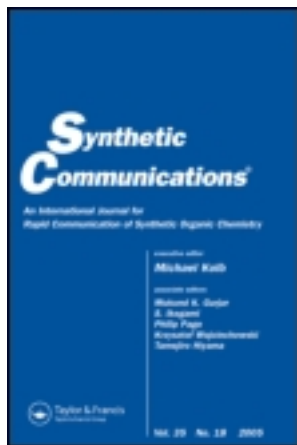


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“Instant Methylide” Modification of the Corey-Chaykovsky Epoxide Synthesis

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ABSTRACT

We report that $\text{Me}_3\text{S}(\text{O})^+\text{I}^-$ (**1**) and $\text{Me}_3\text{S}^+\text{I}^-$ (**2**) form stable, dry mixtures with $\text{KO}t\text{-Bu}$ and NaH , respectively, which remain stable upon prolonged storage (> 1 year). The corresponding methylides ($\text{Me}_2\text{SO}=\text{CH}_2$ and $\text{Me}_2\text{S}=\text{CH}_2$) are generated upon addition of DMSO or DMSO/THF solutions of carbonyl compounds, cleanly affording epoxides via the Corey–Chaykovsky reaction in good yields and short reaction times (as short as 20 min when 1–2 mmol of various ketones and aldehydes were treated with a mixture of **1** and $\text{KO}t\text{-Bu}$ at 50–60°C).

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Key Words: Epoxide synthesis; Corey–Chaykovsky reaction; Sulfonylide.

The Corey–Chaykovsky reaction is the standard method for preparing monosubstituted and 2,2-disubstituted epoxides from aldehydes and ketones, respectively. In the original report,^[1] the methylene transfer agents, dimethylsulfoxonium methylide (DMSY)^[2] and dimethylsulfonium methylide, were formed by treating $\text{Me}_3\text{S}(\text{O})^+\text{I}^-$ (**1**) and $\text{Me}_3\text{S}^+\text{I}^-$ (**2**) with NaH in anhyd. DMSO or DMSO/THF. Subsequent condensations with aldehydes and ketones were performed at 50°C for 1–2 h using DMSY and at 0–25°C for 0.5–1 h using dimethylsulfonium methylide, affording the corresponding epoxides in 56–97% yields.

Modifications of the reaction have been reported in which methylides were obtained by deprotonation of either sulfonium^[3] or sulfoxonium^[4] salts in nonaqueous media using various bases (including KO*t*-Bu),^[4] by phase-transfer catalysis in heterogeneous alkaline media,^[5] using basic microcrystalline solids in slightly hydrated solid–liquid media,^[6] using solvent free conditions,^[7] and by fluorodesilylation of dialkyl[(trimethylsilyl)methyl]sulfonium salts in nonbasic media.^[8] A method for generation of $\text{Me}_3\text{S}^+\text{HSO}_4^-$ and reaction in situ with ketones and benzaldehyde has also been described.^[9] Much recent attention has focused on asymmetric variations of the reaction using chiral sulfur benzylides that are formed under a variety of conditions.^[10]

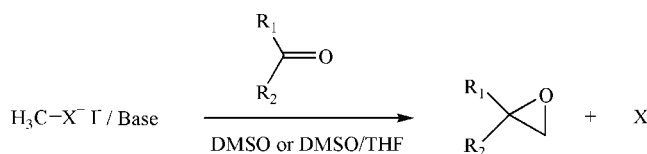
Reminiscent of Schlosser–Schaub alkyltriphenylphosphonium salt–base mixtures (“instant ylides” for Wittig olefination of carbonyl compounds),^[11] we have found that **1** and **2** form stable, dry mixtures with KO*t*-Bu and NaH, respectively, which remain stable upon prolonged storage (>1 year). The corresponding methylides are generated upon addition of DMSO or DMSO/THF solutions of carbonyl compounds to the salt–base mixture, affording the corresponding epoxides in yields of 55–98% after stirring either at room temperature or below (when using equimolar mixtures of **1** and KO*t*-Bu, or **2** and NaH), or briefly heating to 50–60°C (when using an equimolar mixture of **1** and KO*t*-Bu) (Sch. 1).

As shown in Table 1, condensation of a number of enolizable and nonenolizable ketones (**3a–g**) and an aldehyde (**4a**) with DMSY occurred at room temperature in DMSO upon treatment with two molar equivalents of an equimolar mixture of **1** and KO*t*-Bu. The corresponding epoxides (**5a–h**) were cleanly afforded in yields of 73–92% and reactions were complete within 2 h when performed on 1–2 mmol of carbonyl compound; similar yields were obtained by stirring the reaction mixtures overnight. By heating the mixtures to 50–60°C, epoxides were



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R₁ = alkyl or aryl; R₂ = alkyl, aryl, or H; X = S(O)Me₂, Base = KO^t-Bu ; X = SMe₂, Base = NaH

Scheme 1.

