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Stereoselective synthesis of electrophilic spirocyclopropanes in ionic liquids

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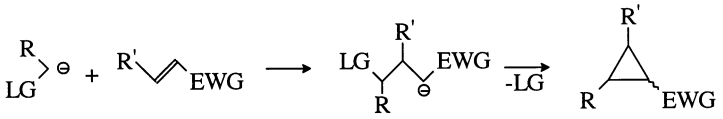
Abstract

The reaction of β-oxosulfides of benzothiazole with Michael acceptors, in liquid tetrabutylammonium bromide and sodium bicarbonate as base, allows a stereoselective synthesis of spirocyclopropanes.

Keywords: cyclopropanation; stereocontrol; ionic liquids; benzothiazole; sulfides.

Cyclopropane derivatives have gained importance in the field of natural and non-natural products for their insecticidal, cytostatic and antiinfective properties, such as those of the antibiotic ciprofloxacin.[1] A widely explored synthesis of electrophilic cyclopropanes involves a cyclization reaction initiated by the conjugate addition of suitable nucleophiles, such as α-halo,[2–4] α-sulfide,[5] α-sulfinate[6] and α-sulfonate carbanions,[7,8] to an electron-deficient alkene, followed by expulsion of the leaving group (Scheme 1). However, this conceptually simple synthetic methodology presents some drawbacks such as the use of toxic solvents, strong bases, lack of stereoselectivity and easy ring cleavage of the electrophilic spirocyclopropanes by nucleophiles.[9]



Scheme 1. LG = Br; Cl; SR; SOR, SO_2R. R = CO_2R; CN; COAr, EWG = CO_2R; NO_2; CN; COAr

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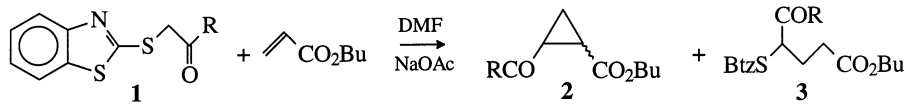
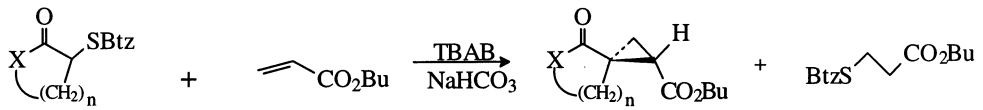
To circumvent some of these problems, in the first instance, we chose as pronucleophiles β-ketosulfides of benzothiazole **1**, which are easily deprotonated by weak bases,[10] butyl acrylate as the Michael acceptor and sodium acetate as the base in DMF or DMA as solvents (Scheme 2).



Scheme 2.

Although the *S*-benzothiazolyl group proved to be a good leaving group, the results were disappointing as the reaction afforded a mixture of cyclopropane isomers **2** and the Michael addition product **3**, in low yield and these were difficult to isolate from the reaction medium.

Owing to our interest in the use of ionic liquids,[11] we substituted DMF (harmful solvent) with tetrabutylammonium bromide (TBAB) in the presence of sodium bicarbonate as base. Surprisingly, in the reactions of cyclic and acyclic carbonyl sulfides of benzothiazole (**5**, **7**, **9**, **11**, **13**) with butyl acrylate, we observed the formation, in one-step, of *trans* spiro or simple cyclopropanes (**6**, **8**, **10**, **12**, **14**) with good yields and a high degree of stereoselectivity (Scheme 3, Table 1, runs 1–5).

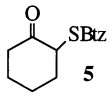
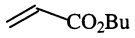
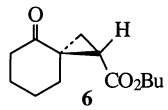
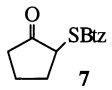
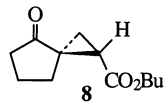
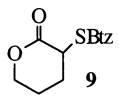
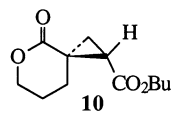
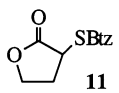
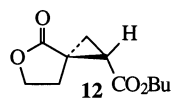
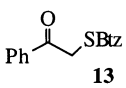
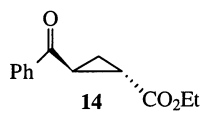
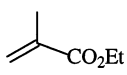
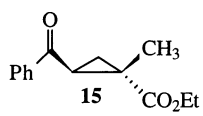
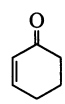
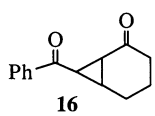


Scheme 3.

Besides water and carbon dioxide, the Michael addition by-product (**4**) of the *S*-benzothiazolyl leaving group and acrylate was also formed. Therefore, the use of a mild base and the formation of neutral by-products, may enable the survival of more reactive cyclopropanes towards acidic or basic reagents. Different Michael acceptors, like methacrylate or enones (runs 6–7), may be successfully used to give trisubstituted and condensed cyclopropanes **15** and **16**, respectively, together with the corresponding, different by-products. In order to account for the observed stereoselectivity, we believe that both steric interactions between the two carbonyl groups and the high solvent polarity may influence the stereoselectivity of these cyclopropanations.[12,13]

An additional merit of these reactions lies in the simple separation procedure[14] of the reaction products from the ionic liquid. Cyclopropanes are isolated by vacuum distillation or Soxhlet extraction with hexane, thus allowing recycling of the ionic liquid. Work is in progress studying the stereospecificity of cyclopropanations under these conditions.

