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The synthesis of azabicyclic heterocycles

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ABSTRACT

An efficient approach to a oxa-azabicyclo[3.2.1] derivatives has been achieved via a double-Mannich reaction of *N,N*-bis(methoxymethyl)-1-phenylethanamine with symmetrical and unsymmetrical ketones.

1. Introduction

Bridged azabicycles have recently found increasing use as key components of biologically active substrates including receptor ligands for the management of cough and anxiety,[1] as GPR119 modulators,[2] and pest control agents.[3] During recent prosecution of a project targeting diabetes, we sought to obtain the previously unknown azabicyclo heterocycle, **1**, which was viewed as a novel component of desired therapeutic agents.

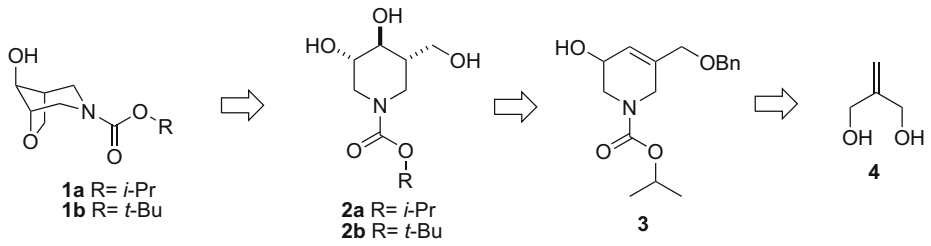
2. Results and discussion

Our initial approach to this oxa-azabicyclo[3.2.1] system is shown in Scheme 1. The hypothesis was that 1-azasugar derivative **2** could undergo an intramolecular etherification upon selective activation of the C-5 hydroxyl group to provide **1**. The 1-azasugars **2** can in turn be derived from the chiral pool[4] or from prochiral[5] precursors such as **3** which is accessible from commercially available 2-methylidene-1,3-propanediol (**4**).

In a modification to a route described by Espeel, the 1-azasugar **2a** was isolated via hydroboration/oxidation, followed by hydrogenolysis of the benzyl ether to provide the desired triol (Scheme 2). Hydroboration occurs from the face opposite of the allylic alcohol resulting in the formation of a single diastereomer.[6] However, attempts to form the oxo-methylene bridge by tosylation of the C-5 hydroxy of **2a**, followed by an intramolecular S_N2 displacement did not provide the desired bicyclic product.[7] When **2a** was subjected to the Appel conditions,[8] the desired oxobridge derivative 1 was isolated in 57% yield.

Although the approach to the bridged alcohol **1** was successful, a more expedient and general approach to this intermediate and other azabicycles was sought. Bis-(aminol) ethers, such as **7**, have been shown to be efficient bis-aminoalkylating agents for the synthesis of tertiary amines including bridged heterocycles.[9,10] A double-Mannich reaction involving such a bis-(aminol) ether and 3-oxotetrahydrofuran (**6**), could provide the azabicyclic ketone **5** in a single step as shown in Scheme 3.

To validate this strategy, we focused our attention on the double-Mannich reaction unsymmetrical ketones. While we were encouraged by the evidence of recent applications of this strategy,[10] there were limitations of the previously published work.[11] First, the R group in **7** would have to allow for an efficient double-Mannich reaction as well as be readily cleavable under relatively mild conditions. Second, reaction conditions that could successfully annulate more challenging unsymmetrical and/or five-membered ring ketones had to be investigated.



Scheme 1. Activation of 1-azasugar to produce bicyclooctane **2**.

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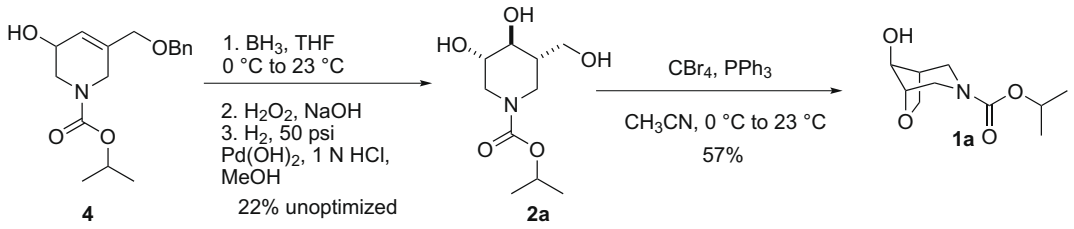
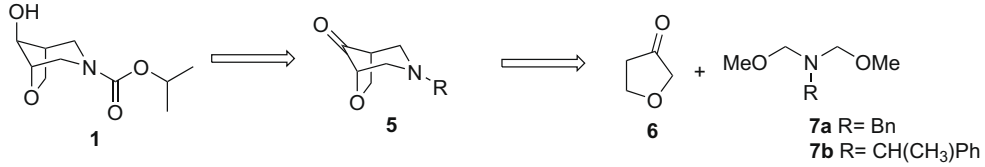
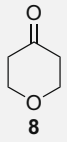
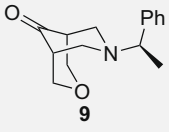
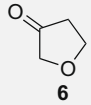
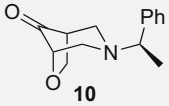
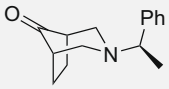
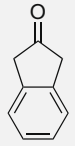
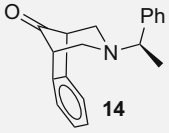
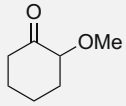
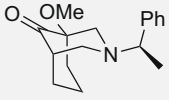


