Reaction of Schiff Bases with Diazenedicarboxylic Esters: Synthesis of 2-Oxo-2,3-dihydroimidazoles

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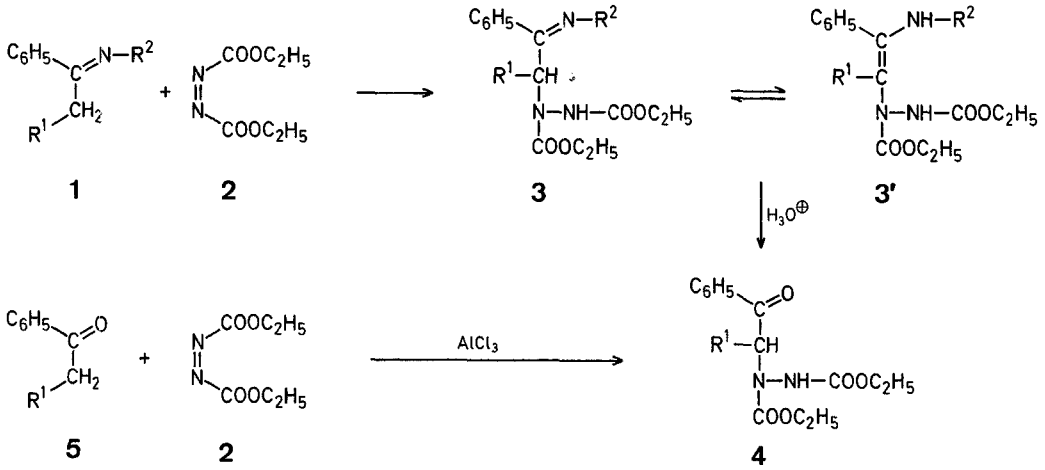
Diazenedicarboxylic esters (azodicarboxylic esters, **2**) exhibit high reactivity[1], in particular in addition reactions. Thus, compounds **2** have been extensively used in cycloaddition reactions[2]. The reaction of diazenedicarboxylic esters (**2**) with *N*-monosubstituted aldehyde hydrazones leads to monoaddition products whereas their reaction with ketone monoalkylhydrazones does not give rise to monoaddition products[3].

N-Arylimines (**1**) of *prim*-alkyl aryl ketones react with diazenedicarboxylic esters (**2**) to give the monoaddition products **3** in consistence with data previously reported on the reactivity of Schiff bases towards electron-deficient compounds[4]. Hydrolysis of compounds **3** with 10% hydrochloric acid affords the carbonyl compounds **4** (Method A) which can also be obtained by reaction of **2** with the free ketone (**5**) corresponding to **1** in the presence of aluminum chloride (Method B).



When compounds **3** are treated with phenyllithium in tetrahydrofuran at 0 °C or with sodium hydride in tetrahydrofuran at room temperature, cyclocondensation takes place to give an *N*-heterocyclic compound (**6** or **9**). Microanalytical, mass-, I.R.-, and ^{1}H-N.M.R.-spectral data are in good agreement with both of these structures. In order to distinguish between structures **6** and **9**, the solid products were heated with potassium hydroxide in ethylene glycol at 200 °C and the resultant 1-amino-2-oxo-2,3-dihydroimidazoles **7** condensed with benzaldehyde to give the hydrazones **8**. This reaction sequences clearly shows that treatment of compounds **3** with phenyllithium or sodium hydride gives rise to the imidazole derivatives **6** and not to the 1,2,4-triazine derivatives **9**.

Diethyl *N*-(2-Anilino-1-methyl-2-phenylethenyl)-hydrazine-*N*,*N*-dicarboxylate (3'a, $R^1 = CH_3$, $R^2 = C_6H_5$):

In a 100 ml flask, 1-phenylimino-1-phenylpropane (**1**; $R^1 = CH_3$, $R^2 = C_6H_5$; 4.2 g, 20 mmol) is dissolved in hexane (50 ml) and diethyl diazenedicarboxylate (**2**; 3.48 g, 20 mmol) is added with stirring. After 2 h at room temperature, the mixture is filtered by suction and the colorless solid product recrystallized from hexane/chloroform (6/1); yield: 4.5 g (59%); m.p. 140–141 °C.

$C_{21}H_{25}N_3O_4$	calc.	C 65.79	H 6.57	N 10.96
(383.4)	found	65.61	6.60	11.09

I.R. (Nujol): ν = 710, 760 (Ar); 1700, 1735 (C=O); 3270, 3320 (NH) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.00, 1.27 (2t, 6H, $2CH_2$—CH_3); 1.85 (s, 3H, C—CH_3); 4.05, 4.23 (2q, 4H, $2CH_2$—CH_3); 6.4–7.6 (m, 10 H_{arom}, NH); 8.05 ppm (s, NH).

