N-Acylethoxymethylene Hydrazones as the Source of a C_1 Fragment

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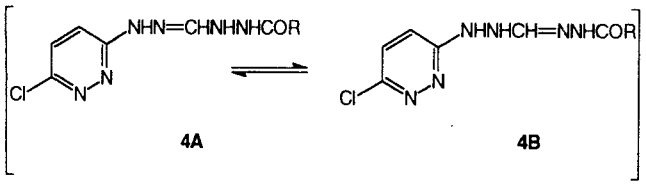
The title compounds were found to be efficient reagents for the ring closure of the appropriate hydrazines or *o*-phenylenediamine. A new C=C bond was formed on their reaction with 1,3-dimethylbarbituric acid.

N-Acylethoxymethylene hydrazones (*N*-acylhydrazonic esters, **2**) are known as intermediates in the synthesis of 1,3,4-oxadiazoles.[1-3] They could be considered as imidol ethers[2] and are easily obtained when hydrazides **1** are treated with triethyl orthoformate.

$RCONHNH_2$ **1** $RCONHN=CHOEt$ **2**

Compounds **2** have not been used so far as reagents in organic synthesis. We have found that hydrazones **2** could serve as a source[4] of C_1 fragments, which could be transferred to the appropriate molecule. In a typical example, 3-chloro-6-hydrazinopyridazine (**3**), was treated in an alcoholic solution with a molar amount of hydrazone **2**, leading to 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine (**5**) as the final product. We assume that the substitution of the ethoxy group in **2** with the hydrazino moiety of the pyridazine molecule gives the corresponding intermediate of type **4A** or **4B**.

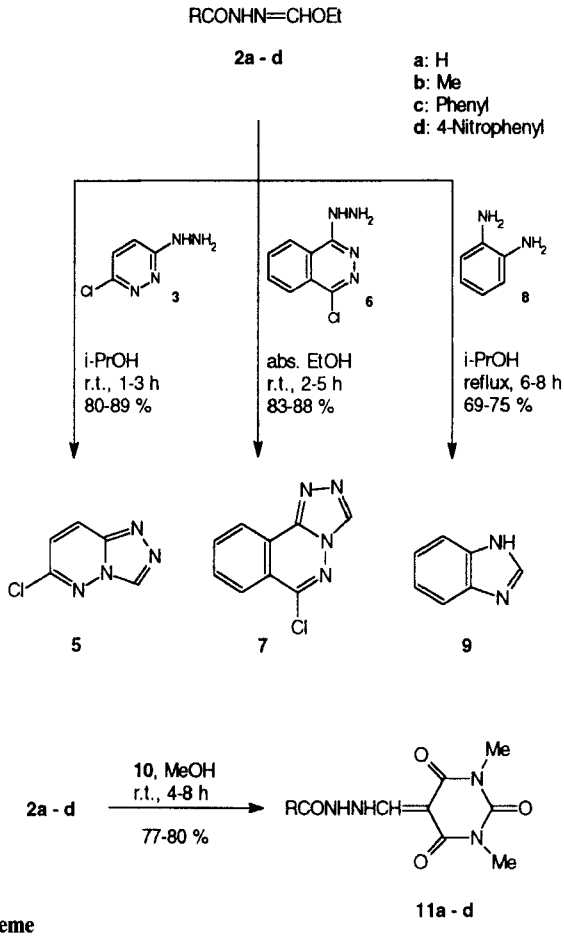


This is in agreement with the fact that compound **2** can react with another molecule of the hydrazide to give bis compound $RCONHN=CHNHNHCOR$.[5-7] In our case, the elimination of the hydrazide **1** from the intermediate **4** resulted in the formation of the cyclized product **5**. One could conclude that the elimination is faster than the first step of the reaction since all attempts to detect intermediate **4** in the reaction mixture by TLC failed.

