New Synthesis of 2-Nitroimidazoles

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1-Triphenylmethylimidazoles are treated with *n*-butyllithium in tetrahydrofuran at 0° to form the 2-lithio derivatives. The latter species react with *n*-propyl nitrate to give 1-trityl-2-nitroimidazoles which, after acid hydrolysis, provide the corresponding 2-nitroimidazoles. 2-Nitroimidazole was obtained from imidazole in overall yields of 27-35%; 4-methyl-2-nitroimidazole was obtained in 40% overall yield from 4-methylimidazole. Imidazole-4,5-dicarboxylic acid was converted, in several steps, to 1-tritylimidazole-4-methanol, and the latter compound was transformed into 2-nitroimidazole-4-methanol in an overall yield of 18%. Protection of the hydroxymethyl function was found to be unnecessary during carbanion formation and nitration. Attempts to nitrate 1-methylimidazole or 1-methoxymethylimidazole by the same procedure failed.

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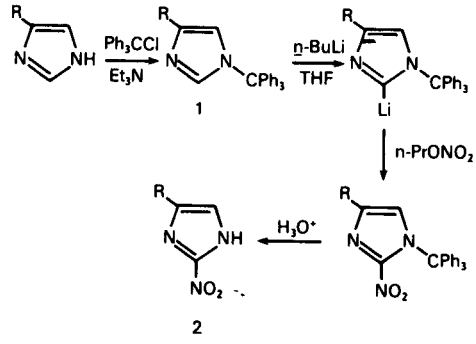
A convenient general method for the synthesis of 2-substituted imidazoles was reported recently by one of us (1), based on the reaction of the 2-carbanion of 1-tritylimidazole with electrophiles. In view of current interest in 2-nitroimidazoles as hypoxic cell sensitizers in radiation therapy (2), as selective cytotoxic agents (3), and as antiparasitic agents (4), we were prompted to investigate the applicability of the new method for the synthesis of 2-nitroimidazoles. To date, simple members of the series have been obtained from 2-aminoimidazoles by diazotization and subsequent displacement of the diazonium group with nitrite ion (5). For several compounds, microbial oxidation of the 2-amino group has also been used (6). Although the displacement reaction provides acceptable yields, it is dependent on the sometimes laborious construction of the 2-aminoimidazole precursor (7) and, occasionally, may take an unexpected turn. Thus, our attempts to prepare 4-methyl-2-nitroimidazole (**2b**) by the published procedure (5d) gave only 2-azido-4-methyl-5-nitroimidazole (8), which had also been obtained in significant amount in the earlier work. The synthesis of 2-nitroimidazoles with useful functionality at C-4 or C-5 has been achieved only by multistep methods (4b,9). Furthermore, the reported compounds are all methylated at N-1 and the inability to remove the methyl group seriously limits the range of analogues which can be prepared for biological testing purposes. Although 2-nitroimidazole (**2a**) has been converted to several Mannich bases (10), direct hydroxymethylation (to give **2c**) or formylation failed. The obvious advantage of the trityl protecting group is its facile removal (1), permitting the subsequent realkylation of nitrogen with various polyfunctional reagents.

No serious obstacles were anticipated in the reaction of the 2-carbanion with sources of the nitro group; indeed, nitration of 2-lithio-1-methylimidazole with nitrogen tetroxide had already been reported (11). Our attempts, however, to react 2-lithio-1-tritylimidazole with nitrogen tetroxide, or with other sources of nitronium ion (*eg.*, nitronium fluoroborate), provided no detectable 2-nitroimidazoles. Presumably, these reagents are sufficiently strong acids to effect removal of the trityl blocking group prior to nitration, even at -78°. The use of nonacidic alkyl nitrates for the side-chain nitration of toluene carbanions has also been described (12); we were gratified to find that such reagents are equally effective in our case. Thus, the reaction of 2-lithio-1-tritylimidazole with *n*-propyl nitrate leads to 2-nitroimidazole (**2a**) in 30% yield (Scheme 1).