Diethyl *N*-(1-Methyl-2-oxo-2-phenylethyl)-hydrazine-*N*,*N*-dicarboxylate (4a, $R^1 = CH_3$):

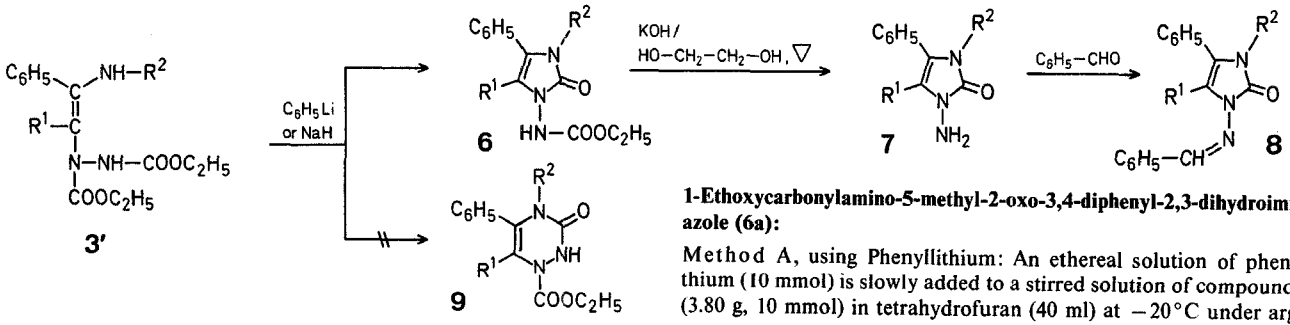
Method A, from **3'a**: To a solution of **3'a** (3.80 g, 10 mmol) in tetrahydrofuran (20 ml), 3 normal hydrochloric acid (50 ml) is added with vigorous stirring. After 24 h, the mixture is extracted with ether (3 × 30 ml) and the organic extract dried with sodium sulfate. The solvent is removed in vacuo and the oily residue (2.70 g, 88%) recrystallized from hexane/chloroform (10/1); yield: 2.1 g (68%); m.p. 86–88 °C.

$C_{15}H_{20}N_2O_5$	calc.	C 58.44	H 6.54	N 9.09
(308.3)	found	58.51	6.49	9.21

I.R. (Nujol): ν = 700, 770 (Ar); 1690, 1725, 1760 (C=O); 3320 (NH) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.23 (m, 6H, $2CH_2$—CH_3); 1.40 (d, 3H, CH—CH_3); 4.20 (q, 4H, $2CH_2$—CH_3); 5.8 (m, 1H, CO—CH—CH_3); 6.90 (s, NH); 7.3–8.1 ppm (m, 5 H_{arom}).

Method B, from **5**: In a 100 ml flask, propiophenone (2.68 g, 20 mmol), diethyl diazenedicarboxylate (3.48 g, 20 mmol), and dioxan (60 ml) are placed and then aluminium chloride (2.66 g, 20 mmol) is added under argon. The mixture is stirred at room temperature for 48 h, acidified with 2 normal sulfuric acid (200 ml), and extracted with ether (3 × 30 ml). The solvent is removed under reduced pressure and the oily residue (3.40 g, 56%) crystallized from hexane/chloroform (10/1); yield: 2.6 g (43%); m.p. 86–88 °C. [The product thus obtained was identical with that prepared using Method A.]



1-Ethoxycarbonylamino-5-methyl-2-oxo-3,4-diphenyl-2,3-dihydroimidazole (6a):

Method A, using Phenyllithium: An ethereal solution of phenyllithium (10 mmol) is slowly added to a stirred solution of compound **3'a** (3.80 g, 10 mmol) in tetrahydrofuran (40 ml) at −20 °C under argon.

