Synthesis of vinyl epoxides *via* a three-component coupling

Martin W. Rowbottom,[a] **Neil Mathews**[b] **and Timothy Gallagher** *[a]†*

[a] *School of Chemistry, University of Bristol, Bristol, UK BS8 1TS*
[b] *Glaxo Wellcome Research and Development, Medicines Research Centre, Stevenage, UK SG1 2NY*

The butadienylsulfonium species 1 undergoes stepwise addition of a stabilised enolate followed by trapping of the initially formed *S*-ylid 2 with an aldehyde to provide vinyl epoxides 3 in a two-step, three-component process.

The vinyl epoxide moiety,[1] as in **3**, represents a valuable functional group, the construction[2] of which also appears to be well-suited to the use of a tandem strategy.[3] In this paper we describe initial studies directed towards a three-component coupling sequence that makes a variety of vinyl epoxides available in a versatile and efficient fashion. The sequence developed is summarised in Scheme 1 and involves, as the key component, buta-1,3-dienyldimethylsulfonium tetrafluoroborate **1**.[4,5]
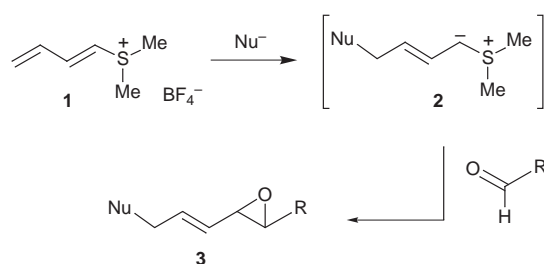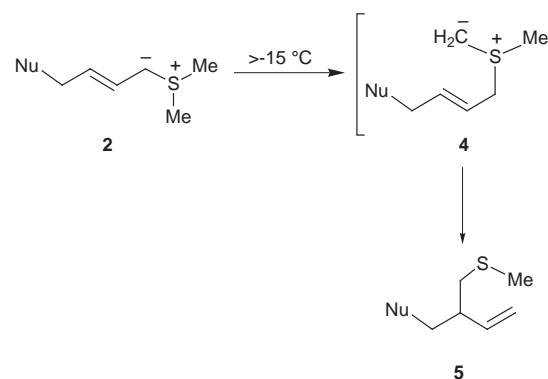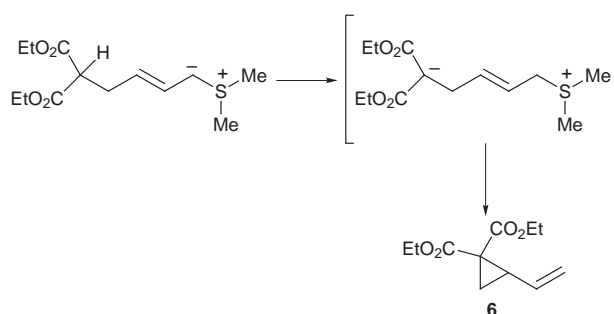

Scheme 1

This electrophilic diene undergoes facile "1,4-addition" of soft nucleophiles (the Na$^+$ salt of a stabilised enolate) to give the sulfur ylid **2**, which is then trapped by the third component—an aldehyde. Work-up followed by chromatography allows isolation of the (*E*)-vinyl epoxide **3** in 31–81% isolated yields.‡ The scope of this tandem reaction sequence has been evaluated in terms of the nucleophilic and carbonyl components used, and the results obtained are illustrated in Table 1.

It is appropriate to comment on the important features associated with the chemistry that is outlined in Scheme 1. The three-component coupling has been carried out in a variety of solvents (EtOH, Et$_2$O, THF), but CH$_2$Cl$_2$ gave consistently higher yields. Nucleophilic addition of the enolate component to **1** only takes place as the reaction mixture is allowed to warm from −40 to −20 °C at which point the aldehyde unit is introduced. The nucleophilic addition step (**1**→**2**) is not efficient at the lower temperature, and an element of care is required. If the reaction mixture is allowed to reach −15 °C (before the aldehyde is added), then the intermediate *S*-ylid **2** undergoes rapid proton transfer (*via* **4**), followed by 2,3-sigmatropic rearrangement to give **5** (Scheme 2).

While the reaction of **2** with aldehydes is generally rapid, attempts to trap this intermediate with either pivaldehyde or cyclohexanone failed; with these electrophiles only the rearrangement pathway corresponding to formation of **5** was observed. With simpler nucleophiles, such as diethyl malonate which contains a second available acidic proton, then internal proton transfer is facile with subsequent loss of Me$_2$S leading to cyclopropane **6**[6] as the major product (Scheme 3). Our attempts to suppress this known[6] cyclopropanation pathway by control of both temperature and the amount of base used have not been successful.

