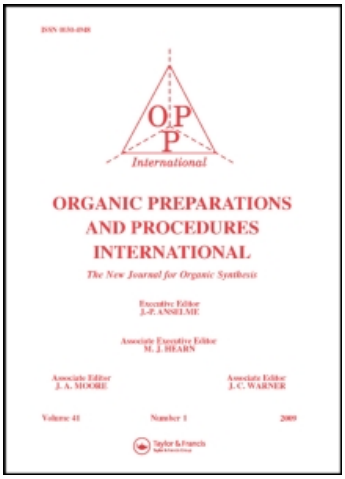

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NOVEL SYNTHESIS OF PYRIDINE-2(1H)THIONES, N-AMINO-2-PYRIDONES AND PYRIDAZINE DERIVATIVES

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NOVEL SYNTHESIS OF PYRIDINE-2(1H)THIONES, N-AMINO-2-PYRIDONES AND PYRIDAZINE DERIVATIVES

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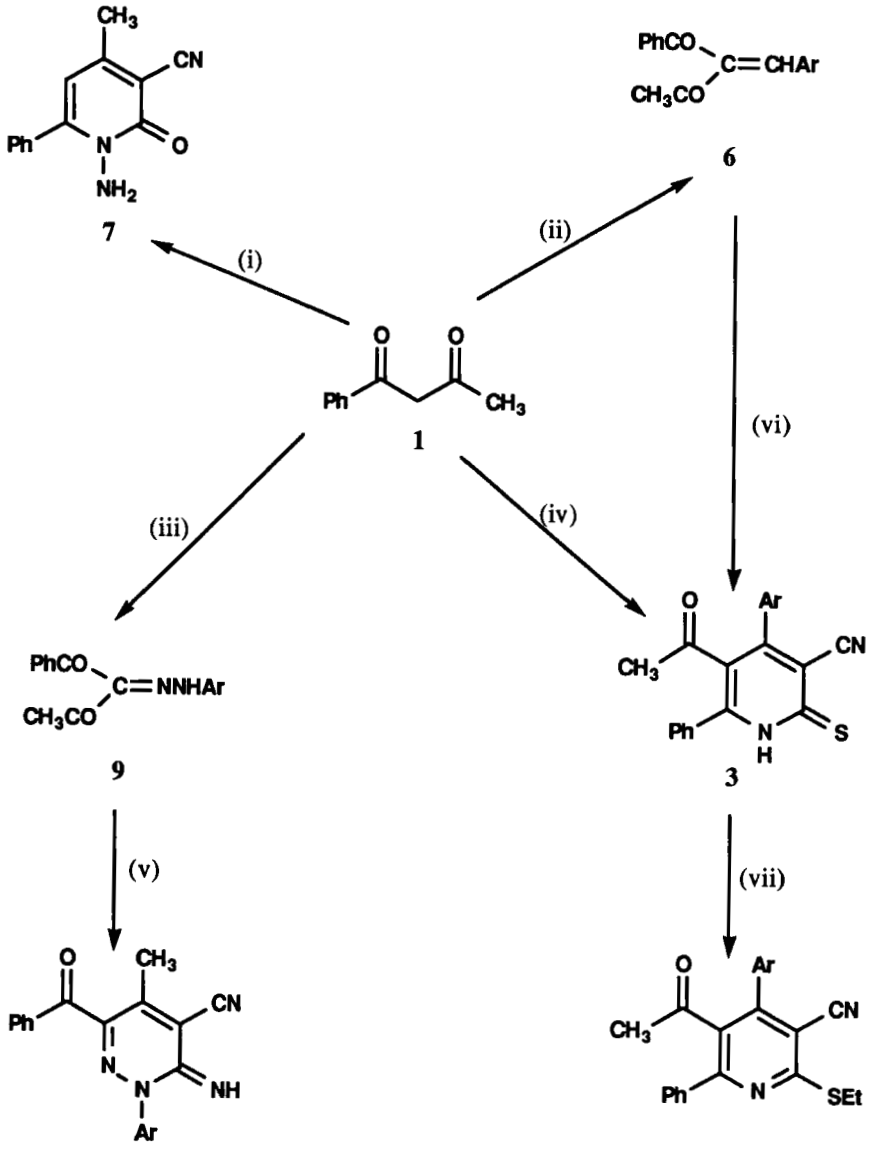
The utility of nitriles in the synthesis of polyfunctionally substituted heterocycles has received considerable recent attention.[1] Over the last few years, our research program has been aimed at developing new routes to polyfunctionally substituted heterocycles of potential biological activity, utilizing readily available starting materials.[2] The present paper describes the reaction of benzoylacetone (**1**) with activated nitriles and α,β-unsaturated nitriles for the synthesis of pyridine-2(1H)thiones, N-aminopyridines and pyridazine derivatives by different synthetic routes.

