Synthesis of Dimethyl 1-(Hetero)aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates from Dimethyl 3-Oxopentane-1,5-dioates

David Pahovnik, Uroš Uršič, Uroš Grošelj, Anton Meden, Jurij Svete, and Branko Stanovnik

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P. O. Box 537, 1000 Ljubljana, Slovenia

Reprint requests to Prof. Dr. Branko Stanovnik. E-mail: Branko.Stanovnik@fkkt.uni-lj.si

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Dimethyl 3-oxopentane-1,5-dioate (dimethyl acetone-1,3-dicarboxylate) (**1**) was transformed first with (hetero)arenediazonium salts **3a** – **j** into dimethyl 2-[(hetero)arylhydrazono]pentane-1,5-dioates **4a** – **j** followed by reaction with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) to afford, without isolation of intermediates **5a** – **j**, dimethyl 1-(hetero)aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates **6a** – **j**. An alternative method represents transformation of **1** with DMFDMA into dimethyl 2-[(dimethylamino)methylidene]-3-oxopentane-1,5-dioate (**7**) followed by treatment with (hetero)arenediazonium salts **3a** – **c**, **j** to give pyridazine derivatives **6a** – **c**, **j**.

Key words: 2-[(Hetero)arylhydrazono]pentane-1,5-dioates, 1-(Hetero)aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates

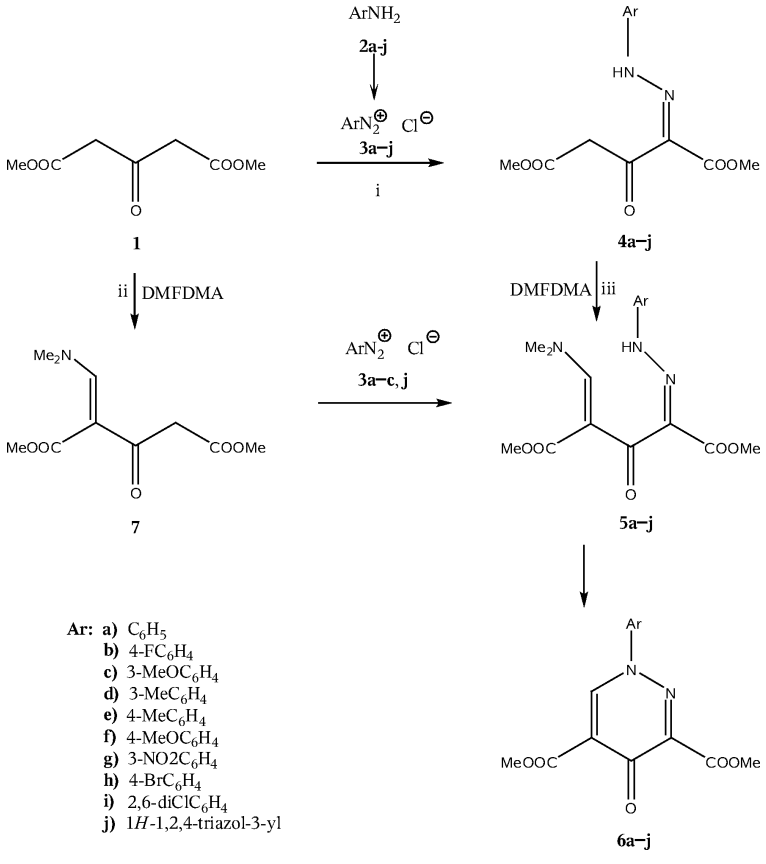
Introduction

In the last decade, a series of 3-(dimethylamino) prop-2-enoates and related enaminones have been prepared as versatile reagents in the synthesis of many functionalized heterocycles [1, 2], including natural products and their analogs [3].

In this study we extend our research in the field of enaminones to the synthesis of pyridazines. There are many syntheses described in the literature, since the pyridazine moiety is of significant importance for the preparation of a variety of products in the pharmaceutical as well as in the agrochemical field [4]. They exhibit many pharmacological activities. They are acetylcholinesterase inhibitors [5a], they act on the cardiovascular [5b] and the inflammatory system [5c], they show antitumor and other activities [5d, e]. Synthetic transformations on this ring system, to yield several diverse analogs for a wide array of applications, have received a considerable boost with the advent of palladium-catalyzed cross-coupling reactions. These reactions facilitate the direct introduction of suitable groups on the pyridazine nucleus *via* carbon-carbon or carbon-heteroatom bond formation [6].