Scheme 2

Scheme 3

While only the (*E*)-alkene geometry has been detected in vinyl epoxides **3**, in all cases both *cis* and *trans* epoxide isomers were produced. Use of unsymmetrical nucleophiles (*e.g.* Table 1, entries 8 and 9) did, however, lead to formation of all four possible diastereomers.§

Finally, at an early point in this study, the quality of the butadienylsulfonium salt **1** that was obtained using the literature procedure[5] was an issue. We have now found that **1** is available as an analytically pure crystalline solid by a simple modification of the original process. This involves purification by continuous extraction (using CH$_2$Cl$_2$) of the crude product, and the yields of vinyl epoxide **3** that are shown in Table 1 are dependent on the use of pure **1**.

In summary, we have demonstrated that vinyl epoxides are readily synthesised using a tandem three-component coupling. Our objective is now to extend the range of viable nucleophiles that can be harnessed to this process in order to then exploit the vinyl epoxide moiety more widely within heterocyclic chemistry.

Experimental

Modified synthesis of buta-1,3-dienyldimethylsulfonium tetrafluoroborate 1[5]

To a stirred solution of 1,4-bis(dimethylsulfonium)but-2-ene dichloride (28.60 g, 115 mmol) in MeOH (200 cm^3) at 0 °C, was added sodium tetrafluoroborate (12.63 g, 115 mmol). After a further 10 min, sodium methoxide (2.36 mol dm^{-3}) was added dropwise until pH 10 was attained, keeping the temperature

Table 1

Entry	Nucleophile (Na$^+$ salt)	Aldehyde	Vinyl epoxide 3^a (% yield)
1	(EtO$_2$C)(EtO$_2$C)C–NHAc	PhCHO	**3a** (58%)
2	(MeCO)(MeCO)C–Me	4-MeOC$_6$H$_4$CHO	**3b** (44%)
3	(MeCO)(MeCO)C–Me	pyridine-CHO	**3c** (43%)
4	(MeCO)(MeCO)C–Me	Me$_2$CHCHO	**3d** (31%)
5	(MeCO)(MeCO)C–Me	C$_7$H$_{15}$CHO	**3e** (53%)
6	(MeCO)(MeCO)C–SPh	PhCHO	**3f** (48%)
7	(EtO$_2$C)(EtO$_2$C)C–Me	PhCHO	**3g** (51%)
8	cyclic β-ketoester, $n = 1,2$	PhCHO	**3h** ($n = 1$, 54%)^b **3i** ($n = 2$, 66%)^b
9	(MeCO)(EtO$_2$C)C–Me	PhCHO	**3j** (81%)^b

^{a} 1:1 Mixture of *cis* and *trans* epoxide isomers and in all cases only (*E*)-alkenes were detected. ^{b} Mixture of the four possible diastereomers.

below 5 °C. After a further 1 h, fluoroboric acid (43 wt% solution in water) was added (to pH 2) and the mixture was filtered, evaporated under reduced pressure and the residue continuously extracted into refluxing CH$_2$Cl$_2$ (500 cm^3) for *ca.* 12 hours. After evaporation under reduced pressure, the residue was purified by recrystallisation from ethanol to give the *sulfonium salt* **1** (15.0 g, 65%) as colourless needles, mp 79–86 °C (ethanol) (Found: C, 35.6; H, 5.6. C$_6$H$_{11}$BF$_4$S requires C, 35.7; H, 5.5%); δ_H (300 MHz; DMSO-d_6) 3.01 (6 H, s, 2 × Me), 5.67 (1 H, br d, J 10.1, 4-H), 5.78 (1 H, br d, J 16.8, 4-H), 6.59 (1 H, m, 3-H), 6.61 (1 H, d, J 14.8, 1-H) and 7.28 (1 H, dd, J 14.8 and 10.9, 2-H); δ_H (300 MHz; D$_2$O) 3.00 (6 H, s, 2 × Me), 5.71 (1 H, m, 4-H), 5.78 (1 H, m, 4-H), 6.41 (1 H, dd, J 14.8 and 0.7, 1-H), 6.58 (1 H, m, 3-H) and 7.30 (1 H, dddd, J 14.8, 10.7, 0.7 and 0.7, 2-H); δ_C (75 MHz; DMSO-d_6) 27.5, 117.7, 127.8, 133.1 and 146.8; δ_C (75 MHz; D$_2$O) 28.8, 116.0, 129.8, 133.3 and 150.2; *m/z* (FAB) 115 (M$^+$, 100%).

