A Mild Synthesis of ^{13}C-Methanol

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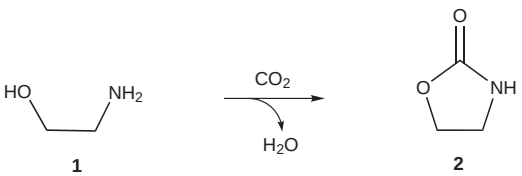
Abstract: The formation of oxazolidinon-2-ones from amino alcohols and carbon dioxide is well known. Until now it was not possible to reduce the fixed carbon dioxide to any basic chemical like formaldehyde or methanol, only the less interesting *N*-methyl compounds were formed with lithium aluminium hydride. Here we show the reduction of a oxazolidin-2-one derivative to methanol and the corresponding sulfone amide after introducing a sulfone group at the nitrogen. With selective labelling of the carbonyl carbon it was possible to produce ^{13}C-labelled methanol.

Key words: carbon dioxide, sulfonation, reduction, oxazolidin-2-ones, methanol

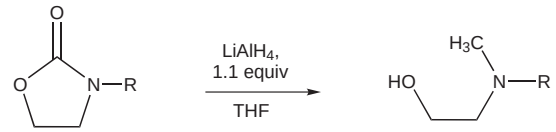
One of the most exciting tasks for chemists since about hundred years is the utilization of carbon dioxide. Carbon dioxide is a thermodynamically extremely stable and inert molecule. While the nature has many creative solutions, chemists failed except a few famous exceptions. These are the formation of urea, salicylic acid and cyclic carbonates as polymer building blocks. The catalytic hydrogenation of carbon dioxide over heterogeneous catalysts is currently a very intense field of investigation.[1] The economic and ecological problems are tremendous as long the hydrogen is produced by the water gas shift reaction. Since it is known that carbon dioxide is one of the greenhouse gases, the reduction of carbon dioxide to basic chemicals becomes more and more important.

While a lot of attempts deal with the activation of carbon dioxide using transition metal complexes, our concept is more classical.[2] It is well known and very well investigated, that amino alcohols **1** are able to bind carbon dioxide to form carbamates, respectively, carbamate salts (Equation 1).[3] By converting the alcohol function to a better leaving group it is possible to form cyclic carbamates **2**, the oxazolidin-2-ones, which are formally condensation products of an amino alcohol and carbon dioxide (Scheme 1).[4]



Equation 1

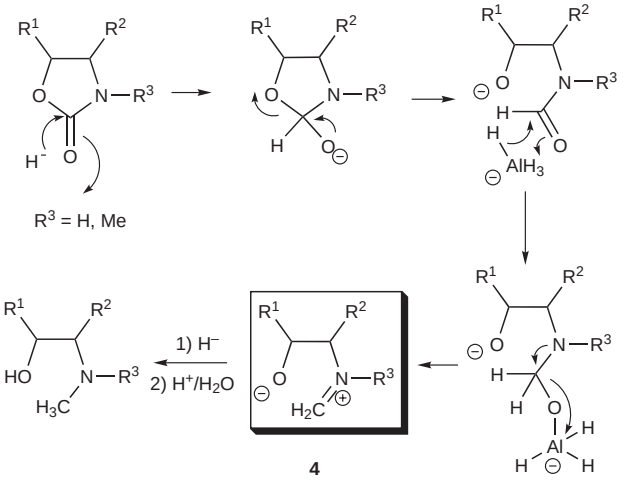
A catalytic process of the reaction of amino alcohols with carbon dioxide to form these five-membered rings is also available.[5] Our goal was now to reduce the fixed carbon dioxide, ideally to methanol. The high stability of the heterocycle makes it currently necessary to use lithium aluminum hydride as a strong reducing agent. However, for R = H and alkyl attached to the nitrogen the reaction gives only the *N*-methyl compounds **3** (Equation 2).[4b]



R = H, Bn, Me

Equation 2

The supposed mechanism for the reaction is given in Scheme 1. The iminium compound **4** is the key intermediate. With the suppression of the formation of this intermediate, it should be possible to release the carbonyl carbon as a reduced species.



