

### Activated Nitriles in Heterocyclic Synthesis: Novel Synthesis of Pyridazines, Pyridines, and Isoxazoles

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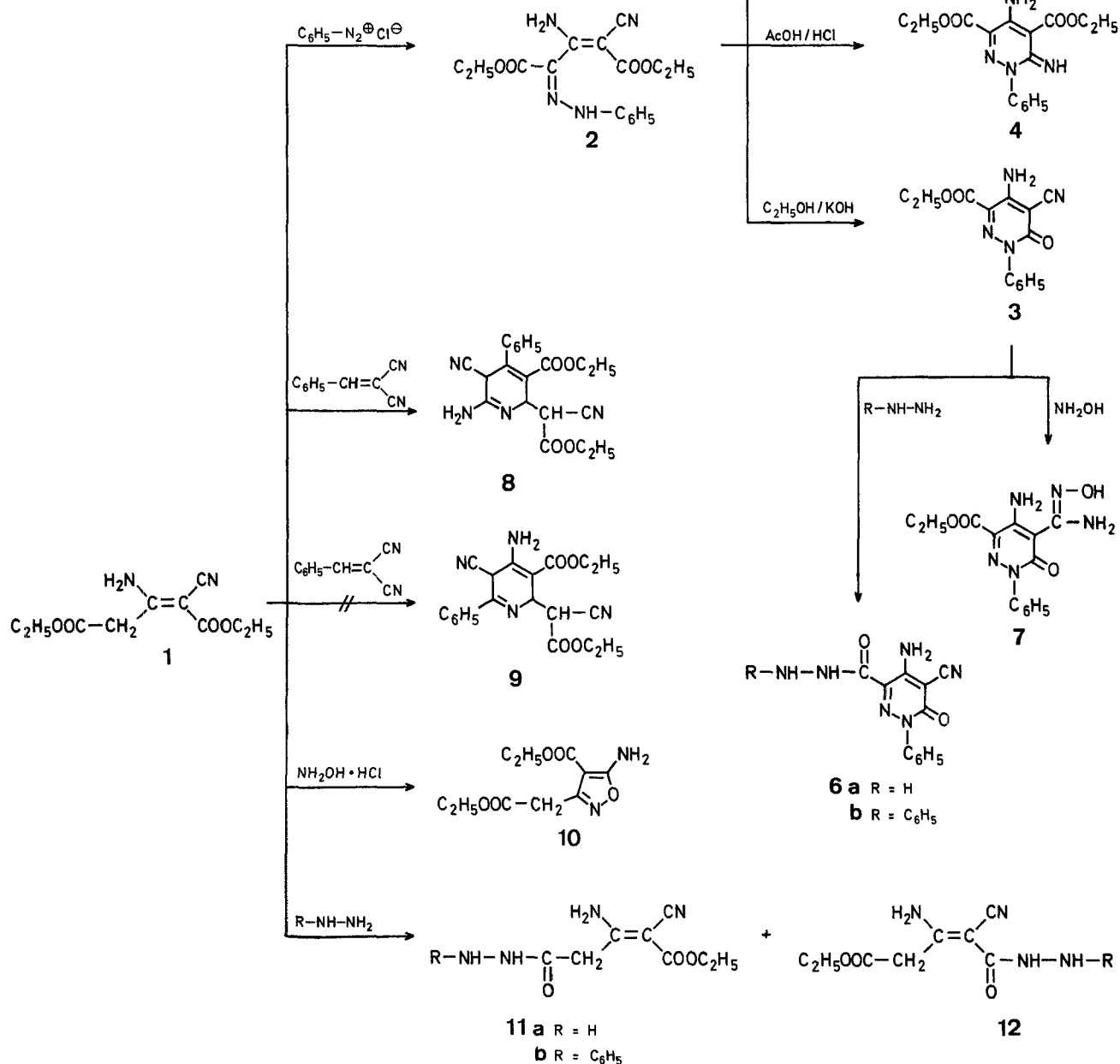
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Although diethyl 3-amino-2-cyano-2-pentene-1,5-dicarboxylate (**1**), readily obtained via dimerisation of ethyl cyanoacetate<sup>1</sup>, is an interesting intermediate for heterocyclic synthesis, very little attention was paid to the potential utility of **1** for the synthesis of azoles and azolines. In continuation of our program directed to the development of new procedures for the synthesis of azoles and azolines from simple starting materials<sup>2</sup>, we report here several new procedures for the synthesis of azolines and azoles utilising **1** as starting material. Thus, it has been found that **1** couples with benzenediazonium chloride in ethanolic sodium acetate to yield the hydrazone **2**. The latter is cyclised to the pyridazin-6-one derivative **3** on treatment with ethanolic potassium hydroxide solution. On the other hand, **1** cyclised readily to the pyridazin-6-imine **4** on treatment with acetic/hydrochloric acid mixture. Compound **2** also afforded the 4-acetylaminopyridazin-6-one derivative **5** on treatment with acetic anhydride. Attempts to synthesise **5** via acylation of **3** under a variety of conditions were unsuccessful. The amino group in **3** proved highly inactive towards electrophilic reagents, which is in analogy to previous observations on 4-aminopyridin-6-one. Compound **3** reacted with hydrazine hydrate and with phenylhydrazine to yield the hydrazide **6a** and the phenylhydrazide **6b**, respectively. When treated with hydroxylamine hydrochloride, in presence of sodium acetate, compound **3** afforded the amidoxime **7**.

