

Synthesis of Methyl 4-Amino-1-aryl-1,4,5,6-tetrahydro-6-oxo-1,2,4-triazine-3-carboxylates

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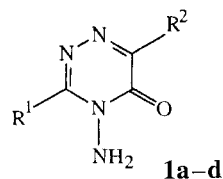
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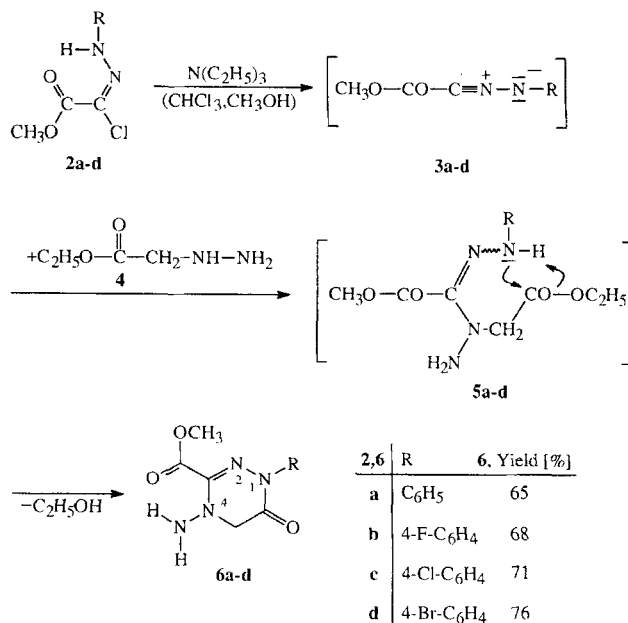
A number of 1,2,4-triazines, especially 4-amino-1,2,4-triazin-5-ones (**1a–d**) was reported to exhibit herbicidal potency [1–5]. A notable example is Metribuzin **1a** which is considered among the best known and widely used herbicides [1–4].



1	R ¹	R ²
a	SCH ₃	C(CH ₃) ₃
b	SH	(CH ₂) _n COOH, n = 1–4
c	H	Alkyl, Aryl
d	Alkyl	Alkyl, Aryl

This background prompted us to synthesize some derivatives of **1** by applying a novel reaction route. The reaction of α -amino esters with nitrile imines (1,3-dipoles) was reported [6] to constitute a convenient and versatile one-pot synthetic route to 4,5-dihydro-1,2,4-triazin-6-ones. The present work deals with the reaction of ethyl 2-hydrazinoacetate (**4**) with nitrile imines **3a–d** which were generated in situ from the corresponding hydrazonoyl chloride precursors **2a–d** by the action of triethylamine [6, 7]. Comparable to amines [8, 9] and α -amino esters [6, 7], ethyl 2-hydrazinoacetate (**4**) is expected to add selectively onto **3** by the attack of the NH group which is more nucleophilic than the NH₂ group. The generated amidrazones **5a–d**, acyclic transients, can undergo in their (Z)-configuration a spontaneous cyclocondensation reaction by elimination of ethanol. The process corresponds to the “6-Exo-Trig” case of the Baldwin rules [10]. Yields between 65 and 76% of the resulting 1,2,4-triazines **6a–d** were obtained under smooth conditions.

The structural assignment of **6a–d** is based on IR, MS, ¹H and ¹³C NMR spectral data and on elemental analysis. The IR spectra in KBr exhibit strong absorption bands in the regions 3300–3350 cm⁻¹ (NH₂), 1740–1770 cm⁻¹ (ester CO), 1650–1670 cm⁻¹ (lactam CO) and 1600–1620 cm⁻¹ (CN and aromatic ring). The electron impact mass spectra of **6a–d** gave prominent peaks for the molecular ions M⁺ (Table 1). A characteristic fragmentation mode involves a consecutive loss of CO



Scheme 1

and H proved by high resolution MS data and metastable scanning.

The ¹H NMR spectra of **6a–d** contain singlets for the geminal protons 5-H, the methoxy and the amino group. The signals of the aromatic protons appear between $\delta = 7.2$ and 7.5 (Table 1). The ¹³C NMR spectra display two signals in the low field region at 158–159 ppm and 160–162 ppm, respectively, which are correlated to C-6 and to the ester carbonyl group. (Table 2). The signal at 142–143 ppm belongs to the carbon atom C-3, while the four signals between 120 and 140 ppm emerge from the aromatic carbon atoms. The two close lying signals between 53 and 55 ppm were assigned to C-5 and the methoxy group. The differentiation made in Table 2 is based on DEPT experiments.

