Improved Dimethylsulfoxonium Methylide Cyclopropanation Procedures, Including a Tandem Oxidation Variant

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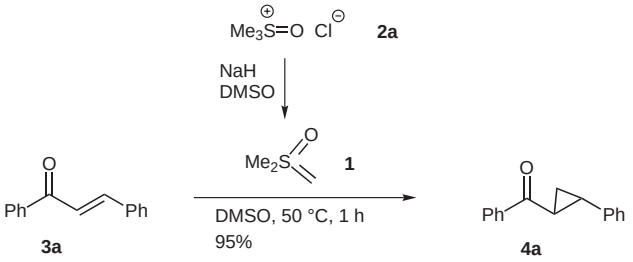
Abstract: A new procedure for the cyclopropanation of α,β-unsaturated carbonyl compounds and related systems is described which employs trimethylsulfoxonium iodide and an organic base in acetonitile to generate dimethylsulfoxonium methylide in situ; in addition, preliminary results are described in which activated alcohols are converted directly into cyclopropyl ketones by a one-pot tandem oxidation–cyclopropanation sequence.

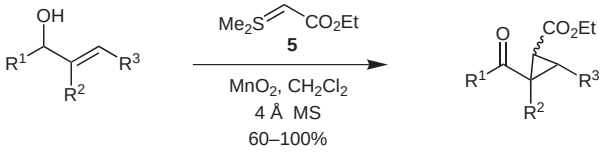
Key words: cyclopropanes, cyclopropanations, tandem oxidation procedures, one-pot procedures

Dimethylsulfoxonium methylide (**1**) has been a mainstay of organic synthesis as a methylene-transfer reagent since its development by Corey and Chaykovsky in the 1960s.[1–4] The standard method for the preparation of this sulfurane reagent involves treatment of the commercially available trimethylsulfoxonium chloride or iodide (**2a**,**b**) with sodium hydride in DMSO,[1] although other solvents (e.g. DMF, THF, dioxane) and bases (e.g. BuLi, *t*-BuOK) have been employed.[2,4] Dimethylsulfoxonium methylide (**1**) has proved particularly valuable for the cyclopropanation of α,β-unsaturated carbonyl compounds and related systems via a conjugate addition–elimination process; in the example shown (Scheme 1), chalcone **3a** is converted into 1-benzoyl-2-phenylcyclopropane (**4a**) in almost quantitative yield by the use of sulfurane **1**.[1c]



Scheme 1

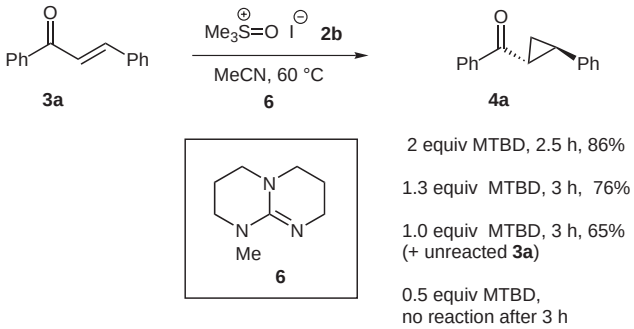
Recently, we have become interested in the preparation of functionalised cyclopropanes and have developed a tandem procedure for the one-pot oxidation–cyclopropanation of allylic alcohols using MnO_2 in conjunction with stabilised sulfuranes such as (carbethoxymethylene)dimethylsulfurane (**5**) (Scheme 2).[5,6]



Scheme 2

In order to complement the above methodology, we wished to explore the use of non-functionalised sulfur ylides to effect methylene transfer. However, in planning this aspect of the investigation, we realised the limitations of the original conditions described by Corey and Chaykovsky. The use of dimsyl sodium in DMSO at 50 °C is fairly stringent, and although a phase-transfer variant has been developed, this also requires prolonged heating in strong base (CH_2Cl_2, TBAI, 50% aq NaOH, 50 °C, 20 h).[4c]

We therefore decided to first investigate simplified procedures for carrying out the cyclopropanation of α,β-unsaturated carbonyl compounds and related systems. Initial studies were carried out using chalcone and trimethylsulfoxonium iodide (**2b**, Scheme 3). A range of organic bases were explored to generate the dimethylsulfoxonium methylide (**1**) in situ and whilst some were totally ineffective (DABCO and Et_3N, no reaction in MeCN at 60 °C after 20 h), under the same conditions others gave good to excellent yields of cyclopropane **4a** (DBU, 2.5 h, 75%; tetramethylguanidine, 19 h, 57%).



