Tetrahedron Letters 50 (2009) 4754–4758

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Substitution of both chloro and sulfinyl groups of aryl 1-chlorocyclopropyl sulfoxides in one-pot via cyclopropylmagnesium carbenoids: a synthesis of multi-substituted cyclopropanes

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ARTICLE INFO

Article history:
Received 18 May 2009
Revised 3 June 2009
Accepted 5 June 2009
Available online 9 June 2009

Keywords:
Magnesium carbenoid
Cyclopropylmagnesium carbenoid
Cyclopropane
One-pot synthesis
Doering–LaFlamme allene synthesis

ABSTRACT

The rearrangement of cyclopropylmagnesium carbenoids, which were generated from aryl 1-chlorocyclopropyl sulfoxides with a Grignard reagent, to allenes was found to be suppressed by adding HMPA as an additive. Alkylation of the cyclopropylmagnesium carbenoids with the Grignard reagent gives mainly alkylated cyclopropylmagnesium chloride instead. The cyclopropylmagnesium chloride intermediate can be trapped with several electrophiles to afford multi-substituted cyclopropanes. This procedure provides a new method for a synthesis of multi-substituted cyclopropanes.

1. Introduction

The synthesis of allenes from *gem*-dihalocyclopropanes, which are derived from olefins with dihalocarbenes, is known as Doering–LaFlamme allene synthesis[1] (or Doering–Moore–Skattebol reaction[2]). The key reaction of this procedure is the cyclopropylidene-allene rearrangement (Doering–LaFlamme-type rearrangement) of the cyclopropylidenes generated from the *gem*-dihalocyclopropanes[3] with alkyllithiums or Grignard reagents.[4]

We are also interested in the reaction of cyclopropylidene carbenoids, especially cyclopropylmagnesium carbenoids **2** generated from aryl 1-chlorocyclopropyl sulfoxides **1** by the sulfoxide-magnesium exchange reaction (Scheme 1). Thus, sulfoxides **1** were synthesized from olefins[5] or α,β-unsaturated carbonyl compounds.[6] Treatment of **1** with PhMgCl[5] or alkylmagnesium chloride[7] in THF or toluene at 0 °C resulted in the formation of cyclopropylmagnesium carbenoids **2**. Doering–LaFlamme-type rearrangement then took place to afford allenes **3** in good yields.[5,7]

During the course of our above-mentioned investigation, we recently found that addition of hexamethylphosphoramide (HMPA) as an additive in the reaction mixture suppressed the cyclopropylidene-allene rearrangement. Alkylation of the cyclopropylmagnesium carbenoid **2** with the used Grignard reagent was preferred instead to give alkylated cyclopropylmagnesium intermediate **4**. This intermediate **4** was proved to be reactive with several electrophiles to give multi-substituted cyclopropanes **5**. This is a new one-pot synthesis of multi-substituted cyclopropanes from easily available aryl 1-chlorocyclopropyl sulfoxides **1**. Details of this procedure are described.

2. Results and discussion

At first, 1-chlorocyclopropyl *p*-tolyl sulfoxide **6** was synthesized as the representative starting material in this study from *tert*-butyl acrylate and chloromethyl *p*-tolyl sulfoxide based on the procedure reported by Toyota.[8] As the study for obtaining an allene as the desired product,[7] sulfoxide **6** was treated with 2 equivalents of *i*-PrMgCl in toluene at 50 °C for 1 min (Table 1, entry 1). This reaction gave allene **7** in 74% as the desired product with isopropylated cyclopropane **8** as a byproduct. Lowering the reaction temperature to 0 °C did not give better result (entry 2).

