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Note

Synthesis of functionaly substituted pyridine and thiophene derivatives

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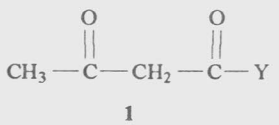
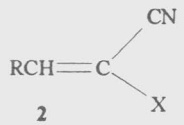
Acetoacetanilides **1** react with the ylidenenitriles **2** to give the substituted pyridines **4,5,10** and **11** respectively. Reaction of **1** with ethyl cyanoacetate and elemental sulphur in ethanolic-triethylamine yield 2-aminothiophenes **14**. Condensation of phenylhydrazone **15** with malononitrile affords pyridine **19**.

Diverse biological activities have been described for functionally substituted pyridines and fused pyridines. For example, pyridoxal phosphate plays an important role in metabolism as a coenzyme for a variety of biological transformations[1]. Nalidixic acid is bactericidal to most of common gram negative bacteria that cause urinary tract infection[2-4]. Moreover, several condensed pyridines have been used as antimalarials and antibactrials[5,6].

In the present note we report the new routes for the synthesis of substituted pyridines and thiophenes using β-ketoanilides **1** and the nitriles[7] **2** as starting components. Reaction of **1a,b** with arylidene-malononitriles **2a-c** in ethanolic-piperidine solution has been reported to give 3-acetylpyridones[8] **4**. Also **1** reacts with **2** in ethanolic-sodium ethoxide to give



1



2

1	Y
a	NHC_6H_5
b	$NHC_6H_4OCH_3$

2	R	X
a	C_6H_5	CN
b	$C_6H_4Cl(p)$	CN
c	$C_6H_4OCH_3(p)$	CN
d	C_6H_5	$CO_2C_2H_5$
e	$C_6H_4Cl(p)$	$CO_2C_2H_5$
f	$C_6H_4OCH_3(p)$	$CO_2C_2H_5$

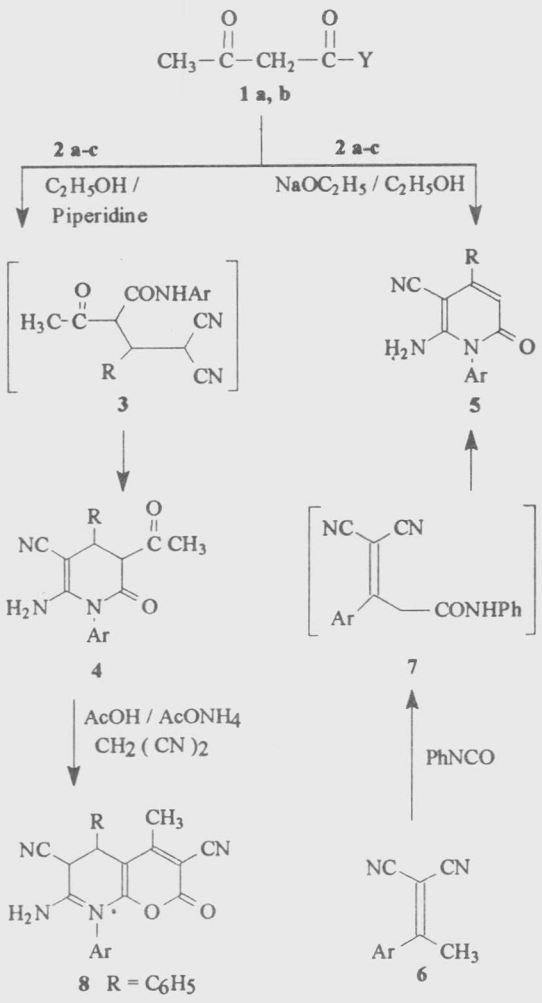
6-aminopyridones **5**. It is assumed to be formed by the addition of an active methylene in **1a,b** to the arylidenes **2a-c** to give the adduct **3**, which is cyclized to yield **4** (Scheme I). Compound **4** finally eliminates its acetyl group to form **5**. Elimination of acetyl group under similar conditions has already been reported[9].

