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A new route to 2-spiropiperidines

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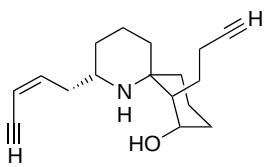
Abstract—An intramolecular Mannich reaction, involving cyclanones together with a ketoprotected aminobutanone in the presence of a Lewis acid, is employed to prepare rapidly 2,2′-spiropiperidine skeletons. This approach is validated through a concise and efficient synthesis of spiro [piperidine-2,2′-adamantane] **4**, an antiviral agent. © 2001 Elsevier Science Ltd. All rights reserved.

A growing number of alkaloids, containing the 2-spiropiperidine framework are being discovered from varied natural sources and biological activities are associated with these compounds. As representative examples, histrionicotoxin **1**, isolated from frog skins of Central and South America, is a very potent nicotinic receptor antagonist;[1] halichlorine **2** isolated from the marine sponge *Halichondria okadai* is an inhibitor of the vascular cell adhesion molecule-1 (VCAM-1),[2] while pinnaic acid **3**, extracted from the Okinawan bivalve *Pinna muricata* exhibits inhibitory activity against phospholipase A_2.[3]



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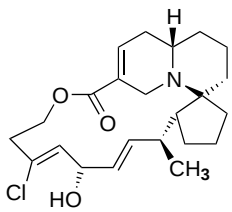

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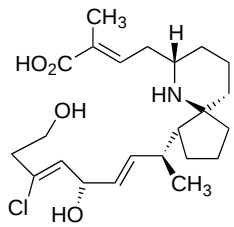

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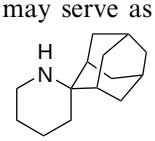
Synthetic compounds with a 2-spiro piperidine skeleton possess also interesting activities. For instance, spiro[piperidine-2,2′-adamantane] **4** proved to be active against influenza viruses,[4] and spiro[piperidine-2,3′(2′H)-benzopyran] **5** showed a significant and selective affinity for the 5-HT_{1A} receptors[5] and therefore may serve as an anxiolytic agent.



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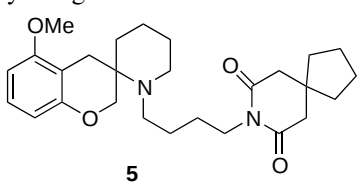

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For these reasons, construction of such spiranic entities draw interest and is the object of important synthetic efforts, attested by many recent reports[6].

For our own, we have described an efficient asymmetric synthesis of substituted piperidines through an intramolecular Mannich type reaction as the cyclization step[7]. This approach, based on the use of various aldehydes and of an α chiral amine, gave efficiently highly substituted piperidine systems in a stereoselective manner (Scheme 1).

In trying to extend the potentiality of this method, we decided to use cyclanones instead of aldehydes as starting carbonyl compound, in order to prepare spiro piperidinic structures. We wish to report herein our preliminary results in this area.

Thus, amine **6**[8] and cyclohexanone were engaged in the cyclization step, following our usual procedure (*p*-TSA 1–2 equiv., 70°C, toluene)[7]. Under these conditions, the reaction led to trace amounts of the desired compound **7** together with many degradation products[9]. So, reaction conditions were modified. First, we noticed that a catalytic amount of acid was absolutely necessary to promote an efficient conversion of the keto compound into the corresponding imine. Then, for the cyclization

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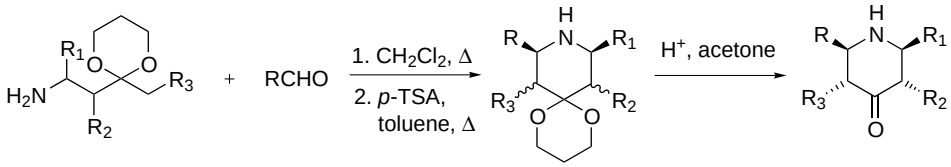


Scheme 1.

step, we decided to use a Lewis acid ($BF_3{\cdot}OEt_2$) in place of *para*-toluene sulphonic acid. By this way, spiropiperidine **7** was obtained in satisfactory yield. Due to its poor stability, this compound was directly transformed into the parent stable spiropiperidone **8**[10] under classical acidic conditions. Confirmation of the spiro structure of **8** was easily obtained by transformation in the known[11] *N*-methylated analog **9** (Scheme 2).

