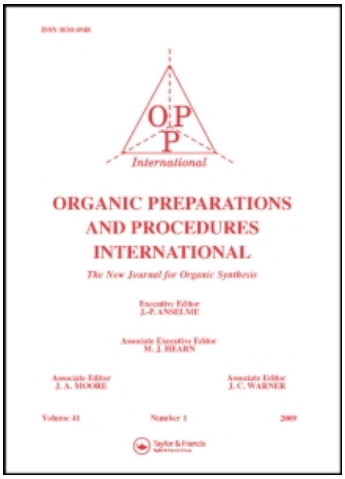

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF 1-(*t*-BUTYLOXYCARBONYL)-3-(BROMOMETHYL)INDOLE

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To cite this Article Venkatachalam, T. K. , Mzengeza, S. and Diksic, M.(1993) 'AN IMPROVED SYNTHESIS OF 1-(*t*-BUTYLOXYCARBONYL)-3-(BROMOMETHYL)INDOLE', Organic Preparations and Procedures International, 25: 2, 249 — 251
To link to this Article: DOI: 10.1080/00304949309457958
URL: http://dx.doi.org/10.1080/00304949309457958

5. Sulfuric acid oxidizes the mercaptan to the sulfenic acid according to the following equation:

$$RSH + H_2SO_4 \rightarrow RSOH + SO_2 + 2\,H_2O$$

6. A. Vogel, "*Practical Organic Chemistry*", 4th Edition, p. 61, Longmans, London, 1978.

7. Thionyl chloride oxidizes the mercaptan to the disulfide,[1a] probably according to the following equations:

$$2\,RSH + SOCl_2 \rightarrow RSS(O)SR + 2\,HCl$$

$$RSS(O)SR + RSH \rightarrow RSSR + RSSOH$$

$$RSSOH + RSH \rightarrow RSSR + H_2O + S$$

$$H_2O + SOCl_2 \rightarrow 2\,HCl + SO_2$$

$$\text{Net: } 4\,RSH + 2\,SOCl_2 \rightarrow 2\,RSSR + 4\,HCl + S + SO_2$$

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AN IMPROVED SYNTHESIS OF

1-(*t*-BUTYLOXYCARBONYL)-3-(BROMOMETHYL)INDOLE

Submitted by (11/16/92)

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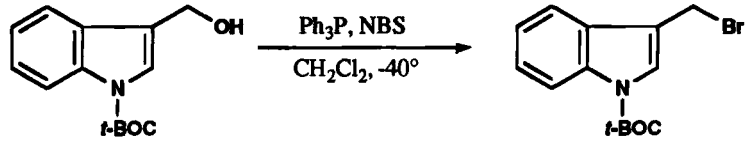
Indolylmethyl bromide **2** has been used in the asymmetric synthesis of α-methyl-L-tryptophan *via* the chiral glycine synthons by Seebach's[1] and Schöllkopf's groups.[2] We have been interested in the asymmetric synthesis of ^{14}C and ^{11}C labelled α-methyl-L-tryptophan.[3] These radiopharmaceuticals are important in the *in vivo* study of the synthesis of the neurotransmitter, serotonin, using both autoradiography[4] and positron emission tomography.[5] Brain serotonin alteration has been implicated in neurological diseases[6] (e. g. schizophrenia, disorders of appetite, mood, sexual behaviour and sleep).[7] All our attempts to prepare indolylmethyl bromide **2** from the corresponding indolylmethyl alcohol **1**



1 **2**

using the procedure reported by Schöllkopf[2] gave either very low yields of the bromide or as in many instances no product at all. The failure of this procedure which involves bromination with bromine and triphenylphosphine is probably due to side-reactions; the hydrogen bromide produced during the reaction cleaves the N-t-Boc. However, the addition of Et_3N to avoid cleavage of the protecting group failed to improve the yield of the product. Furthermore, the literature[1,2] methods require three days and neither characterization and yields nor analytical data of the indolylmethyl bromide were reported.[1,2] Herein, we report a reproducible procedure which gives good yields of **2**.

