NOVEL SYNTHESES OF FUSED-IMIDAZOLES III.[1] SIMPLIFIED CONSTRUCTION OF THE IMIDAZO[2,1-b]THIAZOLINE SYSTEM

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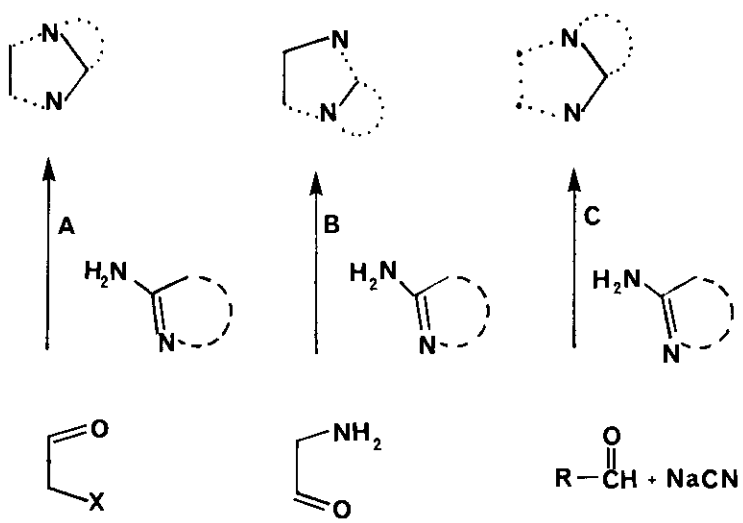
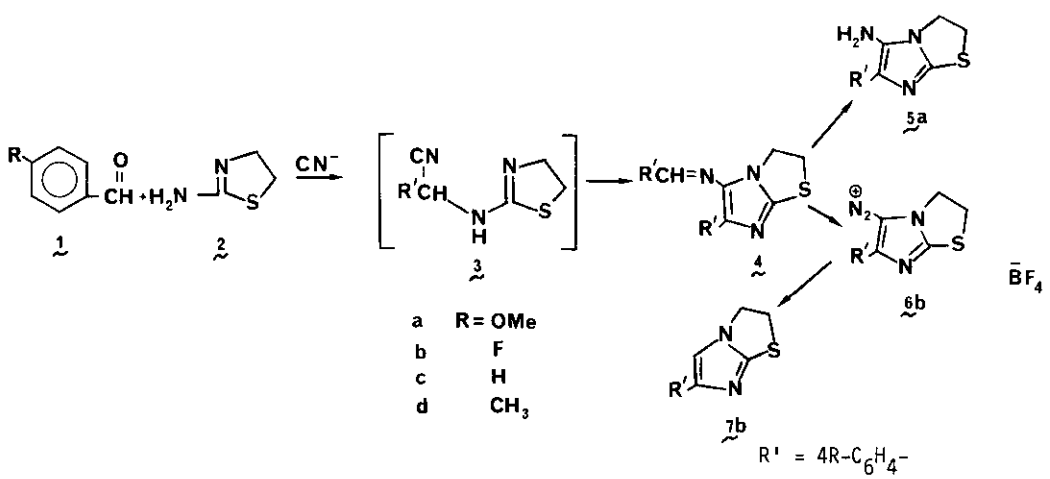
Abstract - A simple, convenient synthesis of 5-aminoimidazo[2,1-b]thiazolines is described, based on the condensation of aminothiazoline with aryl carboxaldehydes in the presence of potassium cyanide.

In connection with our ongoing interest in drugs containing the imidazole moiety[1] we have been exploring various approaches toward this heterocycle. We have noted with interest that despite the biological importance of imidazole derived molecules in nature, there are few new approaches to imidazoles or fused imidazoles found in the literature.[2] For example, the most commonly utilized synthesis of the imidazole moiety still involves initial construction of the C4-C5 bond and its subsequent condensation with the unit containing N1-C2-N3, as shown via transformation A, or alternatively, the construction of C4-C5-N1 and its annulation with C3-N4 via path B.



In our investigations of novel modes of imidazole ring construction we have discovered a highly effective strategy which is capable of the separate and simultaneous introduction of the C4 and C5 substructural moieties of the imidazole nucleus, i.e., the transformation shown via path C. This route offers the potential of a short route to amino substituted imidazole derivatives, compounds that were approached previously via primary synthesis of the parent heterocycle, followed by a two step nitration/reduction procedure,[3a] or by use of more complex precursors.[3b] Our approach is similar in concept to well known syntheses of aminopyrimidines based on nucleophilic cyclization of internal nitrile residues.[4] A similar procedure with the use of amidines has been suggested by Taylor[5], however, no relevent literature references could be found. It was applied to the synthesis of 5-aminoimidazo[1,2-b]thiazolines as described below.

