Conversion of Phenols into Aryl *Tert*-Butyl Ethers Under Mitsunobu Conditions Utilizing Neighboring Group Contribution

Annette Wolfgardt and Franz Bracher*

Department of Pharmacy – Center for Drug Research, Ludwig-Maximilians-University, Butenandtstr. 5–13, 81377 Munich, Germany

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Abstract: Under Mitsunobu conditions *N*-Boc-2-(hydroxymethyl)piperidine acts as a source of *tert*-butyl residue for the conversion of phenols into aryl *tert*-butyl ethers under neutral conditions. This reactivity can be attributed to a neighboring group contribution which strongly depends on the structure of the employed *N*-Boc-aminoalcohol. Five other, closely related *N*-Boc-aminoalcohols investigated here did not show this special reactivity, and gave the regular Mitsunobu coupling products.

Keywords: *N*-Boc-aminoalcohols, *tert*-butyl ether, Mitsunobu reaction, neighboring group contribution, protecting group, stereoselective reaction.

INTRODUCTION

In a project aimed at the synthesis of new cholesterol biosynthesis inhibitors we intended to connect selected phenols with *N*-Boc-protected piperidine moieties through an ether linkage. In order to accomplish the coupling under mild reaction conditions, we selected the well established Mitsunobu reaction [1] for the synthesis of the ether moiety starting from the phenols and *N*-Boc-2-(hydroxymethyl)piperidine (**2**).

In this communication we report on an unexpected formation of aryl *tert*-butyl ethers under Mitsunobu conditions, and give evidence that a neighboring group contribution is the driving force in this reaction.

RESULTS AND DISCUSSION

The phenol **1a**, easily prepared from 3-hydroxybenzaldehyde and the corresponding *N*-methylbenzylamine by reductive amination with sodium cyanoborohydride as reducing agent, was reacted with *N*-Boc-2-(hydroxymethyl) piperidine (**2**) under Mitsunobu conditions (triphenylphosphane and diisopropyl azodicaboxylate, DIAD) [1]. To our surprise, the attempted *N*-Boc-protected piperidinomethyl ether **3** (R = Cl) could not be detected in the reaction mixture, but we isolated the aryl *tert*-butyl ether **4a** in 29 % yield. In the same manner the bromo and nitro analogs **4b** and **4c** were obtained (Scheme **1**). This is in contrast to an earlier report on a successful coupling of a phenol with **2** under comparable conditions [2]. In order to exclude that *tert*-butanol, which might have been a contaminant or decomposition product of the *N*-Boc-piperidine **2**, was the actual source of the *tert*-butyl residue, we performed a control experiment in which **1a** was reacted with *tert*-butanol and the Mitsunobu reagents under identical conditions, but not even traces of **4a** were detected. This is in line with the known reluctance of tertiary alcohols to undergo Mitsunobu-type couplings [3]. Consequently, the *N*-Boc-2-(hydroxymethyl)piperidine **2** acts as the *tert*-butyl group donor under Mitsunobu conditions.

For this unexpected reaction we propose a mechanism that includes a neighboring group contribution (Scheme **2**). In the first step, the hydroxymethyl group of **2** undergoes the standard initial step of Mitsunobu activation, i.e. the formation of the oxyphosphonium intermediate **5** accompanied by a phenolate. Nucleophilic attack of the carbonyl oxygen of the Boc group at the activated side chain methylene carbon should lead to a fragmentation of the molecule yielding triphenylphosphane oxide, the cyclic carbamate **6**, and a *tert*-butyl cation, which itself combines with the phenolate to give the aryl *tert*-butyl ether. In fact, we could detect the carbamate **6** in the reaction mixture by GC-MS. An authentic sample of **6** was easily obtained from 2-(hydroxymethyl) piperidine, but by replacing phosgene [4] by less hazardous triphosgene in analogy to a known protocol [5].

The moderate to poor yields of the aryl *tert*-butyl ethers can be explained by competing decomposition of the *tert*-butyl cation under deprotonation to give isobutene. A related route to aryl *tert*-butyl ethers *via* an *intra*molecular transfer of a *tert*-butyl residue from a Boc-anhydride intermediate has been described, but this method requires activation by a Lewis acid (magnesium perchlorate) [6]. The loss (but not further utilization) of a *tert*-butyl cation by an intramolecular attack at the carbonyl oxygen of a Boc-protected sugar ending up with a cyclic carbonate has been observed [7]; a similar mechanism has been claimed for iodocyclisations of homoallylic *tert*-butyl carbonates [8].

