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Improvement in the One-Carbon Chain Extension of Esters with Dimethylsulfoxonium Methylide

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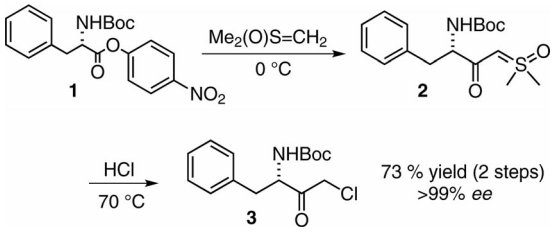
A recent report suggests that the reaction of dimethylsulfoxonium methylide with esters does not produce a chain-extended sulfur ylide as previously reported, but rather affords the corresponding carboxylate salt. We have investigated this assertion by using a combination of ab initio molecular orbital calculations, spiking studies, and isotopic labeling. The formation of carboxylate is unambiguously demonstrated to arise through hydrolysis involving adventitious water, principally derived from moisture in commercial trimethylsulfoxonium chloride. Careful vacuum drying of this reagent diminishes the competing hydrolytic pathway resulting in higher yields for the chain-extension reaction than previously reported.

Introduction

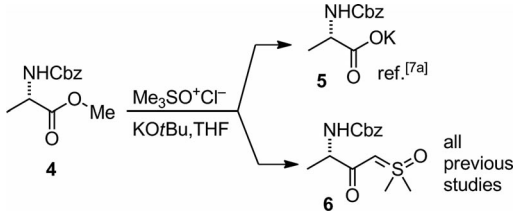
The one-carbon chain extension of esters to stabilized sulfur ylides[1] using dimethylsulfoxonium methylide[2,3] was reported in 2004 as an alternative to the use of diazomethane, a toxic and explosive gas. As illustrated for the case of phenylalanine-derived ester **1** in a later *Organic Syntheses* procedure,[4] sulfur ylides such as **2** are readily converted into α-chloroketones exemplified by **3** upon treatment with anhydrous HCl (Scheme 1).



Scheme 1. Synthesis of an α-chloroketone by using dimethylsulfoxonium methylide.

Subsequently, the process research group at Merck demonstrated that stabilized sulfur ylides generated in this way can be activated by transition-metal catalysis, which greatly expands their utility.[5] Ester-derived sulfur ylides have now been utilized in the manufacture of several pharmaceutical intermediates.[6] Most notably, MK-7246, a CRTH2 antagonist for the potential treatment of respiratory disease, has been prepared on a 100 kg scale.[6a]

Given this background, we were initially astonished by a recent report of Leggio, Linguori, and co-workers at the University of Calabria.[7a] When the Calabria group attempted the chain-extension of Cbz-alanine methyl ester (**4**, Cbz = benzyloxycarbonyl), they were unable to obtain previously reported chain-extended sulfur ylide **6**. Instead, the product (isolated after acidification) was Cbz-alanine **5** (Scheme 2). In addition, the Calabria group found that a variety of other esters afforded the carboxylic acid as the product. We elected to investigate this observation. As pointed out in a recent essay,[8] such unexpected experimental results have played a critical role in the advancement of organic synthesis; one ignores such "outliers" at one's own risk.



Scheme 2. Reaction of **4** with in situ generated dimethylsulfoxonium methylide.

Results and Discussion

The Calabria report suggests that the oxygen atom in the carboxylic acid product originates from the oxo moiety of the dimethylsulfoxonium methylide. To gain a better understanding of this result, a computational study was initiated to examine the mechanisms for O versus C attack of the ylide on the ester. The initial phase of the QM study evaluated the site of highest nucleophilicity of the reagent. At

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the M06–2X/aug-cc-pVDZ level of theory, the geometry-optimized structure and its corresponding HOMO are shown in Figure 1. The structure shows significant pyramidalization in the methylene fragment, consistent with the conventional view that the methylene carbon atom retains significant carbanionic character. It is clear from Figure 1 that the HOMO is largely localized on the methylene carbon atom, and this identifies it as the most nucleophilic center of the molecule.

