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Acylation Mechanisms of DMSO/[D_6]DMSO with Di-*tert*-butylketene and Its Congeners[‡]

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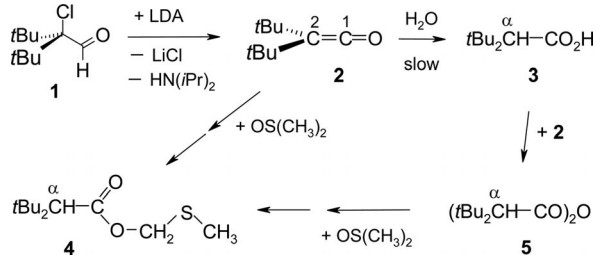
Dedicated to the memory of Professor Hans Behringer

Keywords: Kinetics / Isotope effects / Ketenes / Reaction mechanisms / Sulfoxides / NMR spectroscopy

Dimethyl sulfoxide (DMSO) and tBu$_2$C=C=O in diglyme require heating to about 150 °C to furnish the Pummerer-type product tBu$_2$CHCO$_2$CH$_2$SCH$_3$ through a novel mechanistic variant. The "ester enolate" tBu$_2$C=C(O$^-$)–O–S$^+$(CH$_3$)$_2$ arising through the reversible addition of DMSO (step 1) to C-1 of tBu$_2$C=C=O must be trapped through protonation (step 2) at C-2 by a carboxylic acid catalyst to form tBu$_2$CH–C(=O)–O–S$^+$(CH$_3$)$_2$ so that the reaction can proceed. The ensuing cleavage (step 3) of the O–S bond and one of the C–H bonds in the –S(CH$_3$)$_2$ group (E2 elimination, no ylide intermediate) results in the formation of tBu$_2$CHCO$_2^-$ and H$_3$CS–CH$_2^+$, whose combination (step 4) generates the final product. With a mixture of DMSO and [D_6]DMSO competing for tBu$_2$C=C=O in diglyme, the small value of the kinetic H/D isotope effect (KIE) k_H/k_D = 1.26 at 150 °C indicates that the cleavage of the C–H/C–D bonds (step 3) does not occur in the transition state with the highest free enthalpy. Therefore, the practically isotope-independent steps 1 and 2 determine the overall rate. The alternative slow initial protonation at C-2 of tBu$_2$C=C=O generating the acylium cation tBu$_2$CHC≡O$^+$ can be excluded. Preparatory studies were undertaken to compare the mechanistic behavior of tBu$_2$C=C=O with that of two related acylating agents: (i) The anhydride (tBu$_2$CHCO)$_2$O affords the same Pummerer-type product more slowly, again with an unexpectedly small KIE of 1.24 at 150 °C, which indicates that the overall rate is limited here by the almost isotope-independent initial *O*-acylation of DMSO in the addition/elimination (AE) mechanism. (ii) The acyl chloride tBu$_2$CHCOCl affords ClCH$_2$SCH$_3$ through a more common mechanistic variant involving neither the ketene nor the acylium cation tBu$_2$CHC≡O$^+$: The modestly enhanced k_H/k_D value of 2.4 at 55 °C shows that the C–H/C–D bond fissions contribute to the overall rate in cooperation with the retarded initial *O*-acylation. Deuterium labeling was quantified through ^{1}H and ^{13}C NMR integrations of deuterium-shifted signals.

Introduction

Di-*tert*-butylketene (tBu$_2$C=C=O, **2** in Scheme 1) is a kinetically sluggish electrophile,[1–4] because the electronic structure of its carbonyl center (C-1) demands the approaching nucleophile to enter from close to the ketene sp^2 plane and thus to collide with one of the two bulky *tert*-butyl (tBu) groups. Therefore, only very potent nucleophiles such as phenyllithium,[5] tBuLi,[6,7] Me$_3$SiLi,[8] or anhydrous KOH in dimethyl sulfoxide (DMSO) (slow at 55 °C[9]), but not tBuMgCl,[9] are able to add to **2** under mild conditions.[1,2] With a convenient preparation[9] of **2** through the elimination of HCl from tBu$_2$CClCH=O (**1**) in hand, it appeared attractive to explore whether DMSO, which is a highly polar and sterically sensitive[10] nucleophile,[11] would be able to add to **2**.



Scheme 1. Preparation and consumption of the ketene **2**.

It may be recalled[12] that tBu$_2$C=C=O (**2**) does not dimerize and is completely stable in a closed vessel. Almost unavoidable trace amounts of adventitious water in even carefully dried DMSO solvent would add slowly (at above 95 °C)[9] to **2**, producing the acid tBu$_2$CHCO$_2$H (**3**) which can slowly consume a second equivalent of **2** with formation of the anhydride (tBu$_2$CHCO)$_2$O (**5**). Therefore, the present study involved reduced concentrations (0.4–3.8 M) of DMSO in anhydrous (H$_3$COCH$_2$CH$_2$)O (diglyme), which is stable[9] against **2** at 150 °C for many hours in the

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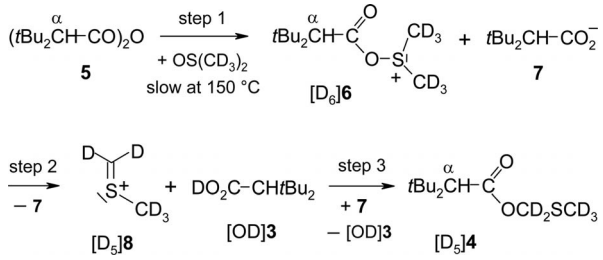
absence of pyridine. Under these conditions, both **2** and **5** afforded the hitherto unknown (methylthio)methyl ester **4**, which is the typical product expected from a Pummerer acylation[13] of DMSO by an anhydride such as **5**. It will now be shown that these two modes of formation of **4** occur through novel mechanistic variants.

