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Efficient Simmons–Smith cyclopropanation with Zn/Cu and CH_2I_2

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An appropriate solvent to perform the original Simmons–Smith reaction was reinvestigated. Among available solvents, cyclopentyl methyl ether (CPME), a recently commercialized ethereal solvent, was found to be the best so far. Compared with Et_2O under reflux – the commonest conditions – reaction completion in CPME at 50 °C was about 10 times faster. The product yields and selectivities were mostly identical to those with Et_2O, but were better in some cases; e.g. 13–56% with 2-cyclohexenol. The good performance of CPME should be mainly due to its moderate polarity and high boiling point. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: Simmons–Smith reaction; zinc carbene; Zn/Cu; CPME

Introduction

The Simmons–Smith reaction is often used for cyclopropanation of olefins via zinc carbene addition.[1,2] The Furukawa modified procedure[3,4] is more often employed because this modified procedure works over a wide temperature range and in various solvent systems, resulting in better product yields. The difference is the use of a readily reactive organometallic reagent (usually diethylzinc) instead of zinc metal, and thus the zinc carbene generation step with diiodomethane is much smoother. For these reasons, the Furukawa procedure is more popular in current organic syntheses, but the use of less expensive metal zinc is economically preferable.

The original Simmons–Smith reaction is usually carried out with copper-activated zinc (Zn/Cu) in Et_2O under reflux conditions with a mixture of diiodomethane and a substrate. The reaction proceeds via generation of the metal carbene, which does not accumulate in the reaction medium (Scheme 1). Completion of the reaction often takes 1–2 days, which can result in lower product yields if the substrate and/or product are not fully stable under the reaction conditions.[5]

In contrast to the reaction in Et_2O, the zinc carbene generation step is quick in THF, while the generated zinc carbene has lower activity with olefins due to stronger solvation with more polar THF.[6] To complete the reaction within shorter times, a suitable polar solvent, being polar between Et_2O and THF, is required.[7] Hydroxy group-directed cyclopropanation is a benefit of the Simmons–Smith reaction, and the selectivity governed by the hydroxyl–zinc carbene interaction is also strongly dependent on solvent polarity. Our investigation regarding the above points led us to the appropriate conditions, which include use of cyclopentyl methyl ether (CPME), a solvent commercialized in 2005.[8]

Experimental

General

Zinc dust (freshly opened) and a diethylzinc hexane solution (1.00 M) were obtained from Kanto Chemical Co. Diiodomethane was purified by passing through a short aluminium column just before use. All ethereal solvents were purified by distillation from a ketyl radical solution under nitrogen. ^1H NMR spectra were recorded on a JEOL ECA-600 using $CDCl_3$ as a solvent and as an internal standard (δ 7.24), and were collected at 600 MHz using a 15 ppm spectral width. Mass spectra were obtained using a JEOL JMS-T100 ESI-TOF-MS instrument. Samples were directly injected as methanol solutions to observe $M + Na^+$ at 1.5 mDa ($R \geq 8000$). Gas–liquid chromatography (GLC) was performed with a Shimadzu 17A and the signals were recorded on a KYA tech Smartchrom.

Cyclopropanation with *In Situ* Activated Zn with CuCl[9]

A suspension of Zn dust (0.77 g) and CuCl (0.12 g) in a solvent (13 ml) was heated at 35 °C for 1 h. After cooling, **1** (1 g) and CH_2I_2 (0.85 ml) were added (molar ratio of substrate:Zn:CH_2I_2 = 1:2.0:4.3) and then the mixture was heated at 50 °C. After the reaction, the mixture was treated with a small amount of water, filtered through a Celite pad, extracted with ether, washed with aqueous NH_4Cl solution (×3) and then $NaHCO_3$ solution (×1) and dried over Na_2SO_4.

Cyclopropanation with Pre-made Zn/Cu

Zn/Cu was prepared from zinc dust (10 g) with $Cu(OAc)_2.H_2O$ (580 mg) in acetic acid (15 ml) at 40 °C in 3 min. The mixture was filtered through a glass filter, and the filter cake was washed with water, dried under vacuum and stored.[2] Substrate **1** (1 g), CH_2I_2 (0.85 ml) and Zn/Cu (0.77 g, 2.3 equiv.) were suspended in a solvent (13 ml) and heated for a specified time. Workup procedure was the same as the above procedure.

