PYRIDAZINES XXXI.[1,2] A FACILE SYNTHESIS OF 3-PYRIDAZINECARBONITRILES VIA 2-(4-TOLUENESULFONYL)-2,3-DIHYDRO-3-PYRIDAZINECARBONITRILES

Dedicated to Prof.K.Komarek on the occasion of his 60th anniversary

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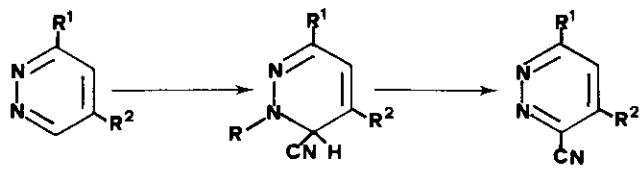
Abstract - Pyridazines 1a-c react with trimethylsilyl cyanide/4-toluenesulfonyl chloride to give 2-(4-toluenesulfonyl)-2,3-dihydro-3-pyridazinecarbonitriles (2a-c) in satisfactory yields. Conversion of compounds 2a-c into 3-pyridazinecarbonitriles 3a-c is conveniently accomplished by action of 1,8-diazabicyclo[5.4.0]undec-7-ene.

In the course of a program directed to the preparation of aza analogs of bio-active pyridine derivatives, straightforward syntheses for 3-pyridazinecarbonitrile and C-alkylated derivatives thereof were required. The preparation methods so far described are characterized by multi-step procedures and/or moderate yields.[3] We now wish to report on the facile synthesis of 3-cyano-pyridazines via sulfonyl Reissert compounds.

Pyridazine (1a) and 3-methylpyridazine (1b) on action of trimethylsilyl cyanide (tmsc)/benzoyl chloride give Reissert compounds in 24% and 41% yield, respectively.[4,5] Likewise, 4-methylpyridazine (1c) under similar conditions affords 2-benzoyl-4-methyl-2,3-dihydro-3-pyridazinecarbonitrile (4) in only 39% yield. In contrast, we now observed the formation of 2-(4-toluenesulfonyl)-2,3-dihydro-3-pyridazinecarbonitriles 2a-c in up to 84% yield, when 1a-c were reacted with tmsc/4-toluene-sulfonyl chloride according to a procedure reported by Veeraraghavan and Popp.[6] The novel compounds can be isolated conveniently from the reaction mixtures;[7] assignment of structures 2a-c rests on elemental analyses and spectroscopic data together with conversions into compounds 3a,[3a] 3b[3c] and 3c, respectively, described below.

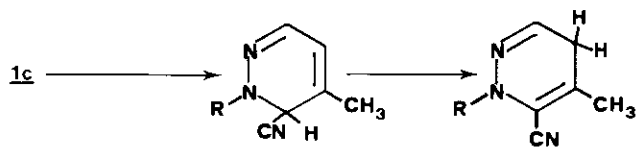
Interestingly, as shown by the formation of 2c, 4-methylpyridazine (1c) is attacked by 4-toluenesulfonyl chloride at N-2. In accordance, also in the reaction with tmsc/benzoyl chloride no indication of an attack at N-1 is observed. Like the Reissert compounds derived from 1a and 1b,[5] compound 4 shows a remarkable tendency to isomerize on silica gel surface, affording compound 5.[8] Compound 2a was found to be stable under these conditions, whereas NMR spectra revealed that compounds 2b and 2c are partially transformed into the pyridazine-carbonitriles 3b and 3c.



1a-c 2a-c 3a-c

R = 4-$CH_3C_6H_4SO_2$

a: $R^1 = R^2 = H$; b: $R^1 = CH_3$, $R^2 = H$; c: $R^1 = H$, $R^2 = CH_3$



4 5

R = C_6H_5CO

It is well documented in the literature [9] that N-alkylsulfonyl or N-arylsulfonyl Reissert analogs on action of a base afford aromatic carbonitriles in absence of a suitable electrophile. We now found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),recently employed in the preparation of 1-cyano-isoquinolines and 2-cyanoquinolines,[10] represents a suitable base for high yield conversions of 2-(4-toluenesulfonyl)-2,3-dihydro-3-pyridazinecarbonitriles into 3-pyridazinecarbonitriles.[11] Thus, the proposed reaction sequence permits the convenient preparation of compounds 3a and 3b (overall yield >75%), starting with commercially available materials. Furthermore, it offers an easy access to so far unknown 4-alkyl-3-pyridazinecarbonitriles as shown by the conversion of compound 1c into 4-methyl-3-pyridazinecarbonitrile (3c).

EXPERIMENTAL

Melting points (uncorrected) were determined with a Kofler hot-stage apparatus. IR spectra were recorded on a Jasco IRA-1 spectrometer (KBr disks; $\tilde{\nu}_{max}$ in cm^{-1}). ^{1}H-NMR spectra were recorded with a Varian EM-390 (90 MHz, $CDCl_3$ as solvent); chemical shifts (J in Hz) are reported in ppm downfield from internal TMS. Mass spectra were obtained on a Varian MAT CH-7. Light petroleum refers to the fraction with bp 50-70°C.Microanalyses were performed by the "Institut für Physikalische Chemie" (University of Vienna, Dr.Zak).