Table 1
Synthesis of cyclopropanes in TBAB[a]

Run	Pronucleophile[b]	Acceptor	t/h	Product[c]	Yield (%)[d]
1	 **5**		0.6	 **6**	60
2	 **7**	" "	2	 **8**	56
3	 **9**	" "	2.3	 **10**	70[e]
4	 **11**	" "	2	 **12**	65
5	 **13**	" "	3.5	 **14**	84[e]
6	" "		6	 **15**	82
7	" "		5.5	 **16**	80

[a] Reactions performed in liquid TBAB at 110 °C. [b] Prepared by reaction of α-bromoketones or lactones with 2-thiobenzothiazole. [c] Structures of all compounds determined by spectroscopic ^{1}H, ^{13}C NMR, IR and mass spectra. [d] GC yields with diethylene glycol dibutyl ether as internal standard. [e] Isolated yields

Acknowledgements

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References

1. In *Houben-Weyl, Methods of Organic Chemistry*; de Meijer, A. Ed.; Thieme Stuttgart–NY, 1997; Vol. E 17 a.
2. (a) Jonczyk, A.; Makosza, M. *Synthesis* **1976**, 387. (b) Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 4215–4218.
3. Saba, A. *Gazz. Chim. Ital.* **1991**, *121*, 55.
4. Le Menn, J.-C.; Tallec, A. *Can. J. Chem.* **1991**, *69*, 761–767.

5. Ahlbrecht, H.; Ibe, *Synthesis* **1988**, 210.
6. Baker, R.; Spillet, M. J. *J. Chem. Soc., Chem. Commun.* **1966**, 757–758.
7. Krief, A.; De Vos, M. I. *Tetrahedron Lett.* **1985**, *26*, 6115–6116.
8. Krief, A.; De Vos, M. I.; Sevrin, M. *Tetrahedron Lett.* **1986**, *27*, 2283–2286.
9. Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72.
10. Calò, V.; Fiandanese, V.; Nacci, A.; Volpe, A. *Tetrahedron* **1996**, *52*, 2155–2166.
11. Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083.
12. Trost, B. M.; Arndt, H. C. *J. Org. Chem.* **1973**, *38*, 3140–3144.
13. Inouye, Y.; Inamasu, M.; Horiike, M.; Ohno, M. *Tetrahedron* **1968**, *24*, 2907–2920.
14. Typical procedure: a Pyrex reaction flask was charged with tetrabutylammonium bromide (5 g) and heated at 110°C. To the stirred molten salt were added the lactone 9 (1.06 g, 4 mmol), butyl acrylate (1.54 g, 12 mmol) and sodium bicarbonate (0.67 g, 8 mmol). After completion of the reaction, the mixture was extracted in a Soxhlet apparatus with hexane for 1 h. After evaporation of the solvent, the residue was chromatographed on silica gel (eluent, hexane/ethyl acetate 5:1) to give, besides **4**, the spirocyclopropane **10** in a 70% yield as a pale yellow liquid. ^{1}H NMR ($CDCl_3$) (δ ppm): 0.88 (3H, t, $J=7.4$ Hz), 1.32 (1H, dd, $J=6.5$ 4.0 Hz), 1.34 (2H, sextet, $J=7.5$ Hz), 1.57 (2H, quintet, $J=7.5$ Hz), 1.73 (1H, dd, $J=8.7$ 4.0 Hz), 1.80–2.03 (4H, m), 2.50 (1H, dd, $J=8.7$ 6.5 Hz), 4.05 (2H, t, $J=6.3$ Hz), 4.32–4.45 (2H, m).^{13}C NMR ($CDCl_3$) (δ ppm): 13.5, 18.9, 22.9, 23.1, 24.2, 27.3, 29.1, 30.5, 64.8, 70.4, 169.9, 171.9. GC–MS (EI) m/z (%):171 (0.9, M^+-55), 152 (29.8), 124 (100), 79 (23.0), 55 (31.0). IR (liquid film) $\nu=2961$, 1719, 1460, 1402, 1349, 1298, 1263, 1153, 1078, 1018, 940, 802, 749 cm^{-1}. The stereochemistry of the spirocyclopropane **10** has been determined by performing a shift reagent experiment: upon addition of 20 mol% of Eu(fod)$_3$ the absorption of the cyclopropane protons at $\delta=1.32$ (H_C), 1.73 (H_B) and 2.50 (H_A) shift to 2.07, 2.72 and 3.69 ppm, respectively. This indicates that H_B and HA are both *cis* to the lactone carbonyl.