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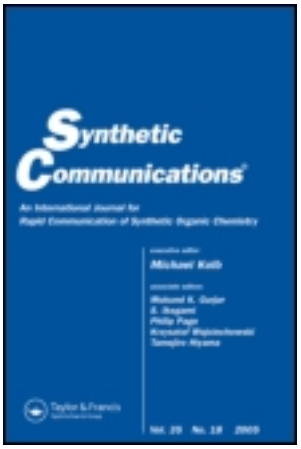

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First Iodine-Catalyzed Deallylation of Reactive Allyl Methylene Esters

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FIRST IODINE-CATALYZED DEALLYLATION OF REACTIVE ALLYL METHYLENE ESTERS

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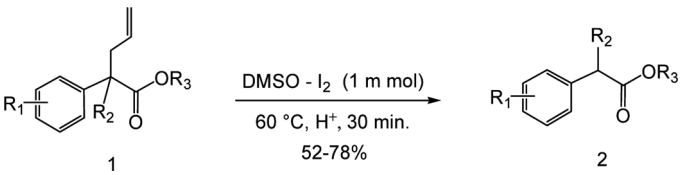
GRAPHICAL ABSTRACT



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Abstract *C-Allyl cleavage has been developed using the inexpensive and mild reagent iodine in dimethylsulfoxide. A variety of compounds with active methylene groups were C-deallylated using this reagent. This method is efficient and operationally simple in comparison to the methods using transition-metal complexes.*

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Keywords C-Allyl cleavage; dimethylsulfoxide; iodine

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INTRODUCTION

Carbon–carbon bonds are the foundation of organic chemistry. Tools for making such bonds are indispensable for the construction of complex molecules. In contrast, C-C bond cleavage reactions receive less attention. Oxidative cleavage,[1] sigmatropic rearrangement[2] and alkene metathesis[3] are key examples on a short list of synthetic methods that involve C-C bond cleavage. The development of efficient methods for the selective cleavage of C-C bonds is a challenging subject in modern organic synthesis.

The dialkylation becomes a significant side reaction in monoalkylation of active methylene esters with reactive alkyl halides or α,ω-dihaloalkanes. It is surprising that no protective group for the acidic hydrogen of malonic esters or acetoacetic ester has been developed. Because of the development of transition-metal-complex–catalyzed deallylation protocols, allyl groups can be introduced as protecting groups for the protection of active methylene groups in the compound. The use of allyl

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protecting groups for the protection of phenols, alcohols, amines, and carboxylic acids has become more common because of effective procedures available for their removal.[4,5]

Transition-metal-complex–catalyzed C-C bond formation and C-C bond cleavage under mild conditions are now well-established methodologies in organic synthesis and are widely used to construct complex molecules. Transition-metal catalysts involving palladium,[6,7] ruthenium,[8] and rhodium[9] have been studied for deallylation of allyl-alkyl ethers, allyl-carboxylates, and allyl amines. However there are very few reports available for C-allyl bond cleavages. C-Deallylation of malonates was reported for a titanium-promoted process[10] and was observed during palladium-catalyzed reactions.[11] The deallylation of allylmalonates has been reported using Ni,[12] Fe,[13] and Ru complexes.[14] Alternative methods for C-allyl cleavages are in demand as many transition-metal-free methods for C-allyl cleavages have been reported for O-allyl and N-allyl cleavages.

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RESULTS AND DISCUSSION

A new process for deallylation of aryl allyl ethers[15a,b] and allyl carboxylates[16] in the presence of a catalytic amount of iodine in dimethylsulfoxide (DMSO) has been recently reported at ambient temperature. Iodine is easily available and handy, workup procedure is simple, and no precautions need to be taken to exclude moisture or oxygen from the reaction system. A wide range of substrates undergo deallylation in the presence of many other functional groups. Earlier use of iodine (1.5 mmol) in deprotection of the prenyl group in prenyl carboxylate has been reported.[17] In this protocol, an allyl group was found to be incompatible. The DMSO-iodine reagent has been used in the deallylation and oxidative cyclization of 2′-allyloxy-chalcones to flavones.[18]

The use of iodine in C-C bond cleavage was reported for retro-Michael addition reaction on the same 1,5-dicarbonyl compounds. Similarly in the course of our investigation into the one-step synthesis of γ-butenolides, a sequence of reactions intended to convert α-allyl-methyl-phenyl-acetate (**1**) into α-methyl-γ-phenyl butenolides (**2**) was performed. A significant quantity of side product (**3**) was observed after the workup of these reactions. The identification of cyclization was α-methyl-γ-phenyl butenolide (**2**) and oxidation was methyl-phenyl-acetate (**3**) (15–20% yield).

