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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.

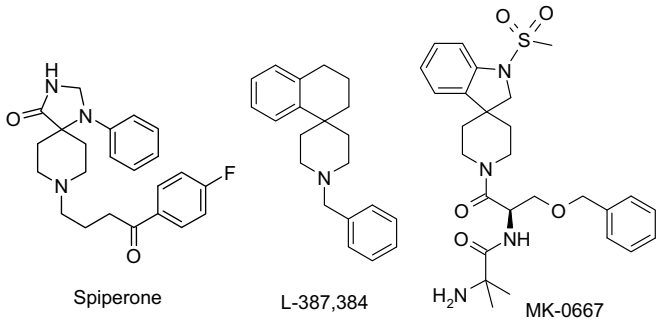

Figure 1. Spiropiperidine-containing bioactive molecules.

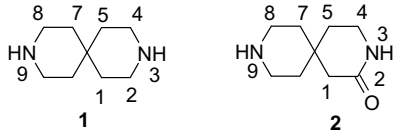

Figure 2. 3,9-Diazaspiro[5.5]undecane **1** and undecan-2-one **2**.

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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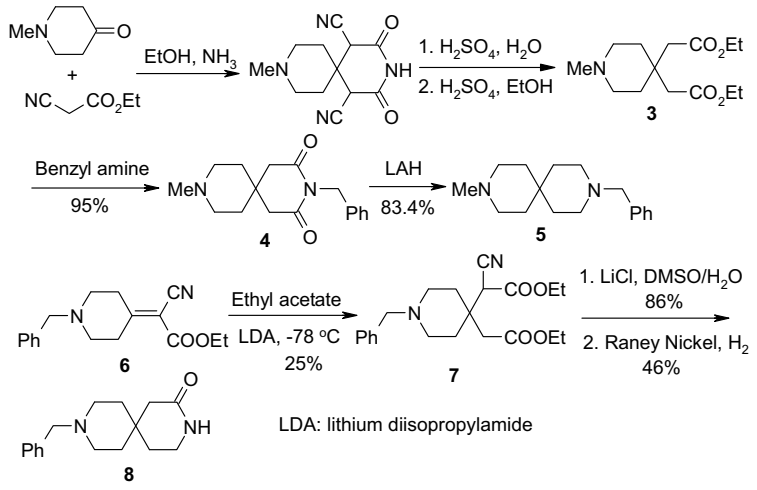
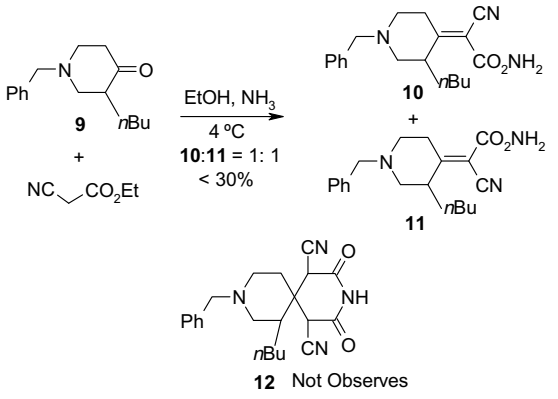


Scheme 1.

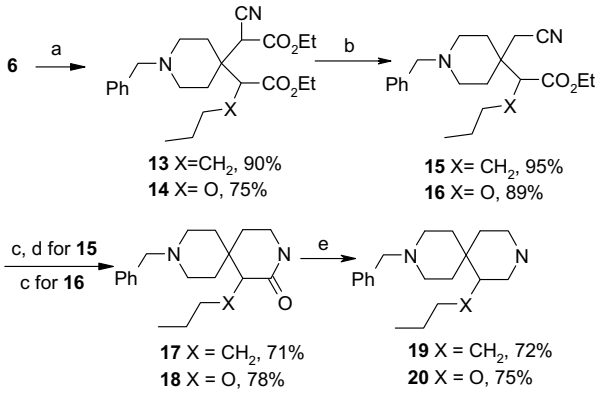
give di-ester **7**, which was converted into diazaspiroundecan-2-one **8** in two steps.

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).

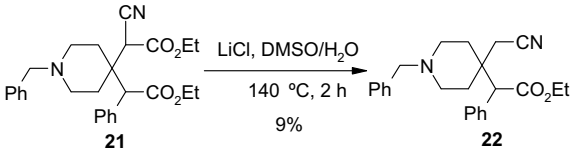


(1)

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**.



