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Jhon J. López & Edwin G. Pérez

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New convergent one pot synthesis of amino benzyl ethers bearing a nitrogen-containing bicycle

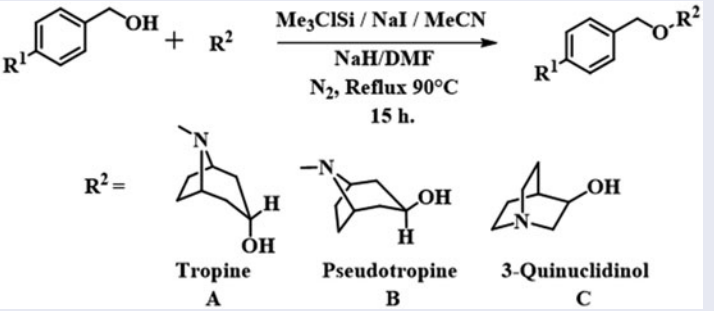
Jhon J. López[a] and Edwin G. Pérez[b]

[a]Department of Organic Chemistry, Faculty of Chemical Sciences, Universidad de Concepción, Concepción, Chile; [b]Department of Organic Chemistry, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile, Santiago, Chile

ABSTRACT

We report herein a new convergent one pot method for the synthesis of amino benzyl ethers containing a bicyclic amine, derived from different substituted benzyl alcohols and bicyclic amino alcohols such as tropine, pseudotropine, and 3-quinuclidinol, using chlorotrimethylsilane and sodium iodide. In order to avoid the competitive reaction with the nitrogen atom, a solution of the separately prepared alkoxide of tropine, pseudotropine, and 3-quinuclidinol was added to the preformed substituted benzyl iodides and allowed to reflux at 90 °C for 15 h under nitrogen atmosphere. This method provides an efficient alternative of the preparation of amino benzyl ethers in organic synthesis with good yields in comparison with existed methods.

GRAPHICAL ABSTRACT



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Amino benzyl ethers; benzyl alcohols; bicyclic amino alcohols; nicotinic acetylcholine receptor; Williamson reaction

Introduction

The benzylation of hydroxyl groups is a fundamental and very versatile reaction in organic synthesis, used primarily as a way to protect these groups[1] as well as to obtain bioactive compounds.[2a–c] One of the most widely used synthetic methods for

CONTACT Jhon J. López jhonlopez@udec.cl Department of Organic Chemistry, Faculty of Chemical Sciences, Universidad de Concepción, Concepción, Chile; Edwin G. Pérez eperezh@uc.cl Department of Organic Chemistry, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile, Santiago, Chile.

JL and EP performed the research and analyzed the data. All the authors designed the research, wrote and critically revised the manuscript.

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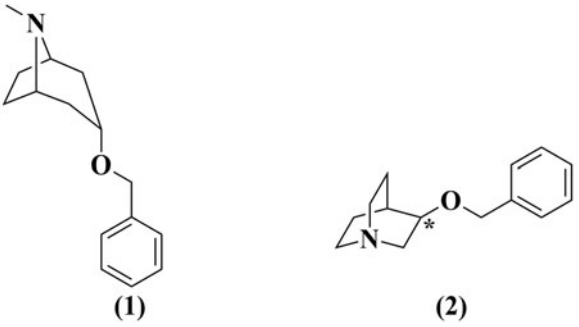


Figure 1. Chemical structures of bioactive bicyclic amino benzyl ethers.[13,14]

preparing alkyl benzyl ethers is the classic Williamson reaction, consisting of coupling between alkoxides and alkyl halides under basic conditions, developed over 160 years ago by the English chemist Alexander Williamson.[3a–b] Since that time, alkyl benzyl ethers have also been prepared using many different methodologies including the use of a tertiary amine as a base,[4] from benzyl bromide and alcohols using $FeSO_4$ as a mediator in the absence of solvent,[5] by reaction of silyl ethers and aromatic aldehydes in the presence of triethylsilane with catalytic amounts of $FeCl_3$,[6] from benzyl chloride and various alcohols using $Cu(acac)_2$ as catalyst,[7] from benzyl trichloroacetimidate or silylation with triethylsilyl chloride[8] in an acidic medium or from 2-benzyloxy-1-methylpyridinium triflate in a neutral medium,[9] from the microwave reaction of benzyl alcohol and various alcohols using $Ph_3PAuNTf_2$ as catalyst,[10] among others.

