Activated Nitriles in Heterocyclic Synthesis. Part III [1]. Synthesis of *N*-Amino-2-pyridone, Pyranopyrazole and Thiazolopyridine Derivatives

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The reaction of 2-cyanoethanoic acid hydrazide and arylidenemalononitrile was studied as a new route for the synthesis of *N*-amino-2-pyridones. Pyrano[2,3-*c*]pyrazole and thiazolo[2,3-*a*]pyridine could be prepared from the reaction of arylideneazolones with the same reagent.

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β-Functional nitriles are versatile reagents and their utility in heterocyclic synthesis has received considerable recent attention [2]. In previous work from our laboratories we have reported novel syntheses of azoles [3,4], azines [5] and azoloazines [6] utilizing β-functional nitriles as starting components. As a part of this work the utility of the readily obtainable 2-cyanoethanoic acid hydrazide (**1**) in heterocyclic synthesis was investigated. The work has resulted in development of several new approaches for the synthesis of otherwise difficultly accessible multifunctional heterocyclic derivatives of utility for further chemical transformations and for biological activity evaluation.

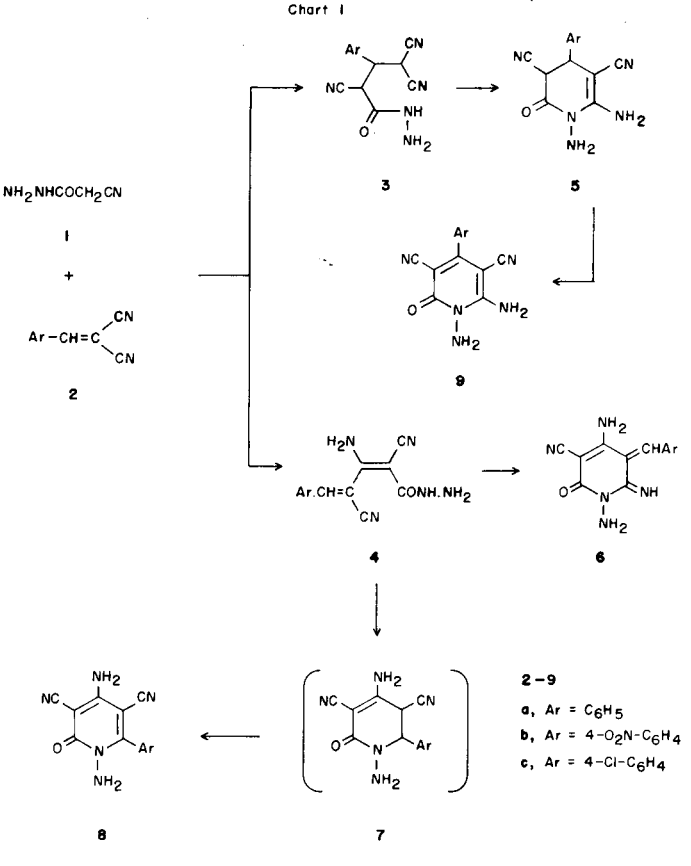
In conjunction of this work, we report here the results of our investigation on the behaviour of 2-cyanoethanoic acid hydrazide (**1**) toward the cinnamonitrile derivatives **2a-c**. It has been found that **1** reacts with benzylidenemalononitrile (**2a**) to yield products, the nature of which depends on the utilized reaction conditions. Thus, when equimolecular amounts of **1** and **2a** were reacted in cold ethanol and in the presence of catalytic amounts of piperidine, a product of mp 305° was obtained in 90% yield. The yield was not effected on reacting **1** and **2a** in a 1:2 ratio. On the other hand when the reaction of **1** and **2a** was conducted in the same medium under reflux for three hours, another product of mp >305° formed on cooling as a 1:1 adduct. This product seemed to be one of either the Michael adduct **3**, the acyclic intermediate **4**, formed *via* the addition of the active methylene to the cyano group or their cyclization products **5-7**. However, ^{1}H nmr clearly revealed the absence of proton linked to sp^3 carbon atoms. Thus, structures **3**, **5** and **7** were eliminated. However, structure **4** was considered most likely as the ir spectrum of the product revealed two cyano group absorptions. Moreover, if this compound was **6**, ylidene proton should have appeared at lower field (*ca.* 8-9 ppm) [7].

The product of mp >320° revealed a molecular formula of $C_{13}H_9N_5O$. This also could be obtained on heating **4** in ethanolic piperidine and is suggested to have structure **8**. The formation of **8** is assumed to proceed *via* cyclization of **4** and **7** which is readily oxidised under the reaction conditions into **8**.