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Table 1. 1-Ethoxycarbonylamino-2-oxo-2,3-dihydroimidazoles **(6)**

6	R^1	R^2	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. (nujol) [cm^{-1}][c] $\nu_{C=O}$	ν_{NH}	^{1}H-N.M.R.[d] ($CDCl_3$/TMS) δ [ppm]
a	CH_3	C_6H_5	88/75	197–198°	$C_{19}H_{19}N_3O_3$ (337.4)	1750, 1695	3180	1.30 (t, 3H, CH_2—CH_3, J=7.5 Hz); 2.13 (s, 3H, 5-CH_3); 4.25 (q, 2H, CH_2—CH_3, J=7.5 Hz); 7.0–7.4 (m, 10H_{arom}); 8.90 (s, NH)
b	CH_3	4-H_3C—C_6H_4—	70/58	141–143°	$C_{20}H_{21}N_3O_3$ (351.4)	1750, 1695	3140	1.26 (t, 3H, CH_2—CH_3, J=7.0 Hz); 2.07 (s, 3H, 5-CH_3); 2.25 (s, 3H, Ar—CH_3); 4.20 (q, 2H, CH_2—CH_3, J=7.0 Hz); 6.9–7.4 (m, 9H_{arom}); 9.05 (s, NH)
c	C_2H_5	C_6H_5	85/71	169–171°	$C_{20}H_{21}N_3O_3$ (351.4)	1765, 1700	3160	1.06 (t, 3H, 5-CH_2—CH_3, J=7.5 Hz); 1.26 (t, 3H, O—CH_2—CH_3, J=7.5 Hz); 2.45 (q, 2H, 5-CH_2—CH_3, J=7.5 Hz); 4.25 (q, 2H, O—CH_2—CH_3, J=7.5 Hz); 6.9–7.4 (m, 10 H_{arom}); 8.65 (s, NH)
d	C_2H_5	2-H_3C—C_6H_4—	86/70	168–170°	$C_{21}H_{23}N_3O_3$ (365.4)	1760, 1705	3180	1.10 (t, 3H, 5-CH_2—CH_3, J=7.5 Hz); 1.28 (t, 3H, O—CH_2—CH_3, J=7.0 Hz); 2.15 (s, 3H, Ar—CH_3); 2.50 (q, 2H, 5-CH_2—CH_3, J=7.5 Hz); 4.25 (q, 2H, O—CH_2—CH_3, J=7.0 Hz); 6.95–7.30 (m, 9H_{arom}); 9.30 (s, NH)
e	C_2H_5	4-H_3C—C_6H_4—	79/63	118–120°	$C_{21}H_{23}N_3O_3$ (365.4)	1745, 1680	3100	1.10 (t, 3H, 5-CH_2—CH_3, J=7.0 Hz); 1.30 (t, 3H, O—CH_2—CH_3, J=7.0 Hz); 2.26 (s, 3H, Ar—CH_3); 2.43 (q, 2H, 5-CH_2—CH_3, J=7.0 Hz); 4.25 (q, 2H, O—CH_2—CH_3, J=7.0 Hz); 6.95–7.35 (m, 9H_{arom}); 9.10 (s, NH)

[a] Crude product/pure product.
[b] The microanalyses of the pure products were in good agreement with the calculated values: C, ±0.20; H, ±0.11; N, ±0.15.
[c] Recorded with a Pye Unicam SP-1000 spectrometer.
[d] Measured at 90 MHz with a Varian EM-390 spectrometer.

Table 2. 1-Amino-2-oxo- **(7)** and 1-Benzylidenamino-2-oxo-2,3-dihydroimidazoles **(8)**

Product	Yield[a] [%]	m.p. [°C]	Molecular formula[b]	I.R. (nujol)[c] [cm^{-1}] $\nu_{C=O}$	ν_{NH}	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]
7a	92/80	208–209°	$C_{16}H_{15}N_3O$ (265.3)	1695	3280, 3320	2.25 (s, 3H, 5-CH_3); 4.45 (s, NH_2); 6.9–7.4 (m, 10H_{arom})
7c	85/73	200–201°	$C_{17}H_{17}N_3O$ (279.3)	1710	3270, 3320	1.0–1.3 (t, 3H, CH_2—CH_3); 2.3–2.7 (q, 2H, CH_2—CH_3); 4.35 (s, NH_2); 6.8–7.4 (m, 10H_{arom})
7d	84/72	121–122°	$C_{18}H_{19}N_3O$ (293.4)	1700	3230, 3310	1.2–1.5 (t, 3H, CH_2—CH_3); 2.15 (s, 3H, Ar—CH_3); 2.4–2.8 (q, 2H, CH_2—CH_3); 4.45 (s, NH_2); 6.9–7.4 (m, 9H_{arom})
7e	81/67	178–179°	$C_{18}H_{19}N_3O$ (293.4)	1710	3230, 3320	1.1–1.4 (t, 3H, CH_2—CH_3); 2.2 (s, 3H, Ar—CH_3); 2.4–2.8 (q, 2H, CH_2—CH_3); 4.4 (s, NH_2); 6.9–7.4 (m, 9H_{arom})
8a	85/71	207–208°	$C_{23}H_{19}N_3O$ (353.4)	1680		2.35 (s, 3H, 5-CH_3); 7.0–7.9 (m, 15H_{arom}); 10.0 (s, CH—N)
8c	87/73	180–181°	$C_{24}H_{21}N_3O$ (367.4)	1700		1.2–1.5 (t, 3H, CH_2—CH_3); 2.5–2.9 (q, 2H, CH_2—CH_3); 6.9–7.9 (m, 15H_{arom}); 10.1 (s, CH=N)
8d	82/68	156–157°	$C_{25}H_{23}N_3O$ (381.5)	1690		1.2–1.5 (t, 3H, CH_2—CH_3); 2.2 (s, 3H, Ar—CH_3); 2.4–2.8 (q, 2H, CH_2—CH_3); 6.8–7.8 (m, 14H_{arom}), 10.0 (s, CH=N)
8e	85/72	197–198°	$C_{25}H_{23}N_3O$ (381.5)	1700		1.15–1.55 (t, 3H, CH_2—CH_3); 2.2 (s, 3H, Ar—CH_3); 2.5–2.9 (q, 2H, CH_2—CH_3); 6.9–8.1 (m, 14H_{arom}); 10.1 (s, CH=N)