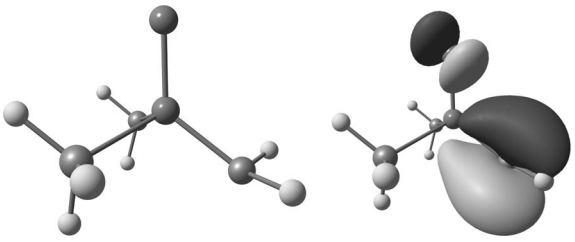


Figure 1. Calculated structure and HOMO of dimethylsulfoxonium methylide.

The second phase of the study evaluated the reaction pathways for the formation of the initial tetrahedral intermediates for O and C addition of dimethylsulfoxonium methylide to methyl acetate at the same level of theory. Transition structures and the resultant tetrahedral intermediates were identified for each pathway. The transition-state free energy for C–C bond formation was calculated to be +16.9 kcal mol^{-1} and afforded a tetrahedral intermediate with free energy of +15.0 kcal mol^{-1}. The energetics for C–O bond formation were considerably less favorable. In this case, the transition-state free energy was +37.8 kcal mol^{-1} and the corresponding tetrahedral intermediate exhibited a free energy of +37.3 kcal mol^{-1}. Given these results, we decided to examine the possibility that the source of the oxygen atom in carboxylate formation was adventitious water.

Proceeding to the laboratory, we examined the reaction of Cbz-alanine methyl ester **4** with 3 equiv. of dimethylsulfoxonium methylide. As in the Calabria studies, the reagent was generated from trimethylsulfoxonium chloride[9] and a commercial solution of potassium *tert*-butoxide in tetrahydrofuran. As shown in entry 1 of Table 1, extractive workup of the basic reaction mixture provided expected product **6** in 73% isolated yield. The reaction mixture was then acidified with a slight excess amount of aqueous HCl and re-extracted to afford Cbz-alanine **5** in 21% isolated yield.

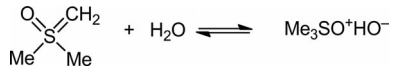
To explore the possible role of water in the formation of **5**, an additional series of reactions were carried out in which increasing amounts of water were intentionally spiked into the sulfur ylide solution prior to the addition of **4**. As shown in Table 1, entries 2–4, the amount of Cbz-alanine side product **5** increased with a concomitant decrease in the yield of **6** along this series.

It is noteworthy that even in the presence of a threefold excess amount of added water, some sulfur ylide **6** continued to be formed. This can be understood in terms of an equilibrium between the sulfur ylide and free water on the one hand and a (presumably THF-soluble) hydroxide species on the other hand, as shown in Scheme 3.

Table 1. Additive effects for reaction of ester **4** with dimethylsulfoxonium methylide.[a]

Entry	Additive[b]	Equivalents	Yield [%]	
			Ylide	Acid
1	none	–	73	21
2	water	1	41	50
3	water	2	32	65
4	water	3	22	73
5	MeOAc	0.5	79	7
6	MMT[c]	0.5	77	n.d.[d]
7	none[e]	–	84	4
8	none[e,f]	–	61	31

[a] All runs contained the substrate (1 equiv.), trimethylsulfoxonium chloride (3 equiv.), and potassium *tert*-butoxide (3 equiv.). [b] Reactions were stirred for 5 h at r.t. with additive prior to the addition of the substrate. [c] MMT = monomethyl terephthalate. [d] n.d.: not determined. [e] Using dried trimethylsulfoxonium chloride with <200 ppm water. [f] Using solid potassium *tert*-butoxide.



Scheme 3. Proposed equilibrium of dimethylsulfoxonium methylide and water.

We reasoned that the 21% of background hydrolysis observed in Table 1, entry 1, might be diminished by pretreatment with a water scavenger. To be useful, the products obtained from such a water scavenger should be water soluble to allow the isolation of the chain-extended sulfur ylide without contamination. Suitable additives for this purpose include methyl acetate (Table 1, entry 5) and terephthalic acid monomethyl ester (Table 1, entry 6). In each case, the yield loss to background hydrolysis was diminished (though not completely eliminated).

