ORGANIC LETTERS

2013
Vol. 15, No. 19
4992–4995

# 1,7-Diazaspiro[5.5]undecane — A Neglected Heterocycle

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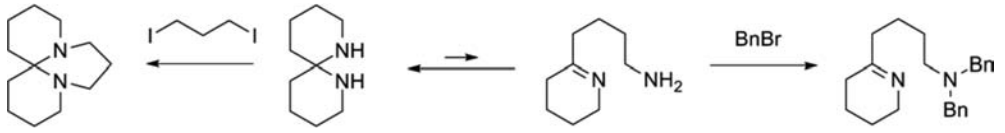
**Received August 12, 2013**

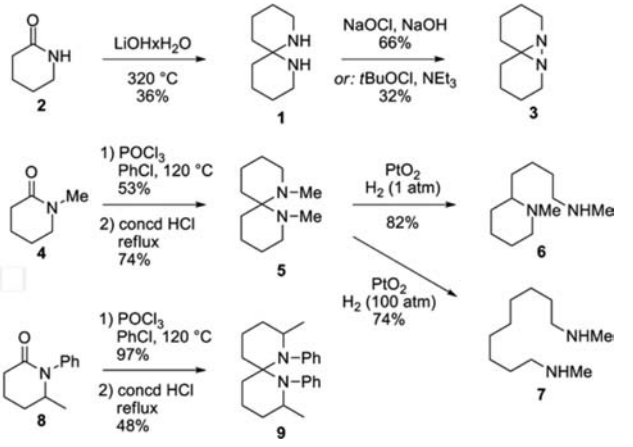
## ABSTRACT




**A convenient and simple three step synthesis of 1,7-diazaspiro[5.5]undecane via Claisen condensation and acid catalyzed decarboxylation and spirocyclization of *N*-Boc-$\delta$-valerolactam is described. Reactions of this spiroaminal with electrophiles including alkyl halides, alkane dihalides, acid chlorides, and sulfonyl chlorides gave either spirocyclic adducts or tetrahydropyridine derivatives. Additionally, the parent heterocycle is a novel bidentate ligand and formed complexes with ruthenium(II) and copper(II).**

In contrast to spiroketals (*O*,*O*-ketals) and spirohemiaminals (*N*,*O*-ketals), little is known about the chemistry of the corresponding spiroaminals (*N*,*N*-ketals).[1,2] Few papers have been published on synthesis and reactions of 1,7-diazaspiro[5.5]undecane (**1**) and its derivatives.[3−6] One simple synthesis is known of the parent compound **1** from piperidin-2-one (**2**) in 36% yield, via heating with lithium hydroxide at 320 °C (Scheme 1).[3] Two *N*-substituted analogues **5** and **9** were synthesized from the corresponding *N*-substituted lactams **4** and **8** in 39% and 47% yield over two steps.[4] Only three reactions are known for spiroaminal **1** and its derivatives. The parent heterocycle **1** can be oxidized to form diaziridine **3**.[3] The dimethyl-analogue **5** was hydrogenated with ring cleavage to form diamine **6** or, under more forcing conditions, to generate diamine **7** via two reductive ring-opening reactions.[5]

**Scheme 1.** Known Syntheses and Conversions of **1** and Simple Analogues[3−5]




In light of the limited information available on this fascinating spirocyclic compound,[3−6] we sought to develop an efficient synthesis of heterocycle **1** and to investigate its reactivity toward electrophiles and as a novel bidentate ligand.

Following the general strategy of the known syntheses,[3−5] we developed a method that allows the synthesis of

(1) (a) Kibayashi, C.; Yamazaki, N. *Sci. Synth.* **2006**, *30*, 639. (b) Pawlenko, S.; Lang-Fugmann, S. In *Houben-Weyl Methods of Molecular Transformations*; Hagemann, H., Klamann, D., Eds.; Georg Thieme Verlag: Stuttgart, 1992; E 14a/3, pp 545−547.

(2) For recent examples of aminals in natural product syntheses, see: (a) Padwa, A.; Flick, A. C.; Lee, H. I. *Org. Lett.* **2005**, *7*, 2925. (b) Bobeck, D. R.; Lee, H. I.; Flick, A. C.; Padwa, A. *J. Org. Chem.* **2009**, *74*, 7389. (c) Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2012**, *134*, 11995.

