Fused Heterocycles

DOI: 10.1002/anie.201305714

Fused Spirocyclic Imidazolone Ketals

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N,*N*-dialkylacetamide acetals (**1**; Figure 1) were first prepared by Meerwein and co-workers from the treatment of acetamides with highly reactive alkylating agents followed by nucleophilic substitution with an alkoxide.[1,2] The π-electron-releasing ability of the lone-pair electrons of the nitrogen atom allows for an equilibrium mixture of **1** and **2** upon preparation.[3] The highly reactive nature of **2** enables its use as a powerful reagent for the formation of γ,δ-unsaturated amides in the Meerwein–Eschenmoser–Claisen rearrangement.[4,5] O-substituted amide acetals are generated in situ through alcoholysis, followed by further rearrangements without isolation. Despite their synthetic usefulness, the scope of acetamide acetals remains limited, owing to the paucity of suitable alkylating agents for their synthesis, and their inherent instability.[6]

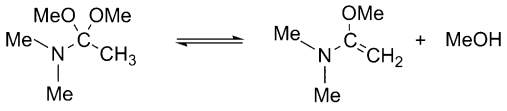


Figure 1. *N*,*N*-dialkylacetamides **1** are in equilibrium with **2**.

The recently reported zwitterionic azolium alkoxides (**3**; Figure 2) are conveniently prepared by the alkylation of commercially available azoles with hexafluoroisobutylene oxide.[7] Deprotonation of **3** directly provides fluoroalkoxy carbenes, which have demonstrated the ability to act as a chelating ligand for transition metals.

The presence of the electron-deficient tertiary alcohols in **3** provides an opportunity to probe oxidation reactions that are not easily accessible with other chelating heterocycles.[8–17] Removal of dihydrogen (H_2) through oxidation leads one to think about the "peroxycarbene" **4**. Although likely not persistent, its valence tautomers (structures **5**–**7**) begin to resemble heteroatom-functionalized architectures of tricyclic-fused natural products and promise both interesting structures and chemistry.[18–21] More specifically, **7** contains a similar functional group to amide acetal **1**, but is derived from an imidazolone rather than acetamide through a most remarkable ketal formation.

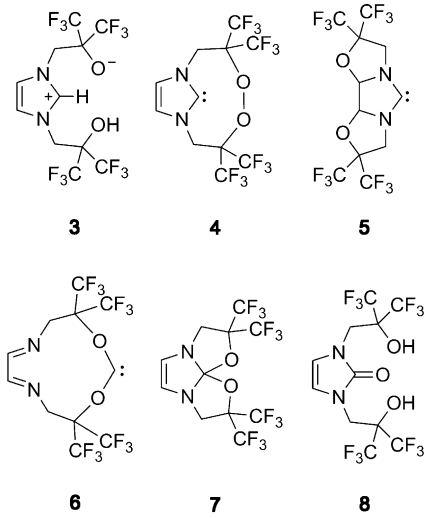
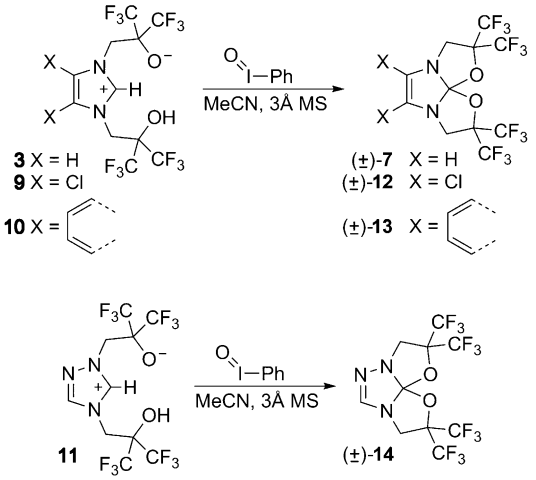


Figure 2. Compounds **4**–**8** are possible oxidation products of zwitterion **3**.

Initial oxidation of **3** with iodosobenzene was found to provide the bis(fluoroalcohol)-substituted imidazolone **8**, along with iodobenzene. This represents the hydrolysis adduct of **7**, produced by adventitious water from the condensation reaction of **3** with iodosobenzene. Conducting the reaction in the presence of 3 Å molecular sieves (3 Å MS) leads to the formation of fused spirocyclic imidazolone-ketal **7** (or **12**–**14**; Scheme 1). Imidazolone **8** is not observed under



Scheme 1. Anhydrous oxidation conditions provide tricyclic spiroketals **7** and **12**–**14**.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201305714.

these latter conditions. It is expected that the spiroketals are more stable than their non-fused counterparts because of the fixed pyramidalization of the imidazole ring nitrogen atoms through ring fusion.