Representative procedure for vinyl epoxide formation. Synthesis of (6R*,7R*) and (6R*,7S*)-(E)-2-acetamido-6,7-epoxy-2-ethoxycarbonyl-7-phenylhept-4-enoic acid ethyl ester 3a

To a stirred solution of diethyl acetamidomalonate (306 mg, 1.41 mmol) in CH$_2$Cl$_2$ (3 cm^3) at r.t., was added sodium hydride (57 mg, 60% dispersion in mineral oil, 1.43 mmol). The mixture was stirred for a further 10 min then was cooled to −40 °C and buta-1,3-dienyldimethylsulfonium tetrafluoroborate (300 mg, 1.5 mmol) was added. The mixture was allowed to slowly warm to −20 °C (over *ca.* 10 min). Benzaldehyde (167 mg, 1.57 mmol) was added and the mixture was allowed to slowly warm to r.t. (over *ca.* 2 hours). The mixture was filtered, evaporated under reduced pressure and the residue was purified by chromatography (eluting with 2:1.5:1.5 petroleum ether (bp 40–60 °C)–dichloromethane–diethyl ether) to give **3a** (309 mg, 58%) as a colourless oil and as a 1:1 (*cis*:*trans* epoxide) mixture

of diastereoisomers (Found: C, 64.0; H, 6.7; N, 3.8. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%); ν_{max}(film)/cm^{-1} 3374 (N–H), 2983, 1745 (ester C=O), 1680 (amide C=O); δ_H (300 MHz; CD_2Cl_2) (samples of each isomer were obtained by careful chromatography and signals assigned to the *trans* epoxide isomer are indicated by *) 1.06 (3 H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.20 (3 H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.24* (6 H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.82 (3 H, s, COMe), 2.00* (3 H, s, COMe), 2.87 (1 H, ddd, *J* 14.2, 8.1 and 1.2, 3-H), 2.97 (1 H, ddd, *J* 14.2, 7.3 and 1.2, 3-H), 3.08* (2 H, dd, *J* 7.5 and 1.2, 3-H), 3.30* (1 H, dd, *J* 7.6 and 1.9, 6-H), 3.60 (1 H, dd, *J* 8.6 and 4.3, 6-H), 3.69* (1 H, d, *J* 1.9, 7-H), 3.89 (1 H, dq, *J* 10.8 and 7.1, $CO_2CH_2CH_3$), 4.04 (1 H, dq, *J* 10.8 and 7.2, $CO_2CH_2CH_3$), 4.13–4.29 (7 H, m, $CO_2CH_2CH_3$ and 7-H), 5.11 (1 H, ddt, *J* 15.4, 8.6 and 1.2, 5-H), 5.45* (1 H, ddt, *J* 15.5, 7.6 and 1.2, 5-H), 5.74* (1 H, m, 4-H), 5.77 (1 H, m, 4-H), 6.60 (1 H, br s, NH), 6.79* (1 H, br s, NH) and 7.24–7.39 (10 H, m, aromatic); δ_C (75 MHz; CD_2Cl_2) 14.1, 14.2, 14.2*, 14.3*, 23.0, 23.2*, 35.9, 35.9*, 59.2, 59.4, 60.5*, 62.5*, 62.9, 63.0, 63.0*, 63.1*, 66.4, 66.4*, 125.8*, 126.7, 128.1, 128.6, 128.6*, 128.9*, 129.2*, 129.6, 131.3, 132.6*, 135.7, 137.6*, 167.7, 167.8, 167.8*, 167.9*, 169.2 and 169.3*; *m/z* (FAB) 398 (M + Na$^+$, 62%), 376 (M + H$^+$, 100) and 217 (92).

When diethyl acetamidomalonate was allowed to react with **1** under the same conditions as described above but in the absence of an aldehyde, **5** (Nu = C(NHAc)(CO$_2$Et)$_2$) was isolated in 48% yield as a colourless oil (Found: C, 54.4; H, 7.5; N, 4.2. $C_{15}H_{25}NO_5S$ requires C, 54.4; H, 7.6; N, 4.2%); ν_{max}(film)/cm^{-1} 3382 (N–H), 2981, 2916, 1740 (ester C=O) and 1674 (amide C=O); δ_H (300 MHz; CDCl$_3$) 1.25 (3 H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.26 (3 H, t, *J* 7.2, $CO_2CH_2CH_3$), 2.02 (3 H, s, Me), 2.06 (3 H, s, Me), 2.18 (1 H, m, 4-H), 2.44 (1 H, dd, *J* 14.6 and 10.1, CH$_2$), 2.47 (2 H, d, *J* 7.1, CH$_2$), 2.68 (1 H, dd, *J* 14.6 and 2.6, CH$_2$), 4.10–4.30 (4 H, m, 2 × $CO_2CH_2CH_3$), 4.99–5.04 (2 H, m, 6-H), 5.52 (1 H, m, 5-H) and 6.77 (1 H, br s, N-H); δ_C (75 MHz; CDCl$_3$) 13.8, 14.0, 16.2, 23.0, 35.7, 40.0, 41.0, 62.5, 62.6, 65.7, 116.2, 140.5, 167.9, 168.0 and 169.0; *m/z* (FAB) 354 (M + Na$^+$, 32%), 332 (M + H$^+$, 100) and 284 (38).

