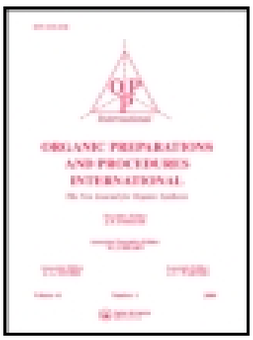


Organic Preparations and Procedures International

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

A CONVENIENT SYNTHESIS OF N-Boc-4-FORMYLPIPERINE

Gary A. Cain & Christopher A. Teleha

To cite this article: Gary A. Cain & Christopher A. Teleha (2000) A CONVENIENT SYNTHESIS OF N-Boc-4-FORMYLPIPERINE, Organic Preparations and Procedures International, 32:1, 96-99, DOI: 10.1080/00304940009356755

To link to this article: http://dx.doi.org/10.1080/00304940009356755

Published online: 18 Feb 2009.

3. L. Lee Melhado and J. L. Brodsky, *J. Org. Chem.*, **53.** 3852 (1988).

4. A. R. Katritzky, S. Rachwal and S. Bayyuk, *Org. Prep. Proced. Int.*, **23**, 357 (1991).

5. M. Somei, F. Yamada, H. Hamada and T. Kawasaki, *Heterocycles,* **29,** 643 (1989).

6. E. E. Gilbert, *J. Energetic Mater.*, **2**, 215 (1984).

7. N. A. Barba and M. S. Nedelko, *Zhur. Org. Khim.*, **19,** 2220 (1983).

8. A. J. Gordon and R. A. Ford, *"The Chemist's Companion"*, Wiley-Interscience, New York-London-Sydney-Toronto, 1972.

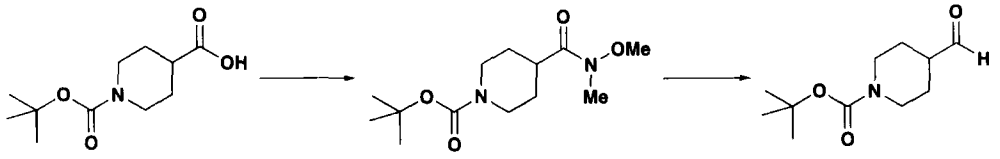
****

A CONVENIENT SYNTHESIS OF N-Boc-4-FORMYLPIPERIDINE

Submitted by (12/16/99) Gary A. Cain* and Christopher A. Teleha

Chemical & Physical Sciences Department
DuPont Pharmaceuticals Company
Experimental Station E336/109
P. O. Box 80336, Wilmington, DE 19880-0336, USA

The title compound, N-Boc-4-formylpiperidine (**3**), has been reported several times in recent years as a useful synthetic intermediate, particularly in the pharmaceutical industry. In the various methods that have been used for its preparation, at least one significant shortcoming exists which makes the reported syntheses unattractive for larger scale preparations. The drawbacks include the need for extremely expensive reagents,[1-2] toxic/environmentally unfriendly reagents,[3] extremely low temperatures,[4] chromatographic purifications,[5] and/or malodorous by-products.[6-8] In addition, some of these reported syntheses proceeded in only moderate overall yields. We report here a convenient, high yielding, cost-effective procedure which does not have the drawbacks of the previously reported procedures.



1 **2** **3**

The starting material, N-Boc-piperidine-4-carboxylic acid (**1**), which is commercially available,[9] can be readily prepared from the inexpensive piperidine-4-carboxylic acid.[1] This carboxylic acid was converted into Weinreb amide[10] **2** on a 50 gram scale by using standard, cost-efficient

peptide coupling conditions[11] (isobutyl chloroformate, N-methylmorpholine, THF). The reaction was rather slow, requiring 3 days at room temperature to go to completion. Nonetheless after simple workup, **2** was isolated in 93% yield and required no purification. Weinreb amide **2** was then selectively reduced by lithium aluminum hydride (LAH) in diethyl ether at -40° to +5° over 3.5 h, followed by a careful aqueous quench at -35°. After workup and concentration, the crude product was distilled (Kugelrohr) at high vacuum to give a 78% yield of target aldehyde **3** of excellent purity.

A noteworthy point in the reduction step was the use of easily handled LAH solid pellets.[12] We find the pellets to be an extremely convenient form of LAH to manipulate. Due to a much lower surface area, the hard pellets are vastly less sensitive to atmospheric moisture than the powder and present a lesser fire hazard than commercial LAH/ether solutions. The pellets can be conveniently weighed out on a bench-top (quickly) and simply dropped with tweezers into the reaction vessel. The size of the pellets makes them particularly advantageous for larger scale reactions. Upon mechanical stirring in ether for 2-3 hours, the pellets dispersed into the highly reactive powdered LAH form. The substrate was then added and the reaction run in typical fashion.

