Oxidation of Methylbenzimidazoles with Ceric Ammonium Nitrate

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A convenient method for the preparation of benzimidazole carboxaldehydes by the oxidation of methylbenzimidazoles with ceric ammonium nitrate is described. A series of methyl, dimethyl, and trimethylbenzimidazoles was treated with ceric ammonium nitrate in sulfuric acid, and the major ethyl acetate soluble products were characterized. In addition to carboxaldehyde products, side reactions yielding benzimidazolediones and nitrobenzimidazoles were also observed.

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Benzimidazole carboxaldehydes are potentially useful synthetic precursors in the development of benzimidazole analogs of biologically active substances (1-2). Difficulties encountered in the preparation of these aldehydes by direct formylation under Vilsmeier-Haack conditions (3) or by oxidation of methylbenzimidazoles with chromium trioxide (4) or persulfate (5) prompted us to investigate the use of an alternate reagent. In this communication we wish to report a convenient, direct method for the preparation of benzimidazole carboxaldehydes by the oxidation of methylbenzimidazoles with ceric ammonium nitrate (CAN) (6).

The results of the CAN oxidation of isomeric methyl, dimethyl, and trimethylbenzimidazoles are shown in Table I. CAN in sulfuric acid was found to be a highly reactive reagent in the presence of benzimidazoles. Extensive oxidation and polymerization reactions were observed for most of the benzimidazoles studied. Purification of the aldehyde products, however, was readily accomplished by a simple recrystallization of the ethyl acetate soluble fraction. In some cases, formation of a bisulfite addition product facilitated the purification. Polymeric side products and benzoic acids formed from further oxidation of aldehydes (6) were not extracted from the alkaline aqueous layer. Of the various positional isomers studied, the 2-methyl substituent was least susceptible to CAN oxidation under the reaction conditions. This observation is consistent with the reported stability of the C-2 methyl of 2-methylbenzimidazole to oxidation by a dichromate-sulfuric acid mixture (8). On the other hand, selenium dioxide converts 2-methylbenzimidazole to benzimidazole-2-carboxaldehyde (9).

In the treatment of 5,6-dimethylbenzimidazole (**3**) with CAN, two oxidation products were isolated. The main product was the desired 6-methyl-5-carboxaldehyde (**11**). A minor compound was identified as the tetrasubstituted quinone 5,6-dimethyl-4,7-benzimidazoledione (**14**). Quinone formation with CAN has been observed for a series of methoxybenzenes (10).

The ability of CAN to function as a nitrating agent was observed in its reaction with the electron rich compound 2-hydroxy-5-methylbenzimidazole (**7**). In this case, no aldehyde product was observed and the major material isolated was the 4,6-dinitro compound **13** (11). Nitration of 2-hydroxy-5,6-dimethylbenzimidazole (**8**) with CAN-sulfuric acid also yielded **13** (9%) presumably by initial oxidation of one of the methyl groups to a carboxylic acid followed by decarboxylation and nitration (12).

Although the CAN-sulfuric acid mixture presents the potential for numerous side reactions, the method is simple and useful for the preparation of aldehydes difficult to obtain by other means.

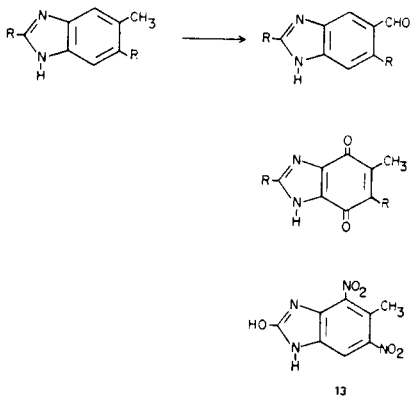

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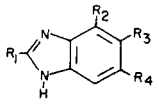
Table I

Reaction of Methylbenzimidazoles with Ceric Ammonium Nitrate (a)



