

Synthesis of Pyridines from β -Substituted α -Phenylacrylonitriles

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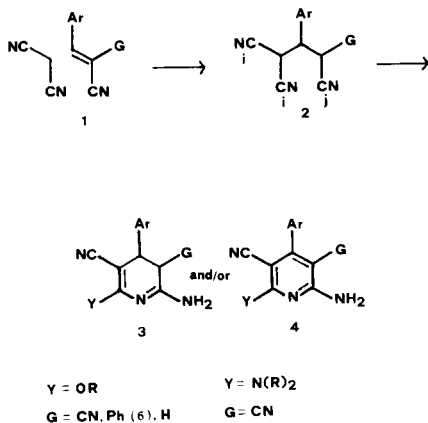
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The reaction of malononitrile with α -phenylcinnamionitriles in ethanolic sodium ethanethiolate is studied as a convenient route to 2-amino-4-aryl-5-cyano-6-ethylthio-3-phenyl-3,4-dihydropyridines (**5**) and the corresponding pyridines **6**. From the study of the structure of **5a** (Ar = Ph) we can conclude that this cyclization reaction proceeds *via* a site-selective addition of the ethanethiolate to the cyano group *i* of the 1,3-tricyano-2-phenylacrylonitrile (**2**).

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The use of reagents such as cinnamionitriles and α -substituted β -aryl or pyridylacrylonitriles by cyano or phenyl groups in the synthesis of 3,4-dihydro-pyridines and pyridines has already been reported (1-4). The reaction is performed by treatment of a cinnamionitrile or α,β -disubstituted acrylonitrile with malononitrile in alcoholic sodium alkoxide (1-3) or amines in chloroform solution (4). Although the reaction mechanism is not completely known, it seems probable that the reaction proceeds through formations of a Michael adduct **2** that is cyclized into a 3,4-dihydropyridine **3** or is cyclized and oxidized (**5**) to pyridine **4** by site-selective addition of the alkoxide to a cyano group *i*.

Figure 1



In order to determine whether the observed site-selectivity was maintained when the cyclization agent is changed, we have studied the reaction of α -phenylcinnamionitriles with malononitrile in ethanolic sodium ethanethiolate. This reaction permitted the synthesis of a series of 2-amino-4-aryl-5-cyano-6-ethylthio-3-phenyl-3,4-dihydro-

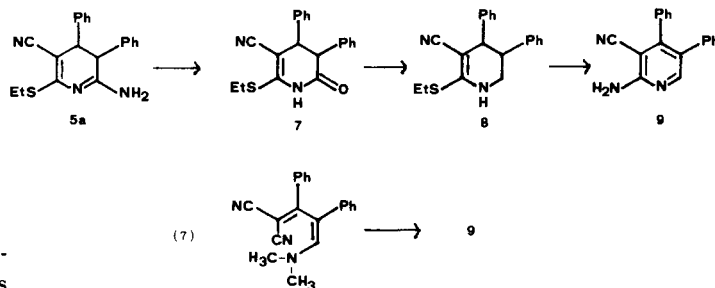
pyridines (**5**) and the corresponding pyridines **6**.

Under the reaction conditions employed, the α -phenyl- β -(*m*-nitrophenyl)acrylonitrile afforded the pyridine directly; the α,β -diphenylacrylonitrile, α -phenyl- β -(*p*-methoxyphenyl)acrylonitrile and α -phenyl- β -(3-pyridyl)acrylonitrile afforded the 3,4-dihydropyridine and with the α -phenyl- β -(2-pyridyl)acrylonitrile a mixture of the 3,4-dihydropyridine and pyridine was obtained. In all cases, the 3,4-dihydropyridine isolated from the reaction mixture was oxidized to the pyridine with DDQ.