Further investigation of reactivity of iodine toward oxidation reactions found that α-allyl-methyl-phenyl-acetate (**1**) when heated with iodine (1.5 mmol) at 145 °C oxidized to benzoic acid (**4**). When α-allyl-methyl-phenyl-acetate (**1**) was subjected to oxidation at 60 °C with iodine (1 mmol) in DMSO in the presence of a drop of concentrated sulfuric acid, phenyl acetic acid was obtained. The C-allyl cleavage could be the first reaction. On the basis of this study of iodine-catalyzed oxidation, it is assumed that successful C-allyl cleavages can be attained using iodine as catalyst in allyl methylene substrates. After many experiments, the first iodine-promoted deallylation of various C-allyl groups was successfully completed. Here the development of this new iodine-catalyzed reaction is reported.

As seen from inspection of Table 1, a wide variety of groups are tolerated on the aryl residue, ranging from the electron-withdrawing nitro group to the synthetically

Table 1. C-Allyl cleavage in α-allyl methyl-phenyl-acetate using I_2-DMSO

Entry	1	R_1	R_2	R_3	3	Yield (%) 3(a-o)[a,b]
1	**1a**	H	H	CH_3	**3a**	78
2	**1b**	4-Cl	H	CH_3	**3b**	71
3	**1c**	4-CH_3O	H	CH_3	**3c**	74
4	**1d**	4-NO_2	H	CH_3	**3d**	61
5	**1e**	2-NO_2	H	CH_3	**3e**	63
6	**1f**	3-NO_2	H	CH_3	**3f**	71
7	**1g**	H	-$CH_2C_6H_5$	CH_3	**3g**	59
8	**1h**	H	-$CH_2CH_2COOCH_3$	CH_3	**3h**	70
9	**1i**	H	-$CH_2CH(CH_3)COOCH_3$	CH_3	**3i**	67
10	**1j**	H	-$CH_2CH{=}CH_2$	CH_3	**3j**	60
11	**1k**	H	H	-$CH_2CH{=}CH_2$	**3k**	58
12	**1l**	H	CH_3	-$CH_2CH{=}CH_2$	**3l**	54
13	**1m**	H	-C_6H_5	CH_3	**3m**	52
14	**1n**	Br	H	CH_3	**3n**	62
15	**1o**	4-$CH_2CH(CH_3)_2$	CH_3	CH_3	**30**	59

[a]Isolated yields of the products.
[b]Products are characterized by spectral analysis.

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useful halides. Even the oxidation-prone methoxy group was tolerated in the reaction. The hydrolysis-prone ester group and carbonyl group in the side chain were well tolerated. The cleavage of C-allyl group was observed in preference to aryl, alkyl, and benzyl groups located at the methylene carbon atom.

Further attention was focused on the C-allyl cleavage reaction of various α-allyl-phenyl-acetates under the present reaction conditions. These reactions involve the selective removal of the allyl group observed in the presence of ester, benzyl, nitro, chloro, and methoxy groups. The entries **11 and 12** demonstrate the possibility of removal of the O-allyl group in preference to the C-allyl group.

Because we observed that the C-allyl group is cleaved at 60 °C using 1 mmol of iodine, we were interested in investigating whether the allyl group can be cleaved at room temperature so that it can be cleaved selectively in the presence of other groups. Therefore we performed the deprotection at room temperature and increasing the molar ratio of iodine to 1:1.5 mmol. The reaction was completed in 12 h. To our surprise, the C-allyl group cleaved cleanly and the methyl-phenyl-acetate was isolated in 90% yield. This reaction also demonstrates that ester groups are not cleaved and no oxidation product was observed. Further attention focused on the selective C-allyl cleavage of the allyl carboxylic ester (Table 1, entries **11 and 12**). As indicated, a considerable difference in reactivity was again observed for both O-allyl and C-allyl group deprotection. The O-allyl cleavage in **1k** and **1l** occurs selectively after 3 h at room temperature while C-allyl cleavage completed in 12 h at room temperature.

Catalytic activity of iodine was studied by considering α-allyl methyl-phenyl-acetate (**1a**) as a model substrate. It was observed that increase in the quantity of iodine gives greater yield (Table 2).