In order to know the effect of additives in this reaction, HMPA was added to the reaction mixture and we observed dramatic change in the reaction (entry 3). Thus, treatment of **6** in toluene with two equivalents of *i*-PrMgCl in the presence of 8 equiv of HMPA at 0 °C for 30 min afforded chlorocyclopropane **9** as the product in 88% yield. No allene **7** and isopropylated cyclopropane **8** were observed. When this reaction was quenched with CH_3OD, cyclopropane deuterated at the carbon bearing the chlorine atom **9** with 86% deuterium content was obtained. This result indicated that the intermediate, cyclopropylmagnesium carbenoid **10** (see

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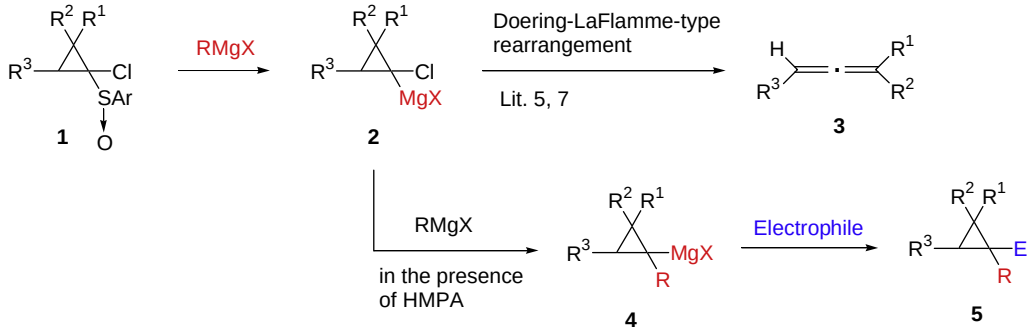
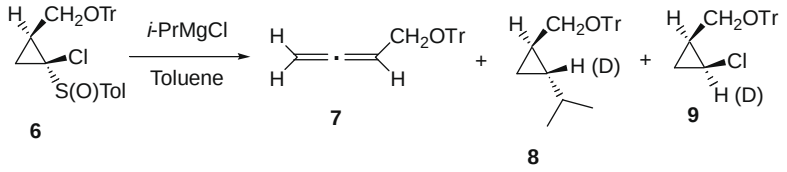
doi:10.1016/j.tetlet.2009.06.019



Scheme 1.

Table 1
Treatment of 1-chlorocyclopropyl *p*-tolyl sulfoxide **6** with *i*-PrMgCl without and with HMPA



Entry	*i*-PrMgCl (equiv)	Conditions	MMPA	**7**/Yield (%)	**8**/Yield (%)	**9**/Yield (%)
1	2	50 °C, 1 min	Non	74	15	0
2	2	0 °C, 30 min	Non	65	27	0
3	2	0 °C, 30 min	8 equiv	0	0	88[a]
4	8	0 °C, 30 min	8 equiv	Trace	85[b]	Trace

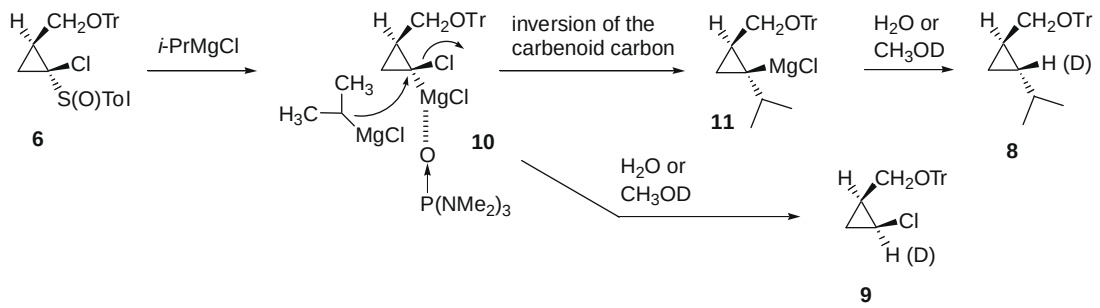
[a] When this reaction was quenched with CH_3OD, deuterated cyclopropane **9** (86% deuterium content) was obtained. About 5% of *trans*-isomer was present as the product.
[b] When this reaction was quenched with CH_3OD, deuterated cyclopropane **8** (99% deuterium content) was obtained. About 9% of *cis*-isomer was present as the product.