Scheme 3

However, the best yields were obtained using the commercially available guanidine base 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (MTBD, **6**)[7,8] which produced the cyclopropanated product **4a** in 86% yield on treatment in MeCN at 60 °C for 2.5 hours

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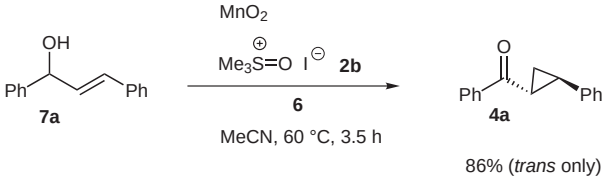
{hexahydro 2*H*-pyrimido[1,2-*a*]pyrimidine (TBD) gave 72% after 2.5 h; polymer-supported TBD gave no reaction after 24 h}. In terms of solvent, the use of MeCN seemed optimal but others were also successful (DMF, 1.5 h, 60 °C, 78%; acetone, 24 h, reflux, 69%; CH_2Cl_2, reflux, 23 h, 72%). The use of 2 equivalents of MTBD gave the highest yields but a lower amount could be employed if longer reaction times were acceptable (Scheme 3). The Corey and Chaykovsky[1c] and the PTC procedure[4c] were both reported to give cyclopropane **4a** as a *cis*/*trans* mixture, and so it is noteworthy that the reactions in Scheme 3 gave only the *trans*-cyclopropane **4a** according to ^{1}H NMR spectroscopy.

With the success of the preliminary study shown in Scheme 3, we went on to explore the scope and limitations of this new cyclopropanation procedure. The results are collected in Table 1.[9,10] As can be seen, chalcone and a range of heterocyclic analogues underwent efficient cyclopropanation (entries 1–6). In addition, several other α,β-unsaturated ketones gave the corresponding cyclopropanes, albeit in variable yields (entries 7–10), although cyclohexenone (entry 11), and substituted derivatives, could not be cyclopropanated using this procedure. The cyclopropanation of an α,β-unsaturated sulfone was accomplished successfully, however (entry 12).[4a]

Having developed a successful method for the in situ generation of dimethylsulfoxonium methylide (**1**) we went on to explore the viability of a manganese dioxide mediated tandem-oxidation process (TOP) in which an allylic alcohol is oxidised and the intermediate α,β-unsaturated carbonyl compound is cyclopropanated in situ. The preliminary study, summarised in Scheme 4, revealed that simply by treatment of alcohol **7a** with manganese dioxide in the presence of trimethylsulfoxonium iodide (**2b**) and MTBD (**6**) in MeCN at 60 °C for 2.5 hours gave an 86% yield of cyclopropyl ketone **4a**. This TOP sequence is advantageous in that it telescopes three processes into a one-pot operation (alcohol oxidation, sulfurane generation and cyclopropanation); it is also operationally straightforward as the work-up consists simply of removal of MnO_2 and other solid by-products by a simple filtration followed by removal of solvent and chromatography.



Scheme 4

Having established that the cyclopropanation conditions are compatible with manganese dioxide, we went on to explore the scope of the procedure with respect to the allylic alcohol (Table 2).[11] As before, reactions proceeding by way of chalcone and heterocyclic analogues proved to be the best substrates. Thus, a range of 1,3-diaryl allylic alcohols underwent one-pot oxidation–cyclopropanation in good to excellent yields (66–86%, entries 1–6). In addition, four other allylic alcohols also gave the corresponding cyclopropyl ketones, albeit in variable yields (entries 7–10). It is noteworthy that in three cases (entries 1, 4 and 8) the oxidation–cyclopropanation yield commencing from the alcohol was the same or marginally higher than the corresponding yield of cyclopropanated product obtained when commencing directly from the ketone. Thus, not only will oxidation–cyclopropanation processes be particularly beneficial in cases where the allylic alcohol, but not the α,β-unsaturated ketone, is commercially available, or when the intermediate carbonyl intermediate is 'difficult', e.g. volatile, toxic or noxious, these one-pot process may even be more efficient when starting from the allylic alcohol.

