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SHORT COMMUNICATION

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

Beena R. Nawghare, Sunil V. Gaikwad, Bharati V. Pawar and Pradeep D. Lokhande*

The Centre for Advanced Studies, Department of Chemistry, University of Pune, Pune 411007, India

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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.

*Corresponding author. E-mail: pdlokhande@chem.unipune.ernet.in

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).

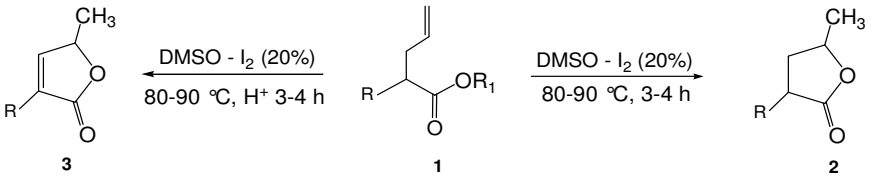
*Compound **2a***. Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 7.5 Hz, 3H), 2.61 (m, 2H), 3.88 (t, 4.42 (t, J = 7.2 Hz, 1H), 4.6 (m, 1H), 7.18 (d, J = 7.2 Hz, 2H), 7.32 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 144.3, 134.5, 134.8, 131.2, 121.3, 77.1, 22.8; IR 1763, 1610, 1511 cm^{-1};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



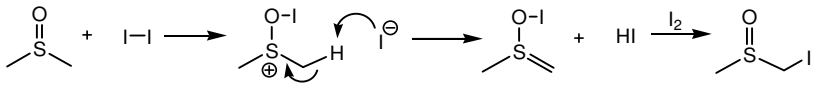
Scheme 1. Cyclization of α-allyl carboxylic esters.

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_6H_5-	C_2H_5	78
2	**1b**	2-NO_2-C_6H_4-	C_2H_5	71
3	**1c**	4-NO_2-C_6H_4-	C_2H_5	74
4	**1d**	CH_3-	CH_3	61
5	**1e**	C_2H_5-	CH_3	63
6	**1f**	C_4H_9-	C_2H_5	71
7	**1g**	$C_{10}H_{21}$-	CH_3	59
8	**1h**	C_6H_5-	CH-$(CH_3)_2$	70
9	**1i**	2-NO_2-C_6H_4-	CH-$(CH_3)_2$	67
10	**1j**	2-NO_2-C_6H_4-	CH_3	72
11	**1k**	$C_6H_5COCHCOOC_2H_5$ |	C_2H_5	60
12	**1l**	4-$(OCH_3)C_6H_4COCHCOOC_2H_5$ |	C_2H_5	58
13	**1m**	3,4-$(OCH_3)_2C_6H_3COCHCOOC_2H_5$ |	C_2H_5	54
14	**1o**	4-$ClC_6H_4COCHCOOC_2H_5$ |	C_2H_5	52

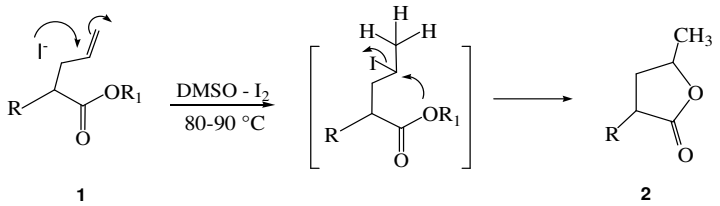
[a]Isolated yields of the product. [b]Products are characterized by spectral analysis.

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^+.

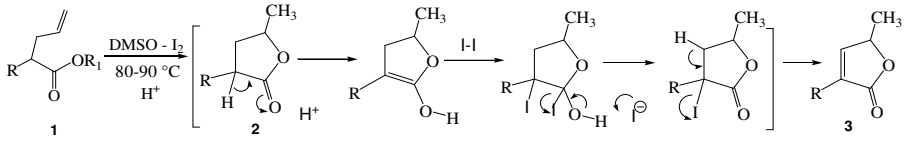
Entry	Substrate	R	R_1	Yield % **3**(**a-e**)[a,b]
1	**1a**	C_6H_5-	CH_3	40
2	**1b**	2-NO_2-C_6H_4-	CH_3	35
3	**1c**	4-NO_2-C_6H_4-	CH_3	30
4	**1d**	CH_3-	CH_3	15
5	**1e**	C_4H_9-	CH_3	25

[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.