Aryl carboxaldehydes 1 (R = OMe, F, H, CH_3) were reacted with cyanide and aminothiazoline 2, at room temperature to furnish Schiff base functionalized 5-aminoimidazo[1,2-b]thiazolines 4 in one step and fair to excellent yields. The driving force for the reaction is most probably the cyclization of the initially formed cyanoamine intermediate because neither Schiff base adducts of the aminothiazoline, nor the open cyanoamines 3 could be detected in the reaction. In an attempt to explore the generality of the reaction benzaldehydes with p-cyano or alkoxycarbonyl substituents were examined. In these instances, however, no imidazole related products could be isolated. The Schiff bases could be readily hydrolyzed to aminoimidazoles 5a, b by acid, or converted directly to diazonium salts 6b, by treatment with $NaNO_2$ and fluoroboric acid.



We were able to remove the diazo functionality and obtain 6-(4-fluorophenyl)imidazo[1,2-b]-thiazole 7b,[6] from 6b by treatment with $TiCl_3$/HCl,[7] the scope of this reaction was not further explored. The transformations shown in Scheme I underscore the potential of this new methodology for the synthesis of substituted fused imidazoles or 5-aminoimidazoles and the scope of the reaction is currently being evaluated in our laboratories.

EXPERIMENTAL

Infrared spectra were obtained in Nujol mulls, or in KBr pellets on a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrophotometer with tetramethylsilane as internal standard. Melting points are uncorrected.

5-Arylideneamino-6-arylimidazo[1,2-b]thiazole (4). 100 mM of the required benzaldehyde was reacted with 50 mM of aminothiazoline and 50 mM sodium cyanide in 30 ml of methanol and 20 ml of water at room temperature overnight. The yellow crystalline precipitate was filtered and recrystallized from chloroform-ether.

p-Anisaldehyde furnished compound 4a in 75% yield; mp 162-164°C; ir (Nujol, cm^{-1}): 2899, 1595, 1497, 1481, 1449, 1235, 1031, 840; nmr ($CDCl_3$, δ): 8.1 (s, 1H, CH = N), 7.85 (d, 2H, J = 12.0 Hz, Ar), 7.55 (d, 2H, J = 12.0 Hz, Ar), 6.80 (d, 4H, J = 12.0 Hz, Ar), 4.10 (m, 2H, CH_2), 3.80 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 3.75 (m, 2H, CH_2). Anal. calcd. for $C_{20}H_{19}N_3O_2S$: C, 65.76; H, 5.24; N, 11.50. Found: C, 66.03; H, 5.41; N, 12.04.

4-Fluorobenzaldehyde furnished compound 4b in 80% yield; mp 195-196.5°C; ir (Nujol, cm^{-1}): 1600, 1539, 1508, 1495, 1468, 1315, 1228, 1221, 827, 750, 695; nmr ($CDCl_3$, δ): 8.30 (s, 1H, CH = N), 7.80 (m, 4H, Ar), 7.05 (m, 4H, Ar), 4.25 (d, 2H, J = 5.3 Hz, CH_2), 3.78 (d, 2H, J = 5.3 Hz, CH_2). Anal. calcd. for $C_{18}H_{13}F_2N_3S \cdot 0.25\ H_2O$: C, 62.34; H, 3.93; N, 12.15. Found: C, 62.34; H, 3.96; N, 12.38.

Benzaldehyde furnished compound 4c in 59% yield; mp 175-177°C; ir (Nujol, cm-1): 1475, 1430, 1315, 1250, 1180, 1140, 1060, 1020, 940, 775, 750, 705, 685; nmr ($CDCl_3$, δ), 8.55 (s, 1, CH), 8.13 (m,Ar), 7.90 (m,Ar), 7.50 (m, Ar), 4.35 (m, 2, CH_2), 3.90 (m, 2, CH_2). Anal. calcd. for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76. Found: C,70.41; H, 5.03; N, 13.68.

p-Tolualdehyde furnished compound 4d in 20% yield, mp 175-177°C; ir (Nujol, cm-1): 1490, 1470, 1450, 1405, 1375, 1320, 1255, 1190, 1170, 1005, 825, 810, 745, 725, 660, nmr ($CDCl_3$, δ), 8.4 (5, CH), 8.0, 7.9, 7.75, 7.65 (s, 1 each, Ar), 7.25 (m, 4 Ar), 4.25 (m, 2, CH_2), 3.85 (m, 2, CH_2), 2.50 (s, 3, CH_3), 2.4 (s, 3, CH_3). Anal. calcd. for $C_{20}H_{19}N_3S$: C, 72.04; H, 5.74; N, 12.60. Found: C, 71.84; H, 5.84; N, 12.53.

