Novel Synthesis of Polyfunctionally Substituted Pyridines and Pyrimidines

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New syntheses of polyfunctionally substituted pyridines and pyrimidines by reaction of 3-amino-3-ethoxy-1-phenyl-2-propen-1-one with cinnamonitriles, or with acyl or aroyl isothiocyanates are reported.

In continuation of our work on new approaches to polyfunctionally substituted heterocycles of potential biological activity from readily obtainable starting materials,[1] we report here some novel syntheses of polyfunctionally substituted pyridines and pyrimidines.

We investigated the chemical behavior of ethyl 3-oxo-3-phenylpropanimidate (**3**), which is obtained from the known[2] reaction of benzoylacetonitrile (**1**) with ethanol and dry hydrogen chloride at 0 °C and neutralization of the resultant hydrochloride **2** with triethylamine. Compound **3** was coupled with arenediazonium salts to yield arylhydrazones **4** and with mercaptoacetic acid to yield the thiazolinone **5**. A synthesis of **5** by heating **1** with mercaptoacetic acid has been reported earlier.[3] Compound **3** reacts with alkylidenemalononitriles **6a–c**[4,5] to give 4-substituted 2-amino-5-aroyl-3-cyanopyridines **7a–c** with elimination of methanol. The formation of **7a–c** from **6a–c** and **3** is assumed to proceed via the intermediacy of the Michael adduct **8**, which cyclizes to **9**. The latter tautomerizes to **10** and then **11**, which finally is aromatized to **7**. To our knowledge, this is the first reported addition of enamines to alkylidenemalononitriles. Addition of active methylene compounds as well as cyclic and acyclic amidines have been reported earlier.[1,6]

Compound **3** reacts with aliphatic and aromatic acyl isothiocyanates to give pyrimidine derivatives **12**, which are assumed to arise via the intermediacy of the addition product **13**, which eliminates water to yield **12**. The formation of oxazine derivatives on cyclization of **13** was eliminated because of the stability of the reaction products toward mild acid treatment; the imino function in the 6-imino-1,3-oxazine derivatives in question would be expected to be hydrolyzed under such conditions.

