SYNTHESIS OF SUBSTITUTED PYRIDINES USING α,β-UNSATURATED NITRILES AND ACTIVE CYANO COMPOUNDS

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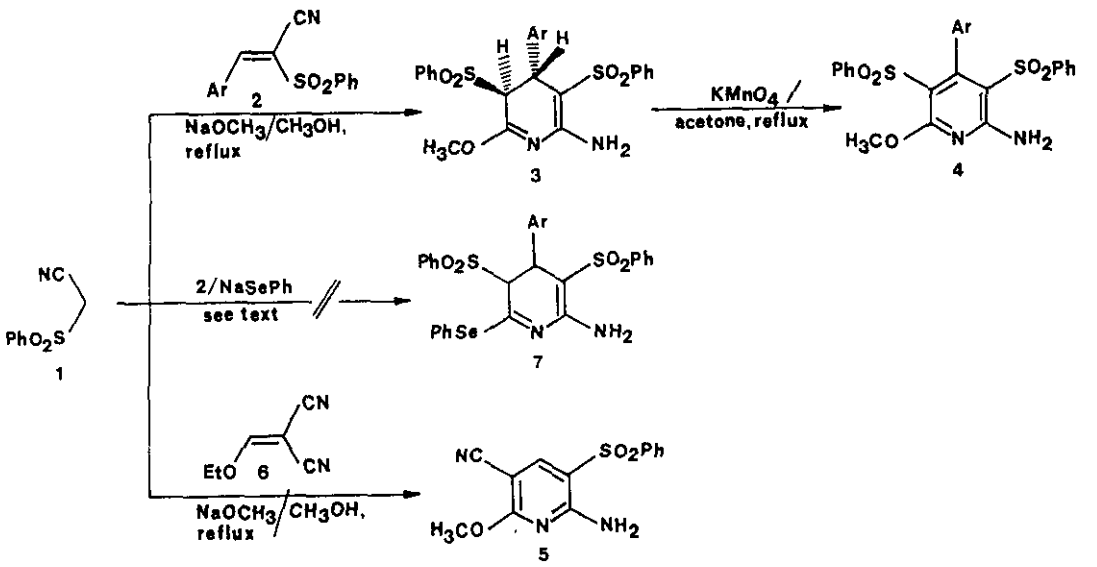
Abstract -- Several unknown 2-amino-substituted 3,4-dihydropyridines and pyridines are prepared by the reaction of α,β-unsaturated nitriles with active cyano compounds in the presence of a nucleophile reagent.

The emergence of α,β-unsaturated nitriles as a major class of compounds being exploited for transformation into heterocycles is evidenced by the increasing number of α,β-unsaturated nitrile related reports.[1-8]

We have previously reported our success in the preparation of 2-amino-substituted pyridines from α,β-unsaturated nitriles and active cyano compounds.[9-13] The reported potential antihypertensive activity of certain benzenesulfonylpyridines[14] have stimulated us to intend the preparation of a series of this type of compounds by condensation of the appropriate propenenitrile derivative with an active cyano compound in the presence of a nucleophile reagent.

As had been hoped, the reaction of benzenesulfonylacetonitrile (1) with α-benzenesulfonylcinnamonitriles (2) in methanol-sodium methoxide afforded the 3,4-dihydropyridines (3) which were quantitatively oxidized to the 2-amino-4-aryl-6-methoxy-3,5-dibenzenesulfonylpyridines (4) with potassium permanganate in refluxing acetone. On the other hand, 2-amino-5-cyano-6-methoxy-3-benzenesulfonylpyridine (5) was obtained when 1 reacts with 2-cyano-3-ethoxypropenenitrile (6) in the same above indicated reaction medium.

Attempts to prepare phenylselenodihydropyridines (7) by using sodium benzeneselenolate as nucleophile failed, the sole isolated product being the 6-methoxy-3,4-dihydropyridine (3) when the reaction was carried out in methanol or the corresponding ethoxy derivative if ethanol was employed as solvent. In 2-propanol, treatment



of 1 with 2 resulted in recovery of both starting materials together with diphenyldiselenide. Use of large excess of sodium benzeneselenolate and more forcing conditions resulted in decomposition of the starting materials.

In a final effort to effect the cyclization, the reaction was carried out in dimethylformamide since it is known that in this solvent the benzeneselenolate anion shows superior reactivity over that observed in protic solvents,[15,16] but again no cyclization reaction ocurred.

