A Practical Synthesis of Differentially Protected 4,4′-Dipiperidinyl Ethers: Novel Ligands of Pharmaceutical Interest

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Abstract: An efficient four-step synthesis (requiring no purification) of Boc-protected 4,4′-dipiperidinyl ethers is described.

Key words: ethers, hydrogenations, piperidines, pyridines, histamine

The design of new ligands for clinical and pharmacological profiling of key targets of biological interest, in particular for disease areas of unmet medical need, is an important goal for the pharmaceutical industry. As part of a program directed towards finding novel histamine-subtype-selective ligands, we identified the novel 4,4′-dipiperidinyl ether template **1** which showed unexpected potency at the histamine H_3 receptor.[1]

Surprisingly, this simple ether template was relatively unknown at the commencement of our studies.[2] For example, we found no reference to the parent diamine, and scarce reports of saturated 4,4′-dipiperidinyl ethers of any substitution in the last 100 years. First reported in 1909,[2a] the 2,2′,6,6′-tetraphenyl decorated compound **2** was a side product from condensation chemistry of acetophenones (Figure 1). The bistropyl ether **3** is known,[2b] which contains the 4,4′- dipiperidinyl ether as a fragment of the structure. In addition, *N*-methyldipiperidinyl ether is found as a spacer group in a series of bicyclic pyrimidine anti-inflammatory agents **4**.[2c,3] A recent paper by Chao et al. highlighted this deficit and reported the synthesis of a series of piperidine containing bis-N-heterocyclic amine ethers by Mitsunobu reaction followed by acid-catalysed pyridyl reduction.[4a] Our findings are reported herein.

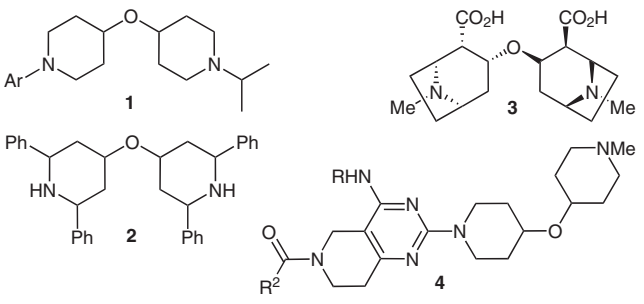
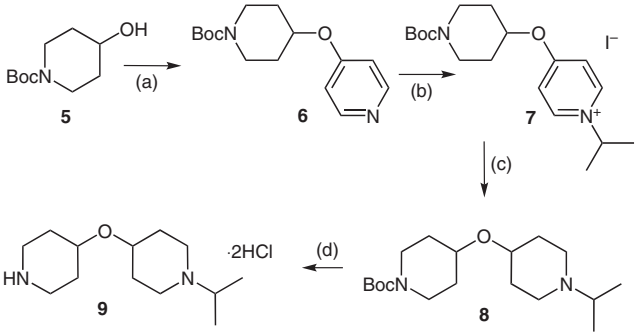


Figure 1 Examples of dipiperidinyl ethers

Our synthesis of the previously unknown ether **9** began by coupling hydroxy piperidine **5** with 4-chloropyridine, followed by formation of the quaternary alkylammonium salt **7**, under standard conditions (Scheme 1).[5] A simple one-pot reduction of the pyridine (step c) then gave dipiperidine ether **8**. Subsequent Boc deprotection afforded **9** which allowed further elaboration of the template by functionalisation of the secondary amine.



Scheme 1 *Reagents and conditions*: (a) 4-chloropyridine·HCl, NaH (60% dispersion), DMSO, 70 °C (79%); (b) *i*-PrI, CH_2Cl_2, r.t. (quant.); (c) $LiBH_4$, ammonium formate, 10% Pd/C, MeOH, reflux; (d) TFA, r.t. then 1 M HCl (93% over 2 steps). *Alternative conditions*: (c) PtO_2, H_2 (3.45 bar, r.t.), EtOH, 6 d (54% **8** + approximately 20% **5** due to ether cleavage); or (c) i. $NaBH_4$, MeOH; ii. ammonium formate, 10% Pd/C, MeOH, reflux (66%).