Results and Discussion

A. DMSO with the Anhydride (tBu$_2$CHCO)$_2$O (5)

Scheme 2 displays a simplified mechanistic version of the Pummerer acylation of sulfoxides by anhydrides,[13,14] formulated for **5** with [D$_6$]DMSO. The first intermediate, [D$_6$]-**6**, may transfer one of its deuterons (step 2) to the carboxylate **7** in an intermolecular E2 elimination[14] reaction, forming the perdeuteriated thionium cation [D$_5$]**8** (2-thioniapropene). [D$_5$]**8** and **7** are believed to recombine in the final step 3 with production of the ester [D$_5$]**4**. A large primary H/D kinetic isotope effect (KIE, up to a k_H/k_D ratio of ca. 4 at 150 °C)[15] would be expected for the E2 elimination in step 2, as supported by known experimental k_H/k_D ratios for the acetylation of other sulfoxides by acetic anhydride at 120 °C (k_H/k_D = 2.9)[16] or at 76 °C (supposed $k_H/k_D \geq$ 4.5).[14a] These values indicate that the C–H (and C–D) bond fission (step 2) contributes to limiting the overall reaction rate in these cases (but not in the case of **5**, as detailed below). The following competition experiment compares this usual Pummerer scenario with the kinetic behavior of anhydride **5**.



Scheme 2. Pummerer acylation of [D$_6$]DMSO with anhydride **5**.

A diglyme (0.59 mL) solution of **5** (0.282 mmol), DMSO (0.500 mmol), and [D$_6$]DMSO (2.11 mmol) in a tightly closed NMR tube was heated at 150 °C for 15 h until **5** had completely disappeared.[17] The in situ ^{13}C NMR analysis revealed the formation of 0.104 mmol (37%) of the two esters **4** and [D$_5$]**4**, along with roughly 0.4 mmol of acid **3**. The two side-products (H$_3$C)$_2$S (0.023 mmol) and (D$_3$C)$_2$S (0.086 mmol) arose through deoxidation reactions of the two dimethyl sulfoxides, but the detached oxygen atoms were not transferred to the sulfur atoms of **4** or [D$_5$]**4**, although such a transfer would be possible[18] at 150 °C.

The differential diagnosis had to be carried out with the isolated product mixture in a more concentrated solution. After separation from the deuterium-free acid **3** (66 mg, 68%), the crude esters (33 mg) were obtained in a millimolar ratio **4**/[D$_5$]**4** of 0.023:0.078 (36% yield), which corresponds[19] to a k_H/k_D ratio of 1.24. This very small intermolecular competitive KIE indicates that the C–H/C–D bond fission (step 2 in Scheme 2) did not occur in the energetically highest transition state, which is then reasonably assigned here to step 1 in which DMSO is required to attack one of the strongly shielded acyl groups of **5**. This changeover of the rate-limiting step establishes a novel mechanistic variant of the Pummerer acylation in which the overall reaction rates of DMSO and [D$_6$]DMSO (but not the faster C–H/C–D bond fissions) are almost equally slow. The large amount of acid **3** observed in situ is informative: If the sulfonium ylide tBu$_2$CHCO$_2$–S$^+$(CD$_3$)CD$_2^-$ had been formed[13,20] from [D$_6$]**6**, it would be expected to be rapidly protonated by **3** to give tBu$_2$CHCO$_2$–S$^+$(CD$_3$)CHD$_2$ and finally [D$_4$]**4** or a less highly deuteriated product; but this was never detected. Consequently, the sulfonium ylide is formed in step 2 either irreversibly[21] (faster decay to afford [D$_5$]**8**) or not at all (faster E2 elimination of [D$_6$]**6**). Furthermore, deuterium was not incorporated into the α-position of the di-*tert*-butyl parts of **4** and [D$_5$]**4** at 150 °C. It is noteworthy that this reaction temperature is higher by at least 70 °C than in the case of acetic anhydride reacting with DMSO.[22] This suggests that step 1 in Scheme 2 is, in fact, slowed down by steric repulsion in **5**, so that the C–H/C–D bond fission in step 2 can no longer co-determine the overall reaction rate.

B. DMSO with the Acyl Chloride tBu$_2$CHCOCl (9)

The closely related acyl chloride **9**[9] is now presented as a contrasting example that tends toward a larger primary KIE. The acylation of DMSO by **9** will again give **6** in step 1 of Scheme 3. The mutual interconversion of **6** and (H$_3$C)$_2$S–Cl$^+$ (**10**) in step 2 may be visualized[23] as involving a sulfurane with a tetracoordinate sulfur atom; the process would be terminated above 0 °C[24a] presumably through an E2-type elimination (step 3) within the ion pair[23] of **10** + **7**, producing the acid **3** together with the thionium chloride **8** and finally (step 4) chloro(methylthio)methane[24a,24b] (**11**). Steps 1 and 2 were formulated as reversible processes in analogy with the main path suggested[23] for the rapid acetylation of DMSO by acetyl chloride, where an experimental k_H/k_D estimate of approximately 5 at 30 °C had been assigned to the C–H/C–D bond-breaking step 3, in rough accord with the values cited above[14a,16] for acetic anhydride. The following competition experiment is thought to slightly modify that mechanistic picture for the present case of **9**.

