SHORT COMMUNICATION

A CONVENIENT METHOD FOR LACTONIZATION OF α-ALLYL ESTERS USING IODINE IN DIMETHYLSULPHOXIDE

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ABSTRACT. A simple method for the synthesis of α-γ-disubstituted-γ-butyrolactones by cyclization of α-allyl esters using iodine in dimethylsulphoxide is reported. This method is efficient and operationally simple in comparison to methods using transition metal complexes.

KEY WORDS: γ-Butyrolactones, α-Allyl esters, Iodine, Dimethyl sulphoxide

INTRODUCTION

γ-Butyrolactones are important building blocks in the synthesis of many natural products [1]. Saturated γ-lactones are encountered frequently in large number of natural products especially flavour components and plant growth regulators [2]. γ-Lactones are also very useful in the synthesis of nucleosides and related bioactive compounds. In particular, some aryl substituted γ-lactones have shown cancer preventive and anti-inflammatory properties [3].

Several routes to prepare γ-lactones and lactone derivatives have been reported [4]. Numerous synthetic methods [5] have been developed for the synthesis of chiral α-methylene butyrolactones, often using transition metals or their [6].

Yamazaki *et al.* reported the use of the allyl group as a protecting group for the acidic hydrogen in malonic ester [7]. Iodine is available as a crystalline solid and is easy to handle and not particularly toxic. The DMSO-I$_2$ reagent has been used in the oxidative cyclization of 2'-hydroxy chalcones to flavones [8], the oxidation of flavanones to flavones [9], isoxazolines to isoxazoles [10], and pyrazolines to pyrazoles [11]. It has also been used for the deprotection of allyl carboxylic esters [12]. Very recently we reported the selective deallylation of allyl ethers and esters using iodine in polyethylene glycol-400 [13]. Allyl ethers of phenols are selectively deprotected using iodine in dimethyl sulphoxide [14].

Initial results of the use of iodine in dimethylsulphoxide for oxidative cyclization of 2'-allyloxy chalcones to flavones encouraged us to use this reagent system for the cyclization of α-allyl esters. 2'-Allyloxy chalcones with iodine (20%) in dimethylsulphoxide result in attack of the allyloxy oxygen towards reactive alkene group. This results in the deallylation of 2'-allyloxy chalcones followed by cyclization to give six membered flavone rings. In α-allylphenyl acetate, the allyl group is attached to a carbon which is bonded to an aryl ring and a carbonyl group. This carbon is sufficiently acidic to give the deallylated product. To study C-deallylation, α-allyl esters were reacted with iodine (20%) in dimethylsulphoxide reagent. But under the initial conditions, it was observed that the oxygen of the ester group attacks the allyl group to form the corresponding γ-butyrolactone. We herein report the results of a study involving the reaction of α-allyl esters with I$_2$-DMSO to yield α-γ-disubstituted-γ-butyrolactones.

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EXPERIMENTAL

General procedure for cyclization of α-allyl esters to α-γ-disubstituted-γ-butyrolactones (2a-o).
To a solution of α-allyl ester **1** (1 mmol) in dimethylsulphoxide (3 mL) was added iodine (0.2
mmol). The reaction mixture was heated in an oil bath at 80-90 °C for 2 hours. After cooling,
the reaction mixture was diluted with water and iodine was removed by addition of a saturated
solution of sodium thiosulphate followed by a water wash. The product was extracted into ethyl
acetate, washed with water, dried over anhydrous Na_2SO_4 and the solvent removed using a
rotary evaporator. The product was purified by column chromatography (hexane/ethyl acetate,
9:1).

Compound 2a. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 7.5 Hz, 3H), 2.61 (m,
2H), 3.88 (t, 4.42 (t, J = 7.2 Hz, 1H), 4.6 (m, 1H), 7.18 (d, J = 7.2 Hz, 2H), 7.32 (m, 3H); [13]C
NMR (75 MHz, $CDCl_3$) δ 174.1, 144.3, 134.5, 134.8, 131.2, 121.3, 77.1, 22.8; IR 1763, 1610,
1511 cm^{-1}; MS(*m/z*) 176 (M[+] ion).

