A quantitative structure–reactivity relationship in decarboxylative Claisen rearrangement reactions of allylic tosylmalonate esters†

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Received (in Cambridge, UK) 18th July 2008, Accepted 29th September 2008
First published as an Advance Article on the web 14th October 2008
DOI: 10.1039/b812306c

First-order rate constants have been determined for the decarboxylative Claisen rearrangement reactions at 293 K of substituted methyl (*E*)-3-phenyl-2-propenyl 2-tosylmalonate esters, which show a linear free-energy relationship indicative of the development of positive charge on the benzylic position in the sigmatropic rearrangement transition-state.

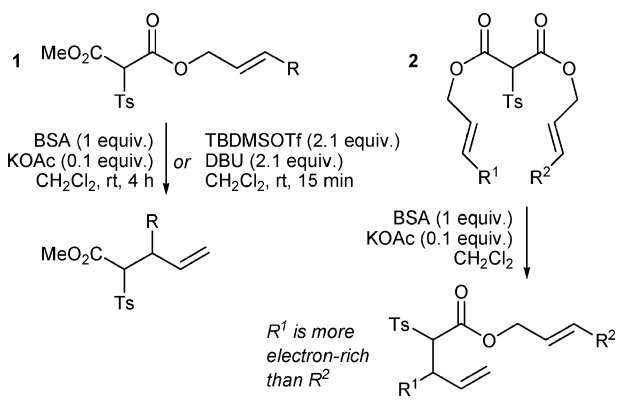
The Ireland–Claisen rearrangement[1] continues to be used widely in synthesis as a strategy-level method for the regiospecific and stereoselective formation of carbon–carbon bonds.[2] During the course of our studies of thermal decarboxylative Claisen rearrangement (dCr) reactions of allylic α-tosylesters,[3–9] we have developed dCr reactions of allylic tosylmalonate esters **1**. These substrates may be converted into the decarboxylated rearrangement products at room temperature using both the KOAc–*N*,*O*-bis(trimethylsilyl)acetamide (BSA) reagent system developed initially,[3,7] and modified conditions involving treatment of **1** with DBU and *tert*-butyldimethylsilyl triflate (TBDMSOTf).[4] Further experimentation showed that malonate substrates **2** possessing two allylic ester groups underwent highly regioselective, room-temperature mono-dCr reactions, in which the allylic group possessing the more electron-rich R substituent rearranged preferentially[9] (Scheme 1). This communication presents ^{1}H nmr-based kinetic measurements of BSA–KOAc-mediated dCr reactions of **1**. The results provide further evidence[10] for significant positive charge build-up on the distal position of the allylic moiety during sigmatropic rearrangement.

Our principal aim in this study was to evaluate the effect of variations in electron density within the R group in tosylmalonates **1** without changing the associated steric demand. Therefore, a series of substrates **1a–f** was synthesised in which R was a 4-substituted or an unsubstituted phenyl group. The syntheses were carried out as previously described:[4] coupling of the appropriate cinnamyl alcohol[11] with methyl malonate (DMAP–DCC) gave the mixed malonate esters, which were *C*-tosylated using *t*BuOK–TsF in DMSO.[12] The *C*-tosylation step provided acceptable yields (62–69%) of substrates **1a–e**, but was hampered in the case of **1f** (isolated in 10% yield) by the formation of a significant quantity (17%) of the γ-lactone **4**. This likely arises through cyclisation of the malonate precursor of **1f** *via* intramolecular nucleophilic attack of the derived enolate on the styryl double bond, which is rendered electrophilic by the electron-withdrawing 4-cyanophenyl group. We have observed similar behaviour previously in an analogous substrate possessing a 4-nitrophenyl residue,[9] and the 4-cyanostyryl moiety was shown to be susceptible to intramolecular nucleophilic attack during *ortho*-Claisen rearrangement of 4-cyanocinnamyl *p*-tolyl ether.[10]

Reference samples of dCr products **3a–f** were prepared from **1** in 66–81% isolated yield using the DBU–TBDMSOTf reagent system (CH_2Cl_2, rt, 40 min); all were formed as diastereoisomeric mixtures in varying ratios (Fig. 1). A further substrate **1** with S = OMe was synthesised also, but its dCr reaction was too rapid to provide useful kinetic data under the conditions studied.

The dCr reactions of **1** to give **3** proceed *via* a stepwise mechanism, in which silyl ketene acetal formation is followed by [3,3]-sigmatropic rearrangement and subsequent decarboxylation. In order to simplify reaction monitoring, we required reaction conditions in which ketene acetal formation was relatively rapid, followed by slower rearrangement and decarboxylation. This was achieved by adding BSA (2.3 equiv.) to CD_2Cl_2 solutions (*ca.* 0.08 M) of **1** containing KOAc (0.1 equiv.) under nitrogen at 293 K, followed by brief agitation and transfer to the nmr probe. Shimming typically took 3–5 min, after which data acquisition began.