In summary, a new one-pot procedure has been developed for the cyclopropanation of α,β-unsaturated carbonyl compounds and related systems which employs trimethylsulfoxonium iodide (**2b**) and MTBD (**6**) to generate dimethylsulfoxonium methylide (**1**) in situ. In addition, preliminary examples are described in which activated alcohols are converted directly into cyclopropyl ketones by a one-pot tandem oxidation–cyclopropanation sequence. We are currently optimising and extending this one-pot cyclopropanation methodology and exploring applications in target molecule synthesis.

Acknowledgment

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References and Notes

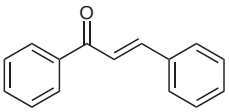
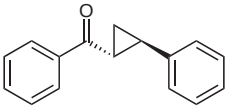
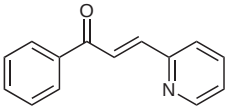
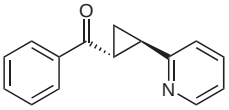
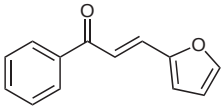
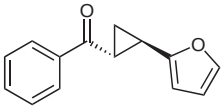
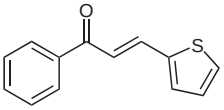
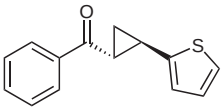
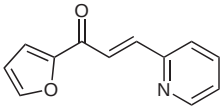
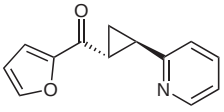
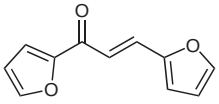
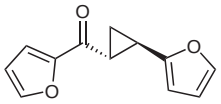
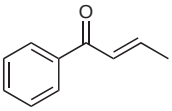
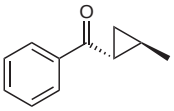
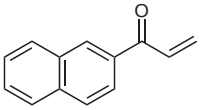
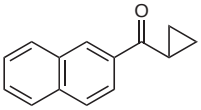
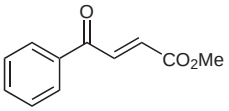
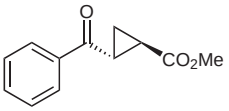
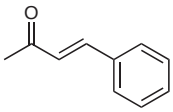
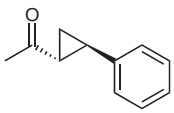
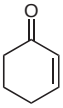
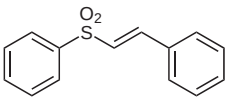
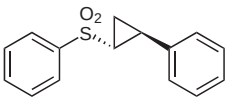
(1) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. (c) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(2) For reviews, see: (a) Trost, B. M.; Melvin, A. S. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, **1975**. (b) Gololobov, Y. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609. (c) Okazaki, R.; Tokitoh, N. In *Encyclopedia of Reagents in Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, **1995**, 2139–2141.

(3) For recent examples, see: (a) Peng, Y.; Yang, J.-H.; Li, W.-D. Z. *Tetrahedron* **2006**, *62*, 1209. (b) Midura, W. H.; Krysiak, J. A.; Cypryk, M.; Mikolajczyk, M.; Wieczorek, M. W.; Filipczak, A. D. *Eur. J. Org. Chem.* **2005**, 653. (c) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565. (d) Demir, A. S.; Sesenoglu, O.; Ülkü, D.; Arici, C. *Helv. Chim. Acta* **2004**, *87*, 106.