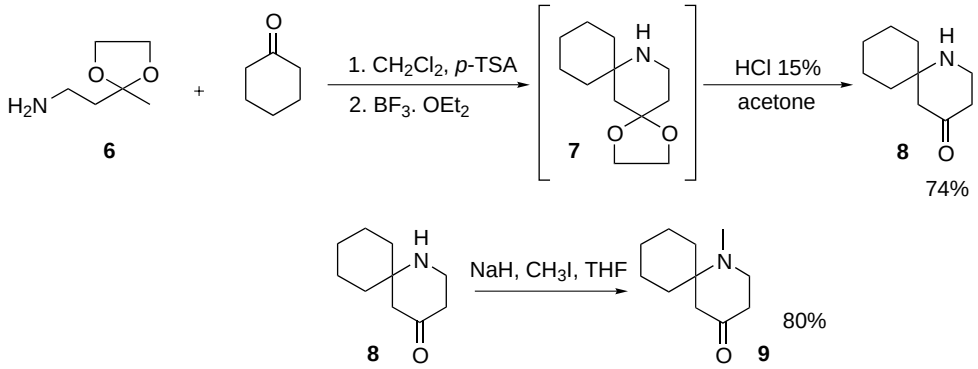
In order to value the widespread of this new approach to 2-spiropiperidines, cyclobutanone, cyclopentanone and cycloheptanone were involved with amine **6** in our cyclization/ketodeprotection sequence. Accordingly, new spiropiperidines **10**–**12**[10] were isolated in 53–70% yield (Scheme 3).

Furthermore, we could also verify that 6-substituted spiropiperidines, such as **13** and **14**, are prepared in the same manner and with the same efficiency, starting from α-methylamine **15**[12] (Scheme 4).

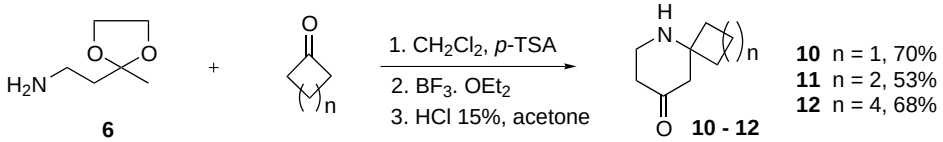
We then focused our attention on a rapid synthesis of compound **4**, for which our method seemed particularly suitable. Thus, reaction of adamantanone with amine **6** in refluxing dichloromethane, in the presence of magnesium sulphate and a catalytic amount of *p*-TSA, led quantitatively to the corresponding imine which was treated in situ by 1.5 equiv. of $BF_3{\cdot}OEt_2$ to give the expected product **16**, as a stable compound, in 83% yield (Scheme 5).

Finally, treatment of spiropiperidine **16** with an excess of ethanedithiol in dichloromethane in the presence of $BF_3{\cdot}OEt_2$ afforded quantitatively the dithiolane derivative **17**. Subsequent hydrogenolysis (Raneynickel W2 in refluxing ethanol) furnished cleanly the desired compound **4** in 92% yield (analytical data identical with those published by Kolocouris et al.[4]).

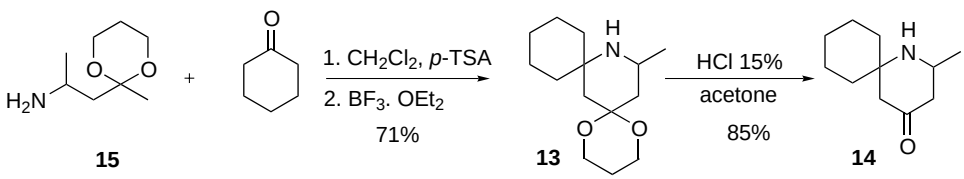
In conclusion, we have described here a facile and efficient entry to the 2-spiropiperidine framework and