In contrast, the benzeneselenolate anion showed to be reactive as cyclization agent when malononitrile (8) and benzylidenemalononitrile (9) were used as reactants. Thus, the reaction of these compounds in ethanol, at room temperature, under nitrogen, afforded in moderate yield the 2-amino-2-aryl-3,5-dicyano-6-phenylselenopyridines (10).

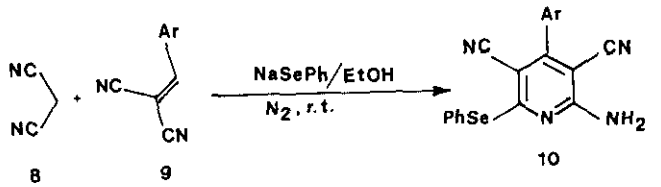


Table 1. Experimental data of Dihydropyridines 3 *and Pyridines* 4, 5 *and* 10 *prepared*

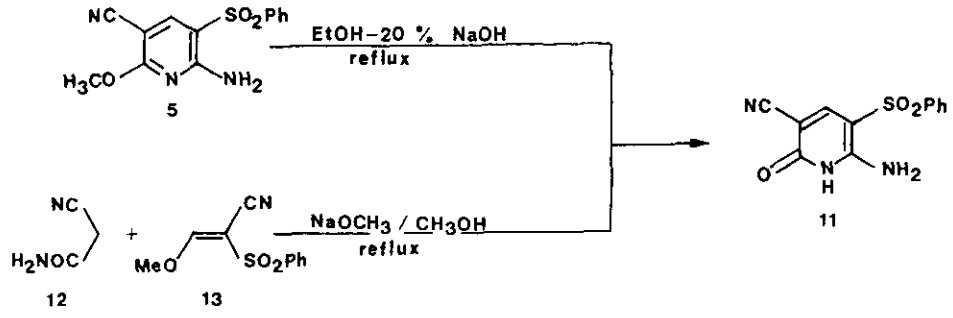
Product No	Ar	Yield (%)	Mp (°C)	Molecular formula	Analyses	Calc. % Found %	
					C	H	N
3a	C_6H_5	66	204 (MeOH)	$C_{24}H_{22}N_2O_5S_2$ (482.6)	59.73 59.61	4.59 4.70	5.80 5.42
3b	4-H_3CO-C_6H_4	74	204-206 (MeOH)	$C_{25}H_{24}N_2O_6S_2$ (512.6)	58.58 58.31	4.72 4.72	5.46 5.43
3c	4-Cl-C_6H_4	58	182-184 (n-PrOH)	$C_{24}H_{21}ClN_2O_5S_2$ (517.0)	55.75 55.50	4.10 4.11	5.42 5.36
3d	4-O_2N-C_6H_4	58	219 (n-PrOH)	$C_{24}H_{21}N_3O_7S_2$ (527.6)	54.64 54.73	4.01 3.99	7.96 7.78
4a	C_6H_5	98	177-178 (EtOH-H_2O)	$C_{24}H_{20}N_2O_5S_2$ (480.6)	59.98 60.08	4.19 4.17	5.83 5.60
4b	4-H_3CO-C_6H_4	96	172-173 (EtOH-H_2O)	$C_{25}H_{22}N_2O_5S_2$ (510.6)	58.81 58.90	4.34 4.02	5.48 5.33
4c	4-Cl-C_6H_4	96	231-232 (EtOH)	$C_{24}H_{19}ClN_2O_5S_2$ (515.0)	55.97 56.12	3.72 3.51	5.44 5.62
4d	4-O_2N-C_6H_4	95	262-263 (MeOH)	$C_{24}H_{19}N_3O_7S_2$ (525.6)	54.85 55.01	3.64 3.53	7.99 7.76
5	----	42	178-180 (EtOH)	$C_{13}H_{11}N_3O_3S$ (289.3)	53.97 53.77	3.83 3.75	14.52 14.91
10a	C_6H_5	40	217-218 (EtOH)	$C_{19}H_{12}N_4Se$ (375.3)	60.81 60.54	3.22 3.13	14.93 15.18
10b	4-H_3CO-C_6H_4	27	246-247 (EtOH)	$C_{20}H_{14}N_4OSe$ (405.3)	59.27 59.68	3.48 3.71	13.82 13.71
10c	3-O_2N-C_6H_4	36	224-225 (EtOH)	$C_{19}H_{11}N_5O_2Se$ (420.3)	54.30 54.64	2.64 2.71	16.66 16.69
10d	3-Pyridyl	35	299-300 (EtOH)	$C_{18}H_{11}N_5Se$ (376.3)	57.45 57.86	2.95 3.01	18.61 18.40

Table 2. Spectroscopic Data of Compounds 3, 4, 5 and 10.