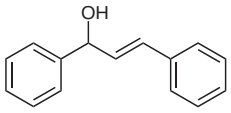
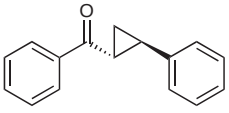
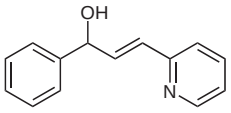
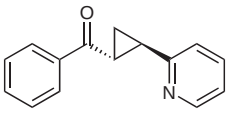
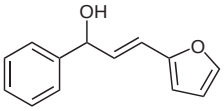
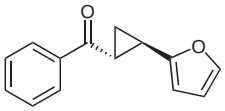
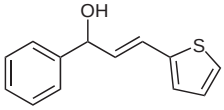
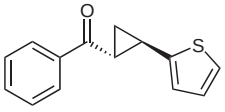
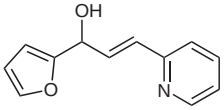
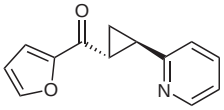
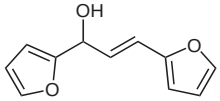
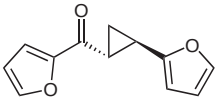
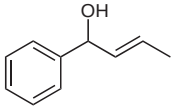
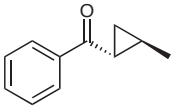
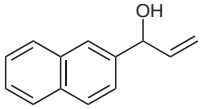
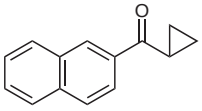
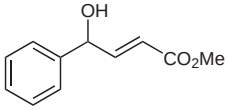
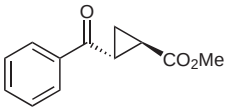
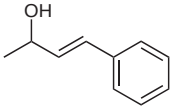
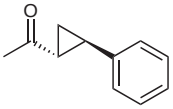
(4) (a) Truce, W. E.; Badiger, V. V. *J. Org. Chem.* **1964**, *29*, 3277. (b) Yanovskaya, L. A.; Dombrovsky, V. A.; Chizhov, O. S.; Zolotarev, B. M.; Subbotin, O. A.; Kucherov, V. F. *Tetrahedron* **1972**, *28*, 1565. (c) Merz, A.; Märkl, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845.

Table 1 Cyclopropanation Using Trimethylsulfoxonium Iodide (**2b**) and MTBD (**6**) in MeCN[a]

Entry	Substrate	Product	Conditions	Time (h)	Yield (%)[b]
1		 **4a**	2.0 equiv MTBD	2.5	86[10]
2		 **4b**	2.0 equiv MTBD	1.5	76
3			2.0 equiv MTBD	2	81
4			2.0 equiv MTBD	2	75
5			2.0 equiv MTBD	2	76
6			2.0 equiv MTBD	2	83
7			1.3 equiv MTBD	3	73
8			1.3 equiv MTBD	2.5	23
9			1.3 equiv MTBD	3	25
10			1.3 equiv MTBD	4.5	33[c]
11		–	1.2 equiv MTBD[d]	24	–[d]
12			1.3 equiv MTBD	27	72

[a] Using 1.2 equiv Me_3SOI in MeCN at 60 °C unless otherwise stated.
[b] Isolated yield; >95% *trans*-isomers by ^1H NMR spectroscopy.
[c] Yield estimated from ^1H NMR spectrum as product and SM are inseparable.
[d] At r.t.; also tried at higher temperatures and in DMF as solvent but without success; no cyclopropanation observed under any conditions.

Table 2 Tandem Oxidation–Cyclopropanation Using MnO_2, Trimethylsulfoxonium Iodide (**2b**) and MTBD (**6**) in MeCN[a]

Entry	Substrate	Product	Conditions	Time (h)	Yield (%)[b]
1		 **4a**	2.0 equiv MTBD	3.5	86
2		 **4b**	2.0 equiv MTBD	2	69[11,12]
3			2.0 equiv MTBD	1.5	76
4			2.0 equiv MTBD	2	77
5			2.0 equiv MTBD	2	66
6			2.0 equiv MTBD	2	71
7			1.3 equiv MTBD	3	39
8			1.3 equiv MTBD	2.5	36
9			1.3 equiv MTBD	3	23
10			1.3 equiv MTBD	3	28[c]

[a] All with 10 equiv MnO_2, 1.2 equiv Me_3SOI in MeCN at 60 °C.
[b] Isolated yield; >95% *trans*-isomers by NMR spectroscopy.
[c] Yields estimated from ^1H NMR spectrum as product and ketone intermediate are inseparable.