This initial strategy was encouraging but capricious yields in the reduction step led us to explore alternative approaches. Stepwise reduction of **7** using $NaBH_4$ in MeOH followed by transfer hydrogenation afforded **8** in reasonable yield. More concisely, **8** could be obtained by direct hydrogenation of **7**, although yields were modest and variable, and significant ether cleavage was observed.

The approach shown in Scheme 1 allowed us to access derivatives containing an *N*-isopropyl substituent. In order to investigate the effect of varying the substituents at both terminal amino groups we required a more versatile late stage intermediate such as **11** (Scheme 2). Direct reduction of **6** would be an attractive solution to this problem but hydrogenation required forcing conditions which gave an undesirable mixture containing starting material, the desired product **11**, and again significant cleavage of the ether to afford the hydroxypiperidine **5** (Table 1, entry 1).[4b]

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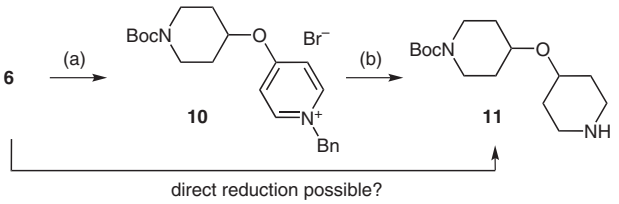
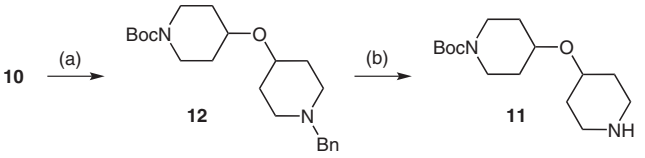
Table 1 Reduction Conditions and Yields

Entry	Substrate	Conditions	Product	Yield (%)[a]
1	**6**	PtO_2, H_2 (3.45 bar), AcOH, EtOH, 3 d	**11** + **5**	n.d.
2	**10**	$LiBH_4$, MeOH, $NH_4^+HCO_2^-$, 10% Pd/C, reflux	**11**	19
3	**10**	PtO_2, H_2 (1.013 bar), EtOH, 2.5 h	–	n.r.
4	**10**	PtO_2, H_2 (3.45 bar), EtOH, 24 h	**11**	60[b]
5	**10**	$NaBH_4$, MeOH, $NH_4^+HCO_2^-$, 10% Pd/C, MeOH, reflux	**11**	69

[a] Yield of desired piperidine product; n.d. = not determined, n.r. = no reaction.
[b] Based on ^1H NMR analysis of crude product mixture. Approximately 30% of *N*-(cyclohexyl)methylpyridinium species was also present.



Scheme 2 *Reagents and conditions*: (a) BnBr, CH_2Cl_2, r.t. (99%); (b) see Table 1



Scheme 3 *Reagents and conditions*: (a) $NaBH_4$, MeOH, r.t., then 10% Pd/C, H_2 (1.013 bar, r.t.), acetone (84%); (b) see text

These observations led us to investigate the reduction of a more suitable pyridine nucleus. Hence, intermediate **6** was converted to the *N*-benzyl quaternary ammonium salt **10** (Scheme 2). Reduction using the 'one-pot' $LiBH_4$, followed by transfer-hydrogenation conditions gave a poor recovery of **11** (Table 1, entry 2). Catalytic hydrogenation of **10** gave either unreacted starting material or was complicated by competing reduction of the benzyl aromatic group to give a mixture of products (entries 3 and 4). The reduction was best accomplished by a two-stage process, using $NaBH_4$ followed by transfer hydrogenation, giving the desired dipiperidine ether in an acceptable yield (entry 5). This four step synthesis of **11** from Boc-piperidinol **5** proceeded without the need for chromatography.