A diglyme (0.55 mL) solution of the acyl chloride **9** (0.35 mmol), DMSO (0.528 mmol), and [D$_6$]DMSO (2.100 mmol) in a tightly closed NMR tube was heated at 55 °C until **9** had vanished (within 6.5 h). The product distribution was measured in situ through ^{13}C NMR integrations that revealed the following millimolar quantities: 0.308 of acid **3**, 0.048 of [α-D]**3**, 0.064 of **11** (18%), 0.110 of [D$_5$]**11** (31%), and 0.021 of **12** (but [D$_5$]**12** was not determined). The product ratio of **11**/[D$_5$]**11** translates[19] into a rate ratio k_H/k_D of 2.4, which amounts to a modest fraction

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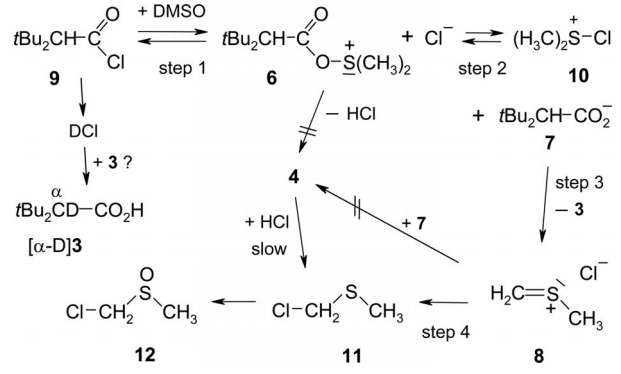
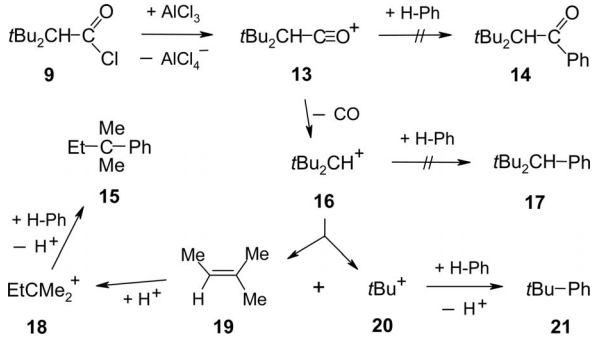


Scheme 3. Pummerer reaction of DMSO with the acyl chloride **9**.

of the maximum KIE (ca. 6.0)[15] at 55 °C. This result appears to indicate that the C–H/C–D bond fissions in step 3 contribute perceptively (though weakly) to the overall rate, so that the preceding steps 1 and 2 should be at least partially reversible. This would mean that, in contrast to the acetylation mentioned above,[23] the present acylation of DMSO with **9** in diglyme, [D_8]dioxane, or [D_8]tetrahydrofuran (THF) (all comparably slow at 55 °C) is retarded by an elevation of the free-enthalpy barrier for step 1 to a level similar to that of the isotope-dependent step 3.

None of the intermediates (**6**, **8**, or **10**) in Scheme 3 could be detected in situ (^{1}H and ^{13}C NMR analysis), but the development of HCl in parallel with the emergence of **11** and acid **3** was recognized through an increasing ^{1}H NMR shift of free DMSO (δ = 2.48 ppm) toward the value for DMSO·HCl[24a] (δ = 2.87 ppm). The much slower subsequent conversion of **11** into the sulfoxide **12**[24b] is known[18] to be mediated by HCl. Hydrolysis of some part of **9** by adventitious moisture is a probable source of HCl, and residual HOD in [D_6]DMSO should similarly give rise to DCl. The occurrence of some [α-D]**3** mentioned above can be understood through a very slow reaction of DCl (first column of Scheme 3) with acid **3** (as formed in step 3), in analogy with the labeling technique reported[25,26] for a related system. During storage of the mixture for some weeks at ambient temperature without workup, the sulfoxide **12** vanished slowly, with appearance[27] of $H_3CS–SO_2–CH_3$.[24a,24c] The ester **4** is probably not generated under the reaction conditions shown in Scheme 3 from the intermediates **6** or **8** (in contrast to Scheme 2), presumably due to a shortage of bases such as **7** in this HCl-producing system; this notion gained support in the following way: A sample (5 mg) of pure ester **4** was added to this aged solution and required significantly longer than 4 h at 55 °C for its cleavage by HCl to give **11** (2nd column of Scheme 3). Therefore, even modest amounts of **4** would have been detected by ^{1}H NMR analysis in situ, which was, however, not the case.

Despite steric repulsion, the conversion of **9** into **6** (step 1 of Scheme 3) is expected to occur through nucleophilic addition of DMSO to **9** and subsequent elimination of a chloride anion (the usual AE mechanism), as judged on the basis that the following two alternative modes can be dismissed: (i) The ketene **2** could not be detected by NMR analysis in situ and is, in fact, unable to react with DMSO at 55 °C, as will be detailed in Section C. (ii) The acylium cation **13** (Scheme 4) is stable at –60 °C but decays "upon warming"[28] with loss of carbon monoxide to give the cations *t*Bu$^+$ (**20**) and $EtMe_2C^+$ (**18**). No simple chemical means of detecting **13** are apparently known; so it was planned to use benzene to trap the cations shown in Scheme 4, because all four conceivable products (**14**, **15**, **17**, and **21**) of these Friedel–Crafts reactions had already been prepared by other routes. For an initial setup of this novel test system, $AlCl_3$ (0.5 equiv. or more) was added to a benzene solution of the acyl chloride **9**, and the reaction was monitored by ^{1}H NMR analysis at approximately 20 °C. Under these conditions, neither **13** nor the expected acylation product **14**[5] could be detected during the slow consumption of **9**, which indicates that the decarbonylation of **13** to generate **16** is faster[29,30] than the acylation of benzene. The subsequent rapid decay of **16** (no formation of **17**[31]) to give the expected[28] *t*Bu$^+$ (**20**) was recognized through the detection of **21**[32] as the main product. Simultaneous protonation[28] of the second fragment **19** led to formation of the *tert*-amyl cation **18**, which was trapped as **15**.[33] In the absence of the Lewis acid catalyst $AlCl_3$, however, **9** was stable in benzene solution at 70 °C for at least 5 h. Likewise, **9** in the more polar diglyme (as a 70 vol.-% component of the solvent mixture) did not react with benzene (23% by volume, 12 equiv.) at 70 °C during 6 h; subsequent addition of DMSO (3.5 equiv.) led to the formation of $ClCH_2SCH_3$ (**11**) and acid **3** as the main products (but neither **15** nor **21**) at 55 °C within 7 h. Thus, the results obtained with the test system outlined in Scheme 4 clearly exclude a spontaneous ionization of **9** in step 1 of Scheme 3 to generate **6** via the acylium ion **13**; this leaves the AE mechanism, as claimed above.



