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Highly regioselective decarboxylative Claisen rearrangement reactions of diallyl 2-sulfonylmalonates

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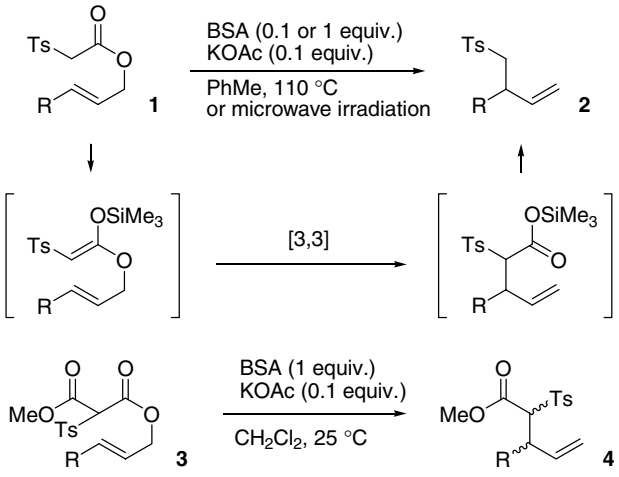
Abstract—The decarboxylative Claisen rearrangement of a range of substituted diallyl 2-sulfonylmalonates is described. The substrates are made by C-carboxylation of the corresponding allyl sulfonylacetates with allyl *para*-nitrophenyl carbonates. The reactions display a high degree of regioselectivity, with allylic substituents possessing electron-rich substituents at the allyl three-position rearranging preferentially.

The Claisen rearrangement continues to be the focus of considerable research effort.[1] Since its introduction in 1972,[2] the Ireland silyl ketene acetal variant in particular has been widely used in complex target-oriented synthesis.[3] This modified process benefits from the ease of preparation of the ketene acetal substrates and the relatively mild conditions for the sigmatropic rearrangement. In addition, it enables overall C-allylation of carboxylic acids using allylic alcohols as the surrogate electrophiles, with regiospecific allylic double-bond transposition. We recently reported[4,5] a novel variant of the Ireland–Claisen rearrangement reaction in which α-tosyl silyl keteneacetals formed in situ from allylic tosylacetates **1** in the presence of sub-stoichiometric amounts of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate undergo thermally induced [3,3]-sigmatropic rearrangement followed by acetate-induced desilylation–decarboxylation to provide homoallylic sulfones **2** in a single step.[6,7] We subsequently[8] showed that introduction of an additional electron-withdrawing α-substituent enables malonyl substrates **3** to undergo decarboxylative Claisen rearrangement (dCr) to provide α-carboxyhomoallyl sulfones **4** at ambient temperature (Scheme 1).

We became interested in the properties of unsymmetrical 2-tolylsulfonylmalonyl dCr substrates such as **5**.



Scheme 1.

These diallyl esters are in principle able to undergo two dCr reaction cycles within the same molecule. We anticipated that substrates such as **5** would be converted into monorearrangement products **6** when subjected to the mild reaction conditions shown to be effective for substrates **3** (Scheme 2). Further reaction of **6** was not expected, since although sulfonylesters **6** are themselves substrates for a second dCr reaction cycle, they lack the additional electron-withdrawing α-substituent necessary for reaction at ambient temperature. Intramolecular competition experiments have been reported previously[9–13] for the Claisen and related rearrangements.