In summary, we have developed a two-step synthesis of high purity N-Boc-4-formylpiperidine **3**. This route is of reasonable cost, requires no chromatographic purification, and proceeds in 73% overall (unoptimized) yield.

EXPERIMENTAL SECTION

Commercial reagents were used without further purification. Melting points were determined on a Thomas/Hoover apparatus in open capillary tubes and are uncorrected. TLC analyses were performed on E. Merck silica gel 60 F_{254} plates in EtOAc/hexane solvent systems with UV detection. Flash chromatography was conducted with E. Merck Kieselgel 60 F_{254} silica gel. Infrared spectra were determined on a Perkin Elmer 1600 Series FT-IR instrument. NMR spectra were recorded using a Varian Unity 300 spectrometer. Mass spectral data were obtained on a Finnigan MAT 8230 or VG 70-VSE with NH_3 chemical ionization. Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ.

N-Boc-Piperidine-4-(N-methoxy-N-methylcarboxamide) (2).- Isobutyl chloroformate (28 mL, 29 g, 210 mmol) was added *via* a syringe over 10 min to a solution of N-Boc-isonipecotic acid **1** (49 g, 210 mmol) and N-methylmorpholine (51 mL, 47 g, 460 mmol) in dry THF (500 mL) at -20° with stirring under N_2. After 30 min, solid N,O-dimethylhydroxylamine hydrochloride (21 g, 210 mmol) was added in one portion. The reaction mixture was allowed to warm slowly to RT and stirred until completion as indicated by ^1H NMR (3 days). After concentration *in vacuo,* the mixture was partitioned between EtOAc (1.5 L) and 1 M HCl (250 mL). The organic phase was separated, extracted with water (100 mL), half-saturated $NaHCO_3$ (100 mL), and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Further drying under high vacuum (1 mm Hg, RT) yielded **2** (53.4 g, 93%), as a colorless oil. IR (neat): 1693, 1663 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.15-4.07 (br m, 2H), 3.67 (s, 3H), 3.14 (s, 3H), 2.82-2.72 (m, 3H), 1.71-1.60 (m, 4H), 1.42 (s, 9H). ^{13}C NMR

($CDCl_3$): δ 175.65, 154.67, 79.43, 61.52, 43.23, 38.12, 32.29, 28.42, 18.98. MS (*m/e*) 295 (base, M + Na^+). HRMS (*m/e*) calc'd for M + H^+: 273.1814, found: 273.1805.

Anal. Calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.35; H, 9.02; N, 9.96

N-Boc-4-Formylpiperidine (3).- Lithium aluminum hydride pellets (9.3 g, 240 mmol) were mechanically stirred in dry diethyl ether (930 mL) at RT under N_2 until dispersed as a fine powder. This mixture was cooled to -50°, then a solution of Weinreb amide **2** (53 g, 200 mmol) in diethyl ether (270 mL) was added over 20 min maintaining the temperature below -40°. The cooling bath was then removed and the mixture allowed to warm in ambient air to +5°. The reaction mixture was immediately cooled to -35°, then Celite (ca. 250 g) was added. The reaction was quenched by cautiously adding a solution of $KHSO_4$ (54 g, 400 mmol) in water (150 mL) under vigorous stirring. The temperature was allowed to warm to 0°, then the mixture was filtered through additional Celite, rinsing the flask and solids well with EtOAc and water. The resulting clear solutions were transferred to a separatory funnel and extracted with 1 M HCl (210 mL). The organic layer was extracted further with saturated aqueous $NaHCO_3$ (210 mL) and brine (210 mL). The aqueous phases were extracted with fresh EtOAc (1 L), then the organic solutions were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Kugelrohr distillation yielded **3** (32.7 g, 78%) as a colorless oil, bp 110-125o (oven T) at 1.9-2.3 mm Hg. IR (neat): 2712, 1726, 1691 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.67 (d, 1H, J = 1 Hz), 4.05-3.92 (m, 2H), 2.98-2.88 (m, 2H), 2.47-2.37 (m, 1H), 1.95-1.85 (m, 2H), 1.62-1.50 (m, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 202.76, 154.56, 79.55, 47.88, 42.78, 28.34, 25.11. HRMS (*m/e*) calc'd for M + H^+: 214.1443, found: 214.1438.