(3) Denisenko, S. N.; Pasch, E.; Kaupp, G. *Angew. Chem.* **1989**, *101*, 1397. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1381.

(4) Büchel, K. H.; Bocz, A. K.; Korte, F. *Chem. Ber.* **1966**, *99*, 724.

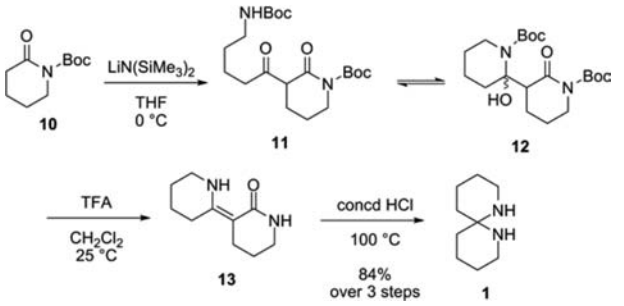
(5) Korte, F.; Bocz, A. K; Büchel, K. H. *Chem. Ber.* **1966**, *99*, 737.

(6) For syntheses of other derivatives of **1**, see: (a) Zondler, H.; Pfleiderer, W. *Helv. Chim. Acta* **1975**, *58*, 2247. (b) Maloň, P.; Barness, C. L.; Buděšinsky, M.; Dukor, R. K.; van der Helm, D.; Keiderling, T. A.; Koblicova, Z.; Pavlikova, F.; Tichy, M.; Blaha, K. *Collect. Czech. Chem. Commun.* **1988**, *53*, 2447. (c) Smolikova, J.; Koblicova, Z.; Blaha, K. *Collect. Czech. Chem. Commun.* **1973**, *38*, 532.

10.1021/ol402301g 
**Published on Web 09/26/2013**

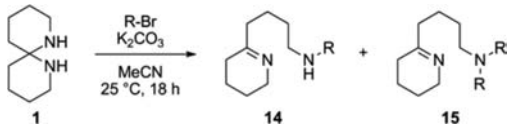
spiroaminal **1** under significantly less harsh reaction conditions. Commercially available Boc-lactam **10** was converted into $\beta$-ketolactam **11** via Claisen condensation,[7] by the slow addition of lithium hexamethyldisilazide ($LiN(SiMe_3)_2$) to a solution of lactam **10** in THF at 0 °C (Scheme 2). The resulting product exists as both $\beta$-ketolactam **11** and hemiaminal **12** in equilibrium and, as a crude product, is prone to decomposition via retro-Claisen reaction. Fortunately, deprotection and dehydration of the mixture directly using trifluoroacetic acid (TFA) gave enamino-lactam **13**, in sufficient purity for the next step. Lactam hydrolysis, decarboxylation, and aminal formation by heating in hydrochloric acid gave, after column chromatography, spiroaminal **1** in 84% yield over the three steps.

**Scheme 2.** Synthesis of 1,7-Diazaspiro[5.5]undecane (**1**)




With spiroaminal **1** in hand, we turned our attention to the synthesis of derivatives by reaction with electrophiles. Among the simplest possible reactions are alkylations, acylations, and sulfonylations.[8] Reaction of spirane **1** with allyl bromide or benzyl bromide, and potassium carbonate in acetonitrile did not yield spirocyclic products but gave the tetrahydropyridines **15a** (62%) and **15b** (72%) respectively (Table 1, entries 1 and 3). Reaction with only 1.1 equiv of electrophile gave the same compounds, but this time monosubstituted analogues **14** were also isolated.