Compounds **5a,b** were also obtained by reacting 1-arylethylidenemalononitriles **6** with phenyl isocyanate in dry dioxane containing catalytic amount of sodium metal[10]. The reactivity of acetyl group in **4** was studied. Thus, **4a** reacted with malononitrile in dry benzene containing catalytic amount of ammonium acetate and acetic acid to give **8** (cf. Scheme I), the structure of which was confirmed from its elemental analysis and IR spectra.

The behaviour of **1** towards ethyl arylidenecyanoacetates was investigated. Thus **1** reacted with **2d,e** to yield products, the type of which depends on the utilized reaction conditions. 3-Acetylpyridone **10** was obtained directly from the reaction of **1** with **2d,e** in ethanolic-piperidine (Scheme II).

On the other hand products with higher molecular weights were obtained from the same reactants on heating in ethanolic-sodium ethoxide. Structure **11** has been suggested for the reaction product, based on ^1H NMR spectra which clearly indicate the absence of acetyl function and the presence of olefinic protons in the product formed. Structure of **11** was also confirmed by its formation from the reaction of **10** with aromatic aldehydes in ethanolic-sodium ethoxide solution. One may assume a reaction pathway for the formation of **11** from **1** and **2d,e** that **1** reacts with **2** to yield a 1:1 adduct **9** followed by cyclization to **10**. Intermediate **10** then condenses with another molecule of aldehyde, which exists in equilibrium with **1** specially in aqueous basic medium[11] to give the chalcones **11** (Scheme II).

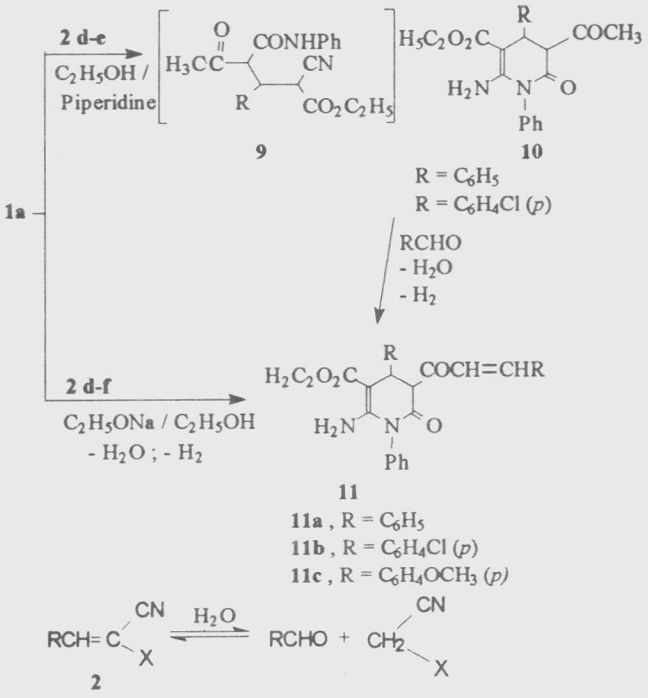
A mixture of **1a,b**, ethyl cyanoacetate and elemental sulphur when heated in ethanolic-triethylamine solution afforded 2-aminothiophenes **14a,b**. IR spectra of **14a,b** indicate clearly that the



4	R	Ar
a	C_6H_5	C_6H_5
b	$C_6H_4Cl(p)$	C_6H_5
c	$C_6H_4OCH_3(p)$	C_6H_5
d	$C_6H_4Cl(p)$	$C_6H_4OCH_3(p)$
e	$C_6H_4OCH_3(p)$	$C_6H_4OCH_3(p)$

5	R	Ar
a	C_6H_5	C_6H_5
b	$C_6H_4Cl(p)$	C_6H_5
c	$C_6H_4OCH_3(p)$	C_6H_5
d	C_6H_5	$C_6H_4OCH_3(p)$
e	$C_6H_4Cl(p)$	$C_6H_4OCH_3(p)$