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(6) For a recent review of tandem oxidation processes, see: Taylor, R. J. K.; Reid, M.; Foot, J. S.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851.
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(8) Blackburn, L.; Pei, C.; Taylor, R. J. K. *Synlett* **2002**, 215.
(9) All known products were characterised by NMR spectroscopy and comparison of key data with those published; novel products were fully characterised.

(10) **Representative Procedure for Cyclopropanation of α,β-Unsaturated Carbonyl Compounds.**
To a stirred solution of trimethylsulfoxonium iodide (**2b**, 0.13 g, 0.6 mmol) and MTBD (**6**, 0.15 g, 1.0 mmol) in MeCN (4 mL) was added (*E*)-1,3-chalcone **3a** (0.10 g, 0.5 mmol) in MeCN (1 mL). The reaction mixture was heated at 60 °C under nitrogen for 2.5 h. After this time the solvent was removed in vacuo and the residue purified by silica column chromatography (PE–EtOAc, 9:1) to afford cyclopropane **4a** (0.095 g, 86%) as a white solid; R_f = 0.38 (PE–EtOAc, 3:1); mp 43–44 °C (lit.[13] 42.0–43.5 °C), with spectroscopic data consistent with those reported.[14]

(11) (*E*)-1-Phenyl-3-pyridin-2-ylprop-2-en-1-ol was prepared by $NaBH_4/CeCl_3$ reduction of (*E*)-1-phenyl-3-(pyridin-2-yl)propenone, see: Bakó, T.; Bakó, P.; Keglevich, G.; Báthori, N.; Czugler, M.; Tatai, J.; Novák, T.; Parlagh, G.; Töke, L. *Tetrahedron: Asymmetry* **2003**, *14*, 1917.

(12) **Representative Procedure for Tandem Oxidation–Cyclopropanation.**
To a stirred solution of trimethylsulfoxonium iodide (0.13 g, 0.6 mmol) activated MnO_2 (Aldrich 21764-6, 0.44 g, 5.0 mmol) and MTBD (**6**, 0.15 g, 1.0 mmol) in MeCN (4 mL) was added (*E*)-1-phenyl-3-(pyridin-2-yl)prop-2-en-1-ol (0.10 g, 0.50 mmol) in MeCN (1 mL). The reaction mixture was heated at 60 °C under nitrogen for 2 h. After this time the reaction mixture was filtered through Celite® and the residue washed with Et_2O. The solvent was removed in vacuo and the residue was purified by silica column chromatography (PE–EtOAc, 6:1) to afford cyclopropane **4b** as a clear oil (0.078 g, 69%); R_f = 0.23 (PE–EtOAc, 3:1). IR (neat): ν_{max} = 1667, 1504, 1568, 1474 1339, 1222 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.78–1.85 (2 H, m, C*H*H and CH*H* overlapping), 2.73–2.78 (1 H, ddd, *J* = 4.0, 6.0, 10.0 Hz, CH), 3.29–3.32 (1 H, ddd, *J* = 4.0, 5.5, 9.0 Hz, CH), 7.93 (1 H, ddd, 1.0, 5.0, 12.0 Hz, ArH), 7.26–7.29 (1 H, m, ArH), 7.44–7.48 (2 H, m, ArH), 7.54–7.60 (2 H, m, ArH), 8.03–8.05 (2 H, m, ArH), 8.49–8.51 (1 H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (CH_2), 28.4 (CH), 29.9 (CH), 121.4 (CH), 122.8 (CH), 128.3 (CH), 128.5 (CH), 133.0 (CH), 136.2 (CH), 137.7 (C) 149.6 (CH), 159.4 (C), 199.2 (CO). MS (CI): *m/z* (%) = 224 (100) [MH^+], 206 (10), 118 (10), 105 (10). HRMS (CI): *m/z* calcd for $C_{15}H_{14}NO$: 224.1075 (2.1 ppm error); found: 224.107078 [MH^+].

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