Soto *et al.* [8] have recently described the reaction of **1** and **2a** and have isolated a product of mp 240° which was formulated as **9**. However, we failed to isolate this product in our laboratories.

In contrast to the behaviour of **2a**, compounds **2b,c** reacted with **1** in cold ethanol to yield products having physical characteristics very similar to those described by Soto *et al.* [8]. These compounds did not change on long refluxing under the reaction conditions utilised to effect conversion of **4** into **8**. The reaction of compounds **2b,c**

Chart I



with **1** may be assumed to proceed *via* Michael addition of the active methylene of **1** to the activated double bond in **2b,c** resulting in the formation of the final isolable products **9b,c**. This is in contrast to the above observed behaviour of **2a**. It seems that the presence of electron-withdrawing substituent in the para position of the aryl moiety in **2** increased the activity of the double bond in **2b,c**, thus Michael addition became the predominating reaction (Chart 1).

The reactivity of the amino function in **8a** toward benzoyl isothiocyanate was investigated. In previous work such reaction could be utilised for synthesis of a variety of aroyl and acyl thiourea derivatives [9]. However, under a variety of conditions compound **8a** was isolated completely unchanged. In order to prepare the required thiourea derivative of **8a**, compound **1** was reacted with benzoyl isothiocyanate to yield **10**. The latter was then treated with **2a** in refluxing ethanol in presence of two drops of piperidine to yield a product of molecular formula $C_{21}H_{14}N_6O_2S$ and for which structure **11** and **12** seemed possible. These are assumed to be formed *via* oxidation of the intermediate adducts **13** and **14** (Chart 2). Since spectral data seemed of little value in discriminating between **11** and **12**, a sample of **11** was prepared *via* condensing **10** with benzaldehyde to yield **15** which reacted with malononitrile to yield **11**. This proved to be different than the product obtained from **2a** and **10**. Thus structure **12** was established for this product.

In previous work, it has been reported that arylidene azolones react with active methylene reagents to yield fused azoles [10,11], which were also directly obtained from cinnamonitrile derivatives and 2-azolin-4-ones. The reactivity of **2** toward a variety of arylidene azolones has been investigated. However, it has been found that in contrast to the reported behaviour of malononitrile, benzoylacetonitrile and ethyl cyanoacetate, compound **1** did not add to the α,β-unsaturated linkage in the benzylidene derivatives **16-18**. In contrast, equimolecular amounts of **1** and **19** reacted smoothly in refluxing ethanol, and in presence of catalytic amounts of piperidine to yield the pyrano[2,3-*c*]pyrazole derivative **21**. Similarly **20** reacted with **1** to yield a product of molecular formula $C_{15}H_{11}N_3O_3S$. Structure **24** was suggested for the reaction product based on ^1H nmr. The formation of **24** in this reaction may be assumed to be