The advantages of the present method are that the succinimide produced can be removed from the reaction mixture by extraction with CCl_4, the reaction is clean and complete in 12 hrs. Recently a similar preparation of a related 3-(bromomethyl)indole has been reported.[8]

EXPERIMENTAL SECTION

Glassware was oven dried at 110° prior to use. Solvents such as methylene chloride, carbon tetrachloride, acetonitrile, hexane and ethyl acetate were distilled from CaH_2 under argon and stored under argon. 1-(t-Butyloxycarbonyl)-3-(hydroxymethyl)indole **1** was obtained from Bis-Chem Inc., Montreal, Canada and it can also be synthetized using Schöllkopf's procedure.[2] N-Bromosuccinimide was recrystallized from water and dried under vacuum for several days prior to use, melting points were determined on a Mel-Temp apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian 400MHz spectrometer using TMS as an internal standard while ^{13}C-NMR spectra were determined on a Varian XL-300 spectrometer. IR spectra were recorded with an Analect AQS-18 FT-IR spectrometer. Mass spectra utilizing chemical ionization were obtained with a HP5980-A quadropole mass spectrometer. The elemental analysis was performed by the Guelph Chemical Laboratories Ltd., Guelpf, Ontario. TLCs were carried out on Analtech Uniplate TLC plates (Cat. No. 47521). Temperature of -40° was obtained using Flexicool cooling probe immersed in acetone solvent.

1-(*t*-Butyloxycarbonyl)-3-(bromomethyl)indole.- To 2.47g (10 mmol) of 1-(*t*-butyloxycarbonyl)-3-(hydroxymethyl)indole (1) under an argon atmosphere in an oven-dried 250 ml RB flask, was added 100 ml of dry methylene chloride using a syringe; the contents were stirred and cooled to -40° for 0.5 hr. Then a solution of 3.14g (12 mmol) of triphenylphosphine in 20 ml of dry methylene chloride was added slowly while the bath temperature was maintained at -40°. The contents were stirred for an additional 0.5 hr and N-bromosuccinimide (1.96 g, 11 mmol) was added portionwise to the mixture and the contents were allowed to stir at -40° for 12 hrs. A deep orange-brown colored solution was obtained. Evaporation of the contents *in vacuo* to 3-5 ml resulted in a sticky mass. To this was added 50 ml of dry CCl_4 and the contents were stirred for 0.5 hr. The precipitate was filtered using a fritted funnel and discarded. The filtrate was evaporated to yield a solid to which 150 ml of hexane/EtOAc (4:1) was added and the resulting suspension was filtered through a silica gel pad (200g) under suction. Rapid filtration of the bromide is necessary to minimize decomposition on the silica gel. The resultant filtrate was evaporated *in vacuo* to yield a white solid, which was recrystallized from dry acetonitrile to give 1.89g (60%) of **2**, mp 98° (dec.), lit[2]. mp 97° (dec.). The compound may be stored under argon in the refrigerator for several days without any sign of decomposition.

Rf of 0.8.(hexane/ethyl acetate, 4:1); IR ($CHCl_3$): 3023, 1734, 1454, 1367, 1272, 1259, 1237, 1226, 1156, 1084, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.12 (d,CH), 7.2-7.7 (m,Ar), 4.65 (s,3CH_2), 1.63 (s,t-Bu); ^{13}C NMR ($CDCl_3$): δ 149.3, 135.7, 128.7, 124.9, 122.8, 119.3, 117.1, 115.4, 84.1, 36.4, 28.1, 24.4; MS (CI; NH_3) m/e: 309(M^+), 311(M+2), 230(M-Br).

Anal. Calcd. for $C_{14}H_{16}BrNO_2$: C, 54.21; H, 5.19; N, 4.52; Br, 25.75

Found: C, 54.53; H, 5.15; N, 4.64; Br, 25.71

ACKNOWLEDGEMENT.- This work was supported in part by the MRC grant SP-30, MA-10232, and the UPHS RO1 NS29629-02. We express our thanks to Dean Jolly and Donald Porter for their continued help, Dr. Joe Tauskela for help with the NMR.

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