A Study on Ester Formylhydrazones

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A series of ester formylhydrazones **2** were synthesized from the reaction of alkyl imidate hydrochlorides **1** with formylhydrazine. Treatment of **2** with hydrazine hydrate, ethyl carbazate and *tert*-butyl carbazate led to the formation of 3-alkyl-4-amino-, 3-alkyl-4-ethoxycarbonylamino- and 3-alkyl-4-*tert*-butoxycarbonylamino-4*H*-1,2,4-triazoles **3-5**, respectively. Reaction of compounds **2** with formylhydrazine gave *N,N'*-diformylhydrazine **6**. Compounds **2** were reacted with 2,5-dimethoxytetrahydrofuran to afford 3-alkyl-4-(1*H*-pyrrol-1-yl)-4*H*-1,2,4-triazoles **8**.

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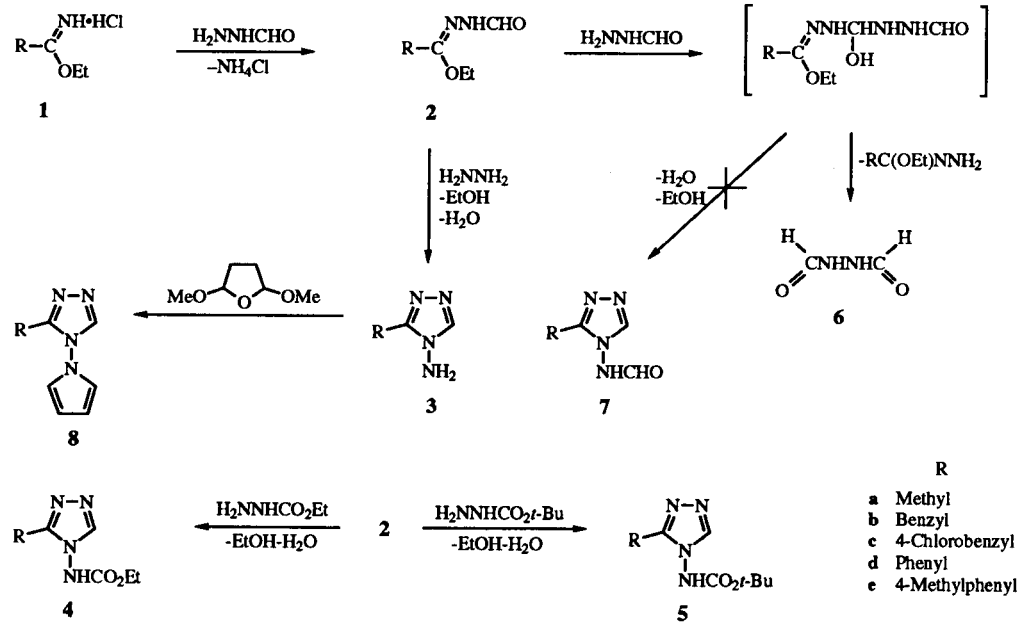
In spite of the fact that some amide ethoxycarbonylhydrazones [1-3], amide *tert*-butoxycarbonylhydrazones [4], amide formylhydrazones [5,6], ester ethoxycarbonylhydrazones [3,7,8] and ester *tert*-butoxycarbonylhydrazones [4,9] have been known, only one specific ester formylhydrazone involving the benzyloxycarbonylamino group has been reported in the literature [10]. On the other hand, only a few methods have been reported for the synthesis of 3-alkyl-4-amino-4*H*-1,2,4-triazoles [11-13]. Taking into consideration, the relationship of some hydrazine derivatives with 1,2,4-triazoles, we propose to synthesize a series of ester formylhydrazones and subsequently the corresponding 4-amino-4*H*-1,2,4-triazole derivatives. Hence, in the present study, alkyl imidate hydrochlorides **1** were reacted with formylhydrazine to afford ester formylhydrazones **2**. Treatment of compounds **2** with hydrazine hydrate, ethyl carbazate and *tert*-butyl carbazate resulted in the formation of 3-alkyl-4-amino-4*H*-1,2,4-triazoles **3**, 3-alkyl-4-ethoxycarbonylamino-4*H*-1,2,4-triazoles **4** and 3-alkyl-4-*tert*-butoxycarbonylamino-4*H*-1,2,4-triazoles **5**, respectively. However, *N,N'*-diformylhydrazine **6** was obtained from the reaction of compounds **2** with formylhydrazine instead of 3-alkyl-4-formylamino-4*H*-1,2,4-triazoles **7**. Moreover, compounds **3** were condensed in relatively good yields with the succinaldehyde equivalent [14] 2,5-dimethoxytetrahydrofuran to give 3-alkyl-4-(1*H*-pyrrol-1-yl)-4*H*-1,2,4-triazoles **8** (Scheme 1).