Keywords: Carboxylation; Claisen rearrangement; Microwave-assisted synthesis; Regioselectivity; Substituent effects.
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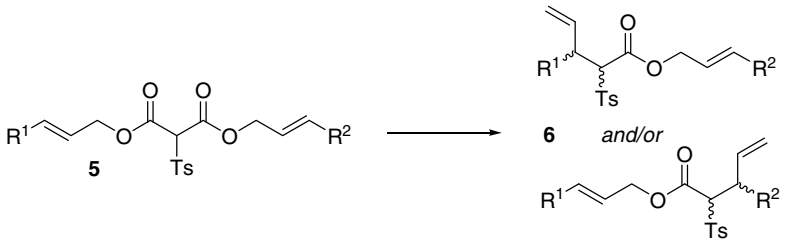
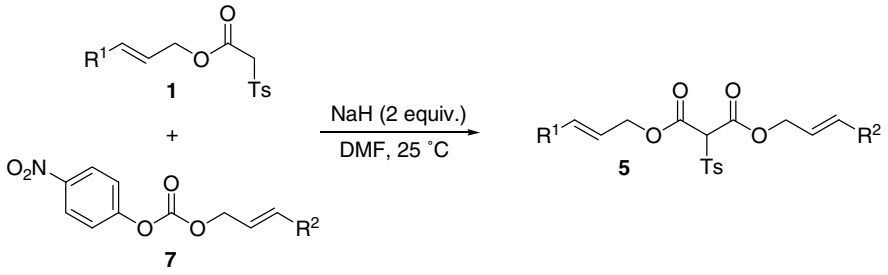


Scheme 2.



Scheme 3.

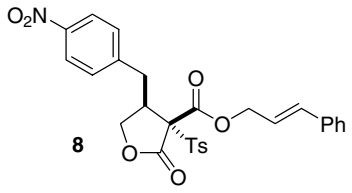
However, the substrates utilised possessed a single ester grouping, which was derived from a doubly allylic secondary alcohol. Additionally, competition in the decarboxylative variant has not been studied to date.

Previously,[8] 2-tolylsulfonylmalonate dCr substrates **3** were synthesised by sulfonylation of the corresponding malonates with tosyl fluoride under basic conditions at high concentration. In the present study, we adopted an alternative synthetic approach based on C-carboxylation. Esters **1** were generated[14] by straightforward acylation of allylic alcohols using commercially available tosylacetic acid (DIC, CH_2Cl_2, 0 °C→25 °C; 65–94% yields). Carbonates **7** were prepared[14] by the reaction of allylic alcohols with 4-nitrophenyl chloroformate (Et_3N, CH_2Cl_2, 0 °C→25 °C; 76–91% yields). Reaction of the sodium salts of **1** with **7** provided diallyl 2-sulfonylmalonates **5** in moderate yields (Scheme 3, Table 1).

Table 1. Synthesis of diallyl 2-sulfonylmalonates **5**

Entry	R^1	R^2	Product	Yield (%)
1	4-$MeOC_6H_4$	*E*-MeCH=CH	**5a**	16
2	4-$MeOC_6H_4$	C_6H_5	**5b**	39
3	*E*-MeCH=CH	C_6H_5	**5c**	30
4	Et	C_6H_5	**5d**	46
5	H	C_6H_5	**5e**	56
6	C_6H_5	$Me_3SiC{\equiv}C$	**5f**	2
7	$Me_3SiC{\equiv}C$	C_6H_5	**5f**	28
8	4-$O_2NC_6H_4$	C_6H_5	**5g**	23
9	$Me_3SiC{\equiv}C$	H	**5h**	17

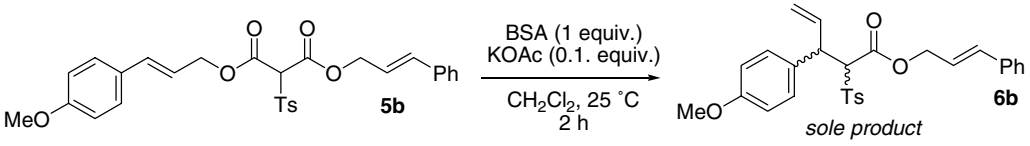
During the synthesis of **5g**, γ-lactone **8** was formed as a by-product in 35% yield (entry 8), presumably by intramolecular 5-*exo-trig* addition of the 2-sulfonylmalonyl enolate to the 4-nitrostyryl group.[15]



With a variety of dCr substrates **5** in hand, their rearrangement behaviour was studied. Substrate **5b** underwent smooth dCr reaction at 25 °C in 2 h, furnishing a 1:1 diastereomeric mixture of rearrangement product **6b** *as a single regioisomer* in high yield (Scheme 4).

