



Original article

Synthesis of pyrazine-2,3-dicarbonitrile and 1,2,4-triazine-5(4H)-one derivatives from furan-2,3-diones



Şevket Hakan Üngören*, Emine Dilekoğlu, İrfan Koca

Department of Chemistry, Faculty of Arts and Sciences, Bozok University, Yozgat 66200, Turkey

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ABSTRACT

The reaction of furan-2,3-diones with S-methylisothiosemicarbazide hydroiodide yielded novel 1,2,4-triazine-5(4H)-ones, and reaction of furan-2,3-diones with diaminomaleonitrile led to the formation of pyrazine-2,3-dicarbonitrile derivatives, and the hydrolysis of these products led to the formation of more new pyrazine-2,3-dicarbonitrile derivatives. These compounds are potential herbicides and pesticides.

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1. Introduction

Azines have many applications in all parts of chemical industry and significantly impact on our daily lives as components of medicines, agrochemicals, natural products and commodity chemicals [1].

Pyrazines are important flavor ingredients in food [2], and exhibit interesting anticancer [2,3] and antituberculosis [2,4–6] activities, and also pyrazine-2,3-dicarbonitriles show varying degrees of herbicidal activity [7].

1,2,4-Triazine-5(4H)-ones constitute an important group of herbicides with a wide range of uses. Most of them are used to increase the efficiency of cultivated plants in the fight against weeds. For example, Metribuzin (Fig. 1), which has excellent selectivity, is a commercial herbicide produced by Bayer (Code No. 94337) and Du Pont (Code No. GPX-G2504) [8]. Some triazines are inhibitors of electron transport in photosynthesis [9]. Also, isomethiozin (Fig. 1), ethiozin, metamitron, and amibuzin show similar activity. Moreover, 6-aza-2'-deoxy-isocytosine (3-amino-1,2,4-triazin-5(2H)-one), is of great biological interest due to its resistance to deaminase [10].

The purpose of this study was the synthesis of new molecules bearing pyrazine-2,3-dicarbonitrile and 1,2,4-triazine-5(4H)-one moieties as a potential herbicides. Herein, we report a simple

synthetic method for the preparation of some azine derivatives from furan-2,3-diones.

2. Experimental

Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. IR spectra (KBr) were measured on a Shimadzu 8400 FTIR spectrometer. ¹H NMR spectra were recorded with a Bruker Avance 400 spectrometer using DMSO-*d*₆ solvents. Elemental analyses (C, H and N) were carried out with a LECO-932 CHNS-O analyzer. The progress of the reactions was monitored by TLC using alumina silica gel Plates 60 F₂₄₅.

Furan-2,3-diones (1), the starting material, were synthesized by the reaction of oxalyl chloride with 1,3-dicarbonyl compounds following previously reported procedures [11–14]. S-Methylisothiosemicarbazide hydroiodide was prepared according to the literature [15].

2.1. General experimental procedure for the synthesis of triazines (3a–d)

Equivalent amounts of furan-2,3-diones and S-methylisothiosemicarbazide hydroiodide were reacted in MeCN at room temperature (Scheme 1). Reactions were completed within a few hours (1–2 h). White-colored products were separated by filtration. Then, the crude products were purified with recrystallization from H₂O or MeCN.

* Corresponding author.

E-mail address: hungoren@erciyes.edu.tr (Ş.H. Üngören).

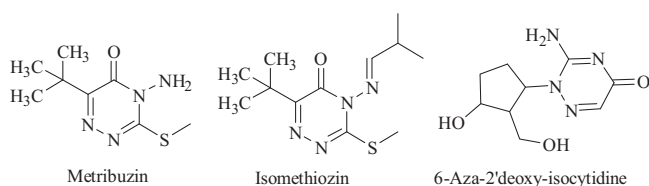


Fig. 1. Some structures of bioactive triazines.

2.2. General experimental procedure for the synthesis of pyrazine-2,3-dicarbonitrile (5a–d and 6a–c).

To a stirred solution of (1a–d) (0.01 mol) in benzene (50 mL), diaminomaleonitrile (1.4 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h (Scheme 2). It was cooled, and the solid product was collected. The crude product was purified with crystallization or column chromatography and dried over P₂O₅.

