DOI: 10.1002/ejoc.200701036

The Use of NMR Chemical Shifts to Predict Reaction Pathways: Methanol Formation from Oxazolidinones

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Keywords: Oxazolidinones / ^{13}C NMR shift / ^{15}N NMR shift / Reduction / Hammett parameter σ_p

The reduction of various *N*-substituted oxazolidin-2-ones with $LiAlH_4$ was investigated to open a pathway for methanol formation. By ^{15}N and ^{13}C NMR analysis and correlation with Hammett σ_p parameters appropriate substituents can be found which direct the reduction into the desired pathway.

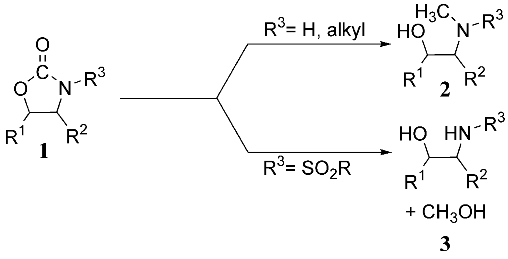
Introduction

The conversion of carbon dioxide to less problematic compounds is one of the most challenging tasks for chemists. Nonreductive fixation of carbon dioxide in form of carbonates or carbamates is very common.[1] Reduction of carbon dioxide to form ground stock chemicals like methanol, formic acid or formaldehyde by heterogeneous or homogeneous catalysts is also a field of intensive research.[2]

A very interesting method to fix carbon dioxide is the condensation of an amino alcohol with carbon dioxide to form a cyclic carbamate, an oxazolidin-2-one (**1**). In a recent paper we could show that it is possible to reduce an oxazolidin-2-one under very mild conditions, when it is sulfonated at the nitrogen atom, to form its corresponding sulfone amide and methanol.[3] However, a major drawback, of the reduction so far is the necessity of using stoichiometric amounts of lithiumaluminium hydride (LAH) as reducing agent. In this paper we describe the strong dependency of the reaction pathway on the substituent at the nitrogen atom and its elucidation by NMR spectroscopy.

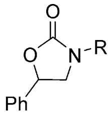
Results and Discussion

Two species are conceivable as products of the reduction of an oxazolidin-2-one **1**, the *N*-methylated amino alcohol **2** and the parent amino alcohol **3**. In the latter case methanol is formed as the most interesting by-product (Scheme 1). In our estimation, the electron-withdrawing power of the substituent at the nitrogen atom is crucial for the product formed. A further reason to investigate the action of the *N*-substituent in detail is the need of refixation of carbon dioxide to the amino alcohol **3**, which should be easier, if the electron density at the nitrogen atom is high. Therefore, we investigated a set of *N*-substituted oxazolidin-2-ones, both in their behaviour against LAH and also in some NMR-spectroscopic properties (Table 1).



Scheme 1. Possible reaction products for the reduction of oxazolidin-2-ones with LAH.

Table 1. Investigated 5-phenyl-2-oxazolidin-2-ones.



Entry	R^3
4	H
5	CH_3
6	$PhCH_2$
7	$4\text{-}FC_6H_4$
8	$4\text{-}F_3CC_6H_4$
9	CH_3SO_2
10	$4\text{-}H_3CC_6H_4SO_2$
11	CF_3SO_2

The alkylated oxazolidin-2-ones **5** and **6** were prepared from 5-phenyloxazolidin-2-one (**1**) by standard alkylation methods using KO*t*Bu as base and the alkyl bromide as electrophile. The *N*-aryloxazolidin-2-ones **7** and **8** were prepared by metal-catalyzed *N*-arylation procedures. The 3-(4-fluorophenyl)-5-phenyloxazolidin-2-one (**7**) was prepared