Scheme 2. Sequence to bycyclooctane derivative **2a**.



Scheme 3. The double-Mannich approach to 3-azabicyclo[3.2.1]octane derivatives.

Table 1
Bis-aminolalkynation of selected cyclic ketones

Entry	Substrate	Conditions	Product	Yield (%)
1	 **8**	(a) $MeSiCl_3$, MeCN (b) $MeSiCl_3$, CH_2Cl_2	 **9**	80 59
2	 **6**	(a) $MeSiCl_3$, MeCN (b) $MeSiCl_3$, MeCN MeOH (2 equiv)	 **10**	Trace 60[a]
3	 **11**	$MeSiCl_3$, MeCN MeOH (2 equiv)	 **12**	78[b]
4	 **13**	(a) $MeSiCl_3$, MeCN (b) $MeSiCl_3$, MeCN MeOH (2 equiv)	 **14**	76 78
5	 **15**	$MeSiCl_3$, MeCN MeOH (2 equiv)	 **16**	45[c]

[a] Compound was carried on and characterized after further transformations.
[b] Product was isolated as ketone-48% and as its dimethylketal derivative-31%.
[c] Product was isolated as ketone-25% and as its dimethylketal derivative-20%.

We found that (*R*)-*N*,*N*-bis(methoxymethyl)-1-phenylethanamine (**7b**) satisfied our requirements. Table 1 illustrates the scope of this chemistry with a variety of cyclic ketones. As shown in entry 1, treatment of 4-oxotetrahydropyranone with the bisaminol ether reagent provided the desired azabicyclic ketone in 80% yield with acetonitrile as the solvent and 59% yield when dichloromethane was used. We then turned our attention to the more challenging case exemplified in Scheme 3.

Treatment of 3-oxotetrahydrofuran (**6**) (entry 2) under the same reaction conditions did not yield the desired azabicyclic product. Instead what was observed by GC–MS analysis were products derived from an intermolecular double-Mannich reaction to give products corresponding to **17** (Fig. 1a). Because the reactivities of the protons distal to the oxygen and proximal to the oxygen are different, there will be an intrinsic difference in the rates of the first Mannich reaction. Depending on this rate, one could expect intermolecular reaction at one of these α-carbons to be faster than the intramolecular cyclization. The challenge here was to find conditions that would allow for the second Mannich to occur only after the starting ketone **6** had undergone the first Mannich reaction. Ultimately, it was found that adding methanol prior to the addition of the furan allowed the reaction to proceed as envisioned to afford the desired product (Fig. 1b).

The addition of methanol improved the reactions with other ketone substrates as well. The double-Mannich reaction of cyclopentanone **11** to form its 3-azabicyclo[3.2.1]octanone derivative **12** has proven to be a difficult transformation.[12] However, as entry 3 shows, the desired azabicycle is formed in high yield under these reaction conditions. The Mannich reaction of 2-indanone **13**, entry 5, gave high yields of the desired product **14** with and without the addition of methanol. Previously published work had shown this substrate to be a poor double-Mannich substrate with *N*,*N*-bis(ethoxymethyl)-1-propylamine, yielding only 11% of the desired substrate.[11] The dramatic improvement observed in this sequence is probably attributed to a Thorpe-Ingold effect[13] imparted by the α-methylbenzyl substituent of the bis(methoxyethyl)amine. Another test case for the efficiency of the Mannich reaction was 2-methoxycyclohexanone **15**. Although subjecting this ketone to the standard protocol afforded the desired azabicycle **16** in a modest 45% yield, it is a significant improvement over previously published work.[11]

The addition of methanol is believed to serve two important roles: it leads to the in situ generation of HCl and this helps promote the first Mannich reaction as well as the protonation of the intermediate which inhibits the second Mannich reaction. The use of HCl instead of trichloromethylsilane in the double-Mannich reaction of bis(aminol) ethers has been shown to stop after a single Mannich addition.[10] Methanol may also attenuate the reactivity of the Lewis acid for a slower generation of the second iminium species. Reduction of ketone **10** gave a single diastereomer **1b**, with the hydroxyl anti to the oxobridge (Scheme 4). Hydrogenolysis of **1b** proved difficult but was efficiently executed using flow hydrogenation.[14] Carbamate formation gave **1** which was confirmed by spectral comparison with the product of the Appel reaction.

