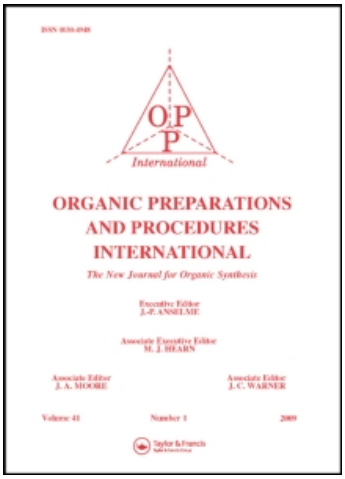

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SYNTHESIS OF SEVERAL N-SUBSTITUTED AMINO-2-PYRIDONES

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OPPI BRIEFS

SYNTHESIS OF SEVERAL N-SUBSTITUTED AMINO-2-PYRIDONES

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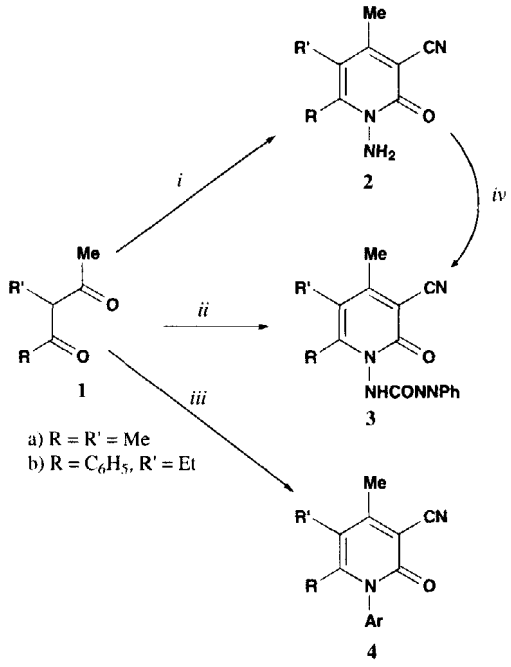
Cyano compounds are of considerable interest in organic synthesis.[1] As part of our program directed toward development of new, simple, and efficient procedures for the synthesis of pyridines of potential synthetic and biological uses,[2] we reported several new approaches for the synthesis of pyridines utilizing readily obtainable nitrile intermediates.[3] Although N-amino-2-pyridones have proved to be useful synthetic intermediates, there are few procedures for their preparation. They are usually obtained in low yield by reaction of hydrazine with 2-pyrones, themselves prepared in low yields from open-chain compounds.[4] We now report a new, one-step synthesis of N-(substituted)amino- and N-aryl-2-pyridones from the reaction of 1-cyanoacetyl-4-phenylthiosemicarbazide and cyanoacetanilide with 2-alkyl substituted 1,3-diketones (**1**).

Compounds **1** react with 1-cyanoacetyl-4-phenylthiosemicarbazide in refluxing ethanol containing catalytic amounts of piperidine to give the N-(1-pyridyl)thiourea derivatives **2a-d**. The structure of compounds **2a-d** was established on the basis of their elemental analysis and spectral data; for example. structure **2a** is supported by its mass (M 312), which agrees with it's molecular formula. The ^{1}H NMR displayed three singlets at δ 2.35, 2.41 and 2.51 assigned for three methyl groups, two broad bands at δ 9.30 and 10.20 assigned to the NH protons and a multiplet at δ 7.00-7.60 assigned for aromatic protons. Compounds **3a-d** can also be prepared by the reaction of the corresponding N-amino-2-pyridones (**2**) with phenylisothiocyanate in refluxing dioxane for 2 hrs. Compounds **2** are prepared by the reaction of cyanoacethydrazide with **1** in refluxing ethanol containing catalytic amounts of piperidine for 4 hrs. Structure **2** was established from elemental analysis and spectral data (MS, IR, ^{1}H NMR). Thus. the mass (M 177) of compound **2a** was compatible with it's molecular formula. The ^{1}H NMR spectrum displayed three singlets at δ 2.03, 2.33 and 2.46 ppm assigned for three methyl groups and a broad band at δ 6.22 ppm assigned to an amino function. The N-(1-pyridyl)urea derivatives **3e-h** are prepared by the reaction of N-amino-2-pyridones **2** with phenyl isocyanate in refluxing dioxane for 3 hrs. Compounds **1** react with cyanoacetanilides in refluxing