Compound **1** readily reacted with benzylidenemalononitrile to yield a product of molecular formula  $C_{20}H_{20}N_4O_4$ . Two isomeric structures seemed possible for the reaction product (**8** or **9**). Structure **8** was established on the basis of the <sup>1</sup>H-N.M.R. spectrum which revealed that two of the aryl protons were shifted downfield by 1.1 ppm as compared to the other three aryl protons. This downfield shift can only be rationalised in terms of deshielding of the two aryl *ortho*-protons by CO group anisotropy. The formation of **8** from **1** and benzylidenemalononitrile might be assumed to proceed via addition of the methylene group of **1** to the activated double bond and cyclisation of the intermediately formed product.

Compound **1** reacted with hydroxylamine hydrochloride in refluxing ethanol to yield the aminoisoxazole derivative **10**. The structure of **10** was inferred from analytical and spectral data.

In contrast to the reported behaviour of enaminonitriles toward the action of hydrazines<sup>4,5</sup>, compound **1** reacted with hydrazine hydrate and phenylhydrazine to yield hydrazides for which structures **11** or **12** seemed possible; structure **11** was considered more likely based on the decrease in activity



of the methylene group in the hydrazides as compared to that in **1**, as demonstrated by their failure to couple with aromatic diazonium salts under conditions similar to those utilised to affect coupling of **1** with the same reagent. The phenylhydrazine **11b** was converted into pyrazole **13** (or possible tautomers) on boiling in xylene. Compound **13** was also directly obtained from reaction of **1** and phenylhydrazine at  $160^\circ\text{C}$  in the absence of solvent.

Melting points are uncorrected.  $^1\text{H-N.M.R.}$  spectra were recorded on a Varian A-90 spectrometer. The I.R. spectra were obtained (KBr) on a Pye-Unicam SP-1000 spectrophotometer. Analytical data were obtained from the analytical data unit at Cairo University and from El-naser Pharmaceutical Chemical Company Analytical data unit. Compound **1** was prepared according to Ref.<sup>1</sup> and afforded analytical and spectral data in agreement with its structure.

**Diethyl 3-Amino-2-cyano-4-phenylhydrazono-2-pentene-1,5-dicarboxylate (2):**

A solution of benzenediazonium chloride [prepared from aniline (0.93 g, 0.01 mol) and the appropriate quantity of hydrochloric acid and sodium nitrite] is added to a stirred solution of **1** (2.26 g, 0.01 mol) in ethanol (50 ml) containing anhydrous sodium acetate (5.0 g). The reaction mixture is left at room temperature for 15 min and the resulting

