Activated Nitriles in Heterocyclic Synthesis: A One-Step Synthesis of Several New Pyrimidine, Pyridine, and Pyrazole Derivatives

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Several new pyrimidine, pyridine, and pyrazole derivatives were obtained from cyanomethylenequinolin-3-yl derivatives 2a,b as starting components.

Activated nitriles are versatile reagents and their chemistry has received considerable recent attention (*1*). In the past decade we were involved in a program aiming to develop synthetic approaches for polyfunctionally substituted heterocycles utilizing readily obtainable nitriles as starting materials (*2*). In conjunction with our interest in the utility of α,β-unsaturated nitriles in heterocyclic synthesis (*3*), we report here the utility of the cyanomethylenequinolin-3-yl derivatives **2a,b**, which are easily prepared through a Knoevenagel condensation of compound **1** with malononitrile and ethyl cyanoacetate, for the preparation of several new pyrimidine, pyridine, and pyrazole derivatives of potential synthetic and biological importance.

Experimental Section

All melting points are uncorrected. IR spectra were recorded (KBr) with a Pye-Unicam SP 1100 spectrophotometer. ^{1}H NMR spectra were obtained on an EM-390 90-MHz spectrophotometer using Me_4Si as internal indicator and chemical shifts are expressed in ppm. Analytical data were obtained from the analytical data unit at Cairo University.

Reaction of 1 (4) with Malononitrile, Ethyl Cyanoacetate, and Cyanoacetamide (2a,b and 7). To a suspension of compound 1 (0.01 mol) in ethanol (30 mL) and malononitrile, ethyl cyanoacetate or cyanoacetamide and 1 mL of triethylamine were added. The reaction mixture was let stand for 4 h (Scheme I). The solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. Table I).

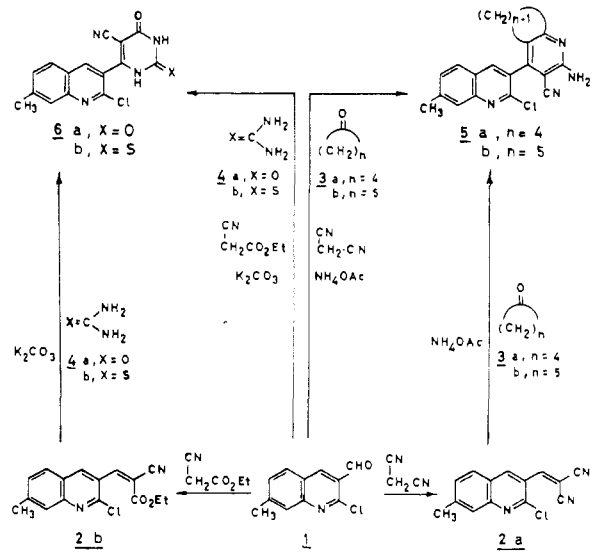
2-Amino-3-cyanopyridines (5a,b). Method A. To a suspension of compound **2a** (0.01 mol) in benzene (20 mL), the cycloalkanone **3a,b** (0.01 mol) and ammonium acetate (0.015 mol) were added. The flask is fitted with a reflux condenser and a water separator. The mixture was refluxed for 6 h and the solvent was then evaporated. The resulting solid precipitate was isolated by suction and crystallized from the proper solvent (cf. Table I).

Method B. To a suspension of compound **1** (0.01 mol) in benzene (20 mL), malononitrile (0.01 mol), the cycloalkanone **3a,b** (0.01 mol), and ammonium acetate (0.015 mol) were added. The mixture was refluxed for 6 h. Work-up is as described above.

4-Oxotetrahydropyrimidines (6a,b) (5). Method A. To a suspension of compound **2b** (0.01 mol) in ethanol (30 mL), urea (**4a**) or thiourea (**4b**) (0.01 mol) and potassium carbonate (0.01 mol) were added. The reaction mixture was refluxed for 5 h. The excess solvent was evaporated in vacuo. The remaining product was acidified with dilute acetic acid. The resulting solid product was collected by filtration and washed with water, and recrystallized from the proper solvent (cf. Table I).

Method B. To a suspension of compound 1 (0.01 mol) in ethanol (20 mL), ethyl cyanoacetate (0.01 mol), urea (**4a**) or thiourea (**4b**) (0.01 mole), and potassium carbonate (0.01 mol)

Scheme I



Scheme II

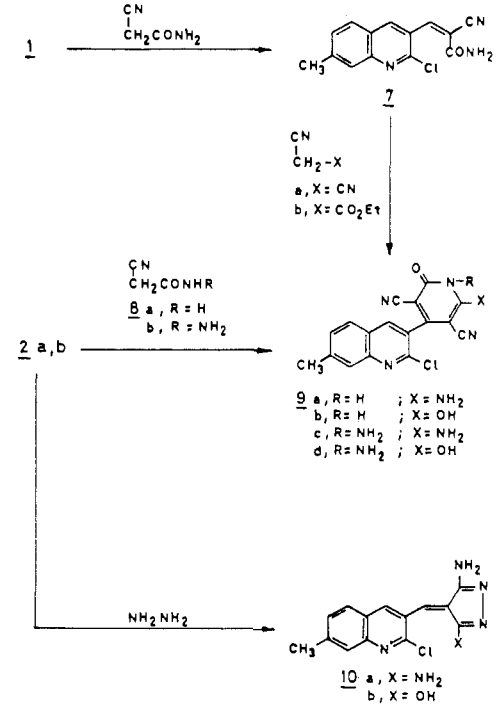


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Table I. List of the Newly Synthesized Compounds