Despite the widely elaborated [4+2] cycloaddition chemistry of 1,2,4,5-tetrazines, only a few examples of cycloadditions to the exocyclic C=C bonds leading to spirodihydropyridazines are known [7]. Recently, [4+2] cycloadditions of 3,6-disubstituted 1,2,4,5-tetrazines to 4′-methylenedihydro-3′*H*-spiro[bicyclo [2.2.1]heptane-2,2′-furans] and 4′-methylene-1′-(4-nitrophenyl)spiro[bicyclo[2.2.1]heptane-3.2′-pyrrolidine], which afforded novel dispirodihydropyridazine derivatives, 11 : 14-isopropylidene-14-methyl-2,3-diaza-8-oxadispiro[5.1.5.2]pentadeca-1,4-dienes and 11 : 14-isopropylidene-11-methyl-2,3,8-triazadispiro[5.1.5.2]pentadeca-1,4-dienes [8], and a one-pot, three-step regio- and stereoselective synthesis of functionalized oxazoline-fused pyridazines by base-assisted "Michael addition-pyridazine cyclization-oxazoline cyclization" cascade reations of 4-chloro-1,2-diaza-1,3-butadienes with 3-(dimethylamino)prop-2-enoates have been reported [9]. Also the coupling of dimethyl 3-oxopentane-1,5-dioate (dimethyl acetone-1,3-dicarboxylate) with a variety of arenediazonium salts, in which the corresponding hydrazones are formed, afforded 5-arylpyridazin-3(2*H*)-one derivatives by cyclization in boiling dichlorobenzene [10].

In this paper we report on the synthesis of dimethyl 1-(hetero)aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates from dimethyl 3-oxopentane-1,5-dioate (dimethyl acetone-1,3-dicarboxylate), as an extension of our research in the field of enaminones and related



Ar: **a)** C_6H_5
b) 4-FC_6H_4
c) 3-$MeOC_6H_4$
d) 3-MeC_6H_4
e) 4-MeC_6H_4
f) 4-$MeOC_6H_4$
g) 3-NO2C_6H_4
h) 4-BrC_6H_4
i) 2,6-diClC_6H_4
j) 1*H*-1,2,4-triazol-3-yl

Scheme 1. Reaction conditions: (i) EtOH/H_2O, 0 °C; (ii) 0 °C, 5 h; r. t., 15 h; (iii) r. t., 3 – 24 h.

reagents and their applications to the synthesis of heterocyclic systems.

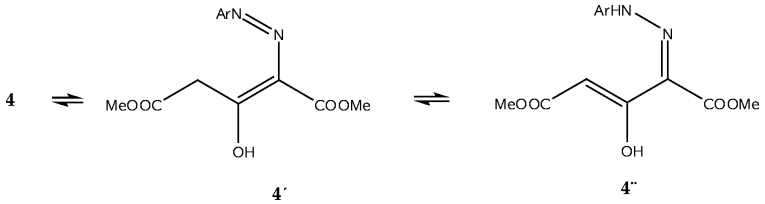
Results and Discussion

Two reaction pathways for the preparation of 1,4-dihydropyridazine derivatives were envisaged (Scheme 1). According to the first method, dimethyl 3-oxopentane-1,5-dioate (dimethyl acetone-1,3-dicarboxylate) (**1**) was treated in ethanol in the presence of sodium acetate at 0 °C with an acidic aqueous solution of diazonium salts **3a** – **j**, prepared from the corresponding aromatic (**2a** – **i**) or heteroaromatic (**2j**) amines, to give the corresponding hydrazones **4a** – **j** in 35 – 94 % yield. They were in the next step treated with dimethylformamide dimethylacetal (DMFDMA) in dichloromethane at room temperature to form the corresponding (dimethylamino) methylidene derivatives **5a** – **j** as intermediates, which immediately cyclize under the reaction conditions to form dimethyl 1-(hetero)aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates **6a** – **j** in 72 – 94 % yield, except for **6j**, which was obtained only in 35 % yield (Scheme 1).

According to the second method, compound **1** was treated with DMFDMA in dichloromethane at room temperature to give dimethyl 2-[(dimethylamino)methylidene]-3-oxopentane-1,5-dioate (**7**) in 78 % yield after purification by column chromatography. To the ice-cold solution of this compound in a 1 : 1 mixture of ethanol and water in the presence of sodium acetate, an aqueous solution of (hetero)arenediazonium salts **3a** – **c**, **i** was added dropwise to form intermediates **5a** – **c**, **i**, which were cyclized without isolation under the reaction conditions into final products **6a** – **c**, **i** in 35 – 42 % yield. They were identical to the products obtained according to the first synthesis.

Structure determination

Dimethyl 2-{2-[(hetero)aryl]hydrazono}-3-oxopentane-1,5-dioates could exist in three tautomeric forms: as hydrazones (**4**), as dimethyl 3-hydroxy-[(hetero)aryldiazenyl]pent-2-ene-1,5-dioates (**4′**), and as dimeth-



Scheme 2. Possible tautomeric forms of dimethyl 2-[(hetero)arylhydrazono]pentane-1,5-dioates **4**.