Benzoylacetone reacts with arylmethylenecyanothioacetamides **2** in refluxing ethanol containing catalytic amounts of ammonium acetate to give the pyridine-2(1H)thione derivatives **3**. Compound **3** can also be prepared in good yield from the reaction of arylmethylenebenzoylacetones (**6**) with cyanothioacetamide in refluxing ethanol-sodium ethoxide solution. Structure **3a** was established by ^{1}H NMR, which exhibited a singlet at δ 2.5 assignable to a methyl group and a broad band at δ 14.2 assignable to an NH group (Tables 1 and 2). The formation of **3** from the reaction of **1** with **2** or of **6** with cyanothioacetamide may be viewed an proceeding by a Michael addition of the methylene function of **1** or of cyanothioacetamide to the activated double bond of **2** or of **6**, respectively, to yield a dihydropyridine structure, which is then oxidized to pyridine-2(1H)thione derivatives **3**. Treatment of the potassium salt of **3** with ethyl iodide gave the corresponding S-ethyl derivatives **8**. The structures of **8** were established from analysis and spectral data. Benzoylacetone reacted with cyanoacethydrazide (**4**)[5] in refluxing ethanol containing catalytic amounts of triethylamine to give the N-aminopyridine-2-one derivative **7**. The structure of **7** was based on elemental analysis and spectral data (Tables 1 and 2). Thus, ^{1}H NMR for **7** revealed in addition to signals from the phenyl and methyl groups, a singlet of δ 5.65 assigned to an amino group and a singlet at δ 6.36 assigned to a pyridine H5 proton.

Compound **1** coupled with aryldiazonium salts to yield the corresponding arylhydrazone derivatives **9**, which reacted with malononitrile in refluxing acetic acid to yield the iminopyridazine



10 a) Ar = C_6H_5 b) Ar = 4-ClC_6H_4
c) Ar = 4-$MeOC_6H_4$ d) Ar = 4-MeC_6H_4
e) Ar = 3-$O_2NC_6H_4$ f) Ar = 3-$MeOC_6H_4$

3, 8 a) Ar = C_6H_5 b) Ar = 4-ClC_6H_4
c) Ar = 4-$MeOC_6H_4$ d) Ar = 4-MeC_6H_4
e) Ar = 2-furanyl f) Ar = 2-thienyl

i) $CNCH_2CONHNH_2$ (**4**), Et_3N ii) ArCHO, piperdine iii) ArN^+_2 Cl^-, AcONa
iv) ArCH=C(CN)$CSNH_2$ (**2**), $AcONH_4$, heat v) $CH_2(CN)_2$, AcOH
vi) $CNCH_2CSNH_2$, NaOEt, heat vii) C_2H_5I, K_2CO_3.

derivatives **10**. Structure **10** was based on elemental analysis and spectral data (Tables 1 and 2). Similar reactions have been reported by us recently.[3]

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were obtained (KBr) on a Pye-Unicam 1000 spectrophotometer and on a Shimadzu IR 200. H NMR spectra were measured on a Varian EM 390 (90 MHz) in DMSO using TMS as internal standard and chemical shifts are expressed as δ. Analyses were obtained from the Microanalytical Data unit at Cairo University. Compounds **2** and **6** were prepared following literature procedures.[4]

4-Substituted-5-Acetyl-3-cyano-6-phenylpyridine-2(1H)thiones (3a-f). Method a.- To a solution of 1 (0.01 mole) and arylmethylenecyanothioacetamide 2 (0.01 mole) in ethanol (30 ml), ammonium acetate (0.015 mole) was added. The mixture was refluxed for 4 hrs. The precipitated solid product was collected and crystallized (Table 1).