That the products were those of methoxycinnamyl sidechain rearrangement was confirmed by X-ray crystallographic analysis[16] of one of the diastereomers **6b** (Fig. 1). Encouraged by this complete regioselectivity, we explored the rearrangement reactions of substrates **5a** and **5c**–**h** (Scheme 5). The results of all the dCr reactions of **5** are collected in Table 2.

Several features of these results merit comment. Firstly, the complete regioselectivity observed for substrate **5b** was seen for many of the other substrates also. It seems unlikely that the remote vinylic substituents on the



Scheme 4.

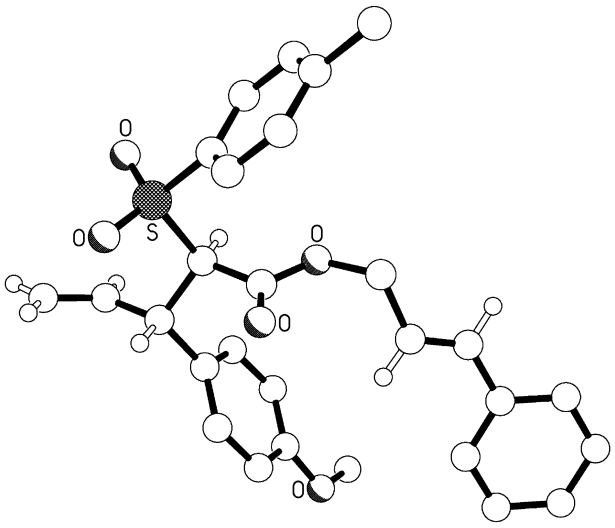


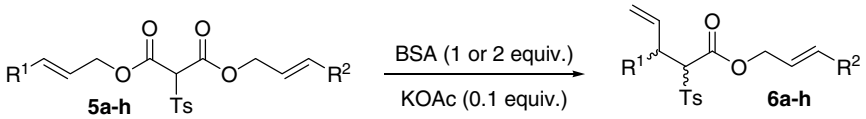
Figure 1. The molecular structure of one of the diastereomers **6b**.

allylic moieties have an influence upon the regiochemistry of silyl ketene acetal formation. Facile interconversion of the regioisomers may take place in a bimolecular fashion, via acetate-mediated desilylation–resilylation or intramolecularly, by a [1,5]-silatropic shift.[17] Following this analysis we interpret the selectivity in terms of the inherent reactivity of the competing allylic groups. The only substrates for which total regioselectivity was not observed were **5d** and **5g** (entries 4 and 7). In these instances the phenyl-substituted side-chain was more reactive.

Overall, a preference for the reaction of electron-rich side-chains was observed. As indicated in Table 2, substrates with less electron-rich side chains required higher reaction temperatures and longer reaction times, and yields of **6** were lower. In the most extreme instance, substrate **5h** was found to be inert to conventional thermal conditions, and use of microwave irradiation was necessary to induce rearrangement, giving **6h** in modest yield.[18]

It seems likely that dCr reaction selectivity is influenced by steric as well as electronic factors. For example, the unexpected skipped diene product **5c**, in which conjugative stabilisation has been lost, may arise from the less sterically congested of the two possible regioisomeric transition states. The electronic effect is demonstrated unambiguously by substrates **5b** and **5g**, in which differing aryl *para*-substituents are distant from the reactive array and therefore will not sterically influence the regioselectivity. For substrates **5f** and **5h** we ascribe the low reactivity of the trimethylsilylethynyl-substituted allyl moiety to the electron-withdrawing nature of silicon.