When α-diallyl ester **(1j)** reacts with iodine in the presence of DMSO, iodine activates the C=C bond and forms a three-membered iodonium intermediate. The

Table 2. Catalytic activity of iodine in C-deallylation

No.	Starting (1)	Product (3)	I_2 (mmol)	Temp. °C	Time (h)	Yield (%)[a,b]
1	**1a**	**3a**	0.1	60	0.5	20
2	**1a**	**3a**	0.2	60	0.5	38
3	**1a**	**3a**	0.5	60	0.5	52
4	**1a**	**3a**	0.8	60	0.5	55
5	**1a**	**3a**	1.0	60	0.5	58
6	**1a**	**3a**	1.2	60	0.5	59

[a]Isolated yields of the products.
[b]Products are characterized by spectral analysis.

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carbonyl oxygen of ester attacks the electron-deficient carbon of iodonium ion, which results in the cleavage of C-C bond, giving allyl vinyl ether. Further attack of iodine shows O-deallylation of allyl vinyl ether resulting in the formation of mono allylic ester **(3j)**. The second C-allyl group is removed by repeating the steps (a) to (d). However, no mechanistic study has been done; this mechanism is proposed on the basis of earlier observations. Recently O-deallylation in allyl ethers was reported using iodine (10 mol%) in polyethyleneglycol-400 as a green reaction solvent.[19]

The treatment of α-allyl-diethylmalonate (**5a**) with 1 mol of iodine in DMSO in the presence of a catalytic amount of sulfuric acid at 60 °C for 30 min gave a deallylated product diethylmalonate (**6a**) in an isolated yield of 58% (Table 3). It is also interesting to find that one allyl group of diethyl malonate (**5b**) selectively cleaved when 1-equivalent of iodine was used. Both allyl groups cleaved with 2 equivalent of iodine (**6b**).

Similar results were observed when allyl derivatives of ethyl-aceto-acetate (**7a–c**) and acetyl acetone (**7d–f**) were treated with iodine. For this, various allylic compounds were prepared using conventional techniques (K_2CO_3, allyl bromide, DMSO) in good yields. These C-allyl compounds were then subjected to cleavage conditions, which involved heating in DMSO with 1 mmol of iodine and monitoring the reaction by thin-layer chromatography (TLC). The results are summarized in Table 4. The reactions were completed in 30 min at 60 °C in the presence of a drop of concentrated sulfuric acid.

The C-allyl cleavage of a series of the allyl substrates (**7a–f**) having an allyl functionality at reactive methylene group proceeded with chemoselectivity at the

Table 3. C-Allyl cleavage in diethylmalonate using I_2-DMSO

Entry	**5**	R_4	**6**	Yield (%))[a, b]
1	**5a**	H	**6a**	58
2	**5b**	$-CH_2CH{=}CH_2$	**6b**	57
3	**5c**	$-CH_2C_6H_5$	**6c**	54
4	**5d**	$-CH_2CH_2COOCH_3$	**6d**	51
5	**5e**	$-CH_2CH(CH_3)COOCH_3$	**6e**	56

[a]Isolated yields of the products.
[b]Products are characterized by spectral analysis.

Table 4. C-Allyl cleavage in reactive methylene compounds using I_2-DMSO

Entry	7	R_5	R_6	R_7	8	Yield (%)[a,b]
1	**7a**	$-COCH_3$	$-OC_2H_5$	H	**8a**	75
2	**7b**	$-COCH_3$	$-OC_2H_5$	$-CH_2CH{=}CH_2$	**8b**	64
3	**7c**	$-COCH_3$	$-OC_2H_5$	$-CH_2C_6H_5$	**8c**	65
4	**7d**	$-COCH_3$	$-CH_3$	H	**8d**	59
5	**7e**	$-COCH_3$	$-CH_3$	$-CH_2C_6H_5$	**8e**	50
6	**7f**	$-COCH_3$	$-CH_3$	$-CH_2CH{=}CH_2$	**8f**	57

[a]Isolated yields of the products.
[b]Products are characterized by spectral analysis.

Table 5. Cyclization of allylic compound to α-pyrone using I_2-DMSO

Entry	9	R_8	R_9	R_{10}	10	Yield (%)[a,b]
1	**9a**	H	H	$-OCH_3$	**10a**	90
2	**9b**	H	$-OCH_3$	$-OCH_3$	**10b**	83
3	**9c**	Cl	$-OCH_3$	$-OCH_3$	**10c**	87

[a]Isolated yields of the products.
[b]Products are characterized by spectral analysis.