A wide range of backbone-functionalized azoles undergo oxidative cyclization (**12**–**14**; Scheme 1). It was observed for phenyl-substituted imidazoles that, in addition to spiroketal fusion, other oxidation products were formed, which were difficult to separate from the product. The quaternary C1 resonances of **7, 12**–**14** ($\delta_C = 134$–145 ppm) suggest that backbone substitution maintains a σ electron-withdrawing effect on the carbon center.

X-ray crystal structures of **12**, **13**, and **14** confirm this tricyclic fusion (Figures 3 and 4). The two imidazole nitrogen atoms pyramidalize *trans* to one another, providing a mixture

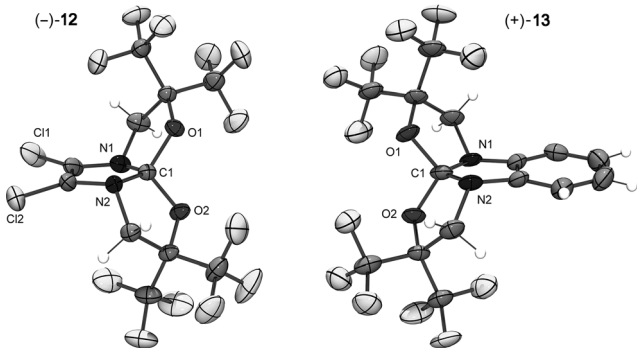

Figure 3. Depiction of (−)-12 and (+)-13 from the crystal structures of their racemates. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths [Å] and angles [°]: (−)-**12**: C1–O1/O2 1.42, C1–N1/N2 1.43; O1-C1-O2 105.0, N1-C1-N2 107.9. (+)-**13**: C1–O1/O2 1.42, C1–N1/N2 1.43; O1-C1-O2 105.0, N1-C1-N2 107.9.

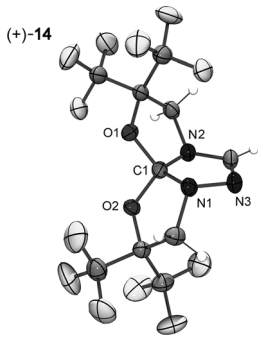

Figure 4. Depiction of (+)-14 from the crystal structure its racemate. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths [Å] and angles [°]: C1–O1/O2 1.42, C1–N1 1.43, C1–N2 1.42; O1-C1-O2 104.7, N1-C1-N2 105.1.

of (±) helical enantiomers, which co-crystallize. Other 5,5,5-fused imidazoles bearing carbon atoms in place of the oxygen atoms exhibit *trans* pyramidalization as well.[22] This conformation is in contrast to saturated C1 centers, where *cis* pyramidalization is favored, and results in imidazole ring puckering.[23,24] The five-membered oxazolidine rings are slightly puckered.

Diastereotopic methylene and CF_3 groups give rise to chemically and magnetically differentiated substituents in the *endo* and *exo* positions (*endo* points into the imidazole plane and *exo* points away from the imidazole ring). The crystal structures reveal that the H_{endo} protons are closer to the imidazole backbone protons than the H_{exo} protons.

The NMR spectra are remarkably rich, owing to the great magnetic chemical shift anisotropy that arises from the diastereotopic positions. The methylene protons ($^2J_{HF}$ ca. 13 Hz) and CF_3 groups ($^4J_{FF}$ ca. 2 Hz) exhibit diastereotopic coupling in both the ^1H and ^{19}F NMR spectra because of ring fusion.

The triazole spiroketal (**14**) has the lowest symmetry, which arises from nitrogen substitution in the imidazole ring backbone. The "C-side" (fused at N4) oxazolidine protons appear upfield to the oxazolidine protons at the "N-side" (fused at N1). These chemical shifts are possibly the result of an electron-withdrawing effect from the in-plane nitrogen atom of the triazole ring. The symmetry down the C1 axis can be distinguished by ^1H-^{13}C HMBC spectroscopy. Further NOE NMR experiments were conducted on **14** to assign the signals for both methylene and CF_3 groups, taking advantage of the spatial difference between H_{endo} and H_{exo} relative to the imidazole backbone proton.[25] Long-range $^4J_{HF}$ couplings (ca. 1.7 Hz) are observable for $^1H_{exo}$ to CF_{3endo}, as determined by ^{19}F decoupling experiments. The $^1H_{endo}$ to CF_{3exo} couplings are too small to observe and are likely attributable to the smaller H-C-C-CF_3 dihedral angle (107°) compared to the former (139°).[25,26]

In conclusion, a new series of stable spirocyclic imidazolone ketals has been produced by the oxidation of **3**. These spiroketals are characterized spectroscopically and, in three cases, by X-ray structure determinations. Preliminary results suggest that spiroketals such as **7** may function as carbene precursors through oxidative insertion of low-valent metals.