Scheme 2), is stable at 0 °C for at least 30 min. This was very interesting result for us because we had presumed that cyclopropylmagnesium carbenoids were unstable above −60 °C to produce allenes.[5]

Further interesting result was obtained when the reaction was conducted with excess of *i*-PrMgCl (entry 4). Thus, treatment of **6** with 8 equiv of *i*-PrMgCl in the presence of 8 equiv of HMPA at 0 °C for 30 min gave isopropylated cyclopropane **8** in 85% yield with trace of **7** and **9**. When this reaction was quenched with CH_3OD, cyclopropane deuterated at the carbon bearing the isopropyl group **8** with 99% deuterium content was obtained.

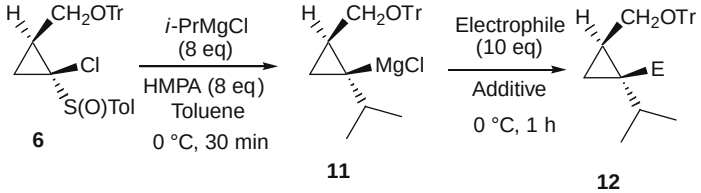
Based on the results mentioned above, the progress and the mechanism of these reactions can be estimated as follows (Scheme 2). At first, the sulfoxide-magnesium exchange reaction of **6** takes place with *i*-PrMgCl with retention of the stereochemistry of the carbon bearing the sulfinyl group[9] to afford cyclopropylmagnesium carbenoid intermediate **10**. This carbenoid is thought to be stabilized by the coordination of HMPA with the magnesium and the rearrangement to allene must be prevented. When this reaction was conducted with slight excess of *i*-PrMgCl, quenching this reaction with water gives *cis*-1-chloro-2-trityloxymethylcyclopropane **9** (Table 1, entry 3). On the other hand, when this reaction was conducted with large excess of *i*-PrMgCl, intermediate **10** is attacked by *i*-PrMgCl with inversion of the carbenoid carbon[10] (or via a magnesium ate complex) to give isopropylated cyclopropylmagnesium chloride **11**. Quenching of this intermediate with water gives *trans*-1-isopropyl-2-trityloxymethylcyclopropane **8** (Table 1, entry 4).

As we were aware that this procedure must become good way for a synthesis of multi-substituted cyclopropanes, the reaction of several electrophiles with the isopropylated cyclopropylmagnesium chloride intermediate **11** was investigated and the results are summarized in Table 2. Thus, sulfoxide **6** was treated with 8 equiv of *i*-PrMgCl in toluene at 0 °C in the presence of HMPA (8 equiv) for



Scheme 2.

Table 2
Treatment of 1-chlorocyclopropyl *p*-tolyl sulfoxide **6** with *i*-PrMgCl in the presence of HMPA followed by electrophiles



Entry	Electrophile	Additive	**12**/Yield (%)	Ratio of diastereomers[a]
1	CH_3I	CuI (10 mol %)	84	20:1
2	$CH_2{=}CHCH_2I$	CuI (10 mol %)	83	10:1
3	$PhCH_2Br$	CuI (10 mol %)	76	10:1
4	PhCOCl	CuI (10 mol %)	65	20:1
5	PhCHO	$Al(CH_3)_2Cl$ (2 equiv)	76	1:1[b]
6	CH_3COCH_3	$Al(CH_3)_2Cl$ (2 equiv)	—[c]	
7	PhCOPh	$Al(CH_3)_2Cl$ (2 equiv)	—[c]	

[a] The ratio of two diastereomers was determined from their ^1H NMR.
[b] The product was obtained as a 1:1 mixture of two diastereomers with respect to the carbon bearing the hydroxyl group.
[c] Compound **8** was obtained as the main product.

