A. A. KIRICHOK, H. TKACHUK, Y. KOZYRIEV, O. SHABLYKIN, O. DATSENKO, D. GRANAT, T. YEGOROVA, Y. B. BAS, V. SEMIRENKO, I. PISHEL, V. KUBYSHKIN, O. KLYMENKO-ULIANOV, D. LESYK, P. K. MYKHAILIUK* (ENAMINE LTD., KYIV AND TARAS SHEVCHENKO NATIONAL UNIVERSITY OF KYIV, UKRAINE)

1-Azaspiro[3.3]heptane as a Bioisostere of Piperidine
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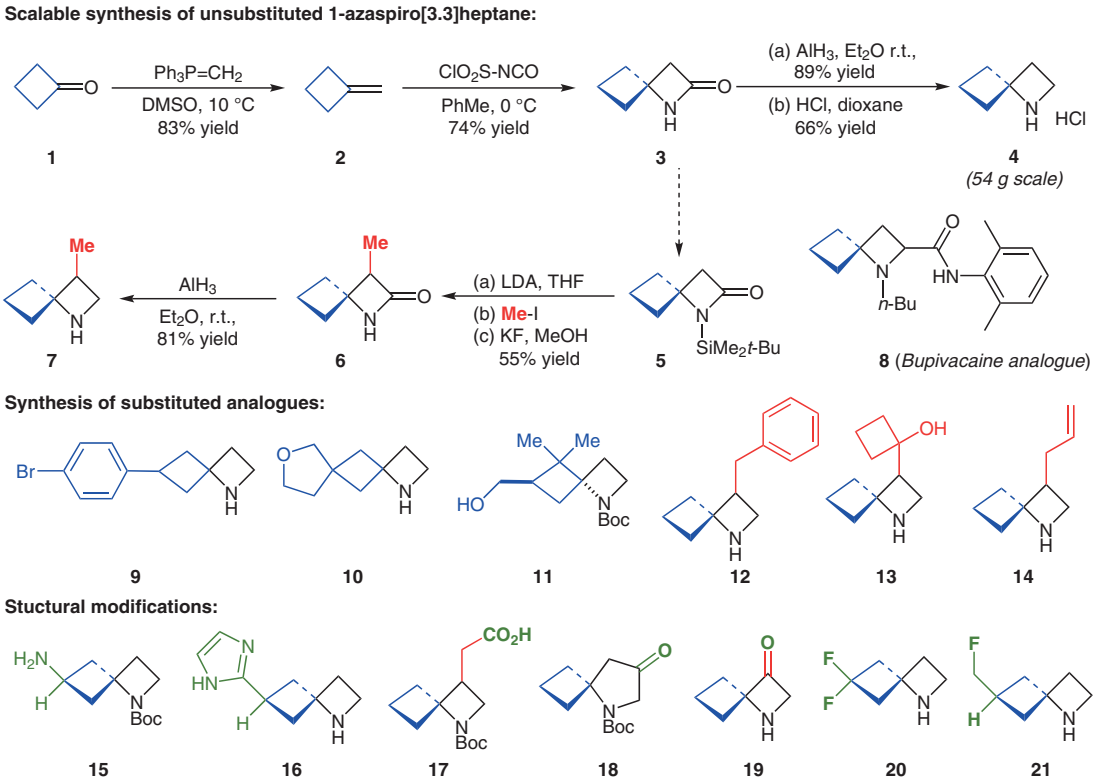
Modular, Scalable Synthesis of 1-Aza[3.3]heptanes



Significance: Over 30 approved drugs currently feature a piperidine ring, though replacement of this moiety with a suitable bioisostere is often utilized as a strategy to increase lipophilicity and improve metabolic stability of a specific target compound. While the use of 2-azaspiro[3.3]heptanes for this purpose was first reported in 2010 (E. M. Carreira and co-workers *Angew. Chem. Int. Ed.* **2010**, *49*, 3524) the isomeric 1-azaspiro[3.3]heptanes are not utilized owing to a lack of robust methods for their preparation. The current report provides a modular, scalable synthetic approach to a series of substituted 1-azaspiro[3.3]heptanes, while also providing a comparative analysis of the geometric parameters with the corresponding 2-substituted piperidines.

Comment: One of the key challenges to establishing the chemistry was in the selective reduction of the lactam derivative formed through the thermal [2+2] cycloaddition between the endocyclic alkene (**2**) and Graf's isocyanate. Borane-based reagents and $LiAlH_4$ afforded both the desired amine though also led to significant amounts of ring cleavage, while alane was successfully employed to smoothly reduce the lactam on multigram scale. Starting with substituted alkene derivatives enabled a range of substituents to be introduced to the cyclobutyl ring (**9**–**11**), while a lithiation/electrophilic trapping sequence was developed on the intermediate lactam (**3**) allowing diversification of the azetidine ring (**12**–**14**). A range of synthetic transformations were also demonstrated (**15**–**21**), while the validity of the bioisostere strategy was highlighted through the synthesis of a bioactive analogue of the local anesthetic bupivacaine (**8**).

SYNFACTS Contributors: Paul Richardson (Pfizer)
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