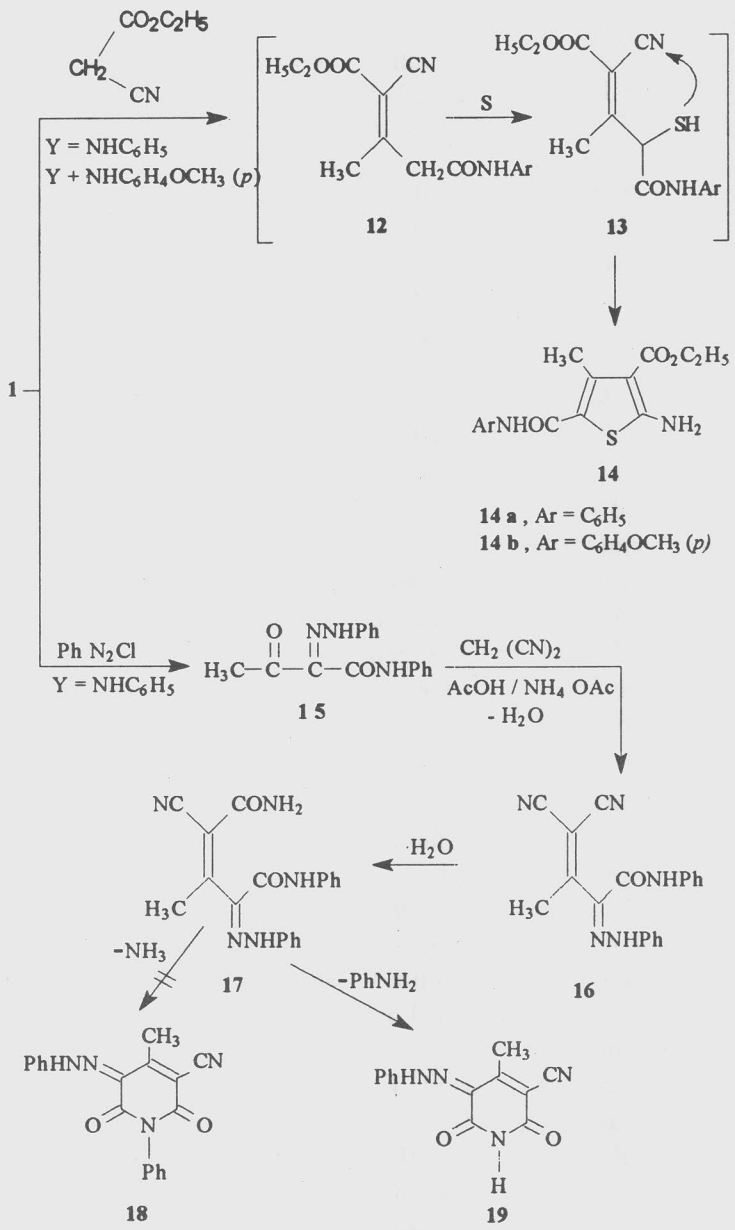
Scheme II



Scheme II

cyano functions are involved in the cyclization process and revealed the presence of amino groups. ^{1}H NMR spectrum of **14a** exhibits in addition to the aromatic protons, signals corresponding to NH, NH_2 and ester groups which is in good agreement with the proposed structures (cf. Scheme III). Formation of **14** is assumed to proceed via condensation of ethyl cyanoacetate with **1** to give an intermediate **12** which reacts with elemental sulphur to afford mercapto derivative **13**. Compound **13** then cyclizes to give product **14**.

