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Convenient Preparation of Optically Pure 3-Aryloxy-pyrrolidines

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Abstract: Chiral 3-methanesulfonyl-1-Boc-pyrrolidine and piperidine were reacted with sodium phenolates, resulting in a mixture of displacement and elimination products. Following carbamate deprotection and pH adjustment, the 3-pyrroline and tetrahydropyridine by-products resulting from elimination were easily removed through aqueous partitioning and/or concentration. Although the pyrrolidines were formed with a high degree of optical purity, slight racemization was observed for the piperidine case because elevated temperatures were required to effect displacement.

Keywords: aryl ethers, pyrrolidines, piperidines

The 3-aryloxypyrrolidine moiety has been incorporated into various biologically active agents, as exemplified by the factor Xa inhibitor DX-9065a **1**[1] and the $5HT_{2c}$ antagonist Org 37684 **2**.[2] Typically, a Mitsunobu reaction between a hydroxypyrrolidine and a phenol is used to construct the basic framework.[3,4] Recognizing the need to ultimately conduct such a process on a large scale, we desired a synthetic approach that would be

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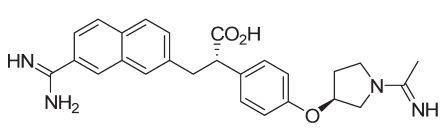
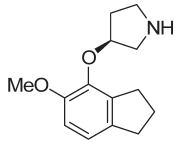
efficient and atom economical, without the generation of phosphine oxide and hydrazide by-products.[5]



1 DX-9065a

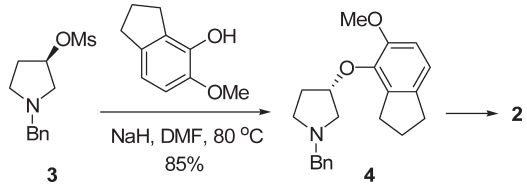


2 Org 37684

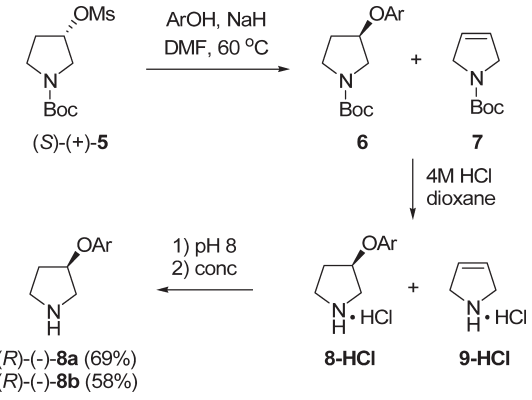
Toward this end, it had been reported in this journal that 3*R*-1-benzyl-3-methanesulfonyloxy-pyrrolidine **3** underwent smooth displacement by the sodium anion of 5-methoxy-4-indanol to afford a precursor (**4**) to Org 37684 (Scheme 1).[2] However, because the conditions required to effect *N*-debenzylation would likely be incompatible with certain functionalities (e.g., chloro), we chose instead to examine etherification of the *N*-Boc-protected mesylate **5**. Several displacement reactions of **5** had been previously reported, including the use of cyanide,[6] enolates,[7] nucleobases,[8] and pyrrolopyrimidines,[9] but phenols seemed to be absent from the range of nucleophilic partners.

Our initial investigation of the displacement of mesylate **5** with the sodium salt of *m*-cresol was at first glance disappointing, as a significant amount (>30%) of elimination by-product was formed (Scheme 2). The by-products were of similar polarity and as a consequence could not be easily separated following the addition step. As a result, the mixture was exposed to anhydrous HCl to deprotect the carbamates in the hope that the by-product could be removed chromatographically at this stage. However, we were delighted to find, after adjusting the pH of the solution to **8** with aqueous $NaHCO_3$, extraction, and concentration, that only amine (−)-**8a** was obtained in 69% yield from **5** in more than 95% chemical purity. Apparently, the elimination by-product **7** on deprotection afforded 3-pyrroline, which either partitioned into the aqueous phase or was evaporated on concentration (bp = 90–91°C at 748 mmHg). Similar results were obtained for displacement of **5** with *o*-cresol, although the steric hindrance afforded by the *ortho* substituent resulted in slightly attenuated yield.

