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# Practical and divergent synthesis of 1- and 5-substituted 3,9-diazaspiro[5.5]undecanes and undecan-2-ones

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ABSTRACT

A divergent synthesis of 1- and 5-substituted 3,9-diazaspiro[5.5]undecanes and undecan-2-ones is described, in which the key step is an efficient Michael addition of a lithium enolate to a tetrasubstituted olefin acceptor. A variety of substituents (butyl, phenyl, and propoxyl) were introduced at C-1(5) in this manner. In addition, an asymmetric synthesis of one member of this series was achieved using an Evans oxazolidinone chiral auxiliary reagent.



Conformationally constrained heterocyclic multi-ring systems have received considerable attention from the practioners of drug discovery.[1] This can be attributed to the ability of such entitites to direct pharmacophores to well-defined 3D space,[2] and to their improved pharmacokinetic (PK) profile as a consequence of reduction in the number of rotatable bonds.[3] Bemis and Murcko analyzed 5120 marketed drugs using graph theory analysis.[4] They found that only 32 frameworks are needed to account for 50% of all known drug molecules. Further analysis of the 32 common frameworks revealed that 23 of them contain at least two fused or linked six-membered rings and only three of them contain more than five rotatable bonds.

Spiropiperidines belong to an important constrained ring system class and are found in a number of bioactive molecules, such as Spiperone—a drug for the treatment of Schizophrenia, L-387,384—a α-opioid ligand,[5] and MK-0667—a GH secretagogue[6] (Fig. 1). Therefore, the design and synthesis of novel spiropiperidines are of continued interest to medicinal chemists.[7]

In connection with one of our drug discovery programs, we were interested in employing 3,9-diaza-spiro[5.5]undecane **1** and undecan-2-one **2** as central templates (Fig. 2). Based on our previous SAR and target homology model, we reasoned that a side chain to the spirocenter would enhance ligand/protein binding affinity. Although 3,9-diazaspiro[5.5]undecane **1** has been used extensively in drug discovery, [8] to the best of our knowledge, there were no reported syntheses of 1- or 5-substituted 3,9-diazaspiro[5.5]undecanes and undecan-2-ones. Presumably, steric hindrance by the spirocenter makes such a substitution highly disfavored. Herein, we report a divergent synthesis of 1- and 5-substituted 3,9-diazaspiro[5.5]undecanes and undecan-2-ones from a common intermediate, and our initial study of their asymmetric syntheses.

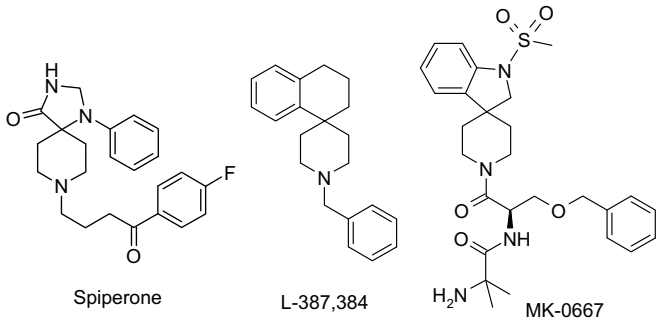


**Figure 1.** Spiropiperidine-containing bioactive molecules.

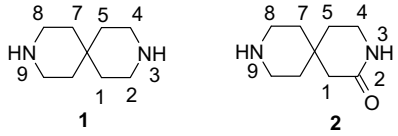


**Figure 2.** 3,9-Diazaspiro[5.5]undecane **1** and undecan-2-one **2**.

Surprisingly, only one synthesis of the unsymmetrically *N*-substituted congeners of both the 3,9-diazaspiro[5.5]undecane[9] and the 3,9-diazaspiro[5.5]undecan-2-one[10] systems has been reported (Scheme 1). Di-ester **3**, the key intermediate leading to 3,9-diazaspiro[5.5]undecane skeleton, was prepared from *N*-methyl 4-piperidone and ethyl cyanoacetate in a three-step sequence involving cycolcondensation, hydrolysis and esterification. Conversion of **3** into the imide **4**, and reduction thereof with lithium aluminum hydride (LAH) gave the diazaspiroundecane **5**. The synthesis of the 3,9-diazaspiro[5.5]undecan-2-one ring system relied upon the conjugate addition of lithio ethyl acetate to **6** to

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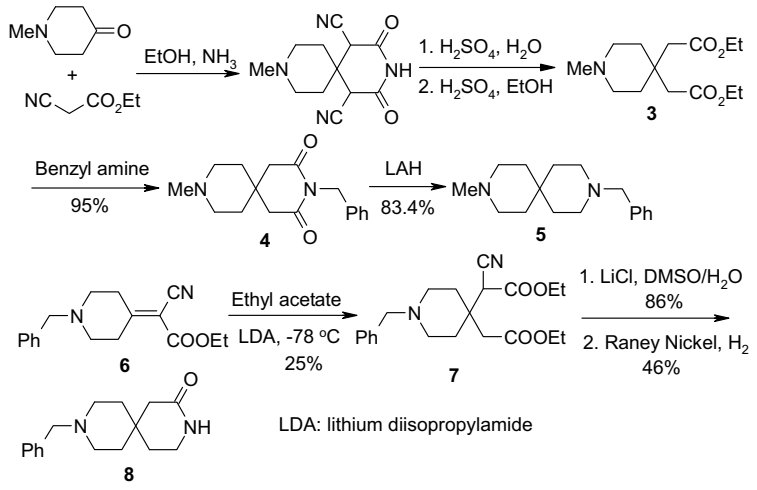
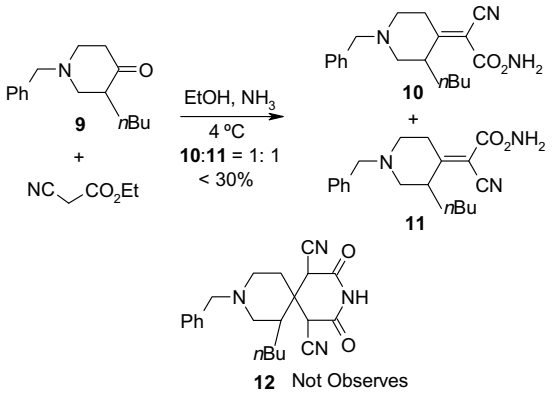