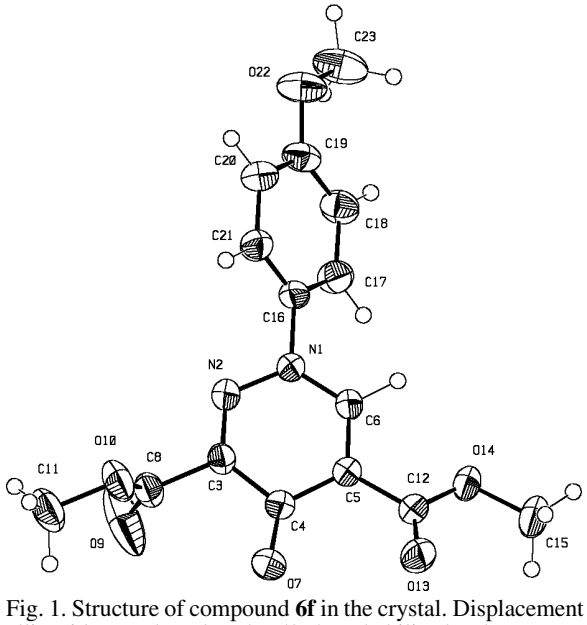


Fig. 1. Structure of compound **6f** in the crystal. Displacement ellipsoids are plotted at the 50 % probability level. H atoms are drawn as circles of arbitrary radii.

yl 3-hydroxy-4-[2-(hetero)arylhydrazono]-pent-2-ene-1,5-dioates (**4″**) (Scheme 2).

For compounds **4a**–**c**, **e** two sets of signals in the ratio of 3.5 : 1 to 10 : 1 were observed in the ^{1}H NMR spectra, while for compounds **4d**, **f**–**j** only one set of peaks was observed. In all compounds the signal at δ = 3.87–3.94 ppm, corresponding to -CH_2- group, is present, while for the minor isomer the signals for the -CH_2- group appeared at lower field at δ = 4.01–4.02 ppm. On the basis of this observation, the structures **4″** are excluded. Between isomers **4** and **4′** one can differentiate on the basis of exchangable protons of NH and OH groups. The NH signals were observed in the range δ = 12.72–13.20 ppm, while the OH signals appeared in the range δ = 14.80–14.96 ppm. The ^{1}H NMR spectra for pyridazine derivatives **6a**–**j** exhibit two singlets for two ester methyl groups at δ = 3.65–3.99 ppm, a singlet for the proton 6-H of the pyridazine ring at δ = 8.31–9.02 ppm and multiplets for aromatic protons in the range δ = 7.31–7.85 ppm.

The structure of compound **6f** was confirmed by X-ray analysis (Fig. 1). The structure of all new compounds, except for **4j**, were determined also by elemental analyses for C, H, and N, and IR spectra. The structure for compound **4j** was confirmed by HRMS and ^{13}C NMR spectroscopy.

Experimental Section

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer in $CDCl_3$ or [D_6]DMSO with TMS as the internal standard. IR spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer and elemental analyses for C, H, and N on a Perkin-Elmer CHN analyzer 2400 II. Dimethyl 2-[(dimethylamino)methylidene]-3-oxopentane-1,5-dioate (**7**) was prepared in essentially the same way as for the corresponding diethyl derivative [11].

*General procedure for the preparation of dimethyl 2-[2-(hetero)arylhydrazono]-3-oxopentane-1,5-dioates (**4a**–**j**)*

*A. Preparation of arenediazonium salts **3a**–**j***

The aromatic amine (**2a**–**j**) (0.005 mol) was suspended in 5 mL of water, and 2.5 mL of conc. aqueous hydrochloric acid was added. The resulting solution was cooled to 0–5 °C, and a solution of $NaNO_2$ (345 mg, 0.005 mol) in 3.75 mL of water was added dropwise. The mixture was stirred for additional 50 min to obtain a solution of the arenediazonium salt (**3a**–**j**).

*B. Preparation of hydrazonopentane-1,5-dioates **4a**–**j***

The solution of the arenediazonium salt (**3a**–**j**) was added dropwise to the ice-cold solution of dimethyl 3-oxo-pentane-1,5-dioate (**1**; 0.721 mL, 0.005 mol) and sodium acetate (3 g) in a mixture of 3 mL of ethanol and 10 mL of water. The mixture was stirred at 0 °C for additional 40 min. A yellow precipitate was collected by filtration, washed with ice-cold water and recrystallized from ethanol.

