Improved Synthesis of Imidazole-2-carboxaldehyde, Imidazole-2-carboxylic Acid, and Ethyl Imidazole-2-carboxylate†

Eduviges Galeazzi, Angel Guzmán, and Jose Luis Nava‡

Syntex, S.A. de C.V., Divisíon de Investigacíon Apartado Postal 272 (CIVAC), 62500 Jiutepec, Morelos, Mexico

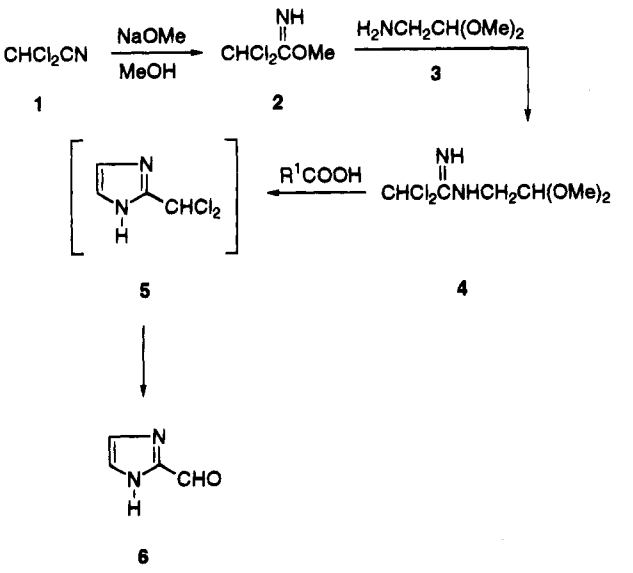
Yanzhou Liu, Michael L. Maddox, and Joseph M. Muchowski*

Syntex Research, Institute of Organic Chemistry, 3401 Hillview Avenue, Palo Alto, California 94304

Received October 3, 1994

In connection with another study,[1] we required substantial amounts of imidazole-2-carboxaldehyde (**6**, Scheme 1) as an intermediate. Several syntheses of this compound have been reported[2–6] and it is commercially available (Aldrich). None of the published syntheses is convenient to carry out on a large scale, and the commercial material is very expensive (>$25/g). It occurred to us that **6** ought to be preparable by hydrolysis of 2-(dichloromethyl)imidazole (**5**) which, in principle, should be obtainable by a Cornforth–Huang[7] type of synthesis from aminoacetaldehyde dimethyl acetal (**3**) and the imidate **2** derived from dichloroacetonitrile (**1**). The generation of **6** in this way is precedented by the facile conversion of the remarkably stable 2,3,6,6-tetrachloro-1,3-diazafulvene[8] into 4,5-dichloroimidazole-2-carboxylic acid and various esters thereof[9] as well as by an analogous series of reactions with 2-(trifluoromethyl)imidazoles,[10,11] including 2-(trifluoromethyl)imidazole itself.[11] In addition, intermediates closely related to the amidine **4** have been utilized in the synthesis of the aldehyde **6**[4] and ethyl imidazole-2-carboxylate (**11**).[12] This publication describes significant improvements in the synthesis of imidazole-2-carboxaldehyde (**6**), imidazole-2-carboxylic acid (**10**), and ethyl imidazole-2-carboxylate (**11**) based on the above precedents. It also discusses the temperature dependent ^{1}H NMR spectra of these compounds in dipolar aprotic solvents.

Scheme 1



When an equimolar mixture of the crude imidate **2** and aminoacetaldehyde dimethyl acetal (**3**) was heated neat at 80 °C for *ca.* 2 h, the crystalline amidine **4** was isolated in high yield. This amidine, upon heating at 70–80 °C (20 h) in formic acid solution and subsequent aqueous hydrolysis, was converted into imidazole-2-carboxaldehyde (**6**) in essentially quantitative yield (85–87% overall). The use of trifluoroacetic acid (TFA) at reflux temperature in the cyclization reaction gave **6** in *ca.* 70% yield. It is assumed that **6** is formed by hydrolysis of the primary cyclization product **5**, but no attempt was made to establish the intermediacy of this compound. This is the most efficient and convenient synthesis of **6** reported to date. It has the additional advantage that both starting materials are relatively inexpensive (*ca.* $0.5/g).[13]

The efficient generation of **6** described above, encouraged us to reexamine the reported cyclization[12] of the trichloroacetamidine **8** which was prepared in nearly quantitative yield merely by mixing equimolar amounts of trichloroacetonitrile and aminoacetaldehyde dimethyl acetal. After 24 h in neat TFA at room temperature, the amidine **8** is no longer present (Scheme 2). Evaporation of the solvent *in vacuo* gave a glassy residue which consisted mainly of 2-(trichloromethyl)imidazole (**9**) as determined by mass spectrometry (no incorporation of trifluoroacetate). It has not yet been possible to purify **9**, but its reactions leave no doubt about its identity. For example, heating the crude material with ethanolic sulfuric acid gave the ethyl ester **11** in 65% yield.[14] It was much more convenient, however, to simply add excess ethanol or water to the TFA solution of **9**, and after heating at reflux temperature (1–4 h) ethyl imidazole-2-carboxylate and imidazole-2-carboxylic acid were obtained in 78 and 93% yields, respectively. This is the most expeditious and efficacious synthesis of **10** and **11** reported to date.