Precedent does exist for rate enhancement in the Ireland–Claisen rearrangement with an electron-donating substituent on the terminal alkene carbon atom of the allylic moiety. Curran has shown[19] that the presence of an oxygen atom in this position leads to an increase in the rate of one or more orders of magnitude. This effect (which has been studied computationally[20]) is rationalised as a 'vinylogous anomeric' ($\pi \rightarrow \sigma^*$) stabilisation[19d,21] of the transition state, in that weakening of the allylic C–O bond facilitates its cleavage upon going to an early transition state,[22,23] in which bond-breaking may be significantly more advanced than bond-making.[24] The observations that an oxygen substituent at the allylic position leads to a similar rate acceleration,[19e] and that solvent effects[19e,23c] and H-bonding additives[19f] are significant provide further support for the idea of a dipolar transition state. Such an argument could equally



Scheme 5.

Table 2. Decarboxylative rearrangement reactions of diallyl 2-sulfonylmalonates **5a**–**h**

Entry[a]	Substrate	Product	R^1	R^2	T (°C)	t (h)	Yield (%)
1	**5a**	**6a**	4-$MeOC_6H_4$	*E*-MeCH=CH	0	2	95
2	**5b**	**6b**	4-$MeOC_6H_4$	Ph	25	2	81
3	**5c**	**6c**	*E*-MeCH=CH	Ph	25	16	79
4[b,c]	**5d**	**6d**	Ph	Et	55	4	84[d]
5[b,c]	**5e**	**6e**	Ph	H	110	16	66
6	**5f**	**6f**	Ph	$Me_3SiC{\equiv}C$	25	16	82
7	**5g**	**6g**	Ph	4-$O_2NC_6H_4$	25	16	29[e]
8[f]	**5h**	**6h**	H	$Me_3SiC{\equiv}C$	130	0.08	26

[a] Reactions were carried out in CH_2Cl_2 using 1.0 equiv of BSA unless otherwise stated.
[b] Toluene was used as a solvent.
[c] 2.0 equiv of BSA was used.
[d] The product was formed as a 3:1 mixture of regioisomers **6d** (R^1 = Ph, R^2 = Et) and **6d** (R^1 = Et, R^2 = Ph).
[e] The product was formed as a 3:1 mixture of regioisomers **6g** (R^1 = Ph, R^2 = 4-$O_2NC_6H_4$) and **6g** (R^1 = 4-$O_2NC_6H_4$, R^2 = Ph).
[f] Reaction was carried out under microwave irradiation conditions.

be applied to our substrates **5a,b**, albeit with the conjugated oxygen further removed from the reacting array.

In summary, electronic selectivity of the decarboxylative Claisen rearrangement in bifunctional substrates has been demonstrated. We have recently completed a quantitative kinetic study of these effects.[25] Current investigations in our laboratory are directed towards effecting the double rearrangement of diallyl 2-sulfonylmalonates **5** and employing the resultant 1,6-dienes in the synthesis of carbocyclic and heterocyclic natural and unnatural products. The results of these investigations will be reported in due course.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.130.

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16. The structure was solved for the more crystalline diastereoisomer of **6b**, which was crystallised selectively from the mixture. In general, mono-dCr reactions of substrates **5** gave products **6** in diastereoisomeric ratios between 1:1 and approximately 2:1. We thank Dr. A. J. P. White (Imperial College) for the analysis. *Crystal data for* **6b**: $C_{28}H_{28}O_5S$, $M = 476.56$, monoclinic, *Pn* (no. 7), $a = 8.1024(11)$, $b = 6.0389(19)$, $c = 25.8931(15)$ Å, $\beta = 91.852(13)°$, $V = 1266.3(4)$ Å^3, $Z = 2$, $D_c = 1.250$ g cm^{-3}, μ(Cu-Kα) $= 1.426$ mm^{-1}, $T = 293$ K, colourless prisms, Bruker P4 diffractometer; 2035 independent measured reflections, F^2 refinement, $R_1 = 0.055$, $wR_2 = 0.128$, 1277 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 120°$], 297 parameters. The absolute structure of **1** was determined by a combination of *R*-factor tests [$R_1^+ = 0.0545$, $R_1^- = 0.0569$] and by use of the Flack parameter [$x^+ = +0.13(9)$, $x^- = +0.87(9)$]. CCDC 658206.
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