The following compounds were prepared in this manner:

*Dimethyl 3-oxo-2-(2-phenylhydrazono)pentane-1,5-dioate (**4a**)*

This compound was prepared from aniline (**2a**; 0.46 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 94 % yield (1.31 g). –

M. p. 87 – 89 °C (86 – 89 °C [10]). – IR (KBr): ν = 3474, 3137, 2949, 1733, 1692, 1530, 1433, 1402, 1329, 1234, 1192, 1173, 1150, 1022, 999, 752 cm^{-1}. – ^1H NMR ($CDCl_3$): two isomers in the ratio 10 : 1; major isomer: δ = 3.71 (s, 3H, MeO), 3.89 (s, 2H, CH_2), 3.92 (s, 3H, MeO), 7.17 – 7.22 (m, 1H, Ph), 7.33 – 7.44 (m, 4H, Ph), 13.07 (s, 1H, NH); minor isomer: δ = 3.76 (s, 3H, MeO), 3.87 (s, 3H, MeO), 4.02 (s, 2H, CH_2), 7.17 – 7.22 (m, 1H, Ph), 7.33 – 744 (m, 4H, Ph), 14.88 (s, 1H, OH).

*Dimethyl 2-[2-(4-fluorophenyl)hydrazono]-3-oxopentane-1,5-dioate (**4b**)*

This compound was prepared from 4-fluoroaniline (**2b**; 0.480 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 92 % yield (1.36 g). – M. p. 101 – 103 °C. – IR (KBr): ν = 3452, 3121, 2995, 1737, 1690, 1509, 1438, 1386, 1333, 1256, 1211, 1147, 1120, 1075, 1015, 836, 803, 516 cm^{-1}. – ^1H NMR ($CDCl_3$): two isomers in the ratio 3.5 : 1; major isomer: δ = 3.71 (s, 3H, MeO), 3.87 (s, 2H, CH_2), 3.92 (s, 3H, MeO), 7.08 – 7.14 (m, 1H, Ar), 7.31 – 7.35 (m, 4H, Ar), 13.10 (s, 1H, NH); minor isomer: δ = 3.76 (s, 3H, MeO), 3.86 (s, 3H, MeO), 4.01 (s, 2H, CH_2), 7.17 – 7.22 (m, 1H, Ar), 7.41 – 7.46 (m, 4H, Ar), 14.91 (s, 1H, OH). – C $C_{13}H_{14}N_2O_5$ (278.26): calcd. C 52.70, H 4.42, N 9.46; found C 52.93, H 4.39, N 9.57.

*Dimethyl 2-[2-(3-methoxyphenyl)hydrazono]-3-oxopentane-1,5-dioate (**4c**)*

This compound was prepared from 3-methoxyaniline (**2c**; 0.60 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 88 % yield (1.35 g). – M. p. 103 – 105 °C. – IR (KBr): ν = 3474, 3218, 3176, 2946, 1737, 1690, 1609, 1594, 1530, 1430, 1333, 1290, 1243, 1213, 1169, 1146, 1050, 1015, 768 cm^{-1}. – ^1H NMR ($CDCl_3$): two isomers in the ratio 5.5 : 1; major isomer: δ = 3.71 (s, 3H, MeO), 3.87 (s, 2H, CH_2), 3.89 (s, 3H, MeO), 3.92 (s, 3H, MeO), 6.74 (ddd, 1H, J = 0.7, 2.4, 8.3 Hz, Ar), 6.87 (ddd, 1H, J = 0.7, 2.1, 8.0 Hz, Ar), 6.99 (dd, 1H, J = 2.3 Hz, Ar), 7.29 (dd, 1H, J = 8.1 Hz, Ar), 13.02 (s, 1H, NH); minor isomer: δ = 3.76 (s, 3H, MeO), 3.85 (s, 3H, MeO), 3.87 (s, 3H, MeO), 4.02 (s, 2H, CH_2), 6.77 (ddd, 1H, J = 0.7 Hz, Ar), 6.97 – 7.00 (m, 1H, Ar), 7.05 (dd, J = 2.2 Hz), 7.29 (dd , 1H, J = 8.0 Hz, Ar), 14.80 (s, 1H, OH). – $C_{14}H_{16}N_2O_6$ (308.29): calcd. C 54.54, H 5.23, N 9.09; found C 54.86, H 5.32, N 9.07.

*Dimethyl 2-[2-(3-methylphenyl)hydrazono]-3-oxopentane-1,5-dioate (**4d**)*

This compound was prepared from 3-methylaniline (**2d**; 0.536 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 89 % yield (1.29 g). – M. p. 85 – 87 °C. – IR (KBr): ν = 3453, 3135, 2947, 1735, 1678, 1532, 1439, 1405, 1334, 1251, 1223, 1186, 1169, 1141, 1026, 1004, 799, 782, 545 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3H, Me), 3.72 (s, 3H, MeO), 3.89 (s, 2H, CH_2), 3.92 (s, 3H, MeO), 7.00 – 7.02 (m, 1H, Ar), 7.14 – 7.17 (m, 2H, Ar), 7.25 – 7.31 (m, 1H, Ar), 13.04 (s, 1H, NH). – $C_{14}H_{16}N_2O_5$ (292.29): calcd. C 57.53, H 5.52, N 9.58; found C 57.43, H 5.63, N 9.57.