*Address correspondence to this author at the Department of Pharmacy – Center for Drug Research, Ludwig-Maximilians-University, Butenandtstr. 5–13, 81377 Munich, Germany; Tel: +49-89-218077301; Fax: +49-89-218077802; E-mail: Franz.Bracher@cup.uni-muenchen.de

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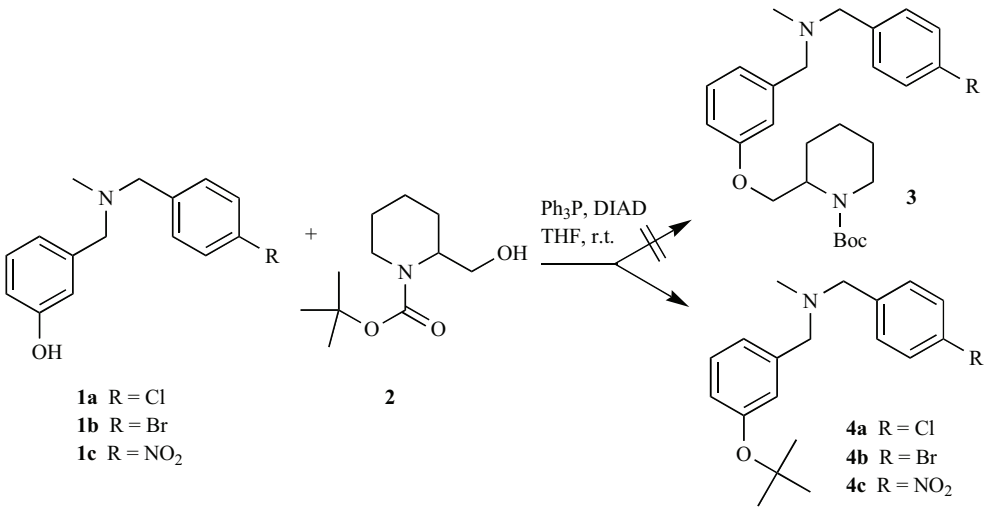
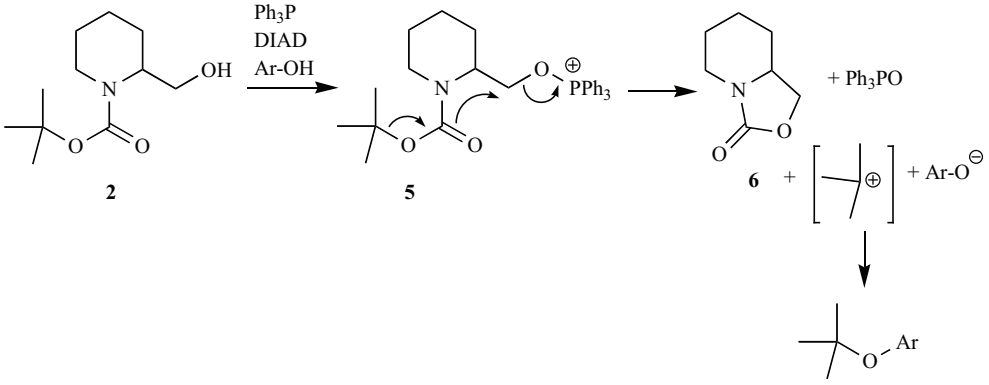


Scheme 1. Unexpected formation of aryl *tert*-butyl ethers.



Scheme 2. Proposed mechanism of the neighboring group contribution.

In order to explore whether this unexpected reactivity found for **2** is common to other *N*-Boc-aminoalcohols, we reacted phenol **1a** in the same manner with the five-membered ring analogue *N*-Boc-2-(hydroxymethyl)pyrrolidine **7**, the side-chain homologue *N*-Boc-2-(2-hydroxyethyl) piperidine **8**, the open-chain *N*-Boc-aminoethanols **9** and **10**, as well as *N*-Boc-3-hydroxypiperidine (**11**), in which an *intra*molecular activation as proposed above cannot take place for steric reasons. In all five experiments we obtained the regular Mitsunobu products (**12** - **16**) resulting from coupling of the phenol **1a** with the hydroxyl groups of the *N*-Boc-aminoalcohols. The ethers derived from the primary alcohols were obtained in 50 to 83 % yield, the secondary alkyl ether **16** in 31 % yield. In neither of these reactions the *tert*-butyl ether **4a** was detected (Scheme **3**).