Scheme 1 Supposed mechanism for reduction of oxazolidin-2-ones with $LiAlH_4$

We therefore introduced an electron-withdrawing group at the nitrogen. This group should hinder the free electron pair of the nitrogen to stabilize the iminium ion **4**. Introducing a trifluoromethyl group at the nitrogen failed with our methods. The second choice was a sulfone moiety as an electron-withdrawing group.[6] Four sulfone-containing moieties were tested: the *p*-toluene sulfonyl group, the

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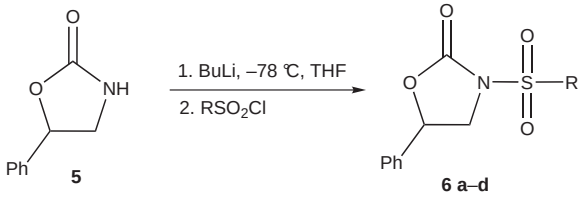
trifluoromethane sulfonyl group, the methane sulfonyl group and the free sulfonic acid (Table 1). The free sulfonic acid turned out as bad choice for the project because of its poor solubility and low stability in DMSO. As oxazolidin-2-one we choose the 5-phenyl-oxazolidin-2-one (**5**). The sulfonic groups were introduced by standard methods, using a strong base and the sulfonic acid chloride as electrophile (Equation 3).[7] The yields were moderate up to excellent (Table 1).



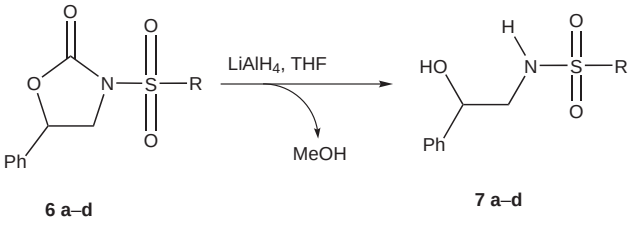
Equation 3

Table 1 Sulfonated Oxazolidin-2-ones

Entry	R	Yield (%)
6a[a]	$-CH_3$	48
6b[a]	$-C_6H_5CH_3$	86
6c	–OH	–[b]
6d[c]	$-CF_3$	19

[a] Purified by recrystallization from EtOH.
[b] Unstable product.
[c] Purified by column chromatography (silica gel, EtOAc–MeOH, 7:1).

The reduction of the N-sulfonated heterocycles with lithium aluminium hydride gave exclusively the sulfone amides **7** (Equation 4).[8]



Equation 4

The more important fact is that the former carbonyl carbon atom becomes the carbon of methanol during the reduction. This could be confirmed by following the reaction with NMR spectroscopy. A 5-phenyl-3-(toluene-4-sulfonyl)-oxazolidin-2-one (**6b**), ^{13}C-labelled at carbonyl carbon, was reduced in the NMR tube and the reaction was followed from –80 °C up to 20 °C (Figure 1). No intermediates could be observed, either with ^{1}H NMR or ^{13}C NMR spectroscopy. But the broad signal B* at δ = 50 ppm should indicate, for our understanding, aggregates of methanolate. After hydrolysis of the reaction mixture with saturated ammonium chloride solution the broad signal became very sharp (C*) and shows a quadruplet in the ^{1}H-coupled carbon spectrum. This carbon signal shows a correlation with a proton signal at δ = 3.4 ppm. To further ascertain methanol as the product, the reaction mixture was analysed by GCMS. Here conformity of the retention time as well as the mass number was found. Because of the absence of any other ^{13}C-labelled species in the ^{13}C NMR spectra, it is assumed that the carbonyl carbon is completely reduced to methanol.[9]

