SYNTHESIS OF HETEROCYCLIC COMPOUNDS. XLV. SYNTHETIC STUDIES USING 2,3-SUBSTITUTED PROPENENITRILES: SYNTHESIS OF 2-AMINO-6-ETHYLTHIOPYRIDINES AND 3,4-DIHYDROPYRIDINES

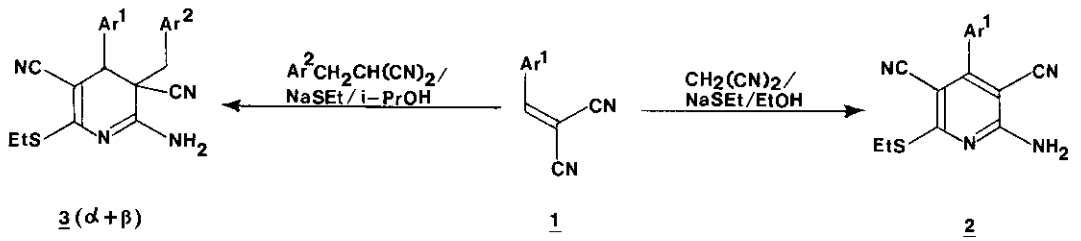
Luis Fuentes*, Juan José Vaquero, Juan Carlos del Castillo, and María Isabel Ardid
Departamento de Química Orgánica. Universidad de Alcalá de Henares, Madrid, Spain

José Luis Soto*
Departamento de Química Orgánica. Facultad de Química, Universidad Complutense, Madrid-3, Spain

Abstract —— The reactions of malononitrile and arylmethylmalononitriles in alcohols-sodium ethanothiolate with 3-aryl-2-cyanopropenenitriles (1) are studied as a method of synthesis of 2-amino-4-aryl-3,5-dicyano-6-ethylthio-pyridines (2) and 2-amino-4-aryl-3-arylmethyl-3,5-dicyano-6-ethylthio-3,4-dihydropyridines (3) respectively. Compounds 3 are isolated as a mixture of diastereoisomers, here designated as α and β. The structure of the 3a(β) isomer (Ar^1= Ar^2= Ph) has been determined by X-Ray crystallography. Pyridines 4 were obtained by hydrogen cyanide elimination from dihydropyridines 3.

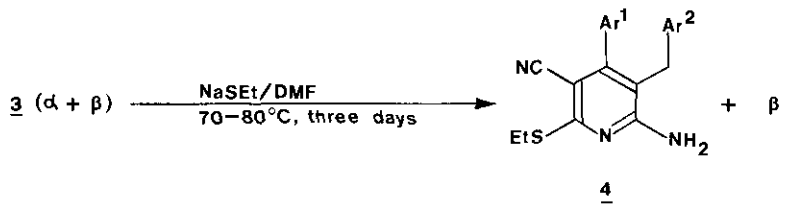
An interesting procedure for the preparation of substituted 2-aminopyridines is the reaction of propenenitriles with active hydrogen nitriles, in presence of a nucleophile reagent. Such pyridines contain attached at 6-position, as substituent, the nucleophile employed.[1-7]

Following our previous works,[1-6] 2-amino-4-aryl-3,5-dicyano-6-ethylthiopyridines (2) were synthesized by treatment of 3-aryl-2-cyanopropenenitriles (1) with malononitrile in ethanol-sodium ethanothiolate. Using 2-propanol as solvent and arylmethylmalononitriles instead of malononitrile, we isolated 2-amino-4-aryl-3-arylmethyl-3,5-dicyano-6-ethylthio-3,4-dihydropyridines (3) as a mixture of diastereoisomers that here we design as α and β.



3(α+β) 1 2

The two pairs of enantiomers, for dihydropyridine 3a (Ar^1= Ar^2= Ph), were separated. Pyridine 4a was obtained by heating the 3a(α) isomer at 70-80 °C in DMF with an excess of sodium ethanothiolate for 3 days. In such conditions the 3a(β) isomer needed 12 days for the same complete transformation. This unlike behavior in the hydrogen cyanide elimination allowed the selective aromatization of α isomer to the pyridines 4a-e, which could be easily separated of the untransformed pair of enantiomers β.



It should also be noted that for 3d, the aromatization of the isomer α was accompanied by the substitution of the halogen atom on 4-position of Ar^1 by the ethylthio group.

