

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>

ONE-POT SYNTHESIS OF 4-[2-(3, 4-DICHLOROPHENOXY)ETHYL]-1-PENTYLPYPERIDINE HYDROCHLORIDE (SB 201823-A)

Oskar Axelsson^a; Dan Peters^a

^a NeuroSearch A/S, Glostrup, DENMARK

To cite this Article Axelsson, Oskar and Peters, Dan(1995) 'ONE-POT SYNTHESIS OF 4-[2-(3, 4-DICHLOROPHENOXY)ETHYL]-1-PENTYLPYPERIDINE HYDROCHLORIDE (SB 201823-A)', *Organic Preparations and Procedures International*, 27: 5, 571 – 572

To link to this Article: DOI: 10.1080/00304949509458505

URL: <http://dx.doi.org/10.1080/00304949509458505>

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.

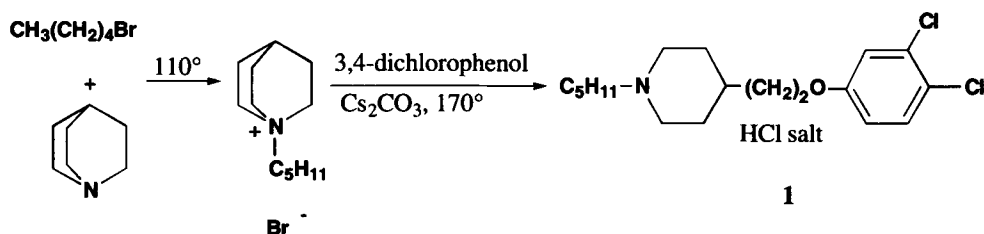
The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any 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.

ONE-POT SYNTHESIS OF 4-[2-(3,4-DICHLOROPHENOXY)ETHYL]-1-PENTYLPIPERIDINE HYDROCHLORIDE (SB 201823-A)

Submitted by Oskar Axelsson* and Dan Peters
(02/13/95)

*NeuroSearch A/S, 26B Smedeland
DK-2600 Glostrup, DENMARK*

The experimental drug 4-[2-(3,4-dichlorophenoxy)ethyl]-1-pentylpiperidine (**1**, SB 201823-A) has been shown to protect against neuronal damage after brain ischemia in rats and to be a blocker of neuronal calcium channels.¹ We needed a sample of this compound for pharmacological evaluation but the published synthesis² used 4-(2-hydroxyethyl)piperidine, which is no longer commercially available, as the starting material. To overcome this problem, we devised a very convenient one-pot, two-step synthesis of **1** in 79% yield starting with quinuclidine, as outlined below.



EXPERIMENTAL SECTION

The NMR spectrum was recorded on a Bruker AM 500 MHz spectrometer with DMSO- d_6 as the solvent and chemical shifts are reported as ppm downfield from TMS. The mass spectrum was obtained on a JEOL JMS AX-505W double focusing mass spectrometer. The IR spectrum was recorded on a Perkin Elmer 1310 IR-spectrometer. Only the most prominent MS and IR peaks are reported. The melting point was determined with a Griffin melting point apparatus which was calibrated using the Aldrich Melting point standards kit.

Procedure.- Quinuclidine (1.11 g, 10 mmol) was quaternized by stirring with 1-bromopentane (1.51 g, 10 mmol) without solvent for 1 hr at 110°. To this salt was then added 3,4-dichlorophenol (2.44 g, 15 mmol) and cesium carbonate³ (3.26 g, 10 mmol). The flask was flushed with nitrogen and the mixture was stirred at 170° (bath temperature) for 15 hrs. After cooling to room temperature, the solid was partitioned in a mixture of ether (50 mL) and water (50 mL). The phases were separated and the aqueous layer was extracted with another 50 mL portion of ether. The combined organic phases were dried over magnesium sulfate. The hydrochloride of **1** (3.0 g, 79%), pure according to TLC ($CH_2Cl_2/EtOH$, 9:1), could then be precipitated by the addition of methanolic HCl (2.5 mL of a 4.3 M solution), mp. 177-178°, lit.² 177-178°.

IR: 2940, 2500, 1470, 1360 cm^{-1} .

$^1\text{H NMR}$: δ 7.51 (d, $J = 8.7$ Hz, 1), 7.25 (d, $J = 3.7$ Hz, 1), 6.95 (dd, $J_1 = 8.7$ Hz, $J_2 = 3.7$ Hz, 1), 4.05 (t, $J = 7.0$ Hz, 2), 3.43 (d, $J = 14.0$ Hz, 2), 2.94 (m, 2), 2.83 (dd, $J_1 = 12.9$ Hz, $J_2 = 10.7$ Hz, 2), 1.88 (d, $J = 13.5$ Hz, 2), 1.75-1.60 (m, 5), 1.149-1.60 (m, 2), 1.35-1.25 (m, 4), 0.89 (t, 6.7 Hz, 3). EI MS: $m/z = 343$ (5%, molecular ion), $m/z = 286$ (base peak).

Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{Cl}_3\text{NO}$: C, 56.77; H, 7.41; N, 3.68. Found: C, 56.80; H, 7.63; N, 3.64

REFERENCES

1. C. D. Benham *et al.*, *Neuropharmacology*, **32**, 1249 (1993).
2. T. H. Brown and D. G. Cooper, World Patent WO 92/02502; *Chem. Abs.*, **116**, 235459 (1992).
3. Cesium carbonate proved to be a much more efficient base than potassium carbonate. With the latter, only a 3% yield of **1** was obtained after 15 hrs at 195°. The crude product from this reaction was of much lower purity and required chromatographic purification.

THE SYNTHESIS OF TRIMETHYLSILYLMETHOXYMETHYL CHLORIDE

Submitted by Arthur G. Schultz* and Yongwen Wang
(02/13/95)

Department of Chemistry
Rensselaer Polytechnic Institute
Troy, NY 12180-3590

The direct oxidation of aliphatic ethers is difficult because of their high oxidation potential (≥ 2.5 V vs. Ag/AgCl).¹ Substitution of a silyl group for a hydrogen atom at the α -position of ethers results in a significant decrease in oxidation potentials (1.6 to 1.7 V).² In connection with a study of photoinduced single electron transfer (SET) reactions in the 2,5-cyclohexadien-1-one series, we desired a practical synthesis of 1,4-cyclohexadiene **2** from methyl 2-methoxy-6-methylbenzoate (**1**).