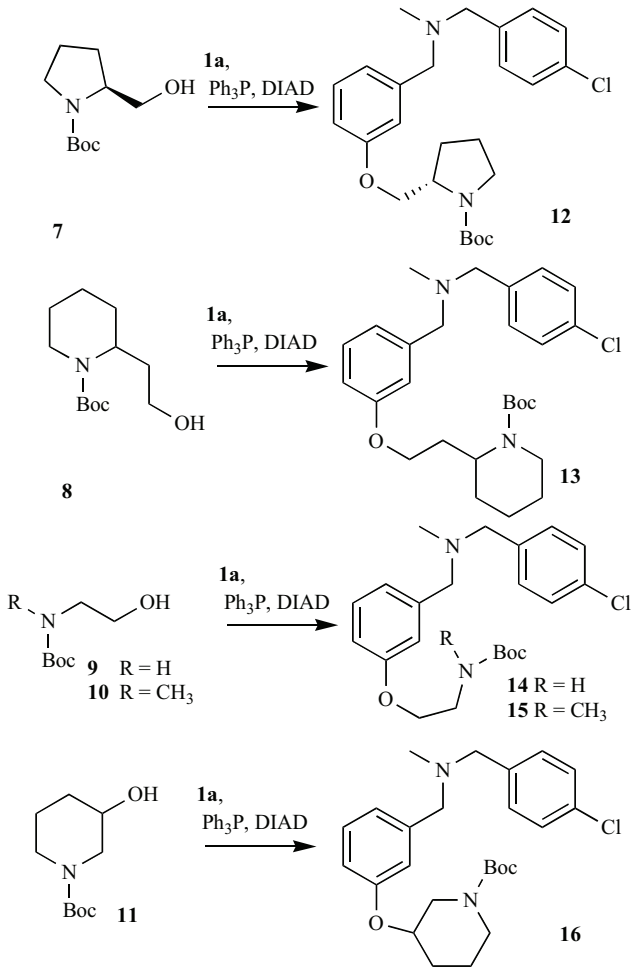
This leads to the conclusion that the unexpected reactivity of **2** with phenols under Mitsunobu conditions is not only due to the proximity of both the primary alcohol and *N*-Boc groups, but is significantly controlled by steric parameters. This is particularly illustrated by the differences in reactivity observed with **2** and its five-membered ring homologue **7**, its side chain homologue **8**, and the failure of flexible open-chain analogues to release the *tert*-butyl residue.

Finally, we demonstrated that this new *tert*-butylation protocol also works with other phenols bearing additional functional groups. Reacting 2-naphthol, vanillin, and ethyl 4-hydroxybenzoate with **2**, triphenylphosphane, and DIAD gave the *tert*-butyl ethers **17** - **19** in 21 to 30 % yields (Scheme **4**). We undertook several attempts to improve the yields of the *tert*-butyl ethers (higher amounts of reagents; higher concentrations; isobutene as a solvent to reduce decomposition of the *tert*-butyl cation), but did not obtain considerably better yields.

In conclusion, we have detected a neighboring group contribution in Mitsunobu reactions leading to the conversion of phenols into aryl *tert*-butyl ethers. In principle, this constitutes a new method for the protection of phenols under very mild, neutral conditions, whereas established protocols require either alkaline conditions (for the conversion to a phenolate, followed by *O*-alkylation with a *tert*-butyl halide [9]), or acidic conditions (mineral acids, Lewis acids) in combination with *tert*-butanol or isobutene [6, 10, 11]. Working under strongly acidic conditions further bears the risk of undesired *C*-alkylation of the substrate phenols [9b, 12]. But due to the poor yields an application of this method will be restricted to the protection of phenols which are both acid- and base-sensitive.

EXPERIMENTAL SECTION

Melting points (uncorrected): Büchi B-540. IR spectra: Perkin Elmer FT-IR Paragon 1000. Mass spectra: JMS



Scheme 3. Control experiments with other *N*-Boc-aminoalcohols leading to regular Mitsunobu products. All experiments were performed in THF at room temperature.

