Copper(II) Acetate Mediated Reactions of Methylenecyclopropane and Diphenyl Diselenide

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Abstract: Phenylselenyl-substituted cyclobutenes and 1,3-butadienes were obtained from a copper(II) acetate mediated reaction between methylenecyclopropanes and diphenyl diselenide.

Key words: methylenecyclopropane, free radical, selenium, copper, electron transfer

Methylenecyclopropanes **1** (MCPs), which are highly strained but readily accessible molecules, are of current interest in synthetic organic chemistry.¹ Relief of their ring strain provides a potent thermodynamic driving force, which facilitates the construction of complex and interesting organic molecules under mild conditions.² During the last decade, much attention has been paid to the reactions of MCPs catalyzed by transition metals³ or Lewis acids.⁴ Recently, free-radical reactions of MCPs have also been widely investigated.⁵

Free-radical addition of diphenyl diselenide to methylenecyclopropanes has been reported.^{5c,g} In this reaction, a phenylselenyl radical, generated from the homolytic cleavage of diphenyl diselenide, was added to the MCP to give the phenylselenyl-substituted homoallylic free radical **3**, which then reacted with another molecule of diphenyl diselenide to produce 2,4-diphenylselenylbut-1ene (**4**) as the final product (Scheme 1). It is well known that carbonium ions can be generated from alkyl radicals by electron transfer in the presence of copper(II) acetate to produce organocopper intermediates, which could potentially produce some interesting compounds via further reactions.⁶ Hence, it is of interest to investigate the reaction of MCPs and diphenyl diselenide in the presence of copper(II) acetate.

Initially, we examined the reaction of diphenylmethylenecyclopropane (1a), diphenyl diselenide and copper(II) acetate under visible light irradiation using chloroform as the solvent. After two hours, only free-radical adduct 4awas obtained in 72% yield (Table 1, entry 1). This unsuccessful result was possibly due to the poor solubility of copper(II) acetate in chloroform. We therefore tried using acetonitrile as solvent as it has a higher polarity. Under similar conditions, 4a and 5a were produced in 15% and





44% yield, respectively (Table 1, entry 2). When the reaction was performed in DMSO, it proceeded very slowly and only trace amounts of **4a** were obtained (Table 1, entry 3). Interestingly, when acetic acid was employed, 2-phenylselenyl-3,3-diphenylcyclobutene **6a** could be obtained in 65% yield (Table 1, entry 4).

Table 1Reaction of Diphenylmethylenecyclopropane (1a), Diphenyl Diselenide and Copper(II) Acetate under Visible-LightIrradiation^a



Entry	Solvent	Time	Yield of 4a	Yield of 5a	Yield of 6a
		(h) ⁶	(%) ^c	(%) ^c	(%) ^c
1	CHCl ₃	2	72	0	0
2	MeCN	5	15	44	0
3	DMSO	8	trace	0	0
4	AcOH	5	0	0	65

^a **1a** (0.3 mmol), $(PhSe)_2 (0.3 \text{ mmol})$, $Cu(OAc)_2 (0.3 \text{ mmol})$ and solvent (2 mL) were employed.

^b The reaction was monitored by TLC (eluent: PE).

^c Isolated yields.

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Cyclobutene derivatives, which are not very easy to prepare, are pivotal skeletons in many natural products with an unusual spectrum of biological activities.⁷ They are also useful building blocks in synthetic organic chemistry.⁷ Selenium compounds are of great interest because of their synthetic applications and biological activities including antitumor, antibacterial activities and other properties.⁸ 2-Phenylselenyl-3,3-diarylcyclobutene (6), containing both a cyclobutene structural unit and a selenium atom, may have potential biochemical activity and applications in organic synthesis.⁹ Thus, a series of 2-phenylselenyl-3,3-diarylcyclobutenes 6 were prepared from various MCPs 1 under similar conditions (Table 2).¹⁰

Table 2 Synthesis of 2-Phenylselenyl-3,3-diarylcyclobutenes^a

\sim	+ (PhSe) ₂	Cu(OAc) ₂ •H ₂ O	R	
R 1		<i>h</i> v (> 300 nm) AcOH, N ₂	SePh 6	
Entry	R		Yield of 6 (%) ^b	
1	Ph (1a)		65 (6a)	
2	p-FC ₆ H ₄ (1b)		60 (6b)	
3	p-ClC ₆ H ₄ (1c)		62 (6c)	
4	p-MeC ₆ H ₄ (1d)		53 (6d)	
5	p-MeOC ₆ H ₄ (1e)		50 (6e)	

^a **1** (0.3 mmol), (PhSe)₂ (0.3 mmol), Cu(OAc)₂ (0.3 mmol) and AcOH (2 mL) were employed.

^b Isolated yields.

Previous literature has indicated that the reaction of MCPs and phenylselenyl chloride would produce 2-phenylselenyl-3,3-diarylcyclobutenes and 2-phenyl-4-chloro-1,1-diarylbut-1-enes. However, the yields of 2-phenylselenyl-3,3-diarylcyclobutenes were low, and when MCPs with an electron-donating group on the benzene ring (**1d** and





1e) were employed, only trace amounts of 2-phenylselenyl-3,3-diarylcyclobutenes were obtained.¹¹ Hence, the present method provides a facile entry to various 2-phenylselenyl-3,3-diarylcyclobutenes.