Analysis of the Reactions

The reactions of **1** were evaluated by ^1H NMR, in which all signals were assignable as mixtures of **1**, **2**, **3** and cyclohexanone. Mixtures of the reactions with cyclooctene (**4**) were analyzed by GLC (TC-5, 25 m × 0.25 mm i.d., 70 °C, retention time 6.0 min for **4** and 10.6 min for **5**). The reaction mixture obtained from geraniol (**6**) was purified by a silica gel column (elution with a mixture of ethyl

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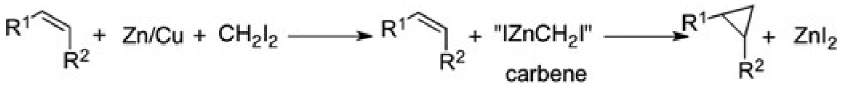


Scheme 1. Reaction process of Simmons–Smith cyclopropanation.

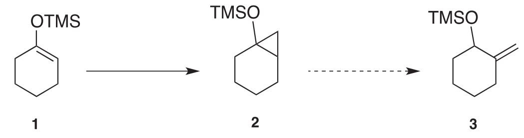
acetate–hexane = 2:8) to isolate product **7**. Here, **8**, **9** and any other side products were not detected before the isolation process (by ^{1}H NMR). ^{1}H NMR analysis of the reaction of **10** did not show any formation of **11b** (<1%) or other side products. Product **11a** was isolated by silica gel column chromatography (elution with ethyl acetate–hexane = 2:8). Stereoselectivity of the reactions of **12** were evaluated by GLC (PEG-20 M, 25 m × 0.25 mm i.d., 110 °C, retention time 16.5 min for **13a** and 17.4 min for **13b**). Yields of the product **13** were determined after silica gel column chromatography (elution with ethyl acetate–hexane = 1:9). In all cases product structures were identified to the known compounds by the ^{1}H NMR spectra and confirmed by mass spectra (see ref. 5 and references therein).

Results and Discussion

Initial attempts to investigate solvent effects on Simmons–Smith cyclopropanation were carried out with 1-(trimethylsiloxy)cyclohexe (**1**), which has an electron-rich double bond and should have sufficient reactivity with the generated zinc carbene. At higher concentrations or at longer reaction times, the product **2** might decompose to give **3** (see scheme in Table 1).[10–12]

The conditions for using zinc need special care, since the reactivity of the zinc metal depends largely on included impurities (e.g. only 0.05% lead), activation method and storage conditions. (For lead-free zinc, copper activation is not necessary, but commercial zinc dust in our hand gives higher activity only after the copper salt treatment).[13] To obtain reproducible results, we first employed an *in situ* activation by mixing Zn and CuCl in the reaction flask before addition of **1** and diiodomethane.[9] *In situ* activation is easy to handle and gives reproducible results, but the activation effect is lower than that of classic pre-made Zn/Cu. Thus the reaction rates with reactive substrate **1** tend to be governed by the zinc carbene generation step (Scheme 1).

Table 1. Simmons–Smith reaction of silyl enol ether **1** to give **2** with *in situ* prepared Zn/Cu at 50 °C



Entry	Solvent	Dielectric constant (ε_r)	Conversion (%) after 2 h
1	1,4-Dioxane	2.21	1
2	Methyl *t*-butyl ether (MTBE)	2.6	10
3	Diisopropyl ether (DIPE)	3.88	4
4	Et_2O[a]	4.20	7
5	Cyclopentyl methyl ether (CPME)	4.76	19
6	Dimethoxyethane (DME)	7.20	2
7	THF	7.58	9

[a]The reaction was carried out under reflux conditions.

Conversion of **1** to **2** at 50 °C (except Et_2O, reflux conditions) was determined in 2 h as given in Table 1. No side product was formed at this stage, and the reaction mixture consisted of only **1** and **2**, as deduced from ^{1}H NMR. At this initial stage, giving low conversions (<20%), the ethereal solvents could be classified into two groups; entries 1–4 and 6, where most zinc and diiodomethane were unreacted after 2 h, and entries 5 and 7, where zinc and diiodomethane were mostly consumed within 10 min. Cyclopropanation efficiency in the former, less polar, ethereal solvents (and dimethoxyethane, DME) must be governed by the zinc carbene generation step, while in the more polar solvents the efficiency should be controlled at the zinc carbene addition step. Among all, CPME of the later group gave the fastest reaction rate, presumably because the generated zinc carbene in less polar CPME is more reactive than in THF.