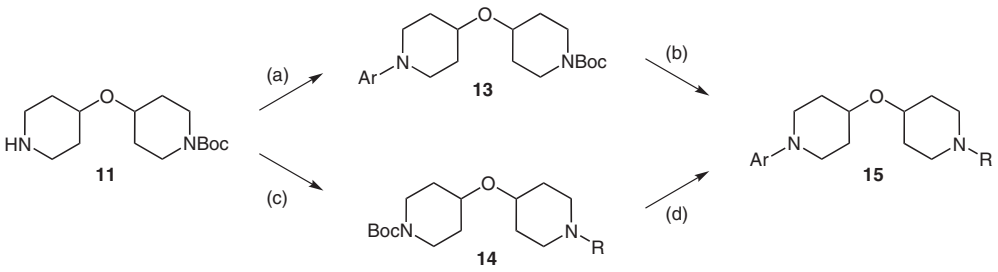
With a viable route to **11** in hand, we scaled up the synthesis to provide bulk material for our medicinal chemistry program. However, a reliable robust synthesis appeared elusive. In one experiment the hydrogenation step required several charges of fresh catalyst before the reaction went to completion. In other cases less than 10% of the desired product was formed even after fresh catalyst and extended reaction times. Analysis of the crude mixtures indicated that removal of the *N*-benzyl group required extended reaction times resulting in competing reactions.[6]

In order to examine the debenzylation step in more detail, borohydride reduction of **10** gave the tetrahydropyridine ether, which was further reduced in situ to *N*-benzylpiperidine **12** (Scheme 3). This was purified either by filtration through silica, or by simply stirring with activated charcoal.[7] For comparison, an additional third batch of untreated **12** was used as a control sample.

These three batches were then exposed to the same reduction conditions, either hydrogenolysis over 10%Pd/C,[8] or the transfer method employed above (see Table 1 entry 7). For all conditions, the untreated material failed to react at all. Both batches of purified **12** behaved similarly: Catalytic hydrogenolysis failed to give any appreciable amount of **11** (at 1.013 bar and 3.45 bar there was maximum 30% conversion as measured by HPLC), however, in comparison the hydrogen-transfer reduction gave a good yield of **11** (74%) from the purified benzylamine.

Two findings were evident from these studies. Firstly, it is clear that the benzyl group in **10** and **12** is recalcitrant towards removal by catalytic hydrogenolysis. Secondly, it appears that some component of the crude reaction mixture was inhibiting the debenzylation step; transfer hydrogenation of purified **12** routinely gave good yields of **11**. We wanted to avoid chromatography on a large scale during this work, and the quantities of activated charcoal required to remove impurities working on >50 gram scale was inconvenient.

For these reasons we re-examined our large-scale synthesis in an effort to eliminate any impurity at source. While exploring different workup procedures for the pyridine ether **6**, it was found that the use of nonchlorinated extraction solvents such as ethyl acetate or diethyl ether ensured that the subsequent reduction steps proceeded cleanly. Using CH_2Cl_2 in the workup gave us slightly higher crude yields of **6**, but with the capricious results discussed earlier. From these findings we inferred that a trace contaminant from step 1 (a, Scheme 1) appeared to poison the catalyst during the production of amine intermediate **11**. We reasoned that a sulfur residue from the DMSO used in the etherification step (a) was carried through during extraction of the product into CH_2Cl_2. Simply switching to a less polar extraction solvent ensured the preparation of **11** proceeded cleanly providing hundreds of grams of this novel template in yields of up to 76% from pyridyl ether **6**.[9]



Scheme 4 *Reagents and conditions*: (a) aryl halide, K_2CO_3, DMSO, 60–120 °C (56–100%); (b) i. 4 M HCl in dioxane or TFA, CH_2Cl_2 (95–100%); ii. $R_2C{=}O$, Et_3N, $NaBH(OAc)_3$ or RX, heat (34–77%); (c) $R_2C{=}O$, Et_3N, $NaBH(OAc)_3$ or RX, heat (47–93%); (d) i. 4 M HCl in dioxane (79–93%); ii. aryl halide, K_2CO_3, DMSO, 60–250 °C (thermal or MW heating, 9–100%), or Buchwald–Hartwig coupling (6–74%).