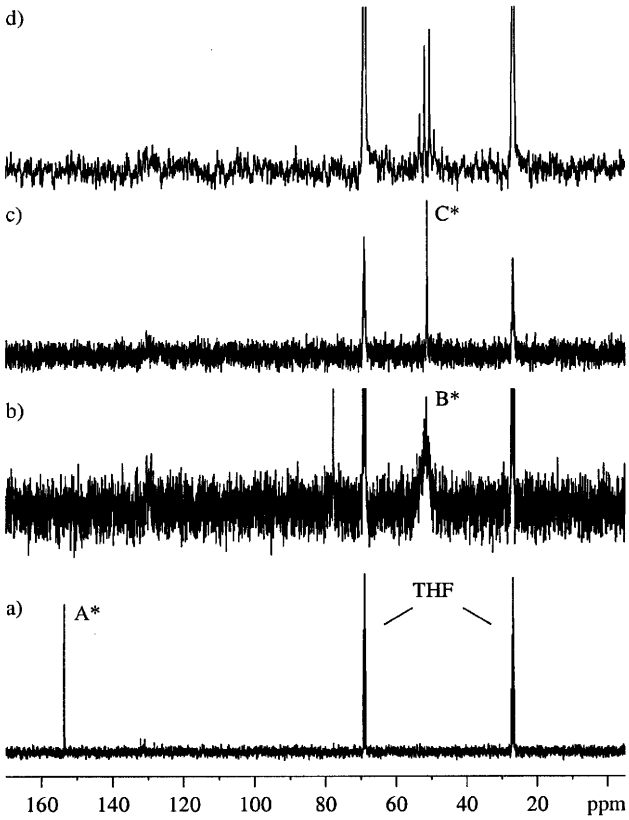


Figure 1 Reduction of **6b** followed by ^{13}C NMR spectroscopy: a) ^{13}C-labelled **6b** in THF-d_8 at –80 °C; b) after addition of $LiAlH_4$ (20 °C); c) after hydrolysis with NH_4Cl in D_2O; d) gated-decoupled-spectrum of state c.

The search for other reducing agents failed up to now. An overview over several tested reducing systems is given in Table 2. The formation of the sulfone amide with sodium hydridoborate causes hydrolysis because of the high basicity of the sodium hydridoborate in protic solvents as the used alcohols. Very interesting is the last entry, were a combination of the amino borane and boron trifluoride as a Lewis acid gives the *N*-methyl compound **8b**. This behavior is not clear, because a predicted activation of the carbonyl function could not be observed by a chemical shift change of the carbonyl group by adding the Lewis acid.[10] The reducing agents $LiEt_3BH$, which is known to reduce carbamates to the corresponding alcohol and amine, did not react in the case of the cyclic carbamate.[11]

Table 2 Tested Borane Reducing Agents Combined with Lewis Acids

Reducing agent[a]	Lewis acid	Solvent	Result
BH_3·THF	–	THF	No reaction
tert-Butylamine borane	–	THF	No reaction
NH_3·BH_3	–	THF	No reaction
NH_3·BH_3	–	CH_2Cl_2	No reaction
$NaBH_4$	–	MeOH	**7b**[b]
$NaBH_4$	–	EtOH	**7b**[b]
NH_3·BH_3	$TiCl_4$	CH_2Cl_2	Mixture[c]
$NaBH_4$	BF_3·OEt_2	CH_2Cl_2	No reaction
NH_3·BH_3	BF_3·OEt_2	CH_2Cl_2	**8b**

[a] Only **6b** tested.
[b] By hydrolysis.
[c] No product isolable.

In this work we have shown that a small change of the electronic properties of a molecule causes dramatic effects of its reactivity. It is, to our knowledge, the first time that an oxazolidin-2-one was reduced to the sulfone amide and methanol instead of the *N*-methyl compounds. This method can be used to produce ^{13}C-labelled methanol. Also a combination of ^{13}C-labelling and deuteration by using lithium aluminum deuteride would be possible by the described procedure. The drawback of the method is the stoichiometric use of $LiAlH_4$, which can reduce carbon dioxide directly.[12] But our technique seems to be much less sensitive to the reaction conditions then in the direct case.