*Dimethyl 2-[2-(4-methylphenyl)hydrazono]-3-oxopentane-1,5-dioate (**4e**)*

This compound was prepared from 4-methylaniline (**2e**; 0.535 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 78 % yield (1.14 g). – M. p. 95 – 97 °C. – IR (KBr): ν = 3445, 3141, 2949, 1727, 1693, 1527, 1433, 1396, 1334, 1323, 1231, 1212, 1183, 997 cm^{-1}. – ^1H NMR ($CDCl_3$): two isomers in the ratio 10 : 1; major isomer: δ = 2.36 (s, 3H, Me), 3.71 (s, 3H, MeO), 3.88 (s, 2H, CH_2), 3.92 (s, 3H, MeO), 7.19 – 7.27 (m, 4H, Ar), 13.10 (s, 1H, NH); minor isomer: δ = 2.36 (s, 3H, Me), 3.75 (s, 3H, MeO), 3.86 (s, 3H, MeO), 4.01 (s, 2H, CH_2), 7.19 – 7.27 (m, 2H, Ar), 7.34 – 7,37 (m, 2H, Ar), 14.96 (s, 1H, OH). – $C_{14}H_{16}N_2O_5$ (292.29): calcd. C 57.53, H 5.52, N 9.58; found C 57.52, H 5.46, N 9.57.

*Dimethyl 2-[2-(4-methoxyphenyl)hydrazono]-3-oxopentane-1,5-dioate (**4f**)*

This compound was prepared from 4-methoxyaniline (**2f**; 0.616 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 84 % yield (1.30 g). – M. p. 70 – 72 °C (70 – 72 °C [10]). – IR (KBr): ν = 3460, 3137, 2948, 2847, 1740, 1698, 1683, 1529, 1514, 1433, 1390, 1342, 1248, 1150, 1122, 1070, 1011, 832, 543 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.70 (s, 3H, MeO), 3.83 (s, 3H, MeO), 3.87 (s, 2H, CH_2), 3.91 (s, 3H, MeO), 6.93 – 6.96 (m, 2H, Ar), 7.29 – 7.32 (m, 2H, Ar), 13.20 (s, 1H, NH).

*Dimethyl 2-[2-(3-nitrophenyl)hydrazono]-3-oxopentane-1,5-dioate (**4g**)*

This compound was prepared from 3-nitroaniline (**2g**; 0.691 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 78 % yield (1.26 g). – M. p. 101 – 103 °C. – IR (KBr): ν = 3445, 3179, 1730, 1698, 1535, 1439, 1349, 1334, 1278, 1259, 1219, 1181, 1159, 1027, 1006, 804, 736 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.75 (s, 3H, MeO), 3.90 (s, 2H, CH_2), 3.95 (s, 3H, MeO), 7.56 – 7.65 (m, 2H, Ar), 8.00 – 8.04 (m, 1H, Ar), 8.19 – 8.21 (m, 1H, Ar), 13.04 (s, 1H, NH). – $C_{13}H_{13}N_3O_7$ (323.26): calcd. C 48.30, H 4.05, N 13.00; found C 48.35, H 3.86, N 13.05.

*Dimethyl 2-[2-(4-bromophenyl)hydrazono]-3-oxopentane-1,5-dioate (**4h**)*

This compound was prepared from 4-bromoaniline (**2h**; 0.860 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 72 % yield (1.29 g). – M. p. 100 – 102 °C. – IR (KBr): ν = 3432, 3137,

2955, 1724, 1688, 1668, 1533, 1489, 1434, 1331, 1320, 1233, 1075, 998, 823 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.71 (s, 3H, MeO), 3.87 (s, 2H, CH_2), 3.92 (s, 3H, MeO), 7.22 – 7.26 (m, 2H, Ar), 7.50 – 7.55 (m, 2H, Ar), 13.01 (s, 1H, NH). – $C_{13}H_{13}BrN_2O_5$ (357.16): calcd. C 43.72, H 3.67, N 7.84; found C 43.80, H 3.67, N 7.81.

*Dimethyl 2-[2-(2,6-dichlorophenyl)hydrazono]-3-oxopentane-1,5-dioate (**4i**)*

This compound was prepared from 2,6-dichloroaniline (**2i**; 0.810 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 88 % yield (1.53 g). – M. p. 69 – 71 °C (69 – 72 °C [10]). – IR (KBr): ν = 3448, 3125, 2954, 1741, 1686, 1515, 1435, 1398, 1340, 1230, 1189, 1174, 1148, 784 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.70 (s, 3H, MeO), 3.94 (s, 2H, CH_2), 3.95 (s, 3H, MeO), 7.11 (dd, 1H, J = 8.1 Hz, Ar), 7.40 (d, 2H, J =8.1 Hz, Ph), 12.92 (s, 1H, NH).