The reductive deamination of dihydropyridine 3a(α) with sodium borohydride in ethanol afforded 3-benzyl-3,5-dicyano-6-ethylthio-4-phenyl-1,2,3,4-tetrahydropyridine (5a); however, the β isomer remained inalterated in the same conditions. The preparation of 5a by this procedure allowed the asignment of the relative position of amino and ethylthio groups in dihydropyridines 3.

Table 1. 2-Amino-4-aryl-3,5-dicyano-6-ethylthiopyridines (2).

Compound No.	Ar^1	Rto. (%)	m.p. (°C)	IR(KBr) ν cm^{-1}	^{1}H-NMR(DMSO-d_6/TMS) δ (ppm)
2a	C_6H_5	53	233-234	3455, 3315, 3205 2210, 1615, 1580 1540, 1520, 1485	1.32 (t, 3H, J=7 Hz); 3.18 (q, 2H, J=7 Hz); 7.38 (5H); 7.80 (2H)
2b	4-MeO-C_6H_4	54	224-225	3430, 3330, 3220 2200, 1630, 1600 1570, 1540, 1505	1.32 (t, 3H, J=7 Hz); 3.18 (q, 2H, J=7 Hz); 3.78 (s, 3H); 6.98 and 7.31 (2d, AB system, J_{ab}=10 Hz); 7.73 (2H)
2c	4-Cl-C_6H_4	43	201-202	3470, 3340, 3200 2200, 1610, 1540 1485	1.30 (t, 3H, J=7 Hz); 3.17 (q, 2H, J=7 Hz); 7.43 (4H); 7.82 (2H)
2d	3-O_2N-C_6H_4	43	224-225	3460, 3320, 3210 2220, 1620, 1580 1525	1.33 (t, 3H, J=7 Hz); 3.20 (q, 2H, J=7 Hz); 7.5-8.4 (4H); 7.86 (2H)

All compounds gave satisfactory microanalyses C, ± 0.3; H, ± 0.4; N, ± 0.4; S, ± 0.2

Table 2. 2-Amino-4-aryl-3-arylmethyl-3,5-dicyano-6-ethylthio-3,4-dihydropyridines (3) and pyridines 4.

Compound No.	Ar^1	Ar^2	Rto. (%)	m.p. (°C)	IR (KBr) ν cm^{-1}	^{1}H-NMR (DMSO-d_6/TMS) δ(ppm)
3a(α+β)	C_6H_5	C_6H_5	71	142-150[a]		
3a(α)			17[d]	206-208[b]	3440, 3340, 3220, 2240, 2190 1515, 1540, 1510	1.31 (t, 3H, J=7 Hz); 2.63 and 3.29 (2d, AB system, J_{ab}=13 Hz); 3.08 (q, 2H, J=7 Hz); 4.28 (s, 1H); 6.8-7.7 (11H); 8.52 (b, 1H)
3a(β)			18[d], 36[e]	161-162[a]	3330, 3150, 2240, 2200, 1640 1560, 1520, 1495	1.31 (t, 3H, J=7 Hz); 3.14 (q, 2H, J=7 Hz); 3.19 (s, 2H); 3.78 (s, 1H); 6.8-7.5 (10H) ; 7.69 (b, 1H); 8.46 (b, 1H)
3b(α+β)	C_6H_5	4-Cl-C_6H_4	70	178-188[b]		
3b(β)			36	199-200[b]	3435, 3330, 3240, 2245, 2190 1635, 1555, 1520, 1490	1.30 (t, 3H, J=7 Hz); 3.12 (q, 2H, J=7 Hz); 3.20 (s, 2H); 3.85 (s, 1H); 6.7-8.0 (10H); 8.50 (s, 1H)
3c(α+β)	C_6H_5	4-MeO-C_6H_4	64	141-148[b]		
3c(β)			37	169-170[b]	3420, 3340, 3240, 2240, 2195 1650, 1560, 1530	1.30 (t, 3H, J=7 Hz); 3.06 (q, 2H, J=7 Hz); 3.07 (s, 2H); 3.68 (s, 4H); 6.6-7.5 (10H); 8.33 (b, 1H)
3d(α+β)	4-Cl-C_6H_4	4-Me-C_6H_4	59	192-200[a]		
3d(β)			29	195-196[a]	3310, 3140, 2240, 2200, 1635 1555, 1520, 1490	1.30 (t, 3H, J=7 Hz); 2.29 (s, 3H); 2.8-3.3 (4H); 3.82 (s, 1H); 6.8-7.6 (9H); 8.56 (s, 1H)
4a	C_6H_5	C_6H_5	20	159-160[c]	3490, 3370, 3210, 2210, 1615 1560, 1435, 1495, 1455, 1430	1.32 (t, 3H, H=7 Hz); 3.17 (q, 2H, J=7 Hz); 3.64 (s, 2H); 6.6-7.5 (12H)
4b	C_6H_5	4-Cl-C_6H_4	15	160-161[c]	3500, 3360, 3210, 2210, 1615 1550, 1490, 1450, 1420	1.31 (t, 3H, J=7 Hz); 3.20 (q, 2H, J=7 Hz); 3.61 (s, 2H); 6.7-8.6 (11H)
4c	C_6H_5	4-MeO-C_6H_4	12	151-152[c]	3500, 3360, 3200, 2200, 1615 1550, 1510, 1490, 1420	1.33 (t, 3H, J=7 Hz); 3.20 (q, 2H, J=7 Hz); 3.58 (s, 2H); 3.66 (s, 3H); 6.6-7.5 (11H)
4d	4-EtS-C_6H_4	4-Me-C_6H_4	19	142-144[c]	3500, 3360, 3210, 2210, 1620 1560, 1545, 1425, 1490, 1435	1.23 (t, 3H, J=7 Hz); 1.32 (t, 3H, J=7 Hz); 2.98 (q, 2H, J=7 Hz); 3.18 (q, 2H, J=7 Hz); 3.60 (s, 2H); 6.5-7.5 (10H)