As a further test of this method, we turned our attention to the 3-hydroxypiperidine system. In our hands, the Mitsunobu reaction of *N*-Boc-protected (*R*)-3-hydroxypiperidine **10** (Aldrich) under standard conditions (DIAD, Ph_3P, THF, rt or 60°C) afforded the corresponding piperidine aryl



Scheme 1. Synthesis of Org 37684 (**2**).[2]



Scheme 2. Formation of pure (3*R*)-*m*-tolyloxy-pyrrolidine (−)-**8**.

ethers **11** in low yield (<30%) and contaminated with inseparable triphenylphosphine oxide.[10−12] However, when mesylate (*R*)-(+)-**12**[13] was subjected to displacement with the sodium anion of *m*-cresol or 3-fluorophenol, a ca. 2:1 mixture of displacement and elimination products **11** and **13** was obtained (Scheme 3). Noteworthy is that higher temperatures were required than for the pyrrolidine case to effect usable conversion of starting material to products, which in turn resulted in lower isolated yields because of some decomposition (at 60°C, only starting mesylate **12** and elimination product **13** were observed). Fortunately, as observed previously for the pyrrolidine case, deprotection, aqueous basification, and concentration led to the formation of amines (−)-**14a** and (−)-**14b** in more than 92% chemical purity.

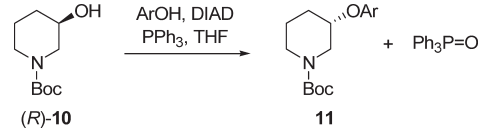
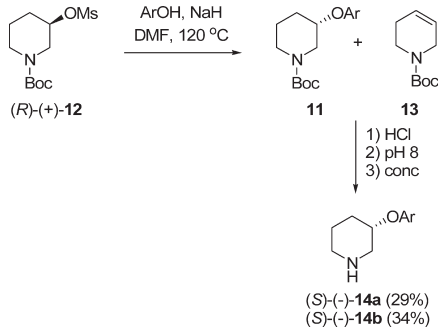


Table 1 contains chemical purity (HPLC) and optical rotation data for chiral mesylates **5** and **12**, as well as *m*-aryloxy substituted heterocycles **8** and **14**. Chemical purity for all crude pyrrolidines and piperidines on concentration was greater than 92%. The sign and magnitude of optical rotation was consistent for the mesylate pairs and also for several final products. In cases where chemical purity was significantly reduced compared to the enantiomeric product (≤2.8%), the magnitude (but not the sign) of rotation was also smaller. Chiral HPLC analysis confirmed that 3-aryloxypyrrolidines **8** were formed with a high degree of optical purity as expected. However, we were surprised to find that slight (ca. 10%) racemization occurred in the case of piperidines **14**, presumably owing to competing displacement by mesylate anion at the elevated temperatures required to effect conversion. Conditions for HPLC optical purity assessment: pyrrolidines **8b**, Chiracel OD-H 0.46 × 25-cm column, mobile phase A CO_2, mobile



Scheme 3. Formation of pure (3*S*)-*m*-tolyloxy-piperidine (−)-**14**.

phase B MeOH + 0.2% isopropylamine, gradient 95% A to 40% A in 15 min, flow rate 4.0 mL/min, injection volume 27 μL, detection DAD 254 nm; piperidines **14b**, Chiracel OD-H 0.46 × 25-cm column, mobile phase A 95% CO_2, mobile phase B 5% MeOH + 0.2% isopropylamine, flow rate 4.0 mL/min, injection volume 30 μL, detection DAD 254 nm.

Table 1. Chemical and optical purity of crude pyrrolidines and piperidines

Entry	Compound	Ar	HPLC purity[a]	α_D^b
1	(*S*)-**5**		94.8%	+22.5
2	(*R*)-**5**		94.5%	−21.0
3	(*R*)-**8a**	3-Me	96.7%	−2.92
4	(*S*)-**8a**	3-Me	96.7%	+2.87
5	(*R*)-**8b**	2-Me	95.4%	−19.9[c]
6	(*S*)-**8b**	2-Me	92.6%	+11.3[c]
7	(*S*)-**12**		96.8%	−2.08
8	(*R*)-**12**		96.8%	+2.68
9	(*R*)-**14a**	3-Me	96.5%	+7.88
10	(*S*)-**14a**	3-Me	96.9%	−7.39
11	(*R*)-**14b**	3-F	92.8%	+3.17[d]
12	(*S*)-**14b**	3-F	95.8%	−6.43[d]

[a]Conditions: ACE_4 5 μm C18, 60 × 150-mm column, acetonitrile with 95% to 10% A gradient over 10 min (A = 0.1 M aq. phosphoric acid), detection 200–400 nm).

[b]Jasco DIP-1000 polarimeter, 589 nm, c = 0.3–1.0 in CH_2Cl_2.

[c]Enantiomeric ratio > 98:2; see *.