Under the conditions described above, mechanistic pathways may be envisaged as shown in Scheme 2. Initially, substrates **1** undergo rapid formation of regioisomeric mixtures of geometric isomeric ketene acetals **5**. Unlike **5y**, isomers **5x** are inert with respect to [3,3]-sigmatropic



Scheme 1 dCr reactions of allylic 2-tosylmalonates.

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† Electronic supplementary information (ESI) available: Experimental procedures, analytical data and nmr spectra (^{1}H, ^{13}C and where appropriate ^{19}F) for the synthesis and characterisation of **1**, **3**, and synthetic intermediates; summarised kinetic data and first-order plots; tabulated integral data *vs.* time for rearrangement reactions of **1a–f**. See DOI: 10.1039/b812306c

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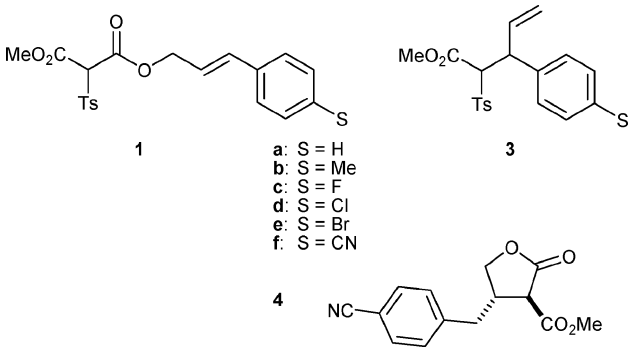
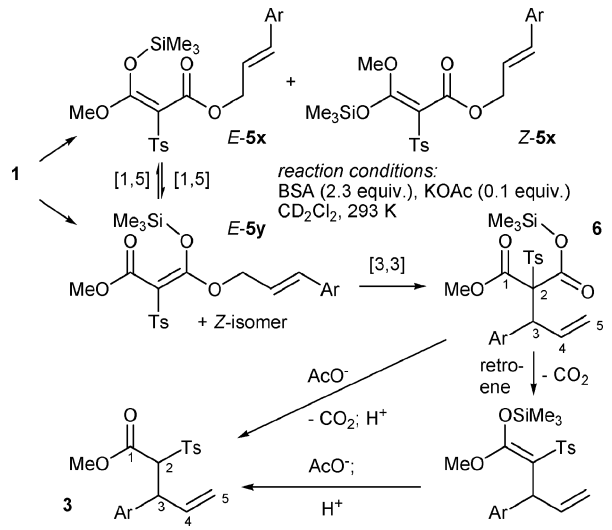


Fig. 1 Structures of **1**, **3** and **4**.



Scheme 2 Mechanistic pathways for the formation of **3**.

rearrangement; *E*-**5x** and *E*-**5y** may interconvert by 1,5-silatropic rearrangement.[13] The lack of complete reaction observed for all the substrates may indicate the formation of a non-reactive species such as *Z*-**5x**. Following [3,3]-sigmatropic rearrangement to silyl esters **6**, further alternatives may be considered. In one scenario, **6** may undergo desilylation by acetate-mediated transesterification–decarboxylation, giving the conjugate bases of **3** which then abstract a proton from **1**. Alternatively, **6** may suffer loss of CO_2 by a formal retro-ene reaction to give ketene acetal derivatives of **3**, which undergo acetate-mediated desilylation and protonation by **1**.

The dCr reactions of **1** were monitored by measuring the changes in integrals of proton signals with respect to time. For substrates **1a**, **1b**, **1d** and **1e**, signal resolution was such that it was most convenient to measure integrals for the methylene protons in **5** (which appeared as broad doublets), the C3 methines in **6** (pairs of broad doublets due to the diastereoisomeric mixture) and the C2 methines in **3** (pairs of sharp doublets due to the diastereoisomeric mixture). For substrates **1c** and **1f** the integrals of the methyl ester CH_3 groups in **5**, **6** and **3** were measured. Care was taken to include signals corresponding to both diastereoisomers in the integrated ranges. The methylene and methoxy CH_3 proton signals in **5** all showed significant broadening, indicative of the interconversion through [1,5]-silatropic shift of regioisomers **5x** and **5y** on the nmr time-scale. Typically, ^{1}H nmr analysis showed depletion of **5**, accumulation, and then depletion of **6**, and accumulation of **3** over the time-periods during which measurements were taken. Fig. 2 shows ^{1}H nmr traces obtained at 60 s intervals for the reaction of **1b**. Full details appear in the ESI.†

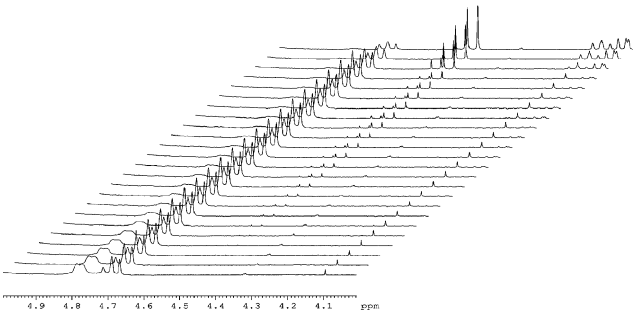


Fig. 2 ^{1}H nmr spectra of dCr reaction of **1b** recorded at 60 s intervals.