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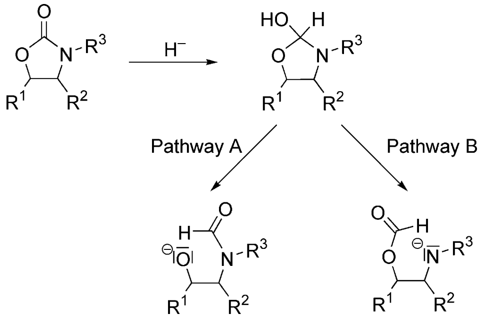
by copper-catalyzed arylation,[4] while the 3-[4-(trifluoromethyl)phenyl]-5-oxazolidin-2-one (**8**) could be prepared in best yields by a palladium-catalyzed *N*-arylation.[5] The sulfonated oxazolidin-2-ones **9**–**11** were prepared by a standard procedure described recently.[3]

Oxazolidin-2-ones with electron-donating or weak electron-withdrawing substituents are exclusively reduced to *N*-methyl compounds **2** by LAH. In contrast, *N*-sulfonated oxazolidin-2-ones react exclusively to the corresponding sulfone amides. Interestingly, the moderate electron-withdrawing 4-(trifluoromethyl)phenyl substituent leads to a 2:1 mixture of the *N*-methyl compound and the *N*-arylated amino alcohol. It seems that with the 4-(trifluoromethyl)phenyl group, a substituent was found which marks the border between the two possible reaction mechanisms **A** and **B**. Further investigation of other aryl substituents would be interesting but fails due the reduciblity of many electron-withdrawing groups, e.g. nitro, cyano or carboxylic.

We had earlier supposed the mechanism for the reaction given in Scheme 2. Whether, after the first reduction step, the proposed oxazolidinol intermediate opens the C(O)–O bond or the C(O)–N bond depends mainly on the polarity of the previous amide-like bond and the influence of the *N*-substituent on this polarity. Furthermore an alkoxide is usually a better leaving group than the nitrogen anion. The stabilization of the intermediate nitrogen anion in pathway B due electron-withdrawing substituents plays therefore an important role. Since the oxazolidinol intermediates cannot be isolated, we use the chemical shifts of the starting oxazolidinones as predictive entities. The polarity of an amide bond has been often investigated by NMR spectroscopic means, both with ^{13}C and with ^{15}N NMR chemical shifts, spin coupling constants and other parameters.[6–10]



Scheme 2. Proposed reaction mechanism for the reduction of oxazolidin-2-ones.

A plot of the ^{15}N NMR chemical shifts vs. the ^{13}C NMR chemical shifts of the carbonyl atom of the oxazolidinones shows a rather good correlation (Figure 1). This correlation demonstrates, that a deshielding of the ^{15}N nuclei is associated with a shielding of the carbonyl carbon atom, while all other ^{13}C NMR chemical shifts are nearly unaffected. Furthermore, we could show that the spectroscopic data correlate well with the preparative results. It is possible to divide the substituents in two groups, and the 4-(trifluoromethyl)phenyl substituent displays the border between the possible reaction pathways, as well as in the chemical and spectroscopic properties. Both the ^{13}C and the ^{15}N chemical shifts of this compound are in about the middle of the respective chemical-shift ranges.

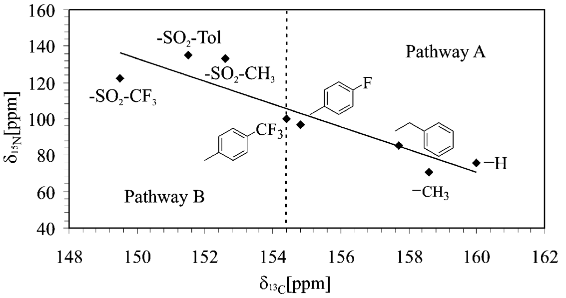


Figure 1. ^{15}N chemical shifts versus ^{13}C chemical shifts (C=O) of the oxazolidin-2-one (Pathway A and B correspond to Scheme 1).