GCmate II Jeol. NMR spectra: JNM-Eclipse+400 (^{1}H NMR: 400 MHz, ^{13}C NMR 100 MHz) and JNM-Eclipse+500 (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz); chemical shifts are reported in parts per million (ppm), tetramethylsilane (TMS, 0.00 ppm) as internal standard. Flash column chromatography: silica gel 60 (0.040-0.063 mm; Merck). Solvents were dried using standard procedures and freshly distilled prior to use.

General Procedure 1: Synthesis of the 3-(aminomethyl)phenols 1a-c

3-Hydroxybenzaldehyde (20 mmol) and the corresponding *N*-methylbenzylamine (8 mmol) were dissolved in methanol (5 mL). Acetic acid (0.4 mL) and sodium cyanoborohydride (16 mmol) were added and the mixture was stirred for 18 h at room temperature. The solvent was evaporated, the residue was suspended in satd. Na_2CO_3 solution (100 mL), and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by flash column chromatography (1:1 hexane/ethyl acetate with 2 % *N*-ethyl-*N*,*N*-dimethylamine).

3-[N-(4-Chlorobenzyl)-N-methylaminomethyl]phenol (1a)

Prepared following General Procedure 1 using *N*-methyl-4-chlorobenzylamine. Yield: 79 %. mp 61-63 °C. IR (KBr) **ν** (cm^{-1}) = 2792, 1589, 1489, 1456, 1273, 1089, 1015. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.30 (m, 4H), 7.16 (t, J = 7.8 Hz, 1H), 6.88 (m, 1H), 6.86 (m, 1H), 6.71 (m, 1H), 3.47 (s, 2H), 3.44 (s, 2H), 2.13 (s, 3H, *N*-CH_3). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 156.5, 141.5, 138.5, 132.8, 130.7, 129.7, 128.6, 121.3, 116.1, 114.4, 61.9, 61.3, 42.3. HRMS calculated for $C_{15}H_{16}ClNO$: 261.0920; found 261.0932.

3-[N-(4-Bromobenzyl)-N-methylaminomethyl]phenol (1b)

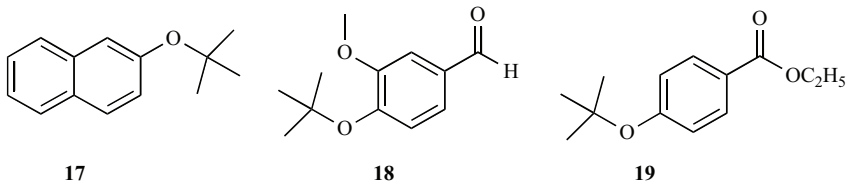
Prepared following General Procedure 1 using *N*-methyl-4-bromobenzylamine. Yield: 83 %. mp 58-60 °C. IR IR (KBr) **ν** (cm^{-1}) = 2789, 1589, 1486, 1458, 1273, 1070, 1011. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.45 (m, 2H), 7.27 (m, 2H), 7.17 (t, J = 7.8 Hz, 1H), 6.90 (m, 1H), 6.85 (m, 1H), 6.70 (m, 1H), 3.46 (s, 2H), 3.45 (s, 2H), 2.13 (s, 3H, *N*-CH_3). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 156.9, 141.6, 139.1, 131.6, 131.1, 129.7, 121.0, 120.8, 116.1, 114.4, 61.9, 61.4, 42.3. HRMS calculated for $C_{15}H_{16}BrNO$: 305.0415; found 305.0401.

3-[N-Methyl-N-(4-nitrobenzyl)aminomethyl]phenol (1c)

Prepared following General Procedure 1 using *N*-methyl-4-nitrobenzylamine. Yield: 89 %. mp 106-108 °C. IR (KBr) **ν** (cm^{-1}) = 2925, 1607, 1585, 1513, 1341, 1099, 1005. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.16 (m, 2H), 7.57 (m, 2H), 7.18 (t, J = 7.9 Hz, 1H), 6.91 (m, 1H), 6.88 (m, 1H), 6.72 (m, 1H), 3.60 (s, 2H), 3.50 (s, 2H), 2.17 (s, 3H, *N*-CH_3). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 156.3, 148.0, 147.5, 141.4, 129.8, 129.8, 123.8, 121.5, 115.9, 114.4, 62.1, 61.3, 42.5. HRMS calculated for $C_{15}H_{16}N_2O_3$: 272.1161; found 272.1160.