The Williamson reaction has also been used to prepare amino benzyl ethers from benzyl halides and bicyclic amino alcohols such as 3-quinuclidinol and tropine.[11,12] Compounds of this type have been shown to possess interesting biological activity. For instance, 3-benzyloxy-8-methyl-8-azabicyclo-[3.2.1]-octane (**1**) inhibits the human neuronal dopamine transporter which is involved in cocaine addiction,[13] and 3-benzyloxy-8-azabicyclo-[2.2.2]-octane (**2**) showed agonist activity at the nicotinic acetylcholine receptor (nAChR) α7 subtype.[14] (Fig. 1).

Additionally, the bicyclic systems of tropine and quinuclidine are chemical moieties present in many bioactive compounds isolated from plants.[15,16] This is a reason for the extensive use of this type of cores as building blocks for the synthesis of molecules with biological activity.[17–19]

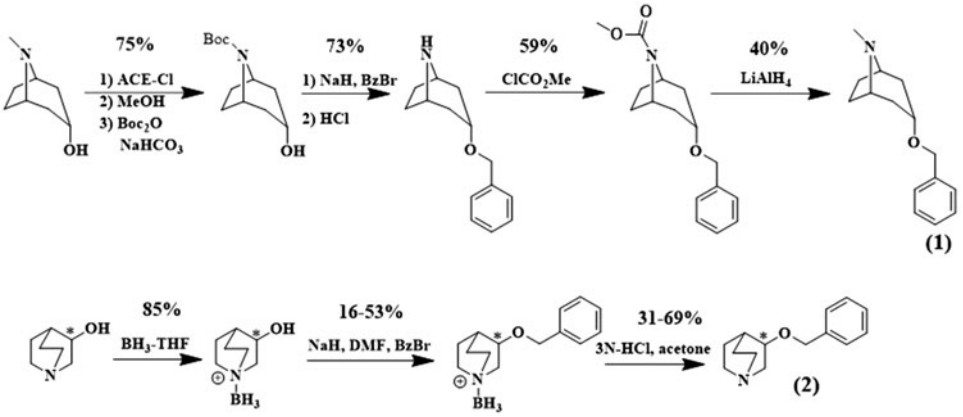
In our current search for new ligands acting on nAChRs, we were interested in the synthesis of new amino benzyl ethers with a nitrogen-containing bicycle. We decided to synthesize 4-methoxybenzyl iodide in situ, from 4-methoxybenzyl alcohol (**4a**), using chlorotrimethylsilane and sodium iodide.[20] In order to avoid the competitive reaction with the nitrogen atom, a solution of the separately prepared alkoxide of tropine was added to the preformed 4-methoxybenzyl iodide. Using this approach, compound **5a** (Figure 1) was obtained in 20% yield after column chromatography and recrystallization. See Table 1.

It is worth mentioning that literature reports for the synthesis of nitrogen-containing bicyclic amino benzyl ethers bearing quinuclidine and tropine rings (no reports were found for pseudotropine) employ multi-step reactions. For instance, in the Schmitt et al. synthesis of **1** the authors used a 4-step process including *N*-protection, alkoxide

Table 1. Bicyclic aminoalcohol benzyl ethers produced under the conditions shown in Scheme 2.