The assignment for the amino and ethylthio groups at the 2 and 6 positions, respectively, was based on the following reactions:

A selective hydrolysis of **5a** performed in acetic acid yielded the 3,4-dihydro-2-pyridone **7**, which was converted to **8** by reduction with sodium borohydride. The 1,2,3,4-tetrahydropyridine **8** was transformed, by treatment with ammonia and later oxidation of the crude product obtained, to 2-amino-3-cyano-4,5-diphenylpyridine (**9**). Compound **9** has been prepared by Ege, *et al.* (7) by the reaction of 4-dimethylamino-2,3-diphenyl-1,3-butadien-1,1-dicarbonitrile with ammonia in methanol.

Figure 2



Hydrolysis of **7** and **8** with hydrochloric acid afforded 3-cyano-4,5-diphenylglutarimide (**10**) and 3-cyano-4,5-diphenyl- δ -valerolactam (**11**). The infrared spectra for both

compounds showed weak bands at 2260 cm^{-1} consistent with the disappearance of cyano group conjugation.

The methylation of **7** with methyl iodide gave the corresponding *N*-methyl derivative **12** in 60% yield.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 and 599 spectrometers. The ^1H -nmr spectra were recorded on a Varian T-60 and FT-80 A apparatus. Mass spectral data were obtained on a Varian Mat mass spectrometer. For the column chromatography silica gel and alumina Merck 60 were used.

Synthesis of 2-Amino-4-aryl-5-cyano-6-ethylthio-3-phenyl-3,4-dihydropyridines and Pyridines (**5**) and (**6**). General Procedure.

To an ethanolic solution of 0.01 mole of sodium ethanethiolate (0.23 g, 0.01 g-atom) of sodium and 0.62 g (0.01 mole) of ethanethiol in 45 ml of absolute ethanol) 0.66 g (0.01 mole) of malononitrile and 0.01 mole of the corresponding α -phenyl- β -arylacrylonitrile were added. The mixture was stirred at $35\text{--}40^\circ$ for 10-12 hours and then allowed to stand for 12 hours at room temperature. The crude product was isolated by combining the solid which precipitated in the reaction mixture with the product isolated from the mother liquors from the chromatography on a silica gel column.

The isolation of pure products was performed in each case as follows:

2-Amino-5-cyano-6-ethylthio-3,4-diphenyl-3,4-dihydropyridine (**5a**).

Following the general procedure and after recrystallization of the crude product in ethanol, 1.5 g of yellow crystals was obtained, mp $202\text{--}203^\circ$ (45%); ir: ν max 3450, 3310, 3200, 2160, 1615, 1565, 1530, 1485, 1450 cm^{-1} ; nmr (DMSO- d_6): δ 1.28 (3H, triplet, SCH_2CH_2), 3.05 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 3.60 (1H, CH), 3.73 (1H, CH), 7.16 (10H, H-aromatics), 7.58 and 7.73 (2H, NH_2); ms: *m/e* 333 (20%, M^+), 304 (100%, $\text{M}^+ - 29$).

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{S}$: C, 72.07; H, 5.70; N, 12.61. Found: C, 72.01; H, 5.51; N, 12.97.

2-Amino-5-cyano-3-deuterio-6-ethylthio-3,4-diphenyl-3,4-dihydropyridine **5a(d)**.

Proceeding as above and by utilization of ethanol- d_4 (15 ml) as the solvent, 0.6 g (3 mmoles) of α -phenylcinnamonnitrile, 0.2 g (3 mmoles) of malononitrile and 3 mmoles of sodium ethanethiolate, 0.4 g of the dihydropyridine deuterated at C-3 was prepared, mp $202\text{--}203^\circ$ (42%); nmr (DMSO- d_6): δ 1.23 (3H, triplet, $\text{CH}_3\text{CH}_2\text{S}$), 3.06 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 3.60 (1H, CH), 7.18 and 7.16 (10H, H-aromatics), 7.63 and 7.78 (2H, NH_2).

2-Amino-5-cyano-6-ethylthio-3-phenyl-4-(*p*-methoxyphenyl)-3,4-dihydropyridine (**5b**).

