Transannular, decarboxylative Claisen rearrangement reactions for the synthesis of sulfur-substituted vinylcyclopropanes†

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Received in XXX, XXX Xth XXXXXXXX 200X, Accepted Xth XXXXXXXX 200X
First published on the web Xth XXXXXXXX 200X
DOI: 10.1039/b000000x

Unsaturated ε-lactones bearing an α-arylsulfonyl or α-arylsulfoximinyl substituent undergo stereoselective transannular decarboxylative Claisen rearrangement to give substituted vinylcyclopropanes.

Since the first report nearly 40 years ago, the Ireland–Claisen rearrangement has become a mainstay of organic synthesis, due to its ability to deliver the products of reliably regiospecific and stereoselective C–C bond formation. The decarboxylative Claisen rearrangement (dCr) reaction is a catalysed variant of the Ireland–Claisen rearrangement which has been developed in our laboratory. In this reaction, exposure of allylic sulfonylacettes 1 to N,O-bis(trimethylsilyl)acetamide (BSA) and KOAc under relatively mild conditions allows access to homoolylic sulfones 2 in good to excellent yields (Scheme 1).

We have demonstrated the utility of the dCr reaction in diverse synthetic contexts, including dearomatisation of heteroaromatic substrates, de novo synthesis of pyridines and natural product total synthesis. We have also studied the relationship between substrate structure and reactivity in the dCr reaction of tosylmalonate substrates.

This communication presents an application of the dCr methodology to α-sulfonyl and α-sulfoximinyl ε-lactones. We envisaged that such cyclic substrates would be able to undergo ring contraction by means of a transannular dCr, to give 2-vinylcyclopropylsulfone and -sulfoximines respectively. Claisen rearrangements of α-unsubstituted ε-lactones have been reported by Funk and Knight. These reactions gave products having cis-disposed carboxylic acid and allyken groups (e.g. 4), arising from the imposition of (E)-geometry on silyl ketene acetal formation, and the constraint of the subsequent rearrangement to a single accessible boat-like transition state (Scheme 2a). In the present work, the relative stereochemistry of the decarboxylated cyclopropanes is dictated by the protonation of the cyclopropyl anion arising from decarboxylation, and was not precedent (Scheme 2b).

The first substrate studied was the readily accessible α-tosyl-ε-lactone 13. MonoproTECTED diol 8 was mesylated, and the resultant sulfonate ester 9 used to alkylate the sodium enolate of tert-butyl sulfonylacate 10; subsequent deprotection and cyclisation gave 13. Subjection of 13 to dCr conditions at room temperature gave carboxylic acid 14 in quantitative yield. Under more forcing conditions, cyclopropylsulfone 15 was the sole product obtained; we ascribe the complete trans selectivity to anion equilibration to the less sterically-hindered product (Scheme 3).

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It seems likely that the facile nature of the Ireland–Claisen rearrangement of 13 in comparison with those of acyclic allylic tosylacetates stems from the favoured adoption of the reactive conformation because of the constraints on the vinylic and allylic moieties imposed by the ring. Presumably, spontaneous decarboxylation is disfavoured in comparison with the malonate substrates studied previously in the dCr reaction, because of the lesser degree of stabilisation of incipient negative charge α- to the sulfur atom. Additionally, the C–C bond to be cleaved upon extrusion of CO₂ is unusually strong due to orbital rehybridisation in the cyclopropane ring.

This chemistry allows access also to cyclopropanes possessing quaternary centres. Subjection of substrates 16a–c (prepared from the corresponding monoprotected Z-allylic mesylates in a manner analogous to 13, using either t-butyl or methyl tosylacetate)† to microwave-assisted dCr conditions once again provided decarboxylated cyclopropylsulfoxones 17a–c and 18a–c in good yield (Scheme 4, Table 1). Mixtures (3:2) of 17 and 18 were formed in all cases, as evidenced by ¹H nmr analysis: in 17a–c, the olefinic –CH=CH₂ signals appeared some 0.8 ppm downfield from the corresponding resonances in 18a–c. The moderate diastereoselectivity is ascribed to steric interactions of the tosyl group with a quaternary centre substituent, which are present regardless of the relative configuration of the sulfone carbon atom.

Scheme 4 Reagents and conditions (i) 1.0 equiv BSA, 0.1 equiv KOAc, DMF, microwave, 160 °C, 10 min.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ar</th>
<th>Products</th>
<th>Total yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16a</td>
<td>–C₆H₅</td>
<td>17a = 18a</td>
<td>87</td>
</tr>
<tr>
<td>16b</td>
<td>–2,4-C₆H₄F₂</td>
<td>17b = 18b</td>
<td>75</td>
</tr>
<tr>
<td>16c</td>
<td>–2,6-C₆H₄F₂</td>
<td>17c = 18c</td>
<td>82</td>
</tr>
</tbody>
</table>

† Isolated yield. Ratio 17:18 = 3:2 in each instance.

The final part of this study looked at asymmetric induction from stereocentres outside the pericyclic array. In our previous work,¹⁵ diastereomeric ratios of up to 87:13 had been realised for acyclic substrates analogous to 1 bearing an N-trisylsulfoximinoyl group in place of the sulfone. Initial experiments focussed on substrates 19 and 20; these are chiral-at-sulfur analogues of the sulfone-containing substrate 13, and were synthesised in analogous manner, using the corresponding sulfoximine-substituted acetate ester in place of tosylacetates.¹⁶ Disappointingly, although dCr reactions of 19 and 20 gave respectively the cyclopropylsulfoximines 21 and 22 in good yield and with complete anti selectivity, in both cases the products were formed as 3:2 diastereoisomeric mixtures; the major isomers were not assigned (Scheme 5).