Received: July 2, 2013
Published online: August 27, 2013

Keywords: fluorinated ligands · fused-ring systems · heterocycles · nitrogen heterocycles · oxidation

[1] H. Meerwein, V. Hederich, H. Morschel, K. Wunderlich, *Justus Liebigs Ann. Chem.* **1960**, *635*, 1–25.
[2] H. Meerwein, W. Florian, N. Schön, G. Stopp, *Justus Liebigs Ann. Chem.* **1961**, *641*, 1–39.
[3] A. Eschenmoser, D. Felix, K. Gschwend-Steen, A. E. Wick, *Helv. Chim. Acta* **1969**, *52*, 1030–1042.
[4] A. Eschenmoser, D. Felix, K. Steen, A. E. Wick, *Helv. Chim. Acta* **1964**, *47*, 2425–2429.
[5] a) R. K. Hill, R. Soman, S. Sawada, *J. Org. Chem.* **1972**, *37*, 3737–3740; b) B. Coates, D. Montgomery, P. J. Stevenson, *Tetrahedron Lett.* **1991**, *32*, 4199–4202.
[6] R. G. Salomon, S. R. Raychaudhuri, *J. Org. Chem.* **1984**, *49*, 3659–3660.
[7] A. J. Arduengo III, J. S. Dolphin, G. Garău, W. J. Marshall, J. C. Nelson, V. A. Petrov, J. W. Runyon, *Angew. Chem.* **2013**, *125*, 5214–5218; *Angew. Chem. Int. Ed.* **2013**, *52*, 5110–5114.
[8] L. P. Spencer, C. Beddie, M. B. Hall, M. D. Fryzuk, *J. Am. Chem. Soc.* **2006**, *128*, 12531–12543.

[9] L. P. Spencer, B. A. MacKay, B. O. Patrick, M. D. Fryzuk, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17094 – 17098.
[10] B. A. MacKay, R. F. Munha, M. D. Fryzuk, *J. Am. Chem. Soc.* **2006**, *128*, 9472 – 9483.
[11] L. P. Spencer, S. Winston, M. D. Fryzuk, *Organometallics* **2004**, *23*, 3372 – 3374.
[12] P. L. Arnold, M. Rodden, C. Wilson, *Chem. Commun.* **2005**, 1743 – 1745.
[13] P. L. Arnold, C. Wilson, *Inorg. Chim. Acta* **2007**, *360*, 190 – 196.
[14] P. L. Arnold, A. J. Blake, C. Wilson, *Chem. Eur. J.* **2005**, *11*, 6095 – 6099.
[15] I. S. Edworthy, M. Rodden, S. A. Mungur, K. M. Davis, A. J. Blake, C. Wilson, M. Schröder, P. L. Arnold, *J. Organomet. Chem.* **2005**, *690*, 5710 – 5719.
[16] P. L. Arnold, I. J. Casely, Z. R. Turner, C. D. Carmichael, *Chem. Eur. J.* **2008**, *14*, 10415 – 10422.
[17] P. L. Arnold, M. S. Sanford, S. M. Pearson, *J. Am. Chem. Soc.* **2009**, *131*, 13912 – 13913.
[18] G. I. Elliott, J. R. Fuchs, B. S. J. Blagg, H. Ishikawa, H. Tao, Z.-Q. Yaun, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 10589 – 10595.
[19] a) D. Romo, A. I. Meyers, *Chem. Commun.* **1997**, 1 – 8; b) D. Romo, A. I. Meyers, *Tetrahedron* **1991**, *47*, 9503 – 9569.
[20] M. W. Carson, G. Kim, M. F. Hentemann, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4582 – 4584; *Angew. Chem. Int. Ed.* **2001**, *40*, 4450 – 4452.
[21] a) E. J. Corey, A. W. Gross, *Tetrahedron Lett.* **1980**, *21*, 1819 – 1822; b) M. Shah, M. J. Tashner, G. F. Koser, N. L. Rash, T. E. Jenkins, P. Cyr, D. Powers, *Tetrahedron Lett.* **1986**, *27*, 5437 – 5440; c) M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, A. Yoshikoshi, *J. Org. Chem.* **1975**, *40*, 1932 – 1941.
[22] a) Y. Cheng, B. Wang, X.-R. Wang, J.-H. Zhang, D.-C. Fang, *J. Org. Chem.* **2009**, *74*, 2357 – 2367; b) S. E. Ealick, D. van der Helm, *Acta Crystallogr. Sect. B* **1975**, *31*, 2676 – 2680; c) S.-P. Yang, D.-Q. Wang, L.-J. Han, H.-T. Xia, *Acta Crystallogr. Sect. E* **2007**, *63*, o4088.
[23] J. W. Runyon, O. Steinhof, H. V. R. Dias, J. C. Calabrese, W. J. Marshall, A. J. Arduengo III, *Aust. J. Chem.* **2011**, *64*, 1165 – 1172.
[24] D. A. Dixon, A. J. Arduengo III, *J. Phys. Chem. A* **2006**, *110*, 1968 – 1974.
[25] See the Supporting Information for NMR studies on **14**.
[26] M. Karplus, *J. Am. Chem. Soc.* **1963**, *85*, 2870 – 2871.