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.99; N, 6.58. Found: C, 61.77; H, 8.75; N, 6.57.

REFERENCES

1. S. I. Klein, B. F. Molino, M. Czekaj, C. J. Gardner, V. Chu, K. Brown, R. D. Sabatino, J. S. Bostwick, C. Kasiewski, R. Bentley, V. Windisch, M. Perrone, C. T. Dunwiddie and R. J. Leadley, *J. Med. Chem.*, **41**, 2492 (1998).

2. G. R. Brown, N. J. Newcombe and A. J. Foubister, WO 98/35959; *Chem. Abstr.*, **129**, 189345 (1998).

3. R. T. Jacobs, C. J. Ohnmacht and D. A. Trainor, EP 0532177 B1; *Chem. Abstr.*, **120**, 244680 (1993).

4. S. M. Sebti, A. D. Hamilton, D. J. Augeri, K. J. Barr, B. G. Donner, S. A. Fakhoury, D. A. Janowick, D. M. Kalvin, J. J. Larsen, G. Liu, S. J. O'Connor, S. H. Rosenberg, W. Shen, R. E. Swenson and B. K. Sorensen, WO 98/50031; *Chem. Abstr.*, **130**, 25339 (1998).

5. D. J. Hoover, B. A. Lefker, R. L. Rosati, EP 0438233 A2; *Chem. Abstr.*, **116**, 152399 (1991).

6. W. J. Hoekstra, WO 99/21832; *Chem. Abstr.*, **130**, 325395 (1999).

7. Y. Mori, S. Takechi and T. Ichihashi; JP 09241206; *Chem. Abstr.*, **127**, 307252 (1997).

8. Y. Ikeda, Y. Ueki, T. Nishihara and Y. Kamikawa, US 5607948; *Chem. Abstr.*, **122**, 266008 (1997).

9. Vendor: Bachem Bioscience, King of Prussia, PA, USA.

10. S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).

11. M. Bodanszky and A. Bodanszky, "*The Practice of Peptide Synthesis*", p. 109, Springer-Verlag, New York, NY, **1984**.

12. Vendor: Aldrich Chemical, Milwaukee, WI, USA.

****

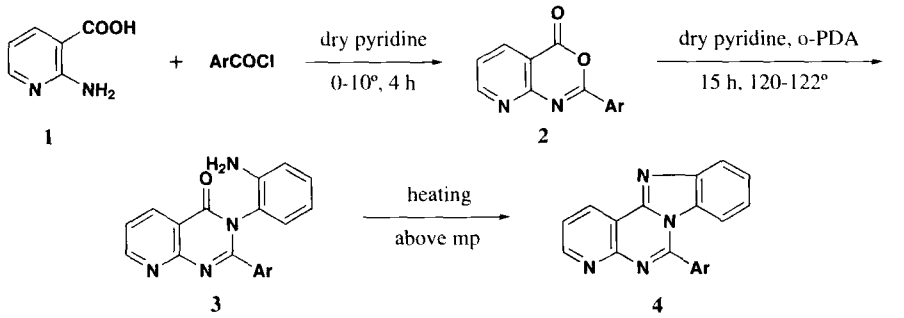
A FACILE METHOD WITH IMPROVED YIELDS IN THE SYNTHESIS OF 6-ARYLPYRIDO[2',3':4,5]PYRIMIDO[1,6-a]BENZIMIDAZOLES†

Submitted by (03/02/99)

G. Suma‡, R. H. Bahekar and A. R. R. Rao*

Medicinal Chemistry Division
University College of Pharmaceutical Sciences
Kakatiya University, Warangal (A. P.) 506 009, INDIA

Methylxanthines are a major class of bronchodilators employed in the treatment of asthma despite a narrow therapeutic index. New heterocyclic compounds designed on the basis of the xanthine skeleton are being investigated as possible bronchodilators with a wider margin of safety.[1] In continuation of our work on the synthesis and bronchodilator activity of some new fused quinazolines,[2] we carried out the preparation of some fused pyridopyrimidines as isosteres of the quinazoline moiety. A literature survey revealed that the title compounds (**4**) have been synthesized with overall yields of about 34%.[3,4] We now report the preparation of the above compounds by a route analogous to the synthesis of benzimidazoquinazolines,[2] involving mild reaction conditions and easy work-up procedures with improved overall yields (46-70%).



1 2 3 4

a) Ar = -C_6H_5 b) Ar = *p*-NO_2-C_6H_4 c) Ar = *p*-Cl-C_6H_4 d) Ar = *p*-Me-C_6H_4