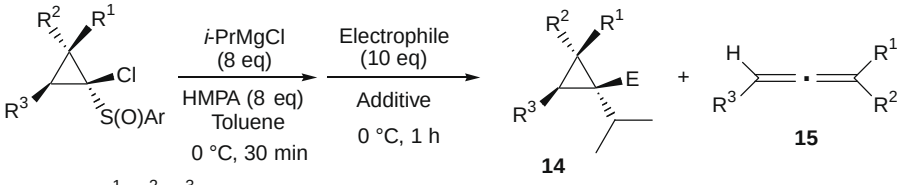
30 min. To this reaction mixture, copper(I) iodide (CuI; 10 mol %) followed by iodomethane (10 equiv) was added and the reaction mixture was stirred at 0 °C for 1 h (Table 2, entry 1). Fortunately, the desired methylated product **12** (E = CH_3) was obtained in 84% yield. The product was proved to be a mixture of two isomers (the ratio 20:1) and structure of the main product was confirmed as shown in Table 2 by NOESY spectrum (NOE was observed between the hydrogen of the introduced methyl group and the hydrogen on the carbon bearing the trityloxy group). It is noteworthy that no methylation was observed when this reaction was conducted without CuI.

Allyl iodide and benzyl bromide reacted well with **11** to give the desired tri-substituted cyclopropanes in 83 and 76% yield, respectively (entries 2 and 3). Benzoyl chloride also reacted with **11** in the presence of CuI to afford a cyclopropane bearing benzoyl substituent (entry 4).[11] The reaction with benzaldehyde without an additive gave only complex mixture; however, it was found that dimethylaluminum chloride worked well as a Lewis acid to give the desired adduct in 76% yield (entry 5). We tried the reaction with acetone and benzophenone without or with dimethylaluminum chloride; however, no adduct was obtained. In these cases, isopropylated cyclopropane **8** was obtained as the main product.

In order to investigate the generality of this reaction, three aryl 1-chlorocyclopropyl sulfoxides (**13a**,[12] **13b**,[6] and **13c**[6]) were synthesized and these sulfoxides were treated with *i*-PrMgCl followed by electrophiles. The results are summarized in Table 3. When 1-chlorocyclopropyl phenyl sulfoxide with no substituent on the cyclopropane ring **13a** was used in this reaction, *gem*-disubstituted cyclopropanes **14** were obtained in up to 77% yield (entries 1–3). The alkylation, benzoylation, and addition to benzaldehyde proceed smoothly in the presence of CuI or dimethylaluminum chloride.

When this reaction was carried out with 1-chlorocyclopropyl *p*-tolyl sulfoxide having two substituents at 2-position on the cyclopropane ring **13b**, the expected isopropylated product **14** was obtained in 66% yield; however, significant amount of allene

Table 3
Treatment of 1-chlorocyclopropyl aryl sulfoxides **13** with *i*-PrMgCl in the presence of HMPA followed by electrophiles



13a $R^1{=}R^2{=}R^3{=}H$, Ar=Ph
b $R^1{=}CH_3$, $R^2{=}CH_2OTr$, $R^3{=}H$, Ar=Tol
c $R^1{=}CH_3$, $R^2{=}CH_2OTr$, $R^3{=}CH_3$, Ar=Tol

Entry		R^1	R^2	R^3	Ar	Electrophile	Additive	**14**/Yield (%)	Ratio of diastereomers[a]	**15**/Yield (%)
1	**13a**	H	H	H	Ph	$PhCH_2CH_2I$	CuI (10 mol %)	68		
2						PhCOCl	CuI (10 mol %)	77		
3						PhCHO	$Al(CH_3)_2Cl$ (2 equiv)	70	Single isomer	
4	**13b**	CH_3	CH_2OTr	H	Tol	H_3O^+		66	10:3	23
5						CH_3I	CuI (10 mol %)	58	5:2	23
6						$CH_2{=}CHCH_2I$	CuI (10 mol %)	64	10:3	25
7						PhCOCl	CuI (10 mol %)	59	5:1	21
8	**13c**	CH_3	CH_2OTr	CH_3	Tol	H_3O^+		15	Single isomer	77

[a] The ratio of two diastereomers was determined from their ^1H NMR.