From the reaction mixture a solid with the constitution of 2-amino-3,5-dicyano-6-ethylthio-4-(*p*-methoxyphenyl)pyridine (**8**) was separated by filtration. The filtrate was chromatographed on a silica gel column. Elution with benzene-ethyl acetate 6:4 gave 0.96 g of **5b**. Recrystallization from ethanol yielded 0.77 g of pure **5b**, mp $188\text{--}189^\circ$ (21%); ir: ν max 3350, 2850-3250, 2190, 1660, 1610, 1585, 1560, 1510, 1440 cm^{-1} ; nmr (DMSO- d_6): δ 1.23 (3H, triplet, $\text{CH}_3\text{CH}_2\text{S}$), 3.05 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 3.55 (1H, CH), 3.65 (4H, CH_3O and CH), 6.63-7.26 (9H, H-aromatics), 7.56 and 7.71 (2H, NH_2).

Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{OS}$: C, 69.42; H, 5.78; N, 11.57. Found: C, 69.62; H, 5.72; N, 12.01.

2-Amino-5-cyano-6-ethylthio-3-phenyl-4-(3-pyridyl)-3,4-dihydropyridine **5c**.

Following the general procedure and using benzene-ethyl acetate as the eluent, 3.5 g of **5c** was obtained. Recrystallization from ethanol yielded 2.1 g of pure product, mp $220\text{--}221^\circ$ (63%); ir: ν max 3500, 3220, 3050, 2195, 1650, 1555, $1510, 1270\text{ cm}^{-1}$; nmr (DMSO- d_6): δ 1.25 (3H, triplet,

$\text{CH}_3\text{CH}_2\text{S}$), 3.06 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 3.76 (2H, CH), 7.10-7.56 (7H, H-aromatics), 8.23-8.40 (2H, H-aromatics), 7.66 and 7.88 (2H, NH_2).

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{S}$: C, 68.26; H, 5.38; N, 16.76. Found: C, 68.34; H, 5.49; N, 16.68.

2-Amino-5-cyano-6-ethylthio-3-phenyl-4-(2-pyridyl)-3,4-dihydropyridine (**5d**).

Following the general procedure, from the reaction mixture 1.96 g of **5d** was isolated. Chromatography of the mother liquor afforded 0.3 g of the corresponding pyridine **6d** by using hexane-ethyl acetate 7:3 as the eluent. When the recrystallization of **5d** from ethanol was tried, this compound showed a great tendency to aromatize so the data are given for the product recrystallized, cooling an acetone solution of the same in a dry ice-acetone bath, mp $208\text{--}209^\circ$ (59%); ir: ν max 3490, 3320, 3210, 2170, 1620, 1590, 1540, 1490, 1445, 1275 cm^{-1} ; nmr (DMSO- d_6): δ 1.21 (3H, triplet, $\text{CH}_3\text{CH}_2\text{S}$), 3.01 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 3.65 (1H, CH), 4.06 (1H, CH), 6.88-7.25 (7H, H-aromatics), 7.45, 7.56, 8.28, 8.35 (2H, H-aromatics), 7.70 (2H, NH_2).

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{S}$: C, 68.26; H, 5.38; N, 16.76. Found: C, 67.90; H, 5.80; N, 16.26.

2-Amino-5-cyano-6-ethylthio-3-phenyl-4-(*m*-nitrophenyl)pyridine (**6e**).

The solid (1.5 g) formed in the reaction mixture combined with that obtained (0.25 g) from chromatography (eluent: hexane-ethyl acetate 6:4) and recrystallized from ethanol yielded 1.51 g of pyridine **6e**, mp $246\text{--}247^\circ$ (40%); ir: ν max 3495, 3380, 3080, 2220, 1610, 1550, 1525, 1440, 1350 cm^{-1} ; nmr (DMSO- d_6): δ 1.36 (3H, triplet, $\text{CH}_3\text{CH}_2\text{S}$), 3.25 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 7.10 (5H, H-aromatics), 7.36-7.63 and 7.80-8.16 (4H, H-aromatics), 6.50 (2H, NH_2).