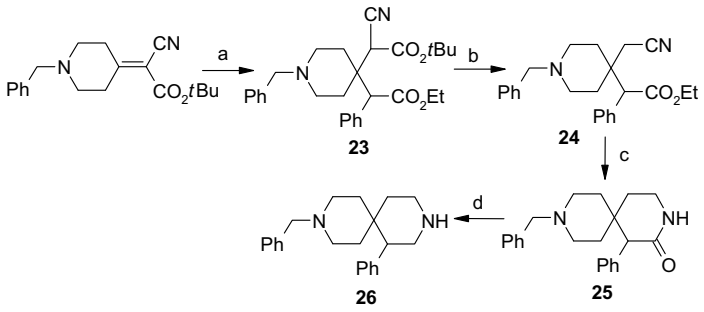
Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, for X = CH_2, ethyl hexanoate; for X = O, ethyl propoxyacetate;(b) LiCl, DMSO, H_2O, 200 °C; (c) $NaBH_4$, $CoCl_2$, MeOH, rt; (d) toluene, reflux; (e) LAH, THF, reflux.



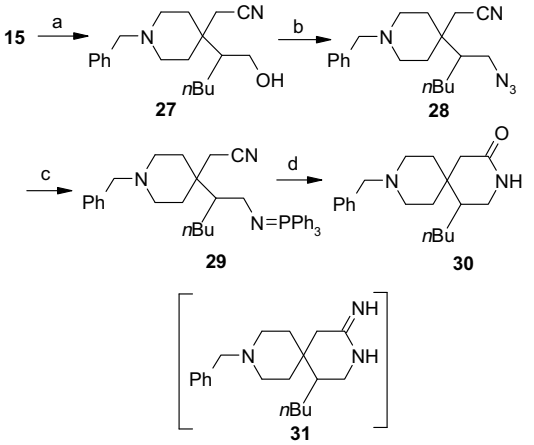
(2)

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**.

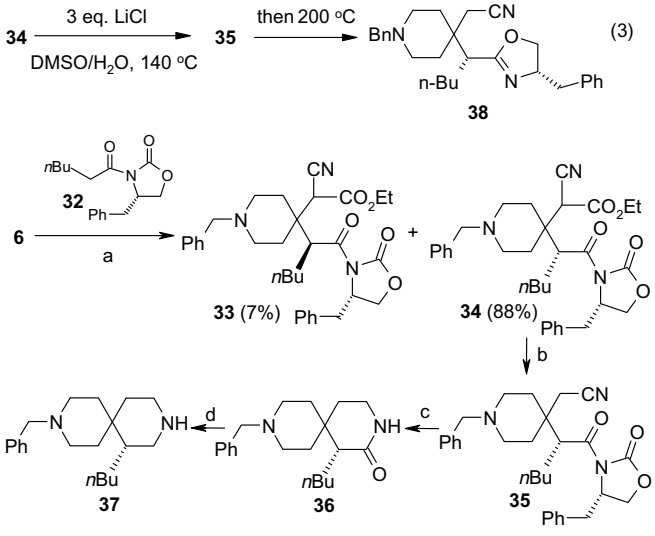


Scheme 3. Reagents and conditions: (a) ethyl phenylacetate, LDA, THF, −78 °C, quant.; (b) hexafluoro-2-propanol, 130 °C, microwave, 1 h, 95%; (c) NaBH4, CoCl2, MeOH, rt, 73%; (d) LAH, THF, reflux, 65%.



Scheme 4. Reagents and conditions: (a) Lithium pyrrolidinoborohydride, THF, rt, 86%; (b) PPh3, diethylazodicarboxylate, diphenyl phosphoryl azide, THF, rt, 54%.

An asymmetric synthesis based on the above methodology was then devised. Michael addition of the lithium enolate[15] of the optically pure ester **32** to **6** occurred in excellent yield (88%) to give a 1:13, readily separable (flash column chromatography), mixture of the stereoisomeric adducts **33** and **34** (Scheme 5). [16] Under the previously employed Krapcho conditions (2 equiv LiCl, DMSO/H_2O, 200 °C, 2 h), **34** was converted into the nitrile **35** in only 25% yield, but this yield was greatly improved when the reaction was effected with ca 1 equiv of LiCl at 140 °C. Interestingly, when the reaction was carried out at 140 °C with 3 equiv of LiCl, the nitrile **35** was formed cleanly, but upon further heating at 200 °C for 50 min, it was completely converted into the oxazoline **38** (Eq. 3), the structure of which was fully confirmed by NMR experiments.[17] Reduction of the nitrile group of **35** as described above gave undecanone **36** (>99.5% ee), which on further reduction with LAH in refluxing THF yielded undecane **37** (79% yield) with minimal racemization (98% ee).