**Table 1.** Alkylation Reactions of **1** with Allyl Bromide and Benzyl Bromide



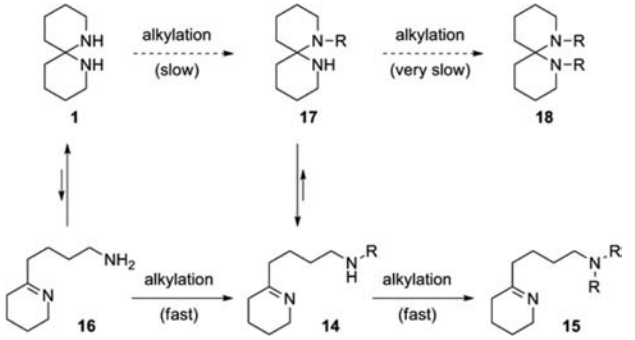

| entry | R | equiv R–Br | products (%)[a] |
|---|---|---|---|
| 1 | allyl | 2.2 | **14a** (trace) + **15a** (62) |
| 2 | allyl | 1.1 | **14a** (12) + **15a** (32) |
| 3 | Bn | 2.2 | **14b** (trace) + **15b** (72) |
| 4 | Bn | 1.1 | **14b** (30) + **15b** (35) |

[a] Isolated yield.

(7) Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. M.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2004**, *69*, 1959.

The monoalkylated products **14a** and **14b** shed some light on the reactivity of 1,7-diazaspiro[5.5]undecane. The NMR spectra of spiroaminal **1** clearly show that this substance has predominantly the spirocyclic constitution.[9] The NMR spectra of compounds **14a** and **14b** are consistent with these substances existing predominantly in the ring-opened imine/amine form. It is a reasonable assumption, though, that for both compounds a small concentration of the other tautomer (i.e., imine/amine **16** is in equilibrium with spiroaminal **1**, and spiroaminal **17** is in equilibrium with imine/amine **14**, respectively, Scheme 3) exists.

**Scheme 3.** Reasonable Mechanism for the Formation of **14** and **15** by Alkylation of **1**, and the Failure To Form Spirane **18**




The consequence of this is obvious: spiroaminal **1** is a sterically rather hindered nucleophile (both amines are 2,2-disubstituted piperidines) and should react slowly, whereas the primary amine **16** is both a good nucleophile and sterically much less hindered and should therefore react rapidly. The first alkylation presumably takes place on the primary amine of isomer **16**, even though its concentration is very low. The equilibrium between the resultant amines **14** and **17** is now clearly on the side of the imine/amine **14**. Following the same reasoning as before, but with increased steric bulk on **17** and increased nucleophilicity on **14**, the product of the second alkylation is consequently **15**, rather than **18**.

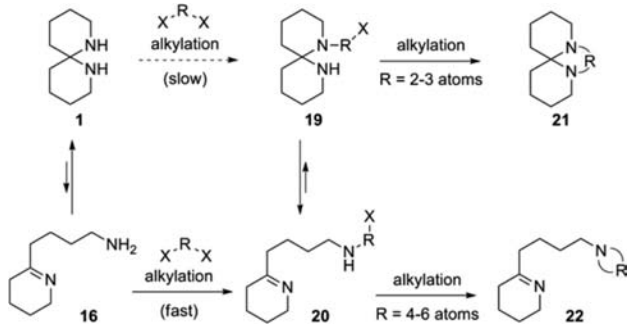
We next turned our attention to alkylation reactions with dielectrophiles. Depending on the dielectrophile structure, the product was either tricyclic diamine **21** or bicyclic imine-amine **22**, and mixtures of these were not observed (Table 2). This interesting result again can be rationalized by considering spiroaminal tautomerism.

Reaction of diaminal **1** with 1,2-dibromoethane, 3-bromo-2-bromomethyl-1-propene, and 1,3-diiodopropane gave rise to the tricyclic adducts **21a**, **21b**, and **21c** respectively. In contrast, reaction of spirane **1** with 1,4-diiodobutane, 1,5-diiodopentane and 1,6-diiodohexane gave the

(8) *Alkylations:* (a) Lawrence, S. A. *Sci. Synth.* **2008**, *40*, 526. *Acylations:* (b) Ziegler, T. *Sci. Synth.* **2005**, *21*, 43. *Sulfonylations:* (c) Drabowicz, J.; Kiełbasiński, P.; Łyżwa, P.; Zając, A.; Mikołajczyk, M. *Sci. Synth.* **2007**, *39*, 77.

(9) Interestingly, this distinguishes spiroaminal **1** from its analogues with 5- and 7-membered rings, which exist predominantly in the form of the ring-opened tautomer (see ref 3).

