Intramolecular C–H insertions adjacent to sulfur for the diastereoselective synthesis of thienofuranones

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A new approach to the diastereoselective synthesis of thienofuranones is described in which an intramolecular 1,5-carbenoid C-H insertion adjacent to sulfur features as a key step.

It is well established that C–H bonds adjacent to oxygen or nitrogen are activated towards insertion by metal carbenoids.^{1–3} By contrast, C–H insertions adjacent to sulfur are extremely rare due to the facile capture of the carbenic intermediate by the heteroatom leading to sulfonium ylide formation.⁴ Indeed, to the best of our knowledge, the only reported example of C–H insertion adjacent to sulfur was noted as a minor pathway during ylide formation.⁵ We reasoned that for substrates such as diazolactone **1**, cyclisation to the strained bicycle **3** was likely to be slow.⁶ Consequently, 1,5-insertion to **2** might compete,⁷ providing a new route to thienofuranones (Scheme 1).

To test that hypothesis, a series of diazolactones 1a-i were prepared following the four step sequence outlined in Scheme $2.^{8-11}$ Notably, the key deacylative diazo-transfer reaction, *viz.* $7\rightarrow 1$, was readily accomplished using a one pot procedure involving *in situ* generation of triflyl azide under phase transfer conditions.¹¹ Each of the diazolactones 1a-i were then treated with 2 mol% dirhodium(π) acetate. Pleasingly, for substrates **1a–f** the products of 1,5-insertion **2a–f** were attained in good to high yield (Table 1).¹²

Reactions displayed excellent diastereoselectivity, with **1a** and **1b** yielding only the *endo,exo* products **2a** and **2b** respectively.¹³ That preference was significantly reduced in the insertion reaction of diazolactone **1g**, which bares two methyl residues at C5 of the furanone. Indeed, exposure of **1g** to $Rh_2(OAc)_4$ gave a complex product mixture from which *endo*-**2g**, *exo*-**2g** and (5*H*)-furanone **8** were each isolated (Scheme 3).

The diminished diastereoselectivity observed for the reaction of **1g**, in comparison to **1a/b**, may be rationalised using the Doyle model for C–H insertion reactions of metal carbenoids.¹⁴ In the transition state leading to *endo* products (see Fig. 1), non-bonding

Table 1 Rhodium catalysed C-H insertion of diazolactones 1a-f



Scheme 2 Reagents and Conditions: (i) 2,2,6-trimethyl-4H-1,3-dioxin-4-one, xylenes, 150 °C; (ii) Mn(OAc)₃, Cu(OAc)₂, KOAc, AcOH, 75 °C; (iii) R³SH, NaHCO₃, DMSO, 100 °C; (iv) NaN₃, (Tf)₂O, ^{*n*}Bu₄NBr, 2 M NaOH–hexane–MeCN (2 : 1 : 1), 0 °C.



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Fig. 1 Possible transition state model for C–H insertion to afford 2-endosubstituted 7-oxa-3-thia-bicyclo[3.3.0]octanes.

interactions between R², the C4 β -hydrogen and R increase when R² = Me. Therefore other pathways, including *exo* C–H insertion and 1,2-insertion, to butenolide **8**, become more important.

To conclude our study we examined two cases where 1,5-insertion was not possible. Thus, exposure of phenyl sulfide **1h** to $Rh_2(OAc)_4$ gave cycloheptatriene **11** in high yield *via* an intramolecular Büchner reaction,¹⁵ while *tert*-butyl sulfide **1i** gave alcohol **12**, presumably *via* hydrolysis of sulfonium ylide **10** (Scheme 4). No products derived from 1,6-carbenoid C–H insertion were observed in either reaction.

In summary, we have shown that 1,5-carbenoid C–H insertion reactions adjacent to sulfur may proceed efficiently and outpace ylide formation when the latter leads to a strained bicyclic ring system. The method has been used to synthesise a series of



thienofuranones and displays excellent diastereoselectivity. We have also shown that intramolecular Büchner reactions can compete with ylide formation in such cases whereas 1,6-carbenoid C–H insertion reactions do not.

