

This article was downloaded by:

On: 27 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t902189982>

EXPEDIENT SYNTHESIS OF *N*-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

To cite this Article Jetter, Michele C. , Boyd, Robert E. and Reitz, Allen B.(1996) 'EXPEDIENT SYNTHESIS OF *N*-TRITYLIMIDAZOLE-4-CARBOXALDEHYDE', *Organic Preparations and Procedures International*, 28: 6, 709 – 710

To link to this Article: DOI: 10.1080/00304949609356738

URL: <http://dx.doi.org/10.1080/00304949609356738>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

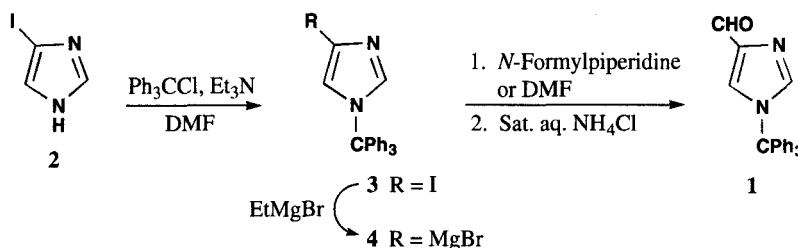
The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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 dimethylformamide⁶ or *N*-formylpiperidine⁷ 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 ¹H NMR spectra were obtained in solutions of deuteriochloroform 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 Microлит 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 NH₄Cl (50 mL) was then added and the aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were dried (Na₂SO₄) 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 (CDCl₃): 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 C₂₃H₁₈N₂O: 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).