Phenylhydrazone **15** when heated with malononitrile in dry benzene containing catalytic amount of ammonium acetate and acetic acid gave 3-cyano-2, 6-dioxo-4-methyl-1, 2, 5, 6-tetrahydropyridine-5-phenylhydrazone **19** and not the anticipated 3-cyano-2, 6-dioxo-4-methyl-1, 2, 5, 6-tetrahydro-1-phenylpyridine-5-phenylhydrazone **18**. The formation of **19** was established on the basis of its spectral (IR, ^{1}H NMR and mass) data. ^{1}H NMR spectrum of **19** exhibited a multiplet showing the presence of two NH groups. If this product was **18**[12] a singlet for NH would be expected. Further, the compound **19** was not identical with an authentic sample of **18** (m.p. and mixed m.p. and finger print region in the IR spectrum). A sequence of reaction of the formation of **19** is shown in Scheme III. Several



Scheme III

alkylheterocycles, such as 4-methylcoumarin[13], 4-methylpyridazines and 4-methyl-3-cyanopyridine-thione[14], reacted readily with cinnamonitriles **2** to yield fused heterocyclic systems, whereas the compound **19** failed to reach with the same reagents under a variety of drastic conditions.

Experimental Section

All melting points are uncorrected.IR spectra were recorded on a pye-unicam SP 1000 instrument; ^{1}H NMR spectra on EM 90-MHz spectrometer in DMSO-d_6 solution using TMS as internal standard (chemical shifts in δ, ppm), mass spectra on MS30 or MS9, (AEI) mass spectrometers operating at 70 eV. Microanalyses were carried out by the Microanalytical Data Unit at Cairo University.

3-Acetyl-6-amino-1, 4-diaryl-1, 2, 3, 4-tetrahydropyridine-5-carbonitriles (4a-e). A mixture of acetoacetanilides **1a** or **1b**-(0.01 mole) and **2a-c** in 50 mL of ethanol containing few drops of piperidine was refluxed for 5 hr. The mixture was then concentrated and cooled. The solid that separated was filtered off, dried and crystallized from ethanol to give **4a-e**. Compounds **4a-c** were previously obtained according to the literature procedure[8].

4b: Yield 2.2 g (60%), m.p. 195° (Found: C, 66.15; H, 3.53; N, 11.54. $C_{20}H_{13}ClN_3O_2$ requires C, 66.21; H, 3.61; N, 11.58%); IR: 3459, 3326, 3243 (NH_2)[15-18], 2184 (CN), 1715, 1708 (CO), 1645 (δNH_2).

4d: Yield 2.6 g (66%), m.p. 228° (Found: C, 63.81; H, 4.33; N, 10.36. $C_{21}H_{18}ClN_3O_3$ requires C, 63.72; H, 4.85; N, 10.62%); IR: 3450, 3320, 3310 (NH_2), 2195 (CN), 1725, 1700 (CO), 1665 (δNH_2).

4e: Yield 2.5 g (65%), m.p. 220° (Found: C, 67.62; H, 5.60; N, 10.53. $C_{22}H_{21}N_3O_4$ requires C, 67.51; H, 5.41; N, 10.74%); IR: 3450, 3350, 3255 (NH_2), 2198 (CN), 1718, 1700 (CO), 1638 (δNH_2).

6-Amino-1, 4-diaryl-2-oxo-1, 2-dihydropyridine 5-carbonitrile 5. Method A: A solution of **1a** or **1b** (0.01 mole) in abs. ethanol (50 mL) containing 0.23 g (0.01 mole) of finely divided sodium metal and 0.01 mole of the arylidenes **2a-c** was refluxed for 6 hr and then left to cool. The solution was then neutralized with dil. HCl. The products so formed were collected by filtration, crystallized from ethanol to give **5a-c**.

Method B: A mixture of **6a** or **6b** (0.01 mole), finely divided sodium metal (0.23 g, 0.01 mole), phenyl isocyanate (1 mL, 0.01 mole) in dry dioxane (40 mL) was refluxed for 4 hr. It was cooled and poured onto cold water and neutralized with dil. HCl. The precipitate was filtered off and crystallized from ethanol to give **5a-e** which were identified by comparison with authentic samples[10].