Entry	Benzyl alcohols (R^1)		Amino alcohols (R^2)	Reaction Time (h)	Yield[a,b] (%)	Amino benzyl ethers
1	**4a**	OCH_3	Tropine	15	44[a] [20][b]	**5a**
2	**4b**	OCH_2CH_3	Tropine	15	66[a] [33][b]	**5b**
3	**4c**	$O(CH_2)_2CH_3$	Tropine	15	73[a] [55][b]	**5c**
4	**4d**	$O(CH_2)_3CH_3$	Tropine	15	61[a] [39][b]	**5d**
5	**4e**	$O(CH_2)_4CH_3$	Tropine	15	40[a] [33][b]	**5e**
6	**4f**	$O(CH_2)_5CH_3$	Tropine	15	58[a] [47][b]	**5f**
7	**4g**	$O(CH_2)_6CH_3$	Tropine	15	61[a] [49][b]	**5g**
8	**4h**	$O(CH_2)_7CH_3$	Tropine	15	77[a] [58][b]	**5h**
9	**4i**	Br	Tropine	15	83[a] [64][b]	**5i**
10	**4j**	H	Tropine	15	51[a] [25][b]	**1**
11	**4g**	$O(CH_2)_6CH_3$	Pseudotropine	15	48[a] [32][b]	**6**
12	**4j**	H	3-Quinuclidinol	15	62[a]	**2**
13	**4a**	OCH_3	3-Quinuclidinol	15	85[a]	**7a**
14	**4b**	OCH_2CH_3	3-Quinuclidinol	15	85[a]	**7b**
15	**4c**	$O(CH_2)_2CH_3$	3-Quinuclidinol	15	87[a]	**7c**
16	**4d**	$O(CH_2)_3CH_3$	3-Quinuclidinol	15	42[a]	**7d**
17	**4e**	$O(CH_2)_4CH_3$	3-Quinuclidinol	15	89[a]	**7e**
18	**4f**	$O(CH_2)_5CH_3$	3-Quinuclidinol	15	57[a]	**7f**
19	**4g**	$O(CH_2)_6CH_3$	3-Quinuclidinol	15	21[a]	**7g**
20	**4h**	$O(CH_2)_7CH_3$	3-Quinuclidinol	15	26[a]	**7h**
21	**4k**	OCH_2Ph	3-Quinuclidinol	15	87[a]	**7i**
22	**4l**	OCH_2-4-Cl-Ph	3-Quinuclidinol	15	65[a]	**7j**
23	**4m**	$N(CH_3)_2$	Tropine	15	0	**8**
24	**4a**	OCH_3	2-Piperidineethanol	15	0	**9**
25	**4a**	OCH_3	2-Morpholinoethanol	15	0	**10**
26	**4j**	H	Nortropine	15	0	**11**

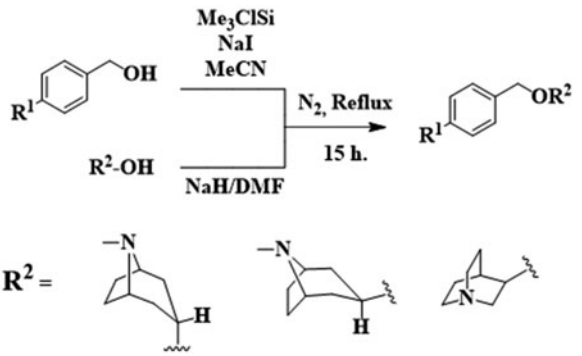
[a]Yield obtained by column chromatography. [b]yield obtained by recrystallization.



Scheme 1. Synthesis of 3-benzyloxy-8-methyl-8-azabicyclo-[3.2.1]-octane (**1**) and 3-benzyloxy-8-azabicyclo-[2.2.2]-octane (**2**).[13,14]

generation, coupling with benzyl bromide, *N*-deprotection and finally *N*-methylation.[13] In a similar fashion, 3-benzyloxy-8-azabicyclo 2 was synthesized by Tatsumi et al. using BH_3-protected 3-quinuclidinol with additional coupling and deprotection steps.[14] **Scheme 1**.

Because of the multiple steps involved in the synthesis of these compounds, the very long reaction times as well as the low overall yields (13 and 32% for **1** and **2**, respectively), we decided to investigate a new route to this kind of products. Thus, in this



Scheme 2. General reaction for the formation of bicyclic amine benzyl ethers.

paper, we present a new methodology which can be used in a simple and efficient way to generate benzyl ethers of bicyclic amines.

Result and discussion

To achieve our goal, we first attempted a reported etherification of 4-methoxybenzyl alcohol and tropine under Mitsunobu conditions.[21] Unfortunately, no product was obtained. Then we decided to synthesize 4-methoxybenzyl iodide in situ, from 4-methoxybenzyl alcohol (**4a**), using chlorotrimethylsilane and sodium iodide.[20] In order to avoid the competitive reaction with the nitrogen atom, a solution of the separately prepared alkoxide of tropine was added to the preformed 4-methoxybenzyl iodide. Using this approach, compound **5a** was obtained in 20% yield after column chromatography and recrystallization. See Scheme 2 and Table 1.

With this result in hand and with the aim of studying the generality of this reaction, we decided to synthesize a series of new compounds coupling different benzyl alcohols (**4a–4j**) with three bicyclic aminoalcohols tropine, pseudotropine and 3-quinuclidinol. See Scheme 2 and Table 1.

