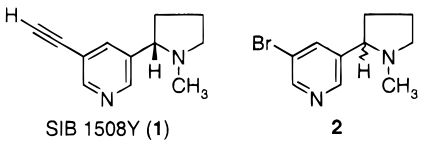
A Novel Method for the Racemization of 5-Bromonicotine

Leo S. Bleicher and Nicholas D. P. Cosford*

Received January 27, 1999

Introduction

While significant progress has been made recently in the field of asymmetric synthesis, not all compounds are amenable to these approaches, and in many cases classical resolution can be more cost-effective on a manufacturing scale.[1−3] We recently reported a convenient synthesis of (*S*)-(−)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)-pyridine maleate [SIB-1508Y (**1**)], a neuronal nicotinic acetylcholine receptor (nAChR) agonist in clinical trials for the treatment of Parkinson's disease.[4] The synthetic route proceeded via classical resolution of racemic 5-bromonicotine (**2**) followed by transformation of (*S*)-**2** to **1**. The need to manufacture kilogram quantities of **1** prompted a reexamination of this preparative sequence and led to the conclusion that an improved classical resolution coupled with racemization and recycling of the excess (*R*)-**2** from the mother liquors might provide a more efficient and cost-effective process. Herein we describe an efficient laboratory scale method for the racemization of (R)-enriched **2** which complements the earlier disclosure on the synthesis of **1**.



SIB 1508Y (**1**) **2**

Results and Discussion

The racemization of nicotine employing base-catalyzed deprotonation/protonation of the tertiary C2′ at elevated temperature has been reported.[5,6] Unfortunately, attempts to racemize **2** using this approach, i.e., KO*t*Bu 10% w/w in DME at reflux for 20 h or KO*t*Bu 10% w/w and phosphazine base P_4-*t*-Bu in hexane (10 mol %) in boiling toluene for 14 h, failed to racemize the substrate. A pyridoxal-catalyzed racemization of nornicotine (desmethyl nicotine) and derivatives has been reported,[7] but this procedure was clearly not applicable to the racemization of the tertiary amine **2**.

Examination of the literature revealed that alkyl chloroformates have been reported to cleave the nicotine C2′−N bond.[8,9] In these studies phenyl or ethyl chloroformate was reacted with nicotine to yield ring-opened

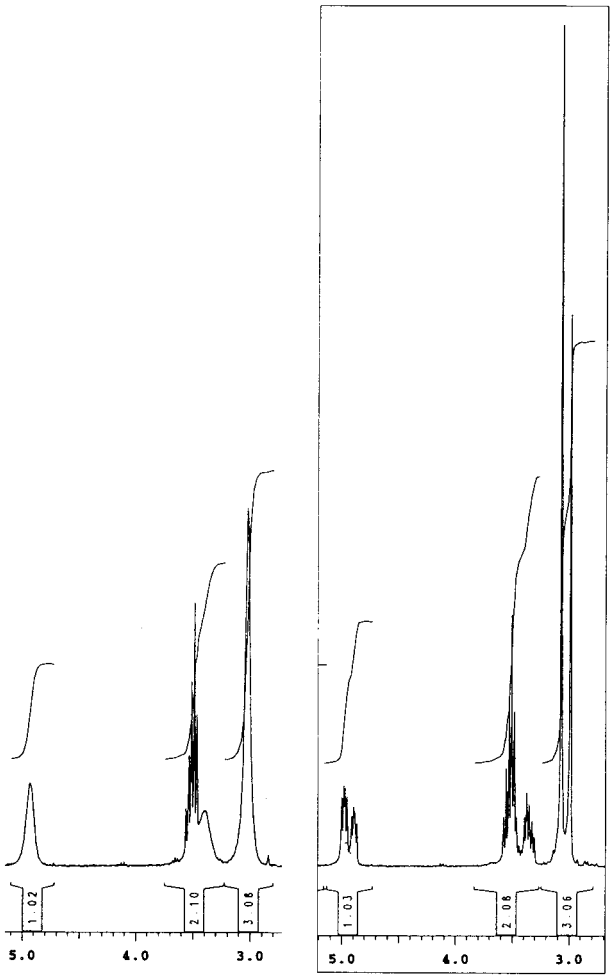


Figure 1. ^{1}H NMR of **3b** at 52 °C (left) and at 22 °C.