General Procedure 2: Synthesis of aryl tert-butyl ethers 4a - 4c

tert-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (**2**; 5 mmol), the corresponding phenol **1a-c** (5 mmol), and



Scheme 4. Further aryl *tert*-butyl ethers obtained from phenols using the reagent combination **2**/Ph_3P/DIAD.

triphenylphosphane (5 mmol) were dissolved in anhydrous THF (7 mL), and diisopropyl azodicarboxylate (DIAD; 5 mmol) was added dropwise and the mixture was stirred for 18 h at room temperature. After evaporation of the volatile components the product was purified by flash column chromatography (hexane with 2% *N*-ethyl-*N*,*N*-dimethylamine).

N-(3-tert-Butoxybenzyl)-1-(4-chlorophenyl)-N-methylmethanamine (4a)

Prepared from **1a** following General Procedure 2. Yield: 29 %. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2977, 2786, 1600, 1489, 1365, 1260, 1145. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.30 (m, 4H), 7.20 (t, J = 7.8 Hz, 1H), 7.05 (m, 1H), 7.00 (m, 1H), 6.86 (m, 1H), 3.47 (s, 4H), 2.13 (s, 3H, N-CH_3), 1.32 (s, 9H, ($C(CH_3)_3$). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 155.9, 140.8, 138.8, 132.7, 130.6, 128.9, 128.6, 124.9, 124.1, 123.0, 78.5, 62.0, 61.2, 42.3, 29.0. HRMS calculated for $C_{19}H_{24}ClNO$: 317.1546; found 317.1554.

1-(4-Bromophenyl)-N-(3-tert-butoxybenyl)-N-methylmethanamine (4b)

Prepared from **1b** following General Procedure 2. Yield: 29 %. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2976, 1601, 1485, 1365, 1260, 1176, 1145 ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.44 (m, 2H), 7.26 (m, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.05 (m, 1H), 7.00 (m, 1H), 6.86 (m, 1H), 3.47 (s, 2H), 3.45 (s, 2H), 2.13 (s, 3H, N-CH_3), 1.32 (s, 9H, ($C(CH_3)_3$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 155.9, 140.8, 139.3, 131.6, 131.0, 128.9, 124.9, 124.1, 123.0, 120.8, 78.5, 62.0, 61.3, 42.3, 29.0. HRMS calculated for $C_{19}H_{24}BrNO$: 361.1041; found 361.1058.

N-(3-tert-Butoxybenzyl)-N-methyl-1-(4-nitrophenyl)methanamine (4c)

Prepared from **1c** following General Procedure 2. Yield: 28 %. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2976, 1601, 1520, 1484, 1245, 1260, 1176, 1145. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.16 (m, 2H), 7.56 (m, 2H), 7.21 (t, J = 7.7 Hz, 1H), 7.07 (m, 1H), 7.02 (m, 1H), 6.87 (m, 1H,), 3.59 (s, 2H), 3.52 (s, 2H), 2.18 (s, 3H, N-CH_3), 1.32 (s, 9H, ($C(CH_3)_3$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 156.0, 148.3, 147.5, 140.5, 129.7, 129.0, 124.9, 124.1, 123.8, 123.2, 78.6, 62.2, 61.2, 42.5, 29.0. HRMS calculated for $C_{19}H_{24}N_2O_3$: 328.1787; found 328.1800.

Tetrahydro-1H-oxazolo-[3,4-a]pyridin-3(5H)-one (6)

2-(Hydroxymethyl)piperidine (2.0 mmol) and triethylamine (6.0 mmol) were dissolved in anhydrous dichloromethane (3 mL). A solution of triphosgene (1.0 mmol) in anhydrous dichloromethane (1 mL) was added dropwise, and the mixture was stirred for 3 h at room temperature. The solvent was evaporated at room temperature and the residue purified by flash column chromatography (1:1 hexane/ethyl acetate with 2 % triethylamine). The fractions were not evaporated to complete dryness, since the product tends towards polymerisation [4]. The mass spectrum corresponded to the one published in lit [4].