compd[a] (color)	mp, °C	yield, %	cryst solv[b]	IR, cm^{-1}	^1H NMR, ppm
2a (yellow)	180	98	a	2215 (CN); 1630 (C=C, C=N)	2.58 (s, 3 H, CH_3); 2.62 (dd, 1 H, quinoline 5-H); 2.84 (d, 1 H, quinoline 6-H); 8.12 (d, 1 H, quinoline 8-H); 8.62 (d, 1 H, quinoline 4-H); 9.12 (s, 1 H, ylidenic CH)
2b (yellow)	116–18	80	a	2212 (CN); 1730 (ester CO); 1610–1630 (C=C, C=N)	1.32 (t, 3 H, CH_3); 2.55 (s, 3 H, CH_3); 4.4 (q, 2 H, CH_2); 9.04 (s, 1 H, ylidenic CH)
5a (yellow)	278	85	b	3320, 3260 (NH_2); 2220 (CN); 1620 (C=N, δ NH_2)	1.92–2.98 (m, 6 H, $-(CH_2)_3-$); 2.56 (s, 3 H, CH_3); 6.92 (s, br, 2 H, NH_2); 7.58 (d, 1 H, quinoline 5-H); 7.82 (s, 1 H, quinoline 6-H); 6-H); (d, 1 H, quinoline 8-H); 8.5 (s, 1 H, quinoline 4-H)
5b (white)	282	80	c		1.58–2.78 (m, 8 H, $-(CH_2)_4-$); 2.56 (s, 3 H, CH_3); 6.8 (s, br, 2 H, NH_2)
6a (yellow)	300	82	a	3280, 3240 (NH); 2210 (CN); 1680, 1695 (CO); 1610 (C=N, δ NH)	2.52 (s, 3 H, CH_3); 7.48 (d, 1 H, quinoline 5-H); 7.8 (s, 1 H, quinoline 6-H); 8.08 (d, 1 H, quinoline 8-H); 8.5 (s, 1 H, quinoline 4-H); 9.00 (s, br, 2 H, 2 NH)
6b (yellow)	255	80	a		2.52 (s, 3 H, CH_3); 8.45 (d, 2 H, quinoline 4-H and NH); 9.22 (s, 1 H, NH)
7 (white)	120	92	a	3400, 3210 (NH_2); 2210 (CN), 1710 (CO); 1630 (C=N, δ NH_2)	2.58 (s, 3 H, CH_3); 8.30 (s, br, 2 H, NH_2); 8.94 (s, 1 H, ylidenic CH)
9a (yellow)	266–68	80	a	3380, 3220 (NH_2 and NH); 2210 (CN); 1705 (CO); 1620 (C=N, δ NH_2 and δ NH)	2.56 (s, 3 H, CH_3); 3.2 (d, 2 H, NH_2); 7.6 (dd, 1 H, quinoline 5-H); 7.81 (d, 1 H, quinoline 6-H); 8.08 (d, 1 H, quinoline 8-H); 8.42 (d, 1 H, quinoline 4-H); 8.94 (s, 1 H, NH)
9b (white)	258–60	80	a		2.55 (s, 3 H, CH_3); 3.32 (s, 1 H, OH); 8.12 (s, 1 H, NH)
9c (yellow)	239–40	85	c		2.52 (s, 3 H, CH_3); 4.38 (s, br, 2 H, NH_2); 8.92 (s, br, 2 H, NH_2)
9d (yellow)	225	85	a		2.54 (s, 3 H, CH_3); 4.32 (s, br, 1 H, OH); 8.82 (s, br, 2 H, NH_2)
10a (yellow)	228	88	c	3420, 3200 (NH_2); 1630 (C=N, δ NH_2)	2.52 (s, 3 H, CH_3); 7.44 (s, br, 4 H, 2 NH_2); 7.68 (d, 1 H, quinoline 5-H); 7.77 (s, 1 H, quinoline 6-H); 7.96 (s, 1 H, quinoline 8-H); 8.18 (s, 1 H, quinoline 4-H); 8.58 (s, 1 H, ylidenic CH)
10b	200–02	92	c		2.56 (s, 3 H, CH_3); 7.42 (s, br, 2 H, NH_2); 8.55 (s, 1 H, ylidenic CH)

[a] Satisfactory elemental analysis were submitted. [b] a, methanol; b, benzene; c, ethanol.

were added. The mixture was refluxed for 5 h. Work-up is as described above.

***2-Oxo-3,5-dicyanopyridones* (*9a-d*) (*6*, *7*).** To a suspension of **2a,b** (0.01 mol) in ethanol (30 mL) **8a,b** (0.01 mol) and 1 mL of triethylamine were added. The reaction mixture was let stand for 1 h and then the solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. Table I). Compound **9a,b** was also prepared from the reaction of **7** with malononitrile and ethyl cyanoacetate as above (Scheme II).

***Aminopyrazoles* (*10a,b*).** A solution of **2a,b** (0.01 mol) in ethanol (30 mL) was treated with hydrazine hydrate (0.01 mol). The reaction mixture was heated under reflux for 2 h. The solid formed while the solution was still boiling was filtered off and crystallized from the proper solvent (cf. Table I).

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Registry No. **1**, 68236-21-5; **2a**, 113110-96-6; **2b**, 113111-02-7; **3a**, 120-92-3; **3b**, 108-94-1; **4a**, 57-13-6; **4b**, 62-56-6; **5a**, 113110-97-7; **5b**, 113111-03-8; **6a**, 113110-98-8; **6b**, 113111-04-9; **7**, 113110-99-9; **8a**, 107-91-5; **8b**, 140-87-4; **9a**, 113111-00-5; **9b**, 113111-05-0; **9c**, 113111-07-2; **9d**, 113111-08-3; **10a**, 113111-01-6; **10b**, 113111-06-1; $NCCH_2CO_2Et$, 105-56-6; $CH_2(CN)_2$, 109-77-3.

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