SCHEME I



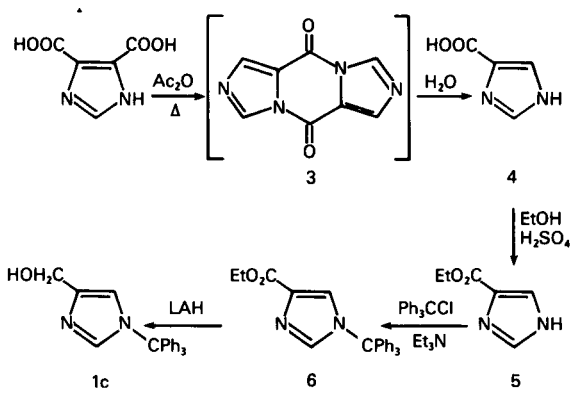
a, R = H; b, R = CH_3; c, R = CH_2OH

Our overall yield of 27%, based on imidazole, may be compared with an overall yield of 9%, based on the aminoacetal precursor of 2-nitroimidazole (5,7). By use of the same nitration method, 4-methyl-1-tritylimidazole (**1b**) (13) was converted into 4-methyl-2-nitoimidazole (**2b**) in 50% yield. Reaction of 2-lithio-1-tritylimidazole with tetranitromethane also leads to 2-nitroimidazole, but this reagent was found inferior to *n*-propyl nitrate with regard to yield and ease of workup.

The starting point for **2c** was 1-tritylimidazole-4-methanol (**1c**), which can be obtained by direct tritylation of imidazole-4-methanol (14). The cost and erratic availability of the latter compound, however, led us to explore alternative sources. Imidazole-4,5-dicarboxylic acid is

readily converted (Scheme 2), *via* **3** and **4**, into ethyl

SCHEME II



imidazole-4-carboxylate (**5**) in 72% yield (15). Tritylation of the ester to form **6** (13) and hydride reduction of **6** provided **1c** in 72% yield. Prior to reaction of **1c** with *n*-butyllithium, the free hydroxyl group was protected as its benzyl ether. This approach proved unsuccessful since there were indications that the strong base could abstract a proton from the methylene group at C-4 (16). Protection of the hydroxyl function by silylation was also explored, but only trace amounts of nitro derivatives were observed. Ultimately, we found that blocking of the hydroxyl was unnecessary since the alkoxide ion (generated by use of an additional equivalent of butyllithium) was an effective deterrent to carbanion formation at the adjacent methylene group. Thus, we obtained in 29% yield, the previously unknown **2c**, a key intermediate for the synthesis of more complex 2-nitroimidazoles (*e.g.*, 2-nitrohistamine and 2-nitrohistidine (17)).

Surprisingly, the nitration of 2-lithio-1-methylimidazole with propyl nitrate failed completely; mass spectral analysis of the reaction mixture suggested the formation of 1-methylimidazole dimers, trimers and products of ring alkoxylation. Parallel results were obtained with 1-methoxymethylimidazole (17). The difference in the influence of the *N*-substituent is puzzling and is under further investigation. It is interesting that the 2-carbanion generated from 1-tritylimidazole is deep red in color while that obtained from 1-methylimidazole is light yellow.

EXPERIMENTAL

General Methods.

Microanalyses and mass spectra were provided by the Microanalytical Services and Instrumentation Section of this Laboratory, under the direction of Dr. D. F. Johnson. Homogeneities and identitites of all compounds were checked by tlc (silica gel GF) and by chemical ionization mass spectrometry. Since nitroimidazoles sometimes react with ammonia carrier gas, mass spectra were run routinely with methane. All reactions involving butyllithium were performed under dry nitrogen or argon in glassware which had been flame-dried. Three-neck reaction flasks were equipped with a gas bubbler, dropping funnel and rubber septum. Butyllithium and propyl nitrate were introduced by syringe through the septum. Although nitroimidazoles show some photosenstivity, protection of reaction flasks or chromatographic columns with aluminum foil had no significant effect on yield. DMF and triethylamine were distilled from potassium carbonate and were stored over 4 Å molecular sieve. Tetrahydrofuran was freshly distilled from lithium aluminum hydride and was stored at 0° under argon for a maximum of 3 weeks. In later runs, Aldrich Gold Label THF was used without further treatment.