In an effort to enhance diastereomeric ratios by increasing the steric demand within the allylic motif, the more highly-substituted substrates 23a–c were evaluated as chiral analogues of 16; these compounds were synthesised analogously to 13 and 16.¹⁷ The dCr reactions of 23 each gave mixtures of four diastereoisomers 24–27. In each case, the resolution of vinylic signals in the ¹H nmr spectra of crude dCr reaction products allowed unambiguous evaluation of the stereoselectivities, and was again invaluable in structure assignment.† In isomers 24 and 25 having syn vinyl and sulfoximine groups, double doublets characteristic of the internal vinyl protons again appeared between 0.5 and 0.8 ppm downfield from those in the two anti isomers 26 and 27, presumably because of anisotropic deshielding by the sulfoximine moiety. These relative stereochemical assignments were supported in the case of products 24b–27b (Ar = 2,4-F₂C₆H₃) by the observation of noe enhancements, which indicated proximity of the sulfoximine α-methylene proton to the vinyl group in the case of the major anti isomer 26b, and to the difluorophenyl group in the case of the syn isomer 24b and 25b. The stereochemistry of the minor syn isomer 25b was unequivocally assigned by X-ray crystallographic analysis,¹⁸ and the structure of major syn isomer 24b was inferred accordingly. The structures of the major and minor anti isomers followed from those of the syn compounds, since the configuration of the quaternary centre is set during the pericyclic process, and is unaffected by the subsequent in situ decarboxylation step. The dCr reactions of 23a–c are shown in Scheme 6, and the results collected in Table 2.

Scheme 5 Non-selective dCr reactions of 19 and 20 Reagents and conditions (i) BSA (1.0 equiv.), KOAc (0.1 equiv.), DMF, microwave, 160 °C, 10 min.

Scheme 6 dCr Reactions of 23 Reagents and conditions (i) BSA (1.0 equiv.), KOAc (0.1 equiv.), DMF, microwave, 160 °C, 10 min.
Table 2 dCr reactions of α-sulfoximinyl-γ-aryl-ε-lactones 23.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ar</th>
<th>Products</th>
<th>Ratio$^a$</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>23a</td>
<td>C$_5$H$_5$</td>
<td>24a:25a:26a:27a</td>
<td>44:22:26:7</td>
<td>78</td>
</tr>
<tr>
<td>23b</td>
<td>2.4-C$_6$H$_4$:F$_2$</td>
<td>24b:25b:26b:27b</td>
<td>44:16:33:7</td>
<td>70</td>
</tr>
<tr>
<td>23c</td>
<td>2.6-C$_6$H$_4$:F$_2$</td>
<td>24c:25c:26c:27c</td>
<td>49:11:36:4</td>
<td>71</td>
</tr>
</tbody>
</table>

$^a$ Ratios based on $^1$H nmr analysis of crude products

$^b$ Isolated yield.

In summary, we have described the first transannular decarboxylicative Claisen rearrangements, and have demonstrated their use in the stereoselective formation of quaternary centres. Extension of this methodology to larger rings, and use in total synthesis will be reported in due course.

We thank EPSRC (grant XXX), Hoffmann–La Roche (supported studentship to S. G.) and Pfizer (supported XXX studentship to S.E.L.) for support.

Notes and references

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$^†$ Electronic Supplementary Information (ESI) available: Experimental details and full spectroscopic data for all novel compounds, crystallographic data for compound 25b. See DOI: 10.1039/b000000x/1

2. For reviews of the Ireland–Claisen rearrangement, see: (a) S. Pereira and M. Srebnik, Aldrichimica Acta, 1993, 26, 17; (b) Y. Chai, S. Hong, H. A. Lindsay, C. McFarland and M. McIntosh, Tetrahedron, 2002, 58, 2905.
17. Substrate 19 was synthesised as the $R_s$ enantiomer; substrate 20 was synthesised as the $S_s$ enantiomer.
18. Crystal data for 25b: C$_{23}$H$_{15}$:F$_2$:NO$_2$:S$_2$, M = 585.75, orthorhombic, Pca$_2$(, no. 29), a = 11.4277(3), b = 11.7915(3), c = 22.8410(5) Å, V = 3077.82(13) Å$^3$, Z = 4, D$_m$ = 1.264 g cm$^{-3}$, μ(Mo-Kα) = 0.218 mm$^{-1}$, T = 173 K, colourless platy needles, Oxford Diffraction Xcalibur 3 diffractometer; 6964 independent measured reflections ($R_{int}$ = 0.0560), $F^2$ refinement, $R_1$ (obs) = 0.0472, $wR_2$(all) = 0.0918, 4734 independent observed absorption-corrected reflections ($|F| > 4σ(|F|)$), 2θ$_{max}$ = 61°. 366 parameters. The absolute structure of 25b was determined by a combination of R-factor tests [$R_1$ = 0.0472, $R_1$ = 0.0479] and by use of the Flack parameter [$x^2$ = 0.00(6), $x^1$ = 1.00(6)], CCDC xxxx.