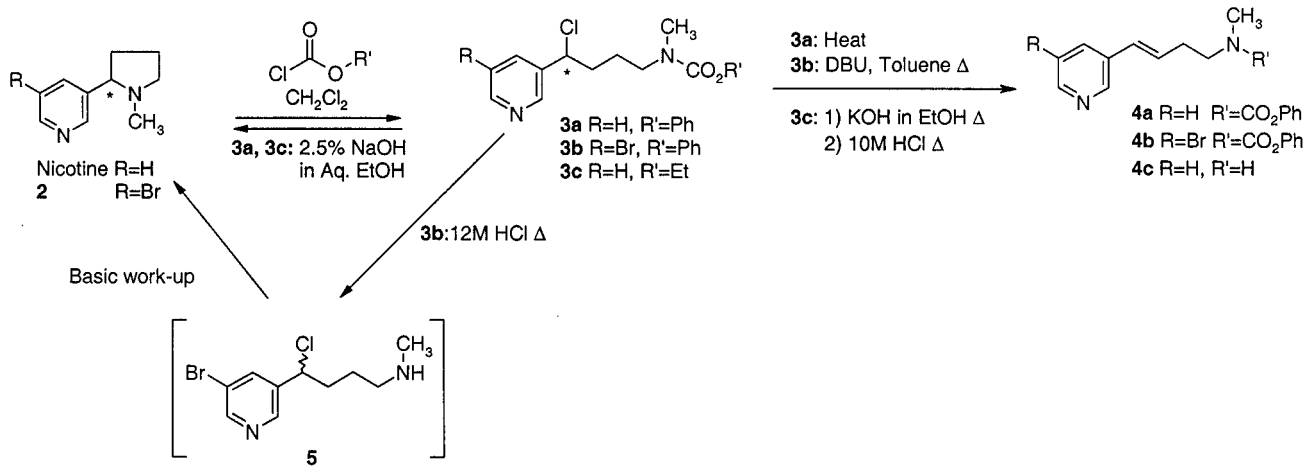
derivatives **3a** or **3c** (Scheme 1). Thermal or strongly basic (KOH/EtOH) elimination of HCl followed by carbamate deprotection provided *trans-meta*-nicotine **4c**. Removal of the carbamate moiety from **3a** or **3c** using 2.5% aqueous NaOH in EtOH gave nicotine with net retention of configuration via a double inversion. Furthermore deprotection of **3c** in boiling 10% aqueous H_2SO_4, upon basification, also gave nicotine with retention of configuration.[8] This implies that neither the ring opening nor ring closure reactions proceed via a discrete carbocation, but that both occur via S_N2-type displacement.

We hypothesized that it might be possible to racemize **3b** by means of acid-catalyzed chloride exchange. Strongly acidic conditions should effect carbamate removal and lead to racemization of **3b** via chloride exchange, and base-induced ring closure of this material would provide racemic **2**. In the event, when (*R*)-enriched **2** (60% ee) was reacted with 1 equiv of phenyl chloroformate, **3b** was formed as a nonracemic viscous oil {$[\alpha]^{18}_D = -20°$ ($c = 5$, EtOH)}. Some concomitant formation of the phenyl carbamate protected 5-bromo-*trans-meta*-nicotine ana-

(1) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. *J. Org. Chem.* **1987**, *52*, 955−957.
(2) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417−9476.
(3) Collet, A.; Brienne, M.-J.; Jacques, J. *Chem. Rev.* **1980**, *80*, 215−230.
(4) Bleicher, L.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109−1118.
(5) Tsujino, Y.; Shibata, S.; Katsuyama, A.; Kisaki, T.; Kaneko, H. *Heterocycles* **1982**, *19*, 2151−2154.
(6) Bowman, E. R.; McKennis, H.; Martin, B. R. *Synth. Commun.* **1982**, *12* (11), 871−879.
(7) Jacob, P. *J. Org. Chem.* **1996**, *61*, 2916−2917.
(8) Acheson, R. M.; Ferris, M. J.; Sinclair, N. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 579−585.
(9) Hootele, C.; Lenders, J. P. *Chimia* **1974**, *28*, 665−666.

10.1021/jo990152g CCC: $18.00
Published on Web 06/24/1999

Scheme 1



logue (**4b**) was observed, and the product ratio was found to be solvent dependent. Interestingly, either methylene chloride or 1,2-dichloroethane as reaction solvent minimized the formation of the alkene **4b**, while performing the reaction in toluene or acetonitrile produced this material in up to 50% yield. In contrast to **3a**, **3b** was stable to mild acid and base. When nonracemic **3b** was heated in concentrated HCl, the phenyl carbamate was removed and the pyridyl chloride was racemized giving intermediate **5**. Basic workup of the reaction allowed racemic **2** to be isolated in 87% yield [based on starting (*R*)-enriched **2**] over the three steps, and this was sufficiently pure to use in an optimized classical resolution procedure.

