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Double-Mannich Annulation of Cyclic Ketones Using *N,N*-Bis(ethoxymethyl)alkylamine Reagents

Jill I. Halliday,[†] Mary Chebib,[‡] Peter Turner,[†] and Malcolm D. McLeod*,[†]

School of Chemistry, F11, and Faculty of Pharmacy, A15, University of Sydney, Camperdown, NSW 2006, Australia

m.mcleod@chem.usyd.edu.au

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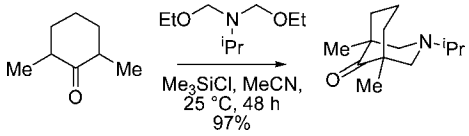
ABSTRACT

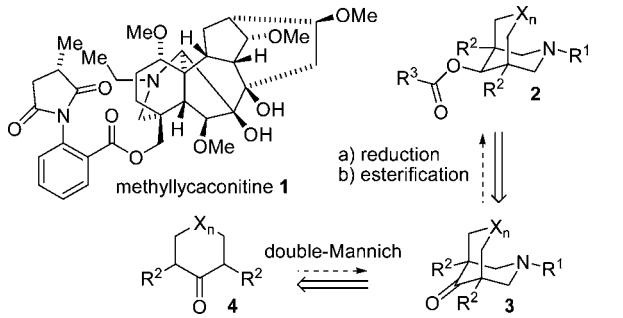


***N,N*-Bis(ethoxymethyl)alkylamines function as effective reagents in the double-Mannich annulation of cyclic ketone substrates, providing efficient access to a series of azabicyclic ketones. These ring systems are a useful scaffold for the four-step synthesis of novel constrained homocholine analogues.**

The development of small molecule ligands for the extensive array of therapeutically important drug targets presents an ongoing challenge to synthetic chemists. As part of our research directed toward the development of nicotinic acetylcholine receptor (nAChR) ligands, we have shown that small molecule analogues of the selective α7 nAChR antagonist methyllycaconitine (**1**, MLA, Scheme 1) act as antagonists in functional assays of nicotinic receptors.[1] To further probe the potential of the acylated homocholine pharmacophore contained in MLA **1**, we sought access to the azabicyclic ring systems represented by bicycle **2** that retain the putative pharmacophore present in **1**, albeit with a different topology. Despite the obvious appeal of the heterocyclic platform, they remain poorly represented in the literature in comparison with ring systems such as 8-azabicyclo[3.2.1]octane derivatives (tropanes).

In considering potential routes to compound **2**, the double-Mannich-based annulation offered an attractive proposal for the single-step synthesis of azabicyclic ring systems such as **3** from cyclic ketones **4** (Scheme 1).[2] Aside from its brevity, the proposed synthesis provides a wide scope for variation of the ring system and substituents of bicycle **2**.

Scheme 1



The direct synthesis of azabicycles such as **3** from cyclic ketones under standard Mannich conditions is limited in

[†] School of Chemistry.
[‡] Faculty of Pharmacy.

(1) Barker, D.; Lin, D. H.-S.; Carland, J. E.; Chu, C. P.-Y.; Chebib, M.; Brimble, M. A.; Savage, G. P.; McLeod, M. D. *Bioorg. Med. Chem.* **2005**, *13* (14), 4565.

(2) (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Cordova, A.. *Acc. Chem. Res.* **2004**, *37*, 102. (d) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (e) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791.

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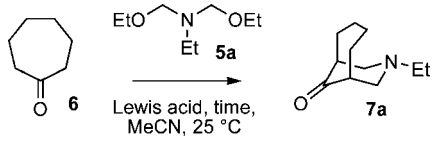
scope, low yielding,[3,4] and in many cases fails to afford the desired azabicyclic ring systems.[5] In some instances, these targets have been obtained by more lengthy indirect synthesis, such as the Mannich reaction of dialkyl cyclohexanone-2,6-dicarboxylate substrates followed by ester hydrolysis and decarboxylation.[3,6] More recently, it has been shown that the use of *N*,*N*-bis(alkoxymethyl)alkylamine reagents developed by Heaney[7] as preformed Mannich reagents can improve the yield of azabicyclic ring systems derived from β-keto esters.[8] Herein, we report the extension of this methodology to cyclic ketone substrates **4** to provide efficient and direct access to azabicycles such as **3** in good yield. We also show that these ring systems provide a suitable template for the development of biologically active homocholine analogues.

From the outset of this investigation, it was apparent that Mannich annulation of cyclic ketones was practically more demanding than that of the previously explored β-keto esters.[8] The use of an acid/base extraction with careful control of pH was required for the direct isolation of the azabicyclic compounds in pure form. Furthermore, the products displayed moderate instability to chromatography on silica gel resulting in low yields and reduced purity so they were used in subsequent reactions without further purification. Initial studies of the double Mannich annulation were conducted with cycloheptanone **6** and *N*,*N*-bis(ethoxymethyl)ethylamine **5a** (1.2 equiv) in acetonitrile under anhydrous conditions to afford azabicycle **7a** (Table 1). In common with previous work on the double-Mannich reaction of β-keto esters,[8] the use of both methyltrichlorosilane (1.0 equiv) and chlorotrimethylsilane (3.0 equiv) as Lewis acid cleanly promoted the reaction. The latter reagent led to a slightly higher yield but required longer reaction time to reach completion (Table 1, entry 4).