Compound 5a–c (1 mmol) was refluxed for 1 min in 18 mL *n*-butanol–water (5:1, v/v) mixture, and then the mixture was allowed to cool to room temperature. The precipitated crude product (6a–c) was filtered and recrystallized from acetonitrile.

3. Results and discussion

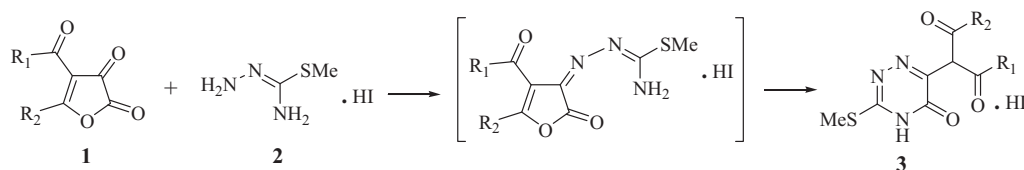
Reaction of 1 with *S*-methylisothiosemicarbazide hydroiodide in MeCN at room temperature gave the 1,2,4-triazine-5(4H)-one

derivatives (3a–d) in 56%–82% yields as shown in Scheme 1. The white-colored crude products precipitated in the form of hydroiodide salts could be crystallized from water or acetonitrile. The compounds are stable for a few weeks in a dark environment after being dried.

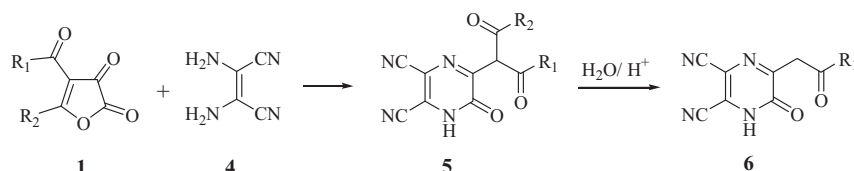
¹H NMR and ¹³C NMR spectra revealed that compounds 3a–d show tautomeric equilibria in DMSO-*d*₆ solutions (Table 1). The ¹³C NMR spectrum of 3a (tautomeric mixture) showed a methine carbon signal at δ 62.0, the carbon signals of Ph–C=O and Ph–C–OH groups belonging to keto–enol tautomers at δ 192.9 and δ 190.9, and the carbon signal of a thiomethyl group at δ 16.5 and δ 14.2. In the ¹H NMR spectrum of 3a, a methine proton at δ 6.56 and δ 6.47, NH proton δ 10.07 and 9.86, SCH₃ protons δ 2.86 and 2.62 were observed. The signal at δ 2.07 as a singlet was assigned to a proton of NR₃·HI. These NMR data of compounds 3a–d can be found in Supporting information. The micro analyses of 3a–d also agree with the proposed structures as shown Table 1.

The reactions of (1a–d) with 2,3-diaminomaleonitrile (4) run via the same reaction mechanism to give pyrazine-2,3-dicarbonitrile derivatives (5a–d) in benzene under reflux conditions for 2 h (see Scheme 2). The products were obtained in moderate to excellent yields as shown in Table 2.

Similar to 3a–d, compounds 5a–d show similar tautomeric forms, such as the keto and enol forms, in DMSO-*d*₆ solutions (Table 2). In the ¹H NMR spectra of 5a–d, OH protons of enol tautomers were clearly observed as a broad band in the range of δ 3.44–5.00, and the methine protons of keto tautomers in the range

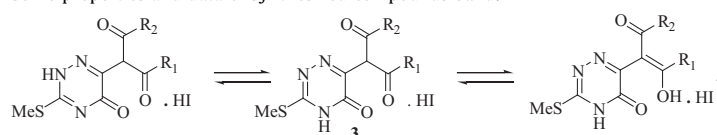


Scheme 1. The reaction route of furan-2,3-diones with *S*-methylisothiosemicarbazide.

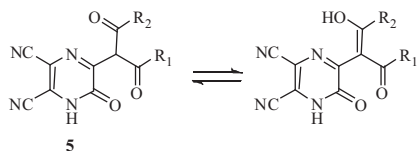


Scheme 2. The synthesis of new pyrazine-2,3-dicarbonitrile derivatives from furan-2,3-diones.