Scheme 4. Decarbonylation of the acylium cation **13** and trapping with benzene.

C. DMSO with the Ketene *t*Bu$_2$C=C=O (2)

Scheme 5 illustrates the competition between DMSO (0.527 mmol) and [D_6]DMSO (2.100 mmol) for the ketene **2** in diglyme (0.55 mL) at 150 °C. Steps 1_H and 1_D generate the zwitterionic "ester enolates" **22** and [D_6]**22**, respectively, which will be trapped by H^+ or D^+ (step 2) to provide the series **6**–[D_7]**6** in line 2 of Scheme 5. Such trapping can be

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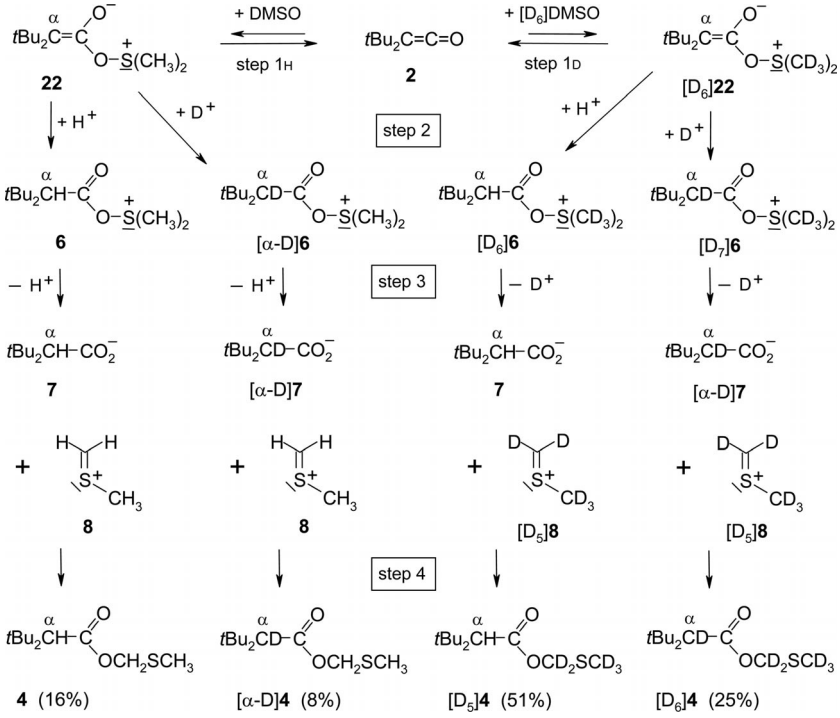
expected to be irreversible, because the isolated product ester **4** does not incorporate deuterium on heating at 110 °C with an excess of solid KOH in [D_6]DMSO for 2 h (continued heating of this mixture to 150 °C for 5.5 h cleaved **4** and afforded the non-deuteriated potassium salt of **3**). Thus, the possibility of α-H/α-D exchange reactions at di-*tert*-butylacetyl groups (reversal of step 2) can be dismissed, as similarly observed[9] with the pivaloin ester of **3**. In step 3, a base such as the carboxylate **7** is required (also in Scheme 2) for the β-elimination reaction of intermediate **6** and its isotopologues (Scheme 5), which will furnish the series of four ion pairs **7** + **8**, the final collapse of which (step 4) should be a fast process affording the product series **4**–[D_6]**4**.

The experimental progress was halted when ketene **2** was almost completely consumed (ca. 6 h), so that the slower acylation of DMSO by the side-product (anhydride **5**)[17] could not seriously interfere with the measurements. An alkaline workup procedure separated the free acids **3** and [α-D]**3** (37 ± 2% α-D) from the four esters **4** (33% α-D). A conspicuously different H/D ratio of 24:76 was found for the pairs of esters (**4** + [α-D]**4**)/([D_5]**4** + [D_6]**4**) through NMR integrations of the OCH_2SCH_3/OCD_2SCD_3 parts (see Table S1 in the Supporting Information). This ratio resembles that of the starting mixture of DMSO/[D_6]DMSO (20:80) and yields[19] a k_H/k_D value of 1.26 for the overall reaction. A more detailed analysis of the deuterium partitioning afforded a ratio of 16:8:51:25 for **4**/[α-D]**4**/[D_5]**4**/[D_6]**4** (bottom line of Scheme 5); this analysis was assisted by results obtained by mass spectrometry, as presented in the Experimental Section.