Recrystallization solvent: a) Toluene-hexane; b) Ethyl acetate-hexane; c) Ethanol-hexane.

d) Yields of α and β pair of enantiomers isolated from the mixture 3a(α+β). e) Yield of the β isomer untransformed on the aromatization.

The microanalyses were in satisfactory agreement with the calculated values C, ± 0.4; H, ± 0.4; N, ± 0.4; S, ± 0.2.

To assign with any degree of certainty the absolute configuration of the pair of enantiomers α and β X-Ray analysis of the compound 3a(β) was done. Crystals of this product grown from toluene-hexane solution are monoclinic, space group $P2_1/n$ with unit cell constants a=11.289(4) Å, b=12.545(1) Å, c=14.153(9) Å, β=90.470(4)°, Z=4, V=2004.0(2) $Å^3$, D_x=1.234 $g.cm.^{-3}$

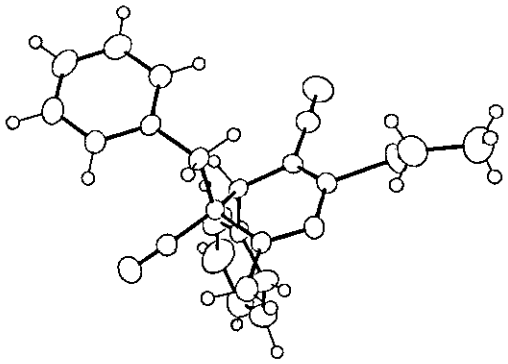


Fig. 1

The intensity data were measured on a CAD-4 automated diffractometer using MoKα radiation (λ=0.7107 Å). The crystal structure was determined using Multan 80 and refined to R=0.058 over observed reflections. Figure 1 shows the structure of the molecule.

EXPERIMENTAL

Melting points were measured with a Buchi (capillary) apparatus and are uncorrected. IR spectra were determined as KBr pellets with a Perkin-Elmer spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian FT-80 (80 Mz) and T-60 (60 Mz) spectrometers. Microanalyses were performed by the Analytical Department of the Institute of Organic Chemistry of CSIC, Madrid. Mass spectrum was obtained in a Varian Mat spectrometer. Column chromatography was performed with silica gel 60 (Merck) and basic alumina 60 (Merck).

2-Amino-4-aryl-3,5-dicyano-6-ethylthiopyridines (2). General procedure: To an ethanolic solution of sodium ethanothiolate (0.01 mol of sodium and 0.01 mol of ethanothiol in 45 ml of absolute ethanol), 0.01 mol of malononitrile and 0.01 mol of the corresponding 3-aryl-2-cyanopropenenitrile (1) were added. The mixture was stirred at room temperature for 45 min. The all crude product was isolated by combining the solid precipitated in the reaction medium with the isolated from the mothers liquors by the chromatography on a silica gel column using hexane-ethyl acetate (6:4) as eluent. Pure compounds 2a-d were obtained by recrystallization from ethanol.