A possible mechanism for the formation of cyclobutene **6** is shown in Scheme 2. The phenylselenyl free radical, generated from the homolytic cleavage of diphenyl diselenide, adds to MCP **1** to form the intermediate **2**, which immediately undergoes homoallylic rearrangement to give **3**.^{5a,c} Compound **3** then reacts with copper(II) acetate to generate an organocopper intermediate **9**,⁶ which undergoes an intramolecular insertion of C=C to C–Cu to produce an intermediate **10** followed by β -elimination to afford the final product **6**.⁶

When monosubstituted MCP **1f** was employed, **7f** was obtained instead of the expected **6f** (Scheme 3). This was presumably due to less steric hindrance around the freeradical intermediate **2**, which allowed for the attack of the copper species prior to the homoallylic rearrangement. Similarly, when alkyl-substituted MCP **1g** was employed, attack of the copper species occurred before the homoallylic rearrangement. Subsequent β -elimination then gave the final product **8g**.



Scheme 3

Scheme 4

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Interestingly, when the reaction was undertaken under heat instead of visible light, the result was quite different. Under these conditions, β -elimination occurred on the intermediate 9 to give the phenylselenyl-substituted buta-1,3-diene 11 (Scheme 4).

Further screening demonstrated that using less solvent decreased the amount of solvent adduct and enhanced the yield of **11a** (Table 3, entry 2).

Table 3 Reaction of Diphenylmethylenecyclopropane (1a),Diphenyl Diselenide and Copper(II) Acetate under Heat^a

Ph		Cu(OAc) ₂ .	H ₂ O	Ph
Ph 1a	+ (PnSe) ₂ -	110 °C solvent, I	N ₂ F	PhSe Ph 11a
Entry	Solvent (volur	ne)	Time (h) ^b	Yield of 11a (%) ^c
1	HOAc (2 mL)		2	42
2	HOAc (0.2 ml	L)	2	68
3	-		3	10 ^d
4	DMSO (2 mL))	6	0

 a 1a (0.3 mmol), (PhSe)_2 (0.3 mmol) and Cu(OAc)_2 (0.3 mmol) were employed.

^b The reaction was monitored by TLC (eluent: PE).

° Isolated yields.

 $^{\rm d}$ Free-radical adduct ${\bf 4a}$ was obtained as the main product in 45% yield.

Under the optimized conditions, a series of phenylselenylsubstituted butadienes were synthesized (Table 4, entries 1–4).¹² When diphenyl disulfide was employed, the corresponding phenylsulfanyl-substituted 1,3-butadienes were obtained (Table 4, entries 5–7). Buta-1,3-dienes are useful building blocks in synthetic organic chemistry.¹³ Here, we have developed a convenient method for the synthesis of phenylselenyl- or phenylsulfanyl-substituted buta-1,3dienes.

Table 4Synthesis of Phenylselenyl- or Phenylsulfanyl-SubstitutedButa-1,3-dienes

	R	Cu(OAc) ₂ ·H ₂ O	RR
1	+ (PnY) ₂ - R	110 °C AcOH, N ₂	PhY R 11
Entry	R	Y	Yield of 11 (%) ^a
1	Ph (1a)	Se	68 (11a)
2	p-FC ₆ H ₄ (1b)	Se	46 (11b)
3	p-ClC ₆ H ₄ (1c)	Se	40 (11c)
4	p-MeC ₆ H ₄ (1d)	Se	54 (11d)
5	Ph (1a)	S	63 (11e)
6	p-FC ₆ H ₄ (1b)	S	48 (11f)
7	p-MeC ₆ H ₄ (1d)	S	52 (11g)

^a Isolated yields.

In conclusion, we have found that the copper(II) acetate mediated reactions of MCPs and diphenyl diselenide or diphenyl disulfide gave different results under different reaction conditions. Under visible light irradiation, phenylselenyl-substituted cyclobutenes were generated, while under heating conditions, phenylselenyl- or phenylsulfanyl-substituted buta-1,3-dienes were obtained. All of these analogues are extremely useful in organic synthesis.

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- (10) **2-Phenylselenyl-3,3-diarylcyclobutene** (6), typical procedure: Under an N₂ atmosphere, a solution of diphenylmethylenecyclopropane (1a, 0.062 g, 0.3 mmol), diphenyl diselenide (0.094 g, 0.3 mmol) and Cu(OAc)₂ (0.060 g, 0.3 mmol) in AcOH (2 mL) was irradiated with a tungsten lamp (300 W). The temperature rose to 40 °C because of the irradiation. The reaction was monitored by TLC (PE). When the reaction was complete, the solvent was evaporated under vacuum and the residue was subjected to preparative TLC (PE) to afford 6a in 65% yield. IR (KBr): 3055, 1575, 1491, 1217, 1025, 750, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.22–7.60 (m, 15 H), 6.12 (t, *J* = 0.8 Hz, 1 H), 3.17 (d, *J* = 0.8 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃):

δ = 46.9, 61.9, 126.4, 127.4, 127.5, 128.0, 128.1, 129.3, 133.9, 134.8, 141.8, 144.1; MS (EI, 70 eV): *m/z* (%) = 362 (12) [M⁺], 281 (14), 205 (100); HRMS (EI): *m/z* calcd for C₂₂H₁₈Se: 362.0574; found: 362.0574.

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