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N-Boc 4-nitropiperidine: preparation and conversion into a spiropiperidine analogue of the eastern part of maraviroc

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ABSTRACT

Previously unreported *N*-Boc 4-nitropiperidine was prepared in two steps from *N*-Boc-piperidone. The synthetic utility of this new intermediate was demonstrated by the development of a new and simple route to spirolactam piperidines. Further synthetic work involving a challenging triazole cyclisation allowed the preparation of a spiropiperidine analogue of the eastern part of maraviroc.

Spiropiperidines have been identified as privileged structures in medicinal chemistry[1] and have attracted increasing interest in the past five years. The most recent reports are representative of their wide range of biological activities as components of new SCD-1 inhibitors,[2] nociceptin receptor ligands,[3] CCR5 antagonists,[4] NPY Y5 receptor antagonists,[5] CGRP receptor antagonists,[6] tryptase inhibitors,[7] PGD2 receptor antagonists[8] and ChK1 kinase inhibitors.[9]

During a research programme aimed at preparing new building blocks, we needed a method to make the spiropiperidines **2** (R = H, Me). No synthetic routes to these compounds could be found in the literature. One report[10] described the preparation of spiropiperidines containing a phenyl substituent on the lactam nitrogen atom. The method was however, complex and lengthy, requiring seven synthetic steps. We anticipated that an alternative methodology starting from Boc-protected 4-nitropiperidine **1** would be simpler and straightforward. It was thought that a Michael addition with an acrylate[11] followed by a reductive cyclisation would give spirolactam **2**, which might in turn be converted into more complex spiro building blocks. The compound **3** (R = Me), a new spiropiperidine analogue of the eastern part of maraviroc (the latest FDA approved anti-HIV drug) was selected as a target to illustrate the potential usefulness of the proposed strategy (Fig. 1). To start our programme, we first needed to prepare the *N*-Boc 4-nitropiperidine **1**.

To our surprise, neither this compound nor any other carbamate-protected analogues had been reported in the literature.[12] *N*-Boc-piperidone **4** (commercially available on bulk scale) was first converted into its corresponding oxime and this was then oxidised with TFAA/H_2O_2[13] to the desired 4-nitro piperidine **1**[14,15] in 55% yield. The nitro ester intermediate **6a** was obtained by a Michael addition of the nitro piperidine **1** to methyl acrylate under mild conditions. Subsequent reduction of the nitro group by catalytic hydrogenation over Raney Nickel gave the corresponding amino intermediate **7a** which spontaneously cyclised to the spirolactam **2a**. The preparation of the nitro ester **6b** was more challenging, requiring the use of TBAF as a base and prolonged reaction time in refluxing THF. Both spirolactams (Scheme 1) were obtained in very good overall yield (greater than 80% over three steps).

Having prepared the new nitropiperidine **1** and developed a simple route to the spirolactams **2a,b**, we next focused on building the more advanced spiropiperidine **3b**. Lactam **2b** was first converted into the corresponding thiolactam **8b** which was then treated with acetyl hydrazide in the presence of mercuric chloride to give intermediate **9b**. The yields were quite moderate, 65% for the first step and 47% for the second, however, the process was straightforward to perform with easy purifications. It was expected that the following intramolecular condensation of the hydrazide carbonyl group with the bridged nitrogen atom would be quite

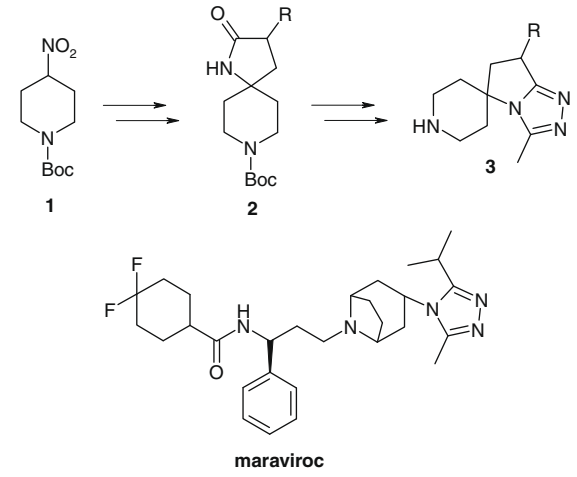

Figure 1. *N*-Boc nitropiperidine as a potential precursor to new spiropiperidines.