The low value of the KIE (k_H/k_D close to 1) demonstrates that the C–H/C–D bond-breaking step 3 is not involved in the overall reaction rate; thus, steps 1 and 2 remain as candidates for this role.[21] In fact, significant rate enhancements were observed with increasing concentrations of both DMSO (step 1) and acid **3** (step 2).[34] A strong acceleration (first $t_{1/2} \approx 20$ min at 150 °C) was also observed when the reaction was performed with benzoic acid (0.7 equiv.) in addition to **3** (as generated from **2** by moisture), wherefrom a 65:35 mixture of **4** and the known[35] ester $PhCO_2CH_2SCH_3$ was obtained, the latter probably arising through either benzoylation of DMSO by a mixed anhydride or trapping of $H_3CSCH_2^+$ (**8**) by $PhCO_2^-$. Thus, the practically isotope-independent steps 1 and 2 co-determine the overall reaction rate; it follows that the transition state of step 2 must be higher in enthalpy than that of the isotope-dependent step 3, so that step 2 becomes irreversible, as expected above.

In a corroboration of the latter results, the acylation of DMSO could be completely suppressed through initial addition of KO*t*Bu (0.3–1.2 equiv.), which neutralized any acids in the reaction vessel. Ketene **2** remained stable in this non-acidic environment at 149 °C for more than 16 h and also for a further 10 h after subsequent addition of sufficient amounts (in excess over KO*t*Bu) first of *tert*-butyl alcohol and then of 2,6-di-*tert*-butylphenol. This inhibition was terminated through the final addition of acid **3** (2 equiv.), which promoted the production of ester **4** together with a small amount of anhydride **5**. The initial inhibition of step 2 demonstrates that conceivable alternative



Scheme 5. Competition between DMSO and [D_6]DMSO for ketene **2**.

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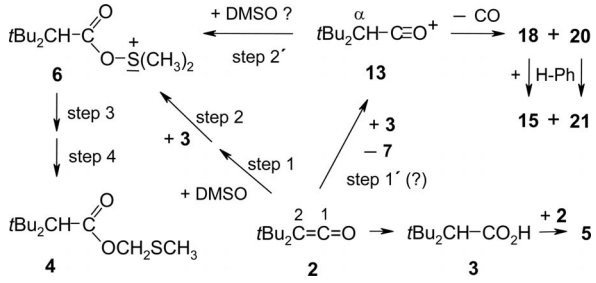
steps, such as an intramolecular or bimolecular proton transfer from *S*-methyl to C-α either within or between molecules of the "ester enolate" **22** (implying a transient sulfonium ylide character), do not occur under the reaction conditions.[20] It also demonstrates the absence of proton transfer from DMSO to C-α of **22**, in agreement with the conclusion that such a transfer can be excluded, because products bearing $–SCH_2D$ or $–SCHD_2$ functions were not observed (as verified in Figure S1 of the Supporting Information) in the above DMSO/[D_6]DMSO competition experiments with ketene **2** at 150 °C after many hours.

Similar mechanistic traits were observed when the small nucleophile methanol was used in place of DMSO. In the presence of solid $NaOCH_3$ (1.4 equiv.) in diglyme, ketene **2** remained totally unreactive towards methanol (11 equiv.) at 110 °C for more than 2 h, whereas a parallel run with acid **3** (1.4 equiv.) in lieu of $NaOCH_3$ at 110 °C was complete within 125 min to produce the known[36] methyl ester, tBu$_2$CHCO$_2$CH$_3$ (yield 60%), together with anhydride **5** (23%) (this methyl ester could not be prepared through a direct esterification of **3** with methanol in diglyme at 110 °C over more than 10 h). These results are compatible with initial nucleophilic addition of methanol to C-1 of **2**, followed by C-2 protonation[37–39] by acid **3**, in analogy with the addition of methanol to dimethylketene at 25 °C as catalyzed[40] by weak carboxylic acids. The results are, however, at variance with the addition reactions of alcohols to less encumbered ketenes under acid-free conditions, in which the alcohol concentrations were included in the rate equations as 2nd or higher reaction orders.[37,38,41] The higher reaction temperatures (110 °C or more) and the inability of ketene **2** to add methanol in diglyme without acid catalysis illustrate the mechanistic consequences of steric shielding in **2**. This inability disappeared upon replacement of diglyme by the more polar[42] solvent DMSO: While ketene **2** still did not react with methanol (36 equiv., 7 vol.-%) in DMSO at 23 °C within at least 2 h, the subsequent addition of solid $NaOCH_3$ (which is barely soluble) started the production of tBu$_2$CHCO$_2$CH$_3$,[36] presumably via the ester enolate tBu$_2$C=C(O$^-$)OCH$_3$ and its subsequent protonation by methanol, so that the reaction appears to be catalyzed by methoxide. This clean conversion was complete after 5 h, which indicates a temperature reduction of much more than 87 °C in comparison with the total kinetic inactivity of $NaOCH_3$ in diglyme at 110 °C as described above. An even stronger acceleration was discovered with the homogeneous solution of $KOCH_3$ (18 equiv., in place of $NaOCH_3$), ketene **2**, and methanol (18 equiv.) in DMSO at 23 °C, which again produced only the methyl ester[36] in less than 48 min.[43] Thus, the addition of methanol to **2** is acid-catalyzed in diglyme solution at 110 °C, but base-catalyzed in DMSO at 23 °C.