† Contribution No. 904 from the Syntex Institute of Organic Chemistry.

‡ Research completed in partial fulfillment for the degree of "Quimico" in the Universidad Autonoma de Hidalgo, Instituto de Ciencias Exactas, HGO. 1994.

(1) Galeazzi, E.; Guzmán, A.; Rodriguez, G.; Muchowski, J. M. *J. Org. Chem.* **1993**, *58*, 974.

(2) Schubert, H.; Rudorf, H-D. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 674.

(3) Iversen, P. E.; Lund, H. *Acta Chem. Scand.* **1966**, *20*, 2649.

(4) English, J. P.; Berkelhammer, G. U.S. Patent 3,812,189, 1974; Chem. Abstr. **1974**, *81*, 49293j.

(5) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381.

(6) Bastiaansen, L. A. M.; Van Lier, P.; Godefroi, E. F. *Org. Synth.* **1981**, *60*, 72. Bastiaansen, L. A. M.; Godefroi, E. F. *J. Org. Chem.* **1978**, *43*, 1603.

(7) Conforth, J. W.; Huang, H. T. *J. Chem. Soc.* **1943**, 1960.

(8) Beck, G.; Döring, F.; Heitzer, H.; Holtschmidt, H. Ger. Offen. 2,454,326, 1976; *Chem. Abstr.* **1976**, *85*, 63071z.

(9) Beck, G.; Sasse, K.; Heitzer, H.; Eue, L.; Schmidt, R. R.; Scheinpflug, H.; Hammann, I.; Brandes, W. Ger. Offen. 2,634,053, 1978; *Chem. Abstr.* **1978**, *88*, 190831j.

(10) Kimoto, H.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 4381.

(11) Kimoto, H.; Cohen, L. A. *J. Org. Chem.* **1979**, *44*, 2902. Although the hydrolysis of 2-(trifluoromethyl)imidazole to imidazole-2-carboxylic acid is a high yielding process, 2-(trifluoromethyl)imidazole is available in exceedingly low yield (<5%) in two steps from imidazole.[10]

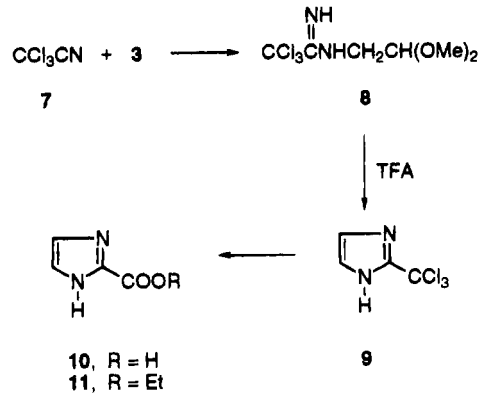
(12) Berkelhammer, G.; Gastrock, W. H.; Remers, W. A.; Tomenfeik, A. S.; Weiss, M. J. U.S. Patent 3,600,399, 1971; *Chem. Abstr.* **1971**, *75*, 18322h.

(13) English and Berkelhammer[4] have described a closely related synthesis of **6** based on the much more costly diethoxyacetonitrile ($13/g, Aldrich) which, however, proceeded in only about 50% overall yield.

(14) Berkelhammer, et al.[12] reported a 33% yield of **9b** using concentrated sulfuric acid in the cyclization step.