[d]Enantiomeric ratio 90:10; see *.

*Conditions for HPLC optical purity assessment; pyrrolidines **8b**, Chiracel OD-H 0.46 × 25 cm column, mobile phase A CO_2, mobile phase B MeOH + 0.2% isopropylamine, gradient 95% A to 40% A in 15 min, flow rate 4.0 mL/min, injection volume 27 μL, detection DAD 254 nm: piperidines **14b**, Chiracel OD-H 0.46 × 25 cm column, mobile phase A 95% CO_2, mobile phase B 5% MeOH + 0.2% isopropylamine, flow rate 4.0 mL/min, injection volume 30 μL, detection DAD 254 nm.

In conclusion, we have developed a phenolate displacement reaction of secondary mesylates situated on carbamate-protected pyrrolidine and piperidine templates. The formation of elimination products in the displacement step was of no consequence with regard to isolation of the free aminoethers. Following deprotection, the by-products were easily removed because of their volatility and/or aqueous solubility. As a result, the 3-aryloxy-pyrrolidines and piperidines were obtained in 29–69% yield with more than 92% chemical purity as well as high optical purity. Slightly reduced optical purity was observed in the piperidine case because of the more demanding conditions to effect displacement. Currently, optimization to effect this transformation under milder conditions to provide enantiopure piperidines is ongoing and will be reported in due course.

EXPERIMENTAL

(*S*)-3-Methanesulfonyloxy-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester 5

To a solution of (*S*)-3-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (10.8 g, 57.41 mmol) in CH_2Cl_2 (80 mL) were added triethylamine (8.8 mL, 63.15 mmol) and methanesulfonyl chloride (4.9 mL, 63.15 mmol). The reaction mixture was stirred at rt for 1 h, then quenched with water (100 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated to afford **5** (15.2 g, quantitative) as an amber oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27 (s, 1H), 3.68–3.50 (m, 4H), 3.05 (s, 3H), 2.29 (m, 1H), 2.17 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.0 (C_q), 81.7–80.9 (d, CH), 79.4 (C_q), 52.7–52.5 (d, CH_2), 44.1–44.0 (d, CH_2), 38.3 (CH_3), 32.5–31.6 (d, CH_2), 28.8 (CH_3). MS m/z 266 [$C_{10}H_{19}NO_5S + 1$].

(*R*)-3-*m*-Tolyloxy-pyrrolidine 8a

To a solution of *m*-cresol (0.39 mL, 3.77 mmol) in DMF (5 mL) was added sodium hydride (60% in oil, 150 mg, 3.77 mmol), and the mixture was stirred at rt for 30 min. A solution of (*S*)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester **5** (1.0 g, 3.77 mmol) in DMF (5 mL) was then added dropwise, and the mixture was heated to 60°C overnight. The mixture was cooled and diluted with EtOAc (10 mL). The organic phase was separated, washed with brine (3 × 50 mL) and 3 *N* KOH (1 × 30 mL), dried ($MgSO_4$), and concentrated to give **6a** and eliminated product **7** (same polarity, ratio 2:1, 1.01 g, 64% in **6a**) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.12 (m, 1H), 6.80–6.68 (m, 3H), 4.89 (br.s, 1H), 3.64–3.52 (m, 4H), 2.33 (s, 3H), 2.17–2.09 (m, 2H), 1.48 (s, 9H). MS m/z

222 [$C_{16}H_{23}NO_3$-55]. To the crude mixture of **6a** and **7** (1.01 g) was added 4 *M* HCl in dioxane (10 mL). The mixture was stirred at rt for 30 min at which time water (20 mL) was added, and the pH of the solution was adjusted to 8 by addition of $NaHCO_3$ in small portions. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phase was dried ($MgSO_4$) and concentrated to furnish **8a** (0.46 g, 69% from **5**) as an amber oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.09 (m, 1H), 6.78–6.61 (m, 3H), 4.85 (br.s, 1H), 3.25–2.96 (m, 4H), 2.32 (2s, 3H), 2.13–1.99 (m, 2H), 1NH not seen. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (C_q), 139.9 (C_q), 129.5 (CH), 122.2 (CH), 116.6 (CH), 112.5 (CH), 70.8 (CH), 52.6 (CH_2), 45.4 (CH_2), 32.7 (CH_2), 21.8 (CH_3). MS m/z 178 [$C_{11}H_{15}NO + 1$].