1-Tritylimidazole (**1a**). Method A.

To 250 ml of dry DMF in a flask equipped with drying tube was added 20.4 g (0.3 mole) of imidazole. The mixture was stirred until solution was complete (*ca.* 10 minutes). A solution of 27.8 g (0.1 mole) of trityl chloride in 60 ml of dry DMF was then added in one portion and the mixture was stirred overnight at ambient temperature. The solvent was removed under reduced pressure and the residual colorless solid was dissolved in a mixture of 150 ml of chloroform and 150 ml of water. After separation, the aqueous layer was extracted with three 50 ml portions of chloroform, the combined extracts were washed several times with water, with saturated brine and dried (sodium carbonate). The solvent was evaporated and the residue was dissolved in 200 ml of hot 95% ethanol. After the solution had cooled, the crystalline product was filtered and dried to give 21.1 g of **1a**. The mother liquor was reduced to one-third volume and chilled to give an additional 6.8 g for a total yield of 90%, mp 221-223° (lit mp 229-230° from xylene (18)). Alternatively, the DMF reaction mixture was diluted with two volumes of water, the product filtered and recrystallized from 95% ethanol, as described above.

Method B.

Imidazole (10.2 g, 0.15 mole) was dissolved in 200 ml of methylene chloride (drying tube) and the solution was chilled in an ice bath. Trityl chloride (46 g, 0.165 mole) was added and the mixture was stirred until solution was complete. Dry triethylamine (42 ml, 0.3 mole) was added slowly to the stirred solution and stirring was continued overnight at ambient temperature. The solvent was evaporated and the residual material was dissolved in 150 ml of hot nitromethane. The solution was chilled in ice, the product was collected and was recrystallized from nitromethane to give 39.5 g (85%) of **1a**, mp 218-220°.

2-Nitroimidazole (**2a**).

A 250 ml flask was charged with 3.1 g (10 mmoles) of 1-tritylimidazole and 100 ml of dry THF. The stirred solution was cooled to 0° and 8.5 ml (11 mmoles) of a 1.3 *M* solution of *n*-butyllithium in hexane (Aldrich Chemical Co.) was added over 2 minutes. The initially colorless solution was stirred at ambient temperature for 2 hours, at which time a dark red color had developed and a white solid (Lithium salt) had separated. A solution of 1.47 g (1.4 ml, 14 mmoles) of *n*-propyl nitrate in 15 ml of dry THF was added dropwise over 5 minutes and stirring was continued for 30-60 minutes at ambient temperature (20). The red color was quickly discharged, the solid dissolved gradually, and the solution became dark brown (21). The solution was cooled to 0°, was diluted with 100 ml of methanol and 10 ml of concentrated hydrochloric acid, and was stirred overnight at ambient temperature to effect removal of the trityl group and hydrolysis of any remaining traces of nitrate ester (22,23). The solvent was evaporated, the residual material was triturated with 10 ml of 50% aqueous ethanol and was filtered. The filtrated was refiltered and was evaporated to dryness. The residual orange-brown solid was chromatographed on 150 g of grade III alumina. Elution of the column with 500 ml of chloroform effected removal of residual triphenylcarbinol and other components. Further elution with 5% methanol in chloroform gave 330 mg (30%) of chromatographically pure **2a**, mp 283-283° dec (lit mp 287-288° dec (5a). The compound was further identified by elemental analysis, and by comparison of uv, ir, nmr and mass spectra with those of an authentic sample. In repeated runs on the same scale, yields of somewhat less pure material ranged from 35-50%.

4-Methyl-1-tritylimidazole (**1b**).