*Dimethyl 2-[2-(1H-1,2,4-triazol-3-yl)hydrazono]-3-oxopentane-1,5-dioate (**4j**)*

This compound was prepared from 3-amino-1*H*-1,2,4-triazole (**2j**; 0.420 g, 0.005 mol) and **1** (0.721 g, 0.005 mol), 35 % yield (0.380 g). – M. p. 213 – 215 °C. – IR (KBr): ν = 3344, 3143, 2997, 1741, 1730, 1721, 1570, 1443, 1353, 1317, 1231, 1215, 1134, 1103, 1059, 1014, 939, 856, 705 cm^{-1}. – MS (EI): m/z = 269 $[M]^+$. – HMRS: m/z = 269.0764 (calcd. 269.0761 for $C_9H_{11}N_5O_5$, $[M]^+$). – ^1H NMR ([D$_6$]DMSO): δ = 3.45 (s, 3H, MeO), 3.68 (d, 1H, J = 17.4 Hz, CH–H_a), 3.76 (s, 3H, MeO), 3.87 (d, 1H, J = 17.4 Hz, CH–C_b) 7.70 (s, 1H, NH), 7.84 (s, 1H, CH), 12.72 (s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 40.6, 51.4, 52.0, 80.2, 130.5, 145.9, 150.1, 162.9, 169.2.

*General procedure for the preparation of dimethyl 1-(hetero) aryl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylates (**6a – j**)*

Procedure A): From dimethyl 2-(2-(hetero)arylhydrazono)-3-oxopentane-1,5-dioates (**4a – j**) and *N*,*N*-dimethylformamide dimethylacetal (DMFDMA).

To a solution of the dimethyl 2-(2-(hetero)arylhydrazono)-3-oxopentane-1,5-dioate (**4a – j**, 0.001 mol) in 1 mL of CH_2Cl_2, DMFDMA (0.2 mL, 0.0015 mol) was added, and the mixture was stirred at r. t. for 3 – 24 h. The volatile components were evaporated *in vacuo*, and the solid was recrystallized from EtOH.

Procedure B): From 2-[(dimethyamino)methylidene]-3-oxopentane-1,5-dioate (**7**) and the (hetero)arenediazonium salt (**3a – j**).

To an ice-cold solution of the (hetero)arenediazonium salt (**3a – j**), prepared from **2a – j** (0.001 mol), an ice-cold solution of **7** (0.23 mL, 0.001 mol) and sodium acetate (0.6 g) in a mixture of etanol (0.6 mL) and water (2 mL) was added. The mixture was stirred at 0 °C for 5 h and then at r. t. for additional 15 h. The precipitate was collected by filtration, washed with water and recrystallized from ethanol.

The following compounds were prepared according to this procedure:

*Dimethyl 1-phenyl-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6a**)*

This compound was prepared by procedure A from **4a** (0.278 g, 0.001 mol) and DMFDMA, 25 h, 82 % yield (0.239 g). – M. p. 158 – 160 °C. – IR (KBr): ν = 3457, 3054, 2954, 1749, 1709, 1635, 1586, 1488, 1436, 1252, 1160, 714 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.95 (s, 6H, 2 × MeO), 7.45 – 7.63 (m, 5H, Ph), 8.94 (s, 2H, 2-H, 6-H). – $C_{14}H_{12}N_2O_5$ (288.26): calcd. C 58.33, H 4.20, N 9.72; found C 58.46, H 3.83, N 9.57.

By procedure B from **7** (0.229 g, 0.001 mol) and **3a** (prepared from **2a** (0.093 g, 0.001 mol)); 53 % yield (0.153 g).

*Dimethyl 1-(4-fluorophenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6b**)*

This compound was prepared by procedure A from **4b** (0.296 g, 0.001 mol) and DMFDMA, 4 h, 80 % yield (0.245 g). – M. p. 135 – 138 °C. – IR (KBr): ν = 3458, 3072, 2971, 1740, 1633, 1538, 1506, 1424, 1346, 1317, 1238, 1222, 1199, 1163, 1053, 980, 842, 545 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.94 (s, 3H, MeO), 3.98 (s, 3H, MeO), 7.21 – 7.26 (m, 2H, Ar), 7.57 – 7.62 (m, 2H, Ar), 8.94 (s, 1H, H_6). – $C_{14}H_{11}FN_2O_5$ (306.25): calcd. C 54.91, H 3.62, N 9.15; found C 55.09, H 3.61, N 9.09.

By procedure B from **7** (0.229 g, 0.001 mol) and **3b** (prepared from **2b** (0.111 g, 0.001 mol)); 42 % yield (0.128 g).