The Simmons–Smith reaction of **1** in CPME was studied at different temperatures. The NMR yield of **2** after 2 h is plotted in Fig. 1. The reaction conversion becomes higher at higher

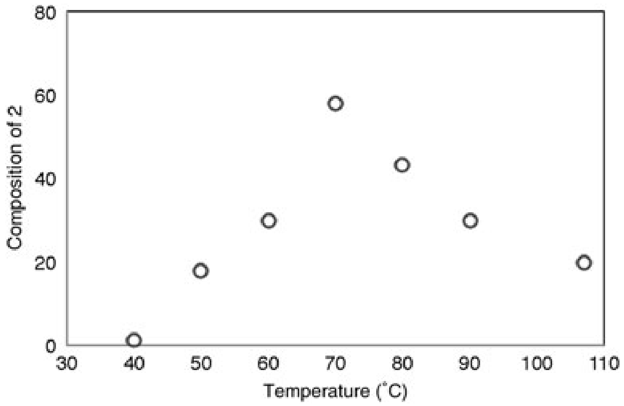


Figure 1. Yield of **2** in a reaction of **1** with *in situ* prepared Zn/Cu in CPME after 2 h.

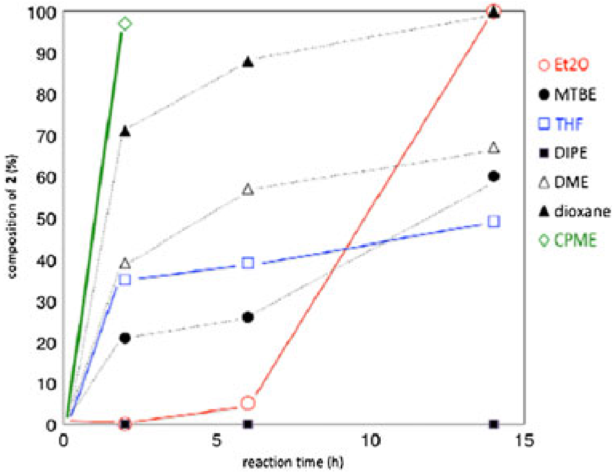
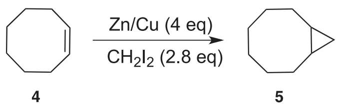
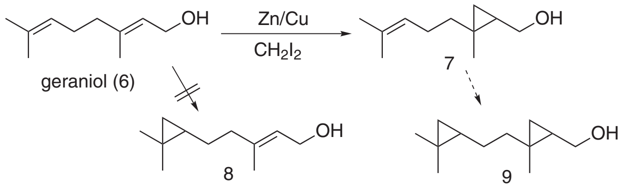


Figure 2. Composition of **2** in the reactions of **1** with pre-made Zn/Cu in various solvents.

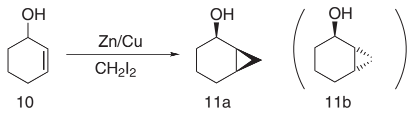
Table 2. Simmons–Smith reaction of cyclooctene with pre-made Zn/Cu



Reaction time (h)	Product composite (%)	
	Et_2O (34 °C)	CPME (50 °C)
2	66	70
4	76	72
6	60	66



Scheme 2. Hydroxy group-directed regioselective cyclopropanation of geraniol.



Scheme 3. Hydroxy group-directed stereoselective cyclopropanation of 2-cyclophexene.

temperature, reaching 59% at 70 °C. At higher temperatures, product **2** is partly converted to **3**, reducing the yield of **2**.

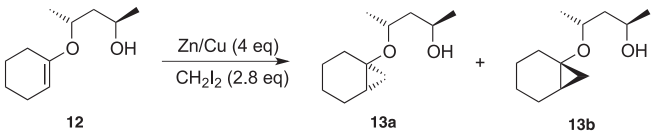
To confirm the superiority of CPME, more active pre-made Zn/Cu was employed, with the intention of establishing a synthetically more useful procedure.[2] The reactions in Et_2O and THF were performed at reflux temperatures, and the other solvents were examined at 50 °C. The results are given in Fig. 2. Reaction in Et_2O took a long time, as previously reported,[10] but this is partly due to the necessity for an induction time. In THF, the reaction was not only slow but also was not completed, probably because the generated carbene is not a fully stable species. Dioxane was similar to Et_2O, but the reaction was basically faster due to the higher reaction temperature. DME and methyl *t*-butyl ether (MTBE) were similar to THF. Differing from the reactions in the other ethereal solvents, the reaction in CPME was completed quickly, in 2 h at 50 °C (97% conversion). At 70 °C (not shown in Fig. 2), the reaction was too fast with the pre-made Zn/Cu in 2 h, resulting in formation of **3** (29%) in addition to **2** (63%).