GC-MS analysis of **6**: A Shimadzu GC 17-A with Shimadzu GCMS OP-5000 was equipped with a Varian Factor Four EZ Guard VF 5 MS column (30 m x 0.25 mm x 0.25 µm). The injector was held at 280 °C and operated in split mode (split ratio: 1:68). The GC-MS conditions were as following: helium 5.0, constant flow of 1.3 mL min^{-1}, linear velocity 42.4 cm sec^{-1}, injection volume 1 µL, MS transfer line temperature 280 °C. The initial GC oven temperature was 100 °C held for 1 min, and ramped with 15 °C min^{-1} to 310 °C (hold time 5 min). The total run time was 20.0 min. The MS was operated at a mass range from 100 to 500 *m/z*. Retention time of **6**: 5.66 min.

Analysis of the reaction leading to **4a**: 5.33 min: reduced DIAD (diisopropyl hydrazodicarboxylate); 5.69 min: **6**; 6.29 min: **2**; 11.08 min: **1a**; 11.15 min: **4a**; 12.86 min: triphenylphosphane oxide.

General Procedure 3: Regular Mitsunobu couplings giving ethers 12 - 16

Phenol **1a** (1.5 mmol), the corresponding *N*-Boc-aminoalcohol (**7**/**8**/**9**/**10**/**11**; 1.5 mmol), and triphenylphosphane (1.5 mmol) were dissolved in anhydrous THF (5 mL). Diisopropyl azodicarboxylate (1.5 mmol) was added dropwise and the mixture was stirred for 18 h at room temperature. After evaporation of the volatile components the product was purified by flash column chromatography (hexane with 2 % triethylamine).

(S)-tert-Butyl 2-{3-[N-(4-chlorobenzyl)-N-methylaminomethyl]phenoxymethyl}pyrrolidine-1-carboxylate (12)

Prepared following General Procedure 3 using (*S*)-*tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (**7**). Yield: 50 % yield. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2975, 1693, 1585, 1489, 1392, 1365, 1167. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.31 (m, 4H), 7.21 (m, 1H), 6.93 (m, 2H), 6.82 (m, 1H), 4.11 (m, 2H), 3.87 (m, 1H), 3.46 (s, 4H), 3.36 (m, 2H), 2.13 (s, 3H, N-CH_3), 2.00 (m, 3H), 1.85 (m, 1H), 1.45 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 159.4, 153.0, 141.5, 138.7, 132.7, 130.6, 129.5, 128.6, 121.6, 115.4, 113.2, 79.5, 68.6, 62.1, 61.3, 56.5, 47.1, 42.3, 28.8, 28.6, 23.7. HRMS calculated for $C_{25}H_{33}ClN_2O_3$: 444.2180; found 444.2160.

tert-Butyl N-{3-[N-(4-chlorobenzyl)-N-methylaminomethyl]phenoxyethyl}-N-methylcarbamate (15)

Prepared following General Procedure 3 using *tert*-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate (**10**). Yield: 73 %. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2928, 1695, 1488, 1451, 1391, 1365, 1154. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.30 (m, 4H), 7.22 (m, 1H), 6.93 (m, 2H), 6.78 (m, 1H), 4.07 (m, 2H), 3.58 (m, 2H), 3.47 (s, 2H), 3.46 (s, 2H), 2.95 (s, 3H, N-CH_3), 2.13 (s, 3H, N-CH_3), 1.43 (m, 9H, $C(CH_3)_3$). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 159.3, 155.9, 141.6, 138.8, 132.7, 130.6, 129.5, 128.6, 121.7, 115.2, 113.2, 79.6, 66.7, 62.1, 61.3, 48.7, 42.4, 35.9, 28.5. HRMS calculated for $C_{23}H_{31}ClN_2O_3$: 418.2023; found 418.2023.

tert-Butyl N-{3-[N-(4-chlorobenzyl)-N-methylamino-methyl]phenoxyethyl}carbamate (14)

Prepared following General Procedure 3 using *tert*-butyl *N*-(2-hydroxyethyl)carbamate (**9**). Yield: 73 %. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2977, 1710, 1585, 1490, 1365, 1252, 1167. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.30 (m, 4H), 7.22 (m, 1H), 6.93 (m, 2H), 6.78 (m, 1H), 5.03 (s, 1H, NH), 4.01 (m, 2H), 3.51 (m, 2H), 3.47 (s, 4H), 2.13 (s, 3H, *N*-CH_3), 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 159.2, 156.2, 141.7, 138.7, 132.7, 130.6, 129.6, 128.6, 121.8, 115.2, 113.2, 79.5, 67.5, 62.1, 61.4, 42.3, 40.6, 28.5. HRMS calculated for $C_{22}H_{29}ClN_2O_3$: 404.1867; found 404.1876.