2-(4-Toluenesulfonyl)-2,3-dihydro-3-pyridazinecarbonitriles 2a-c

A mixture of 1a (25 mmol,2.00 g),1b or 1c[13] (25 mmol,2.35 g), respectively, $AlCl_3$ (10 mg) and tmsc (45 mmol,4.46 g) in anhydrous CH_2Cl_2 (30 ml) was stirred under dry nitrogen for 20 min. Then a solution of 4-toluenesulfonyl chloride (43 mmol,8.20 g) in anhydrous CH_2Cl_2 (60 ml) was added dropwise during 3 h. Stirring was continued for 5 h, then the solvent was removed in vacuo and the residue was treated with EtOH (50 ml) to give 2a (5.50 g, 84%), 2b (5.50 g, 80 %) or 2c (4.30 g, 63%), respectively, as crystalline solids; analytically pure samples were obtained by recrystallisation from ethyl acetate/ light petroleum (2a,2c) or EtOH/H_2O (2b).

Compound 2a: colourless crystals, mp 113-118°C. IR: 1360,1170 (SO_2N); NMR: 8.00 (part of an AA'BB'-system, J≈8,2H,C_6H_4-H), 7.60-7.30 (m,3H,C_6H_4-H,H-6), 6.30-6.10 (m,2H,H-5,H-4), 5.90-5.70 (m,1H,H-3), 2.40 (s,3H,CH_3); MS: M^+ at m/z 261 (3%), 91 (100%). Anal.calcd.for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08. Found: C, 55.23; H, 4.32; N, 16.13.

Compound 2b: colourless crystals, mp 118-120°C.IR:1360,1175 (SO_2N); NMR: 8.10-7.40 (AA'BB'-system, J≈8,4H,C_6H_4-H), 6.40-6.00 (m,2H,H-5,H-4), 5.70 (d,J=6,1H,H-3), 2.40 (s,3H,C_6H_4-CH_3), 2.10 (s,3H,CH_3); MS: M^+ at m/z 275 (1%), 105 (100%). Anal.calcd.for $C_{13}H_{13}N_3O_2S$: C,56.71; H, 4.76; N, 15.26. Found: C, 56.68; H, 4.84; N, 15.10.

Compound 2c: colourless crystals, mp 112-114°C (dec). IR: 1350,1165 (SO_2N); NMR: 8.00 (part of an AA'BB'-system,J≈8,2H,C_6H_4-H), 7.50-7.30 (m,3H,C_6H_4-H,H-6), 6.00-5.80 (m,1H,H-5), 5.60 (s,1H,H-3), 2.40 (s,3H,C_6H_4-CH_3), 2.00 (d,J=1,3H,CH_3); MS: M^+ at m/z 275 (9%),43 (100%). Anal.calcd.for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.72; H, 4.82; N, 15.21.

3-Pyridazinecarbonitriles 3a-c

A mixture of 2a (8 mmol,2.09 g), 2b or 2c (8 mmol,2.20 g), respectively, and DBU (10 mmol,1.52 g) in dry THF (20 ml) was stirred under dry nitrogen for 1 h. Then a saturated aqueous solution of NH_4Cl (20 ml) was added and the mixture poured into water (20 ml). The solution was extracted with ethyl acetate and the combined organic layers were filtered over silica gel, yielding 3a (771 mg, 92 %), 3b (942 mg,99%) or 3c (675 mg,71%), respectively, as crystalline solids; analytically pure samples were obtained by recrystallisation from toluene/light petroleum.

Compound 3a: colourless crystals, mp 43-44°C (Lit.[3a]: mp 43-44°C). IR: 2250 (C≡N); NMR: 9.45 (dd, $J_{5,6}$ ≈4, $J_{4,6}$≈1, 1H,H-6), 8.10-7.60 (m,2H,H-5,H-4); MS: M^+ at m/z 105 (63%), 50 (100%).

Compound 3b: colourless crystals, mp 86-87°C (Lit.[3c]:mp 90-91°C). IR: 2250 (C≡N); NMR: 7.90-7.40 (AB-system,J≈8,2H,H-5,H-4), 2.80 (s,3H,CH_3); MS: M^+ at m/z 119 (50%), 64 (100%).

Compound 3c: colourless crystals, mp 43-44°C. IR: 2260 (C≡N); NMR: 9.30 (d,J=5,1H,H-6), 7.50 (d,J=5, 1H,H-5), 2.60 (s,3H,CH_3); MS: M^+ at m/z 119 (50%), 63 (100%). Anal.calcd.for $C_6H_5N_3$:C, 60.50; H, 4.23; N, 35.27. Found: C, 60.33; H, 4.39; N,35.30.