To quantify the electronic properties of the investigated substituents, the Hammett substituent constants can be included in the discussion about the changed reaction pathway. Therefore, we correlated the ^{13}C and ^{15}N NMR chemical shifts with the Hammett values σ_p from literature[11] (Figure 2). Again, ^{13}C and ^{15}N chemical shifts correlate with different signs. In this plot a principle trend can be observed, and it should be possible to predict the reaction pathway by means of the σ_p value, although the theoretical understanding of ^{15}N chemical shifts is complex.[12] Notable to mention is the fact, that the CF_3SO_2 group has the highest σ_p value as well as the highest group electronegativity of all substituents compared in this paper. For the ^{13}C chemical shift, this special property is accompanied by the overall strongest shielding of the carbonyl carbon atom of all oxazolidin-2-ones. To investigate this phenomenon in more detail, solid-state NMR experiments directed towards the anisotropy of the carbonyl shielding are in progress.

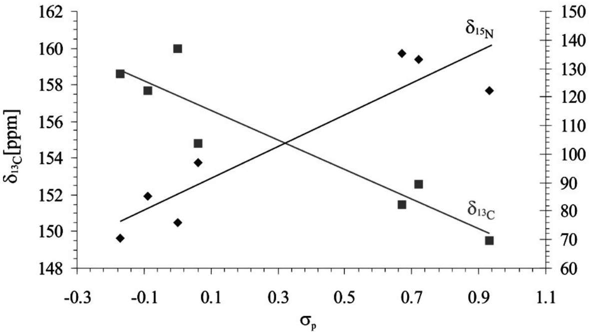


Figure 2. Correlation of Hammett's substituent constants with the ^{13}C chemical shifts of the carbonyl carbon atom and the ^{15}N chemical shifts.

Conclusions

It was possible to find a substituent which marks a border between two possible reaction pathways. Furthermore, we were able to correlate spectroscopic data with the chemical behavior of the 5-phenyloxazolidin-2-ones which make a prediction of the reaction pathway possible.

Experimental Section

The synthetic procedures were carried out according to the literature citations given. NMR measurements were performed with Bruker DRX-400 and DRX-600 instruments. The ^{15}N chemical shifts were obtained by 2D $^{1}H,^{15}N$-HMQC measurements and are referenced through internal TMS versus nitromethane using the Ξ scale. Up to 32 scans per t_1 increment were recorded using a relaxation delay up to 5 s. Further parameters were exactly as given in ref.[13] ^{13}C chemicals shifts were obtained directly and referenced to internal TMS.

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[1] T. Sakakura, J.-C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365–2387.

[2] I. Omae, *Catal. Today* **2006**, *115*, 33–52.

[3] J. Fröhlich, S. Berger, *Synlett* **2005**, *16*, 2522–2524.

[4] R. K. Dieter, L. A. Silks, J. A. Fishpaugh, M. E. Kastner, *J. Am. Chem. Soc.* **1985**, *107*, 4679–4692.

[5] S. Cacchi, G. Fabrizi, A. Goggiamani, G. Zappia, *Org. Lett.* **2001**, *3*, 2536–2541.

[6] J. Done, J. P. Gouesnard, B. Mechin, N. Naulet, G. J. Martin, *Org. Magn. Reson.* **1980**, *13*, 127–131.

[7] W.-N. Chou, M. Pomerantz, M. K. Witzcakl, *J. Org. Chem.* **1990**, *55*, 716–721.

[8] J. P. Marchal, D. Canet, *Org. Magn. Reson.* **1981**, *15*, 344–346.

[9] Y. X. Lei, G. Cerioni, Z. Rappoport, *J. Org. Chem.* **2001**, *66*, 8379–8394.

[10] A. J. BeMet, V. Somayaji, R. S. Brown, B. D. Santarsierot, *J. Am. Chem. Soc.* **1991**, *113*, 7563–7571.

[11] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–191.

[12] B. Mothana, F. Ban, R. J. Boyd, A. Thompson, C. E. Hadden, *Mol. Phys.* **2005**, *103*, 1113–1129.

[13] S. Berger, S. Braun, *200 and More NMR Experiments*, Wiley-VCH, Weinheim, **2004**, p. 612.

Received: November 4, 2007