Chart 2

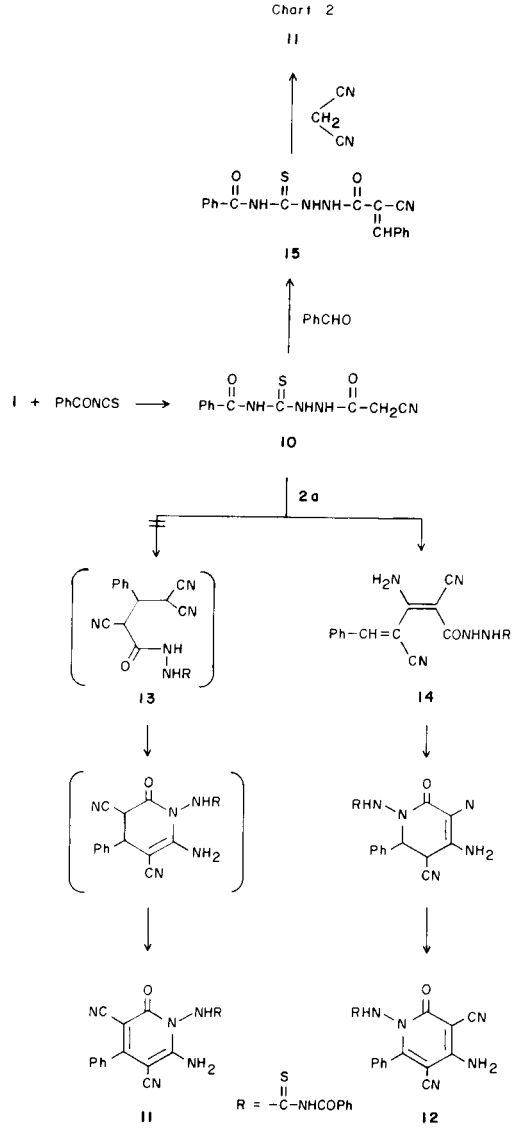
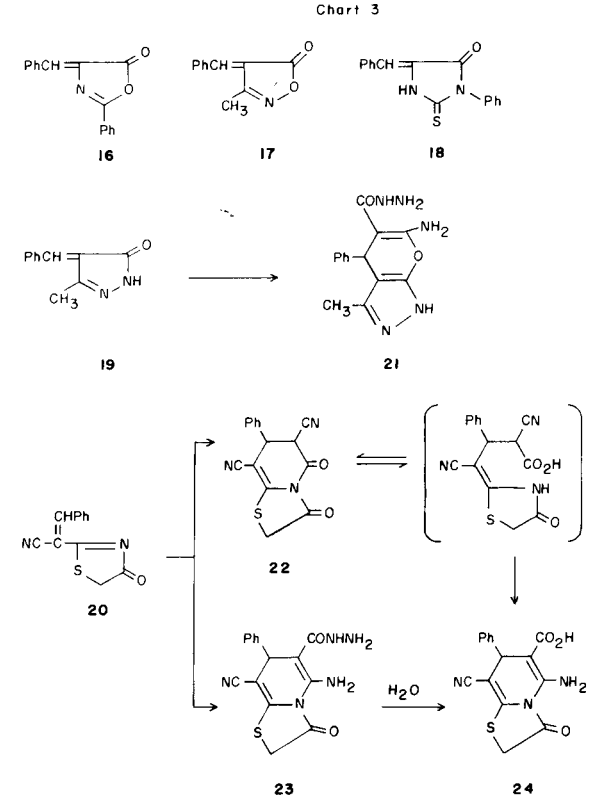


Chart 3



formed *via* addition of **1** to the double bond and cyclisation either into **22** or **23** which then affords the final isolable end product.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using a Pye Unicam Sp-1000 spectrophotometer or a Shimadzo-200. The ^{1}H nmr spectra were measured on a Varian EM-390 90 MHz using TMS as an internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the analytical Data Unit at Cairo University.

3-Amino-2,4-dicyano-5-phenylpent-2,4-dienoic Acid Hydrazide (**4a**).

To a suspension of **2a** (0.01 mole) and 2-cyanoethanoic acid hydrazide (**1**) (0.01 mole) in ethanol (50 ml), 0.5 ml of piperidine was added. The reaction mixture was warmed with stirring until the dissolution of the solid materials, then left to stand at room temperature for two hours. The colourless crystalline product, so formed, was filtered off and crystallised from ethanol, mp 305°, yield 90%; ir: 3460, 3410, 3320-3000 (NH and NH_2), 2220, 2200 (two conjugated CN), 1680-1580 cm^{-1} (NH_2 and CO); ^{1}H nmr (DMSO-d_6): 5.65 (br s, 2H), 7.37-7.60 (br s, 7H) and 8.45 (br, 2H).

Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.7; H, 4.4; N, 27.7. Found: C, 61.5; H, 4.3; N, 27.9.

1,4-Diamino-3,5-dicyano-6-phenyl-2-pyridone (**8a**).

a) From **2a** and **1**.

Equimolecular amounts (0.01 mole) of **2a** and **1** were refluxed in ethanol (50 ml) in presence of piperidine (0.5 ml) for 3 hours. The solid crystalline product, so formed, was filtered off and crystallised from ethanol, mp >320°, yield 85%; ir: 3480, 3440, 3360, 3250, 3200 (NH_2), 2200 (conjugated CN), 1650-1590 cm^{-1} (NH_2 and CO); ^{1}H nmr (DMSO-d_6): 5.6 (br s, 2H, NH_2), 7.35-7.6 (s, 5H, C_6H_5) and 8.5 (br s, 2H, NH_2).

Anal. Calcd. for $C_{13}H_9N_5O$: C, 62.2; H, 3.6; N, 27.8. Found: C, 62.0; H, 3.6; N, 27.8.

b) From Compound **4a**.

To a suspension of compound **4a** (1.0 g) in ethanol (30 ml) a catalytic amount of piperidine (0.5 ml) was added. The reaction mixture was refluxed for 2 hours, the product, so formed, was filtered off and identified (mp, mixed mp and ir) as **8a**.

1,6-Diamino-3,5-dicyano-4-aryl-2-pyridones **9b,c**.