D. DMSO with the Acylium Cation tBu$_2$CH–C≡O$^+$ (13)?

The hydration of ketene **2** through protonation at C-2 to generate the intermediate **13** (step 1′ in Scheme 6) is subject to rate-limiting general acid catalysis in pure water at 25 °C, which convinced the authors[25] of "a modest steric barrier" for the approach of H_3O^+ from regions perpendicular to the ketene sp^2 plane. This raises the question of whether the results described in Section C might also be compatible with the alternative mechanism depicted in Scheme 6. In this approach, *initial* protonation of **2** by the acid **3** in step 1′, followed by addition of DMSO to **13** in step 2′ would result in the formation of the same intermediate **6** as shown in Scheme 5. Considering the evidence[25,44] of a decreasing proton-transfer efficiency to C-2 of ketene **2** in a less polar environment than pure water, a solvent such as diglyme, used in the present work, might not appear to be of great promise for promoting the generation of **13** by the very weak[45] acid **3**. Instead, the concomitant[25] consumption of **2** by formic or acetic acid may be viewed as being caused by an initial *nucleophilic* addition[46] of the acid at C-1 of **2**, combined with a proton transfer to C-2 producing anhydrides; under this supposition, formation of an anhydride such as **5** cannot serve as unequivocal evidence for the involvement of an acylium intermediate such as **13**. In fact, attempts to detect **13**, as described in Section B, with benzene (11 equiv.) in a diglyme solution of **2** and acid **3** (1.3 equiv.) at 147 °C (ca. 1 h) furnished only **5**, and no trace of the aromatic products (**15** and **21** in the right column of Scheme 6) derived from the carbocations **18** and **20** as generated through decarbonylation[28] of **13**. Because the decarbonylation was fast[30] at room temperature (and should be much faster at 147 °C), one has to conclude that step 1′ does not occur in diglyme with benzene in the absence of DMSO.



Scheme 6. Mechanistic alternatives of the Pummerer acylation of DMSO with ketene **2** (steps 1–4 are depicted in Scheme 5).

The possibility remains that the highly polar co-solvent DMSO,[42] even when used in a smaller amount than discussed in Section C, might still promote the proton-transfer step 1′. In this case, the intermediacy of **13** could perhaps be unveiled through its monomolecular decarbonylation reaction (Scheme 6), especially if the competing bimolecular trapping of **13** (step 2′) could be repressed by employing a deliberately small concentration of DMSO. Thus, ketene **2** in diglyme containing benzene (21 equiv.), DMSO (1.1 equiv., 0.3% by volume), and acid **3** (up to 0.6 equiv.) were heated at 149 °C for 11 h, affording a trace of the Pummerer ester **4** along with mainly the anhydride **5** but, again, none of the aromatic compounds derived from carbocations **18** or **20**. Hence, the conjectured step 2′ must

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be faster than the rapid[30] decarbonylation of **13**, under the proviso that step 1′ takes place. If so, the consumption of **13** by DMSO in a faster step 2′ would leave the slow step 1′ as the sole[47] rate-limiting step in a very slow overall reaction. As a consequence, the employed concentration of DMSO would not influence the overall reaction rate (kinetic reaction order zero), which contradicts the experimental observations described in Section C; this contradiction disproves the above proviso and, with it, the acylium mechanism, at least as the main pathway in Scheme 6. Instead, the results of Section C remain consistent with the rate-determining steps 1 and 2 in Schemes 6 and 5.

Conclusions

The results presented here are compatible with the usually assumed mechanistic variants of Pummerer acylations by anhydrides and by acyl chlorides, except for the lower than usual kinetic isotope effects k_H/k_D, which indicate that the role of the rate-determining steps has shifted toward the starting (isotope-independent) events. A second novel variant concerns an initiating DMSO addition to the ketene tBu$_2$C=C=O, followed by an intermolecular proton-transfer step from carboxylic acids that contributes to the overall reaction rate, whereas the subsequent steps do not contribute. The latter mechanistic variant seems to be without precedence,[4,48,49] because the previously reported reactions of two other stable ketenes with sulfoxides were apparently not conducted in this way: (i) The initiating zwitterionic intermediate formulated[50] for Cl$_2$C=C=O reacting with α,β-unsaturated sulfoxides[48,51] is thought to rearrange through a (formal) [3,3]-sigmatropic migration; (ii) Ph$_2$C=C=O (reported[52] to be unsusceptible to protonation at C-2) and acidified DMSO follow a different route to produce benzilic acid;[53] the corresponding product tBu$_2$C(OH)CO$_2$H expected from ketene **2** is known[54] but could not be found in the present investigations.

Neither methanol nor DMSO furnish stable adducts with the ketene tBu$_2$C=C=O in acid-free diglyme solution, in contrast to the alcohol-catalyzed alcohol addition reactions to some less encumbered ketenes reported in the literature. This remarkable dependence on carboxylic acid catalysis of acylations of DMSO or methanol by tBu$_2$C=C=O in diglyme is not due to C-2 protonation (acylium route) as the first step. The base-catalyzed acylation of methanol or pivaloin by tBu$_2$C=C=O is possible in DMSO solution.

Experimental Section

Chemicals: Improved preparations of tBu$_2$C=C=O (**2**), tBu$_2$CHCO$_2$H (**3**), anhydride **5**, and acyl chloride **9** have already been described, together with the solvent dependence of their ^{1}H NMR spectra.[9] Pure commercial samples of DMSO, [D$_6$]DMSO, diglyme, and [D$_8$]THF were dried with molecular sieves in two stages.