Two mechanisms are possible for the formation of compounds **3-5** starting from a nucleophilic attack at the azomethine carbon or the aldehyde carbon as shown in Scheme 2. The instability of an isomeric 1,2-dihydro-1,2,4,5-tetrazine **9** structure at an elevated reaction temperature [15] and the formation of compounds **8** reveal the impossibility of the formation of type **9** compounds from the reaction of compounds **2** with hydrazine hydrate. A reliable basis is ^{1}H-nmr spectra to differentiate of a type **9** compound from com-

Scheme 1



Scheme 2

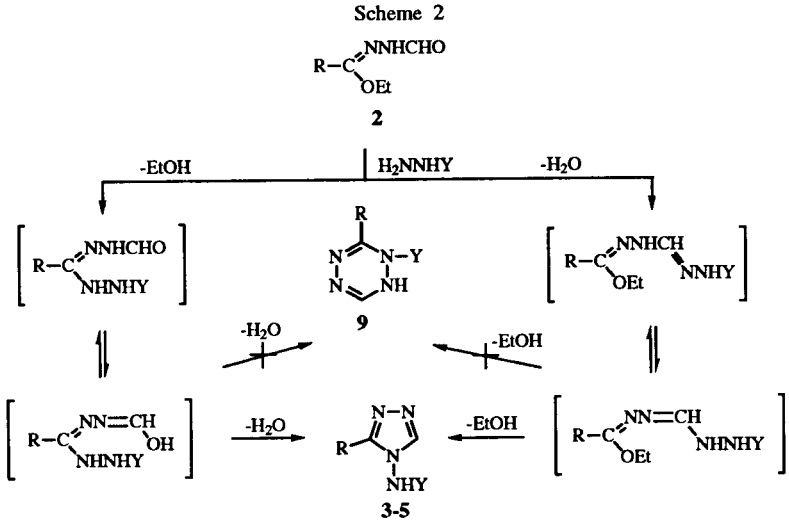


Table 1
Physical Data of Compounds **2-6,8**

Compound No.	Yield (%)	Mp (°C) (recrystallization solvent)	Molecular Formula (Molecular Weight)	Analysis (%) Calcd./Found C	H	N
2a	46	97-98 (petroleum ether, 40-60°)	$C_5H_{10}N_2O_2$ (130.15)	46.14 45.97	7.75 7.94	21.53 21.80
2b	40	89-90 (petroleum ether, 40-60°)	$C_{11}H_{14}N_2O_2$ (206.24)	64.06 63.97	6.84 6.89	13.58 13.45
2c	48	98-99 (petroleum ether, 40-60°)	$C_{11}H_{13}ClN_2O_2$ (240.68)	54.89 55.15	5.44 5.45	11.64 11.94
2d	45	80-81 (petroleum ether, 40-60°)	$C_{10}H_{12}N_2O_2$ (192.21)	62.48 62.30	6.29 6.31	14.58 14.55
2e	44	98-99 (petroleum ether, 40-60°)	$C_{11}H_{14}N_2O_2$ (206.24)	64.06 64.34	6.84 6.82	13.58 13.33
3a	35	57-59 [a] (ethyl acetate)	$C_3H_6N_4$ (98.11)	36.72 36.64	6.16 6.20	57.11 57.29
3b	57	137-138 [b] (ethyl acetate)	$C_9H_{10}N_4$ (174.20)	62.05 61.86	5.79 5.73	32.17 32.46
3c	58	162-163 (ethyl acetate)	$C_9H_9ClN_4$ (208.64)	51.81 51.62	4.35 4.20	26.85 26.82
3d	47	91-92 [c] (ethyl acetate)	$C_8H_8N_4$ (160.18)	59.98 60.03	5.03 4.94	34.98 34.79
3e	49	123-124 (ethyl acetate)	$C_9H_{10}N_4$ (174.20)	62.05 62.32	5.79 5.87	32.17 32.18
4a	62	160-161 (ethyl acetate)	$C_6H_{10}N_4O_2$ (170.17)	42.35 42.55	5.92 5.74	32.93 32.98
4b	40	153-154 (ethyl acetate)	$C_{12}H_{14}N_4O_2$ (246.26)	58.52 58.53	5.73 5.78	22.75 22.90
4c	41	189-190 (ethyl acetate)	$C_{12}H_{13}ClN_4O_2$ (280.70)	51.35 51.10	4.67 4.71	19.96 20.07
5a	60	162-163 (ethyl acetate)	$C_8H_{14}N_4O_2$ (198.22)	48.47 48.26	7.12 7.16	28.27 28.55
5c	48	185-186 (ethyl acetate)	$C_{14}H_{17}ClN_4O_2$ (308.75)	54.46 54.57	5.55 5.62	18.15 18.01
6	39-45	158-159 [d] (ethanol/ethyl acetate)	$C_2H_4N_2O_2$ (88.06)	27.28 27.13	4.58 4.55	31.81 32.00
8b	67	134-135 (acetone/water)	$C_{13}H_{12}N_4$ (224.26)	69.62 69.78	5.39 5.53	24.99 25.22
8c	58	162-163 (acetone/water)	$C_{13}H_{11}ClN_4$ (258.70)	60.35 60.53	4.29 4.13	21.66 21.82
8e	54	188-189 (ethyl acetate)	$C_{13}H_{12}N_4$ (224.26)	69.62 69.70	5.39 5.32	24.99 24.95

[a] Lit [11] reported 60°. [b] Lit [12] reported 140°. [c] Lit [12] reported 92°. [d] Lit [18] reported 159-160°.

Table 2

^{1}H-NMR Data for Compounds **2-6,8** [a]

