), 169.76 (N-C=O), 165.79-115.95 (Aromatic C), 65.76 (diketo, C-H), 57.52 ppm (CH\textsubscript{3}O), 23.19, 19.29 ppm (CH\textsubscript{3}).

Anal. Caled. For C\textsubscript{33}H\textsubscript{30}N\textsubscript{2}O\textsubscript{5}: C, 74.51; H, 5.61; N, 5.24. Found: C, 74.45; H, 5.56; N, 5.31.
2-(4-methoxybenzoyl)-N’-(diphenylmethylene)-3-(4-methoxyphenyl)-3-oxo-N-phenyl-proponohydrazide (5c): Compound 5c was obtained from 1 (0.30 g, 0.88 mmol) and benzophenone phenylhydrazone 3c (0.24 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from propan-2-ol. The yield 0.31 g (60%); mp 142°C. IR: 1674, 1678 cm\(^{-1}\) (C=O). 

\[^1\]H NMR (CDCl\(_3\)): \(\delta = 8.01-6.82\) (m, 25H, Ar-H, N=CH, keto-CH), 3.82 ppm (s, 6H, CH\(_3\)O). 

\[^1\]3C NMR (CDCl\(_3\)): \(\delta = 192.61\) (Ar-CO), 170.46 (N-C=O), 166.46-115.85 (Aromatic C), 66.05 (diketo, C-H) and 57.47 ppm (CH\(_3\)O).


2-(4-methoxybenzoyl)-N’-[4-ethoxyphenyl)methylene]-3-(4-methoxyphenyl)-3-oxo-N-phenyl-proponohydrazide (5d): Compound 5d was obtained from 1 (0.30 g, 0.88 mmol) and 4-ethoxybenzaldehyde phenylhydrazone 3d (0.21 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from ethanol. The yield 0.27 g (55%); mp 202°C. IR: 1670, 1676 cm\(^{-1}\) (C=O). 

\[^1\]H NMR (CDCl\(_3\)): \(\delta = 9.05-6.62\) (m, 19H, Ar-H, N=CH, keto-CH), 4.02-3.91 (q, 2H, J = 6.96 Hz, OCH\(_2\)), 3.85, 3.81 (s, 6H, CH\(_3\)O), 1.40, 1.37, 1.33 ppm (t, J = 13.08 Hz, -C-CH\(_3\)). 

\[^1\]3C NMR (CDCl\(_3\)): \(\delta = 192.85\) (Ar-CO), 170.15 (N-C=O), 165.79-115.97 (Aromatic C), 65.68 (diketo, C-H), 57.51 (CH\(_3\)O), 16.65 ppm (CH\(_3\)).

Anal. Calcd. For C\(_{33}\)H\(_{31}\)N\(_2\)O\(_6\): C, 71.86; H, 5.62; N, 5.08. Found: C, 72.15; H, 5.34; N, 5.09.

2-(4-methoxybenzoyl)-N’-(4-chlorophenyl)methylene]-3-(4-methoxyphenyl)-3-oxo-N-phenyl-proponohydrazide (5e): Compound 5e was obtained from 1 (0.30 g, 0.88 mmol) and 2-chlorophenyl phenylhydrazone 3e (0.20 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from n-butanol. The yield 0.25 g (53%); mp 216°C. IR: 1690, 1698 cm\(^{-1}\) (C=O). 

\[^1\]H NMR (CDCl\(_3\)): \(\delta = 8.04-6.89\) (m, 19H, Ar-H, N=CH, keto-CH), 3.86 ppm (s, 6H, CH\(_3\)O). 

\[^1\]3C NMR (CDCl\(_3\)): \(\delta = 192.64\) (Ar-CO), 170.38 (N-C=O), 165.89-116.01 (Aromatic C), 57.51 ppm (CH\(_3\)O).

Anal. Calcd. For C\(_{31}\)H\(_{25}\)N\(_2\)O\(_5\)Cl: C, 68.82; H, 4.62; N, 5.18. Found: C, 68.86; H, 4.52; N, 5.09.

2-(4-methoxybenzoyl)-N’-(1-naphthylmethylene)-3-(4-methoxyphenyl)-3-oxo-N-phenyl-proponohydrazide (5f): Compound 5f was obtained from 1 (0.30 g, 0.88 mmol) and benzaldehyde-1-naphthyl phenylhydrazone 3f (0.19 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from n-propyl alcohol. The yield 0.33 g (68%); mp 213°C. IR: 1659, 1671, 1698 cm\(^{-1}\) (C=O). 

\[^1\]H NMR (CDCl\(_3\)): \(\delta = 8.06-6.93\) (m, 22H, Ar-H, N=CH, keto-CH), 3.86 ppm (s, 6H, CH\(_3\)O). 

\[^1\]3C NMR (CDCl\(_3\)): \(\delta = 192.83\) (Ar-CO), 170.23 (N-C=O), 165.87-116.04 (Aromatic C), 65.46 (diketo, C-H), 57.52 ppm (CH\(_3\)O).