Product No	Ir (KBr) ν (cm^{-1})	^{1}H-Nmr (TMS) [a,b] δ (ppm)	Ms m/z(relative intensity,%)
3a	3460,3340,1640,1610,1550,1445,1340, 1315,1290,1130,1080	[c] 3.75(s,4H); 4.70(s,1H); 5.57(br.,2H); 6.5-8.1(m, 15H); [d] 3.25, 3.66(two s,3H); 4.20(s,1H); 4.52, 4.66(two s,1H); 6.6-7.9(m,15H); 8.04(s,1H);8.54(s,1H)	482 (M^+, 1); 340 (100); 275 (87).
3b	3400,3310,3240,3200,1635,1605,1585, 1540,1505,1445,1315,1275,1130,1080	[d] 3.24, 3.63(two s,3H); 3.68(s,3H); 4.11, 4.18(two s,1H); 4.54, 4.65(two s,1H); 6.3-7.9(m,14H); 8.05(s,1H); 8.51(s,1H)	
3c	3470,3360,1640,1615,1550,1490,1450, 1345,1290,1135,1085	[c] 3.75(s,4H); 4.67(s,1H); 5.63(br.,2H); 6.5-8.0(m,14H). [d] 3.25, 3.68(two s,3H); 4.25(s,1H); 4.51, 4.68(two s,1H); 6.4-7.9(m,14H); 8.14(s,1H); 8.58(s,1H)	
3d	3470,3410,3360,3320,1640,1610,1540, 1510,1445,1345,1130,1080	[c] 3.76(s, 4H); 4.82(s,1H); 5.77(br.,2H); 6.9-7.9(m,14H) [d] 3.27, 3.70(two s,3H); 4.31, 4.41(two s,1H); 4.64, 4.83 (two s,1H); 6.8-8.4(m, 16H); 8.65(s,1H)	
4a	3460,3350,1605,1550,1525,1450,1360, 1315,1210,1160,1145,1100,1080	3.70(s, 3H); 6.6-7.7(m, 17H)	
4b	3460,3340,1580,1510,1460,1340,1290, 1240,1140,1060,1020	3.73(s, 3H); 3.76(s, 3H); 6.54, 6.68(A_2B_2, J=7 Hz, 4H); 7.1-7.8(m, 12H)	
4c	3460,3345,1600,1545,1505,1480,1440, 1340,1300,1260,1140,1080	3.75(s, 3H); 6.72, 6.98(A_2B_2, J=8 Hz, 4H); 7.1-7.8(m, 12H)	
4d	3460,3340,1590,1540,1510,1440,1340, 1300,1200,1150,1070	3.73(s, 3H); 7.2-8.1(m, 16H)	
5	3465,3350,2210,1605,1530,1465,1445, 1300,1150,1090	3.91(s, 3H); 7.4-8.1(m, 11H); 8.42(s, 1H)	
10a	3490,3470,3210,2210,1615,1545,1520, 1420,1260,1000	7.3-7.7(m, 10H); 7.82(br., 2H)	376 (M^+, 100); 375 (94)
10b	3480,3355,3230,2230,2210,1640,1610, 1550,1510,1420,1290,1260,1190,1020	3.82(s, 3H); 6.9-7.7(m, 9H); 7.76(br., 2H)	
10c	3400,3330,3240,2220,1650,1630,1550, 1520,1355,1260	7.3-8.5(m, 9H); 7.94(br., 2H)	
10d	3380,3320,3120,2220,1650,1580,1550, 1520,1430,1420,1270,1200,1065	7.2-8.2(M, 7H); 8.6-8.9(m, 2H); 7.90(br., 2H)	

[a] Compounds **4a-c** in $CDCl_3$, compounds **4d, 5, 10** in DMSO-d_6. [b] The insolubility of **3b** in $CDCl_3$ made necessary to obtain the ^{1}H-nmr in DMSO-d_6. In this solvent compounds **3a-d** are present in two isomeric forms. [c] In $CDCl_3$. [d] In DMSO-d_6.

The products here described were identified on the basis of their spectral data and relevant transformation reactions. Thus,the assignment of the amino and methoxy groups at the 2 and 6 positions in pyridine 5 was made by hydrolyzing 5 with aqueous sodium hydroxide to the pyridone 11, which was unambiguously synthesized by the condensation of cyanoacetamide (12) with 3-methoxy-2-benzenesulfonylpropenenitrile (13).



