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Carbon–carbon bond formation on solid support. Application of the classical Julia–Lythgoe olefination

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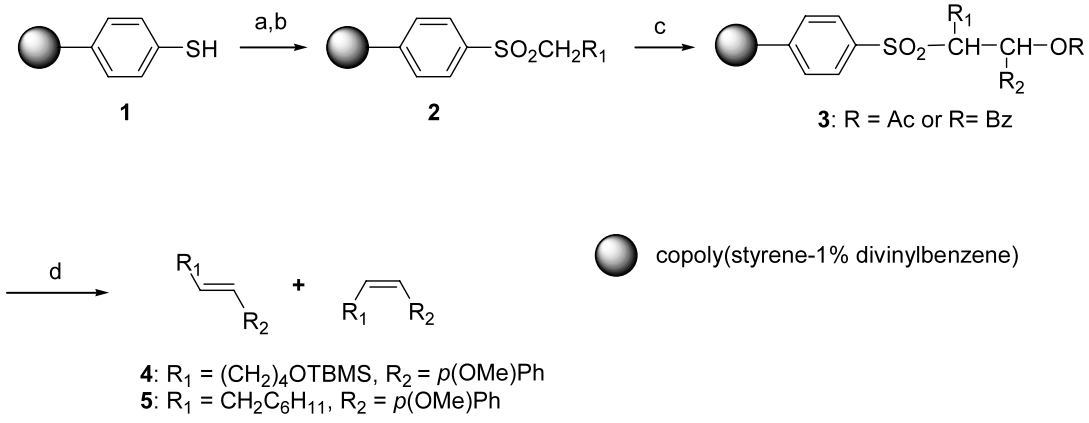
Abstract—Reductive elimination of β-benzoyloxysulfones, obtained via solid-phase organic synthesis, with samarium diiodide in the presence of DMPU favors the formation of *trans*-alkenes.

One of the consequences of the continuous interest in combinatorial chemistry has been the study of solid-phase applications of most existing organic reactions.[1–4] Naturally the carbon–carbon forming processes have received considerable attention. Surprisingly, however, the Julia–Lythgoe olefination,[5–9] one of the standard connective procedures used in synthesis, has, to the best of our knowledge, not been examined in this context. Yet the classical process which involves (a) the synthesis and metallation of a phenylsulfone, (b) the addition of the sulfonyl anion to the aldehyde, (c) the in situ acylation of the resulting β-alkoxysulfone, and (d) the reductive elimination of the resulting β-acyloxysulfone with a single electron donor, is ideally suited for that purpose, since: (i) at two stages, i.e. the synthesis of the phenylsulfone and the addition of the aldehyde, molecular diversity is introduced in the process, and (ii) the loss of a sulfone moiety during the olefin formation (stage d) allows for the development of a sequence in which the phenylsulfone part functions as a traceless linker.[10]

Our long standing interest in the development of analogues of calcitriol[11–13] coupled with a more recent



Scheme 1. *Reagents and conditions*: (a) 12 equiv. KO*t*Bu, THF/DMSO (2/1), rt, 90 min; 2 equiv. R_1CH_2OTs, THF/DMSO (2/1), rt, 18 h; (b) 4 equiv. *m*-CPBA, CH_2Cl_2, rt, 3 h; (c) 5 equiv. *n*Buli, toluene, 0°C to rt, 1 h; 2 equiv. R_2CHO, THF, rt, 18 h; 10 equiv. of Ac_2O (cat. DMAP) or PhCOCl, THF, rt, 18 h; (d) 7 equiv. SmI_2, THF, HMPA or DMPU, rt, 24–48 h.

Keywords: Julia–Lythgoe coupling; solid-phase organic synthesis; samarium diiodide.
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Table 1. Reductive elimination (samarium diiodide, THF) of polymer-bound β-acyloxysulfones **3**.