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Notes and references

- For examples of oxygen activated C–H insertions, see: J. Adams and R. Frenette, *Tetrahedron Lett.*, 1987, 28, 4773; J. Adams, M. A. Poupart, L. Grenier, C. Schaller, N. Ouimet and R. Frenette, *Tetrahedron Lett.*, 1989, 30, 1749.
- 2 For examples of nitrogen activated C-H insertions, see: T. C. Smale, *Tetrahedron Lett.*, 1984, **25**, 2913; P. Brown and R. Southgate, *Tetrahedron Lett.*, 1986, **27**, 247.
- For reviews of diazo/carbenoid reactivity, see: M. P. Doyle, *Chem. Rev.*, 1986, **86**, 919; J. Adams and D. M. Spero, *Tetrahedron*, 1991, **47**, 1765–1808; A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385; T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091; M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911.
- 4 A. Padwa and S. F. Hornbuckle, Chem. Rev., 1991, 91, 263.
- 5 A. Padwa, S. F. Hornbuckle, G. E. Fryxell and P. D. Stull, J. Org. Chem., 1989, 54, 817.
- 6 For formation of a four-membered cyclic sulfonium ylide, see: H. M. L. Davies and L. V. Crisco, *Tetrahedron Lett.*, 1987, 28, 371.
- 7 Other examples of cyclisation reactions being biased towards an abnormal course through the inclusion of a five membered ring in the tethering chain include: D. C. Harrowven, N. L'Helias, J. D. Moseley, N. J. Blumire and S. R. Flanagan, *Chem. Commun.*, 2003, 2658; J. W. Dankwardt and L. A. Flippin, *J. Org. Chem.*, 1995, **60**, 2312.
- 8 R. J. Clemens and J. A. Hyatt, J. Org. Chem., 1985, 50, 2431.
- 9 B. B. Snider and B. A. McCarthy, *Tetrahedron*, 1993, **49**, 9447; M. P. Bertrand, H. O. Mahamat, C. Moustrou and J. M. Surzur, *J. Org. Chem.*, 1989, **54**, 5684.
- 10 C. S. Lee, K. I. Lee and A. D. Hamilton, *Tetrahedron Lett.*, 2001, 42, 211; C. S. Lee, K. I. Lee and A. D. Hamilton, *Tetrahedron Lett.*, 2001, 42, 2929.
- 11 N. A. Swain, R. C. D. Brown and G. Bruton, J. Org. Chem., 2004, 69, 122; R. C. D. Brown, C. J. R. Bataille, G. Bruton, J. D. Hinks and N. A. Swain, J. Org. Chem., 2001, 66, 6719.
- 12 Procedure for the rhodium-catalysed C–H insertion of compound **1a**: To a solution of diazolactone **1a** (58 mg, 0.18 mmol) in CH₂Cl₂ (4 mL) at room temperature was added Rh₂(OAc)₄ (2 mg, 2 mol%) and the resulting pink, slowly effervescing (N₂) reaction mixture was stirred for 24 h. The reaction was concentrated *in vacuo* to afford crude furofuranone as a pink gum (61 mg). Purification (SiO₂) eluting with 10–20% EtOAc in hexane gave compound **2a** as a white crystalline solid (38 mg, 0.13 mmol, 72%); mp 136–138 °C (EtOAc/hexane); v_{max} (neat)/cm⁻¹ 1761; δ_{H} (400 MHz, CDCl₃) 7.43–7.30 (10H, m, PhH), 5.43 (1H, d, *J* 6.9, PhCHO–), 4.87 (1H, d, *J* 9.0, PhCHS–), 3.58 (1H, t, *J* 9.0, -O₂CCH–), 3.41 (1H, dddd, *J* 9.0, 6.9, 5.8, 1.0, -SCH₂CH–), 3.27 (1H, dd, *J* 12.6, 5.8, -SCHH–), 3.08 (1H, d, *J* 12.6, -SCHH–); δ_{C} (100 MHz, CDCl₃) 174.5, 139.5, 135.4, 129.1, 128.9, 128.7, 128.5, 125.8, 85.2, 56.8, 54.6, 53.9, 37.0; *m*/z (CI) 314 ([MNH₄]⁺, 100%), 297 ([MH⁺], 96).
- 13 The stereochemistry of 2a was determined by X-ray crystallography; details to be published elsewhere.
- 14 M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri and M. M. Pearson, J. Am. Chem. Soc., 1993, 115, 958.
- 15 E. Büchner and T. Curtius, Chem. Ber., 1885, 18, 2374.