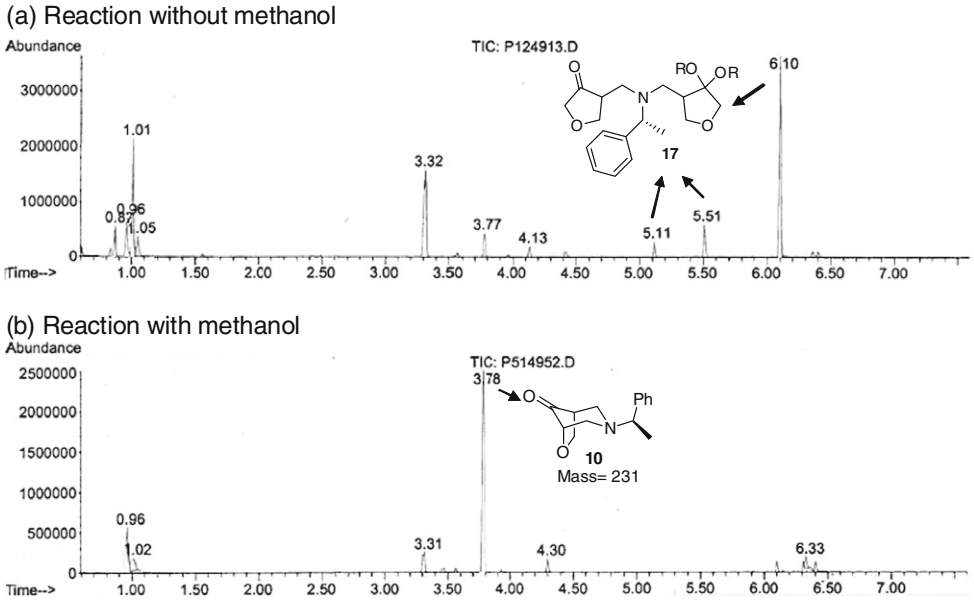
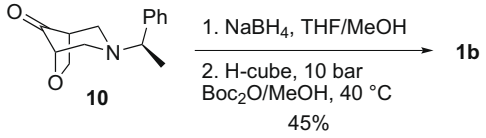


Figure 1. Comparison of double-Mannich reaction of 3-oxotetrahydrofuran with and without methanol.



Scheme 4. Synthesis of 8-hydroxy-6-oxa-3-azabicyclo[3.2.1]octane **1b**.

3. Conclusion

In conclusion, two distinct syntheses of 3-azabicyclo[3.2.1]octanol were accomplished. The more concise route relied on an unprecendented double-Mannich reaction with 3-oxotetrahydrofuran. The use of methanol as an additive was also found to be critical to the success of this transformation.

4. Experimental

Compound **1a**: Characterized as its acetate derivative (R_f 0.4 EtOAc/heptanes 1:2) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.25 (d, J = 6.35 Hz, 6H) 2.15 (s, 3H) 2.53–2.65 (m, 1H) 3.06–3.12 (m, 1H) 3.24–3.31 (m, 1H) 3.75–4.05 (m, 4H) 4.14–4.23 (m, 1H) 4.89–4.97 (m, 1H) 5.03 (t, J = 5.49 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 170.3, 156.9, 100.0, 70.7, 70.7, 70.9, 69.8, 69.7, 69.1, 69.0, 45.1, 43.4, 43.2, 35.2, 22.5, 21.1.