Table 1. Reaction conditions for epoxide synthesis using “instant methyldide” salt-base mixtures.

Carbonyl substrate	Prod. no. ^a	Me ₃ SOI/KO ^t -Bu room temp yield (%) (time, h)	Me ₃ SOI/KO ^t -Bu 50–60°C yield (%) (time, h)	Me ₃ SI/NaH 0–25°C yield (%) (time, h)
	5a	86 (0.50) 80 (16)	87 (0.67)	81 (2.0) 98 (16)
	5b	86 (0.67) 87 (16)	89 (0.33)	84 (1.5) 89 (16)
	5c	86 (0.40) 82 (16)	92 (0.33)	96 (4.9)
	5d	87 (0.5) 90 (16)	80 (0.33)	72 (6.0)
	5e	82 (0.42) 92 (16)	84 (0.33)	79 (16)
	5f	80 (0.50)	81 (0.33)	70 (2.0) ^b
	5g	73 (1.0)	80 (0.75) 73 (1.0) ^c	55 (16)
4a C ₁₁ H ₂₃ – CHO	5h	78 (1.2)	94 (0.25)	76 (16)
4b Ph-CH=CH-CHO	5i	—	—	80 (6.0)

^aYields are for isolated products using 1–2 mmol carbonyl substrate as starting material.

^bObtained as a 1:1.4 mixture of diastereomers, as determined by ¹H NMR integration.

^cUsing 6.4 mmol of **3g**.



obtained in yields of 73–94% and most reaction times were shortened to 20 min.

Condensations with dimethylsulfonium methylide were carried out at ice bath temperature by adding DMSO/THF solutions of carbonyl compounds to an equimolar mixture of **2** and NaH, followed by slow warming to room temperature. Reactions were complete within 6 h, or could be stirred at room temperature overnight, and cleanly afforded epoxides in yields of 55–98%; although yields of epoxides from several enolizable substrates (**3d–g**, **4a**) were slightly lower than those obtained when using **1** and KO*t*-Bu.

This “instant methylide” modification of the Corey–Chaykovsky reaction offers a quick, convenient, and experimentally simple preparation of monosubstituted and 2,2-disubstituted epoxides, with advantages over conventional procedures: ease of handling (the mixture of sulfoxonium or sulfonium salt and base can be stored indefinitely under anhydrous conditions without significant loss of activity); methylides are generated in the presence of the carbonyl substrate; and reaction times are relatively short (as short as 20 min when treating 1–2 mmol of carbonyl substrate with a mixture of **1** and KO*t*-Bu at 50–60°C).

Cyclopropanation of conjugated carbonyl compounds and in situ reactions of epoxides prepared by this method are currently being examined.

EXPERIMENTAL

Reactions were performed under a dry nitrogen atmosphere using glassware that was oven-dried at 120°C. All solvents, reagents, and carbonyl substrates are commercially available. Tetrahydrofuran (THF) was freshly distilled under nitrogen from dark blue or purple solutions of sodium and benzophenone; all other solvents and reagents were used without purification. Analytical TLC was performed using Hard Layer Silica Gel GHLF UNIPLATES with inorganic binder (Analtech, Inc.) and Riedel-deHaen TLC plates, silica gel (60 F 254), 0.2 mm thickness on aluminum (available from Aldrich Chem. Co.). Plates were visualized by UV, I₂, and/or 10% phosphomolybdic acid in absolute ethanol. ¹H spectra were recorded at 300 MHz and ¹³C spectra were recorded at 75 MHz on a Bruker Avance™ DPX300 spectrometer with the use of CDCl₃ as solvent. Chemical shifts were measured relative to internal TMS. After an aqueous work-up, epoxides were afforded in good yield (avg. yield in Table 1 is 83%) from

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either ketones or aldehydes (including enolizable substrates), and the crude products generally were obtained pure enough to be used directly for further reactions, as determined by TLC, ^{13}C and ^1H NMR analyses. Epoxides **5a-i** (Table 1) have been reported previously, and our NMR data are in agreement with the published data.