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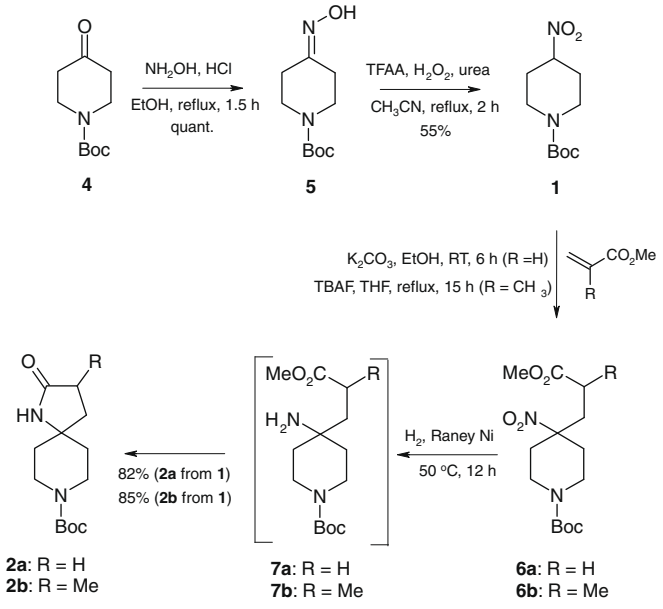
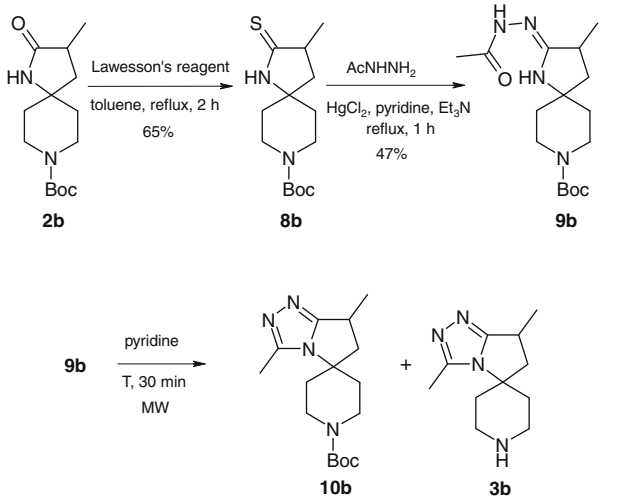


Scheme 1. Preparation of 4-nitropiperidine **1** and spirolactams **2a,b**.

challenging. Indeed, a wide range of known conditions was initially screened under both conventional and microwave heating but all failed. In most cases, unreacted starting material was recovered, even under quite forcing conditions (toluene, 200 °C, microwave). On evaluation of other solvents than those commonly employed in the literature to carry out this cyclisation, the breakthrough came with pyridine. Heating a solution of intermediate **9b** in pyridine for 30 min at 130 °C under microwave irradiation gave a 30% yield of the desired triazole **10b** along with unreacted starting material. More forcing conditions (180 °C, microwave) improved the conversion and also resulted in partial cleavage of the Boc group. To our delight, carrying out the reaction at 240 °C under microwave[16] heating resulted in the complete consumption of intermediate **9b** with the desired deprotected product **3b** being obtained in 80% yield (Scheme 2 and Table 1).

In conclusion, we have reported the first preparation of *N*-Boc 4-nitropiperidine **1**. We have demonstrated the synthetic utility of this new building block by preparing simple and more advanced novel spiropiperidines, including an analogue of the eastern part of maraviroc. Further applications of *N*-Boc 4-nitropiperidine are currently being investigated and the results will be reported in due course.



Scheme 2. Conversion of **2b** into the spirotriazole **3b**.

Table 1
Product distribution (LC–MS) upon thermal treatment of compound **9b**

T (°C)	**9b**	**10b**	**3b**
130	70	30	0
180	50	30	20
240	0	0	80

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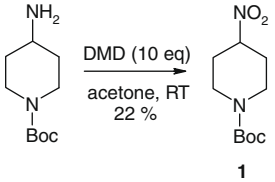
References and notes