5c: Yield 1.9 g (60%), m.p. 205° (Found: C, 71.80; H, 4.82; N, 31.21. $C_{19}H_{15}N_3O_2$ requires C, 71.91; H, 4.76; N, 13.24%); IR: 3350, 3200 (NH_2), 2195 (CN), 1710 (CO), ^1H NMR: 3.65 (s, 3H, OCH_3), 6.75-7.80 (m, 9H, ArH and 1H, CH), 9.85 (s, 2H, NH_2)[10]; MS: m/z 317 (M^+).

5d: Yield 2.0 g (63%), m.p. 180° (Found: C, 72.11; H, 4.38; N, 13.51. $C_{19}H_{15}N_3O_2$ requires C, 71.91; H, 4.76; N, 13.24%); IR: 3350, 3250, 3200 (NH_2), 2210 (CN), 1710 (CO); ^1H NMR: 3.68 (s, 3H, OCH_3), 6.76-7.82 (m, 9H, ArH and 1H, CH), 10.2 (s, 2H, NH_2); MS: m/z 317 (M^+).

5e: Yield 2.2 g (62%), m.p. 175° (Found: C, 64.52; H, 4.33; N, 12.00. $C_{19}H_{14}ClN_3O_2$ requires C, 64.87; H, 4.01; N, 11.94%); IR: 3425-3230 (NH_2), 3195 (CN), 1695 (CO), 1640 (δNH_2).

7-Amino-4-methyl-2(*H*)-oxo-5, 8-diphenyl-5,6-dihydropyrano[2,3-*b*]pyridine-3, 6-dicarbonitrile 8. To a mixture of **4a** (0.01 mole), ammonium acetate (0.3 g) and acetic acid (0.5 mL) in dry benzene (50 mL), malononitrile (0.01 mole) was added. The reaction mixture was refluxed for 6 hr. The resulting solid product was filtered and crystallized from ethanol-DMF to give **8**, yield 2.3 g (60%), m.p. >300° (Found: C, 72.70; H, 4.43; N, 14.64. $C_{23}H_{16}N_4O_2$ requires C, 72.62; H, 4.24; N, 14.73%); IR: 3458, 3410, 3326 (NH_2), 2203 (CN), 1685 (CO), 1663 (δNH_2).

Ethyl 3-acetyl-6-amino-2-oxo-1-phenyl-1,2,3,4-tetrahydropyridine-5-carboxylates 10a,b. To a solution of **1a** (0.01 mole) in abs. ethanol (50 mL) containing 0.5 mL of piperidine **2d** or **2e** (0.01 mole) were added. The reaction mixture was refluxed for 1 hr, and cooled. The precipitate thus separated was filtered and crystallized from ethanol to give **10a,b**.

10a: Yield 2.5 (66%),m.p. 143° (Found: C, 69.65; H, 5.91; N, 7.35. $C_{22}H_{22}N_2O_4$ requires C, 69.83; H, 5.86; N, 7.40%); IR: 3450, 3330 (NH_2), 1730, 1720, 1650 (CO).

10b: Yield 3.3 g (80%), m.p. 130° (Found: C, 63.90; H, 5.01; N, 6.52. $C_{22}H_{21}ClN_2O_4$ requires C, 64.00; H, 5.13; N, 6.79%); IR: 3465, 3269 (NH_2), 1737, 1720, 1649 (CO); ^1H NMR: 1.2 (t, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.2 (q, 2H, CH_2), 4.3 (s, 1H, pyridine H-4), 5.85 (s, 1H, pyridine H-3), 7.10-7.52 (m, 11H, 9H, ArH and 2H, NH_2).

3-Aryl-1-(6-amino-4-aryl-1, 2-dihydro-5-ethoxycarbonyl- 2 -oxo-1-phenylpyridine-3-yl)prop - 2-enone 11a-c. Method A: A suspension of **1a** (0.01 (mole) and **2d-f** (0.1 mole) in ethanol (50 mL) containing 0.01 mole of sodium metal were refluxed for 10 hr and then cooled. The reaction mixture was neutralized with HCl and the solid precipitated was filtered off, recrystallized from ethanol to give **11a-c.**

Method B: Compounds **11a,b** could also be prepared from **10a,b** and aromatic aldehydes and by usual work-up as reported in Method A.

