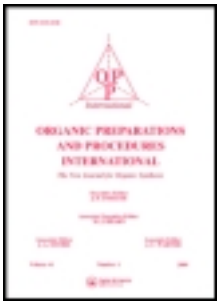


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

EXPEDIENT SYNTHESIS OF N [1]-TRITYLIMIDAZOLE-4-CARBOXALDEHYDE

Michele C. Jetter [a] , Robert E. Boyd [a] & Allen B. Reitz [a]

[a] Drug Discovery Division, The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477

Published online: 18 Feb 2009.

To cite this article: Michele C. Jetter , Robert E. Boyd & Allen B. Reitz (1996): EXPEDIENT SYNTHESIS OF N [1]-TRITYLIMIDAZOLE-4-CARBOXALDEHYDE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 28:6, 709-710

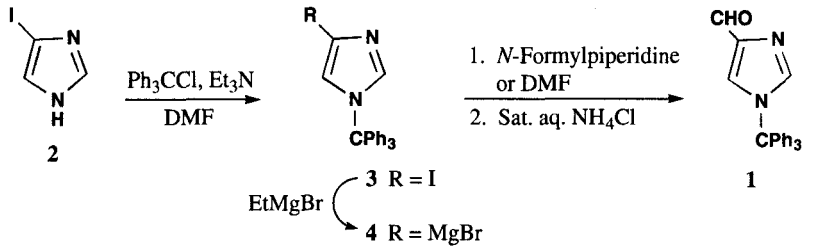
To link to this article: http://dx.doi.org/10.1080/00304949609356738

EXPEDIENT SYNTHESIS OF N^1-TRITYLIMIDAZOLE-4-CARBOXALDEHYDE

Submitted by Michele C. Jetter*, Robert E. Boyd, and Allen B. Reitz
(04/25/96)

Drug Discovery Division
The R. W. Johnson Pharmaceutical Research Institute
Spring House, PA 19477

N^1-Tritylimidazole-4-carboxaldehyde (**1**) is an important reagent for the synthesis of various 4-substituted imidazoles, and two routes to this compound have been reported.[1] It can be prepared *via* tritylation of 4(5)-(hydroxymethyl)imidazole and subsequent oxidation.[1a] However, this procedure requires synthesis of the 4(5)- (hydroxymethyl)imidazole either from fructose or from 1,3-dihydroxy-2-propanone.[2,3] An alternate route for the synthesis of **1** involves tritylation of 4(5)-iodoimidazole (**2**) to give N^1-trityl-4-iodoimidazole (**3**), followed by lithiation and formylation with dimethylformamide.[1b] However, mixtures of the 2- and 4-carboxaldehydes are produced, which are difficult to separate.[1b] Alternatively, a synthesis of N^1-sulfamoyl-4-imidazolecarboxaldehyde has been recently published,[4] but our own work required trityl protection on the imidazole ring. Lindell and Turner have shown that imidazo-4(5)-yl anions can be generated by reaction of **3** with EtMgBr to give



Grignard reagent **4**.[5] We now report that reaction of C-4(5) anion **4** with either dimethylformamide[6] or *N*-formylpiperidine[7] affords **1** in >75% yield. The details for the reaction employing *N*-formylpiperidine are given in the experimental section (81% yield). A similar result was obtained when dimethylformamide was used as the formylating reagent under identical reaction conditions and scale (77% yield), with the exception that 1.2 mol-equiv. of dimethylformamide was employed. In addition to high yield, these reactions are fairly rapid and easy to perform with no reaction time greater than 1 hr, and purification is readily achieved *via* flash chromatography. Because of these advantages, we believe that this procedure is the best means of obtaining **1** that has been reported to date.

EXPERIMENTAL SECTION

Melting points are uncorrected. The ^{1}H NMR spectra were obtained in solutions of deuterochloroform using a Bruker AC-300 instrument (300 MHz) using TMS as internal standard. N^1-Trityl-4-iodoimidazole (**3**) was readily obtained from 4(5)-iodoimidazole by a published procedure.[1b] Flash column chromatography was conducted according to the standard literature method.[8] Solvents were used as

commercially obtained without any further purification or drying. Elemental analysis was determined by Robertson Microlit Laboratories.

N^1-Tritylimidazole-4-carboxaldehyde (1).- To a solution of N^1-trityl-4-iodoimidazole (**3**, 2.18 g, 0.005 mol) in 50 mL of dry THF was added 2.0 mL (0.006 mol) of a 3.0 M solution of EtMgBr in diethyl ether. The reaction mixture was stirred at room temperature for 30 min, after which time TLC analysis (7:3 hexane:ethyl acetate) showed complete consumption of the starting material. *N*-Formylpiperidine (0.57 g, 0.56 mL, 0.005 mol) was added to the solution *via* syringe, and the reaction mixture was stirred for 1 hr. Saturated aqueous NH_4Cl (50 mL) was then added and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel, eluting with a 7:3 mixture of hexane/ethyl acetate. The product was obtained as 1.37 g (81%) of a white solid, mp 198-199°, lit.[1a] mp 197-199°. ^1H NMR ($CDCl_3$): δ 9.85 (s, 1H, HC=O), 7.61 (s, 1H, ImH), 7.54 (s, 1H, ImH), 7.1-7.38 (m 15H, ArH).

Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.82; H, 5.40; N, 8.17

REFERENCES

1. a) J. L. Kelley, C. A. Miller and E. W. McLean, *J. Med. Chem.*, **20**, 721 (1977); b) K. L. Kirk, *J. Het. Chem.*, **22**, 57 (1985).

2. J. R. Totter and W. J. Darby, *Org. Syn., Coll. Vol. 3*; E. C. Horning, ed., Wiley: New York, 1955, p 460.

3. R. Weidenhagen and R. Hermann, *Ber.*, **68**, 1953 (1935).

4. J. Winter and J. Retey, *Synthesis*, 245 (**1994**).

5. R. M Turner, S. D. Lindell and S. V. Ley, *J. Org. Chem.*, **56**, 5739 (1991).

6. G. A. Olah, G. K. S. Prakash and M. Arvanaghi, *Synthesis*, 228 (**1984**).

7. G. A. Olah and M. Arvanaghi, *Angew. Chem. Int. Ed.*, **20**, 878 (1981).

8. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

****