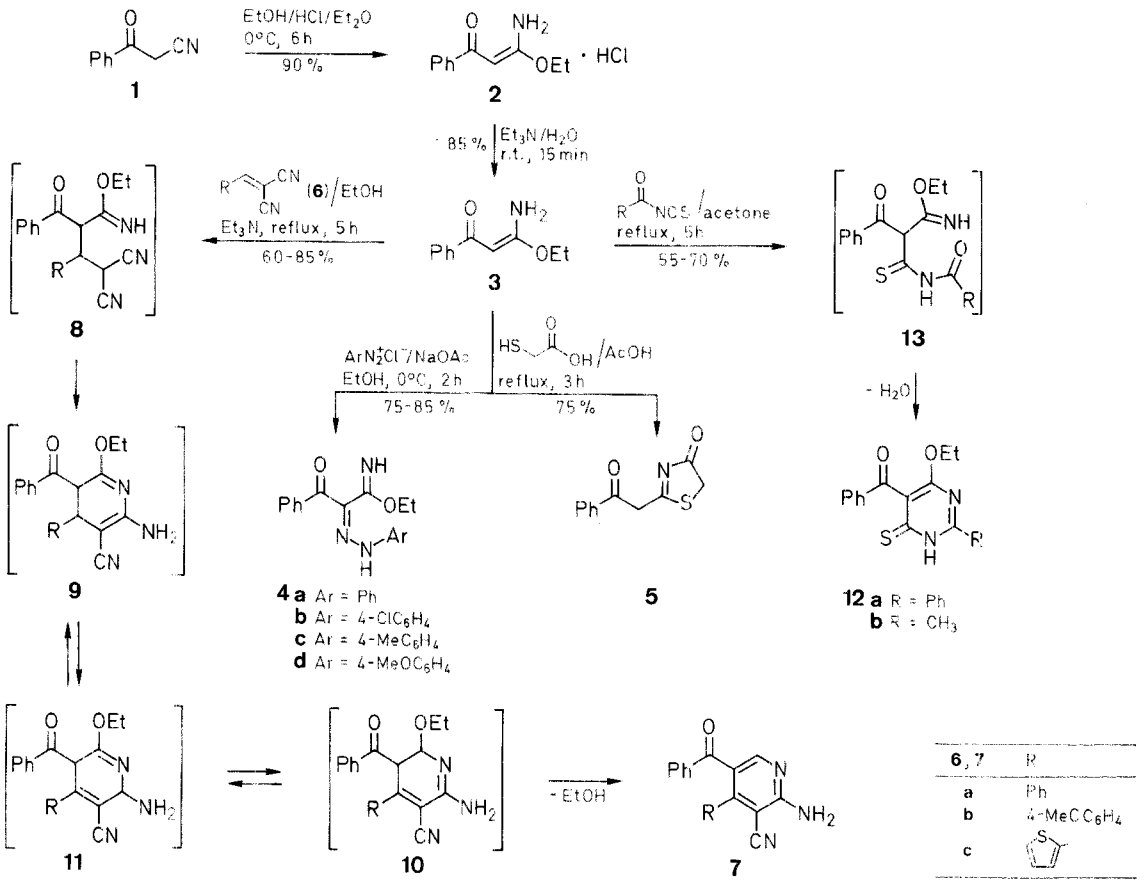

Table. Compounds **4**, **7**, and **12** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	MS (70 eV) m/z (M^+)	IR (KBr) ν(cm^{-1})	^{1}H-NMR (DMSO/TMS) δ, J(Hz)
4a	85	75 (EtOH)	$C_{17}H_{17}N_3O_2$ (295.3)	295	1600 (C=N); 1630 (C=O); 3140 (NH)	1.34 (t, 3H, J = 13, CH_3); 3.45 (s, 1H, NH); 4.25 (q, 2H, J = 12.8, CH_2); 6.95–7.93 (m, 10H_{arom}); 10.02 (br s, 1H, NH)
4b	80	93 (EtOH)	$C_{17}H_{16}ClN_3O_2$ (329.8)		1600 (C=N); 1640 (C=O); 3280 (NH)	1.44 (t, 3H, J = 13, CH_3); 4.23 (q, 2H, J = 12.8, CH_2); 6.94 (d, 2H, J = 14, H_{arom}); 7.14–7.75 (m, 7H, 5H_{arom}, 2NH); 7.84 (d, 2H, J = 14, H_{arom})
4c	85	105 (EtOH)	$C_{18}H_{19}N_3O_2$ (309.4)		1600 (C=N); 1650 (C=O); 2950 (CH_3); 3200–3400 (NH)	1.25 (t, 3H, J = 12.5, CH_3); 2.45 (s, 3H, CH_3); 4.04 (q, 2H, J = 13, CH_2); 6.83–8.03 (m, 9H_{arom}); 9.71 (s, 1H, NH); 11.34 (s, 1H, NH)
4d	75	84 (EtOH)	$C_{18}H_{19}N_3O_3$ (325.4)		1600 (C=N); 1650 (C=O); 2950 (OCH_3); 3250 (NH)	1.45 (t, 3H, J = 12.8, CH_3); 3.64 (s, 3H, OCH_3); 4.34 (q, 2H, J = 13, CH_2); 6.53–7.93 (m, 11H, 9H_{arom}, 2NH)
7a	75	237 (dioxane)	$C_{19}H_{13}N_3O$ (299.3)		1600 (C=N); 1660 (C=O); 2200 (CN); 2900–3100 (NH_2)	7.42–7.71 (m, 11H, 10H_{arom}, H-6$_{pyridine}$)
7b	85	295 (EtOH/DMF)	$C_{20}H_{15}N_3O_2$ (329.3)	328	1600 (C=N); 1650 (CO); 2200 (CN); 2950 (CH_3); 3300–3600 (NH)	3.92 (s, 3H, OCH_3); 7.14 (d, 2H, J = 14.5, H_{arom}); 7.63 (m, 6H, 5H_{arom}, H-6$_{pyridine}$); 7.73 (d, 2H, J = 14.5, H_{arom})
7c	60	272 (EtOH)	$C_{17}H_{11}N_3OS$ (305.3)	304	1570 (C=N); 1650 (CO); 2210 (CN); 3070–3160 (NH)	7.21–8.73 (m, 9H, 5H_{arom}, 3$H_{thiophene}$, H-6$_{pyridine}$)
12a	70	204 (EtOH)	$C_{19}H_{16}N_2O_2S$ (336.4)	336	1590 (C=N); 1680 (CO); 3300–3600 (NH)	1.23 (t, 3H, J = 11, CH_3); 4.55 (q, 2H, J = 11.5, CH_2); 7.42–8.44 (m, 10H_{arom}); 10.54 (br s, 1H, NH)
12b	55	186 (EtOH)	$C_{14}H_{14}N_2O_2S$ (274.3)		1590 (C=N); 1670 (CO); 2900 (CH_3); 3150–3250 (NH)	1.24 (t, 3H, J = 12, CH_3); 2.22 (s, 3H, CH_3); 4.33 (q, 2H, J = 12.3, CH_2); 7.23–7.93 (m, 5H_{arom}); 10.6 (br s, 1H, NH)