tert-Butyl 3-{3-[N-(4-chlorobenzyl)-N-methylamino-methyl]phenoxyethyl}piperidine-1-carboxylate (13)

Prepared following General Procedure 3 using *tert*-butyl 2-(hydroxyethyl)piperidine-1-carboxylate (**8**). Yield: 83 % yield. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2977, 2932, 1697, 1418, 1366, 1240, 1167. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.30 (m, 4H), 7.20 (m, 1H), 6.91 (m, 2H), 6.74 (m, 1H), 4.47 (m, 1H), 3.92 (m, 3H), 3.46 (s, 4H), 2.80 (m, 1H), 2.23 (m, 1H), 2.12 (s, 3H, *N*-CH_3), 1.84 (m, 1H), 1.60 (m, 6H), 1.36 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 159.5, 155.2, 141.5, 138.7, 132.7, 130.6, 129.5, 128.6, 121.3, 115.1, 113.2, 79.2, 65.6, 62.2, 61.3, 48.2, 42.3, 39.0, 30.0, 29.4, 28.5, 26.1, 19.5. HRMS calculated for $C_{27}H_{37}ClN_2O_3$: 472.2493; found 472.2491.

tert-Butyl 3-{3-[N-(4-chlorobenzyl)-N-methylamino-methyl]phenoxy}piperidine-1-carboxylate (16)

Prepared following General Procedure 3 using *tert*-butyl 3-hydroxypiperidine-1-carboxylate (**11**). Yield: 31 %. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2929, 1694, 1488, 1422, 1365, 1258, 1146. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.30 (m, 4H), 7.22 (m, 1H), 6.94 (m, 2H), 6.80 (m, 1H), 4.26 (m, 1H), 4.03–3.00 (m, 4H), 3.47 (s, 4H), 2.14 (s, 3H, *N*-CH_3), 2.00 (m, 1H), 1.81 (m, 1H), 1.46 (m, 2H), 1.34 (m, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 157.9, 155.0, 141.7, 138.7, 132.7, 130.6, 129.6, 128.6, 121.7, 116.5, 114.4, 79.6, 71.3, 62.1, 61.3, 47.8, 43.9, 42.4, 30.4, 28.4, 22.6. HRMS calculated for $C_{25}H_{33}ClN_2O_3$: 444.2180; found 444.2179.

General Procedure 4: Synthesis of aryl tert-butyl ethers 17 - 19

tert-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (**2**; 1.5 mmol), the corresponding phenol (1.5 mmol), and triphenylphosphane (1.5 mmol) were dissolved in anhydrous THF (5 mL). Diisopropyl azodicarboxylate (1.5 mmol) was added dropwise and the mixture was stirred for 18 h at room temperature. After evaporation of the volatile components the product was purified by flash column chromatography (9:1 hexane/ethyl acetate).

2-(tert-Butoxy)naphthalene (17)

Prepared following General Procedure 4 from 2-naphthol. Yield: 30 % yield. The spectroscopic data correspond to those published in lit [9d].

4-(tert-Butoxy)-3-methoxybenzaldehyde (18)

Prepared following General Procedure 4 from vanillin. Yield: 21 %. The spectroscopic data correspond to those published in lit. [13].

Ethyl 4-(tert-butoxy)benzoate (19)

Prepared following General Procedure 4 from ethyl 4-hydroxybenzoate. Yield: 21 %. Viscous oil. IR (NaCl, film) ν (cm^{-1}) = 2979, 1715, 1605, 1367, 1275, 1159, 1098. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.93 (m, 2H), 7.01 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.39 (s, 9H, $C(CH_3)_3$), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 166.6, 160.5, 131.0, 125.2, 122.9, 79.8, 61.1, 29.0, 14.6. HRMS calculated for $C_{13}H_{18}O_3$: 222.1256; found 222.1265.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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Declared none.

REFERENCES

[1] Mitsunobu, O. The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. *Synthesis,* **1981**, 1-28.