In the future, the influence of the lithium ion will be investigated. Also a catalytic reduction of the heterocycle would be very interesting and is a subject of current work.

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(7) **Sulfonation of Oxazolidin-2-one (5).**
Oxazolidin-2-one (500 mg, 3.07 mmol) was dissolved in dry THF (10 mL) under N_2 atmosphere. At –80 °C *n*-BuLi (1.93 mL, 3.07 mmol, 1.6 M solution in THF) was added slowly to the solution. After the solution was allowed to warm up to –30 °C, *p*-toluenesulfonyl chloride (585 mg, 3.07 mmol) in dry THF (5 mL) was added. After stirring at r.t. for 4 h, the reaction mixture was hydrolyzed with sat. NH_4Cl solution, extracted with EtOAc (4 × 20 mL), the organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was recrystallized from EtOH to yield the N-sulfonated oxazolidin-2-one (**6b**, 836 mg, 86%); mp 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.47 (s, Ph–CH_3), 3.89 (dd, $^2J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 7.8 Hz, CH_A–NH), 4.42 (dd, $^2J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 8.1 Hz, CH_B–NH), 5.52 (dd, $^3J_{HH}$ = 8.1 Hz, O–C*H*), 7.37 (m, Ph), 7.95 (d, $^3J_{HH}$ = 8.1 Hz, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 21.7 (Ph–*C*H_3), 51.6 (*C*H_2–N), 75.3 (Ph–*C*H), 125.6, 128.3, 128.9, 129.1, 133.8, 136.2, 145.7 (Ph), 151.5 (*C*=O). MS (ES^+): *m/z* = 318 $[M^+]$.

(8) **Reduction of Sulfonated Oxazolidin-2-one (6b)**
Under an N_2 atmosphere, $LiAlH_4$ (15 mg, 0.39 mmol) was dissolved in dry THF (5 mL). While cooling the suspension (0 °C), the *N*-tosyloxazolidin-2-one (200 mg, 0.63 mmol) in THF (5 mL) was added slowly and refluxed for 2 h. After cooling to r.t. the mixture was hydrolyzed with sat. NH_4Cl solution, extracted with Et_2O (4 × 15 mL) and the solvent removed to yield the sulfone amide **7b** (149 mg, 81%); mp 115–117 °C.
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.42 (s, Ph–CH_3), 3.03 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 8.5 Hz, CH_A–NH), 3.85 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 3.5 Hz, CH_B–NH), 4.80 (dd, $^3J_{HH}$ = 8.5 Hz = 3.5 Hz, C*H*–Ph), 7.29 (m, Ph), 7.72 (d, $^3J_{HH}$ = 8.1 Hz, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 21.5 (Ph–*C*H_3), 50.2 (*C*H_2–NH), 72.8 (*C*H–Ph), 125.8, 127.1, 128.3, 128.7, 129.8, 136.8, 140.8 and 143.6 (Ph). MS (ES^+): *m/z* = 292 $[M]^+$.

(9) **Determination of the Yield of Methanol in the Unlabelled Case.**
The reaction was performed like described (200 mg, 0.63 mmol **6b**). After hydrolysis the reaction mixture was filtered off and filled with H_2O to a volume of 10 mL. An aliquot (0.5 mL) was taken and a ^{1}H NMR spectrum was measured. As integral reference we used sodium benzoate (453.5 mg in 10 mL H_2O), because of its good solubility and the well separated *ortho*-protons of the aromatic ring. Then, 200 µL of a standard solution were added and the integrals of the methyl group signals of the methanol and the *ortho*-proton signals of the benzoate were compared to find a methanol yield of 73% (0.46 mmol).

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