To a mixture of **1** (1.0 g, 0.01 mole) in ethanol (30 ml) was added the appropriate benzylidenemalononitrile **2b,c** (0.012 mole). The reaction mixture was gently heated to 40°, then two drops of piperidine were added. After a few minutes standing at room temperature, a precipitate was formed. The solid material deposited was filtered off, washed with ethanol and crystallised from ethanol-DMF (1:1), yield 80%. Compounds **9b,c** were found to be identical (mp, ir and ^{1}H nmr) with the products previously described by Soto *et al.* [8].

Reaction of Benzaldehyde with 1-Cyanoacetyl-4-thiosemicarbazide (**10**).

To a mixture of **10** (0.1 mole, prepared as has been previously described) (**12**) and benzaldehyde (0.12 mole) in ethanol (100 ml), a catalytic amount of piperidine was added. The reaction mixture was refluxed for 3 hours, and the solvent was evaporated *in vacuo*. The remaining solid product was collected by filtration and crystallised from ethanol. Compound **15** formed yellow crystals, mp >280°, yield 80%; ir: 3400-3100 (NH), 2215 (conjugated CN), 1690, 1680 cm^{-1} (2 CO); ^{1}H nmr (DMSO-d_6): 7.45-7.7 (m, 8H), 7.85-8.15 (m, 4H), 8.35 (s, 1 H, ylidene CH) and 11.8 (br s, 1H, NH).

Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.71; H, 4.0; N, 16.0. Found: C, 61.61; H, 4.1; N, 16.2.

Reaction of **10** with **2a**.

A solution of **10** (0.1 mole) in ethanol (100 ml) was treated with compound **2a** (0.1 mole) and 1 ml of piperidine. The reaction mixture was refluxed for 3 hours. The solid product, so formed, was filtered off and crystallised from DMF, compound **12**, mp >300°, yield 88%; ir: 3450-3000 (NH and NH_2), 2230 (CN), 1670 (CO) and 1650 cm^{-1} (NH_2); ^{1}H nmr (DMSO-d_6): 7.5-7.8 (2 br s, 10H) and 8.05-8.45 (br, 4H).

Anal. Calcd. for $C_{21}H_{14}N_6O_2S$: C, 60.86; H, 3.38; N, 20.29. Found: C, 60.6; H, 3.5; N, 20.32.

Reaction of **15** and Malononitrile.

To a solution of **15** (0.1 mole) in ethanol (100 ml) was added malononitrile (0.12 mole) and piperidine (0.5 ml). The reaction mixture was refluxed for 5 hours. The solvent was removed *in vacuo* and the formed solid product was filtered off and crystallised from ethanol. Compound **11** formed pale yellow crystals, mp 235°, yield 85%; ir: 3500, 3150 (NH and NH_2), 2220 (CN), 1675-1640 cm^{-1} (CO).

Anal. Calcd. for $C_{21}H_{14}N_6O_2S$: C, 60.86; H, 3.38; N, 20.29; S, 7.73. Found: C, 60.5; H, 3.7; N, 19.9; S, 7.6.

Reaction of Each of Compounds **19** and **20** with **1**.

To a suspension of compound **1** (0.01 mole) and compound **19** or compound **20** (0.01 mole) in ethanol (30 ml), one ml of piperidine was added. The reaction mixture was refluxed for five hours, the solvent was then evaporated *in vacuo* and the remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallised from the appropriate solvent to give **21** and **24**.

Compound **21** was crystallised from dioxane, mp 265° (yielded 90%); ir: 3500-2400 (NH, NH_2 and OH), 1620 cm^{-1} (NH_2); ^{1}H nmr (DMSO-d_6): 2.1 (s, 4H, integrated for 3 protons after deuterium oxide exchange), 4.85 (s, 1H, pyrane CH), 5.9-7.1 (br, 4H, $2NH_2$) and 7.2 (s, 5H, C_6H_5).

Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C, 58.95; H, 5.26; N, 24.56. Found: C, 58.89; H, 5.21; N, 24.52.

Compound **24** was crystallised from DMF, mp 205°, yield 82%; ir: 3600-2500 (NH_2 and carboxylic group dimer), 2220 (conjugated CN), 1730 (carboxyl CO) and 1700 cm^{-1} (ring CO); ^{1}H nmr (DMSO-d_6): 3.3 (s, 1H, pyridine CH-4), 4.2 (s, 2H, CH_2), 7.3-7.8 (m, 6H, C_6H_5 and NH), 7.95 (s, 1H) and 11.5 (br s, 1H).

Anal. Calcd. for $C_{15}H_{11}N_3O_3S$: C, 57.5; H, 3.5; N, 13.4; S, 10.2. Found: C, 57.6; H, 3.6; N, 13.2; S, 9.8.

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