The coupling of *p*-substituted C2-C8 alkyloxy benzyl alcohols (**4b–4h**) with tropine proceeded to give the ethers **5b–5h** in yields ranging from 33% to 58% after purification by column chromatography and recrystallization from $CHCl_3$: MeOH. Unsubstituted benzyl alcohol (**4j**) afforded the previously reported compound **1** in 25% yield, double that reported in the four-step general synthesis shown in Scheme 1. Moreover, the reaction of *p*-bromobenzyl alcohol (**4i**) with tropine produced the desired ether in 64% yield. See Table 1, entry 9.

Besides, *p*-heptyloxybenzyl alcohol (**4g**) was combined with pseudotropine and ether 6 was obtained as the exclusive product under the same reaction conditions. Figure 2 shows that the proton (equatorial position) present in C-3 of the compound **5g** only can interact with the vecinal equatorial hydrogens atoms (C-2 and C-4) generating a narrow band (chemical shifts 3.92 p.p.m), characteristic of tropine ethers.[22] However, the proton (axial position) present in C-3 of the compound 6 generate strong interactions (large band; chemical shifts 4.07–4.13 p.p.m) with vecinal axial hydrogen atoms (C-2 and C-4 or C-1 and C5), characteristic of pseudotropine ethers.[22] The signs at 4.00 ppm correspond to the protons of the methylene group of the aliphatic chain in

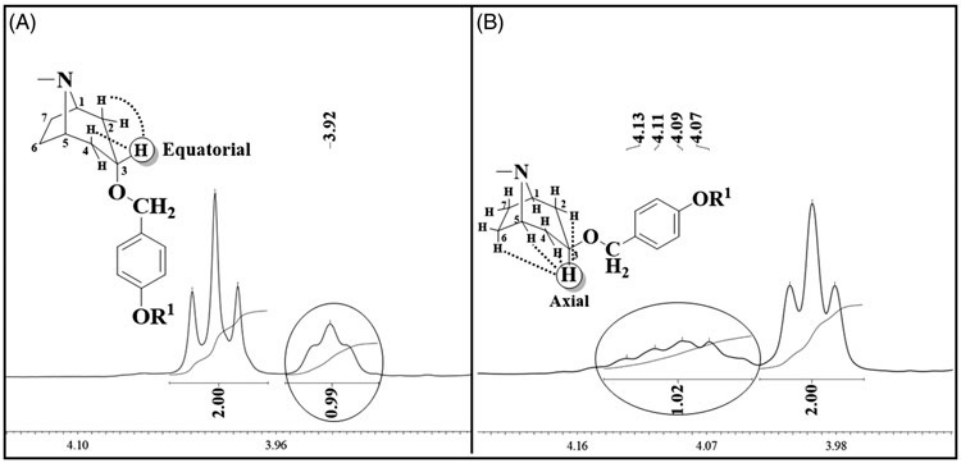


Figure 2. Comparison of the ^{1}H-NMR spectra of **5g** and **6** showing the different multiplicity of the signal of the proton attached Tropine (A) and pseudotropine (B) C-3.

position *p* with respect to the aromatic ring. This result suggests that these conditions do not lead to the inversion of configuration.

With the aim of extending this methodology to other bicyclic aminoalcohols, we chose 3-quinuclidinol to synthesize ethers such as **2**. Thus, **2** was obtained in 62% yield combining the above mentioned quinuclidinol with benzyl alcohol (**4j**) under the same conditions shown in Scheme 2. Again, this yield is twice as high as that reported in the three-step synthesis shown in Scheme 1.

Furthermore, the same *p*-substituted C1-C8 alkyloxy benzyl alcohols (**4a–4h**) were coupled with 3-quinuclidinol furnishing ethers **7a–7h** in yields ranging from 21% to 87% after purification by column chromatography. See Table 1, entries 12–21. In addition, 3-quinuclidinol was coupled with *p*-benzyloxybenzyl alcohol (4k) and *p*-(4-chlorobenzyloxy) benzyl alcohol (**4l**) furnishing the corresponding ethers in 87 and 65% yield, respectively.

Unfortunately, the reaction between *p-N,N*-dimethylbenzyl alcohol and tropine did not produce the expected ether, there was also no reaction between a secondary amine (Nortropine) and benzyl alcohol and the attempted couplings of the monocyclic 2-piperidineethanol and 2-morpholinoethanol with *p*-methoxybenzyl alcohol were also unsuccessful. See Table 1, entries 23–26.