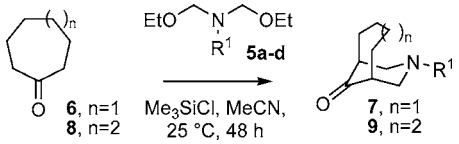
Table 1. Investigation of Double-Mannich Reaction Conditions



entry	Lewis acid (equiv)	time (h)	yield (%)
1	$MeSiCl_3$ (1.0)	24	72
2	$MeSiCl_3$ (1.0)	48	67
3	Me_3SiCl (3.0)	24	62
4	Me_3SiCl (3.0)	48	77

These conditions were employed with a variety of *N*,*N*-bis(ethoxymethyl)alkylamine reagents **5a**−**d** (1.2 equiv) with chlorotrimethylsilane (3.0 equiv) and cycloheptanone **6** or cyclooctanone **8**, giving good yields of the double Mannich products **7** and **9** (Table 2).

Table 2. Synthesis of 8-Azabicyclo[4.3.1]decan-10-ones and 9-Azabicyclo[5.3.1]undecan-11-ones



entry	substrate	reagent	R^1	product	yield (%)
1	**6**	**5b**	*i*-Pr	**7b**	85
2	**6**	**5c**	*t*-Bu	**7c**	81
3	**6**	**5d**	*n*-Pr	**7d**	85
4	**8**	**5a**	Et	**9a**	82
5	**8**	**5b**	*i*-Pr	**9b**	95
6	**8**	**5c**	*t*-Bu	**9c**	77
7	**8**	**5d**	*n*-Pr	**9d**	74

The scope of this transformation was further explored by the use of a variety of substituted cyclic ketones **10**−**16** (Table 3). The introduction of alkyl substituents was well tolerated by the reaction. Double-Mannich annulation of 2-methylcyclohexanone **10** or 2,6-dimethylcyclohexanone **11** gave good yields of the desired products **17** and **18**, respectively (entries 1−5). Reaction of 2-allylcyclohexanone **12** incorporating an unsaturated side chain also afforded the product **19** in good yield (entry 6).

The tolerance for other substituents was more variable. The reaction of 2-benzyloxycyclohexanone **13** containing exocyclic oxygenation adjacent to the ketone gave product **20** in poor yield (entry 7). In contrast pyran-4-one **14** gave the oxa-azabicycle **21** in 75% without evidence of β-elimination of the endocyclic oxygen (entry 8). Further variation in substitution was examined for the reaction of 2,6-diphenylcyclohexanone **15** and 2-indanone **16** to form products **22** and **23** respectively, in low yield. Thus, the double Mannich annulation is generally tolerant of variation in nitrogen substituent, ketone ring size, alkyl and heteroatom ring substitution but less tolerant of unsaturated or heteroatom substituents adjacent to the carbonyl group.

The heterocyclic ketones produced by this method offer promise as scaffolds for the development of constrained homocholine analogues (Scheme 2). Reduction of azabicyclic ketone **7c** with sodium borohydride selectively afforded

(3) Jeyaraman, R.; Avila, S. *Chem. Rev.* **1981**, *18*, 149.

(4) (a) House, H. O.; Wickham, P. P.; Muller, H. C. *J. Am. Chem. Soc.* **1962**, *84*, 3139. (b) Ohki, E.; Oida, S.; Ohashi, Y.; Yoshida, A.; Kamoshita, K.; Takagi, H. *Chem. Pharm. Bull.* **1974**, *22*, 1014. (c) Bailey, B. R., III; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Lazzara, R.; Brachmann, J.; Van der Helm, D.; Powell, D. R.; Pantaleo, N. S.; Ruenitz, P. C. *J. Med. Chem.* **1984**, *27*, 758. (d) Afsah, E. M.; Metwally, M. A.; Khalifa, M. M. *Monatsh. Chem.* **1984**, *115*, 303. (d) Kim, D.-I.; Schweri, M. M.; Deutsch, H. M. *J. Med. Chem.* **2003**, *46*, 1456.

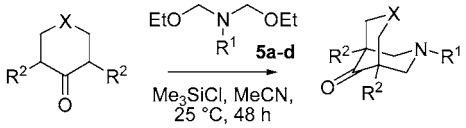
(5) Weatherbee, C.; Adcock, W. E.; Winter, D. *J. Org. Chem.* **1957**, *22*, 465.