Anal. Calcd. for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$: C, 63.82; H, 4.25; N, 14.89. Found: C, 64.16; H, 4.23; N, 15.30.

Oxidation of the Dihydropyridines **5a-d** to Pyridines. General Procedure.

The corresponding 3,4-dihydropyridine (3 mmoles) and 0.71 g (3 mmoles) of DDQ in 40 ml of ethanol were heated under reflux for 2 hours. The mixture was cooled and filtered on an alumina column (10-12 g) to separate the pyridine.

2-Amino-5-cyano-6-ethylthio-3,4-diphenylpyridine (**6a**).

After the reaction was finished *via* the general procedure, 0.8 g of **6a** was obtained by filtration from the cooled reaction mixture. The filtrate was chromatographed on alumina affording an additional 0.16 g of **6a**. Recrystallization from ethanol yielded 0.95 g of white flakes, mp $273\text{--}274^\circ$ (95%); ir: ν max 3460, 3340, 3180, 2200, 1600, 1540, 1525, 1430 cm^{-1} ; nmr (DMSO- d_6): δ 1.35 (3H, triplet, $\text{CH}_3\text{CH}_2\text{S}$), 3.23 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 7.08 (10H, H-aromatics), 6.30 (2H, broad, NH_2).

Anal. Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{S}$: C, 72.50; H, 5.13; N, 12.68. Found: C, 72.28; H, 5.17; N, 12.90.

2-Amino-5-cyano-6-ethylthio-3-phenyl-4-(*p*-methoxyphenyl)pyridine (**6b**).

Proceeding as indicated in the general procedure and after recrystallization of the crude product from ethanol, 0.94 g of white needles of **6b** was obtained, mp $205\text{--}206^\circ$ (92%); ir: ν max 3460, 3350, 3200, 2210, 1615, 1550, 1510, 1440, 1420 cm^{-1} ; nmr (DMSO- d_6): δ 1.32 (3H, triplet, $\text{CH}_3\text{CH}_2\text{S}$), 3.16 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 3.58 (3H, CH_3O), 6.43-7.20 (9H, H-aromatics), 6.22 (2H, broad, NH_2).

Anal. Calcd. for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{OS}$: C, 69.78; H, 5.29; N, 11.62; S, 8.85. Found: C, 70.04; H, 5.54; N, 11.76; S, 8.64.

2-Amino-5-cyano-6-ethylthio-3-phenyl-4-(3-pyridyl)pyridine (**6c**).

The crude product upon recrystallization from ethanol yielded 0.94 g of white needles of **6c**, mp $230\text{--}231^\circ$ (94%); ir: ν max 3370, 3300, 3180, 2210, 1635, 1600, 1594, 1570, 1550, 1525, 1480, 1460, 1445, 1420, 1410 cm^{-1} ; nmr (DMSO- d_6): δ 1.33 (3H, triplet, $\text{CH}_3\text{CH}_2\text{S}$), 3.16 (2H, quartet, $\text{CH}_3\text{CH}_2\text{S}$), 6.70-7.23 (6H, H-aromatics), 7.33 and 7.45 (1H, H-aromatic), 8.03-8.26 (2H, H-aromatics), 6.40 (2H, broad, NH_2).

Anal. Calcd. for $C_{19}H_{16}N_4S$: C, 68.65; H, 4.85; N, 16.85. Found: C, 69.11; H, 5.03; N, 16.94.

2-Amino-5-cyano-6-ethylthio-3-phenyl-4-(2-pyridyl)pyridine (**6d**).