5-Amino-6-arylimidazo[1,2-b]thiazoles (5a,b). 8.0 mM of the Schiff bases were covered with 100 ml of 10% hydrochloric acid solution and 25 ml of methanol. The mixture was extracted exhaustively with ether until the presence of aldehyde was no longer observable in the ethereal extract by TLC. The yellow crystalline residue was filtered and furnished pure hydrochloride salt of the amine in 95% yield. 5a hydrochloride had mp 210°C; ir (Nujol, cm^{-1}): 3333, 1575, 1550, 1504, 1449, 1370, 1250, 1198, 1156, 870; nmr (DMSO, δ): 7.53 (d, 2H, J = 13.0 Hz, Ar), 7.10 (d, 2H, J = 13.0, Ar), 4.33 (m, 4H, CH_2CH_2), 3.86 (s, 3H, CH_3O). Anal. calcd. for $C_{12}H_{13}N_3O \cdot HCl$: C, 57.26; H, 5.60; N, 16.69. Found: C, 56.82; H, 5.45; N, 16.42. The acetyl derivative was prepared in 87% yield by treatment with acetic anhydride in pyridine, recrystallyzed from ethanol-ether, mp 182-183.5°C; ir (Nujol, cm^{-1}): 3226, 1639, 1587, 1449, 1250, 1026, 840; nmr ($CDCl_3$, δ): 8.80 (s, 1H, NH), 7.50 (d, 2H, J = 9.0 Hz, Ar), 6.80 (d, 2H, J = 9.0 Hz, Ar), 3.75 (s, 3H, CH_3O), 3.70 (m, 4H, CH_2CH_2), 2.00 (s, 3H, CH_3CO). Anal. calcd. for $C_{14}H_{15}N_3O_2S$: C, 58.17; H, 5.23, N, 14.53. Found: C, 58.06; H, 5.34; N, 14.42. 5b hydrochloride had mp 200°C; ir (Nujol, cm^{-1}): 3278, 3125, 1481, 1449, 1351, 1235, 1149, 840; nmr (DMSO, δ): 7.80 (m, 2H, Ar), 7.30 (m, 2H, Ar), 4.35 (m, 4H, CH_2CH_2). Anal. calcd. for $C_{11}H_{10}FN_3S \cdot HCl$: C, 48.66; H, 4.08; N, 14.48. Found: C, 48.75; H, 4.26; N, 15.39. The acetyl derivative was prepared in 90% yield with acetic anhydride in pyridine, recrystallyzed from chloroform-ether (1:1), mp 222-224°C; ir (Nujol, cm^{-1}): 3125, 1613, 1563, 1481, 1361, 1307, 1220, 1149, 837; nmr ($CDCl_3$, δ); 7.60 (m, 2H, Ar), 7.05 (m, 2H, Ar) 3.90 (m, 4H, CH_2CH_2), 2.15 (s, 3H,CH_3CO). Anal. calcd. for $C_{13}H_{12}FN_3OS$: C, 56.30; H, 4.36; N, 15.15. Found: C, 56.10; H, 4.42; N, 14.73.

Formation of Diazo Compound 6b. 5 g (13.7 mM) of the Schiff base 4b was covered with 45 ml of ethanol. The reaction was cooled in an ice bath with stirring, 8 ml of tetrafluoroboric acid was added followed by a cold solution of 1.1 g (15.9 mM) of sodium nitrite in 10 ml of water. After 10 min, 10 ml of concentrated HCl at 0°C was added and the reaction was stirred for 1 h at ice bath temperature and for 1 h at room temperature. Filtration, followed by trituration with ether yielded the diazonium salt as a rust colored solid, (3.7g, 78%), mp 99°C (dec); ir (KBr, cm^{-1}): 2120, 1590, 1515, 1445, 1420, 1400, 1315, 1290, 1250, 1200, 1155, 1050, 830, 760, 720, 690, 640, 620; nmr (CD_3CN, δ): 7.80 (m, 2H, Ar), 7.25 (m, 2H, Ar), 4.55 (d, 2H, J = 6.2 Hz, 2, CH_2), 4.05 (d, 2H, J = 6.2 Hz, CH_2). Anal. calcd. for $C_{11}H_8N_4SBF_5 \cdot H_2O$: C, 37.52; H, 2.86. Found: C, 37.86; H, 3.01.

6-(4-Fluorophenyl)imidazo[1,2-b]thiazoline (7b). 1.0 ml of 15% $TiCl_3$ at 0°C was treated with 1.0 ml of acetonitrile. To this stirred solution was added 154 mg of 6b dissolved in 3 ml of acetonitrile. After 1 h the solution was basified with 5% potassium carbonate to pH 9. The reaction mixture was extracted with methylene chloride, dried over sodium sulfate and the solvent removed in vacuo to yield 7b (85 mg, 89%), mp 151-153°C; ir (KBr, cm^{-1}): 1450, 1400, 1350, 1300, 1240, 1140, 1080, 920, 830, 745, 670; nmr ($CDCl_3$, δ): 7.50 (m, 2H, Ar), 6.90 (m, 2H, Ar), 7.02 (s, 1H, C = CH) 4.05 (d, 2H, J = 6.0 Hz, CH_2), 3.65 (d, 2H, J = 6.0 Hz, CH_2). Anal. calcd. for $C_{11}H_9FN_2S$: C, 59.98; H, 4.12; N, 12.72. Found: C, 60.02; H, 4.29; N, 12.68.

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