Formal Methylene Insertion into the C H Bond of α-Carbonyl Aldonitrones with Dimethylsulfoxonium Methylide

Formal Methylene Insertion into the C–H Bond of *α*-Carbonyl Aldonitrones with Dimethylsulfoxonium Methylide

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Abstract

A methylene group was introduced into the C–H bond of *α*-carbonyl aldonitrones by the reaction with dimethylsulfoxonium methylide, producing one-carbon homologated *C*-methyl ketonitrones. This formal methylene insertion was applied to one-pot synthesis of quaternary C3-methyl isoxazolidines via successive 1,3-dipolar cycloaddition with alkenes bearing an electron withdrawing group.

Keywords: Nitrone, Sulfur-Ylide, Methylene Insertion,

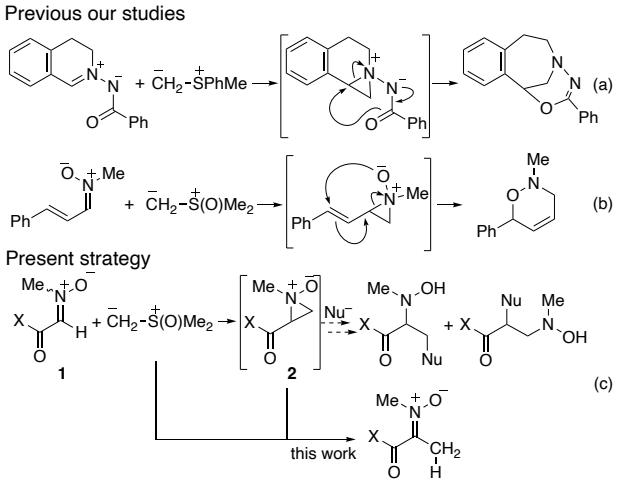
1. Introduction

Sulfur-ylides have been widely utilized as reagents for formal methylene insertion since the discovery of the epoxidation of carbonyl compounds, namely the Corey-Chaykovsky reaction, in the 1960s.[1] Later, imines and related compounds were also found to undergo aziridine formation in analogy with carbonyl compounds.[1,2] Previously, we reported the nucleophilic addition of sulfur ylides to *C*,*N*-cyclic-*N*'-acyl azomethine imines and to *α,β*-unsaturated nitrones that furnish 3-benzazepine derivatives and 3,6-dihydro-2*H*-1,2-oxazines, respectively (Scheme 1a,b).[3] In both the reactions, three-membered aziridinium rings were anticipated to form as well, although unusual results were obtained in the subsequent intramolecular transformations.

To ensure further utilization of the 1,3-dipole-ylide chemistry, we utilized *α*-carbonyl aldonitrones **1**, with the expectation that the attached carbonyl moiety will enhance the electrophilicity of the nitrone moiety and even alter its behavior. For example, intermolecular transformation to the resulting aziridinium intermediate **2** using subsequent nucleophiles might render it possible to obtain non-natural *α*- or *β*-amino acid derivatives through the use of glyoxylic acid derivative **1** (X = OR or NR_2) (Scheme 1c). Herein, we describe the formal methylene insertion reaction into the C–H bond of *α*-carbonyl aldonitrones with dimethylsulfoxonium methylide (Scheme 1c, this work) contrary to our expectations.[4–6] Monitoring of the reaction with ^{13}C NMR suggested additional reaction pathways along with that via aziridinium ring **2** formation. The products, *α*-carbonyl ketonitrones, were successfully employed in the one-pot 1,3-dipolar cycloaddition reaction to afford C3-methyl substituted isoxazolidines.