With supplies of intermediate **11** in hand, we were now able to explore variation at both the R and Ar positions (Scheme 4), a key focus of our medicinal chemistry program. Amine **11** was reacted with appropriate aryl halides via direct displacement to afford excellent yields of Boc-protected amines of formula **13**. These were deprotected and alkylated to give compounds of formula **15**. This initial route via **13** provided a method to obtain and screen a range of different alkyl groups (*R*), but a modification to the synthetic route (Scheme 4, path c and d) was required to allow late stage variation of the aryl group. To this end, precursor **11** was first alkylated to give **14**, followed by deprotection and derivatisation with the appropriate aryl halides either by direct displacement (e.g., using K_2CO_3, DMSO, at elevated temperature in the microwave[10] or Buchwald displacement[11]). Unoptimised yields ranged from no reaction in the case of secondary pyridinecarboxamides,[12] to quantitative for activated 2-chloropyridines or 4-fluoroacetophenone.

This chemistry could also be applied to the synthesis of templates with alternative ring sizes (Scheme 5). The azetidine-containing scaffold **18** was readily prepared from commercially available azetidinol **16**. Switching to the Boc-protected amine **19** and generating the benzyl salt of **20** (analogous to dipiperidine intermediate **10**) resulted in successful reduction to give pyrrolidinyl ether **21**. Similarly, *ent*-**21** could also be prepared from (3*S*)-**19** (not shown), and comparable results were observed with the racemic azepine alcohol **22**. It is noteworthy that none of these steps were optimised, yet they still provided good yields of these amine templates.

In conclusion, we have developed an efficient synthesis of the 4,4′-dipiperidinyl ether template **11**, a novel scaffold for the preparation of histamine H_3 ligands.[1] The current route provides access to this template on multigram scale, requires no chromatography, and solves several synthetic problems encountered in the preparation. Importantly, this key dipiperidine intermediate is monoprotected and is suitable for further elaboration. The template can be derivatised as desired through a variety of synthetic methods. The chemistry is amenable to ring sizes from four to seven, and proceeds with retention of stereochemistry in chiral alcohols. Further details of our medicinal chemistry program will be discussed elsewhere.

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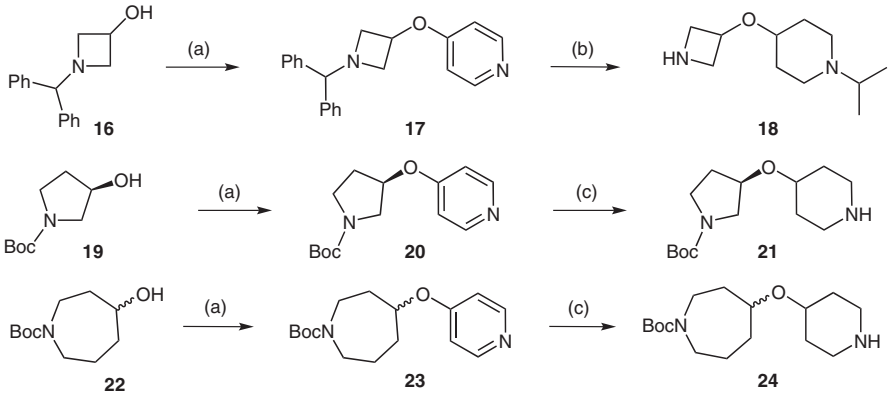

Scheme 5 *Reagents and conditions*: (a) 4-chloropyridine·HCl, NaH (60% dispersion), DMSO, 70 °C (54–92%); (b) *i*-PrI, CH_2Cl_2, r.t., then $NaBH_4$, MeOH, $NH_4^+HCO_2^-$, 10% Pd/C, MeOH, reflux (quant.); (c) BnBr, CH_2Cl_2, r.t., then $NaBH_4$, MeOH, $NH_4^+HCO_2^-$, 10% Pd/C, MeOH, reflux (33–73%).

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(4) (a) Chao, J.; Israiel, M.; Zheng, J.; Aki, C. *Tetrahedron Lett.* **2007**, *48*, 791. (b) The authors have reported similar findings in their two-step synthesis of **10**, which proceeds in 37–40% yield and requires chromatography after both steps.

(5) All products gave satisfactory MS and ^{1}H NMR (400 MHz) spectra.

(6) For example, on a 50 gram scale, extended reaction times resulted in the deprotected amine reacting with excess ammonium formate in the reaction mixture to give *N*-formyl piperidines.