To 125 ml of dry DMF in a flask equipped with a drying tube and a large stirring bar was added 5 g (61 mmoles) of 4-methylimidazole. Trityl chloride (14.94 g, 68 mmoles) was added followed by dropwise addition of 21 ml (150 mmoles) of triethylamine. A colorless precipitate formed rapidly and the mixture gradually became a thick slurry. After 16 hours at ambient temperature, the precipitate was filtered, washed with cold water and dried. Two recrystallizations from ethyl acetate afforded 16.3 g (82%) of **1b**, mp 219.5-220°. Dilution of the DMF filtrate with water provided an additional 1-2 g of product; nmr (deuteriochloroform): δ 2.23 (3, d, J = 0.85 Hz, CH_3), 6.56 (1, qn, J = 0.85 and 1.0 Hz, H-5), 7.0-7.35 (m, Ph_3C), 7.40 (1, d, J = 1.0 Hz, H-2).

Anal. Calcd. for $C_{23}H_{20}N_2$ (324): C, 85.15; H, 6.21; N, 8.64. Found: C, 85.23; H, 6.30; N, 8.48.

Compound **1b** was also obtained in 72% yield by use of method B as for **1a**, mp 221-223°.

4-Methyl-2-nitroimidazole (**2b**).

The carbanion was generated as in the preparation of **2a**, using 6.0 g (18.5 mmoles) of **1b** and 15.5 ml (20 mmoles) of *n*-butyllithium reagent. To the carbanion solution was added 4 ml (40 mmoles) of *n*-propyl nitrate. The solution was stirred at ambient temperature for 3 hours and was then warmed (water bath) until the solid had completely dissolved. The brown solution was cooled in ice and was diluted with 100 ml of 1*N* hydrochloric acid. The solution was stirred overnight at ambient temperature, THF was removed *in vacuo*. The aqueous filtrate was reduced to half volume and was extracted with five 30 ml portions of ethyl acetate. The combined extracts were dried (magnesium sulfate) and concentrated to *ca.* 10 ml. The solution was refrigerated overnight and the product separated as a yellowish powder, 0.65 g, mp 205-207°. Concentration of the filtrate afforded an additional 0.52 g for a total yield of 50%. The compound was recrystallized from ethyl acetate, mp 205-207° (lit mp 211-212° (5d)); nmr (perdeuteriomethanol): δ 2.23 (3, s, CH_3), 7.16 (1, s, H-5).

Imidazole-4-carboxylic Acid (**4**) (24).

A suspension of 20 g (0.128 mole) of imidazole-4,5-dicarboxylic acid in 750 ml of acetic anhydride was stirred and refluxed until solution was nearly complete (*ca.* 5 hours) (25). A small amount of gray solid was removed by filtration and the light brown filtrate was evaporated to dryness. To the residual material was added 300 ml of water; the mixture was stirred overnight and was then heated on steam for 1 hour. To the solution was added 300 ml of ethanol and decolorizing charcoal (Norit). The mixture was heated on steam for 30 minutes and was filtered hot. The solution was refrigerated overnight and a crop of pale yellow crystals was collected and dried (9.85 g). The mother liquor was concentrated to dryness, the residual was dissolved in 100 ml of 50% aqueous ethanol, and the solution was chilled overnight to give an additional 1.61 g of **4**, for a total yield of 80%, mp 279-281° dec (lit mp 271° dec (26)). This material, although slightly colored, is satisfacory for conversion to the ester. Further purification can be effected by recrystallization from 50% aqueous ethanol.

Ethyl Imidazole-4-carboxylate (**5**).

To a suspension of 25 g (0.22 mole) of **4** in 450 ml of absolute ethanol was added 25 ml of concentrated sulfuric acid. The mixture was stirred and refluxed (under nitrogen) for 36 hours, at which point solution was complete and tlc showed the absence of **4**. The solution was chilled in an ice bath and was neutralized to *ca.* *p*H 8 with 100 ml of 5*N* sodium hydroxide. The solvent was removed *in vacuo* and the residue was dissolved in the minimum volume of boiling water (200-300 ml). The ester separated upon cooling of the solution; concentration of the mother liquor gave an additional crop for a total yield of 28 g (90%) of **5**, mp 156-158°. A sample was recrystallized from 80% ethanol, mp 159-160° (lit mp 157-158° (26)).