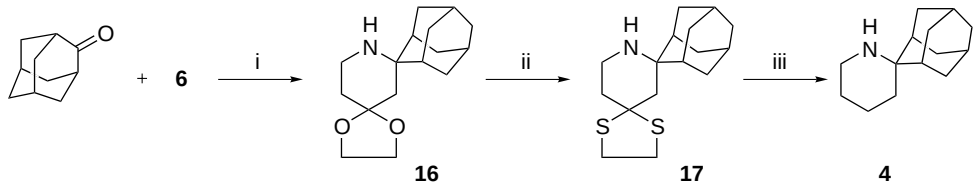
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5. (i) CH_2Cl_2, *p*-TSA then $BF_3{\cdot}OEt_2$, 83%; (ii) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 95%; (iii) Raney-Ni, EtOH, 92%.

we have validated our approach through a concise and competitive synthesis of antiviral spiropiperidine **4** (three steps from adamantanone, 73% overall yield). Our efforts are now devoted to the extension of this new route to the field of enantioselective synthesis of natural products and analogs.

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9. Several attempts of cyclization using other protic acids were not successful either.
10. General experimental procedure: to a stirred solution of cyclanone (1.1 mmol) in CH_2Cl_2 (20 ml) was added $MgSO_4$ (ca. 500 mg), a solution of amine **6** (1 mmol) in CH_2Cl_2 (5 mL), then *p*-TSA (0.05 mmol). The resulting suspension was refluxed until complete disappearance (TLC monitoring) of the amine (2–3 h) then cooled to room temperature before addition of a solution of $BF_3{\cdot}OEt_2$ (1.5 mmol) in CH_2Cl_2 (5 mL). The mixture was heated at reflux for 10 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ (15 mL) was added, followed by an extraction with ethyl acetate (4×20 mL). The combined extracts were dried, filtered and evaporated. The residue, solubilized in acetone (15 mL) was treated at room temperature (3 days) with 15% hydrochloric acid (6 mL). The organic solvent was eliminated under reduced pressure and the residue such obtained was diluted with an excess of 3 M aqueous NaOH. The spiropiperidine was then extracted with CH_2Cl_2 (4×20 mL). The combined organic extracts were washed with brine and dried. Concentration, followed by column chromatography (ethyl acetate/methanol, 3/1) afforded pure spiropiperidone.
    Selected data **8**: IR (cm^{-1}) ν_{max} 3418, 2928, 2855, 1714, 1456; ^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (t, 2H, $J=6.5$ Hz), 2.23 (t, 2H, $J=6.5$ Hz), 2.18 (s, 2H), 2.09 (s, 1H), 1.53–1.20 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.7, 56.3, 53.8, 42.4, 40.2, 35.9, 25.4, 21.2. Compound **10**: IR (cm^{-1}) ν_{max} 3301, 2958, 2846, 1708, 1458, 1412, 1299. ^1H NMR (400 MHz, $CDCl_3$): δ 3.07 (td, 2H, $J=6.0$, 1.5 Hz), 2.85 (t, 2H, $J=6.0$ Hz), 2.52 (s, 2H), 2.05–1.70 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.9, 60.2, 52.3, 41.8, 41.1, 39.5, 12.8. Compound **11**: IR (cm^{-1}) ν_{max} 3390, 2957, 1714, 1694, 1651, 1454; ^1H NMR (400 MHz, $CDCl_3$): δ 3.15 (t, 2H, $J=6.0$ Hz), 2.34 (t, 2H, $J=6.0$ Hz), 2.32 (s, 2H), 2.22 (s, 2H), 1.80–1.50 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.4, 66.3, 53.8, 42.8, 42.6, 42.5, 38.1, 23.8. Compound **12**: IR (cm^{-1}) ν_{max} 3390, 2923, 2854, 1694, 1591, 1455. ^1H NMR (400 MHz, $CDCl_3$): δ 3.12 (t, 2H, $J=6.0$ Hz), 2.30 (t, 2H, $J=6.0$ Hz), 2.21 (s, 2H), 1.92 (s, 1H), 1.64–1.30 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.1, 60.1, 55.1, 42.5, 41.0, 39.5, 29.7, 22.0.
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