Anal. Calcd. For C\(_{35}\)H\(_{28}\)N\(_2\)O\(_5\): C, 75.53; H, 5.03; N, 5.03. Found: C, 75.31; H, 5.04; N, 5.14.

2-(4-methoxybenzoyl)-N’-[4-(ethoxyphenyl)methylene]-3-(4-methoxyphenyl)-3-oxo-N-phenyl-proponohydrazide (5g): Compound 5g was obtained from 1 (0.30 g, 0.88 mmol) and anisaldehyde phenylhydrazone 3g (0.20 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from ethanol. The yield 0.21 g (45%); mp 192°C. IR: 1680, 1685, 1693 cm\(^{-1}\) (C=O). 

\[^1\]H NMR (CDCl\(_3\)): \(\delta = 3.79-3.68\) (s, 9H, CH\(_3\)O), 7.96-6.57 ppm (m, 19H, Ar-H, N=CH, keto-CH). 

\[^1\]C NMR (CDCl\(_3\)): \(\delta = 191.30\) (Ar-CO), 168.62 (N-C=O), 164.15-113.69 (Aromatic C), 64.02 (diketo, C-H), 55.66 ppm (CH\(_3\)).

Anal. Calcd. For C\(_{32}\)H\(_{28}\)N\(_2\)O\(_6\): C, 71.50; H, 5.19; N, 5.20. Found: C, 71.30; H, 5.40; N, 5.25.
2-(4-methoxybenzoyl)-N'-(4-(dimethylamino)phenyl)methylen-3-(4-methoxy phenyl)-3-oxo-N-phenyl-proponohydrazide (5h): Compound 5h was obtained from 1 (0.30 g, 0.88 mmol) and 4-dimethylamino-benzaldehyde phenylhydrazone, 3h, (0.19 g, 0.88 mmol). Following the general procedure reported above, a white solid was obtained. It was recrystallized from ethanol. The yield 0.33 g (70%); mp 228°C. IR: 1650, 1655 cm\(^{-1}\) (C=O).

1HNMR (CDCl\(_3\)): \(\delta= 8.07-6.48\) (m, 19H, Ar-H, N=CH, keto-CH), 3.87 (s, 6H, CH\(_3\)O), 2.94 ppm (s, 6H, CH\(_3\)).

Anal. Calcd. For C\(_{33}\)H\(_{31}\)N\(_3\)O\(_5\): C, 72.13; H, 5.64; N, 7.65. Found: C, 72.27; H, 5.59; N, 7.75.

4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-2-phenyl-2,3-dihydro-1\(H\)-3-pyrazolone (7i):

To a solution of 5a (0.22 g, 0.45 mmol) or 5b-g in water (10 mL) was added 5 mL of acetic acid. Then the mixtures were heated under reflux for 30 min. The residual oils were cooled and treated with ether/petroleum ether (40-60 °C) and the crude products were extensively washed with dry n-hexane. All the products were obtained as the same yellow solid. Compound 7i was obtained in 68-75% yield; mp 161°C. IR: 3300 (N-H), 1604, 1600 cm\(^{-1}\) (C=O).

1HNMR (CDCl\(_3\)): \(\delta= 12.68\) (s, 1H, N-H), 8.00-6.59 (m, 13H Ar-H), 3.75 ppm (s, 6H, CH\(_3\)O).

13CNMR (CDCl\(_3\)): \(\delta= 192.18\) (Ar-CO), 164.87 (Ph-N-C=O), 152.89 (C=N-H) 139.79-115.11 (Aromatic C), 103.81 (OC-C=CO), 57.29 ppm (CH\(_3\)O).


2-(2,4-dimethyl)-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-2-phenyl-2,3-dihydro-1\(H\)-3-pyrazolone (7j):

To a solution of 5h (0.26 g, 0.49 mmol) in water (10 mL) was added 5 mL of acetic acid. Then the mixture was heated under reflux for 30 min. The residual oil was cooled and treated with ether/petroleum ether (40-60 °C) and the crude product was extensively washed with dry n-hexane. A yellow solid was obtained. Compound 7j was obtained in 63% yield; mp 169°C. IR: 3350 cm\(^{-1}\) (N-H). 1602, 1600 (C=O), 1580 (C=C).