Compound No.	CH_3	CH_3	CH_2	CH_2	NH_2	CH	Ar-H (Benzenoid ring)	NH
2a	1.40 (t, 3H)	2.04 (s, 3H)	-	4.10 (q, 2H)	-	8.42 (s, 1H)	-	9.80 (s, 1H)
2b	1.36 (t, 3H)	-	3.72 (s, 2H)	4.12 (q, 2H)	-	8.40 (s, 1H)	7.20 (s, 5H)	9.60 (s, 1H)
2c	1.24 (t, 3H)	-	3.70 (s, 2H)	4.00 (q, 2H)	-	8.40 (s, 1H)	7.16 (s, 4H)	9.80 (s, 1H)
2d	1.40 (t, 3H)	-	-	4.04 (q, 2H)	-	8.65 (s, 1H)	7.20-7.70 (m, 5H)	9.50 (s, 1H)
2e	1.30 (t, 3H)	2.40 (s, 3H)	-	4.00 (q, 2H)	-	8.60 (s, 1H)	7.00-7.55 (m, 4H)	9.55 (s, 1H)
3a	-	2.40 (s, 3H)	-	-	5.72 (s, 2H)	8.00 (s, 1H)	-	-
3b	-	-	4.16 (s, 2H)	-	5.80 (s, 2H)	8.20 (s, 1H)	7.20 (s, 5H)	-
3c	-	-	4.10 (s, 2H)	-	5.90 (s, 2H)	8.30 (s, 1H)	7.22 (s, 4H)	-
3d	-	-	-	-	6.05 (s, 2H)	8.40 (s, 1H)	7.30-8.10 (m, 5H)	-
3e	-	2.48 (s, 3H)	-	-	5.96 (s, 2H)	8.45 (s, 1H)	7.22 (d, 2H), 7.94 (d, 2H)	-
4a	1.40 (t, 3H)	2.32 (s, 3H)	-	4.24 (q, 2H)	-	8.60 (s, 1H)	-	10.84 (s, 1H)
4b	1.40 (t, 3H)	-	3.92 (s, 2H)	4.00 (q, 2H)	-	8.56 (s, 1H)	7.16 (s, 5H)	10.76 (s, 1H)
4c	1.25 (t, 3H)	-	3.95 (s, 2H)	4.10 (q, 2H)	-	8.50 (s, 1H)	7.20 (s, 4H)	10.72 (s, 1H)
5a	1.50 (s, 9H, $3CH_3$)	2.30 (s, 3H)	-	-	-	8.70 (s, 1H)	-	10.40 (s, 1H)
5c	1.40 (s, 9H, $3CH_3$)	-	3.95 (s, 2H)	-	-	8.75 (s, 1H)	7.20 (s, 4H)	10.50 (s, 1H)
6	-	-	-	-	-	7.90 (s, 2H, 2CH)	-	9.90 (s, 2H, 2NH)
8b	-	-	4.00 (s, 2H)	-	-	8.50 (s, 1H) [b]	7.20 (s, 5H)	-
8c	-	-	3.94 (s, 2H)	-	-	8.80 (s, 1H) [c]	7.20 (s, 4H)	-
8e	-	2.30 (s, 3H)	-	-	-	8.80 (s, 1H) [d]	7.20 (d, 2H), 7.40 (d, 2H)	-