(Methylthio)methyl 2-*tert*-Butyl-3,3-dimethylbutanoate (4): An NMR tube (5 mm) was charged with crude di-*tert*-butylketene (**2**; ca. 116 mg, 0.75 mmol), anhydrous diglyme (0.400 mL), dry DMSO (0.300 mL, 4.22 mmol), [D$_{12}$]cyclohexane (0.03 mL), and a trace of tetramethylsilane (TMS). The tightly closed tube was heated at 148 °C for 15 h with occasional NMR analysis. The ketene **2** disappeared within 10 h, rapidly generating some anhydride **5** (from **3**) and then the ester **4** (1:2.6); the major part of **5** was also transformed more slowly into **4** and acid **3**. The mixture was dissolved in Et$_2$O and shaken with aqueous 1 M NaOH. Acidification of the aqueous layer afforded acid **3** (27 mg, 21%). The organic layer was washed until neutral, dried with Na$_2$SO$_4$, and distilled at 105–115 °C (bath temp.)/3 mbar to yield the liquid ester **4** (101 mg, 57%). ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.11 (s, 18 H), 2.22 (s, 1 H, *tert*-CH), 2.24 (s, 3 H, SCH$_3$), 5.10 (s, 2 H, OCH$_2$S) ppm. ^{1}H NMR (diglyme + DMSO): δ = 1.10, 2.18, 2.20, 5.11 ppm. ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 15.62 (SCH$_3$), 30.70 [2× C(*C*H$_3$)$_3$], 35.08 [2× *C*(CH$_3$)$_3$], 64.42 (br., *tert*-*C*H), 67.31 (sharp, OCH$_2$S), 174.22 (C=O) ppm; assigned through ^{13}C/^{1}H correlation (HSQC) spectroscopy. ^{13}C NMR (100.6 MHz, diglyme + DMSO): δ = 15.20, 30.75, 35.28, 64.3 (br.), 67.3, 173.77 ppm. IR (film on diamond, ATR): $\tilde{\nu}$ = 2958, 2910, 2873, 1731 (s), 1476, 1370, 1349, 1220, 1109 (s), 1047, 969 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 232 (18) [M$^+$], 155 (85) [tBu$_2$CHCO$^+$], 57 (100) [tBu$^+$]. C$_{12}$H$_{24}$O$_2$S (232.39): calcd. C 62.02, H 10.41, S 13.80; found C 62.30, H 10.37, S 12.98.

Chloro(methylthio)methane (11):[24a,24b] ^{1}H NMR (diglyme, 400 MHz): δ = 2.253 (s, 3 H, CH$_3$), 4.88 (s, 2 H, CH$_2$) ppm. ^{13}C NMR (diglyme, 100.6 MHz): δ = 14.66 (CH$_3$), 52.90 (CH$_2$) ppm.

(1,1-Dimethylpropyl)benzene (15): ^{1}H NMR (CDCl$_3$, 400 MHz):[33] δ = 0.68 (t, ^3J = 7.4 Hz, 3 H, CH$_3$-3), 1.28 (s, 6 H, 2× 1-CH$_3$), 1.65 (q, ^3J = 7.4 Hz, 2 H, CH$_2$), 7.16 (disturbed t, ca. 1 H, *p*-H), 7.29 (disturbed m, ca. 2 H, 2× *m*-H), 7.32 (disturbed m, ca. 2 H, 2× *o*-H) ppm. ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 9.12 (CH$_3$-3), 28.44 (2× 1-CH$_3$), 36.88 (CH$_2$), 37.87 (C-1), 125.41 (*p*-C), 125.93 (2× *o*-C), 127.96 (2× *m*-C), 149.44 (*i*-C) ppm; assigned through HSQC spectroscopy.

***tert*-Butylbenzene (21):** ^{1}H NMR (CDCl$_3$, 400 MHz):[32a] δ = 1.32 (s, 9 H), 7.16 (disturbed t, ca. 1 H, *p*-H), 7.30 (disturbed m, ca. 2 H, 2× *m*-H), 7.39 (dm, ^3J = 7.5 Hz, ca. 2 H, 2× *o*-H) ppm. ^{13}C NMR (CDCl$_3$, 100.6 MHz):[32b] δ = 31.36 [C(*C*H$_3$)$_3$], 34.65 [*C*(CH$_3$)$_3$], 125.24 (2× *o*-C), 125.29 (*p*-C), 128.05 (2× *m*-C), 151.09 (*i*-C) ppm; assigned through HSQC spectroscopy.

Analytical Procedures for Deuterium Quantification: The most direct analytical method would employ quantitative ^{1}H NMR spectroscopy to determine the degree of deuterium labeling. With reference to the 18-proton integrals of the tBu$_2$ singlets of compounds **3**, **4**, and **11**, integral deficiencies between the NMR signals could indicate the H/D ratio. However, this simple technique would only be reliable for those substances for which integrals are not disturbed by impurities. Therefore, a different technique had to be chosen for the small batches of unpurified samples (prepared in situ, or obtained as the crude material after workup) as investigated in the present work. In this situation, ^{13}C NMR integration is the method of choice in view of its large spectral dispersion (less probable disturbances) and of the various deuterium-induced ^{13}C NMR chemical shifts $\Delta = \delta$(isotopologue) – δ(unlabeled) that offer multiple chances of integrating separate signals for the labeled and unlabeled components.

As depicted in Scheme 7, several large ^{13}C NMR upfield shifts Δ, expressed in units of ppb (1:10^9), could be used for the integrations of signal pairs as induced by the CH/CD, CH$_2$/CD$_2$, or CH$_3$/CD$_3$ pairs in the following mixtures: **3**/[α-D]**3** (63:37, from ketene **2**), **4**/[D$_5$]**4** (22:78, from anhydride **5**), (**4** + [α-D]**4**)/([D$_5$]**4** + [D$_6$]**4**) (24:76, from ketene **2**), and **11**/[D$_5$]**11** (37:63, from the acyl chloride **9**). The strongly broadened C-α signal (a conformational problem)[9] of **4**