Compound 2c [15]. White crystals, yield 74%, m.p. 103–106 ºC. IR(KBr pellet): 1764, 1611,
158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 6.9 Hz, 2H), 7.43 (d, J = 6.9 Hz, 2H), 4.65
(m, 1H), 3.8 (t, J = 6.9 Hz, 1H), 2.61 (m, 2H), 1.46 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz,
CDCl3): δ 175.44; 147.12; 143.93; 128.65; 123.93; 75.15; 45.07; 37.21; 20.99. B: 175.16;
147.12; 143.44; 128.97; 123.79; 75.20; 47.28; 39.23; 20.71.

Compound 3c [15]. Yellow crystals, yield 56%, m.p. 130–133 ºC. IR (KBr pellet): 3074, 1743,
1600, 1511, 856 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J = 6.9 Hz, 2H), 8.09 (d, J = 6.9
Hz, 2H), 7.78 (d, J = 1.7 Hz, 1H); 5.23 (m, J = 1.7 Hz, 1H); 1.56 (d, J = 6.9 Hz, 3H), ^{13}C NMR
(75 MHz, $CDCl_3$): δ 170.51; 152.14; 147.86; 135.43; 129.53; 127.82; 123.73; 77.08; 18.99;
calcd for $C_{11}H_9NO_4$: C, 60.28; H, 4.14; N 6.39; found: C, 60.28; H, 4.08; N 6.39.

RESULTS AND DISCUSSION

Earlier we reported the use of DMSO-I_2 for the synthesis of flavones from 2'-allyloxy chalcones
[16] in which the allyl group is first deprotected and the resulting 2'-allyloxychalcones then
oxidatively cyclized to flavones. We thought this type of cyclization would be possible in α-allyl
esters using the same reagent. To test this hypothesis, α-allyl carboxylic esters (**1**) were reacted
with iodine (20%) in dimethyl sulphoxide in order to generate the γ-butyrolactone. The reaction
was complete in 3-4 hours at 80-90 °C. It was observed that the reaction resulted in cyclization
to give the product α-γ-disubstituted-γ-butyrolactone (**2**) (Scheme 1).
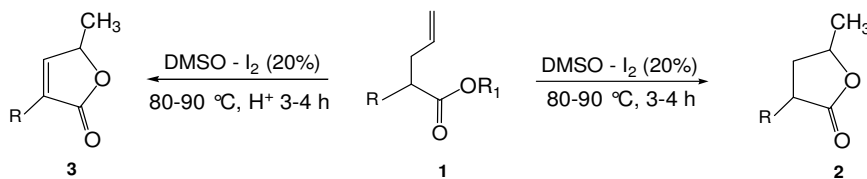
Scheme 1. Cyclization of α-allyl carboxylic esters.

Table 1. Cyclization of α-allyl esters to α-γ-disubstituted-γ-butyrolactones by using I$_2$-DMSO.

| Entry	Substrate	R	R$_1$	Yield % 2(a-o)[a,b]
1	1a	C$_6$H$_5$-	C$_2$H$_5$	78
2	1b	2-NO$_2$-C$_6$H$_4$-	C$_2$H$_5$	71
3	1c	4-NO$_2$-C$_6$H$_4$-	C$_2$H$_5$	74
4	1d	CH$_3$-	CH$_3$	61
5	1e	C$_2$H$_5$-	CH$_3$	63
6	1f	C$_4$H$_9$-	C$_2$H$_5$	71
7	1g	C$_{10}$H$_{21}$-	CH$_3$	59
8	1h	C$_6$H$_5$-	CH-(CH$_3$)$_2$	70
9	1i	2-NO$_2$-C$_6$H$_4$-	CH-(CH$_3$)$_2$	67
10	1j	2-NO$_2$-C$_6$H$_4$-	CH$_3$	72
11	1k	C$_6$H$_5$COCHCOOC$_2$H$_5$	C$_2$H$_5$	60
12	1l	4-(OCH$_3$)C$_6$H$_4$COCHCOOC$_2$H$_5$	C$_2$H$_5$	58
13	1m	3,4-(OCH$_3$)$_2$C$_6$H$_3$COCHCOOC$_2$H$_5$	C$_2$H$_5$	54
14	1o	4-ClC$_6$H$_4$COCHCOOC$_2$H$_5$	C$_2$H$_5$	52

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

There are different methods reported for allyl cyclization using iodine. In most cases, iodocyclization gives the desired product [17]. In the synthesis of flavones from 2'-hydroxychalcones, Silva and co-worker reported that traces of HI were observed [18]. In the presence of HI, our cyclization method results in generation of γ-methyl-butyrolactones. Presumably, this reaction is initiated by the HI which is formed in situ [19]. The generation of HI can be explained by the following reaction (Scheme 2).
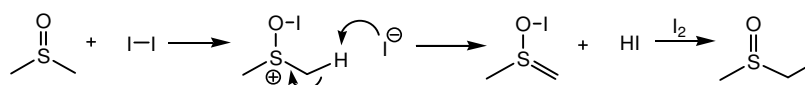
Scheme 2. Formation of HI.