Entry	R_1	R_2	R	Cosolvent	Yield[a] (%)	*E*:*Z* ratio[b]
1	$(CH_2)_4OTBDMS$	*p*(OMe)Ph	Ac	HMPA	25	50:50
2	$(CH_2)_4OTBDMS$	*p*(OMe)Ph	Ac	DMPU	25	65:35
3	$CH_2C_6H_{11}$	*p*(OMe)Ph	Ac	HMPA	25	50:50
4	$CH_2C_6H_{11}$	*p*(OMe)Ph	Bz	HMPA	29	60:40
5	$CH_2C_6H_{11}$	*p*(OMe)Ph	Bz	DMPU	27	94:6

[a] Overall yield of chromatographically purified material for the following consecutive steps: preparation of thiophenol, coupling with tosylate, oxidation, coupling with aldehyde, benzylation and finally reductive elimination (average yield = ±80%); based on an initial 1.95 mmol/g loading of 4-bromopolystyrene.

[b] Determined via ^1H NMR integration

interest in the generation of small libraries in this area[14,15] led us to investigate the potential of the 'classical' Julia–Lythgoe coupling[16] on solid phase.†

The required solid-phase linked phenylsulfone derivative **2** was obtained starting from the corresponding thiophenol resin **1** (Scheme 1).‡,§ The latter is prepared starting from Novabiochem®'s 4-bromopolystyrene following Fréchet's procedure (*n*-BuLi, S_8, $LiAlH_4$).[19]

After deprotonation of **1** (large excess of KO*t*Bu[20]) the intermediate thiolate was isolated by filtration and subsequently treated with the primary tosylate R_1CH_2OTs ($R_1 = (CH_2)_4OTBDMS$ or $CH_2C_6H_{11}$, 2 equiv., THF/DMSO (2/1), 18 h, 25°C).

After extensive washing (DMF, MeOH, CH_2Cl_2) the resin was oxidized with *m*-CPBA[21,22] (CH_2Cl_2) to the corresponding sulfone **2**. After deprotonation of **2** (*n*BuLi, toluene), the α-sulfonyl carbanion was isolated and reacted with the aldehyde (2 equiv. of anisaldehyde, THF) and the resulting alkoxide directly converted to the corresponding acetate (5 equiv. of Ac_2O, DMAP, THF) or benzoate (benzoyl chloride). In recent adaptations of the classical Julia–Lythgoe olefination the one-electron reducing agent Na(Hg) has been replaced by samarium diiodide.[23–25] In further optimizations co-solvents as HMPA or DMPU have been added.[26] Those were the conditions that we have applied successfully in the reductive elimination of the acylated solid-phase bound phenyl sulfone derivatives **3** which led to the release of a mixture of *E* and *Z* olefins **4** and **5**.[27] The obtained results under different conditions are outlined in Table 1. They show that the observed stereoselectivities are low except for entry 5 involving the use of DMPU as cosolvent and the benzoate as acylated derivative.

A typical procedure (entry 4) is as follows: to 650 mg of resin (0.767 mmol, loading = 1.18 mmol/g) 100 ml 0.1 M SmI_2 in THF[28] was added under argon atmosphere via a double tip needle. After a short period, 5 ml (28.7 mmol) of freshly distilled HMPA were added. The resulting blue–green solution was stirred at room temperature for 48 h. To the above solution, which had turned milky white and turbid, some drops of a 2N HCl solution were added. The mixture was filtered and a saturated $Na_2S_2O_3$ solution added. The mixture was extracted with ether and the combined organic phases were washed with H_2O and brine and finally were dried. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silicagel using iso-octane as eluent, affording 64 mg of alkenes (0.278 mmol).

Application of this sequence to the generation of vitamin D related compounds will be reported in due course.

† The modified process[16] involving reaction of a metallated heteroarylsulfone, whereby the separate reductive elimination step is omitted, has not been considered so far in this work.

‡ An alternative pathway would involve the alkylation of a sulfinate-functionalized resin.[17,18]

§ Reactions were monitored by FT-IR: thiophenol resin **1**: 2566 cm^{-1}; sulfone **2**: 1144 cm^{-1}, 1309 cm^{-1}; acetate **3**: 1745 cm^{-1}; benzoate **3**: 1721 cm^{-1}.