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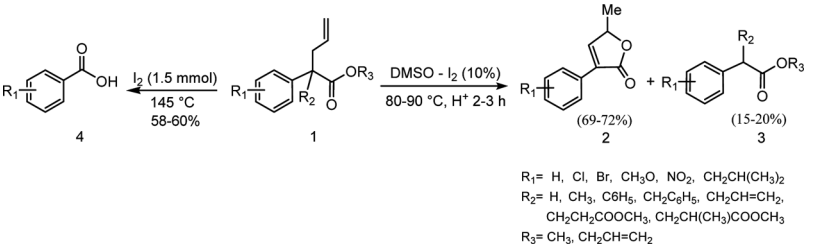
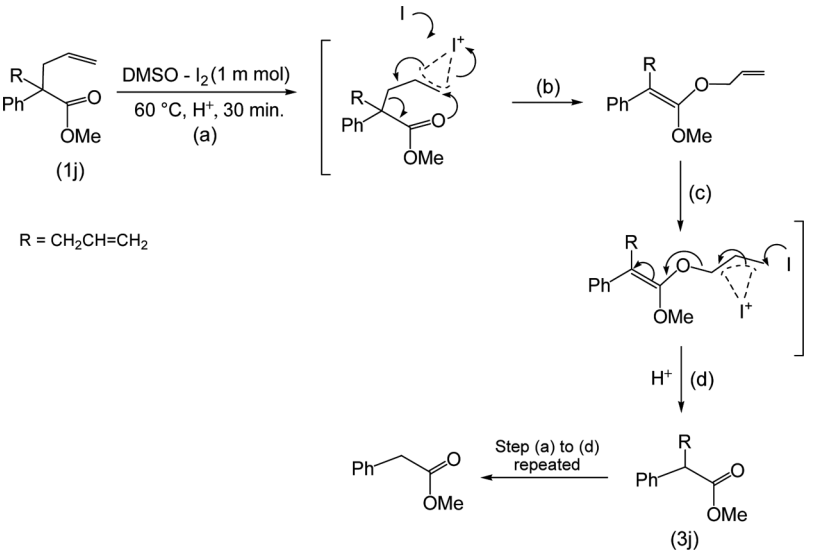
allyl end. Treatment of substances **7a–f** afforded products **8a–f** in 50–75% yields. For bis-allyl substrate (**7b,7f**), 2 equivalents of iodine is necessary for double deallylation, however, mono-deallylation proceeded smoothly. The reaction of **7c,7e** occurred smoothly at the allyl end eventhough benzyl group was located at the same carbon atom (Table 4).

α-Pyrones are found in a large number of natural products[20] that display a wide variety of biological activities.[21] The synthesis of 2-pyrones is either by traditional approaches[22] or by new approaches[23] and transition-metal-catalyzed procedures.[24]

Pursuing the competitive deallylation,we further investigated the effect of the side chain substituent in the cyclization of 5,6,7-member ring, which successfully involved allyl functionality (Table 5). We often observed the formation of cyclic product α-pyrone along with the desired deallylated product. When the percentage

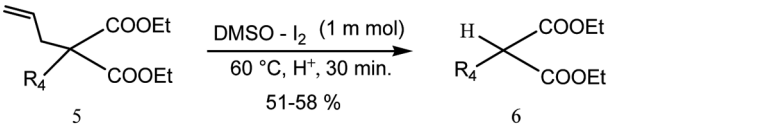


Scheme 1. Cyclization and oxidation of α-allyl methyl-phenyl-acetate.

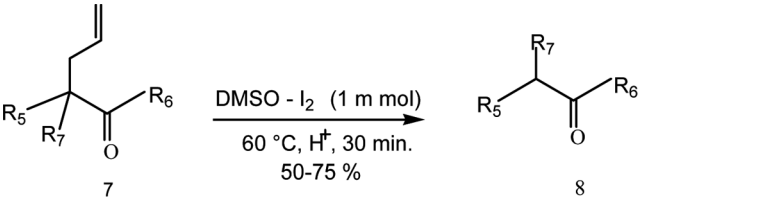


Scheme 2. Plausible mechanism for C-allyl cleavage.

mole of iodine increases at the same temperature, α-pyrone was the sole product with a yield of 90% (Scheme 5). Iodine acted as Lewis acid, which promotes the cyclization.



Scheme 3. C-Allyl cleavage in diethylmalonate.