Method b - A mixture of 1 (0.01 mole), 6 (0.01 mole) and sodium ethoxide (0.01 mole) in absolute ethanol (30 ml) was refluxed for 5 hrs. The reaction mixture was cooled and poured slowly into

TABLE 1. Mps, Yields and Elemental Analyses of Compounds **3a-f, 7, 8a-f** and **10a-f.**

Compound	Solv. of cryst.	mp. (°C)	Yield (%)	Elemental Analysis (%) (Calcd.) Found		
				C	H	N
3a	EtOH	182-184	60	(72.7) (72.5)	(4.2) (4.5)	(8.5) (8.7)
3b	EtOH	274-276	70	(65.8) (65.5)	(3.6) (3.9)	(7.7) (7.4)
3c	EtOH	195-196	80	(70.0) (69.7)	(4.4) (4.2)	(7.8) (7.5)
3d	MeOH	212-214	50	(73.3) (73.3)	(4.7) (4.5)	(8.1) (7.8)
3e	MeOH	155-156	40	(67.5) (67.2)	(3.8) (4.0)	(8.8) (8.5)
3f	EtOH-DMF	234-236	55	(64.3) (64.0)	(3.6) (3.9)	(8.3) (8.0)
7	EtOH	207	60	(69.3) (69.1)	(4.9) (4.7)	(18.7) (18.4)
8a	MeOH	128-130	50	(73.7) (73.5)	(5.0) (4.7)	(7.8) (7.5)
8b	MeOH	167-168	40	(67.3) (67.0)	(4.3) (4.0)	(7.1) (6.8)
8c	dioxane	140-141	50	(71.1) (70.8)	(5.2) (4.9)	(7.2) (6.9)
8d	benzene	120-121	35	(74.2) (73.9)	(5.4) (5.1)	(7.5) (7.3)
8e	MeOH	121	40	(69.0) (69.2)	(4.6) (4.3)	(8.0) (7.7)
8f	EtOH	146	60	(65.9) (66.1)	(4.4) (4.6)	(7.7) (7.4)
10a	EtOH	186-188	70	(72.6) (72.3)	(4.5) (4.2)	(17.8) (17.5)
10b	EtOH	205-206	60	(65.4) (65.1)	(3.7) (4.0)	(16.1) (15.7)
10c	EtOH	177	80	(69.8) (69.6)	(4.7) (4.5)	(16.3) (16.0)
10d	EtOH	160	60	(73.2) (72.9)	(4.9) (5.1)	(17.1) (16.8)
10e	EtOH	238-240	70	(63.5) (63.2)	(3.6) (3.9)	(19.5) (19.2)
10f	EtOH	130-132	50	(69.8) (70.0)	(4.7) (5.0)	(16.3) (16.0)

ice/water and acidified with dilute hydrochloric acid. The precipitated solid was collected, washed with water and crystallized from the appropriate solvent (Table 1).

1-Amino-4-methyl-6-phenyl-3-cyano-2-pyridone (7).- Hydrazide **4** (0.01 mole)[5] and benzoylacetone 1 (0.01 mole) were dissolved in ethanol (30 ml) and a few drops of piperidine added. The mixture was refluxed for 4 hrs. The precipitated solid product was collected and crystallized from ethanol (Table 1).