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27. Spectral data for compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H, *Z*-isomer), 0.05 (s, 6H, *E*-isomer), 0.88 (s, 9H, *Z*-isomer), 0.90 (s, 9H, *E*-isomer), 1.54 (m, 4H+4H, *E*+*Z*-isomers), 2.20 (m, 2H, *E*-isomer), 2.34 (m, 2H, *Z*-isomer), 3.60 (t, $J=6.3$ Hz, 2H, *Z*-isomer), 3.63 (t, $J=6.4$ Hz, 2H, *E*-isomer), 3.80 (s, 3H, *E*-isomer), 3.81 (s, 3H, *Z*-isomer), 5.57 (dt, $J=11.6$ Hz, $J=7.2$ Hz, 1H, *Z*-isomer), 6.07 (dt, $J=15.8$ Hz, $J=7.0$ Hz, 1H, *E*-isomer), 6.32 (d, $J=15.5$ Hz, 1H, *E*-isomer), 6.35 (d, $J=10.1$ Hz, 1H, *Z*-isomer), 6.83 (d, $J=8.7$ Hz, 2H, *E*-isomer), 6.87 (d, $J=8.7$ Hz, 2H, *Z*-isomer), 7.22 (d, $J=8.6$ Hz, 2H, *Z*-isomer), 7.27 (d, $J=8.7$ Hz, 2H, *E*-isomer); ^{13}C NMR (500 MHz, $CDCl_3$) δ −5.4 (CH_3, *E*+*Z*-isomers), 18.3 (C, *E*+*Z*-isomers), 25.6 (CH_2, *E*-isomer), 25.9 (CH_3, *E*+*Z*-isomers), 26.2 (CH_2, *Z*-isomer), 28.3 (CH_2, *Z*-isomer), 32.3 (CH_2, *E*-isomer), 32.4 (CH_2, *Z*-isomer), 32.7 (CH_2, *E*-isomer), 55.1 (OCH_3, *Z*-isomer), 55.2 (OCH_3, *E*-isomer), 62.9 (CH_2, *Z*-isomer), 63.0 (CH_2, *E*-isomer), 113.4 (CH, *Z*-isomer), 113.8 (CH, *E*-isomer), 126.9 (CH), 128.1 (CH), 128.6 (CH), 129.1 (CH), 129.8 (CH), 130.6 (C, *Z*-isomer), 130.6 (C, *E*-isomer), 131.3 (CH), 158.0 (C, *Z*-isomer), 158.5 (C, *E*-isomer); IR (KBr): 2953, 2930, 2856, 1608, 1511, 1463, 1248, 1175, 1175, 1102, 1038, 836, 775; MS (EI$^+$) $m/z=263$, 248, 147, 121, 91, 75. Anal. calcd for $C_{19}H_{32}O_2Si$ (320.589): C, 71.18; H, 10.08. Found: C, 70.91; H, 10.31.
    Spectral data for compound **5**: ^{1}H NMR ($CDCl_3$) *Z*-isomer: δ 0.91 (m, 2H), 1.12–1.27 (m, 3H), 1.28–1.36 (m, 1H), 1.63–1.77 (m, 5H), 2.21 (td, $J=7.1$ Hz, $J=1.7$ Hz, 2H), 3.81 (s, 3H), 5.60 (dt, $J=11.7$ Hz, $J=7.2$ Hz, 1H), 6.37 (d, $J=11.7$ Hz, 1H), 6.87 (d, $J=8.7$ Hz, 2H), 7.22 (d, $J=8.7$ Hz, 2H); *E*-isomer: 0.94 (m, 2H), 1.11–1.27 (m, 3H), 1.37 (m, 1H), 1.63–1.77 (m, 5H), 2.07 (td, $J=7.2$ Hz, $J=1.0$ Hz, 2H), 3.80 (s, 3H), 6.07 (dt, $J=15.2$, $J=7.3$ Hz, 1H), 6.29 (d, $J=15.8$ Hz, 1H), 6.82 (d, $J=8.8$ Hz, 2H), 7.28 (d, $J=8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$) *Z*-isomer: δ 27.8 (CH_2), 28.1 (CH_2), 34.7 (CH_2), 37.7 (CH_2) 40.2 (CH), 56.7 (OCH_3), 114.9 (CH), 130.0 (CH), 131.4 (CH), 131.8 (CH), 132.0 (C), 159.5 (C); IR (KBr): 2924, 2851, 1607, 1510, 1448, 1264, 176, 1036, 839, 739, 705; MS (EI$^+$) $m/z=230$, 147. Anal. calcd for $C_{16}H_{22}O$ (230.35): C, 83.43; H, 9.63. Found: C, 83.28; H, 9.68.
28. Samarium(II) iodide is commercially available from Aldrich®.