Table. Compounds 2-7, 9-11, and 13 prepared

Product	Yield [%]	m.p. [°C] (solvent)	Colour	Molecular formula <sup>a</sup>	I.R. (KBr) $\nu$ [cm <sup>-1</sup> ]	<sup>1</sup> H-N.M.R. (DMSO- <i>d</i> <sub>6</sub> ) $\delta$ [ppm]
2	80	110° (C <sub>2</sub> H <sub>5</sub> OH)	yellow	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> (330.3)	3500-3200 (NH); 2220 (CN); 1730, 1720 (CO)	1.16 (t, 6H); 4.2 (2q, 4H); 6.5 (br s, 2H, D <sub>2</sub> O-exchangeable); 7.2-8.0 (m, 5H); 10.92 (br s, 1H, D <sub>2</sub> O-exchangeable)
3	65	228-230° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> (284.3)	3400-3200 (NH); 2220 (CN); 1715 (CO); 1670 (CO)	1.20 (t, 3H); 4.00 (q, 2H); 7.5 (m, 5H); 8.16 (s, 2H, D <sub>2</sub> O-exchangeable)
4	50	220° (C <sub>2</sub> H <sub>5</sub> OH)	brown	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> (330.3)	3260-3200 (NH); 1700 (CO); 1660-1630 (C=N)	—
5	78	185° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub> (326.3)	3800-3300, 3200 (NH); 2220 (CN); 1740 (CO); 1710 (CO); 1680 (CO)	—
6a (R = H)	79	258-261° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>12</sub> H <sub>10</sub> N <sub>6</sub> O <sub>2</sub> (270.3)	3440-3300 (NH <sub>2</sub> , NH); 2220 (CN); 1740 (CO); 1680 (CO)	4.43 (br s, 2H); 7.3-7.7 (m, 5H); 8.5 (br, 2H); 10.0 (br s, 1H)
6b (R = C <sub>6</sub> H <sub>5</sub> )	63	360° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>18</sub> H <sub>14</sub> N <sub>6</sub> O <sub>2</sub> (346.3)	3360, 3100, 3050 (NH); 2220 (CN); 1740 (CO); 1680 (CO)	—
7	58	345-347° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>14</sub> H <sub>15</sub> N <sub>5</sub> O <sub>4</sub> (317.3)	3560 (CN); 3480, 3400, 3350 (NH <sub>2</sub> , NH); 1740 (CO); 1680 (CO)	—
8	82	110° (C <sub>2</sub> H <sub>5</sub> OH)	yellow	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O <sub>4</sub> (380.4)	3400, 3200 (NH); 2200, 2180 (CN); 1700 (CO); 1670 (CO); 1670 (NH <sub>2</sub> )	1.20 (2t, 6H); 3.5 (s, 1H); 4.16 (q, 4H); 4.70 (s, 1H); 6.25 (s, 2H); 7.2-8.0 (m, 5H); 12.50 (br, 1H)
10	50	130° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub> (242.2)	3420, 3340, 3200 (NH <sub>2</sub> ); 2990, 2970 (CH <sub>2</sub> , CH <sub>3</sub> ); 1725, 1690 (CO); 1660 (NH <sub>2</sub> )	—
11a (R = H)	80	175-176° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>8</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> (212.2)	3300 (NH <sub>2</sub> ); 2220 (CN); 1750 (CO); 1650 (NH)	1.16 (t, 3H); 4.20 (q, 2H); 4.5 (s, 2H); 6.2 (br, 4H); 11.2 (br, 1H)
11b (R = C <sub>6</sub> H <sub>5</sub> )	55	170° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>14</sub> H <sub>16</sub> N <sub>4</sub> O <sub>3</sub> (288.3)	3460, 3400, 3200 (NH <sub>2</sub> , NH); 2990, 2950 (CH <sub>2</sub> , CH <sub>3</sub> ); 2200 (CN); 1715 (CO); 1670 (CO); 1640 (NH <sub>2</sub> ); 1620 (C=C)	1.33 (t, 3H); 4.30 (q, 2H); 4.5 (br s, 2H); 5.8 (br s, 2H); 11.0-11.5 (br, 2H)
13	60	228-230° (C <sub>2</sub> H <sub>5</sub> OH)	colourless	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> (271.3)	3320, 3220 (NH); 2960, 2880 (CH <sub>2</sub> , CH <sub>3</sub> ); 2200 (CN); 1670 (CO); 1610 (C=C)	1.25 (t, 3H); 4.21 (q, 2H); 5.5 (s, 2H); 7.2-7.8 (m, 5H); 11.2 (br s, 1H)

<sup>a</sup> Satisfactory microanalyses obtained: C  $\pm$  0.47, H  $\pm$  0.47, N  $\pm$  0.20.

solid product is collected by filtration and crystallised from ethanol; yield: 2.7 g (80%).

**4-Amino-5-cyano-3-ethoxycarbonyl-6-oxo-1-phenyl-1,6-dihydropyridazine (3):**

A solution of **2** (2.0 g, 0.006 mol) in ethanol (20 ml) is treated with 10% sodium hydroxide solution (2 ml). The reaction mixture is refluxed for 30 min then evaporated in vacuo. The remaining product is triturated with water, neutralised, and the resulting solid product is collected by filtration and crystallised from ethanol; yield: 1.1 g (65%).