0022-3263/95/1960-1090$09.00/0

Scheme 2



The ^{1}H NMR spectra of **6** and **11** are interesting in that they show significant solvent and temperature dependence. For example, in CD_3OD or $CDCl_3$ H-4 and H-5 of the ester **11** appear as temperature independent (at least in $CDCl_3$) singlets at δ 7.25 and 8.03, respectively. The equivalence of H-4 and H-5 under these conditions must be a consequence of a rapid intermolecular proton exchange between N-1 and N-3 of the imidazole nucleus. In contrast, in dipolar aprotic strong H-bond accepting solvents such as DMSO-d_6 or DMF-d_7 H-4 and H-5 appear as a pair of equiintense singlets which coalesce to a single absorption on heating. For example, for the aldehyde **6** these protons appear as two broad singlets in DMSO-d_6 at δ 7.36 and 7.43[15] and two sharp singlets at δ 7.32 and 7.60 in DMF-d_7. Similarly, the ester **11** showed two broad singlets at δ 7.14 and 7.35 in both solvents.[15] Under these conditions of slow exchange[17] the inherent dissymmetry present in **6** and **11** becomes visible and the rotational barriers about the imidazolyl–CO bond can be measured. In DMF-d_7 **6** and **11** have coalescence temperatures T_c of 361 and 329 K with $\Delta G^{\ddagger}$ = 16.9 and 15.4 kcal/mol, respectively. These rotational barriers are significantly higher than for N-substituted pyrrole-2-carboxaldehydes (*ca.* 11 kcal/mol)[18] but are not unreasonable for such compounds. An analogous phenomenon has been reported by Papadopoulos and Holstein[19] who showed that the ^{13}C NMR spectra of imidazole-2-carboxylic acid and various imidazole-2-carboxamides in DMSO-d_6 show distinct absorptions for C-4 and C-5 which coalesce to a singlet on warming.

Experimental Section

Proton magnetic resonance spectra were recorded at 200, 300, or 500 MHz and are reported in ppm (δ) downfield from internal tetramethylsilane. See Antonio et al.[20] for general information regarding the instrumentation used to obtain the physical constants of the compounds described herein.

***N*-(2,2-Dimethoxyethyl)dichloroacetamidine (4).** A 1 M sodium methoxide solution (20 mL, 20 mmol) was added dropwise to a stirred solution of dichloroacetonitrile (13.7 g, 124.5 mmol) in anhydrous methanol (20 mL) cooled in a dry ice–acetone bath. After 1.5 h at −78 °C and 1 h at room temperature, the solvent was removed *in vacuo* at ambient temperature to give the crude imidate (15 g) as an oil; IR ($CHCl_3$) 3330, 1670 cm^{-1}; ^{1}H NMR (200, $CDCl_3$) δ 3.87 (s, 3H), 5.97 (s, 1H), 8.27 (bs, 1H, exchanged with D_2O).

A mixture of the above imidate and aminoacetaldehyde dimethyl acetal (11.1 g, 105.7 mmol) was heated in an oil bath at 80 °C (internal temp) for 1.45 h. The crude product was taken up in ethyl acetate and subjected to purification by column chromatography on Florisil using ethyl acetate to elute the crystalline product **4** (20.1 g, 88% yield): mp 85–89 °C; IR ($CHCl_3$) 3494, 3328, 1638, 1601 cm^{-1}; ^{1}H NMR (200, $CDCl_3$) δ 3.33 (d, 2H, J = 5.3 Hz), 3.44 (s, 6H), 4.56 (t, 1H, J = 5.3 Hz), 6.12 (s, 1H). Anal. Calcd for $C_6H_{12}Cl_2N_2O_2$: C, 33.50; H, 5.62; Cl, 32.96; N, 13.02. Found: C, 33.34; H, 5.50; Cl, 32.73; N, 12.71.

Imidazole-2-carboxaldehyde (6). A solution of the amidine **4** (5.00 g, 23.2 mmol) in 95–97% formic acid (10 mL) was heated in an oil bath at 70–80 °C for 20 h. The solvent was removed *in vacuo*, benzene was added to the residue, and the mixture was evaporated to dryness (repeated three times). The residue was dissolved in water (9 mL), and solid sodium bicarbonate was added to raise the pH of the solution to 8. The aldehyde precipitated immediately. The mixture was cooled in the refrigerator overnight, and the product was collected by filtration and dried *in vacuo*. The imidazole-2-carboxaldehyde obtained in this way (2.21 g, 99% yield) was pure by ^{1}H NMR spectroscopy. A small amount on sublimation at 80–90 °C/2 mm gave the analytically pure aldehyde, mp 204–205 °C, lit.[6] mp 206–207 °C.