The lack of reactivity of 3a towards sodium borohydride in sharp contrast with the deamination suffered by certain 2-amino-3,4-dihydropyridines[13] in the same conditions, was interpreted by us, as a result owing to the structure of 6-amino-3,4-dihydropyridine for compounds 3, which was last confirmed by X-Ray diffraction analysis of 3b[17].

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 and are uncorrected. Mass spectra were recorded on a Varian Mat 711 instrument. Ir spectra were recorded on a Perkin-Elmer 700. ^{1}H-Nmr spectra were obtained on a Varian FT 80 and Bruker WP 60 WC spectrometers.

2-Amino-5-cyano-6-methoxy-3-benzenesulfonylpyridine (5): To a solution of sodium methoxide (1.08 g;20 mmol) in dry methanol (40 ml), benzenesulfonylacetonitrile (1.81 g; 10 mmol) and 2-cyano-3-ethoxypropenenitrile (6) (1.22 g; 10 mmol) are added. The mixture is heated under reflux with stirring for 5 h and then allowed to stand overnight at room temperature. The precipitate formed (1.8 g) is collected. The filtrate was poured into cool water (100 ml) and 0.6 g more of product is obtained. The combined solids are recrystallized from ethanol to yield 1.2 g of pyridine 5.

6-Amino-3-cyano-5-benzenesulfonyl-2-pyridone (11). Method A: To ethanol (5 ml) containing 20 % aqueous sodium hydroxide (2 ml) is added compound **5** (145 mg; 0.5 mmol). The mixture is heated under reflux with stirring for 1 h. The solution is poured over ice-water (50 ml) weakly acidified by hydrochloric acid. The precipitate formed is collected and recrystallized from ethanol; yield 110 mg (80 %), mp 280 °C (dec.).

Method B: A solution of sodium methoxide (108 mg; 2 mmol), 3-methoxy-2-benzenesulfonylpropenenitrile (446 mg; 2 mmol) and cyanoacetamide (168 mg; 2 mmol) in methanol (15 ml) is heated under reflux for 3 h, after which time the mixture is poured over ice-water (50 ml) and then acidified by hydrochloric acid. The precipitate thus formed is collected and recrystallized from methanol; yield 110 mg (20 %), mp 280 °C (dec.). Anal. Calcd for $C_{12}H_9N_3O_3S$: C, 52.37; H, 3.30; N, 15.27; S, 11.65. Found: C, 52.15; H, 3.50; N, 15.51; S, 11.41; ir (KBr): 3500-2600, 2230, 1650, 1310, 1285, 1145, 1095 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ=7.2-8.2 (m, 7H, H_{arom}+ NH_2); 8.32 (s, 1H); 11.59 (br., 1H, NH).

6-Amino-4-aryl-2-methoxy-3,5-dibenzenesulfonyl-3,4-dihydropyridines (3). General procedure: A mixture of sodium methoxide (5 mmol), benzenesulfonylacetonitrile (0.9 g; 5 mmol) and the respective α-benzenesulfonylcinnamonitrile (5 mmol) in absolute methanol (50 ml) is allowed to reflux for 24 h and then poured into ice-water. The precipitate is collected and recrystallized to afford **3**.

2-Amino-4-aryl-6-methoxy-3,5-dibenzenesulfonylpyridines (4). General procedure: A mixture of the corresponding 3,4-dihydropyridine **3** (1 mmol) and potassium permanganate (474 mg; 3 mmol) in acetone (30 ml) with water (drops) is heated under reflux for 3 h. The reaction mixture is then filtered through active carbon, the solvent evaporated and the residue recrystallized.

2-Amino-4-aryl-3,5-dicyano-6-phenylselenopyridines (10). General procedure: In a typical procedure, diphenyl diselenide (0.78 g; 2.5 mmol) is dissolved in absolute ethanol (15 ml) and nitrogen is bubbled through the solution for 1 h. Then, sodium borohydride (0.19 g; 5 mmol) is added in batches while stirring under nitrogen until the bright yellow solution turns colorless. After addition of malononitrile (0.33 g; 5 mmol) and the respective benzylidenemalononitrile (5 mmol) the reaction mixture was maintained at room temperature for 6 h, and then allowed to stand overnight in the refrigerator. The solid formed is separated by filtration and recrystallized.

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