(*S*)-3-*o*-Tolyloxy-pyrrolidine 8b

Prepared from *o*-cresol (0.39 mL, 3.77 mmol) and (*R*)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester **5** (1.0 g, 3.77 mmol) by the procedure outlined previously to yield **8b** (0.39 g, 58% from **5**) as an amber oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dd, 2H), 6.86 (dd, 1H), 6.77 (dd, 1H), 4.88 (br. s, 1H), 3.63 (br. s, 1H), 3.29–3.02 (m, 4H), 2.20 (s, 3H), 2.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3 (C_q), 131.8 (CH), 128.1 (C_q), 127.0 (CH), 122.0 (CH), 112.0 (CH), 75.1 (CH), 50.3 (CH_2), 44.1 (CH_2), 31.5 (CH_2), 16.7 (CH_3). MS m/z 178 [$C_{11}H_{15}NO + 1$].

(*S*)-3-Methanesulfonyloxy-piperidine-1-carboxylic Acid *tert*-Butyl Ester 12

To a solution of (*S*)-3-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (4.0 g, 19.9 mmol) in dichloromethane (30 mL) were added triethylamine (3.0 mL, 21.9 mmol) and methanesulfonyl chloride (1.7 mL, 21.86 mmol). The reaction mixture was stirred at rt for 1 h, then quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated to provide **12** (5.6 g, quantitative) as a colorless oil that solidified on standing: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (br.s, 1H), 3.69–3.61 (m, 2H), 3.49–3.29 (m, 2H), 3.06 (s, 3H), 2.02–1.77 (m, 3H), 1.58–1.46 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9 (C_q), 80.3 (C_q), 75.6 (CH), 39.0 (CH_3), 30.6 ($2CH_2$), 28.5 ($2CH_2$), 21.8 (CH_3). MS m/z 224 [$C_{11}H_{21}NO_5S$-55].

(*R*)-3-*m*-Tolyloxy-piperidine 14a

To a solution of *m*-cresol (0.78 g, 7.16 mmol) in DMF (5 mL) was added sodium hydride (60% in oil, 0.29 g, 7.16 mmol) portionwise at 0°C. The mixture was

stirred at rt for 1 h, at which time a solution of (*S*)-3-methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester **12** (2.0 g, 7.16 mmol) in DMF (5 mL) was added dropwise. The mixture was heated to 120°C overnight, then cooled and poured into EtOAc (50 mL), washed with *3 N* KOH (30 mL) and brine (2 × 50 mL), dried (Na_2SO_4), and concentrated to afford **11a** and eliminated product **13** (same polarity, ratio 2: 1, 1.29 g, 41% in **11a**) as a brown oil. MS m/z 236 [$C_{17}H_{25}NO_3$-55]. To the crude mixture of **11a** and **13** (1.29 g) was added 4 *M* HCl in dioxane (5 mL). The mixture was stirred at rt for 1 h, at which time water (10 mL) was added and the pH of the solution adjusted to 8 by addition of $NaHCO_3$ in small portions. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the organic phase was dried ($MgSO_4$) and concentrated to provide **14a** (0.40 g, 29% from **12**) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.16 (dd, 1H), 6.78–6.72 (m, 3H), 4.38–4.32 (m, 1H), 4.22–4.00 (br.s, 1H), 3.22–3.20 (m, 1H), 2.95–2.80 (m, 3H), 2.30 (s, 3H), 2.05–1.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2 (C_q), 140.0 (C_q), 129.8 (CH), 122.0 (CH), 117.0 (CH), 112.9 (CH), 71.8 (CH), 50.3 (CH_2), 46.0 (CH_2), 29.9 (CH_2), 23.7 (CH_2), 21.9 (CH_3). MS m/z 192 [$C_{12}H_{17}NO + 1$].

(*R*)-3-(3-Fluoro-phenoxy)-piperidine 14b

Prepared from 3-fluorophenol (0.8 g, 7.16 mmol) and (*S*)-3-methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester **12** (2.0 g, 7.16 mmol) by the procedure outlined previously to give **14b** (0.48 g, 34% from **12**) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.17 (m, 1H), 6.74–6.70 (dd, 1H), 6.68–6.62 (m, 2H), 4.32–4.26 (m, 1H), 3.43–3.25 (br.s, 1H), 3.21–3.18 (m, 1H), 2.95–2.78 (m, 3H), 2.05–1.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5–162.8 (d (C-F), C_q), 159.0 (C_q), 130.3 (CH), 111.8 (CH), 108.0 (CH), 103.9 (CH), 72.2 (CH), 50.1 (CH_2), 46.0 (CH_2), 29.9 (CH_2), 23.9 (CH_2). MS m/z 196 [$C_{11}H_{14}FNO + 1$].

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