[a] Satisfactory microanalyses: C ±0.3, H ±0.2, N ±0.3.

All melting points are uncorrected. Microanalyses were performed by the microanalytical unit Cairo University. Mass spectra were recorded at 70 eV on a EI Direct IT 170 instrument. IR spectra were recorded on a Pye Unicam SO-1100 spectrophotometer and ^{1}H-NMR spectra on Varian EM-390-90 MHz and Bruker WP 80 spectrometers.

3-Amino-3-ethoxy-1-phenyl-2-propen-1-one (Ethyl 3-Oxo-3-phenylpropanimidate, 3):

Hydrochloride **2**: Dry HCl is passed through an ice-cooled solution of benzoylacetonitrile (**1**; 1.45 g, 0.01 mol) and absolute EtOH (0.7 mL, 0.012 mol) in anhydrous Et_2O (30 mL) for 6 h. The resultant solution is allowed to stand at 0 °C for 10 h. The solid product thus formed is isolated by suction and recrystallized from EtOH to give **2** as pale yellow crystals; yield: 2 g (90%); mp 138 °C (Lit.[2] mp 140 °C).

Free Compound **3**: A solution of hydrochloride **2** (2 g) in H_2O (50 mL) is neutralized by shaking with Et_3N (4 mL) for 15 min. The solid product thus formed is isolated by suction and recrystallized from EtOH to give **3** as pale yellow crystals; yield: 1.6 g (85%); mp 90 °C (Lit.[2] mp 89.5 °C).

Ethyl 2-Arylhydrazono-3-oxo-3-phenylpropanimidates 4a–d; General Procedure:

A solution of the arenediazonium chloride (prepared from 0.01 mol substituted aniline, aq. HCl, and $NaNO_2$) is gradually added to an ice-cooled solution of compound **3** (1.9 g, 0.01 mol) in EtOH (50 mL) containing NaOAc (5.0 g). The mixture is kept at 0 °C for 2 h. The resultant solid product is isolated by suction, washed with H_2O, and recrystallized from the solvent given in the Table.

4-Oxo-2-phenacyl-4,5-dihydrothiazole 5:

A solution of compound **3** (1.9 g, 0.01 mol) and mercaptoacetic acid (0.92 g, 0.01 mol) in AcOH (50 mL) is refluxed for 3 h. The solvent is then removed under reduced pressure and the residue is triturated with H_2O (100 mL). The solid product is isolated by suction and recrystallized from EtOH to give **5** as pale yellow crystals; yield: 1.6 g (75%); mp 213 °C (Lit.[3] mp 212 °C).

4-Substituted 2-Amino-5-benzoyl-3-cyanopyridines 7a–c; General Procedure:

To a solution of compound **3** (1.9 g; 0.01 mol) in absolute EtOH (50 mL), the appropriate benzylidenemalononitrile **6a, b, c**[4,5] (0.01 mol) and anhydrous Et_3N (1 mL) are added. The mixture is refluxed for 5 h and then evaporated under reduced pressure. The remaining product is poured onto ice (100 g) and acidified with 10% aqueous HCl to pH 4. The resultant solid product is isolated by suction and recrystallized from the solvent given in the Table.

2-Substituted 5-Benzoyl-4-ethoxy-6-thioxo-1,6-dihydropyrimidines 12a, b; General Procedure:

A suspension of compound **3** (1.9 g; 0.01 mol) in acetone (40 mL) is stirred with the appropriate isothiocyanate solution [prepared[8,9] by refluxing NH_4SCN (0.012 mol) and the respective acid chloride (0.01 mol) in acetone (40 mL) for 15 min]. The mixture is refluxed for 5 h, then evaporated under reduced pressure. The remaining product is triturated with H_2O (75 mL), then isolated by suction, and recrystallized from the solvent given in the Table.

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