2. Experimental

Representative procedure for formal methylene insertion reaction into the C–H bond of 2-(diisopropylamino)-*N*-methyl-2-oxoethan-1-imine oxide (**1b**): To a EtCN (2 mL) solution of



Scheme 1. (a, b) Previous our studies and (c) present strategy for the transformation of 1,3-dipoles by sulfur ylides

the nitrone **1b** (93 mg, 0.50 mmol), dimethylsulfoxonium methylide[7] (0.99 mL, 0.76 M in THF, 0.75 mmol) was added at rt under an Ar atmosphere and the reaction mixture was stirred at rt for 31 h. After the addition of brine, the resulting mixture was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The chemical yield of the corresponding one-carbon homologated ketonitrone **3b** in the crude mixture was determined to be 80% based on the analysis of the ^1H NMR spectrum in $CDCl_3$ acquired using 1,1,2,2-tetrachloroethane (21 μL, 0.20 mmol) as an internal standard. The residue was purified first by silica gel column chromatography (AcOEt/MeOH = 3/1, v/v) and then by recycle HPLC (AcOEt/MeOH = 3/1, v/v) to give **3b** (59 mg, 59% yield).

Representative procedure for one-pot preparation of C3-methyl isoxazolidine **5bC**: To a EtCN (1.5 mL) solution of nitrone **1b** (65 mg, 0.35 mmol), dimethylsulfoxonium methylide (0.87 mL, 0.60 M in THF, 0.52 mmol) was added at rt under an Ar atmosphere. After the reaction mixture was stirred at this temperature for 31 h, *N*-methylmaleimide (**4C**) (233 mg, 2.10 mmol) was added, and the reaction mixture was heated at 100 °C (oil bath temperature) for 2.5 d. After cooling to rt, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 10/1, 6/1, 4/1, 3/1 v/v) to give the isoxazolidine **5bC** (72 mg, 66% yield).

3. Results and Discussion

Firstly, the reaction of a *N*,*N*-(dibenzyl)glyoxylamide-derived aldonitrone **1a** with dimethylsulfoxonium methylide was examined with the view of the formation of an aziridine *N*-oxide **2a**.[8] To our surprise, a one-carbon homologated ketonitrone **3a** was obtained as a 1/1 mixture of *E*- and *Z*-isomers (eq. 1). When *N*,*N*-diisopropylamide-substituted nitrone **1b** was subjected to this reaction, the corresponding ketonitrone **3b** was produced with complete *E*-selectivity.[9] Using 1.5 equiv. of the sulfur-ylide at rt, the chemical yield increased up to 80% (NMR yield). After intensive purification by recycle HPLC, **3b** was isolated in 59% yield (eq. 2).

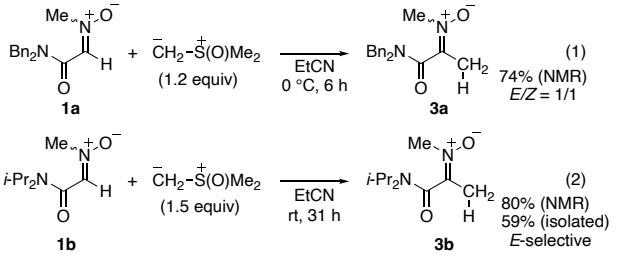
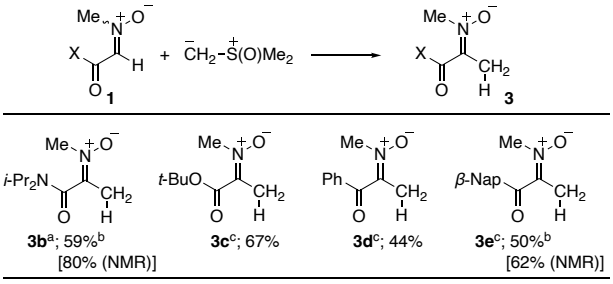