Starting Benzimidazole						Product						% Starting
Compound No.	R_1	R_2	R_3	R_4	Time (min)	Compound No.	R_1	R_2	R_3	R_4	% Yield	Material Recovered
1	H	H	CH_3	H	45	**9**(b)	H	H	CHO	H	29	-
2	CH_3	H	CH_3	H	75	**10**	CH_3	H	CHO	H	60	-
3	H	H	CH_3	CH_3	15	**11**(c)	H	H	CHO	CH_3	34	-
4	CH_3	H	CH_3	CH_3	15	**12**(d)	CH_3	H	CHO	CH_3	25	-
5	CH_3	H	H	H	45	(e)					-	65
6	H	H	CH_3	NO_2	60	(e)					-	82
7	OH	H	CH_3	H	45	**13**(e)	OH	NO_2	CH_3	NO_2	18	-
8	OH	H	CH_3	CH_3	45	**13**(e)	OH	NO_2	CH_3	NO_2	9	-

(a) Treatment of unsubstituted benzimidazole and 1-methylbenzimidazole with CAN under the reaction conditions for 35 minutes yielded in each case 50% starting material recovered. (b) This aldehyde has been reported without experimental detail by Mathias and Overberger (7) to be a product of the cyclization of 3,4-diaminobenzaldehyde. (c) 5,6-Dimethyl-4,7-benzimidazoledione (**14**) was identified as a minor product (< 10% by nmr analysis). (d) 2,5,6-Trimethyl-4,7-benzimidazoledione (**15**) was identified as a minor product (<10% by nmr analysis). (e) No ethyl acetate extractable aldehydes or quinones were observed by nmr analysis.

EXPERIMENTAL

Melting points were determined in capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained in potassium bromide discs using a Perkin-Elmer spectrophotometer Model 257. ^1H nmr spectra (60 MHz) were determined using a Jeolco C-60HL NMR spectrometer and are expressed in ppm (δ) relative to tetramethylsilane. Electron impact mass spectra were obtained with a Du Pont 21-490 mass spectrometer operating at 70 eV and interfaced with a Du Pont 21-094 data system. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee and by the Heterocyclic Chemical Corporation, Harrisonville, Missouri. Starting methylbenzimidazoles were available commercially or were prepared from the appropriate phenylenediamine by cyclization with formic acid, acetic acid, or phosgene following established procedures.

Benzimidazole-5-carboxaldehyde (**9**).

Ceric ammonium nitrate (43.8 g., 80 mmoles) was added in small portions with stirring over a 5 minute period to a solution of 5-methylbenzimidazole (**1**, 1.32 g., 10 mmoles) in 87 ml. of 40% sulfuric acid w/w. The resulting orange solution was heated on a steam bath (80-90°) with occasional swirling until the color turned to a pale yellow (45 minutes). The mixture was then cooled, neutralized with solid potassium carbonate, and stirred with refluxing ethyl acetate (3 x 100 ml.). The combined ethyl acetate layers were washed with brine, dried (magnesium sulfate), and evaporated to yield a pale yellow solid. Recrystallization from ethyl acetate gave 0.42 g. (29%) of pure **9**, m.p., 163-165°; ir: 1690 cm^{-1} (aldehyde); nmr (DMSO-d_6): δ 7.9 (s, 2H, Ar-H), 8.37 (s, 1H, Ar-H), 8.63 (s, 1H, C-2 CH), and 10.2 (s, 1H, CHO); mass spectrum m/e (relative intensity): 146 (100%; $[M]^+$), 145 (97%; $[M-1]^+$), and 117 (64%; $[M-CHO]^+$); **9**·HCl: m.p. 240° dec. (ethanol:ether, 1:1); nmr (DMSO-d_6): δ 9.83 (s, 1H, C-2 CH).

Anal. Calcd. for $C_8H_7ClN_2O$: C, 52.60; H, 3.85; N, 15.34. Found: C, 52.78; H, 3.77; N, 15.26.

2-Methylbenzimidazole-5-carboxaldehyde (**10**).

Following the procedure described above for the preparation of **9**, 2,5-dimethylbenzimidazole (**2**, 2.70 g., 19 mmoles) was treated with CAN (71 g., 130 mmoles). The crude product obtained on work-up was recrystallized from acetone:hexane (1:2) to yield 60% of pure **10**, m.p. 218° dec.; ir: 1685 cm^{-1} (aldehyde); nmr (DMSO-d_6): δ 2.63 (s, 3H, CH_3), 7.8 (s, 2H, Ar-H), 8.22 (s, 1H, Ar-H), and 10.23 (s, 1H, CHO); mass spectrum m/e (relative intenstiy): 160 (100%; $[M]^+$), 159 (95%; $[M-1]^+$), and 131 (58%; $[M-CHO]^+$).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.45; H, 4.99; N, 17.08.