To unambiguously demonstrate the incorporation of water into Cbz-alanine **5**, an isotopic labeling study was additionally carried out. Following the conditions of Table 1, entry 4, 3 equiv. of ^{18}O-labeled water (97% isotopic enrichment) was introduced into a solution of 3 equiv. of dimethylsulfoxonium methylide in THF prior to the introduction of ester substrate **4**. LC–MS analysis was carried out on the reaction mixture prior to quench. Careful quantification of the resulting mass spectra indicated that the Cbz-alanine produced in the reaction contained 92% ^{18}O and 8% ^{16}O, which further confirmed the role of water in the reaction.[10]

An effort was made to determine the principal source of water in these reactions by using automated Karl–Fischer (KF) titration. Notably, the commercial trimethylsulfoxonium chloride was found by KF to contain 0.74 wt.-% of water. Because of the relatively low molecular weight of water relative to that of this salt and the fact that three molar equivalents of the salt were used in these reactions, this contribution alone delivers 0.16 mol of water per mol of ester substrate **4**. In duplicate runs, the water content of starting ester **4** was <260 ppm and the solvent THF con-

tained only 68 ppm of water by KF. Thus, neither is expected to contribute significantly to background hydrolysis.

On the basis of the above results, a sample of trimethylsulfoxonium chloride was vacuum dried for 6 d at 55 °C and 20 Torr. KF analysis of the dried salt showed that the moisture content had dropped to <200 ppm. When the reaction was again run under the standard conditions but with the use of this dried salt (Table 1, entry 7), the yield of chain-extended sulfur ylide **6** increased to 84% and only 4% of Cbz-alanine **5** was isolated after acidification.

KF analysis was not suitable for determining the amount of water in the commercial THF solution of potassium *tert*-butoxide that was utilized as base. Our results suggest that the water content in this solution is low. However, for a related reaction researchers at Merck noted that when the commercial solution was replaced with solid potassium *tert*-butoxide, significant carboxylic acid side product was formed.[11] This suggests that such solid potassium *tert*-butoxide may contain significant amounts of potassium hydroxide as a contaminant. Consistent with this proposal, when the reaction was re-run with the use of dried trimethylsulfoxonium chloride and solid potassium *tert*-butoxide (Table 1, entry 8), the yield of carboxylic acid **5** increased from 4 to 31%.

Conclusions

Taken together, our experimental results provide compelling evidence that carboxylic acid side product **5** formed during the preparation of **6** is the result of a facile hydrolysis reaction involving adventitious water. We suggest that optimal yields of chain-extended sulfur ylides will be obtained if (1) trimethylsulfoxonium chloride is dried prior to use and (2) commercial potassium *tert*-butoxide solution in THF rather than the solid reagent is utilized as base.

It seems feasible that trimethylsulfoxonium chloride obtained from different commercial sources may contain differing levels of water depending on how scrupulously the salt is dried.[12] We can only speculate regarding the origin of the results observed by the Calabria group but note that a water content of as little as 2% in trimethylsulfoxonium chloride would account for their observations.[13] Although the mechanistic proposal put forward by these researchers was shown to be incorrect, their observation of a hydrolytic side product has led to an improved understanding and enhanced yields for the one-carbon chain extension of esters.[14]

Experimental Section

General Methods: Cbz-Alanine methyl ester was obtained from Chem-Impex, Inc., and was used as received. Trimethylsulfoxonium chloride was obtained from Sigma–Aldrich or Acros Organics and was used as received except where otherwise indicated. All remaining reagents were from Sigma–Aldrich and were used as received. To be consistent with ref.[7a], glassware was not dried prior to use. Automated Karl–Fischer titrations were carried out in triplicate with a Mettler Toledo DL39 Karl–Fischer Coulometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained in solvent $CDCl_3$ with a Bruker Avance 3 NMR spectrometer.

Computational Method: Geometry optimizations and transition-state searches were performed at the M06–2X/aug-cc-pVDZ level of theory by using the Gaussian 09 suite of programs.[15] Extra-tight convergence criteria (acc2e = 12, opt = tight) and an ultrafine grid (grid = ultrafine) were used for final optimization and the frequency and thermal calculations. The identity of the transition structure was identified by a single imaginary frequency. The identity of the transition structure was confirmed by an IRC calculation leading to the corresponding tetrahedral intermediate.