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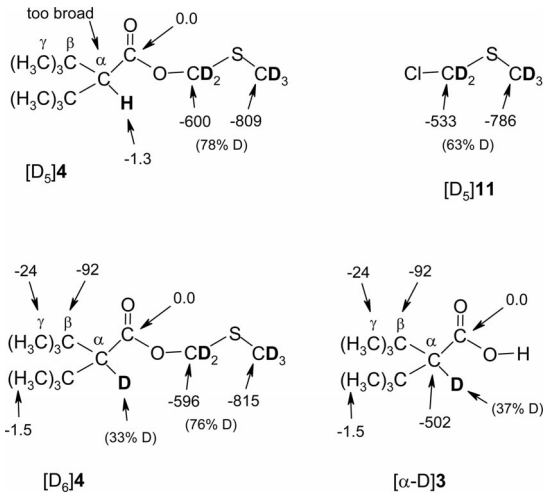
and its isotopologues was unsuitable for these analyses. Table S1 (see the Supporting Information) presents the detailed results and illustrates their reliability through consistent integral ratios as measured at two or more molecular positions.[19]



Scheme 7. Deuterium-induced ^{13}C and ^{1}H NMR isotope shifts $\Delta = \delta$(isotopologue) – δ(unlabeled) in ppb (averaged values); C-α signals in **4** and [D_5]**4** were too broad.

Accurate ^{13}C integral ratios were obtained through the application of the method of inverse-gated broad-band decoupling, which employs {^{1}H} decoupling only during the short acquisition period of the pulsed Fourier transform technique, used to suppress the undesired nuclear Overhauser enhancements of the integrals of proton-bearing carbon atoms. In addition, the relaxation delay period was set long enough (20–60 s) for a practically complete ^{13}C nuclear spin relaxation toward the thermal equilibrium before the next pulse. ^{1}H NMR integrals do not normally require such a time-consuming procedure and can be recorded under standard conditions. The α-H signals of a mixture of **4** and [D_5]**4** are separated by $\Delta = –1.3$ ppb (Scheme 7), as induced by the deuterium atoms of the OCD_2S group over a distance of five single bonds. Although a complete separation of this ^{1}H signal pair could not be achieved, its integral ratio of approximately 24:76 for (**4** + [α-D])**4**/([D_5]**4** + [D_6]**4**) equals the ^{13}C integral ratio mentioned above for that mixture (these two sums have to be taken because the ^{13}C NMR regions of the $–CD_2SCD_3$ parts of [D_5]**4** and [D_6]**4** are practically indistinguishable, as shown in Scheme 7; likewise, the NMR regions of the $–CH_2SCH_3$ parts of **4** and [α-D]**4** are practically identical). For the α-H portions (in **4** + [D_5]**4**) in relation to all α-D components ([α-D]**4** + [D_6]**4**), the γ-H (in *t*Bu) signal pair with $\Delta = –1.5$ ppb in Scheme 7 (integral ratio 71:29) supports the overall α-H/α-D = 67:33 ratio as measured by ^{13}C NMR analysis for (**4** + [D_5]**4**)/([α-D]**4** + [D_6]**4**) in the same experiment (Table S1 in the Supporting Information). Thus, deuterium-induced ^{1}H NMR isotope shifts can be recommended for a quick, perhaps semiquantitative, preview before starting a long-term ^{13}C NMR spectroscopic measurement.

In the presence of unlabeled **4**, these NMR methods cannot differentiate [D_6]**4** from a mixture of [D_5]**4** plus [α-D]**4**, so that the presence of [α-D]**4** and the precise portion of [D_6]**4** cannot be guaranteed at this point. Therefore, auxiliary mass-spectrometric analyses with chemical ionization (isobutane) at temperatures at or below 45 °C were carried out as follows: A first run with **4** + [D_5]**4** (obtained from the anhydride **5**) confirmed the absence of α-D in the fragment $t\text{Bu}_2\text{CHCO}^+$ (the acylium cation **13**),[55] the ^{13}C satellite of which had the expected intensity. Consequently, the $[M + 1]^+$ peak of **4** could not contain an α-D contribution and must have been composed of $M + {}^{13}C + H^+$ contributions alone. The $M^+/[M + 5]^+$ = **4**/[D_5]**4** intensity ratio of 25:75 for this sample emerged, which is in agreement with the value of 22:78 derived from NMR analysis. Next, the product mixture obtained with ketene **2** was found (always after corrections for ^{13}C satellites) to generate the mass fragments $t\text{Bu}_2\text{CHCO}^+$ and $t\text{Bu}_2\text{CDCO}^+$ in a 66:34 ratio, which is also consistent with the above NMR ratio of α-H/α-D = 67:33. In addition, the NMR-based ratio (**4** + [α-D]**4**)/([D_5]**4** + [D_6]-**4**) = 24:76 was also found for both the $M^+/[M + 5]^+$ = **4**/[D_5]**4** and the $[M + 1]^+/[M + 6]^+$ = [α-D]**4**/[D_6]**4** fractions; these latter two equalities require the same proportion (33%) of α-D labeling to be present in both (**4** + [α-D]**4**) and ([D_5]**4** + [D_6]**4**). Consequently, the first of these two sum terms (the 24% portion) is distributed by 67:33, so to become (16% + 8%), while the second sum term (the 76% portion) divides into (51% + 25%), which are the portions reported in Scheme 5 (last line). It may be noticed that due to the usual uncertainties about mass peak assignments, peak superpositions, and $M + H^+$ contributions, mass spectrometry alone (without NMR analysis) of these unpurified samples would not have provided these results with a comparable reliability.

Supporting Information (see footnote on the first page of this article): Table S1 of deuterium-induced ^{13}C and ^{1}H NMR shifts; general procedure for determining intermolecular competitive kinetic H/D isotope effects (with Figure S1).

Acknowledgments

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