a) R = R' = Me
b) R = Me, R' = Et
c) R = C_6H_5, R' = Me
d) R = C_6H_5, R' = Et

a) R = R' = Me, X = S
b) R = Me, R' = Et, X = S
c) R = C_6H_5, R' = Me, X = S
d) R = C_6H_5, R' = Et, X = S
e) R = R' = Me, X = O
f) R = Me, R' = Et, X = O
g) R = C_6H_5, R' = Me, X = O
h) R = C_6H_5, R' = Et, X = O

a) R = R' = Me, Ar = C_6H_5
b) R = Me, R' = Et, Ar = C_6H_5
c) R = C_6H_5, R' = Me, Ar = C_6H_5
d) R = C_6H_5, R' = Et, Ar = C_6H_5
e) R = R' = Me, Ar = 4-ClC_6H_4
f) R = Me, R' = Et, Ar = 4-ClC_6H_4
g) R = R' = Me, Ar = 4-$CH_3C_6H_4$
h) R = Me, R' = Et, Ar = 4-$CH_3C_6H_4$
i) R = C_6H_5, R' = Me, Ar = 4-$CH_3C_6H_4$
j) R = R' = Me, Ar = 4-$CH_3OC_6H_4$
k) R = Me, R' = Et, AR = 4-$CH_3OC_6H_4$
l) R = C_6H_5, R' = Me, Ar = 4-$CH_3OC_6H_4$
m) R = C_6H_5, R' = Et, Ar = 4-$CH_3OC_6H_4$

i) $CNCH_2CONHNH_2$, EtOH, piperidine, heat
ii) $PhNHC(=X)NHNHCOCH_2CN$
iii) $CNCH_2CONHAr$, EtOH, piperidine, heat
iv) PhNCS, dioxane, heat

ethanol containing catalytic amounts of piperidine for 10 hrs to give the interesting N-aryl-2-pyridone derivatives **4**, the structures of which were based on elemental analysis and spectral data (MS, IR, ^1H NMR). The mass (M 238) of compound **4a** was compatible with it's molecular formula and its ^1H NMR spectrum displayed three singlets at δ 1.97, 2.17 and 2.41 assigned for three methyl groups and a multiplet at δ 7.23-7.58 assigned for phenyl protons. The results describe the ready availability of several otherwise difficulty accessible N-arylpyridines, N-(1-pyridyl)urea and thiourea derivatives. These compounds showed promise in biological tests.

EXPERIMENTAL SECTION

All mps are uncorrected. IR spectra were obtained as KBr discs on a Pye Unicam instrument. ^1H NMR spectra were measured on a Varian 400 or Wilmad 270 MHz spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

N-Aryl-2-pyridone Derivatives (4a-m).- To a mixture of cyanoacetanilide[5] (0.01 mol) and **1**[6] (0.01 mol) in ethanol (50 mL), 0.5 mL of piperidine were added. The mixture was refluxed for 10 hrs, and the resulting solid was collected and crystallized (Table 1).

N-Amino-2-pyridone Derivatives (2a-d).- A mixture of **1** (0.01 mol) and cyanoacethydrazide (0.01 mol) was dissolved in ethanol (30 mL) containing 0.5 mL of piperidine. The mixture was refluxed for

3 hrs, and then allowed to cool. The resulting solid was collected and crystallized (Table 1).

N-(1-Pyridyl)urea and -thiourea Derivatives (3a-h). Method A.- To a solution of N-amino-2-pyridones **2** (0.01 mol) in dioxane (50 mL), phenyl isothiocyanate or phenylisocyanate (0.01 mol) was added. The resulting mixture was refluxed for 3 hrs and the solid product collected by filtration and crystallized from the appropriate solvent (Table 1).

Method B.- A mixture of 1-cyanoacetyl-4-phenylthiosemicarbazide[7] (0.01 mol) and **1** (0.01 mol) was dissolved in ethanol (50 mL), and 0.5 mL of piperidine added. The mixture was refluxed for 3 hrs, and the solid was collected and crystallized from the appropriate solvent (Table 1).