(7) This latter procedure was chosen to mimic the contact with the Pd/C catalyst experienced during hydrogenolysis experiments, which in some cases would drive the reduction over time.

(8) More vigorous conditions were avoided due to our previous observation that the phenyl methyl group in **10** was labile to reduction (see Table 1, footnote b).

(9) Synthesis of Compounds **6**, **10**, and **11**
Sodium hydride (20.88 g) was suspended in DMSO (600 mL) under argon and 4-chloropyridine hydrochloride (31.0 g), suspended in DMSO (150 mL), was added slowly over 45 min. The reaction was then stirred for 10 min, and **5** (35 g), dissolved in DMSO (150 mL), was added over 15 min. The reaction was stirred at r.t. overnight. Saturated $NaHCO_3$ solution (150 mL) was then added slowly and the reaction stirred for 20 min. The mixture was evaporated to a minimum, redissolved in EtOAc (600 mL), and washed with sat. $NaHCO_3$ (150 mL) and H_2O (150 mL), followed by H_2O (5 × 250 mL). The organic layer was then dried ($MgSO_4$). The solution was filtered and evaporated to give a yellow solid, which was triturated with hexane and then dried at 50 °C overnight to give **6** as a pale yellow solid (38.0 g). MS (ES+): *m/z* = 279 [MH^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (2 H, d, *J* = 4.8 Hz), 6.87 (2 H, d, *J* = 4.8 Hz), 4.57 (1 H, m), 3.68 (2 H, m), 3.37 (2 H, m), 1.90 (2 H, m), 1.78 (2 H, m), 1.47 (9 H, s).
Compound **6** (37.5g) was dissolved in CH_2Cl_2 (400 mL). Benzyl bromide (32.26 mL) was added, and the reaction was stirred at r.t. for 4 h. The solvent was removed in vacuo, and the crude residue was redissolved in a minimum quantity of CH_2Cl_2. Diethyl ether was added to the stirred CH_2Cl_2 solution until the product precipitated. The pale pink solid was isolated by filtration and dried at 50 °C under high vacuum overnight to give **10** (60.0 g) as a pink solid. MS (ES+): *m/z* = 369 [M^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (2 H, d, *J* = 7.5 Hz), 7.58 (2 H, m), 7.50 (2 H, d, *J* = 7.5 Hz), 7.41 (3 H, m), 6.04 (2 H, s), 5.00 (1 H, m), 3.71 (2 H, m), 3.38 (2 H, m), 2.03 (2 H, m), 1.74 (2 H, m), 1.47 (9 H, s).
Compound **10** (55.2 g) was stirred in MeOH (300 mL) under argon at 0 °C and $NaBH_4$ (pellets, 9.3 g) was added portionwise over 1 h. The reaction was allowed to warm to r.t. for a further 90 min, and then acetone (50 mL) was added. The reaction was stirred for 1 h. The solvent was evaporated and residue partitioned between sat. aq $NaHCO_3$ solution and EtOAc (200 mL of each). The aqueous phase was separated and re-extracted with EtOAc (3 × 100 mL). The combined organics were dried over $MgSO_4$ with activated charcoal added, filtered, and evaporated to give the enol ether as a yellow-to-pink oil (40.6 g).
The crude oil (59.2 g) was dissolved in MeOH (900 mL) and ammonium formate (100.2 g) was added followed by 10% Pd/C (paste, 30 g). The reaction was heated to 60 °C (bath temperature, when internal temperature achieved 30 °C effervescence was observed), maintained at 55 °C for 1.5 h. The reaction was filtered and concentrated. The residue was re-dissolved in EtOAc (1 L) and washed with sat. K_2CO_3 solution (3 × 400 mL), dried ($MgSO_4$), and evaporated to give an oil which crystallized on standing to give **11** as a white solid (39.0 g). MS (ES+): *m/z* = 285 [MH^+]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (2 H, m), 3.65–3.38 (2 H, m), 3.06 (4 H, m), 2.60 (2 H, m), 1.91–1.67 (4 H, m), 1.59–1.31 (13 H, m).

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