*Dimethyl 1-(3-methoxyphenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6c**)*

This compound was prepared by procedure A from **4c** (0.308 g, 0.001 mol) and DMFDMA, 4 h, 70 % yield (0.222 g). – M. p. 174 – 177 °C. – IR (KBr): ν = 3448, 2960, 1750, 1734, 1630, 1609, 1586, 1433, 1268, 1216, 1164, 1063, 980, 716 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.88 (s, 3H, MeO), 3.95 (s, 3H, MeO), 3.99 (s, 3H, MeO), 6.98 – 7.02 (m, 1H, Ar), 7.13 – 7.15 (m, 2H, Ar), 7.40 – 7.46 (m, 1H, Ar), 8.93 (s, 1H, H_6). – $C_{15}H_{14}FN_2O_6$ (318.28): calcd. C 56.60, H 4.43, N 8.80; found C 56.89, H 4.32, N 8.73.

By procedure B from **7** (0.229 g, 0.001 mol) and **3c** (prepared from **2c** (0.112 g, 0.001 mol)); 35 % yield (0.110 g).

*Dimethyl 1-(3-methylphenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6d**)*

This compound was prepared by procedure A from **4d** (0.292 g, 0.001 mol) and DMFDMA, 3 h, 76 % yield (0.230 g). – M. p. 135 – 137 °C. – IR (KBr): ν = 3447, 3125,

2958, 1752, 1733, 1630, 1434, 1325, 1246, 1209, 1165, 1063, 988, 804, 718 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.46 (s, 3H, Me), 3.95 (s, 3H, MeO), 3.99 (s, 3H, MeO), 7.26 – 7.29 (m, 1H, Ar), 7.36 – 7.44 (m, 3H, Ar), 8.92 (s, 1H, H_6). – $C_{15}H_{14}N_2O_5$ (302.28): calcd. C 59.60, H 4.67, N 9.27; found C 59.66, H 4.55, N 9.17.

*Dimethyl 1-(4-methylphenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6e**)*

This compound was prepared by procedure A from **4e** (0.292 g, 0.001 mol) and DMFDMA, 24 h, 73 % yield (0.220 g). – M. p. 130 – 131 °C. – IR (KBr): ν = 3461, 2959, 1742, 1705, 1645, 1530, 1507, 1313, 1242, 1198, 1161, 1128, 1049, 968, 955, 824, 817 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.43 (s, 3H, Me), 3.94 (s, 3H, MeO), 3.98 (s, 3H, MeO), 7.31 – 7.34 (m, 2H, Ar), 7.46 – 7.49 (m, 2H, Ar), 8.90 (s, 1H, 6-H). – $C_{15}H_{14}N_2O_5$ (302.28): calcd. C 59.60, H 4.67, N 9.27; found C 59.66, H 4.55, N 9.17.

*Dimethyl 1-(4-methoxyphenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6f**)*

This compound was prepared by procedure A from **4f** (0.308 g, 0.001 mol) and DMFDMA, 22 h, 58 % yield (0.183 g). – M. p. 117 – 120 °C. – IR (KBr): ν = 3451, 3125, 2960, 1748, 1739, 1629, 1526, 1512, 1430, 1312, 1253, 1230, 1203, 1168, 1057, 854 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.87 (s, 3H, MeO), 3.94 (s, 3H, MeO) 3.98 (s, 3H, MeO), 7.00 – 7.03 (m, 2H, Ar), 7.49 – 7.52 (m, 2H, Ar), 8.85 (s, 1H, 6-H). – $C_{15}H_{14}N_2O_6$ (318.28): calcd. C 56.60, H 4.43, N 8.80; found C 56.58, H 4.29, N 8.79.

*Dimethyl 1-(3-nitrophenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6g**)*

This compound was prepared by procedure A from **4g** (0.323 g, 0.001 mol) and DMFDMA, 26 h, 70 % yield (0.234 g). – M. p. 180 – 182 °C. – IR (KBr): ν = 3447, 3102, 2960, 1751, 1633, 1537, 1437, 1351, 1328, 1236, 1203, 1168, 984, 817, 713 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.96 (s, 3H, MeO), 34.01 (s, 3H, MeO), 7.76 – 7.81 (m, 1H, Ar), 8.01 – 8.03 (m, 1H, Ar), 8.33 – 8.36 (m 1H, Ar), 8.51 – 8.57 (m, 1H, Ar), 9.02 (s, 1H, 6-H). – $C_{14}H_{11}FN_3O_7$ (333.25): calcd. C 50.46, H 3.33, N 12.61; found C 50.24, H 3.20, N 12.55.