Scheme 4. C-Allyl cleavage in reactive methylene compounds.

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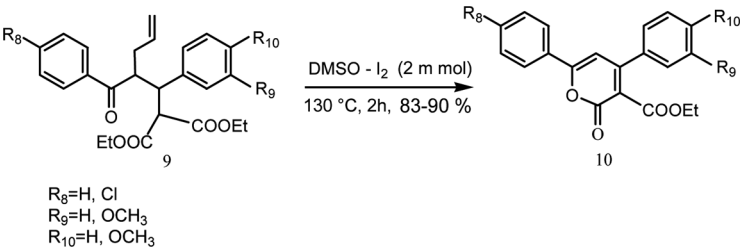
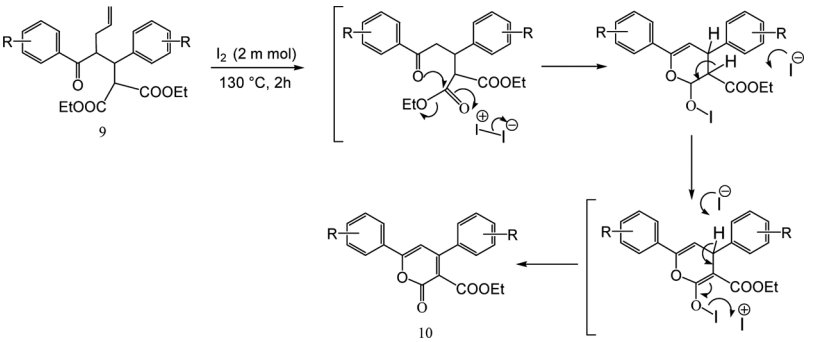


Scheme 5. Cyclization of allylic compound to α-pyrone.



Scheme 6. Plausible mechanism for synthesis of α-pyrone.

CONCLUSION

An efficient C-deallylation procedure for a variety of allylic compounds using iodine in DMSO reagent has been successfully developed. The reaction proceeds using a weak oxidizing agent in a short time. The ease of handling the reagent encourages using it for allyl deprotection in reactive methylene compounds.

EXPERIMENTAL

TLC was performed on E-Merck precoated 60 F_{254} plates, and the spots were rendered visible by exposure to ultraviolet light and iodine. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu 8000 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on Varian spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and with reference to tetramethylsilane (TMS) as internal standard. Mass spectra (GCMS) were recorded on a Shimadzu Q 5050 spectrometer.

General Procedure for C-Deallylation

Iodine (1 mmol) was added to a solution of allyloxy compound (**1**)(1 mmol) in DMSO (3 ml). The reddish reaction mixture was heated in an oil bath at 60 °C for

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30 min. After cooling, the reaction mixture was diluted with ice-cold water, and iodine was removed by addition of saturated solution of sodium thiosulfate and washing with water. The product **3** was extracted with ethyl acetate and dried over Na_2SO_4, and the solvent was evaporated. The product was purified by column chromatography (hexane / ethyl acetate, 9:1).

General Procedure for Cyclization of Allylic Compound to α-Pyrone

Iodine (2 mmol) was added to a solution of allyloxy compound (**9**) (1 mmol) in DMSO (3 ml). The reddish reaction mixture was heated in an oil bath at 130 °C for 2 h. After cooling, the reaction mixture was diluted with ice-cold water and iodine was removed by addition of saturated solution of sodium thiosulfate and washing with water. The product **10** was extracted with ethyl acetate and dried over Na_2SO_4, and the solvent was evaporated. The product was purified by column chromatography (hexane / ethyl acetate, 9:1).

Methyl 2-Phenylpent-4-enoate (1a)

IR: 1630, 1742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.02 (m, 1H), 3.67 (s, 3H), 4.51 (m, 2H), 5.22 (dd, $J = 10.2$, 20.4 Hz, 2H), 5.93 (m, 1H), 7.28 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 62.6, 62.2, 39.9. MS (m/z): 190 (M+ion). Anal. calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%. Found: C, 75.98; H, 7.21%.

Methyl 2-(4-Nitro phenyl)acetate (2d)

IR: 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H), 3.68 (s, 2H), 7.28 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 63.5, 42.3. MS (m/z): 195 (M+ion). Anal. calcd. for $C_9H_9NO_4$: C, 55.39; H, 4.65%. Found: C, 55.58; H, 4.4%.

Please see the Supplemental Material, available online, for further details.

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