REFERENCES

1. Boukouvalas, J.; Loach, R.P. *J. Org. Chem.* **2008**, 73, 8109.
2. Koch, S.S.C.; Chamberlin, A.R. *J. Org. Chem.* **1993**, 58, 2725.
   2a. Dabs, P.; Stussi, R.; *Helv. Chim. Acta* **1978**, 61, 990.
3. Lambert, J.D.; Rice, J.E.; Hong, J.; Hou, Z.; Yang, C.S. *Bioorg. Med. Chem. Lett*. **2005**, 15, 873.

4. Roberto, B.; Enrico, M.; Silvia, P. *J. Org. Chem.* **1999**, 64, 2954 and references therein. (a) Carosi, L.; Hall, D.G. *Can. J. Chem.* **2009**, 87, 650.
5. For review papers see: Grieco, P.A. *Synthesis* **1975**, 2, 67. 5a. Lee, E.; Lim, J.L.; Yoon, C.H.; Sung, Y.S.; Kim, Y.K. *J. Am. Chem. Soc*. **1997**, 119, 8391.
6. Drewes, S.E.; Hoole, R.F.A. *Synth. Commun.* **1985**, 15, 1067.
7. Yamazaki, T.; Kasatkin, A.; Kawanaka, Y.; Sato, F. *J. Org. Chem*. **1996**, 61, 2266.
8. Ghiya, B.J.; Soni, P.A.; Doshi, A.G. *Ind. J. Chem.* **1986**, 25B, 759.
9. Wasim, F.; Jawaid, F.; Manchanda, W.; Shaidawara, R.W. *J. Chem. Res*. **1984**, 9, 298.
10. Gaikwad, D.D.M. *Synthesis of Oxygen, Nitrogen Heterocyclic Compound*, M. Phil. Thesis, University of Pune, Pune, India, **2003**.
11. Lokhande, P.D.; Waghmare, B.Y.; Sakate, S.S. *Indian J. Chem*. **2005**, 44B, 2338.
12. Lokhande, P.D.; Taksande, K.N.; Sakate, S.S. *Tetrahedron Lett*. **2006**, 47, 643.
13. Lokhande, P.D.; Konda, S.G.; Humne, V.T. *Green Chemistry* **2011,** 13, 2354.
14. Lokhande, P.D.; Nawghare, B.R. *Indian J. Chem*. **2012**, 51B, 328.
15. Pour, M.; Spulak, M.; Balsanek, V.; Kunes, J.; Kubanova, P.; Buchtab, V. *Bio. Med. Chem.* **2003**, 11, 2843.
16. Lokhande, P.D.; Sakate, S.S.; Taksande, K.N.; Nawghare, B.R. *Tetrahedron Lett*. **2005**, 46, 1573. (a) Lokhande, P.D.; Nawghare, B.R; Sakate, S.S. *J. Heterocycl. Chem*. **2011**, DOI: 10.1002/jhet.1580.
17. Mphahlele, M.J. *Molecules* **2009**, 14, 4814. (a) Maeda, K.; Miller, R.A.; Szumigala, R.H.; Shafiee, A.; Karady, S.; Armstrong, J.D. *Tetrahedron Lett*. **2005**, 46, 1545. (b) Inoue, T.; Kitagawa, O.; Ochiai, O.; Taguchi, T. *Tetrahedron: Asymmetry* **1995**, 6, 691. (c) Tsuboi, S. *J. Org. Chem*. **1998**, 63, 1102. (d) Liu, J.T.; Yun, L. *Tetrahedron Lett*. **2006**, 47, 6075. (e) Paolucci, C.; Righi, P. *Tetrahedron Lett*. **2007**, 63, 12763.
18. Silva, A.M.S.; Pinto, D.C.G.A.; Cavaleiro, J.A.S. *Tetrahedron Lett*. **1994**, 35, 5899.
19. Floyd, M.B.; Du, M.T.; Fabio, P.F.; Jacob, L.A.; Johnson, B.D. *J. Org. Chem.* **1985**, 50, 5022. (a) Zoretic, P.A. *J. Org. Chem.* **1975**, 40, 1867. (b) Schipper, E.; Cinnamon, M.; Rascher, L.; Chiang, Y.H.; Oroshnik, W. *Tetrahedron Lett*. **1968**, 6201.
20. Amonkar, C.P.; Tilve, S.G.; Parameswaran, P.S. *Synthesis* **2005**, 2314.