*Dimethyl 1-(4-bromophenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6h**)*

This compound was prepared by procedure A from **4h** (0.357 g, 0.001 mol) and DMFDMA, 47 h, 81 % yield (0.296 g). – M. p. 150 – 152 °C. – IR (KBr): ν = 3462, 3089, 3059, 2951, 1752, 1748, 1620, 1536, 1480, 1446, 1402, 1349, 1317, 1232, 1198, 1171, 1119, 1051, 1006, 847, 757, 720 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.95 (s, 3H, MeO), 3.99 (s, 3H, MeO), 7.49 – 7.52 (m, 2H, Ar), 7.66 – 7.69 (m, 2H, Ar), 8.90 (s, 1H, H_6). – $C_{14}H_{11}BrN_2O_5$ (367.15): calcd. C 45.80, H 3.02, N 7.63; found C 45.97, H 3.11, N 7.53.

Table 1. Crystal data, data collection and structure refinement for compound **6f**.

	Compound **6f**
Formula	$C_{15}H_{14}N_2O_6$
Rel. formula weight	636.56
Crystal color	yellow
Crystal shape	block
Dimensions, mm^3	$0.25 \times 0.19 \times 0.15$
Crystal system	triclinic
Space group	$P\bar{1}$
a, Å	9.1746(2)
b, Å	9.5436(2)
c, Å	9.9562(2)
α, deg	103.6445(11)
β, deg	96.9588(10)
γ, deg	113.5046(9)
V, $Å^3$	753.86(3)
Z	2
$F(000)$, e	332
ρ, $Mg\,m^{-3}$	1.402
μ, mm^{-1}	0.11
hkl range	$\pm11, \pm12, -12/+11$
$(sin\theta/\lambda)_{max}$, $Å^{-1}$	0.648
Temperature, K	293(1)
Wavelength, Å	0.71073
θ_{max}, deg.	27.55
No. of integr. refl.	11945
No. of indep. refl.	3430
R_{int}	0.043
No. of observed refl.	2541
Threshold criterion	$I \geq 2.0\sigma(I)$
No. of param.	208
Final R/R_w	0.047/0.041
$(\Delta/\sigma)_{max}$	0.0001
$\Delta\rho_{max/min}$, e $Å^{-3}$	0.32/−0.31

*Dimethyl 1-(2,6-dichlorophenyl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6i**)*

This compound was prepared by procedure A from **4i** (0.347g, 0.001 mol) and DMFDMA, 24 h, 81 % yield (0.290 g). – M. p. 199 – 200 °C. – IR (KBr): ν = 3448, 3041, 2954, 1754, 1736, 1717, 1626, 1595, 1530, 1461, 1438, 1325, 1246, 1200, 1167, 1037, 787, 697, 650 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.93 (s, 3H, MeO), 3.96 (s, 3H, MeO), 7.43 – 7.55 (m, 3H, Ar), 8.94 (s, 1H, 6-H). – $C_{14}H_{10}Cl_2N_2O_5$ (357.15): calcd. C 45.80, H 3.02, N 7.63; found C 45.97, H 3.11, N 7.53.

By procedure B from **7** (0.229 g, 0.001 mol) and **3i** (prepared from **2i** (0.162g, 0.001 mol)); 38 % yield (0.137 g).

*Dimethyl 1-(1H-1,2,4-triazol-3-yl)-4-oxo-1,4-dihydropyridazine-3,5-dicarboxylate (**6j**)*

This compound was prepared by procedure A from **4j** (0.269 g, 0.001 mol) and DMFDMA, 24 h, 39 % yield

(0.108 g). – M. p. 205 – 208 °C. – IR (KBr): ν = 3445, 3102, 2961, 2888, 1754, 1706, 1620, 1440, 1395, 1323, 1210, 1196, 1181, 1106, 850, 578 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 3.65 (s, 3H, MeO), 3.79 (s, 3H, MeO), 5.99 (s, 1H, CH), 8.31 (s, 1H, 6-H), 14.22 (s, 1H, NH). – $C_{10}H_9N_5O_5$ (279.21): calcd. C 43.02, H 3.25, N 25.08; found C 43.09, H 3.53, N 25.42.

By procedure B from **7** (0.229 g, 0.001 mol) and **3j** (prepared from **2j** (0.088 g, 0.001 mol)); 42 % yield (0.128 g).

*X-Ray structure analysis for compound **6f***

Single crystal X-ray diffraction data of compound **6f** were collected at r. t. on a Nonius Kappa CCD diffractometer using the Nonius Collect Software [12]. DENZO and SCALEPACK [13] were used for indexing and scaling of the data, and the structure was solved by means of SIR97 [14]. Refinement was done using the XTAL3.4 [15] program package. The crystal structure was refined on F^2 using full-matrix least-squares procedures. The non-hydrogen atoms were refined anisotropically, while the positions of the hydrogen atoms were geometrically calculated, and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina [16] weighting scheme was used in both cases. An ORTEP-III [17] drawing of the content of the asymmetric unit showing the atom-labeling scheme is presented in Fig. 1. The resulting crystal data and details concerning data collection and refinement for compound **6f** are quoted in Table 1.

CCDC 674009 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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