Table 1 shows that C–H methylene insertion occurs regardless of the substituent at the carbonyl terminus. For example, one carbon-homologation of nitrone **1c** derived from *t*-butyl glyoxylate proceeded efficiently. When **1c** was treated with dimethylsulfoxonium methylide in THF at 0 °C, the corresponding ketonitrone **3c** was obtained in 67% yield.[10] The methylene insertion was applied to a phenylglyoxal-derived nitrone. 2-(Methyloxidoimino)-1-phenylethanone (**1d**) was treated with the sulfur ylide to afford the corresponding *α*-benzoyl ketonitrone **3d** in 44% yield. The *β*-naphthyl substituted aldonitrone **1e** also afforded the corresponding ketonitrone **3e** in good yield. In all these cases, (*E*)-isomers were selectively produced.[9,11]

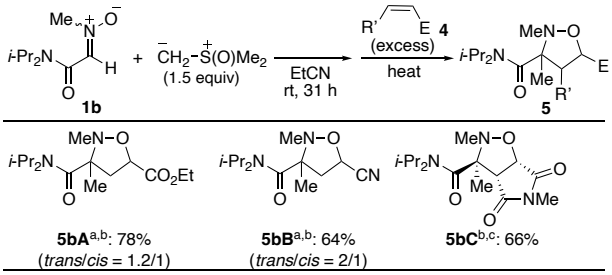
Table 1. Formal methylene insertion of *α*-carbonyl aldonitrones **1**



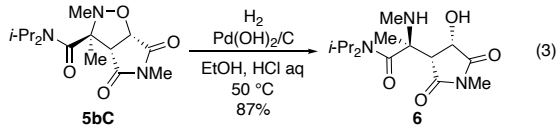
[a]1.5 equiv. of sulfur ylide was used in EtCN at rt for 31 h. [b]Isolated yield was poor due to difficulty in purification. [c]1.0 equiv. of sulfur ylide was used in THF at 0 °C for 1–2 h.

Quaternary *α*-methyl *α*-amino acids are an intriguing class of non-natural amino acids in medicinal and biological chemistry. These amino acids increase the proteolytic stability of a peptide because of their remarkable resistance to enzymatic degradation and hence are often incorporated into peptides to replace natural amino acids to perform conformational and structural stability studies, which ultimately reveal the differences in bioactivity.[12] To access unnatural *α*-methyl *α*-amino acid, 1,3-dipolar cycloaddition of nitrones derived from pyruvic acid derivatives is a useful way.[13] Because our method easily provides various derivatives of pyruvic acid-based (= *α*-carbonyl) ketonitrones, it is expected to be effective in providing access to *α*-methyl *α*-amino acid derivatives. Starting from the readily available glyoxylic acid-derived aldonitrones, one-pot synthesis of isoxazolidines bearing quaternary C3-methyl carbons through one carbon-homologation can be effective in minimizing chemical waste, saving time, and simplifying synthetic procedures.[14] Accordingly, a one-pot methylene insertion–1,3-dipolar addition sequence was examined using aldonitrone **1b**, dimethylsulfoxonium methylide, and alkenes bearing an electron withdrawing group as shown in Table 2. The reaction with ethyl acrylate (**4A**) as a dipolarophile successfully afforded isoxazolidine **5bA**, which can be regarded as an *α*-methylated glutamic acid equivalent, in 78% yield. Acrylonitrile (**4B**) was also employed to give **5bB** in 64% yield. When *N*-methylmaleimide (**4C**) was used as a dipolarophile, diastereoselective formation of the corresponding isoxazolidine **5bC** was achieved in 66% yield. Cycloadduct **5bC** could be readily converted to a densely functionalized quaternary glutamic acid derivative **6** by hydrogenation (eq. 3), demonstrating the utility of synthesizing *α*-methylated *α*-amino acids.

Table 2. One-pot synthesis of C3-methyl isoxazolidines **5**



[a]Dipolarophiles **4** were used as solvent at 80 °C. [b]As to determination of relative stereochemistries, see Supporting Information. [c]6 equiv. of dipolarophile **4C** was used in EtCN at 100 °C.