TABLE 2. Spectral Data for Compounds **3a-f, 7, 8a-f** and **10a-f**

Cmpd	IR (KBr) cm^{-1}	^1H NMR (δ)
3a	3450 (NH); 2225 (CN) and 1700 (CO).	2.22 (s, 3H, C H_3); 6.92-7.65 (m , 10 H, $2C_6H_5$); 14.1 (s, br, 1H, NH).
3b	3300-3200 (NH); 2220 (CN) and 1680 (CO).	2.18 (s, 3H, CH_3); 7.15-7.70 (m, 9H, $C_6H_5$and C_6H_4); 14.30 (s, br, 1H, NH).
3c	3400 (NH) and 2215 (CN).	2.32 (s, 3H, CH_3); 3.69 (s, 3H, OCH_3); 6.88-7.75 (m, 9H, C_6H_5 and C_6H_4); 14.20 (s, br, 1H, NH).
3d	3420 (NH); 2220 (CN) and 1690 (CO).	2.28 (s, 3H, CH_3); 2.62 (s, 3H, CH_3); 6.98-7.58 (m, 9H, C_6H_5 and C_6H_4); 14.12 (s, br, 1H, NH).
3e	3250 (NH); 2220 (CN) and 1695 (CO).	2.25 (s, 3H, CH_3); 680-7.80 (m, 8H, C_6H_5 and furan 3,4,5-H); 14.0 (s, br, 1H, N.3H).
3f	3380-3420 (NH); 2220 (CN) and 1685 (CO).	2.29 (s, 3H, CH_3); 6.90-7.90 (m, 8H, C_6H_5 and thiophen 3,4,5-H); 14.10 (s, br, 1H, NH).
7	3400, 3330 (NH_2); 2220 (CN) and 1660 (CO).	2.46 (s, 3H, CH_3); 5.60 (s, br, 2H, NH_2); 6.40 (s, 1H, pyridine H-5); 7.38-7.70 (m , 5H, C_6H_5).
8a	2220 (CN) and 1700 (CO).	1.42 (t, 3H, CH_3); 2.28 (s, 3H, CH_3); 3.46(q, 2H, CH_2); 6.98-7.84 (m, 10 H, $2C_6H_5$).
8b	2220 (CN) and 1700 (CO).	1.44 (t, 3H, CH_3); 2.30 (s, 3H, CH_3); 3.46(q, 2H, CH_2); 6.96-7.80 (m , 9H, C_6H_5 and C_6H_4).
8c	2220 (CN) and 1690 (CO).	1.48 (t, 3H, CH_3); 2.28 (s, 3H, CH_3); 3.48 (q, 2H, CH_2); 3.88 (s, 3H, OCH_3); 7.0-7.92 (m , 9H, C_6H_5 and C_6H_4).
8d	2220 (CN) and 1690 (CO) .	1.54 (t, 3H, C H_3); 2.30 (s, 3H, CH_3); 3.49 (q, 2H, CH_3); 2.65 (s, 3H, CH_3); 6.98-7.6 (m, 9H, C_6H_5 and C_6H_4).
8e	2215 (CN) and 1700 (CO).	1.62 (t, 3H, CH_3); 2.35 (s, 3H, CH_3); 3.60 (q, 2H, CH_2); 690-7.75 (m, 8H, C_6H_5 and furan 3,4,5-H).

TABLE 2. (Continued)

Cmpd	IR (KBr) cm^{-1}	^1H NMR (δ)
8f	2215 (CN) and 1700 (CO).	1.60 (t, 3H, CH_3); 2.30 (s, 3H, CH_3); 3.48 (q, 2H, CH_2); 6.85-7.80 (m, 8H, C_6H_5 and thienyl 3,4,5-H).
10a	3500-3330 (NH); 2220 CN) and 1690 (CO).	2.50 (s, 3H, CH_3); 6.90-7.70 (m, 10H, $2C_6H_5$).
10b	3330 (NH); 2210 (CN) and 1685 (CO).	2.48 (s, 3H, CH_3); 685-7.72 (m, 9H, C_6H_5 and C_6H_4).
10c	3400 (NH); 2220 (CN) and 1680 (CO).	2.54 (s, 3H, CH_3); 3.78 (s, 3H, OCH_3); 6.92-7.80 (m, 9H, C_6H_5 and C_6H_4).
10d	3450 (NH); 2220 (CN) and 1700 (CO).	2.32 (s, 3H, CH_3); 2.58 (s, 3H, CH_3); 7.18-7.56 (m, 9H, C_6H_5 and C_6H_4).
10e	3400 (NH); 2220 (CN) and 1690 (CO).	2.34 (s, 3H, CH_3); 7.20-7.58 (m, 9H, C_6H_5 and C_6H_4).
10f	3400 (NH) , 2220 (CN) and 1685 (C0).	2.54 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3);6.90-7.78 (m, 9H, C_6H_5 and C_6H_4).

4-Substituted-5-acetyl-3-cyano-2-(ethylthio)-6-phenylpyridine-2(1H)thiones (8a-f).- A mixture of **3** (0.01 mole), K_2CO_3 (0.015 mole) and ethyl iodide (0.02 mole) in dry DMF (30 ml) was stirred at room temperature for 24 hrs and then diluted with cold water. The resulting solid was collected and crystallized (Table 1).

3-Arylhydrazono-4-phenylbutan-2,4-diones (9a-f).- A solution of 1 (0.01 mole) in ethanol (100 ml) containing sodium acetate (3.0 g) was cooled to 0°, stirred and treated gradually with a cooled solution of aryldiazonium chloride (prepared from 0.01 mole of amine and the appropriate quantities of HCl and $NaNO_2$). The solid product formed on standing was collected and crystallized from the appropriate solvent.

2-Substituted-6-benzoyl-4-cyano-5-methyl-2,3-dihydropridazine-3-imines (10a-f).- A suspension of **9** (0.01 mole) and malononitrile (0.01 mole) in acetic acid (30 ml. was refluxed for 5 hrs and then evaporated under vacuum. The resulting solid product was collected and crystallized (Table 1).

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