**Scheme 1.**

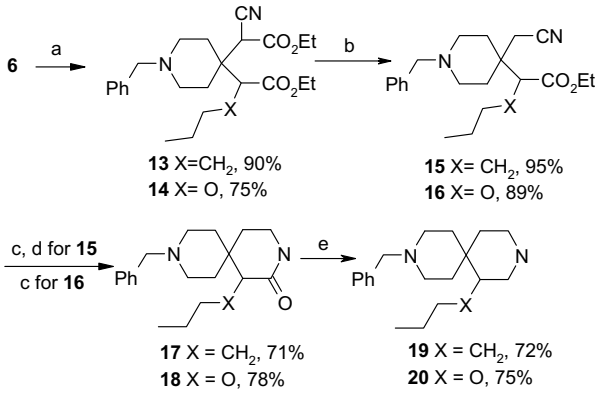
give di-ester **7**, which was converted into diazaspiroundecan-2-one **8** in two steps.

Our initial synthetic target was the 1-butyl congener of the 3,9-diazaspiro[5.5]undecane system. Thus, the reaction of **9** with ethyl cyanoacetate in saturated ethanolic ammonia solution, as described in the literature,[10] gave a complex mixture, from which small amounts of the monocondensation products **10** and **11** could be isolated, but not containing any of the desired product **12** (Eq. 1).

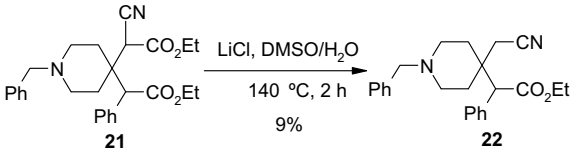



(1)

This result prompted us to examine the reported 3,9-diazaspiro[5.5]undecan-2-one synthesis, but the low yield (25%) reported in the Michael addition step (**6**→**7**) was of concern to us because the 1-substitued congeners of the spirocyclic system were required in multi-gram amounts. On the assumption that the poor yield was associated with temperature control in the enolate generation step, a pre-cooled (−78 °C) THF solution of ethyl caproate or ethyl propoxyacetate was added to a stirred solution of a THF solution Lithium diisopropylamide (LDA) and **6** at −78 °C. The Michael addition products **13** and **14** were thus obtained in 90% and 75% yields, respectively, (Scheme 2). Krapcho de-ethoxycarbonylation (2 equiv of LiCl, DMSO/$H_2O$, 200 °C) of the Michael adducts occurred selectively and in high yield, to give the mono-esters **15** and **16**. Catalytic reduction (Raney Nickel, $H_2$) of the nitrile group of **15** and **16** took place in modest yields at best, but reduction with a large excess of $NaBH_4$ (15 equiv), in the presence of $CoCl_2$ in methanol solution,[11] occurred cleanly and efficiently to give the spirocyclic lactams **17** and **18** directly. Final LAH reduction of the lactams readily provided the 3,9-diazaspiro[5.5]undecanes **19** and **20**.




**Scheme 2.** Reagents and conditions: (a) LDA, THF, −78 °C, for X = $CH_2$, ethyl hexanoate; for X = O, ethyl propoxyacetate;(b) LiCl, DMSO, $H_2O$, 200 °C; (c) $NaBH_4$, $CoCl_2$, MeOH, rt; (d) toluene, reflux; (e) LAH, THF, reflux.




(2)

An attempt to apply the methodology described in Scheme 2 to the synthesis of the phenyl analog turned out to be problematic in the de-ethoxycarbonylation step. The required mono-ester **22** was obtained in very low yield, perhaps due to the loss of the benzylic ethoxycarbonyl group.[12] This problem was solved as shown in Scheme 3, via the *t*-butyl ester **23**. Microwave irradiation of a hexafluoroisopropanol solution of this diester (1 h/130 °C) gave the mono-ester **24** nearly quantitatively.[13] This compound was converted into **25** and **26** by the methods described above.

Cyanoester **15** also served as a flexible intermediate for the synthesis of 5-substituted-3,9-diazaspiro[5.5]undecan-2-ones (Scheme 4). Thus, selective reduction of the ester with lithium pyrrolidinoborohydride[14] gave alcohol **27**, which was converted into the azide **28** via a Mitsunobu reaction. Staudinger reduction of **28** gave the iminophosphorane **29**, which upon vigorous acidic hydrolysis (concd HCl/100 °C, 3 d) produced the diazaspiroundecanone **30** via the easily detectable (liquid chromatography–mass spectrometry) intermediate amidine **31**.