Compound **1b**: To a solution of **10** (700 mg, 3.03 mmol) in THF/EtOH (24.8 mL (1:1)) was added $NaBH_4$ (694 mg, 18.2 mmol). The mixture was stirred for 18 h and concentrated. The residue was partitioned between 20 mL of TBME and 1 N NaOH (1:1). The mixture was stirred for 30 min and the layers separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give a clear oil (694 mg). The oil was dissolved in methanol (24 mL) and Boc_2O (734 mg, 3.33 mmol) was added. The solution was passed through a $Pd(OH)_2$ cartridge using an H-Cube® Continuous-flow Hydrogenation Reactor at 50 bar and 50 °C. The crude material was concentrated, dissolved in pyridine (10 mL), and acetic anhydride (1 mL) was added. After 16 h, the mixture was concentrated and purified by flash column chromatography (ISCO combiflash) (R_f 0.42 EtOAc/heptanes 1:1) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.47 (s, 9H) 2.15 (s, 3H) 2.54–2.64 (m, 1H) 3.05 (dd, J = 24.9, 13.4, 1H) 3.23 (dd, J = 33.0, 12.9, 1H) 3.75–4.00 (m, 5H) 4.10–4.25 (m, 1H), 5.02 (t, J = 5.37 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 170.4, 157.0, 80.2, 70.7, 70.7, 69.8, 69.7, 45.4, 44.6, 43.8, 42.8, 35.2, 28.6, 28.6, 21.1.

Compound **2a**: ^{1}H NMR (D_2O, 500 MHz) δ ppm 1.11 (d, J = 6.20 Hz, 6H) 1.50–1.57 (m, 1H) 2.57 (q, J = 13.3 Hz, 2H) 3.19–3.24 (m, 1H) 3.30–3.33 (m, 1H) 3.44–3.52 (m, 1H) 3.67 (dd, J = 11.5, 3.3 Hz, 1H) 4.02 (br s, 1H) 4.65–4.73 (m, 1H); ^{13}C NMR (D_2O, 125 MHz) 156.8, 100.0, 73.7, 70.9, 60.3, 47.7, 45.0, 43.7, 21.4.

Compound **9**: To a stirred solution of bis-methoxymethyl-(1-phenyl-ethyl)-amine (750 mg, 3.58 mmol) and tetrahydro-4*H*-pyran-4-one **8** (150 mg, 1.50 mmol) in MeCN was added $MeSiCl_3$ (400 μL, 3.41 mmol) at room temperature. The resulting mixture was stirred for 50 h, then the reaction was quenched with aqueous sodium bicarbonate and the reaction mixture was diluted with EtOAc. The bi-layer was separated and the aqueous portion was extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ISCO combiflash, EtOAc/heptane 0–100%) to provide desired compound (317 mg, 88%). The same reaction was also performed in CH_2Cl_2 (Yield, 215 mg, 60%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.39 (d, J = 6.83 Hz, 3H) 2.52 (tt, J = 6.01, 2.90 Hz, 2H) 2.88–2.99 (m, 2H) 3.05–3.11 (m, 1H) 3.14–3.20 (m, 1H) 3.54 (q, J = 6.83 Hz, 1H) 3.89 (dt, J = 11.16, 3.32 Hz, 2H) 4.20 (t, J = 9.64 Hz, 2H) 7.20–7.39 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 212.2, 143.5, 128.2, 127.1, 126.9, 73.4, 73.3, 63.0, 55.2, 54.7, 49.6, 49.5, 18.8.

Compound **10**: To a stirred solution of bis-methoxymethyl-(1-phenyl-ethyl)-amine (1.0 g, 11.6 mmol) and methanol (1.00 mL) in MeCN (19 mL) was added $MeSiCl_3$ (2.34 mL, 19.7 mmol) dropwise at room temperature. To this solution was added 3-oxotetrahydrofuran (**6**) dropwise and the resulting mixture was stirred for 16 h. Water (5 mL) was added and the mixture was basified with 1 N NaOH to pH >9. Diethyl ether (30 mL) was added and after 10 min the layers were separated. The ether layer was washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ISCO combiflash, EtOAc/heptane 1:1) to provide the desired compound (1.6 g, 60%) as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.32–1.34 (m), 2.15 (t, J = 4.6 Hz), 2.26 (t, J = 4.5 Hz) 2.45–2.56 (m) 2.61–2.76 (m) 3.04–

3.11 (m) 3.33 (s) 3.34 (s) 3.47 (q, J = 6.6 Hz) 3.57 (q, J = 6.7 Hz) 3.66–3.67 (m) 3.75–3.79 (m) 3.96–4.02 (m) 4.13 (d, J = 6.8 Hz) 4.19 (d, J = 6.8 Hz) 4.45 (dd, J = 7.2, 2.1 Hz) 7.15–7.36 (m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 213.2, 145.4, 143.1, 128.6, 128.5, 128.2, 127.6, 127.5, 126.9, 101.9, 70.9, 68.3, 64.1, 62.9, 59.3, 53.0, 51.5, 50.1, 48.6, 45.5, 40.8, 40.5, 18.9, 17.8.