5,6-Dimethyl-4,7-benzimidazoledione (**14**).

5,6-Dimethylbenzimidazole (**3**, 1.46 g., 10 mmoles) was treated with CAN (43.8 g., 80 mmoles) following the procedure described above for the preparation of **9**. The crude product obtained on work-up contained a mixture of the aldehyde **11** and quinone **14** in an approximate ratio of 10:1 (as determined by integration of the methyl region in the nmr spectrum). Fractional crystallization (acetone:hexane, 1:1) gave an enrichment of **14** in the first fraction. Recrystallization from dimethylformamide:ether (1:2) gave pure **14** (35 mg., 2%), m.p. 245° dec.; ir: 1660 cm^{-1} (1,4-quinone); nmr (DMSO-d_6): δ 1.97 (s, 6H, CH_3), 8.0 (s, 1H, C-2H, shifts to 10.0 on adding a drop of deuterium chloride); mass spectrum m/e (relative intensity): 176 (100%; $[M]^+$).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.49; H, 4.89; N, 15.99.

6-Methylbenzimidazole-5-carboxaldehyde (**11**).

The main product from the treatment of **3** with CAN as described above was aldehyde **11**. The solid found in the mother liquor after the separation of **14** by fractional crystallization was recrystallized from acetone:hexane (1:2) to give 0.54 g. (34%) of pure **11**, m.p. 173-175°; nmr (DMSO-d_6): δ 2.7 (s, 3H, CH_3), 7.45 (s, 1H, C-7 H), 8.1 (s, 1H, C-4 H), 8.37 (s, 1H, C-2 H, shifts to 9.2 on adding a drop of deuterium chloride), and 10.17 (s, 1H, CHO); mass spectrum m/e (relative intensity): 160 (100%; $[M]^+$), 159 (58%; $[M-1]^+$), and 131 (26%; $[M-CHO]^+$).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.12; H, 5.17; N, 17.54.

2,6-Dimethylbenzimidazole-5-carboxaldehyde (**12**).

Following the procedure for the preparation of **9**, 2,5,6-trimethylbenzimidazole (**4**, 3.2 g., 20 mmoles) was treated with CAN (87.6 g., 160 mmoles). Crude aldehyde **12**, separated from quinone **15** by fractional crystallization (acetone:hexane, 1:1), was recrystallized from ethyl acetate (0.87 g., 25%): m.p. 181-183°; nmr (DMSO-d_6: dueterium oxide, 5:1) δ 2.53 (s, 3H, C-2 CH_3, shifts to 2.87 on adding a drop of deuterium chloride), 2.70 (s, 3H, C-5 CH_3), 7.27 (s, 1H, C-7 H), 7.87 (s, 1H, C-4H), and 10.03 (s. 1H, CHO); mass spectrum m/e (relative intensity): 174 (100%; $[M]^+$), 173 (87%; $[M-1]^+$), 145 (48%; $[M-CHO]^+$).

Anal. Calcd. for $C_{10}H_{10}N_2O \cdot \frac{1}{2}H_2O$: C, 65.60; H, 6.01; N, 15.30. Found: C, 65.81; H, 6.26; N, 15.38.

2-Hydroxy-4,6-dinitro-5-methylbenzimidazole (**13**).

Treatment of 2-hydroxy-5-methylbenzimidazole (**7**, 0.45 g., 3.0 mmoles) with CAN (13.1 g., 24 mmoles) following the procedure described above for the preparation of **9** yielded crude **13**. Recrystallization from dimethylformamide:ether (1:2) gave 128 mg. (18%) of pure **13**, m.p. 330° dec. [lit. (11) m.p. 320° dec.]; ir: 1530 cm^{-1} (C-NO_2); nmr (DMSO-d_6): δ 2.33 (s, 3H, CH_3), and 7.37 (s, 1H, Ar-H); mass spectrum m/e (relative intensity): 238 (100%; $[M]^+$). Reduction with hydrogen over 5% palladium/carbon gave the diamine, m.p. 270° dec.; m/e 178 (100%; $[M]^+$).

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