Acknowledgements

Notes and references

† E-mail: t.gallagher@bristol.ac.uk
‡ Garst[5] has observed "1,4-addition" of a ketone enolate to **1** followed by *intramolecular* trapping of the resulting *S*-ylid (analogous to **2**) to give an epoxide. This reaction necessarily involves the (*Z*)-isomer of the intermediate allylic *S*-ylid but no evidence has been obtained in our studies for the operation of this pathway with any of the ketone-based nucleophiles shown in Table 1.
§ With **3h–j**, signals corresponding to the four diastereomers were apparent in the ^{1}H NMR spectrum but these components could not be separated and were fully characterised as the mixture.

1 For leading references to the applications/reactivity of vinyl epoxides, see: B. M. Trost, *Angew. Chem.*, *Int. Ed. Engl.*, 1989, **28**, 1173; J. A. Marshall, *Chem. Rev.*, 1989, **89**, 1503; T. Hudlicky and J. W. Reed, in *Comprehensive Organic Synthesis*, eds. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 899; S. V. Ley, *Pure Appl. Chem.*, 1994, **66**, 1415. For more recent applications, see A. S. Batsanov, A. L. J. Byerley, J. A. K. Howard and P. G Steel, *Synlett*, **1996**, 401; C. Larksarp and H. Alper, *J. Am. Chem. Soc.*, 1997, **119**, 3709; U. M. Lindstrom, R. Franckowiak, N. Pinault and P. Somfai, *Tetrahedron Lett.*, 1997, **38**, 2027; J. Shim and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 3067; U. M. Lindstrom and P. Somfai, *Synthesis*, **1998**, 109.

2 Epoxidation is widely used to prepare vinyl epoxides: M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang and Y. Shi, *J. Org. Chem.*, 1998, **63**, 2948 and citations therein. Leading references to other preparative methods; (*a*) from glycidic esters: P. S. Vankar, I. Bhattacharya and Y. D. Vankar, *Tetrahedron: Asymmetry*, 1996, **7**, 1683; (*b*) from allyl S, Te and As salts: Z.-L. Zhou, Y.-S. Sun, L.-L. Shi and Y.-Z. Huang, *Tetrahedron Lett.*, 1990, **31**, 7657; J. D. Hsi and M. Koreeda, *J. Org. Chem.*, 1989, **54**, 3229; A. Osuka and H. Suzuki, *Tetrahedron Lett.*, 1983, **24**, 5109; J. B. Ousset, C. Mioskowski and G. Solladie, *Tetrahedron Lett.*, 1983, **24**, 4419; M. J. Hatch, *J. Org. Chem.*, 1969, **34**, 2133; R. W. LaRoochelle, B. M. Trost and L. Krepski, *J. Org. Chem.*, 1971, **36**, 1126; (*c*) from chlorohydrins and related precursors: S. Jayaraman, S. Hu and A. C. Oehlschlager, *Tetrahedron Lett.*, 1995, **36**, 4765; M. Julia, J. N. Verpeaux and T. Zahneisen, *Bull. Soc. Chim. Fr.*, 1994, 539; K. Mallaiah, J. Satyanarayana and H. Junjappa, *Tetrahedron Lett.*, 1993, **34**, 3145; (*d*) using other asymmetric oxidation methods: R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH Publishers, New York, 1993, pp. 103–158.

3 T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York, 1992; R. A. Bunce, *Tetrahedron*, 1995, **51**, 13103; P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195.

4 H. Braun, N. Mayer and G. Kresze, *Liebigs Ann. Chem.*, 1972, 111; H. Braun, N. Mayer, G. Strobl and G. Kresze, *Liebigs Ann. Chem.*, 1973, 1317; H. Braun, G. Huber and G. Kresze, *Tetrahedron Lett.*, 1973, 4033.

5 M. E. Garst, *J. Org. Chem.*, 1979, **44**, 1578; M. E. Garst and P. Arrhenius, *J. Org. Chem.*, 1983, **48**, 16.

6 H. Braun and G. Huber *Tetrahedron Lett.*, **1976**, 2121.

7 D. A. Fletcher, R. F. McMeeking and D. J. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.

Communication 8/07805J