**Scheme 4.** Plausible Mechanism for the Formation of Compounds **21** and **22** by Alkylation of **1** with Dihalides



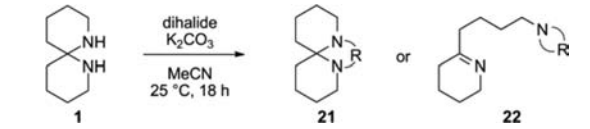

bicyclic imino-amines **22a**, **22b**, and **22c**. Clearly, the first alkylation step (Scheme 4) does not differ from the allylation or benzylation discussed above. But the resultant intermediate **19**/**20** can now undergo a second intramolecular alkylation step. By reaction with the secondary amine in **20**, it forms imino-amine **22**. This is the case for dihalides that can form 5-membered or larger rings. It is not observed, however, for dihalides that would result in 4-membered or smaller rings. These result in tricyclic spiroaminals, most likely via alkylation of the second amine via the spiroaminal tautomer **19**. The exclusive formation of either **21** or **22** can therefore be explained by ring strain (which prevents the formation of **22** with 4-membered or smaller cyclic amines) and fast ring closing of **20** to **22** (which prevents formation of tricyclic spiroaminals **21** for α,ω-diiodoalkanes with four or more carbon atoms, which would have resulted in 7- to 9-membered heterocycles).

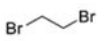
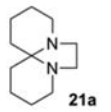
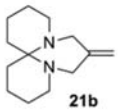
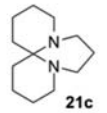
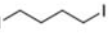
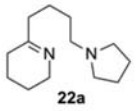
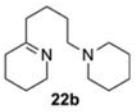
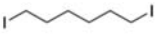
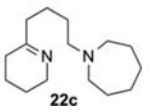
Reaction of diaminal **1** with acetyl chloride and 4-toluenesulfonyl chloride again resulted in spirocycle scission (Scheme 5). With the first amine converted into a rather non-nucleophilic amide, the next best nucleophile is now the imine, which leads (via an iminium ion intermediate) to *N*-acylated or *N*-toluene-4-sulfonated enamines **24** respectively.

The formation of an acylated or *N*-toluene-4-sulfonated spiroaminal as an intermediate is less likely to occur, and its reaction with acetyl or toluene-4-sulfonyl chloride even more so. The NMR spectra of compounds **23** and **24** show clearly the ring opened tautomer structures. In addition to that, an X-ray crystal structure determination of sulfonamide **23b** confirms this structure to be present for the solid state, too.

Consistent with the reactions of spirane **1** with the dihalides in entries 1−3 in Table 2, reaction of **1** with bromide **25** gave the corresponding adduct **26**, retaining the spiroaminal unit as a single diastereoisomer (Scheme 6). Clearly, the product **26** was formed via *N*-alkylation followed by Michael addition. In contrast, reaction of the isomeric bromide **27** with spirane **1** gave the doubly alkylated amino-imine **15c**. Presumably the difference between the two reaction pathways is that the examined system **19** apparently undergoes 5-*exo*-*trig* cyclizations

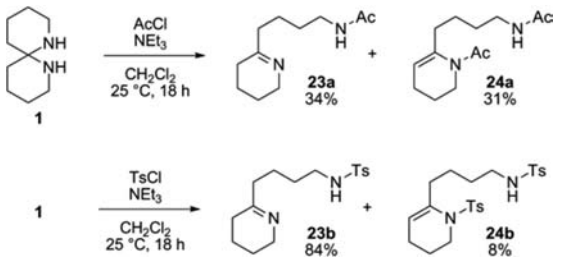
**Table 2.** Alkylation Reactions of **1** with Dihalides




| entry | dihalide | product | isolated yield (%) |
|---|---|---|---|
| 1 |  |  | 37[a] |
| 2 |  |  | 81 |
| 3 |  |  | 69 |
| 4 |  |  | 61 |
| 5 |  |  | 63 |
| 6 |  |  | 43 |

[a] Reaction conditions: 70 °C, 3 h.