Following the general procedure and upon chromatography, a crude product was obtained which was recrystallized from ethanol yielding 0.93 g of white crystals, mp 228-229° (93%); ir: ν max 3480, 3340, 3180, 2210, 1610, 1555, 1535, 1470, 1440, 1410 cm^{-1} ; nmr (DMSO- d_6): δ 1.33 (3H, triplet, CH_3CH_2S), 3.15 (2H, quartet, CH_3CH_2S), 6.70-7.16 (7H, H-aromatics), 7.26 and 7.42 (1H, H-aromatic), 8.22 and 8.28 (1H, H-aromatic), 6.35 (2H, broad, NH $_2$).

Anal. Calcd. for $C_{19}H_{16}N_4S$: C, 68.65; H, 4.85; N, 16.85. Found: C, 68.71; H, 4.48; N, 17.28.

5-Cyano-6-ethylthio-3,4-diphenyl-3,4-dihydro-2-pyridone (**7**).

A solution of 2 g (6 mmoles) of **5a** in ethanol-acetic acid (30:15 ml) was heated under reflux for 4 hours. The mixture was cooled and poured over ice-water. The resulting solid was filtered and washed with water. Recrystallization from ethanol yielded white crystals (1.7 g), mp 156-157° (84%); ir: ν max 3190, 3090, 2210, 1680, 1605, 1495, 1465, 1455 cm^{-1} ; nmr (DMSO- d_6): δ 1.17 (3H, triplet, CH_3CH_2S), 3.01 (2H, quartet, CH_3CH_2S), 4.00 and 4.20 (2H, AB system, $J = 7$ Hz, CH), 7.06 (10H, H-aromatics), 10.60 (1H, broad, NH).

Anal. Calcd. for $C_{22}H_{18}N_2SO$: C, 71.85; H, 5.39; N, 8.38; S, 9.58. Found: C, 71.94; H, 5.76; N, 8.70; S, 9.90.

5-Cyano-6-ethylthio-3,4-diphenyl-1,2,3,4-tetrahydropyridine (**8**).

To 40 ml of absolute ethanol 0.23 g (6 mmoles) of sodium borohydride and 1 g (3 mmoles) of **7** were added. The reaction mixture was stirred under reflux for 8 hours, then concentrated to 15 ml and poured over ice-water. The crude product upon recrystallization from ethanol yielded 0.67 g of colourless crystals, mp 190-191° (70%); ir: ν max 3360, 2180, 1605, 1590, 1550, 1490, 1455 cm^{-1} ; nmr (trifluoroacetic acid- d): δ 1.55 (3H, triplet, CH_3CH_2S), 3.40 (2H, quartet, CH_3CH_2S), 3.53-4.90 (4H, CH and CH_2), 6.96 and 7.03 (10H, H-aromatics).

Anal. Calcd. for $C_{20}H_{20}N_2S$: C, 75.00; H, 6.25; N, 8.75. Found: C, 75.10; H, 6.45; N, 8.92.

2-Amino-3-cyano-4,5-diphenylpyridine (**9**).

A solution of 1.28 g (4 mmoles) of **8** in 20 ml of ethylene glycol was heated under reflux for 15 hours while dry ammonia was bubbled into the solution. The mixture was cooled and poured over ice-water (150 ml). The resulting solid was chromatographed on a silica-gel column; elution with hexane:ethyl acetate (6:4) afforded the starting compound **8**. Elution with ethanol and further removal of the solvent yielded a residue. A mixture of this crude product in 30 ml of ethanol with 0.7 g (3 mmoles) of DDQ was heated under reflux for 6 hours and the mixture was chromatographed on an alumina column using hexane-ethyl acetate (6:4) to give 0.14 g of **9**, mp 222-223° (13%); ir: ν max 3410, 3320, 3160, 2220, 1655, 1585, 1575, 1545, 1480 cm^{-1} .

2-Cyano-3,4-diphenylglutarimide (**10**).