15 (23%) was also observed (entry 4). This result indicated that the corresponding highly substituted cyclopropylmagnesium carbenoid was prone to rearrange to allene. Although the cyclopropylmagnesium carbenoid has this nature, tetra-substituted cyclopropanes **14** were synthesized in up to 64% yield (entries 5–7). It is noteworthy that the produced cyclopropanes **14** have two quaternary carbons.

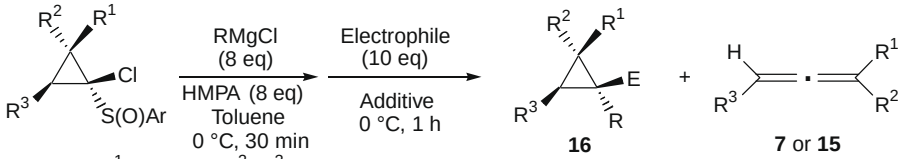
Finally, tri-substituted cyclopropylmagnesium carbenoid was generated from **13c** (entry 8). In this case, it was found that the desired isopropylated product was obtained in only 15% yield and the yield of allene **15** was 77%. This result indicates that the substituents on the cyclopropylmagnesium carbenoid retard the alkylation, perhaps by steric hindrance, and also promote the Doering–LaFlamme-type rearrangement.

Finally, investigation of this reaction with ethylmagnesium chloride, cyclopentylmagnesium chloride, and phenylmagnesium chloride was carried out using aryl 1-chlorocyclopropyl sulfoxides **6** and **13a–c** as the substrates and the results are summarized in Table 4. Ethylmagnesium chloride and cyclopentyl magnesium chloride reacted with **13a** to afford the alkylated cyclopropylmagnesium intermediates, which could be trapped with iodoalkane, benzoyl chloride, and benzaldehyde to afford *gem*-disubstituted cyclopropanes in up to 73% yield (entries 1–6). This procedure also worked well with 1-chlorocyclopropyl *p*-tolyl sulfoxide **6** (entries 7–14).

The reaction of **6** with phenylmagnesium chloride was found to be troublesome (entry 15). Phenylation of the cyclopropylmagnesium carbenoid intermediate was found to be slow in the reaction of **6** with phenylmagnesium chloride under the conditions which smoothly gave cyclopropylmagnesium carbenoid **10**; and allene **7** was produced in 25% yield. We concluded that phenylmagnesium halides were not suitable in this procedure. In entries 16–25 the reactions of **13b** and **13c** with ethylmagnesium chloride and cyclopentylmagnesium chloride followed by electrophiles are summarized. As shown, the results are quite similar with those of the reactions of **13b** and **13c** with *i*-PrMgCl shown in Table 3, entries 4–8.

In conclusion, we have found that HMPA suppresses the cyclopropylidene-allene rearrangement. Base on this finding, we established a procedure for the synthesis of multi-substituted cyclopropanes from aryl 1-chlorocyclopropyl sulfoxides in one-pot via the formation and alkylation of cyclopropylmagnesium carbenoids as the key reactions. This is the first example for the double substitution of chlorine and sulfinyl groups on a cyclopropane ring via cyclopropylmagnesium carbenoid intermediate.[13] Cyclopropanes are unambiguously one of the most important and fundamental compounds in organic and synthetic organic chemistries.[14] The results presented herein will contribute greatly to the synthesis of multi-substituted cyclopropanes and to the chemistry of magnesium carbenoids.

