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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Vivek Humne & Pradeep Lokahnde (2014) Efficient Deallylation of Allyl Phenyl Ethers by Molecular Iodine in PEG-400 and Their Utility for Flavone Synthesis, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:7, 929-935, DOI: <u>10.1080/00397911.2013.837489</u>

To link to this article: http://dx.doi.org/10.1080/00397911.2013.837489

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Synthetic Communications[®], 44: 929–935, 2014 Copyright © Taylor & Francis Group, LLC ISSN: 0039-7911 print/1532-2432 online DOI: 10.1080/00397911.2013.837489

EFFICIENT DEALLYLATION OF ALLYL PHENYL ETHERS BY MOLECULAR IODINE IN PEG-400 AND THEIR UTILITY FOR FLAVONE SYNTHESIS

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GRAPHICAL ABSTRACT



Abstract *Rapid and efficient deallylation of allyl phenyl ethers by molecular iodine* (20 mol%) in polyethylene glycol-400 at 60 °C has been reported. This method has short reaction time, readily available catalyst, and reuse of reaction medium with good yield. The utility of this methodology has been extended to flavone synthesis.

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications[®] for the following free supplemental resource(s): Full experimental and spectral details.]

Keywords Allyl phenyl ether; deallylation; flavones; molecular iodine; PEG-400

INTRODUCTION

Protection and deprotection are the significant processes in organic transformation. Allyl is a commonly used protecting group for various functionalities, especially phenols, alcohols, acids, and amines.^[1] The stability to acidic and basic conditions, is the most beneficial feature of allyl protection. Allyl protection is useful in carbohydrate^[2] and peptide synthesis^[3,4] and in other polyfunctional molecules.^[5] In general, deprotection of allyl group has been carried out by direct cleavage of C-O bond using transition metals such as palladium,^[6] ruthenium(II),^[7] iridium(I),^[8] titanium,^[9] and zirconium.^[10] Other reagents used for deprotection process are 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),^[11] SeO₂,^[12] and NBS-hv.^[13]

Received July 11, 2013.

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However, these procedures have several drawbacks such as harsh conditions, toxicity, use of stoichiometric proportion, and difficulty of loading the catalyst. Therefore, development of rapid, efficient, and ecofriendly protocol for the cleavage of allyl group is exceedingly desirable.

Over the past few decades, molecular iodine has been widely used in pharmaceutical and organic syntheses because of its inexpensive, nontoxic, and environmentally benign characteristic nature.^[14] Recently, polyethylene glycol (PEG) is used as a green solvent^[15] and has many applications, particularly in substitution, oxidation, and reduction reactions.^[16] Many recent reviews cover the application of PEG in biotechnology and medicine.^[17,18] As a part of a continuing effort in our laboratory to study iodine-mediated transformations,^[19,20] we became interested in the possibility of developing a novel and efficient method of deallylation of allyl phenyl ether by molecular iodine in PEG-400 and the synthetic application is extended to flavone synthesis.

RESULTS AND DISCUSSION

Deallylation of allyl phenyl ether by molecular iodine in PEG-400 was studied by taking **1a** as a model reaction (Scheme 1). First, substrate **1a** was treated with 5 mol% of iodine, and o-deallylated product **2a** was obtained in 46% yield with recovery of starting substrate after 12 h. Subsequent loading of 20 mol% of iodine reduces reaction time and increases yield (Scheme 1). However, use of 100 mol% of iodine does not alter the results. Several solvents such as MeOH, dichloromethane (DCM), dimethylformamide (DMF), and ethylene glycol were examined for best reaction medium. However, trace amounts of product (18%) were observed in ethylene glycol after 18 h. After replacing ethylene glycol by PEG-400, o-deallylated product isolated with excellent yield. On the basis of this result, we established that PEG-400 is a good solvent for deallylation.