Compound **7** 0.84 g (2.5 mmoles) was dissolved in 35 ml of a mixture of 4:3 ethanol-11.6 *N* hydrochloric acid and was heated under reflux for 9

hours. The solvent was evaporated and the residue was chromatographed on a silica gel column using benzene-ethyl acetate (8:2) to give 0.3 g of **10**. Recrystallization from benzene yielded crystals of mp 220-222° (40%); ir: ν max 3200, 3090, 2880, 2260, 1730, 1700, 1500, 1475, 1455, 1365, 1300, 1280, 1230 cm^{-1} ; nmr (DMSO- d_6): δ 3.92-4.46 (2H, multiplet, CH), 4.74-5.29 (1H, multiplet, CH), 7.06 and 7.15 (10H, H-aromatics), 11.53 (1H, broad, NH).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.82; N, 9.65. Found: C, 74.69; H, 5.29; N, 9.54.

2-Cyano-3,4-diphenyl- δ -valerolactam (**11**).

A solution of **8** (1.07 g, 3.3 mmoles) in 30 ml of a mixture of 5:1 ethanol-11.6 *N* hydrochloric acid was heated under reflux for 6 hours. The solvent was evaporated and the residue was recrystallized from ethanol-water yielding 0.83 g of white crystals, mp 166-167° (91%); ir: ν max 3340, 2260, 1680, 1610, 1490, 1460 cm^{-1} ; nmr (DMSO- d_6): δ 2.75-4.55 (5H, -CH and CH_2), 7.20 (10H, H-aromatics), 8.39 (1H, broad, NH).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 78.26; H, 5.79; N, 10.14. Found: C, 78.23; H, 6.21; N, 10.41.

5-Cyano-6-ethylthio-3,4-diphenyl-1-methyl-3,4-dihydro-2-pyridone (**12**).

Over an ethanol-sodium ethoxide solution [9.2 mg (0.004 g-atom) of sodium metal in 90 ml of absolute ethanol], 1.32 g (4 mmoles) of **7** and 1.42 g (0.01 mole) of methyl iodide were added. The mixture was stirred at room temperature for 60 hours, after which time the mixture was concentrated to 30 ml and poured over 400 ml of ice-water made weakly acidic by hydrochloric acid. The crude product was chromatographed on a silica gel column; elution with hexane-ethyl acetate (8:2) gave a product which recrystallized from ethanol, yielded 0.8 g of white flakes, mp 123-124° (60%); ir: ν max 2200, 1690, 1590, 1490, 1450, 1295 cm^{-1} ; nmr (DMSO- d_6): δ 1.10 (3H, triplet, CH_3CH_2S), 2.83 (2H, quarter, CH_3CH_2S), 3.33 (3H, NCH_3), 4.14 and 4.26 (2H, AB system, $J = 7$ Hz), 7.10 (10H, H-aromatics).

Anal. Calcd. for $C_{22}H_{20}N_2OS$: C, 72.41; H, 5.74; N, 8.04; S, 9.19. Found: C, 72.39; H, 6.16; N, 8.37; S, 9.42.

REFERENCES AND NOTES

- (1) M^a. A. Cabrerizo and J. L. Soto, *An. Quim.*, **70**, 951 (1974).
- (2) L. Fuentes, A. Lorente and J. L. Soto, *ibid.*, **73**, 1359 (1977).
- (3) M. C. Chacón, M. C. Pardo, J. L. Soto, A. Lorente and L. Fuentes, *J. Heterocyclic Chem.*, in press.
- (4) L. Fuentes, J. J. Vaquero and J. L. Soto, *An. Quim.*, **76**, 68 (1980).
- (5) The order of these steps is being investigated.
- (6) The assignment of the relative positions for the amino and alkoxy groups is described in J. J. Vaquero's Thesis, reference 8.
- (7) G. Ege, H. O. Frey and E. Schuck, *Synthesis*, 376 (1979).
- (8) J. J. Vaquero, *Thesis*, University of Alcalá de Henares, Madrid, Spain (1981).