Ethyl 1-Tritylimidazole-4-carboxylate (**6**).

To 200 ml of dry DMF in a flask equipped with drying tube and stirring bar was added 8.4 g (60 mmoles) of **5**. The mixture was stirred for 10 minutes to effect solution and 17 g (61 mmoles) of trityl chloride was added. When solution was complete, 10 ml (71 mmoles) of triethylamine was added. The mixture was stirred overnight at ambient temperature and the solvent was removed *in vacuo*. The residual solid was dissolved in a mixture of 100 ml of saturated sodium bicarbonate and 100 ml of chloroform. The aqueous layer was extracted with three 40 ml portions of chloroform, the combined extracts were washed with saturated brine and dried (sodium carbonate). The solvent was evaporated and the residual solid was dissolved in 200 ml of boiling 95% ethanol; 40 ml of water was added and the solution was heated until clear. As the solution cooled, **6** separated as large crystals which were collected and dried (21.7 g, mp 165-167°). Concentration of the mother liquor and careful dilution with water gave an additional 1.2 g for a quantitative yield. An analytical sample was recrystallized from 80% ethanol, mp 168-169°; nmr (deuteriochloroform): δ 1.37 (3, t, J = 7 Hz, $-OCH_2CH_3$), 4.37 (2, q, J = 7 Hz, $-OCH_2CH_3$), 7.0-7.35 (m, Ph_3C), 7.50 (1, d, J = 1 Hz, H-2), 7.64 (1, d, J = 1 Hz, H-5) (13); ir (potassium bromide): 1727 cm^{-1} (C=O).

Anal. Calcd. for $C_{25}H_{22}N_2O_2$ (382): C, 78.53; H, 5.76; N, 7.33. Found: C, 78.41; H, 5.77; N, 7.04.

1-Tritylimidazole-4-methanol (**1c**).

A suspension of 1.14 g (30 mmoles) of LAH in 100 ml of dry THF was cooled to 0° and a solution of 10 g (26.2 mmoles) of **6** in 100 ml of THF was added over 15 minutes with stirring. The mixture was stirred at ambient temperature for 1 hour and was then cooled to 0°. Water (1.14 ml) was added slowly, followed by 1.7 ml of 10% sodium hydroxide and finally, another 2.85 ml of water. The mixture was stirred for 30 mintues and was filtered. The filter cake was washed with three 30 ml portions of hot THF and was then extracted with three 150 ml portions of hot 95% ethanol. The combined ethanol extracts were cooled to give, after filtration and drying, 4.95 g of colorless crystals. Concentration of the mother liquor afforded an additional 1.47 g. The original THF filtrate and washings of the filter cake were combined, concentrated and the residue was chromatographed on silica gel (elution with ethyl acetate) to give 1.27 g of **1c**, for a total yield of 86%, mp 239-240°. The mp was unchanged after two recrystallizations from 95% ethanol; recrystallization from chloroform-ethyl acetate (1:3) gave mp 237.5-238° (lit mp 228-230° (14) and 234-236° (27), both from dioxane); nmr (deuteriochloroform): δ 4.60 (2, s, $-CH_2OH$), 6.81 (1, d, J = 1 Hz, H-5), 7.0-7.35 (m, Ph_3C), 7.45 (1, d, J = 1 Hz, H-2); (perdeuteriomethanol): δ 4.47 (2, d, J = 0.61 Hz, $-CH_2OH$), 6.85 (1, sx, J = 0.61 and 1.5 Hz, H-5), 7.05-7.30 (m, Ph_3C), 7.39 (1, d, J = 1.5 Hz, H-2).

Anal. Calcd. for $C_{23}H_{20}N_2O$ (340): C, 81.18; H, 5.88; N, 8.24. Found: C, 80.96; H, 6.13; N, 8.44.

2-Nitroimidazole-4-methanol (**2c**).