Compound **12**: Ketone: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.37 (d, J = 6.59 Hz, 3H) 1.79–1.89 (m, 2H) 1.98–2.12 (m, 3H) 2.16–2.21 (m, 1H) 2.49 (d, J = 10.49 Hz, 1H) 2.56 (d, J = 10.49 Hz, 1H) 2.91 (ddd, J = 10.49, 4.39, 2.93 Hz, 1H) 3.08 (ddd, J = 10.37, 4.27, 2.93 Hz, 1H) 3.60 (q, J = 6.67 Hz, 1H) 7.23–7.27 (m, 1H) 7.31–7.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 Hz) MHz) δ ppm 144.2, 128.2, 127.2, 126.9, 62.1, 59.8, 57.9, 45.5, 22.6, 22.5, 19.3; GC–MS (M^+) 229.

Dimethylacetal: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.31 (d, J = 6.83 Hz, 3H) 1.62–1.77 (m, 4H) 1.98 (d, J = 1.46 Hz, 1H) 2.13 (d, J = 2.20 Hz, 1H) 2.30–2.34 (m, 1H) 2.37–2.41 (m, 1H) 2.46 (d, J = 10.00 Hz, 1H) 2.69–2.76 (m, 1H) 3.19 (s, 3H) 3.24 (s, 3H) 3.42 (q, J = 6.51 Hz, 1H) 7.20–7.23 (m, 1H) 7.30 (t, J = 7.56 Hz, 2H) 7.34–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 146.2, 128.1, 127.2, 126.5, 108.0, 63.6, 53.7, 51.1, 49.2, 47.4, 38.1, 38.0, 25.5, 20.3; GC–MS (M^+) 275.

Compound **14**: (R_f 0.6 EtOac/heptanes 1:20) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.24 (d, J = 6.83 Hz, 3H) 2.73 (d, J = 10.73 Hz, 1H) 2.80 (d, J = 10.98 Hz, 1H) 3.13–3.16 (m, 2H) 3.34–3.38 (m, 2H) 3.62 (q, J = 6.83 Hz, 1H) 6.87 (dd, J = 6.59, 2.93 Hz, 2H) 7.17–7.20 (m, 3H) 7.23–7.28 (m, 2H) 7.34–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 215.3, 143.9, 139.9, 139.8, 128.4, 127.7, 127.6, 127.2, 127.0, 122.5, 122.4, 57.7, 54.7, 53.6, 53.4; GC–MS (M^+) 277.

Compound **16**: Ketone (R_f 0.69 EtOAc/heptanes 1:2).

Diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 1.33 (d, J = 6.59 Hz), 1.45–1.48 (m) 1.61 (br s) 1.59 (d, J = 6.83 Hz) 1.81–1.96 (m), 2.12–2.14 (m) 1.98–2.04 (m), 2.35 (dd, J = 10.25, 2.44 Hz) 2.48–2.56 (m) 2.73–2.89 (m) 3.12 (s) 3.22–3.26 (m) 3.32 (s), 3.33(s), 3.35(s) 7.21–7.33 (m) 7.31 (d, J = 2.68 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 145.7, 128.2, 127.2, 126.6, 100.5, 78.5, 78.3, 65.3, 65.1, 56.9, 55.3, 54.0, 49.14, 49.11, 49.0, 48.9, 37.4, 37.3, 31.5, 27.7, 27.4, 21.4, 21.3, 20.3, 20.4; GC–MS (M^+) 319.

Dimethylacetal (R_f 0.63 EtOAc/heptanes 1:2).

Diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm [1.39 (d, J = 6.59 Hz) 1.40 (d, J = 6.59 Hz), total 3H] 1.63–1.67 (m, 1H) 1.92–2.02 (series of m) 2.16–2.20 (m), 2.25–2.29 (m), total 4H] [2.41–2.48 (m) 2.55–2.61 (m), total 3H] [2.97 (td, J = 12.69, 6.10 Hz) 3.12 (dd, J = 10.73, 2.20 Hz) 3.32–3.20 (m), 3.38–3.35 (m), total 3H], [3.40 (s), 3.31 (s), total 3H], 3.40–3.44 (m, 1H) 7.23–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 214.4, 143.5, 143.3, 128.3, 127.1, 127.0, 80.3, 64.1, 63.9, 61.3, 60.8, 57.6, 56.6, 51.3, 48.7, 48.6, 38.1, 37.8, 33.7, 33.4, 21.4, 19.5; GC–MS (M^+) 273.

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14. Hydrogenolysis of the substrate was performed on an H-Cube® Continuous-flow Hydrogenation Reactor manufactured by ThalesNano.