1. Wilson, R. A.; Chan, R.; Wood, R.; Brown, R. C. D. *Org. Biomol. Chem.* **2005**, *3*, 3228–3235. and references cited therein.
2. Uto, Y.; Kiyotsuka, Y.; Ueno, Y.; Miyazawa, Y.; Kurata, H.; Ogata, T.; Deguchi, T.; Yamada, M.; Watanabe, N.; Konishi, M.; Kurikawa, N.; Takagi, T.; Wakimoto, S.; Kono, K.; Ohsumi, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 746–754.
3. Caldwell, J. P.; Matasi, J. J.; Fernandez, X.; McLeod, R. L.; Zhang, H.; Fawsi, A.; Tulshian, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1164–1167.
4. Rotstein, D. M.; Gabriel, S. D.; Makra, F.; Filonova, L.; Gleason, S.; Brotherton-Pleiss, C.; Setti, L. Q.; Trejo-Martin, A.; Lee, E. K.; Sankuratri, S.; Ji, C.; de Rosier, A.; Dioszegi, M.; Heilek, G.; Jekle, A.; Berry, P.; Weller, P.; Mau, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5401–5406.
5. Takahashi, T.; Haga, Y.; Sakamoto, T.; Moriya, M.; Okamoto, O.; Nonoshita, K.; Shibata, T.; Suga, T.; Takahashi, H.; Hirohashi, T.; Sakuraba, A.; Gomori, A.; Iwaasa, H.; Ohe, T.; Ishihara, A.; Ishii, Y.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3511–3516.
6. Burgey, C. S.; Potteiger, C. M.; Deng, J. Z.; Mosser, S. D.; Salvatore, C. A.; Yu, S.; Roller, S.; Kane, S. A.; Vacca, J. P.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6368–6372.
7. Costanzo, M. J.; Yabut, S. C.; Tounge, B.; Maryanoff, B. E.; Zhang, H. WO Patent 200906720, 2009; *Chem. Abstr.* **2009**, *151*, 8305.
8. Stearns, B. A.; Truong, Y. P.; Hutchinson, J. H. WO Patent 2009061676, 2009; *Chem. Abstr.* **2009**, *150*, 515047.
9. Converso, A.; Hartingh, T.; Garbaccio, R. M.; Tasber, E.; Rickert, K.; Fraley, M. E.; Yan, Y.; Kreatsoulas, C.; Stirdivant, S.; Drakas, B.; Walsh, E. S.; Hamilton, K.; Buser, C. A.; Mao, X.; Abrams, M. T.; Beck, S. C.; Tao, W.; Lobell, R.; Sepp-Lorenzino, L.; Zugay-Murphy, J.; Sardana, V.; Munshi, S. K.; Jezequel-Sur, S. M.; Zuck, P. D.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1240–1244.
10. Van Parys, M.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1981**, *90*, 749–755.
11. Bryce, M. R.; Gardiner, J. M.; Horton, P. J.; Smith, S. A. *J. Chem. Res. (S)* **1989**, 116–124. and references cited therein.
12. The only reference that we could find was a publication on the preparation of various *N*-alkylated 4-nitropiperidines, the synthetic applications of which have never been explored see Piotrowska, H.; Sas, W.; Winiarski, J. *Roczniki Chemii* **1977**, *51*, 2417–2420. A patent also reports the preparation of 4-nitropiperidine by simple nitration of piperidine but provides no experimental procedures, see CN 1772735, 2006; *Chem. Abstr.* **2006**, *145*, 62786.
13. Emmons, W. D. *J. Am. Chem. Soc.* **1953**, *75*, 4623–4624.
14. To a 35% aqueous solution of H_2O_2 (27.3 mL, 0.318 mol) in MeCN (150 mL) at 0 °C was added TFAA (200.2 mL, 1.43 mol). This solution was added dropwise over 40 min to a stirring, refluxing solution of oxime **2** (34.00 g, 0.159 mol), urea (3.24 g, 0.054 mol) and $NaHCO_3$ (241.6 g, 2.88 mol) in MeCN (500 mL). The solution was refluxed for a further 4 h. It was then cooled and filtered. The filtrate was diluted with EtOAc (2 L) and washed with H_2O (2 × 500 mL). The organic layer was dried, filtered and concentrated to a residue which was purified by chromatography (hexane/EtOAc: 100/0–70/30) to give product **1** as a yellow oil (20.1 g, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.06 (m, 2H), 2.23 (m, 2H), 3.02 (m, 2H), 4.05 (m, 2H), 4.52 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 27.9, 29.5, 43.0, 79.6, 80.5, 154.0.
15. We initially tried to prepare compound **1** by dimethyldioxirane oxidation of 4-amino 1-Boc-piperidine. Whilst this method allowed us to prepare the first analytical sample of compound **1**, the yield was low and a large excess of dimethyldioxirane was required.



16. The microwave-assisted reactions were run in a Biotage Initiator™ microwave oven.