The carbanion was generated as in the preparation of **2a**, using 3.31 g (9.7 mmoles) of **1c** and 16.2 ml (21 mmoles) of *n*-butyllithium reagent. To the carbanion solution was added 2.2 ml (22 mmoles) of *n*-propyl nitrate. Workup, including detritylation, followed the procedure previously described. The crude product was triturated with water-ethanol (4:1), the filtrate was refiltered and was evaporated to dryness. The residual brown solid was chromatographed on 150 g of silica gel; the column was first eluted with 1000 ml of ethyl acetate, followed by 5% methanol in ethyl acetate to elute **2c**. There was obtained 358 mg (29%) of a yellow solid which proved to be homogeneous by tlc and mass spectrum. A sample was recrystallized from ethyl acetate-ethanol, mp 170-172°; nmr (perdeuteriomethanol): δ 4.52 (2, s, CH_2OH), 7.16 (1, s, H-5).

Anal. Calcd. for $C_4H_5N_3O_3$: C, 33.56; H, 3.52; N, 29.36; for $C_4H_5N_3O_3$ + 10% C_2H_5OH: C, 34.01; H, 3.76; N, 28.63. Found: C, 34.09; H, 3.69; N, 28.78 (28).

Test for Completeness of Carbanion Formation.

Reactions between 1-tritylimidazoles and *n*-butyllithium generally required 2-3 hours at ambient temperature to effect full conversion to the

carbanion. The progress of proton abstraction was followed by conversion of the carbanion to the 2-aldehyde with DMF, which reaction has been found to be quantitative (1). A small aliquot of the THF solution was withdrawn and was added to 0.5 ml of dry DMF; the red color was discharged immediately. To this mixture was added 0.5 ml of water and 0.5 ml of ether. The mixture was shaken and the ether extract was applied to a tlc plate (silica gel GF) together with the original 1-tritylimidazole. The plate was developed with ether and the butyllithium reaction was continued until starting material was no longer evident.

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(13) Tritylation of 4-methylimidazole, **5**, and imidazole-4-methanol (ref 14) appear to produce single position isomers, all of which are considered to have the 1,4-orientation because of steric preference. These structural assignments are consistent with differentiation based on 2,4- and 2,5-proton coupling constants: H. R. Matthews and H. Rapoport, *J. Am. Chem. Soc.*, **95**, 2297 (1973); furthermore the δ values for the ring protons in **1b**, **1c**, and **6** resemble more closely those for 1-methyl-4-X-imidazoles than for the 1-methyl-5-X series: Y. Takeuchi, K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **43**, 3570 (1978).

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(15) Compound **5** is also obtainable by direct ethanolysis of **3**, but with significantly reduced yield.

(16) When an aliquot of the carbanion-containing reaction mixture was quenched with deuterium oxide, the recovered starting material had undergone partial isotope exchange at the C-4 methylene group.

(17) Work in progress.

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(19) In order to avoid the necessity of drying and distilling DMF, this alternative method for tritylation was developed by O. Olubajo in this laboratory.

(20) Injection of neat propyl nitrate from a syringe in one portion proved equally effective.

(21) The rate of solution of the solid varied with the run. Stirring was continued for 30 minutes following complete solution.

(22) Hydrolysis was also effected by reflux for several hours.

(23) Efforts to isolate the intermediate 1-trityl-2-nitroimidazoles were abandoned because of the lability of the *N*-trityl bond.

(24) This procedure is a modification of one previously developed in this laboratory by J. C. Reepmeyer which, in turn, is a modification of the published procedure: S. Kasina and J. Nematollahi, *Synthesis*, 162 (1975).

(25) The diacid is sparingly soluble in acetic anhydride. Efforts to reduce further the volume of solvent and to increase time of reflux resulted in reduced yields and darker products.

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(28) This compound retains polar solvents tenaciously in a nonstoichiometric relationship. A sample, which had been recrystallized several times from ethyl acetate-ethanol, gradually lost ethanol as it was dried at 25° *in vacuo* for one week. Attempts to remove ethanol completely at elevated temperatures resulted in darkening of the sample.