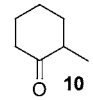
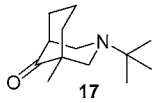
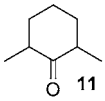
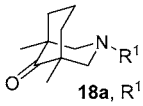
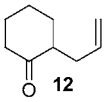
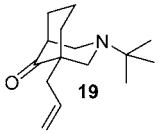
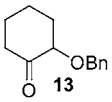
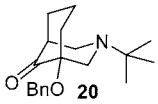
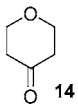
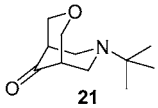
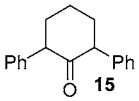
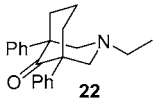
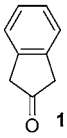
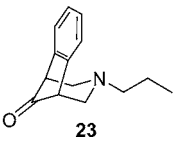
(6) (a) Blicke, F. F.; McCarty, F. J. *J. Org. Chem.* **1953**, *24*, 1379. (b) Shimizu, B.; Ogiso, A.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 766. (c) Takahashi, M.; Tanino, K.; Kuwajima, I. *Chem. Lett.* **1993**, 1655.

(7) (a) Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron Lett.* **1990**, *31*, 4229. (b) Heaney, H.; Papageorgiou, G. *Tetrahedron* **1996**, *52*, 3473.

(8) (a) Brocke, C.; Brimble, M. A.; Lin, D. S.-H.; McLeod, M. D. *Synlett* **2004**, 2359. (b) Brimble, M. A.; Brocke, C. *Eur. J. Org. Chem.* **2005**, 2385. (c) Buckley, B. R.; Page, P. C. B.; Heaney, H.; Sampler, E. P.; Carley, S.; Brocke, C.; Brimble, M. A. *Tetrahedron* **2005**, *61*, 5876.

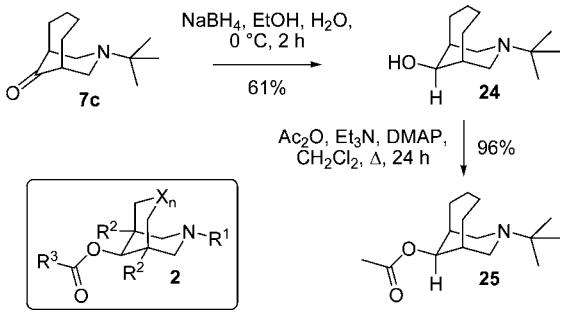
Table 3. Double-Mannich Alkylation of Substituted Cyclic Ketones



entry	substrate	reagent	product	yield (%)
1	 **10**	**5c**	 **17**	94
2	 **11**	**5a**	 **18a**, R^1 = Et	97
3	**11**	**5b**	**18b**, R^1 = *i*-Pr	97
4	**11**	**5c**	**18c**, R^1 = *t*-Bu	86
5	**11**	**5d**	**18d**, R^1 = *n*-Pr	96
6	 **12**	**5c**	 **19**	75
7	 **13**	**5c**	 **20**	5
8	 **14**	**5c**	 **21**	75
9	 **15**	**5a**	 **22**	35
10	 **16**	**5d**	 **23**	11

azabicycle **23** (61%),[9,10] which was acetylated to afford ester **25** (96%). The ester **25** contains an embedded acylated homocholine pharmacophore in common to the previously reported nAChR antagonist methyllycaconitine **1**. A preliminary biological evaluation of compound **25** has been performed against recombinant $\alpha4\beta2$ nAChR expressed in *Xenopus* oocytes and shows that it acts as an antagonist as previously observed for analogues of **1**.[1,11] Although ligand **25** is of modest potency, the ability to readily vary the substituents of generalized target structure **2** provides ample scope for optimization of biological activity.

Scheme 2



In this study, we have shown that the use of *N,N*-bis(ethoxymethyl)alkylamines in the double-Mannich reaction provides efficient single-step access to a range of azabicycles from cyclic ketones in good to excellent yield. The enhanced efficiency of this methodology can be attributed to the use of preformed reagents as a latent source of iminium ions, which bypass a number of unfavorable equilibria associated with the traditional Mannich reaction[2] and favor intramolecular reactions over unproductive intermolecular processes.[5] Finally, these azabicyclic frameworks provide a useful scaffold for the synthesis of novel small molecule homocholine analogues with demonstrated biological activity at nAChRs.

Acknowledgment. We thank The University of Sydney for supporting this work.

Supporting Information Available: Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C spectra for all new compounds. The ORTEP diagram and CIF file for the X-ray crystal structure of alcohol **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The stereochemistry of alcohol **24** was confirmed by a 2D NOESY experiment and X-ray crystallography. The ORTEP diagram and CIF of this crystal structure are given in the Supporting Information.

(10) House, H. O.; Muller, H. C.; Pitt, C. G.; Wickham, P. P. *J. Org. Chem.* **1963**, *28*, 2407.

(11) For the experimental details of related functional assays see ref 1. Ester **25** (100 μM) shows no agonist activity on its own but acts as an antagonist inhibiting 65 ± 3% of the response elicited by the agonist acetylcholine (60 μM). Further analogue synthesis and biological evaluation are under investigation will be reported elsewhere.