Preparation of the Sulfoxonium/Sulfonium Salt and Base Mixtures

Appropriate amounts (see below) of the powdered salt and base were thoroughly mixed, placed in glass, screw cap bottles, and then stored in desiccators with no significant loss in activity for samples stored > 1 year:

Me_3SI (4.29 g; 21.0 mmol) + NaH (dry; 0.500 g; 20.8 mmol)
= 4.3 mmol methyllide/g

Me_3SOI (5.90 g; 26.8 mmol) + $\text{KO}t\text{-Bu}$ (3.00 g; 26.7 mmol)
= 3.0 mmol methyllide/g

General Procedure Using an Equimolar Mixture of Me_3SOI (1) and $\text{KO}t\text{-Bu}$

An anhyd. DMSO (8 mL) solution of the carbonyl compound (1–2 mmol) was added all at once to a dry mixture (1.5 to 2 molar equivalents) of **1** and $\text{KO}t\text{-Bu}$ in a small round-bottomed flask at room temperature. The resulting clear solution was stirred for either 20–45 min while the flask was immersed in an oil bath heated to 50–60°C, or overnight at room temperature (or until TLC analysis revealed the absence of carbonyl compound). The mixture was then treated with water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed either with water or brine (3 × 50 mL), dried over anhyd. MgSO_4 , filtered, and evaporated in vacuo to afford the corresponding epoxide.

General Procedure Using an Equimolar Mixture of Me_3SI (2) and NaH

A solution of the carbonyl compound (1–2 mmol) in anhyd. DMSO (6 mL) and THF (1–3 mL) was added in small portions over 5–10 min to



a mixture (3 molar equivalents) of **2** and NaH in anhyd. THF (1–2 mL) that was stirring in a small round-bottomed flask immersed in an ice water bath. The mixture was slowly warmed to room temperature and the resulting clear solution was stirred either overnight or until TLC analysis revealed the absence of carbonyl compound. The mixture was then treated with water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed either with water or brine (3 × 50 mL), dried over anhyd. MgSO₄, filtered, and evaporated in vacuo to afford the corresponding epoxide.

2,2-Diphenyloxirane (5a)^[1c]: M.p. 54–55°C (lit. 55–56°C). ¹H NMR δ 7.20 (m, 10H), 3.10 (s, 2H). ¹³C NMR δ 140.03, 128.71, 128.39, 127.92, 62.26, 57.29.

2-Methyl-2-phenyloxirane (5b)^[12]: ¹H NMR δ 7.35 (m, 5H), 2.95 (d, 1H, *J* = 5 Hz), 2.78 (d, 1H, *J* = 5 Hz), 1.71 (s, 3H). ¹³C NMR δ 141.60, 128.73, 121.85, 125.71, 57.40, 57.14, 22.21.

2-Methyl-2-(4-methylphenyl)oxirane (5c)^[13]: ¹H NMR δ 7.20 (d, 2H), 7.10 (d, 2H), 2.90 (d, 1H), 2.80 (d, 1H), 2.30 (s, 3H), 1.65 (s, 3H). ¹³C NMR δ 138.57, 137.54, 129.42, 125.64, 57.47, 57.09, 22.28, 21.48.

2-Hexyl-2-methyloxirane (5d)^[4a]: ¹H NMR δ 2.54 (d, 1H), 2.49 (d, 1H), 1.59–1.10 (m, 13H), 1.20 (s), 0.80 (t, 3H). ¹³C NMR δ 57.07, 53.86, 36.64, 31.67, 29.22, 25.11, 22.46, 20.76, 13.95.

1-Oxaspiro[2.6]nonane (5e)^[1c]: ¹H NMR δ 2.60 (s, 2H), 1.75–1.50 (m, 12H). ¹³C NMR δ 60.58, 55.70, 35.84, 28.86, 24.54.

6-*t*-Butyl-1-oxaspiro[2.5]octane (5f)^[1c,6a]: (Single diastereomer), prepared using **1** and KO^{*t*}-Bu. ¹H NMR δ 2.64 (s, 2H), 1.94–1.68 (m, 4H), 1.44–1.24 (m, 4H), 1.12–1.00 (m, 1H), 0.89 (s, 9H). ¹³C NMR δ 58.37, 53.82, 47.14, 33.37, 32.48, 27.58, 24.82.

1,7,10-Trioxadispiro[2.2.4.2]dodecane (5g)^[14]: ¹H NMR δ 4.00 (s, 4H), 2.70 (s, 2H), 2.00–1.30 (m, 8H). ¹³C NMR δ 108.00, 64.30, 57.68, 53.88, 32.75, 30.37.

2-Undecyloxirane (5h)^[15]: ¹H NMR δ 2.90 (m, 1H), 2.74 (dd, 1H), 2.45 (dd, 1H), 1.6–1.2 (m, 20H), 0.88 (t, 3H). ¹³C NMR δ 52.33, 47.01, 32.43, 31.86, 29.58, 29.50, 29.40, 29.29, 25.92, 22.63, 14.03.

2-Styryloxirane (5i)^[5b,5f,6a]: ¹H NMR δ 7.42–7.15 (m, 5H), 6.78 (d, 1H), 5.85 (dd, 1H), 3.50 (m, 1H), 3.00 (dd, 1H), 2.75 (dd, 1H). ¹³C NMR δ 135.93, 134.40, 128.48, 127.91, 126.81, 126.28, 52.47, 49.05.

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