We have compared the reactivity of hydrazones **2** and triethyl orthoformate (TOF) with the same substrate. Thus, the reaction between **3** and TOF did not take place under the reaction conditions used for the transformation of **3** with **2a–d** (Table 1). The desired product **5** was formed from **3** and TOF either at higher temperature or on prolonged standing of the reaction mixture at room temperature, as observed by TLC.

The same type of ring closure, mentioned above for **3** using **2a–d**, was also carried out with 1-chloro-4-hydrazinophthalazine (**6**). A tricyclic product (6-chloro-1,2,4-triazolo[3,4-*a*]phthalazine, **7**) was isolated in 83–88% yield. In addition, benzimidazole (**9**) could easily be obtained on treatment of *o*-phenylenediamine (**8**) with **2a–d** (Scheme, Table 1).

We believe that the compounds of type **2**, being more reactive than TOF, could be applied in similar reactions as very convenient reagents. It should be emphasized that only equimolar amounts of **2** have been used in our



Scheme

Table 1. Compounds **5**, **7** and **9** Prepared

Compound	Substrate	RCONHN=CHOEt	Reaction Time (h)	Yield (%)
5[a]	3	2a	1	80
		2b	1	81
		2c	1	81.5
		2d	3	89
7[b]	6	2a	4	83
		2b	2	83
		2c	4.5	86
		2d	5	88
9[c]	8	2a	6	72
		2b	6	69
		2c	8	74
		2d	8	75

[a] mp 200–202°C; Lit[9] mp 203.5°C.
[b] mp 162–164°C; Lit[11] mp 164–165°C.
[c] mp 171–173°C; Lit[12] mp 170–172°C.

studies and not an excess of the reagent, which is usually the case when TOF is employed. Furthermore, hydrazides **1** (**a** = R = H, **b** = R = methyl, **c** = R = phenyl, **d** = R = 4-nitrophenyl), which are also formed in the above process, could be used again to start the reaction sequence.

Ethoxymethylene compounds **2a–d** were also found to attack position 5 of 1,3-dimethylbarbituric acid (**10**). The condensation products **11a–d**, possessing a new C=C bond, have been prepared in 77–80% yield. The corresponding reaction conditions and spectroscopic data of the isolated products are shown in Table 2 and Table 3.

Table 2. Reactions of Ethoxymethylene Hydrazones **2a–d** with **10**

Product[a]	Reaction Time (h)	Yield (%)	mp (°C)[b,c]
11a	8	80	249–250
11b	4	77	253–254
11c	4	78	259–261
11d	8	78	257–258

[a] Satisfactory microanalyses obtained: C ± 0.21 (except **11a** C ± 0.45), H ± 0.29, N ± 0.30.
[b] Uncorrected.
[c] Solvents for crystallization: MeOH–DMF for **11a**, **11c** and **11d**; MeOH for **11b**.

Table 3. Spectroscopic Data of Products **11a–d**

Compound	MS (M^+) *m/z*	IR (KBr) cm^{-1}	^1H NMR (DMSO-d_6) δ, *J* (Hz)
11a	226 ($C_8H_{10}N_4O_4$)	3270, 3140, 1718, 1640, 1475	11.38 (br s, 2H, NHNH), 8.14 and 8.23 (s, 2H, CH= and CHO), 3.17 (s, 6H, 2× NMe)
11b	240 ($C_9H_{12}N_4O_4$)	3240, 3160, 1709, 1635, 1510, 1465	11.33 (br s, 2H, NHNH), 8.10 (s, 1H, CH=), 3.17 (s, 6H, 2×NMe), 1.93 (s, 3H, MeCO)
11c	302 ($C_{14}H_{14}N_4O_4$)	3240, 2830, 1703, 1625, 1525, 1490, 1470	12.07 (br s, 2H, NHNH), 8.38 (s, 1H, CH=), 7.87–8.11 (m, 2H, H-2 and H-6), 7.50–7.80 (m, 3H, H-3, H-4 and H-5), 3.20 (s, 6H, 2× NMe)
11d	347 ($C_{14}H_{13}N_5O_6$)	3150, 3000, 1708, 1640, 1520, 1470	8.12 and 8.40 (d, *J* = 8.8, 4H, C_6H_4), 8.31 (s, 1H, CH=), 3.19 (s, 6H, 2× NMe)