Reactions were monitored over at least two half-lives for all substrates apart from **1c**, for which data were gathered over *ca.* 1.5 half-lives. Plots of $[A]/[A]_0$ *versus* t were obtained for **1a–f**, where $[A]$ is the integral for the observed protons in **5** (methylene or methyl ester, as described above), normalised by taking into account the number of protons giving rise to the signal being integrated, and $[A]_0$ is the sum of the normalised integrals for **5**, **6** and **3**. First-order rate constants k_S were obtained by fitting the data according to the equation $[A] = [A]_0 e^{-kt} + B$ using nonlinear least squares,[14] where B is non-zero because of the formation of an unreactive species alluded to above. The rate constant data collected in Table 1 were further analysed by plotting $\lg[k_S/k_H]$ *versus* σ^+_{Spara}, which gave a straight-line plot and a ρ-value of *ca.* −2.3 (Fig. 3). The k_S values for the reactions of **5** derived from **1a–f**, and the corresponding σ^+_{Spara} values[15] are shown in Table 1; full details are provided in the ESI.†

Several features of the data presented above are worthy of note. Firstly, the first-order rate constants measured at 293 K are all significantly higher than those reported for the *ortho*-Claisen rearrangement reactions of 4-substituted cinnamyl *p*-tolyl ethers carried out under significantly more forcing conditions.[10] This is well established semi-quantitatively,[2] and may be rationalised in terms of the driving-force intrinsic in the carbonyl-forming Ireland–Claisen process, in contrast to the dearomatising nature of the [3,3]-sigmatropic rearrangement step in the *ortho*-Claisen variant. Secondly, the variation of rate constant as a function of the cinnamyl substituent observed in the present work is significantly larger than that reported previously, as evidenced by a ρ-value over five times greater than that found for the *ortho*-Claisen rearrangements.

Table 1 Measured rate constants for dCr reactions of **1** at 293 K

Substrate	S	σ^+_{Spara}	$10^5\ k_S/s^{-1}$	$\lg[k_S/k_H]$
1a	H	0	41.4	0
1b	Me	−0.311	250.8	0.78
1c	F	−0.073	110.6	0.43
1d	Cl	0.114	12.5	−0.52
1e	Br	0.15	9.8	−0.63
1f	CN	0.659	1.9	−1.34

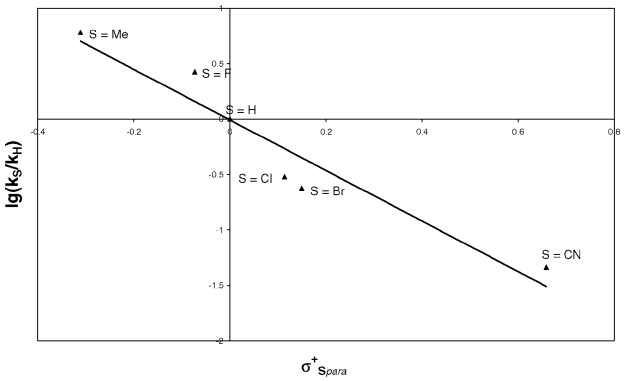


Fig. 3 Plot of $\lg[k_S/k_H]$ *vs.* σ^+_{Spara} for dCr reactions of **1a–f**.

Indeed, the value for ρ determined in the present work is similar in magnitude to that found for the hydrolysis of substituted benzyl chlorides in aqueous ethanol.[16]

Acceleration of the Ireland–Claisen rearrangement of substrates possessing an electron-donating substituent on the distal position of the allylic moiety has been documented. Curran *et al*. have shown[17] that the presence of an oxygen atom in this position leads to an increase in rate of one or more orders of magnitude. This effect has been studied computationally,[18] and has been described in terms of "vinylogous anomeric" ($\pi \rightarrow \sigma^*$) stabilisation[17d,19] of an early transition-state.[20,21] In this model, there is significant weakening of the allylic C–O bond, such that its scission may be significantly more advanced than formation of the new C–C bond. This induces positive charge character on the distal allylic carbon atom, which is stabilised by more electron-donating substituents attached at that position.[22] In the present work, the rate enhancement observed for ketene acetals **5** possessing electron-rich Ar is consistent with this analysis. The notion of a dipolar transition-state is further supported by published observations that an oxygen substituent at the allylic position leads to reaction acceleration in the Claisen rearrangement,[17e] and that solvent[17e,21c] and hydrogen-bonding additives[17f] significantly affect the rate.

In summary, we have shown that the first-order rate constants for dCr reactions of **1** show a pronounced dependency on σ^+ for the *para*-aryl substituent S, and therefore on the electron-density of the aryl group. This is indicative of significant positive charge development at the benzylic position during rearrangement, and the magnitude of the effect is substantially greater than that found in previous investigations of structure–rate relationships in [3,3]-sigmatropic processes.

This research was supported by Evangelisches Studienwerk e.V. Villigst (scholarship to N.K.S.). We thank Dr John C. de Mello for valuable assistance with data analysis, and Mr Richard N. Sheppard and Mr Peter R. Haycock for nmr measurements.

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