Conclusion

In summary, a procedure for the racemization of (*R*)-enriched **2** was devised. This protocol constitutes a novel use of chloroformate-induced ring opening and halogen exchange-mediated racemization of substituted pyrrolidine derivatives. The method promises to significantly increase yields obtainable in the resolution sequence and highlights key differences in reactivity between pyridine ring substituted and unsubstituted nicotine derivatives. In view of the recent surge of interest in nicotine analogues as potential therapeutic agents, the methodology described herein should prove to be of utility in the preparation of a variety of novel nicotinic agonists and antagonists.[10]

Experimental Section

General. All reactions, unless otherwise noted, were conducted under an inert atmosphere. Purchased reagents and solvents were used as received. Column chromatography was performed on silica gel (35−70 μm). Melting points were obtained in unsealed capillaries and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in the indicated solvents, and the chemical shifts are reported in ppm downfield from tetramethylsilane, solvent ($CDCl_3$ $\delta_C = 77.00$, $\delta_H = 7.25$; DMSO-d_6 $\delta_C = 39.43$, $\delta_H = 2.5$; CD_3OD $\delta_C = 49.05$, $\delta_H = 3.30$) or added tetramethylsilane served as internal references. Optical rotations were obtained at 589 nm (sodium D line) using a 1.9 dm cell at 20 °C. Chiral gas chromatographic separations were conducted on a 20 m × 0.25 mm capillary column coated with permethylated hydroxypropyl β-cyclodextrin phase at 130 °C under isothermal conditions with a flow rate of 3.0 mL/min (carrier gas He), using flame ionization detection.

Phenyl *N*-{4-Chloro-4-[3-(5-bromopyridinyl)]butyl}-*N*-methylcarbamate (3b). A solution of **2** (60% ee favoring the *R*-isomer) (60.2 g, 0.250 mol) was dissolved in dry CH_2Cl_2 (200 mL) while stirring at ambient temperature. Phenyl chloroformate (32.7 mL, 0.26 mol) was added via syringe over 30 min, and the mixture was stirred at room temperature for 3 h. Water (10 mL) was added and the solution concentrated in vacuo to give **3b** as a viscous opaque brown oil (108 g). This material was carried on to the next step without further purification. A portion of this material was purified by chromatography on silica eluting with CH_2Cl_2:MeOH 98:2 to give a transparent oil. This compound exists as rotamers; pairs of signals at δ 4.9 and 3.0 coalesce in ^{1}H NMR at 52 °C (Figure 1). ^{1}H NMR at 22 °C ($CDCl_3$) δ 8.62 (m, 1H), 8.52 (m, 1H), 7.90 (m, 1H), 7.36 (m, 2H), 7.20 (m, 1H), 7.08 (m, 2H), 4.98 and 4.89 (app dd, J = 5,9 Hz, 1H), 3.51 and 3.38 (m, 2H), 3.08 and 3.00 (s, 3H), 2.11 (m, 2H), 1.87 (m, 1H), 1.75 (m, 1H); ^{13}C NMR at 22 °C ($CDCl_3$) δ 155.0, 151.2 (app d, J = 6 Hz), 150.9, 150.7, 146.3 (app d, J = 4 Hz), 139.0, 138.7, 137.1 (app d, J = 4 Hz), 129.3 (app d, J = 4 Hz), 125.3 (app d, J = 7 Hz), 121.6, 120.8 (app d, J = 5 Hz), 59.0, 53.4, 48.1, 47.8, 36.7, 34.8, 34.3, 25.3, 24.6; $[\alpha]^{18}_D = -20°$ (c = 5, EtOH). Anal. Calcd for: C, 51.34; H, 4.56; N, 7.04. Found: C, 51.36; H, 4.59; N, 7.06.

Racemic 5-Bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (2). 5-Bromo-3-(1-chloro-4-(methyl(phenoxycarbonyl)amino)butyl)pyridine (**3b**) (88 g crude) was taken up in 10 M HCl (600 mL) and heated at reflux (internal temperature 105 °C) for 6 h. The solution was made basic by the addition of NaOH (500 mL of a 40% solution) while cooling with a dry ice−acetone bath to maintain temperature below 50 °C. This mixture was extracted with CH_2Cl_2 (1.2 L) and then dried over Na_2SO_4 and concentrated in vacuo. This material was purified by filtration through silica eluting with EtOAc:hexane 50:50 ⇒ 100:0 to give **2** as a transparent golden oil (43.6 g, 87% from starting (*R*)-**2**) and was shown to be racemic and identical to an authentic sample of **2**.

JO990152G

(10) Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40* (26), 4169−4194.