**Diethyl 4-Amino-6-imino-1-phenyl-1,6-dihydropyridazine-3,5-dicarboxylate (4):**

A solution of **2** (5.0 g, 0.16 mol) in acetic acid (20 ml) and hydrochloric acid (3.0 ml; 37%) is refluxed for 3 h. The reaction mixture is then allowed to cool and poured onto water (80 ml). The solid product, so formed, is collected by filtration and crystallised from ethanol; yield: 2.5 g (50%).

**4-Acetylamino-5-cyano-3-ethoxycarbonyl-6-oxo-1-phenyl-1,6-dihydropyridazine (5):**

A solution of **2** (5.0 g, 0.16 mol) in acetic anhydride (20 ml) is boiled under reflux for 10 h, evaporated in vacuo, and then poured onto water (80 ml). The solid product so formed is collected by filtration and crystallised from ethanol; yield: 3.9 g (78%).

**4-Amino-5-cyano-3-hydrazinocarbonyl-6-oxo-1-phenyl-1,6-dihydropyridazine (6a) and 4-Amino-5-cyano-6-oxo-1-phenyl-3-phenylhydrazinocarbonyl-1,6-dihydropyridazine (6b):**

A solution of **3** (2.84 g, 0.01 mol) in ethanol (15 ml) is treated with hydrazine hydrate (0.9 ml) or phenylhydrazine (1.1 g, 0.015 mol), heated

to boiling, and then left to cool to room temperature. The solid product so formed is collected by filtration and crystallised from ethanol; yield of **6a**: 2.19 g (79%); yield of **6b**: 2.2 g (63%).

**4-Amino-5-aminohydroxyiminomethyl-3-ethoxycarbonyl-6-oxo-1-phenyl-1,6-dihydropyridazine (7):**

A solution of **3** (2.84 g, 0.01 mol) in ethanol (15 ml) is treated with hydroxylamine hydrochloride (0.68 g, 0.01 mol) and anhydrous sodium acetate (3.0 g). The reaction mixture is refluxed for 3 h and then poured onto water (80 ml). The solid product so formed is collected by filtration and crystallised from ethanol; yield: 1.3 g (58%).

**2-Amino-3-cyano-5-ethoxycarbonyl-6-(cyanoethoxycarbonyl)-methyl-4-phenyl-3,6-dihydropyridine (8):**

A solution of **1** (2.20 g, 0.01 mol) in ethanol (20 ml) is treated with benzylidenemalononitrile (0.01 mol) and ethylamine (0.5 ml). The reaction mixture is refluxed for 3 h. The solvent is then evaporated, the remaining product is triturated with water (80 ml), collected by filtration, and recrystallised from ethanol; yield: 3.1 g (82%).

**5-Amino-4-ethoxycarbonyl-3-ethoxycarbonylmethyl-1,2-oxazole (10):**

A solution of **1** (2.2 g, 0.01 mol) in ethanol (20 ml) is treated with hydroxylamine hydrochloride (0.01 mol) and sodium acetate (3.0 g) and then refluxed for 4 h after which it is poured onto water (50 ml). The solid product so formed is collected by filtration and crystallised from ethanol; yield: 1.2 g (50%).

**Ethyl 3-Amino-2-cyano-5-hydrazino-5-oxo-2-pentenoate (11a) and Ethyl 3-Amino-2-cyano-5-oxo-5-phenylhydrazino-2-pentenoate (11b):**

A solution of **1** (2.26 g, 0.01 mol) in ethanol (20 ml) is treated with hydrazine hydrate (0.6 ml, 0.01 mol) or with phenylhydrazine (1.1 g, 0.01

mol). The reaction mixture is refluxed for 1 h and then left to cool. The solid product so formed is collected by filtration and crystallised from ethanol; yield of **11a**: 1.79 g (80%); yield of **11b**: 1.60 g (55%).

**5-(Cyanoethoxycarbonyl)-methylene-3-oxo-1-phenyltetrahydropyrazole (13; R = C<sub>6</sub>H<sub>5</sub>):**

Compound **11b** (2.9 g, 0.01 mol) [or a mixture of **1** (2.26 g, 0.01 mol) and phenylhydrazine (1.1 g, 0.01 mol)] is heated at 160 °C for 4 h then left to cool. The resulting product is dissolved in boiling ethanol and left to cool. The solid product so formed is collected by filtration and crystallised from ethanol; yield: 1.6 g (60%).

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