The newly established conditions, pre-made Zn/Cu, CPME and 50 °C, were used in the cyclopropanation of cyclooctene (**4**), which has a less electron-rich, simple double bond (Table 2). The reactions were compared between Et_2O at 34 °C and CPME at 50 °C. The reaction conversion was determined by GLC after 2, 4 and 6 h. For cyclooctene – a stable and less reactive substrate – the advantage to using CPME was minimal, but compared with conventional Et_2O the equivalent product yield was obtained in a shorter time.

Another important function of the Simmons–Smith reaction is hydroxy group-directed cyclopropanation, which will result in chemoselectivity, regioselectivity and stereoselectivity. Regioselective cyclopropanation was demonstrated with geraniol (**6**) and resulted in cyclopropanation at C2–C3 (Scheme 2). The substrate (**6**) was consumed completely within 1 h to give **7** in 71% isolated yield. The yield became lower (58%) when the reaction was carried out for 2 h. In either case, over-reaction at the C6–C7 double bond is very minor (<1%). Lack of reactivity at the 6, 7- position indicates that the hydroxy-directed regioselective cyclopropanation was successful in CPME, the same as in Et_2O.[14] Stereoselective cyclopropanation was examined with 2-cyclohexenol (Scheme 3). The reaction under conventional Simmons–Smith conditions with Et_2O is known to give high stereoselectivity (**11a**/**11b** > 99/1), but with poor yield (e.g. 13%).[15] Under the present conditions, the *cis* product **11a** was obtained predominantly (>99% purity) in a moderate 56% yield.

Finally, the Simmons–Smith reaction using CPME was applied to an asymmetric cyclopropanation based on a remote hydroxy direction with **12**. The diastereoselectivity obtained was a moderately high 80% diastereomer excess (% de = 100 × |**13a** − **13b**|/(**13a** + **13b**)) both in Et_2O at reflux temperature (49% yield) and in THF at 60 °C (69% yield, Table 3).[16,17] Use of CPME at 50 °C did not result in improvement (72% de, 40% yield), but reverse addition of the zinc carbenoid to a substrate solution at 50 °C resulted in the

Table 3. Product composite and diastereomer excess (% de)[a] with a chiral enol ether



Method	Et_2O	THF	CPME
SS reaction	49% (80% de)	69% (80% de)	40% (72% de)
Reverse SS reaction[b]	—	—	25% (84% de)
Furukawa	78% (18% de)	65% (94% de)	90% (32% de)
Furukawa with ZnI_2 (1 equiv.)	65% (68% de)	56% (90% de)	87% (78% de)

[a] %de = |**13a** − **13b**|/(**13a** + **13b**) × 100.

[b] The reaction was carried out by the addition of a pre-made zinc carbene with Zn/Cu to a reactant solution.

highest diastereomer excess, at 84% de, while the yield became 25%. Formation of this pre-made zinc carbene by mixing Zn/Cu and CH_2I_2 was not possible in Et_2O, and the zinc carbene pre-made in THF was unreactive for conversion of **12** to **13**. The low yields in CPME were attributable to instability of **12** to isomerize to the corresponding cyclohexanone acetal under the reaction conditions.

The Furukawa procedure was more effective for fragile substrates since the reaction could be run at lower temperatures. For example, the reaction of **12** with $ZnEt_2$ (5 equiv.) and CH_2I_2 (10 equiv.) gave 78% yield (17% de) of **13** in Et_2O (0 °C), and 65% yield (94% de) in THF (20 °C).[16,17] The low diastereomer excess in Et_2O was improved to 68% de by the addition of ZnI_2, while yield of **13** became lower (65%). The reaction in CPME (0 °C) was noteworthy because the yield was highest (90%). The low diastereomer excess (32% de) was improved by the addition of ZnI_2 (1 equiv.) to 78% de. Here, the loss in efficiency was minimal (87% yield of **13**).

Conclusions

In the present study, CPME was found to be a suitable solvent for the Simmons–Smith reaction. The favorable properties in cyclopropanation should come from moderate solvation power; CPME stabilizes zinc carbene during its formation but does not stabilize it enough to preserve its reactivity to olefins. In addition, CPME has general advantages; it can easily be dehydrated and can be used in a wide temperature range, from −140 to 106 °C.[8] The observed high product yields may indicate additional predominance of CPME in coordination to zinc reagents.[18]

Acknowledgments

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