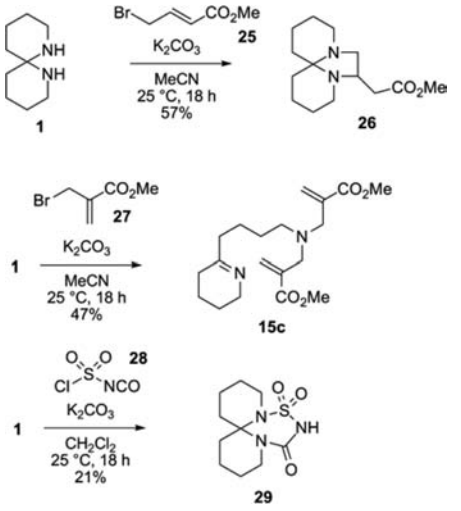
**Scheme 5.** Reactions of **1** with Acetyl Chloride and 4-Toluenesulfonyl Chloride




easily, while 6-*endo*-*trig* cyclizations seem to be a disfavored process. Reaction of spirane **1** with chlorosulfonyl isocyanate (**28**) resulted in the formation of a thiatriazine ring system. The structure of tricyclic sulfonyl-urea **29** was confirmed by an X-ray crystallographic structure determination.

Preliminary experiments also demonstrate the utility of spiroaminal **1** as a bidentate ligand in transition metal complexes. The molecule can bind to a metal with either retention or scission of the spirane ring system, as X-ray

**Scheme 6.** Reactions of **1** with Unsymmetric Dielectrophiles



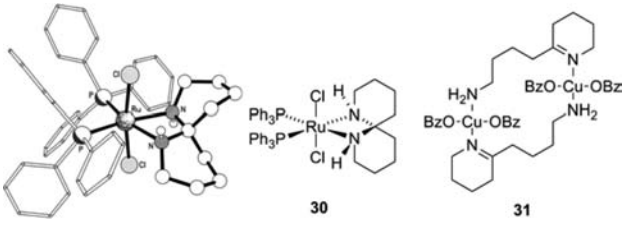




**Figure 1.** Ruthenium complex **30** and copper complex **31**.

crystal structure determinations of two complexes have shown. Reaction of spiroaminal **1** with $(Ph_3P)_3RuCl_2$ gave the corresponding monomeric complex $(Ph_3P)_2RuCl_2$(**1**) (**30**) which retained the intact spiroaminal unit (Figure 1), via formation of a four-membered chelate structure (Ru−N−C−N−ring). The spiroaminal adopts an unusual double boat conformation in complex **30**. In contrast, reaction of spiroaminal **1** with copper(II) benzoate gave a binuclear complex $[(BzO)_2Cu(\mathbf{16})]_2$ (**31**) with two imine/amine ligands **16** bridging two copper cores, each copper atom being coordinated by the amine of the one ligand and the imine of the other.

In conclusion, we describe an improved synthesis of 1,7-diazaspiro[5.5]undecane (**1**) and the formation of derivatives by reaction of **1** with mono- and dihalo-alkanes, acetyl chloride, and 4-toluenesulfonyl chloride. Most of these reactions resulted in conversion of the spiroaminal into 3,4,5,6-tetrahydropyridines. Reaction with 1,2- and 1,3-dihalides, (*E*)-methyl 4-bromobut-2-enoate (**25**), and chlorosulfonyl isocyanate (**28**), however, resulted in *N*,*N*′-substitution and formation of tricyclic adducts **21a**−**c**, **26**, and **29**, retaining the spirane core. Two transition metal coordination complexes of **1** were formed, a ruthenium complex (**30**) of the spiroaminal itself, and a binuclear copper complex (**31**) of the ring-opened tautomer **16**.

The synthesis of core-substituted analogues of **1** and analyses of the conformational and tautomeric preferences of spiroaminals like **1** are the subject of current investigations and will be reported in due course.

**Acknowledgment.** We thank the European Research Council (ERC) for generous grant support, GlaxoSmithKline for the Glaxo endowment, and P. R. Haycock and R. N. Sheppard (both Imperial College London) for high-resolution NMR spectroscopy.

**Supporting Information Available.** Experimental procedures and analytical data for all new compounds and X-ray crystallographic data (CIF) for **23b**, **29**, **30**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.