1HNMR (CDCl\(_3\)): \(\delta= \) (not detectable, N-H), 7.71-6.62 (m, 11H, Ar-H), 3.77 (s, 6H, CH\(_3\)O), 2.34 ppm (CH\(_3\)).

13CNMR (CDCl\(_3\)): \(\delta= 192.69\) (Ar-CO), 164.78, 152.62 (C-NH) 139.43-115.08 (Aromatic C), 103.47 (OC-C=CO), 57.30 (CH\(_3\)O), 21.81, 21.26 ppm (CH\(_3\)).

Anal. Calcd. For C\(_{26}\)H\(_{24}\)N\(_2\)O\(_4\): C, 72.90; H, 5.61; N, 6.54. Found: C, 72.64; H, 5.41; N, 6.36.

**Results and Discussion**

A number of proponohydrazide derivatives were obtained in good yields (65-75% ) from the reaction of 1 and the corresponding 3a-h. The reactions of 1 and 3a-h were realized in boiling xylene. The recycling of 1 to the 3-aminooxazine derivatives 4a-h was not carried out by reacting under different conditions such as temperature and solvent. Instead of 4a-h compounds, the corresponding 5a-h compounds were isolated. The proposed reaction pathway from 1 to 5 is shown in Scheme 1. The elucidation of the structures of 5a-h was deduced mainly from elemental analysis and IR, \(^1\)HNMR and \(^13\)C NMR spectroscopic data. The molecular skeleton of 5 was previously determined by X-ray analysis\(^{32}\). It was stated that when various phenylhydrazones were added to 4-benzoyl-5-phenyl-furan-2,3-dione with the reaction of Michael type addition in benzene, 1\(H\)-pyrazole-3-carboxylic acid and pyrazolo[3,4-d] pyridazinone compounds were obtained\(^7\). In our study, compounds 1 and 3a-h did not give ring products similar to pyrazole and pyridazinones compounds. The reason for that might be the inductive effect of the methoxy group in the position attached to C-5 of 1. Thermal decomposition and decarbonylation of compound 1 leads to 2 as an intermediate and then it reacts easily with various 3a-h nucleophilic addition. In the IR spectrum
of compound 5a, the carbonyl absorption bands were at about 1660, 1657 and 1654 cm$^{-1}$ respectively. Important structural information about 5a was obtained from the $^1$H NMR spectrum. In the $^1$H NMR, there is no detectable signal for the OH group and it is possible to see the C-H-signal (at 6.93 ppm) in only the diketo form. The enol form was not observed in CDCl$_3$ solution of 5a in solid state. This is agreement with earlier results obtained from various dibenzoylacetic acid derivatives$^7$, which showed no tendency toward enolization under the measurement conditions. In the $^{13}$C NMR spectrum of 5a, the peak at 65.57 ppm represents C-H in the diketo form. The cyclization reactions of compounds 5a-h in H$_2$O/AcOH solution led to the formation of pyrazolone derivatives 7i and 7j, respectively. The reaction pathway is illustrated in Scheme 2. According to the reaction mechanism, compounds 7 are obtained by variation of the R$_3$ group attached to proponohydrazide derivatives. In the first step, R$_1$ and R$_2$ groups attached to proponohydrazides are removed as ketones, which are by-products. Therefore, the variation of R$_1$ and R$_2$ groups does not have any effect on the formation of pyrazolones. In acidic solution, the same type of pyrazolone 7i was always obtained from the hydrolysis of proponohydrazides 5a-g. Compound 7j was only obtained from 5h. The ring closure of 5 to the different pyrazolones generates 6 as an intermediate that cannot be isolated. With rearrangement of this intermediate, compound 6 is cyclized to 7 by losing H$_2$O. Pyrazolone derivatives are formed by the nucleophilic attack of the NH$_2$-N-R$_3$ group on the anisoyl carbonyl moiety at proponohydrazide (see Scheme 2). Their structures were confirmed by elemental analysis and spectral data. In the $^1$H NMR spectrum, compound 7i has a singlet signal at 12.68 ppm assignable to the N-H band on the pyrazolone molecule. In the $^{13}$C NMR spectrum, anisoyl carbonyl and another carbonyl group were observed at 192.18 and 164.87 ppm, respectively.

![Scheme 1](image_url)
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\begin{align*}
\text{Ar: MeO-Ph} & \quad + \text{H}_2\text{O (H}^+) & \quad \xrightarrow{\text{R}_1-\text{CO-R}_2} & \quad \text{R}_3 \\
\text{Scheme 2} & & & & \\
\end{align*}
\]

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References

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