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

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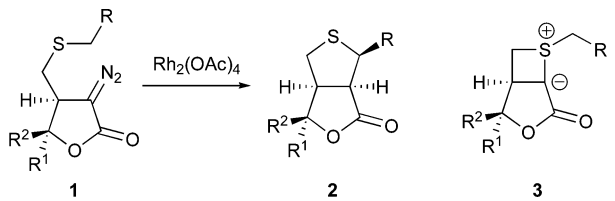
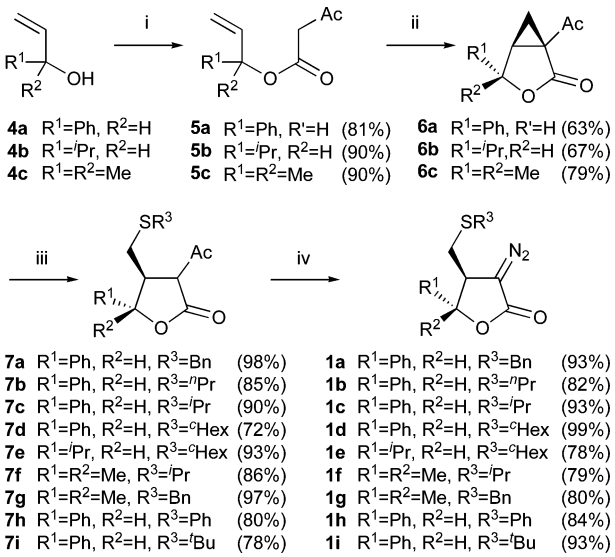
A new approach to the diastereoselective synthesis of thienofuranones is described in which an intramolecular 1,5-carbenoid C–H insertion adjacent to sulfur features as a key step.

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**→**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(II) acetate. Pleasingly, for substrates **1a–f** the products of 1,5-insertion **2a–f** were attained in good to high yield (Table 1).[12]



Scheme 1

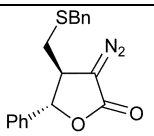
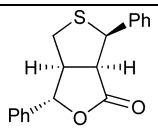
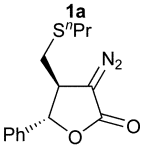
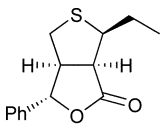
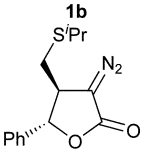
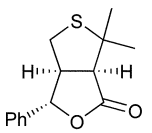
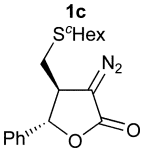
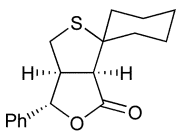
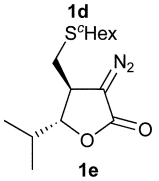
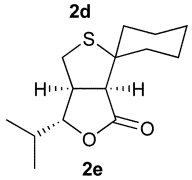
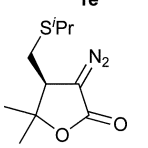
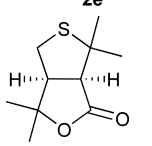


Scheme 2 *Reagents and Conditions*: (i) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylenes, 150 °C; (ii) $Mn(OAc)_3$, $Cu(OAc)_2$, KOAc, AcOH, 75 °C; (iii) R^3SH, $NaHCO_3$, DMSO, 100 °C; (iv) NaN_3, $(Tf)_2O$, $^nBu_4NBr$, 2 M NaOH–hexane–MeCN (2 : 1 : 1), 0 °C.

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**

Entry	Diazolactone	Thienofuranone	Yield (%)[a]
1	 **1a**	 **2a**	72
2	 **1b**	 **2b**	84
3	 **1c**	 **2c**	75
4	 **1d**	 **2d**	59 (from **7d**)
5	 **1e**	 **2e**	75
6	 **1f**	 **2f**	51

[a] Isolated yield.

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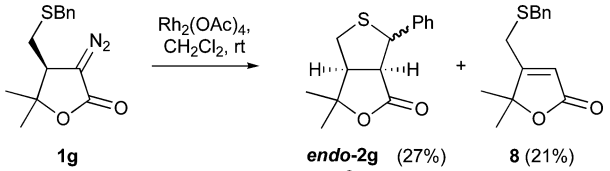


Scheme 3

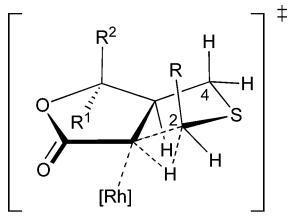
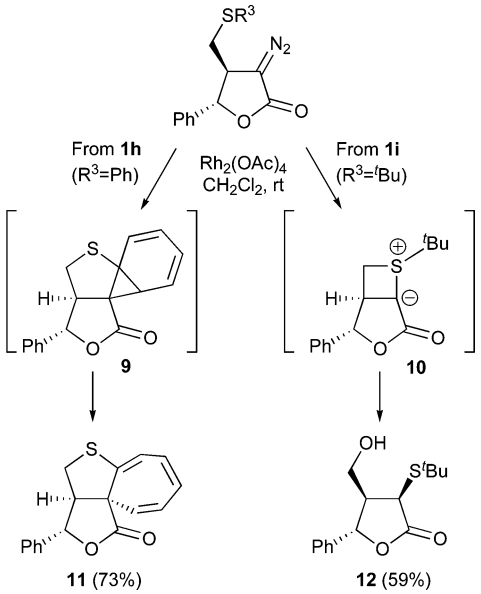


Fig. 1 Possible transition state model for C–H insertion to afford 2-*endo*-substituted 7-oxa-3-thia-bicyclo[3.3.0]octanes.

interactions between R^2, the C4 β-hydrogen and R increase when R^2 = 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.



Scheme 4

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Notes and references

1 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.

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12 Procedure for the rhodium-catalysed C–H insertion of compound **1a**: To a solution of diazolactone **1a** (58 mg, 0.18 mmol) in CH_2Cl_2 (4 mL) at room temperature was added $Rh_2(OAc)_4$ (2 mg, 2 mol%) and the resulting pink, slowly effervescing (N_2) reaction mixture was stirred for 24 h. The reaction was concentrated *in vacuo* to afford crude furofuranone as a pink gum (61 mg). Purification (SiO_2) 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); ν_{max} (neat)/cm^{-1} 1761; δ_H (400 MHz, $CDCl_3$) 7.43–7.30 (10H, m, Ph*H*), 5.43 (1H, d, *J* 6.9, PhC*H*O–), 4.87 (1H, d, *J* 9.0, PhC*H*S–), 3.58 (1H, t, *J* 9.0, $–O_2CCH–$), 3.41 (1H, dddd, *J* 9.0, 6.9, 5.8, 1.0, $–SCH_2CH–$), 3.27 (1H, dd, *J* 12.6, 5.8, –SC*H*H–), 3.08 (1H, d, *J* 12.6, –SCH*H*–); δ_C (100 MHz, $CDCl_3$) 174.5, 139.5, 135.4, 129.1, 128.9, 128.9, 128.7, 128.5, 125.8, 85.2, 56.8, 54.6, 53.9, 37.0; *m*/*z* (CI) 314 ($[MNH_4]^+$, 100%), 297 ($[MH]^+$, 96).

13 The stereochemistry of **2a** was determined by X-ray crystallography; details to be published elsewhere.

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