Reaction of 2a with Sodium Borohydride

A mixture of 2a (1 mmol,261 mg), EtOH (5 ml) and $NaBH_4$ (1 mmol,38 mg) was stirred for 10 h. After addition of H_2O (15 ml), EtOH was removed in vacuo; the remaining mixture was extracted with CH_2Cl_2, the combined organic layers were dried and evaporated. The resulting oil then was subjected to medium pressure column chromatography (silica gel, ethyl acetate/light petroleum 1:3). Fraction I yielded 2-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-3-pyridazinecarbonitrile (85 mg,32%) as colourless crystals, mp 159-160°C. IR: 1360,1170 (SO_2N); NMR: 8.00-7.40 (AA'BB'-system, J≈8,4H,C_6H_4-H), 7.20-7.10 (m,1H,H-6), 5.40-5.20 (m,1H,H-3), 2.50 (s,3H,CH_3), 2.40-2.20 (m,4H,H-5,H-4); MS: M^+ at m/z 263 (3%), 91 (100%). Anal.calcd.for $C_{12}H_{13}N_3O_2S$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.87; H, 5.02; N, 16.06.

Fraction II yielded 3a (30 mg,29%), shown to be identical with 3a prepared as described above by tlc (silica gel, ethyl acetate/light petroleum 1:1) and ^{1}H-NMR data.

2-Benzoyl-4-methyl-2,3-dihydro-3-pyridazinecarbonitrile (4)

A solution of 1c[13] (25 mmol,2.35 g) in anhydrous CH_2Cl_2 (40 ml) was treated with tmsc (37 mmol, 3.66 g) and benzoyl chloride (37 mmol,5.20 g) in the presence of $AlCl_3$ (10 mg) according to a described procedure,[5] yielding 4 (2.20 g,39%) as a brown solid. An analytical sample was prepared by recrystallisation from ethyl acetate/light petroleum: yellow needles, mp 104-110°C. IR: 1660 (C=O); NMR: 7.90-7.40 (m,5H,C_6H_5-H), 7.20 (d,J=4,1H,H-6), 6.05 (d,J=4,1H,H-5), 5.90 (s,1H,H-3), 2.10 (s,3H,CH_3); MS: M^+ at m/z 225 (1%), 107 (100%). Anal.calcd.for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.14; H, 5.15; N, 18.37.

Conversion of Compound 4 into the 2,5-Dihydropyridazine derivative 5

a) Compound 4 (1 mmol,225 mg) was repeatedly subjected to chromatography on silica gel, using ethyl acetate/ light petroleum (1:4) as the eluent. Evaporation of the solvent, followed by recrystallisation from ethyl acetate/light petroleum yielded 5 (50 mg,22%) as orange crystals, mp 125-127°C (dec). IR: 2240 (C≡N), 1660 (C=O); NMR: 7.90-7.30 (m,5H,C_6H_5-H), 7.00-6.90 (X-part of an ABX-system,1H,H-6), 3.10-2.90 (AB-part of an ABX-system,2H,H-5), 2.15 (s,3H,CH_3); MS: M^+ at m/z 225 (5%), 105 (100%). Anal.calcd.for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.22; H, 5.10; N, 18.60.

b) A mixture of 4 (1 mmol,225 mg) and DBU (1.4 mmol,214 mg) in CH_2Cl_2 (10 ml) was stirred for 10 h. The solvent was distilled off in vacuo and the residue was chromatographed on silica gel (ethyl acetate/CH_2Cl_2 1:4). The so obtained oil was crystallized from ethyl acetate/light petroleum, yielding 90 mg of 5 (40%).

REFERENCES AND NOTES

1) Pyridazines XXX: N.Haider and G.Heinisch, Synthesis, in press.

2) Presented in part at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Ontario, Canada 1985.

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5) W.Dostal and G.Heinisch, J.Heterocyclic Chem., in press.

6) S.Veeraraghavan and F.D.Popp, J.Heterocyclic Chem., 1981, 18, 775.

7) Since compounds 2a-c are of low stability at ambient temperature, it is recommended to employ the crude products without further purification in the preparation of compounds 3a-c.

8) This 2,5-dihydropyridazine derivative is formed also on treatment of 4 with 1,8-diazabicyclo-[5.4.0]undec-7-ene (see experimental).

9) For a recent review see: J.V.Cooney, J.Heterocyclic Chem., 1983, 20, 823.

10) D.L.Boger, C.E.Brotherton, J.S.Panek and D.Yohannes, J.Org.Chem., 1984, 49, 4056.

11) Initial attempts to convert compounds 2 into carbonitriles 3 by employment of $NaBH_4$ as a base [12] met with limited success, since in the reactions with N-(4-toluenesulfonyl)-2,3-dihydro-3-pyridazinecarbonitriles the reducing properties of this reagent leeds to formation of substantial amounts of tetrahydropyridazines as shown by the isolation of 2-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-3-pyridazinecarbonitrile in 32 % yield (see experimental). Accordingly, under these conditions, which were successfully used in a high yield synthesis of isoquinaldonitrile,[12] the desired compounds 3a-c are obtained only in moderate yields.

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