Experimental section

Materials and methods

All solvents and all deuterated solvents were purchased from Merck, reagents from Aldrich, Merck and AK Scientific. Column chromatography was performed with silica gel (Merck, type 60, 0.063–0.2 mm). NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (Bruker, MA, USA). All chemical shifts in NMR experiments were reported as ppm downfield from TMS. Melting points were determined on a Reichert Galen III hot plate microscope apparatus and are uncorrected.

Procedures

Preparation of substituted benzaldehydes[23,24]

The Williamson method was initially used to couple 4-hydroxylbenzaldehyde and alkyl halides to produce the corresponding alkyloxy benzaldehydes. In round-bottomed flask 100 mL fitted with a magnetic stir bar is charged with K_2CO_3 (6 g, 43.4 mmol), ethanol (30 mL), 4-hydroxylbenzaldehyde (6 g, 49.1 mmol), and alkyl halides (4.0 mL, 49.1 mmol). The mixture was refluxed for 18 h under nitrogen with stirring. The resulting suspension was vacuum filtered, and the solvent removed under reduced pressure on a rotary evaporator. Finally, the compound was purified by column chromatography (silica gel from 0.063 to 0.2 mm, CH_2Cl_2) to affording the substituted benzaldehydes.

Preparation of benzyl alcohols[18]

In a round bottom flask of 250 mL, substituted benzaldehydes (2.8 g, 20.57 mmol) and 100 mL of methanol are added. Subsequently, the reaction mixture was allowed to stir and then $NaBH_4$ was slowly added (excess). The mixture was allowed to stir for 2 h. Subsequently, 50 ml of acetone were added to neutralize excess $NaBH_4$. Then the reaction mixture was concentrated under reduced pressure on a rotary evaporator. After 50 mL was added water to the reaction mixture, which was extracted with chloroform (3×20 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure.

The product was purified by chromatography column (from 0.063 to 0.2 mm silica gel, CH_2Cl_2) affording the benzyl alcohols. Compounds **4a–4m** were prepared from the respective substituted benzaldehydes commercial, 4-bromo benzaldehyde, benzaldehyde, 4-dimethylamino benzaldehyde, and 4-metoxy benzaldehyde.

Preparation of benzyl ethers amino tropane ring

To a solution of different benzyl alcohols (7.82 mmol) in acetonitrile (27 mL), chlorotrimethylsilane (8.73 mmol) was added and then sodium iodide (8.05 mmol) was slowly added. This mixture was allowed to reflux with constant stirring at 90 °C for 2 h, under nitrogen. In another testing column, tropine was added (11.73 mmol) and dissolved in DMF (25 mL), then NaH (11.73 mmol) was added slowly and allowed to stir for 2 h. After this time, the mixture containing tropine (tropine alkoxide), was slowly added to the reaction mixture, benzyl alcohol previously cooled and is allowed to reflux at 90 °C for 15 h under nitrogen atmosphere. Then the reaction mixture was concentrated under reduced pressure and the product purified by column chromatography using as solvent methanol-triethylamine-dichloromethane elution (9:1:0.5) and then recrystallized using various solvents such as chloroform, ethyl acetate, and methanol.

Preparation of benzyl ethers amino quinuclidine ring

Using the same procedure as for benzyl ethers, amino tropane ring was prepared. Compounds were purified using single column chromatography using a solvent dichloromethane-methanol-triethylamine elution (9:1:0.5).

Conclusions

In conclusion, we have developed a new methodology to generate bicyclic amino benzyl ethers from different substituted benzyl alcohols and bicyclic amino alcohols (with a tertiary amine) using commercial and low-cost reagents such as chlorotrimethylsilane, sodium iodide, and sodium hydride in acetonitrile and *N,N*-dimethylformamide, refluxing under nitrogen. The simple procedure makes it an attractive, selective, and a useful method to prepare bicyclic amino benzyl ethers from benzyl alcohols and three different bicyclic amino alcohols.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relatioship that could be construed as a potential conflict of interest.

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ORCID

Jhon J. López http://orcid.org/0000-0002-2678-3627
Edwin G. Pérez http://orcid.org/0000-0002-3777-6297

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