[a] The spectra for **2a-e** were recorded in deuteriochloroform and for **3-7** in dimethyl sulfoxide-d_6. [b] 6.20 (t, 2H, 2CH) and 6.52 (t, 2H, 2CH). [c] 6.20 (t, 2H, 2CH) and 6.50 (t, 2H, 2CH). [d] 6.20 (t, 2H, 2CH) and 6.70 (t, 2H, 2CH).

Table 3

IR and UV Data for Compounds **2-6,8**

Compound No.	IR, ν (cm^{-1}) [a] NH	NH_2	C=O	C=N	[b]	UV, λ_{max} (nm)/ε x 10^{-3} (in ethanol)
2a	3165	-	1685	1630	-	211 (1.94)
2b	3160	-	1675	1615	762, 690	235 (5.91)
2c	3163	-	1665	1620	810	224 (9.26)
2d	3165	-	1672	1615	765,690	208 (8.74), 265 (9.40)
2e	3140	-	1680	1620	820	208 (7.96), 266 (8.74)
3a	-	3250, 3180	-	1630, 1650	-	203 (2.05)
3b	-	3235, 3115	-	1640, 1520	730, 693	214 (3.75)
3c	-	3280, 3170	-	1640, 1530	805	223 (4.47)
3d	-	3260, 3110	-	1635, 1520	760, 680	204 (5.04), 225 (6.02)
3e	-	3285, 3190	-	1615, 1560	820	214 (5.80), 2.97 (7.78)
4a	3140	-	1740	1580, 1550	-	202 (2.41)
4b	3140	-	1735	1555, 1520	760, 690	214 (3.72)
4c	3150	-	1735	1555, 1520	790	222 (9.05)
5a	3120	-	1730	1550, 1520	-	202 (2.10)
5c	3115	-	1730	1550, 1520	790	223 (13.93)
6	3140	-	1650	-	-	210 (2.46)
8b	-	-	-	1615, 1530	740, 690	212 (2.67)
8c	-	-	-	1605, 1540	810	225 (5.34)
8e	-	-	-	1620, 1510	825	238 (7.85)

[a] Potassium bromide pellets. [b] Substituted aromatic ring.

pounds **4** and **5**. Indeed, the nitrogen protons of compounds **4** and **5** appeared at δ 10.40-10.84 ppm, as expected from their structures. But, a nitrogen proton of a dihydrotetrazine appears at a lower δ value as reported recently [9,15].