A possible mechanism for cyclization of α-allyl carboxylic esters (1) to α-γ-disubstituted-γ-butyrolactone (2) is presented below (Scheme 3).
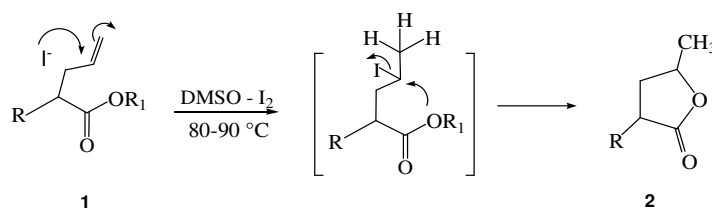
Scheme 3. A proposed mechanism for lactonization of α-allyl carboxylic esters.

α-Substituted-γ-methyl-butenolides are very important compounds in the synthesis of natural products. α-Phenyl-γ-methyl-butenolide has antifungal activity [20] against filamentous fungi.

α-Butyl-γ-methyl-butenolide can be used as a precursor for the synthesis of blastmycinone, blastmycinolactol.

Previous studies reported the synthesis of flavones from 2'-allyloxy chalcones [16]. In this reaction, deallylation with oxidative cyclization of 2'-allyloxy chalcones gives flavones at 130 °C in 30 min. The same reaction can be accomplished at 60 °C in presence of a drop of concentrated sulphuric acid. In order to examine the effect of acid in reducing the temperature of the cyclization reaction of α-allyl carboxylic esters (**1**), a drop of concentrated sulfuric acid was added to the iodine in dimethylsulphoxide (Scheme 2). The reaction was completed in 3 h giving 40% yield. The plausible mechanism for the formation of α-substituted-γ-methyl-butenolide from α-allyl carboxylic esters (**1**) is shown in Scheme 4.

Table 2. Cyclization of α-allyl esters to α-substituted-γ-methyl-butenolide by using I_2-DMSO/H^+.

Entry	Substrate	R	R_1	Yield % **3(a-e)**[a,b]
1	**1a**	C_6H_5-	CH_3	40
2	**1b**	$2\text{-}NO_2\text{-}C_6H_4$-	CH_3	35
3	**1c**	$4\text{-}NO_2\text{-}C_6H_4$-	CH_3	30
4	**1d**	CH_3-	CH_3	15
5	**1e**	C_4H_9-	CH_3	25

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

Table 3. Effect of Quantity of iodine.

Entry	Compound	Iodine (mmol)	Yield **2a**(%)[a,b]
1	**1a**	0.10	35
2	**1a**	0.15	52
3	**1a**	0.20	78
4	**1a**	0.25	79

[a]Isolated yields of the product. [b]Products are characterized by spectral analysis.
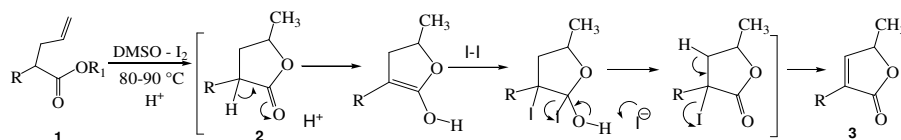
Scheme 4. The plausible mechanism for the formation of α-substituted-γ-methyl-butenolide.

In conclusion, we report a method for preparing α-γ-disubstituted-γ-butyrolactones by cyclization of α-allyl esters using iodine in dimethylsulphoxide. The efficiency, ready availability, and ease of handling encourages using the reagent for lactonization of various α-allyl- esters. The DMSO-I_2 reagent in the presence of a catalytic amount of H^+ is useful for the synthesis of α-substituted-γ-methyl-butenolides.

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