11a: Yield 3.2 g (70%), m.p. 235° (Found: C, 74.66; H, 5.11; N, 6.34. $C_{29}H_{24}N_2O_4$ requires C, 74.98; H, 5.21; N, 6.03%); IR: 3400, 3350, 3200 (NH_2), 1725, 1685, 1675 (CO), 1665 (NH_2); MS: m/z 464 (M^+).

11b: Yield 3.2 g (60%), m.p. 252° (Found: C, 65.11; H, 4.45; N, 5.36. $C_{29}H_{22}Cl_2N_2O_4$ requires C, 65.30; H, 4.16: N, 5.25%); IR: 3350, 3200 (NH_2), 1680, 1670, 1665 (CO), 1655 (δNH_2); ^1H NMR:

1.13 (t, 3H, CH_3), 2.0 (s, 3H, CH_3), 4.16 (q, 2H, CH_2), 7.10 (d, *J*=9 Hz, 1H, CH), 7.40-7.76 (m, 13H, ArH), 8.20 (d, *J*=9 Hz, 1H, CH), 10.32 (s, 2H, NH_2).

11c: Yield 3.1 g (60%), m.p. 225° (Found: C, 71.23; H, 5.40; N, 5.12. $C_{31}H_{28}N_2O_6$ requires C, 70.98; H, 5.38; N, 5.34%); IR: 3360, 3330, 3250 (NH_2), 1700, 1685, 1675 (CO), 1660 (δNH_2), 1610 (C=C).

Ethyl 2-amino-5-arylcarboxyanilido-4-methyl-thiophene-3-carboxylates 14a-c. Equimolecular amounts of the anilide **1a** or **1b** (0.01 mole), ethyl cyanoacetate and elemental sulphur (0.01 mole) in ethanol (50 mL) were refluxed together with triethylamine (1 mL) for 1 hr. The solid obtained on cooling was filtered off and crystallized from ethanol to yield **14a,b**.

14a: Yield 2.1 g (70%) m.p. 172° (Found: C, 59.15; H, 5.47; N, 9.08. $C_{15}H_{16}N_2O_3S$ requires C, 59.19; H, 5.30; N, 9.20%); IR: 3480, 3350, 3275 (NH_2, NH), 1678 (CO), 1640 (δNH_2); ^1H NMR: 1.10-1.40 (t, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.56-4.16 (q, 2H, CH_2), 6.8-7.04 (m, 7H, 5H, ArH and 2H, NH_2), 9.60 (s, 1H, NH); MS: m/z 305 (M^+).

14b:Yield 2.4 g (73%), m.p. 155° (Found: C, 57.21; H, 5.68; N, 8.54. $C_{16}H_{18}N_2O_4S$ requires C, 57.47; H, 5.43; N, 8.38%); IR: 3475, 3325 (NH_2, NH), 1675 (CO), 1660 (δNH_2); MS: m/z 334 (M^+).

3-Cyano-2, 6-dioxo-4-methyl-1, 2, 5, 6-tetrahydropyridine-5-phenylhydrazone 19. To a mixture of 2-acetyl-*N*-phenylethanamide-2-phenylhydrazone **15** (0.01 mole) in dry benzene (50 mL), 0.5 g of ammonium acetate and glacial acetic acid (8 mL) was added malononitrile (0.01 mole). The reaction mixture was refluxed for 6 hr. Evaporation of benzene left a solid product which was crystallized from DMF to give **19**, yield 1.6 g (63%), m.p. 265° (Found: C, 61.13; H, 4.24; N, 21.76. $C_{13}H_{10}N_4O_2$ requires C, 61.41; H, 3.96; N, 22.04%); IR: 3470, 3350 (NH), 2200 (CN), 1685, 1660 (CO), 1650 (C=N); ^1H NMR: 2.6 (s, 3H, CH_3), 7.36-7.52 (m, 5H, ArH), 7.6-7.8 (m, 2H, 2NH); MS: m/z 254 (M^+).

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