TABLE 1. Mps, Yields and Elemental Analysis for Compounds **2-4**

Compd[a]	Yield (%)	mp. (°C)	Elemental Analysis Found (Calcd.) C	H	N	M^+ (m/z)
2a	68	165	60.78 (61.02)	5.98 (6.21)	23.52 (23.73)	177
2b	85	160	62.58 (62.83)	6.55 (6.81)	22.00 (21.99)	191
2c	82	190	70.09 (70.29)	5.25 (5.44)	17.33 (17.57)	239
2d	80	180	70.92 (71.15)	6.11 (5.93)	16.32 (16.60)	—
3a	83	190	61.32 (61.54)	4.88 (5.13)	17.77 (17.95)	312
3b	79	195	62.33 (62.58)	5.28 (5.52)	16.93 (17.18)	—
3c[b,c]	72	210	67.09 (67.38)	4.55 (4.81)	14.66 (14.97)	—
3d[b]	65	217	68.21 (68.04)	4.88 (5.15)	14.15 (14.43)	—
3e[d]	90	230	65.00 (64.86)	5.50 (5.41)	19.10 (18.92)	—
3f[d]	90	308	66.08 (65.81)	5.65 (5.81)	18.26 (18.06)	—
3g	90	215	70.26 (70.39)	4.87 (5.03)	15.34 (15.64)	—
3h	90	240	70.79 (70.97)	5.12 (5.38)	15.20 (15.05)	—
4a	58	150	75.38 (75.63)	5.67 (5.88)	11.50 (11.76)	238
4b	82	255	75.89 (76.19)	6.18 (6.35)	10.91 (11.11)	252
4c[d]	69	245	79.84 (80.00)	5.15 (5.33)	9.07 (9.33)	300
4d	63	262	80.00 (80.25)	5.50 (5.73)	9.00 (8.92)	—
4e	72	180	65.81 (66.06)	4.55 (4.77)	9.99 (10.28)	—
4f[e]	80	220	66.82 (67.02)	5.03 (5.24)	9.55 (9.77)	—
4g	82	162	75.80 (76.19)	6.11 (6.35)	10.83 (11.11)	—
4h	75	220	76.43 (76.69)	6.49 (6.77)	10.27 (10.53)	266
4i[d]	85	228	79.99 (80.25)	5.66 (5.73)	9.00 (8.92)	314
4j[c]	81	182	71.50 (71.64)	6.00 (5.97)	10.19 (10.45)	—
4k	85	245	72.00 (72.34)	6.20 (6.38)	10.00 (9.93)	—
4l	82	151	76.30 (76.36)	5.60 (5.45)	8.50 (8.48)	—
4m	76	210	76.28 (76.52)	6.20 (6.09)	7.88 (8.12)	—

a) Unless otherwise noted, all compounds are colorless and were crystallized from EtOH b) Yellow
c) From MeOH d) From EtOH-DMF e) From DMF

TABLE 2. IR and ^{1}H NMR Data for Compounds **2-4**

Cmpd	IR (cm^{-1})	^{1}H NMR (δ)
2a	3450, 3380 (NH_2), 2200 (CN), 1670 (CO)	2.04 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.22 (s, br, 2H, NH_2)
2c	3420, 3380 (NH_2), 2225 (CN), 1660 (CO)	1.92 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 6.50 (s, br, 2H, NH_2), 7.40- 7.68 (m, 5H, C_6H_5)
3a	400, 3250 (NH), 2220 (CN), 1730 (CO)	2.35 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.00-7.60 (m, 5H, C_6H_5), 9.30 (s, br,1H, NH), 10.20 (s, br, 1H, NH)
3e	3470, 3300 (NH), 2222 (CN), 1710 (CO)	2.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3 2.48 (s, 3H, CH_3), 7.05- 7.58 (m, 5H, C_6H_5), 9.55 (s, br, 1H, NH), 10.40 (s, br, 1H, NH)
4a	2220 (CN), 1660 (CO)	1.97 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.23-7.58 (m, 5H, C_6H_5)
4g	2216 (CN), 1659 (CO)	1.96 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.15-7.38 (m, 4H, C_6H_4)
4j	2220 (CN), 1660 (CO)	1.90 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 7.20-7.60 (m, 4H, C_6H_4)

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