Table 1 Analytical data of the methyl 4-amino-1-aryl-1,4,5,6-tetrahydro-6-oxo-1,2,4-triazine-3-carboxylates (**6a–d**)

Compound	<i>m.p.</i> °C	MS M ⁺ (<i>m/z</i>)	Elemental Anal.			¹ HNMR ^{a)}					
			Calcd./Found C(%)	H(%)	N(%)	5-H (s)	OCH ₃ (s)	NH ₂ (s)	Aryl (AA'BB'C or AA'BB')		
									<i>o</i> -H	<i>m</i> -H	<i>p</i> -H
6a C ₁₁ H ₁₂ N ₄ O ₃ (248.3)	159–160	248	53.22 53.11	4.87 4.92	22.56 23.34	4.18	3.87	4.21	7.48	7.37	7.25
6b C ₁₁ H ₁₁ FN ₄ O ₃ (266.2)	184–185	266	49.63 49.42	4.16 4.28	21.04 20.86	4.20	3.88	4.23	7.45	7.05	–
6c C ₁₁ H ₁₁ ClN ₄ O ₃ (282.7)	134–135	282/284	46.74 46.71	3.92 4.07	19.81 20.02	4.20	3.88	4.23	7.46	7.32	–
6d C ₁₁ H ₁₁ BrN ₄ O ₃ (327.2)	139–140	326/328	40.39 40.48	3.39 3.37	17.13 16.91	4.20	3.88	4.23	7.46	7.32	–

^{a)} δ values in CDCl₃, TMS as internal standard

Table 2 ¹³C NMR Data of the methyl 4-amino-1-aryl-1,4,5,6-tetrahydro-6-oxo-1,2,4-triazine-3-carboxylates (**6a–d**) (δ values in CDCl₃, TMS as internal standard)

Compound	1,2,4-Triazine			Ester CO/OCH ₃	C _i	Aryl			¹ J(C,F)/Hz	² J(C,F)/Hz	³ J(C,F)/Hz
	C-3	C-5	C-6			C _o	C _m	C _p			
6a	142.8	54.5	158.7	161.1/53.1	139.9	124.8	128.7	127.2			
6b	142.9	54.5	158.7	162.1/53.2	135.9	126.6	115.5	159.8	215.5	22.6	8.6
6c	143.0	54.5	158.6	160.9/53.2	138.4	125.8	128.7	132.4			
6d	143.0	54.6	158.7	160.9/53.3	139.1	126.3	132.2	121.4			

Experimental

Melting points were measured on a Gallenkamp Electrothermal Apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 577 spectrophotometer. ¹H and ¹³C NMR spectra were measured in CDCl₃ on a Bruker AM 400 instrument. EI MS spectra were obtained by using a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses were carried out by the M. H. W. Laboratories, Arizona, U.S.A.

The methyl 2-arylhydrazono-2-chloroacetates (**2a–d**) were prepared following a reported procedure [7]. Ethyl 2-hydrazinoacetate (**4**) is commercially available as hydrochloride.

General Procedure for the Preparation of the Methyl 4-amino-1-aryl-1,4,5,6-tetrahydro-6-oxo-1,2,4-triazine-3-carboxylates (**6a–d**)

To a solution of the appropriate 2-arylhydrazono-2-chloroacetate (**2a–d**), (20.0 mmol) in 40 ml of chloroform was added a solution of ethyl 2-hydrazinoacetate hydrochloride (3.71 g, 24.0 mmol) in methanol (40 ml). Triethylamine (10.1 g, 100 mmol) was added dropwise under stirring and cooling in an ice-bath. The reaction mixture was stirred for 2–3 h at 0–4 °C and then for 4 h at ambient temperature. The organic solvent was evaporated in vacuo, and the residue was washed with water (3 × 10 ml) and cold ethanol (5 ml), and recrystallized from chloroform/petrol ether (*b.p.* 40–60 °C). The crystalline products **6a–d** can be further purified on preparative TLC plates (silica gel GF₂₅₄, chloroform/methanol 95 : 5). The yields amount to 65–76% (Scheme 1). The Tables 1–3 contain the analytical and spectroscopic characterization.

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