2-Amino-4-aryl-3-arylmethyl-3,5-dicyano-6-ethylthio-3,4-dihydropyridines (3). General procedure: To a solution of 0.02 mol of sodium in 60 ml of 2-propanol, 0.02 mol of ethanothiol, 0.01 mol of the arylmethylmalononitrile and 0.01 mol of the 3-aryl-2-cyanopropenenitrile were added. The reac-

tion mixture was stirred at room temperature for 36 h and then the dark solution was poured over ice-water (200 ml) weakly acidified with hydrochloric acid. The precipitate was filtered and washed to neutral pH. The mixture of α and β isomers was separated by chromatography of the crude product through an alumina column with hexane-ethyl acetate (8:2) as the mobile phase.

For 3a, the two isomers α and β were separated by shaking 4.02 g of the mixture four times with ethyl ether (20 ml). The solid remaining in the flask was recrystallized from ethyl acetate-hexane yielding 0.93 g of the pure pair of enantiomers α. The residue obtained after removing the ether under reduced pressure yielded, by recrystallization from toluene-hexane, 1.02 g of pure β pairs of enantiomers.

2-Amino-4-aryl-3-arylmethyl-5-cyano-6-ethylthiopyridines (4) and dihydropyridines 3 (β isomer). General procedure: The mixture of α and β diastereoisomers isolated for each dihydropyridine 3 by the procedure above indicated was stirred and heated to 70-80 °C for 3 days in DMF (30 ml) with an excess of sodium ethanothiolate (molar ratio 1:10) generated "in situ" from equimolar amounts of sodium hydride and ethanothiol. Afterwards, the dark solution was poured over ice-water (150 ml). Pyridines 4 and dihydropyridines 3 (β isomer) were separated from the crude product by chromatography through an alumina column; the former eluated with hexane-ethyl acetate (9:1) and the latter with hexane-ethyl acetate (8:2).

By following this procedure, from 0.372 g (1 mmol) of 3a(α) isomer, 0.3 g of the pyridine 4a were obtained; yield: 87%. In the same conditions, but heating for 12 days, from 0.372 g (1 mmol) of 3a(β), 0.120 g of the same pyridine were obtained; yield: 35 %.

3-Benzyl-3,5-dicyano-6-ethylthio-4-phenyl-1,2,3,4-tetrahydropyridine (5a): To 30 ml of absolute ethanol 0.104 g (3 mmol) of sodium borohydride and 0.372 g (1 mmol) of 3a(α) were added. The reaction mixture was stirred under reflux for 3 h and then poured over ice-water (60 ml) acidified by hydrochloric acid. The precipitate formed, upon recrystallization from ethanol-hexane, yielded 0.294 g of colourless crystals, mp 153-154 °C (82%). Anal. Calcd for $C_{22}H_{21}N_3S$: C, 73.50; H, 5.89; N, 11.69. Found: C, 73.26; H, 6.15; N, 11.94; IR (KBr): 3350, 2230, 2170, 1555, 1495, 1450 cm^{-1}; ^{1}H-NMR (TFA-d_1) δ 1.44 (t, 3H, J=7 Hz), 2.8-3.2 (q, 2H, J=7 Hz), 2.21 and 3.03 (2d, 2H, J=13 Hz), 3.47 (s, 2H), 4.17 (s, 1H), 7.0-7.6 (10H); mass spectrum, m/e (relative intensity) 359 (M^+, 100), 330 (90), 268 (57), 155 (77), 144 (59), 91 (71).

ACKNOWLEDGMENTS

The authors are grateful to Dr. J. L. Balcázar, Facultad de Ciencias, Universidad de Alcalá de Henares, Madrid and Dr. F. Florencio, Instituto Rocasolano, Departamento de Rayos X, CSIC, Madrid for the X-Ray Analysis. This work was supported by Comisión Asesora de Investigación Científica y Técnica of the Presidencia de Gobierno of Spain.

REFERENCES

1. M. A. Cabrerizo and J. L. Soto, An. Quím., 1974, 70, 951.

2. L. Fuentes, A. Lorente and J. L. Soto, ibid., 1977, 73, 1359.
3. M. C. Chacón, M. C. Pardo, J. L. Soto, A. Lorente and L. Fuentes, J. Heterocyclic Chem., 1982, 19, 421.
4. L. Fuentes, J. J. Vaquero and J. L. Soto, An. Quím., 1980, 76, 68.
5. L. Fuentes, J. J. Vaquero and J. L. Soto, J. Heterocyclic Chem., 1982, 19, 1109.
6. L. Fuentes, A. Lorente and J. L. Soto, J. Heterocyclic Chem., 1979, 16, 273.
7. S. Kambe, K. Saito, A. Sakurai and H. Midorikawa, Synthesis, 1981, 7, 531.

Received, 3rd August, 1984