Reactions of Cbz-Alanine Methyl Ester with Dimethylsulfoxonium Methylide: Reactions in Table 1 were carried out in glass tubes equipped with Teflon screw caps. The tubes were charged with trimethylsulfoxonium chloride (772 mg, 6.00 mmol), a solution of potassium *tert*-butoxide (1.00 M in THF, 6.00 mL, 6.00 mmol), and additional anhydrous THF (6.00 mL). The mixture was stirred for 2 h at 60 °C and was then cooled to 0 °C with continued stirring. The tube was briefly opened and water (if any) was then added by syringe. For reactions involving the use of a water scavenger, a solution of methyl acetate or terephthalic acid monomethyl ester (1.00 mmol) in THF (2 mL) was added and stirring was continued for 5 h. The tube was briefly opened to allow addition of a solution of Cbz-alanine methyl ester (474 mg, 2.00 mmol) in THF (2.00 mL). After 4 h stirring at 0 °C all reactions were complete as determined by HPLC (see the Supporting Information). The mixture was added to water (15 mL) and extracted into ethyl acetate (3× 15 mL). Distillation of the solvent by using a rotary evaporator afforded chain-extended sulfur ylide **6**. The remaining aqueous solution was acidified with 1 N HCl (8.0 mL) and was further extracted with ethyl acetate (3× 15 mL). Distillation of the solvent by using a rotary evaporator afforded Cbz-alanine **5**. After drying, the ^{1}H NMR and ^{13}C NMR spectra of **5** and **6** matched those in the literature.[1,6a] Typical spectra are included in the Supporting Information. Data for **5**: white solid m.p. 85–86 °C. $C_{11}H_{13}NO_4$ (223.23): calcd. C 59.19, H 5.87, N 6.27; found C 59.23, H 5.77, N 6.26. Data for **6**: snow-white solid, m.p. 136–138 °C. $C_{14}H_{19}NO_4S$ (297.37): calcd. C 56.54, H 6.44, N 4.71; found C 56.71, H 6.44, N 4.65.

Isotopic Labeling Study: The reaction was carried out as above with the exception that ^{18}O-labeled water (108 μL, 6 mmol, 97% isotopic enrichment) was added prior to the introduction of ester **4**. After the reaction, the mixture was not subjected to aqueous quench but was immediately analyzed by LC–MS by using an Agilent 1100 series HPLC system and utilizing an Agilent Poroshell SB-C18 column at 40 °C. Both mobile phases were acidic to ensure that Cbz-alanine was present as the free acid (mobile phase A 0.1% formic acid in water and mobile phase B 0.1% formic acid in acetonitrile). The resulting mass spectra were analyzed in comparison with those of authentic samples of the unlabeled products. Careful quantification indicated that the Cbz-alanine produced in the reaction contained 92% ^{18}O and 8% ^{16}O. Full details of the analysis and associated mass spectra are included in the Supporting Information.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra, additional computational details, and details of the isotopic labeling study.

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[9] When trimethylsulfoxonium iodide was used in place of the chloride, partial loss of the Cbz protecting group was observed. This is presumably related to the deprotection of the 9-fluorenylmethoxycarbonyl (Fmoc) protecting groups observed in ref.[7b]
[10] For a detailed description of this experiment, see the Supporting Information.
[11] See ref.[6a] and especially reference 39 therein.
[12] Although we exclusively used potassium *tert*-butoxide as the base, much of the Calabria work utilized sodium hydride as the base. When NaH was used as the base, the most likely source of water would seem to be the sulfoxonium salt.
[13] Trimethylsulfoxonium chloride used for the reactions in Table 1 was obtained from Sigma–Aldrich. For comparison, a sample obtained from Acros Organics exhibited a similar moisture content of 0.82%.
[14] Two factors seem to have contributed to the fact that this side reaction has not been widely recognized. At the completion of the reaction, the carboxylic acid is present as the potassium carboxylate salt and remains in the aqueous phase during extractive workup. Thus, it is not seen as a contaminant in the isolated product. In addition, the chain-extended sulfur ylide contains an unusually strong UV chromophore; depending on the wavelength, its extinction coefficient is typically two orders of magnitude greater than that of the carboxylic acid. Consequently it does not register as a significant side product in HPLC analysis of the reaction mixture.
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