It is interesting that the treatment of compounds **2a-e** with formylhydrazine always led to the formation of compound **6**. This indicates that this reaction predominantly occurs *via* a nucleophilic addition to the aldehyde group of **2** and subsequently an elimination (Scheme 1).

EXPERIMENTAL

Melting points were determined on a Büchi oil heated melting point apparatus and are uncorrected. Experimental data for compounds **2-6,8** are given in Table 1. The ^{1}H-nmr spectra (δ, ppm) were run on a Varian 60A spectrometer using tetramethylsilane as the internal reference (Table 2). The ir spectra (ν, cm^{-1}) were recorded on a Perkin Elmer 377 spectrophotometer in potassium

bromide discs (Table 3). The uv absorption measurements were carried out with 1.10^{-5}-1.10^{-4} ethanolic solutions and the spectra were measured between 200 and 400 nm with a Shimatzu-1201 spectrophotometer using 10 mm quartz cells (Table 3). The elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. The starting compounds **1** were synthesized by routes previously reported [16,17]. The necessary chemicals were obtained from Fluka and Merck.

General Method for the Synthesis of Compounds **2**.

The corresponding alkyl imidate hydrochloride **1** (0.01 mole) was dissolved in 50 ml of absolute ethanol with ice-bath cooling and formylhydrazine (0.01 mole) dissolved in 50 ml of absolute ethanol was added to the solution. After stirring for 6 hours at 0-5°, the precipitate was filtered. The filtrate was evaporated at 30-35° under reduced pressure. The solid residue was extracted with hot petroleum ether (40-60°) and recrystallized from the same solvent to give pure compound **2**.

General Method for the Synthesis of Compounds **3**.

The corresponding ester formylhydrazone **2** (0.01 mole) was refluxed with a solution of hydrazine hydrate (0.025 mole) in 60 ml of water for 5-6 hours. The resulting solution was evaporated at 40-45° under reduced pressure or crystallized by cooling to obtain the crude product. This solid product was recrystallized from ethyl acetate to give the desired compound.

General Procedure for the Synthesis of Compounds **4** and **5**.

The corresponding ester formylhydrazone **2** (0.01 mole) was treated with ethyl carbazate (0.01 mole) or *tert*-butyl carbazate (0.01 mole) and the mixture was heated at 110-120° for 1.5 hours. After cooling to room temperature, 2-3 ml of ethyl acetate was added to the viscous reaction mixture. On cooling the mixture in a deep-freeze, a white solid appeared. This was recrystallized from ethyl acetate to afford the desired compound.

Treatment of Compounds **2** with Formylhydrazine.

An ester formylhydrazone **2a**, **2b**, **2c**, **2d** or **2e** (0.01 mole) was heated with formylhydrazine (0.01 mole) at 110-120° for 2 hours and then allowed to cool. The crude oil which formed solidified when allowed to stand in the deep-freeze with 2-3 ml of ethyl acetate. Recrystallization of the product from ethanol-ethyl acetate (1:1) gave pure **6**.

General Route for the Synthesis of Compounds **8**.

The corresponding 3-alkyl-4-amino-4*H*-1,2,4-triazole **4** (0.01 mole) was refluxed with a solution of 2,5-dimethoxytetrahydrofuran (0.01 mole) in 5 ml of glacial acetic acid for 1 hour. The resulting solution was evaporated at 45-50° under reduced pressure and dried *in vacuo*. The solid residue was recrystallized from an appropriate solvent to give compound **8**.

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