Table 4
Treatment of 1-chlorocyclopropyl aryl sulfoxides **13** with Grignard reagent in the presence of HMPA followed by electrophiles



6 R^1=CH_2OTr, R^2=R^3=H, Ar=Tol
13a R^1=R^2=R^3=H, Ar=Ph
b R^1=CH_3, R^2=CH_2OTr, R^3=H, Ar=Tol
c R^1=CH_3, R^2=CH_2OTr, R^3=CH_3, Ar=Tol

Entry	R^1	R^2	R^3	Ar	R	Electrophile	Additive[a]	**16**/Yield (%)	Ratio of diastereomers[a]	**7** or **15**/Yield (%)
1	H	H	H	Ph	CH_3CH_2	$PhCH_2CH_2I$	CuI	57		
2						PhCOCl	CuI	59		
3						PhCHO	$Al(CH_3)_2Cl$	54	Single isomer	
4						$PhCH_2CH_2I$	CuI	60		
5						PhCOCl	CuI	67		
6						PhCHO	$Al(CH_3)_2Cl$	73	Single isomer	
7	CH_2OTr	H	H	Tol	CH_3CH_2	H_3O^+		74	10:1	
8						CH_3I	CuI	61	5:1	
9						CH_2=$CHCH_2I$	CuI	68	5:1	
10						PhCOCl	CuI	60	5:1	
11						H_3O^+		73	10:1	
12						CH_3I	CuI	62	7:1	
13						CH_2=$CHCH_2I$	CuI	62	10:1	
14						PhCOCl	CuI	58	20:1	
15					Ph	H_3O^+		38	Single isomer	25
16	CH_3	CH_2OTr	H	Tol	CH_3CH_2	H_3O^+		61	5:1	31
17						CH_3I	CuI	53	10:3	34
18						CH_2=$CHCH_2I$	CuI	49	10:3	34
19						PhCOCl	CuI	55	4:1	32
20						H_3O^+		64	5:1	29
21						CH_3I	CuI	58	5:2	25
22						CH_2=$CHCH_2I$	CuI	45	5:1	30
23						PhCOCl	CuI	50	7:1	25
24	CH_3	CH_2OTr	CH_3	Tol	CH_3CH_2	H_3O^+		10	Single isomer	84
25						H_3O^+		13	Single isomer	76

[a] Ten mol % of CuI or 2 equiv of $Al(CH_3)_2Cl$ was used as the additive.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research No. 19590018 from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and TUS Grant for Research Promotion from Tokyo University of Science, which are gratefully acknowledged.

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11. A synthesis of **12** (E = PhCO; Table 2, entry 4) is reported as a representative example of this procedure. To a flame-dried flask, 0.5 ml of toluene, *i*-PrMgCl (2.0 M solution in diethyl ether; 0.4 ml, 0.8 mmol), and HMPA (0.14 ml; 0.8 mmol) were successively added at 0 °C under argon atmosphere. After stirring for 10 min, a solution of cyclopropyl sulfoxide **6** (49 mg; 0.1 mmol) in 0.5 ml of toluene was added to the mixture dropwise with stirring and the whole mixture was stirred at 0 °C for 30 min. To the reaction mixture were successively added copper (I) iodide (2 mg; 0.01 mmol) and benzoyl chloride (0.132 ml; 1 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by adding satd aq NH_4Cl. The whole was extracted three times with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash column chromatography (hexane/AcOEt) to give **12** (E = PhCO) (30 mg; 65%) as colorless crystals. Main product; mp 133–133.5 °C (Et_2O–hexane), IR (KBr); 2947, 2868, 1674, 1597, 1490, 1292, 1221, 1059, 988, 708 cm^{-1}; ^{1}HNMR δ 0.73–0.75 (1H, m), 0.77 (3H, d, J = 6.8 Hz), 0.78 (3H, d, J = 6.8 Hz), 1.00 (1H, dd, J = 5.4, 6.0 Hz), 1.56–1.60 (1H, m), 2.42 (1H, septet, J = 6.8 Hz), 2.71 (1H, dd, J = 8.0, 10.5 Hz), 3.20 (1H, dd, J = 4.7, 10.5 Hz), 7.15–7.30 (17H, m), 7.42–7.45 (1H, m), 7.91–7.93 (2H, m). Anal. Calcd for $C_{33}H_{32}O_2$: C, 86.05; H, 7.00. Found: C, 85.79; H, 6.99.
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