[a] Crude product/pure product.
[b] The microanalyses of the pure products were in good agreement with the calculated values: C±0.24; H±0.14; N±0.13.
[c] Recorded with a Pye Unicam SP-1000 spectrometer.
[d] Measured at 90 MHz with a Varian EM-390 spectrometer.

The resultant clear solution is stirred at 0°C for 4 h, then hydrolyzed with 0.1 normal sulfuric acid (200 ml), and extracted with ether (3 × 30 ml). The extract is dried with sodium sulfate, the solvent removed under reduced pressure, and the residual crude product (2.97 g, 88%) recrystallized from hexane/chloroform (6/1); yield 2.53 g (75%); m.p. 197–198°C.

$C_{19}H_{19}N_3O_3$	calc.	C 67.63	H 5.68	N 12.45
(337.4)	found	67.43	5.79	12.56

M.S.: m/e=337 (M^+).

Method B, using Sodium Hydride: To a stirred solution of compound **3'a** (3.80 g, 10 mmol) in tetrahydrofuran (50 ml), sodium hydride (0.30 g, 12.5 mmol) is added at room temperature and stirring is continued for 8 h. The mixture is then hydrolyzed with 0.1 normal sulfuric acid (200 ml) and extracted with ether (3 × 30 ml). The extract is dried with sodium sulfate, the solvent removed under reduced pressure, and the residual crude product (2.8 g, 85%) recrystallized from hexane/chloroform (6/1); yield: 2.37 g (72%); m.p. 197–198°C.

1-Amino-5-methyl-2-oxo-3,4-diphenyl-2,3-dihydroimidazole (7a):
Compound **6a** (3.37 g, 10 mmol) is mixed with potassium hydroxide (3.50 g, 62.5 mmol) in ethylene glycol (40 ml). The mixture is refluxed for 5 h, then cooled, and poured into water (250 ml). The mixture is extracted with ether (3 × 30 ml), the extract washed with water (80 ml) and dried with sodium sulfate, and the solvent removed under reduced pressure. The residual colorless solid is recrystallized from ethanol; yield: 2.10 g (80%); m.p. 208–209°C.

$C_{16}H_{15}N_3O$	calc.	C 72.44	H 5.70	N 15.84
(265.3)	found	72.58	5.67	15.75

I.R. (Nujol): ν=720, 770 (Ar); 1695 (C=O); 3280, 3320 (NH_2) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ=2.23 (s, CH_3); 4.43 (s, NH_2); 6.9–7.4 ppm (m, $10H_{arom}$).

1-Benzylidenamino-5-methyl-2-oxo-3,4-diphenyl-2,3-dihydroimidazole (8a):

Compound **7a** (2.65 g, 10 mmol) is dissolved in boiling methanol (150 ml), and benzaldehyde (25 ml) is gradually added to the solution. The resultant colorless precipitate is isolated by suction and recrystallized from methanol; yield: 2.53 g (71%); m.p. 207–208 °C.

$C_{23}H_{19}N_3O$	calc.	C 78.17	H 5.42	N 11.89
(353.4)	found	78.03	5.51	11.98

M.S.: m/e=353 (M^+).

I.R. (Nujol): ν=710, 775 (Ar); 1680 (C=O) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ=2.35 (s, CH_3); 7.0–7.9 (m, $15H_{arom}$); 10.00 ppm (s, CH=N).

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