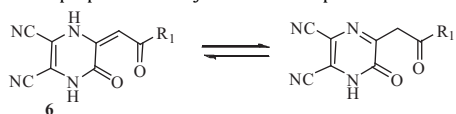
Table 1
Some properties and data of synthesized compounds 3a–d.



Entry	R ₁	R ₂	Mp (°C)	Mol. Formula (Mol. wt.)	Yields (%)	Elemental Analyses (%)			
						C	H	N	S
3a			139	C ₁₉ H ₁₆ N ₃ O ₃ S 493.3	82	Calcd. 46.26 Found 46.32	3.27 3.19	8.52 8.69	6.50 6.41
3b			146	C ₂₁ H ₂₀ N ₃ O ₅ S 553.4	65	Calcd. 45.58 Found 45.42	3.64 3.68	7.59 7.39	5.79 5.96
3c			144	C ₂₁ H ₂₀ N ₃ O ₃ S 521.4	71	Calcd. 48.38 Found 48.16	3.87 3.86	8.06 8.21	6.15 6.20
3d			149	C ₁₆ H ₁₈ N ₃ O ₅ S 491.3	56	Calcd. 39.11 Found 39.21	3.69 3.57	8.55 8.30	6.53 6.46

Table 2Some properties and data of compounds **5a–d**.

Entry	R ₁	R ₂	Mp (°C)	Mol. Formula (Mol. wt.)	Yields (%)	Elemental Analyses (%)		
						C	H	N
5a			106	C ₂₁ H ₁₂ N ₄ O ₃ 368.3	88	Calcd. 68.48 Found 68.61	3.28 3.21	15.21 15.11
5b			143	³ C ₂₃ H ₁₆ N ₄ O ₅ ·C ₄ H ₈ O ₂ 516.5	85	Calcd. 62.69 Found 62.76	4.68 4.68	10.85 10.96
5c			163	C ₂₃ H ₁₆ N ₄ O ₃ 396.4	89	Calcd. 69.69 Found 69.42	4.07 4.26	14.13 14.35
5d			84	C ₁₈ H ₁₄ N ₄ O ₅ 366.3	63	Calcd. 59.02 Found 59.19	3.85 3.91	15.29 15.19

^a This compound was purified using ethyl acetate as eluent from column chromatography.**Table 3**Some properties and synthesized compounds **6a–c**.

Entry	R ₁	Mp (°C)	Mol. Formula (Mol. wt.)	Yields (%)	Elemental Analyses (%)		
					C	H	N
6a^a		243	C ₁₄ H ₈ N ₄ O ₂ 264.2	44	Calcd. 63.64 Found 63.69	3.05 3.01	21.20 21.31
6b		266	C ₁₅ H ₁₀ N ₄ O ₃ 294.3	56	Calcd. 61.22 Found 60.98	3.43 3.35	19.04 19.13
6c^a		267	C ₁₅ H ₁₀ N ₄ O ₃ 278.3	34	Calcd. 64.74 Found 64.89	3.62 3.71	20.13 19.98

^a This compounds were synthesized earlier with different method [16].

of δ 4.58–5.89 and NH protons of keto and enol forms in the range of δ 12.15–13.15 as two singlet peaks were also observed. The absorptions of CN groups were observed at 2214 cm⁻¹. These NMR data of compounds **5a–d** can be found in Supporting information.

Simply heating an *n*-butanol/water solution (5:1) of **5a–c** led to the formation of new pyrazine-2,3-dicarbonitrile derivatives (**6a–c**). On cooling of the solution, the orange crude products precipitated in moderate yields and a highly pure state (Table 3).

In the ¹H NMR spectra of **6b**, NH proton at δ 13.83, aliphatic =CH proton at δ 6.71, CH₂ protons at δ 4.57, OCH₃ protons at δ 3.85 and δ 3.83 were observed. The ¹³C signals of =CH and CH₂ groups were detected at δ 91.1 and 43.6, respectively. These NMR data of compounds **6a–c** can be found in Supporting information.

4. Conclusion

We have easily synthesized new 1,2,4-triazine and pyrazine-2,3-dicarbonitrile derivatives in moderate to good yields as potential herbicides. The synthesized compounds are similar derivatives of some commercial herbicides, and might contribute to the development of pesticides. For this purpose, performances of the compounds will be tested in future works.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cclet.2013.08.001>.

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