NMR spectra were recorded with JEOL JNM FX 90Q and Varian EM 360L instruments. IR spectra were obtained with a Perkin-Elmer 727B spectrometer. Mass spectra were recorded with a VG-Analytical AutoSpec Q instrument. Melting points were determined on a Kofler micro hot stage. Elemental analyses (C, H, N) were performed with a Perkin-Elmer 2400 CHN Analyzer. TLC was carried out on Fluka silica gel TLC plates (F_{254}).

Ethoxymethylene derivatives **2a**,[7] **2b**,[7] **2c**[5] and **2d**[5] as well as 3-chloro-6-hydrazinopyridazine (**3**),[8] 6-chloro-1,2,4-triazolo[4,3-*b*] pyridazine (**5**),[9] 1-chloro-4-hydrazinophthalazine (**6**),[10] 6-chloro-1,2,4-triazolo[3,4-*a*] phthalazine (**7**)[11] and benzimidazole (**9**),[12] were prepared by known procedures. *o*-Phenylenediamine was obtained from Fluka.

Transformation of 3-Chloro-6-hydrazinopyridazine (3) into 6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazine (5); Typical procedure:
To 3-chloro-6-hydrazinopyridazine (**3**, 144.5 mg; 1 mmol) in 2-propanol (5 mL) was added ethoxymethylene hydrazone **2d** (237 mg; 1 mmol) and the mixture was stirred at r.t. for 3 h. The mixture was evaporated to dryness and the residue extracted with $CHCl_3$ (2 × 10 mL). The insoluble material was hydrazide **1d** (151 mg; 83% yield). $CHCl_3$ extracts were combined, evaporated to dryness and treated with hexane (3 mL). Compound **5** was filtered off (137 mg; 89% yield).

6-Chloro-1,2,4-triazolo[3,4-*a*]phthalazine (7); Typical Procedure:
Ethoxymethylene hydrazone **2d** (118.5 mg; 0.5 mmol) and 1-chloro-4-hydrazinophthalazine (**6**, 97 mg; 0.5 mmol) in abs. EtOH (6 mL) were stirred at r.t. for 5 h. The reaction mixture was evaporated to dryness and extracted with $CHCl_3$ (3 × 10 mL). The insoluble part was hydrazide **1d** (76 mg; 84% yield). The combined chloroform extracts were evaporated to dryness, water (10 mL) was added and cyclized product **7** was separated by filtration (90 mg; 88% yield)

1*H*-Benzimidazole (9); Typical Procedure:
A mixture of **2c** (192 mg; 1 mmol) and *o*-phenylenediamine (**8**; 108 mg; 1 mmol) in 2-propanol (6 mL) was heated under reflux for 8 h. The reaction mixture was evaporated to dryness and water was added (2 mL). 1*H*-Benzimidazole (**9**) was filtered off (87 mg; 74% yield); the filtrate was evaporated to dryness, treated with abs. EtOH (1 mL) and kept at −15°C for 2 h. Insoluble hydrazide **1c** was separated by filtration (102 mg; 75% yield).

Reaction of the Ethoxymethylene Hydrazones 2a–d with 1,3-Dimethylbarbituric Acid; General Procedure:
A mixture of the hydrazone **2a–d** (1 mmol) and 1,3-dimethylbarbituric acid (**10**, 156 mg; 1 mmol) in MeOH (4 mL) was stirred at r.t. for 4–8 h (Table 2). The reaction mixture was evaporated to dryness and treated with abs. EtOH (2 mL). Products **11a–d** were filtered off in 77–80% yield and crystallized from the appropriate solvent (Table 2).

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