***N*-(2,2-Dimethoxyethyl)trichloroacetamidine (8).** Aminoacetaldehyde dimethyl acetal (10.9 mL, 10.5 g, 100 mmol) was added dropwise to a stirred solution of trichloroacetonitrile (14.4 g, 100 mmol) in THF (25 mL) at −35 to −40 °C (argon atmosphere). The cooling bath was removed and when the temperature reached ambient, the reaction mixture was diluted with ethyl acetate, and the solution was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave an oil (24.55–24.7 g, 98–99% yield) which was pure and which crystallized spontaneously: mp 44–45 °C; IR ($CHCl_3$) 3442, 3343, 1671, 1643 cm^{-1}; ^{1}H NMR (200, $CDCl_3$) δ 3.45 (s, 6H), 3.50 (d, 2H, J = 5.3 Hz), 4.57 (t, 1H, J = 5.3 Hz), 5.47 (bs, 1H, lost with D_2O), 7.35 (bs, 1H, lost with D_2O). Anal. Calcd for $C_6H_{11}Cl_3N_2O_2$: C, 28.87; H, 4.42; Cl, 42.62; N, 11.22. Found: C, 28.95; H, 4.49; Cl, 42.53; N, 11.02.

2-(Trichloromethyl)imidazole (9) and Ethyl Imidazole-2-carboxylate (11). The amidine **8** (2.00 g, 8.0 mmol) was added at 0 °C to TFA (2 mL). The solution was then left at room temperature for 24 h. The solvent was removed *in vacuo*, benzene was added to the residue, and the mixture was evaporated to dryness *in vacuo* (repeated once) to give impure **9** as a glass: ^{1}H NMR (200, DMSO-d_6) δ 7.83 (s); *m/e* (rel intensity) 188 (2), 186 (4), 184 (5), 153 (12), 151 (69), 149 (100), 86 (49), 69 (78), 51 (72), 45 (58), 35 (54).

A solution of crude **9** obtained as described above, in absolute ethanol (20 mL) containing concentrated sulfuric acid (2 mL), was heated at reflux temperature for 24 h. The ethanol was removed *in vacuo* and 5% aqueous $NaHCO_3$ was added to the residue to give a pH 6 solution. Ethanol (50 mL) was added, and the solution was evaporated (repeated twice). The residue was slurried with hot ethyl acetate, the mixture was filtered through a pad of Celite and Florisil, and the filtrate was evaporated *in vacuo* giving ethyl imidazole-2-carboxylate (**11**) as a solid (0.73 g, 65% yield) which was pure by ^{1}H NMR spectroscopy and was identical to the material obtained as described below.

Absolute ethanol (20 mL) was added to the TFA solution of **9** (prepared from 2.00 g of **8**), and the solution was heated at reflux

(15) For the aldehyde **6**, H-4 and H-5 have been reported[5,6,16] to appear as a singlet at δ 7.41–7.46 in DMSO-d_6. One of these spectra was recorded[5] at 100 MHz at which field strength the singlets we observe should easily have been observed. It may be that the solvent contained traces of acid causing rapid exchange (see below). The ester **11** is reported[5] to show a singlet for H-4 and H-5 at δ 7.32 in DMSO-d_6 (100). When we added a small amount of D_2O and a trace of CF_3COOD to the DMF-d_7 solution of **11**, the two singlets of δ 7.14 and 7.35 collapsed to a sharp singlet at δ 7.26.

(16) Gebert, U.; von Kerekjarto, B. *Liebigs Ann. Chim.* **1968**, *718*, 249.

(17) Chapman, O. L.; King, R. W. *J. Am. Chem. Soc.* **1964**, *86*, 1256. See also, Davis, J. C.; Deb, K. K. In *Advances in Magnetic Resonance*; Waugh, J. S., Ed.; Academic Press: New York, 1970; Vol. 4, pp 201–270.

(18) Jaureguiberry, C.; Fournie-Zaluski, M. C.; Rogues, B.; Combrisson, S. *Org. Magn. Reson.* **1973**, *5*, 165.

(19) Papadopoulos, P. E.; Hollstein, U. *Org. Magn. Reson.* **1982**, *19*, 188.

(20) Antonio, Y.; De La Cruz, M. E.; Galeazzi, E.; Guzmán, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15.

temperature for 4 h. The solvent was removed *in vacuo*, ethyl acetate was added to the residue, and the solution was filtered through a pad of Act. I neutral alumina. Evaporation of the filtrate *in vacuo* gave **11** as a solid (0.87 g, 78% yield) which was pure by ^{1}H NMR. Crystallization of a specimen from ethyl acetate gave material with mp 175–177 °C, lit.[21] mp 178–179 °C.

(21) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 3403.

Imidazole-2-carboxylic Acid (10). Water (5 mL) was added to a TFA solution of **9** (prepared as described above from 2.00 g of **8**), and the solution was heated at reflux temperature for 1 h. The solvent was removed *in vacuo*, benzene was added to the residue, and the mixture was evaporated to dryness *in vacuo* (repeated twice). The solid residue was crystallized from 2-propanol–THF to give pure **10** (0.84 g, 94% yield), mp 166–167 °C, lit. mp[11] 163–164 °C.

JO941648V