[2] Mendel, D.; Marquardt, A. L.; Joseph, S.; Waid, P.; Yee, Y. K.; Tebbe, A. L.; Ratz, A. M.; Herron, D. K.; Goodson, T.; Masters, J. J.; Franciskovich, J. B.; Tinsley, J. M.; Wiley, M. R.; Weir, L. C.; Kyle, J. A.; Klimkowski, V. J.; Smith, G. F.; Towner, R. D.; Froelich, L. L.; Buben, J.; Craft, T. J. Anthranilamide inhibitors of factor Xa. *Bioorg. Med. Chem. Lett.,* **2007**, *17*, 4832-4836; no experimental details and analytical data are presented in this publication.

[3] (a) Shi, Y.-J.; Hughes, D. L.; McNamara, J. M. Stereospecific synthesis of chiral tertiary alkyl-aryl ethers *via* Mitsunobu reaction with complete inversion of configuration. *Tetrahedron Lett.* **2003**, *44*, 3609-3611. (b) Mayer, C. D.; Kehrel, M.; Bracher, F. An improved approach to *N*-substituted maleimides and phthalimides by microwave-promoted Mitsunobu reaction. *Org. Prep. Proced. Int.,* **2008**, *40*, 574-579.

[4] Hall, H. K. Jr.; El-Shekeil, A. Anti-Bredt molecules. 3. 3-Oxa-1-azabicyclo[3.3.1]nonan-2-one and 6-oxa-1-azabicyclo[3.2.1]octan-7-one, two atom-bridged bicyclic urethanes possessing bridgehead nitrogen. *J. Org. Chem.,* **1980**, *45*, 5325-5328.

[5] Bracher, F.; Berns, C. Triphosgene in organic chemistry: A novel synthesis of the antiinflammatory prodrug droxicam. *J. prakt. Chem.,* **1997**, *339*, 477-478.

[6] Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. Unusual and unexpected reactivity of t-butyl dicarbonate (Boc_2O) with alcohols in the presence of magnesium perchlorate. A new and general route to t-butyl ethers. *Org. Lett.,* **2005**, *7*, 427-430.

[7] Crich, D.; Hu, T.; Cai, F. Does neighboring group participation by non-vicinal esters play a role in glycosylation reactions? Effective probes for the detection of bridging intermediates. *J. Org. Chem.,* **2008**, *73*, 8942-8953.

[8] Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. Carbonate extension. A versatile procedure for functionalization of acyclic homoallylic alcohols with moderate stereocontrol. *J. Org. Chem.,* **1982**, *47*, 4013-4018.

[9] (a) Masada, H.; Oishi, Y. A new synthesis of aryl *t*-butyl ethers. *Chem. Lett.,* **1978**, 57-58. (b) Bandgar, B. P.; Kasture, S. P. Protection of phenols as *t*-butyl ethers under mild conditions. *J. Chem. Res., (S)* **2000**, 252-253. (c) Rai, N. P.; Arunachalam, P. N. Effi-

cient synthesis of *tert*-butyl ethers under solvent-free conditions. *Synth. Commun.,* **2007**, *37*, 2891-2896. (d) Mahammed, K. A.; Keshava Murthy, P. S.; Mohana Raju, K. A convenient synthesis of *tert*-butyl ethers under microwave conditions. *Indian J. Chem.,* **2008**, *47B*, 575-578.

[10] (a) Holcombe, J. L.; Livinghouse, T. A new and specific method for the protection of phenols as the corresponding *tert*-butyl ethers. *J. Org. Chem.,* **1986**, *51*, 111-113. (b) Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. Convenient preparations of t-butyl esters and ethers from t-butanol. *Tetrahedron Lett.,* **1997**, *38*, 7345-7348.

[11] Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Locatelli, M.; Melchiorre, P.; Sambri, L. Alcohols and di-*tert*-butyl dicarbonate: How the nature of the Lewis acid catalyst may address the reaction to the synthesis of *tert*-butyl ethers. *J. Org. Chem.,* **2006**, *71*, 9580-9588.

[12] Hansen, M. M.; Riggs, J. R. A novel protecting group for hindered phenols. *Tetrahedron Lett.,* **1998**, *39*, 2705-2706.

[13] Ploypradith, P.; Cheryklin, P.; Niyomtham, N.; Bertoni, D. R.; Ruchirawat, S. Solid-supported acids as mild and versatile reagents for the deprotection of aromatic ethers. *Org. Lett.,* **2007**, *9*, 2637-2640.