To gain insights into the present one carbon-homologation, the reaction was monitored by ^{13}C NMR spectroscopy. When the deuterated aldonitrone **1b**-*d* was treated with dimethylsulfoxonium methylide in THF-d_8, deuterated ketonitrone **3b**-*d*[15] was produced along with non-deuterated ketonitrone **3b**, as confirmed by ^{13}C NMR analysis (Figure 1a). In addition, non-deuterated nitrone **3b** was predominantly formed when the one carbon-homologation reaction was carried out in the presence of excess H_2O (5 equiv.) (Figure 1b). If the reaction proceeds via the formation of aziridine **2b**, followed by 1,2-deuterium shift, similar to the House–Meinwald rearrangement of epoxides (Scheme 2, path a)[16] or via nucleophilic addition of the sulfur ylide, followed by 1,2-deuterium shift, similar to the Büchner–Curtius–Schlotterbeck reaction of diazo compounds (path b),[17] the deuterated ketonitrone **3b**-*d* might be predominantly produced. ^{13}C NMR analysis revealed the intermolecular introduction of hydrogen. The exact mechanism of the present formal methylene insertion is not yet clear. Paths a and b could not still be ruled out because the relatively acidic deuterium-hydrogen exchange of the generated **3b**-*d* might furnish **3b**. In addition to paths a and b, an alternative path c could be proposed, which includes oxy-enamine **7** formation via dedeuteration and subsequent tautomerization.[4] Excess H_2O promotes intermolecular protonation to furnish **3b** more selectively.

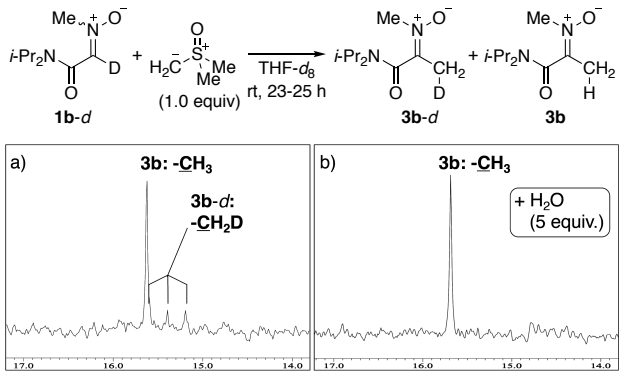
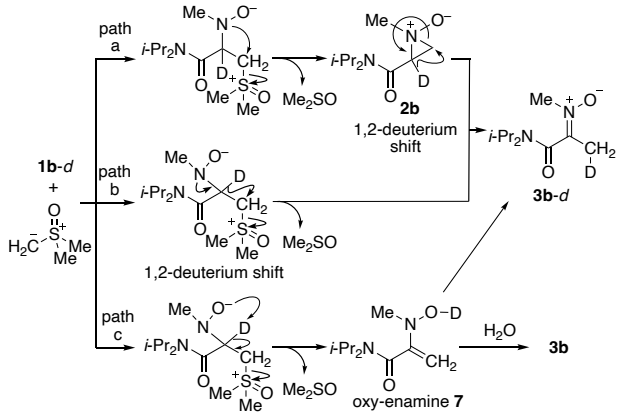


Figure 1. Monitoring one-carbon homologation of **1b**-*d* by ^{13}C NMR spectroscopy



Scheme 2. Possible pathways of one-carbon homologation

4. Conclusion

In conclusion, we demonstrated a new method to homologate *α*-carbonyl aldonitrones using a sulfur ylide. The obtained ketonitrones were further utilized for the one-pot 1,3-dipolar cycloaddition to furnish C3-methyl-substituted isoxazolidines. ^{13}C NMR spectral analysis suggested the additionally alternative pathway of the oxy-enamine formation–protonation. The developed protocol provides efficient access to *α*-methyl *α*-amino acid derivatives.

Acknowledgement

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