Scheme 5. Reagents and conditions: (a) LDA, THF, −78 °C, then 21, −78 °C, 88% yield for the R-isomer; (b) LiCl, DMSO, H_2O, 140 °C, 89%; (c) $NaBH_4$, $CoCl_2$, MeOH, rt, 80% yield, >99.5% ee; (d) LAH, THF, reflux, 79% yield, 98% ee.

In summary, a practical and divergent synthesis of 1- and 5-substituted 3,9-diazaspiro[5.5] undecanes and 3,9-diazaspiro[5.5]undecan-2-ones is described, in which the key synthetic step involves an efficient Michael addition of the lithium enolates of α-substituted acetic acid esters to tetrasubstituted olefin acceptors such as **6**.[18] Similar methodology using the Evans oxazolidinone chiral reagent **32** permitted the synthesis of the highly optically enriched 5-butyl-3.9-diazaspiro[5.5]undecan-2-one **36**.

Acknowledgments

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18. *Selected spectral data—compound* **30**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.20 (m, 5H), 6.85 (s, 1H), 3.51 (s, 2H), 3.41 (dd, J = 1.5, 4.7 Hz, 1H), 3.10–3.02 (m, 1H), 2.70–2.60 (m, 2H), 2.41–2.13 (m, 4H), 1.80–1.13 (m, 11H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 138.6, 129.6, 128.6, 127.4, 63.7, 49.3, 49.2, 42.5, 41.5, 38.6, 35.2, 33.8, 31.8, 30.9, 26.1, 23.2, 14.4; IR (neat film) 3421, 3195, 3060, 2948, 2932, 2869, 2799, 2762, 1670, 1505, 1451, 1411, 1366, 1341, 1313, 1121, 736 cm^{-1}; HRMS Cacld for $C_{20}H_{31}N_2O$ [M+H]$^+$ 315.2436. Found: 315.2433. Compound **36**: $[\alpha]_D^{25}$ +32.4 (c 1.7, CH_2Cl_2); ee >99.5% (determined by chrialpak AD analytical column with 85:15 hexane/EtOH at 1.4 mL/min rate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.21 (m, 5H), 6.13 (br s, 1H), 3.49 (s, 2H), 3.28–3.20 (m, 2H), 2.60–2.55 (m, 2H), 2.35–2.25 (m, 2H), 2.12–2.08 (m, 1H), 1.83–1.72 (m, 1H), 1.53–1.23 (m, 11H), 0.89 (t, J = 7.1H, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2, 138.7, 129.6, 128.6, 127.4, 63.8, 50.9, 49.6, 49.5, 38.6, 34.5, 34.1, 33.7, 31.7, 28.0, 26.7, 23.5, 14.4; IR (neat film) 3681, 3402, 3207, 3019, 2956, 2873, 2811, 2771, 2400, 1656, 1496, 1454, 1369, 1343, 1297, 1163, 1106, 1029, 991, 909, 701 cm^{-1}; HRMS Calcd for $C_{20}H_{31}N_2O$ [M+H]$^+$ 315.2436. Found: 315.2431. Compound **37**: $[\alpha]_D^{25}$ +55.0 (c 2.3, CH_2Cl_2); ee 98% (determined by chrialpak AD analytical column with 95:05 hexane/EtOH at 1.4 mL/min rate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.22 (m, 5H), 4.53 (br s, 1H), 3.49 (s, 2H), 3.02–2.88 (m, 2H), 2.85–2.76 (m, 1H), 2.62–2.52 (m, 3H), 2.26–2.09 (m, 2H), 2.02–1.88 (m, 2H), 1.60–1.40 (m, 3H), 1.36–0.95 (m, 8H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 129.5, 128.6, 127.3, 63.9, 49.1, 45.6, 44.7, 41.6, 35.5, 33.3, 31.8, 31.2, 28.1, 26.5, 23.4, 14.5; IR (neat film) 3285, 3061, 3026, 2929, 2858, 2804, 1494, 1453, 1394, 1365, 1342, 1135, 1083, 1029, 993, 794, 738, 698 cm^{-1}; HRMS Calcd for $C_{20}H_{33}N_2$ [M+H]$^+$ 301.2644. Found: 301.2614.