To understand the role of PEG-400, we performed deallylation of **1a** in various glycols such as triethylene glycol, PEG-600, PEG-4000, PEG-6000, and PEG-8000 (Table 1). Poor yield (22%) was observed in triethylene glycol. However, as the molecular weight of PEGs increases (entries 5–7, Table 1), the viscosity increases. Therefore, temperature of the solvent has been increased to 100 °C for liquefaction of PEG. Almost the same results have been observed in other PEGs. In general, PEG formed the complex with the cation, which activates the anion in the same medium.^[21]

To determine the reusability of the solvent, the reaction mixture was extracted by ethyl acetate. The combine organic layer was dried over anhydrous sodium sulfate and evaporated. The resulting mother liquor was subjected to vacuum distillation to



Scheme 1. Cleavage of aryl ally ethers.

DEALLYLATION OF ALLYL ETHERS BY IODINE

		6.	
Entry	Glycol	Time (h)	Yield (%) ^a
1	Ethylene glycol	18	18
2	Triethylene glycol	16	22
3	PEG-400	0.25	96
4	PEG-600	0.25	95
5	PEG-4000	0.3	90
6	PEG-6000	0.3	90
7	PEG-8000	0.35	88

Table 1. Deallylation of 1a in different glycols

^aIsolated yields of the products.

remove water and PEG remains in the bottom part of the container. The recovered PEG was used for five cycles without loss of activity (Table 2). With this result, we next turned to study the variety of allyl phenyl ethers (Table 3). Substrates having electron-withdrawing and electron-donating groups were smoothly deallylated.

In this context, cleavage of 2'-allyloxy chalcones **3a–e** using 20 mol% of iodine in PEG-400 has been studied. Interestingly, deallylation with oxidative cyclization of 2'-allyloxy chalcones was carried out and gave the corresponding flavones in 45 min (Scheme 2, Table 4). A variety of 2'-allyloxy chalcones were studied by molecular iodine in PEG-400. Surprisingly, chloro-substituted flavone was afforded in shorter time (Table 4, entries a, b). Gratifyingly, all the corresponding substituted flavones were obtained in good yield.

The infrared (IR) spectrum of **4a–f** shows that the frequency at 1656 cm^{-1} corresponds to the carbonyl group. In the ¹H NMR spectrum, allylic protons and a double doublet at 6.87 and 7.45 ppm of coupling constant 15.8 Hz regarding the C-2 and C-3 of chalcone disappeared. The characteristic signal of flavone was observed at 6.97 ppm due to its C-3 position. Eventually the formation of product was confirmed by elemental analysis, which was well correlated to calculate the molecular formula of the product.

In our previous work, we successfully achieved selective o-deallylation by using a catalytic amount of iodine in PEG-400.^[22a] The role of PEG is possibly to form a complex with the cation, much like crown ether, and these complexes cause the anion to be activated.^[22b] When iodine was employed for the deallylation process, it activates the C=C bond of allyl functionality and forms a three-membered iodonium

Run	Yields (%	
1	95	
2	92	
3	90	
4	90	
5	88	

 Table 2. Recycling of PEG-400 on deallylation of 1a with 10 mol% of iodine as catalyst at room temperature

^aAll reactions were carried out with 1 mmol of substrate.

Entry	Substrate (1a–i)	Product (2a-i)	Yield (%) ^{<i>a,b</i>}
a		CI	96
b	Me	Me	92
c		OH	88
d		CH ₃	89
e		OH	92
f		CI	94
g	H ₃ C	H ₃ C OH	90
h		OH H	95
i	O ₂ N	O ₂ N OH	90

Table 3. Deallylation of allyl phenyl ethers using iodine (20 mol%) in PEG-400 at room temperature

^{*a*}Isolated yields of the products.

^bSpectral data and mp of the products are matches with the authentic sample.

intermediate, which is stabilized by oxygen atoms of PEG. Similar to this, the formation of flavones proceed first through deallylation^[22a] of chalcone, and then oxidative cyclization is achieved by complex formation of iodine cation stabilized by PEG (Fig. 1). The color of the solution remains unchanged, which suggested regenerated iodine.



Scheme 2. Synthesis of flavones.

EXPERIMENTAL

All reagents were of commercial quality, and reagent-quality solvents were used without further purification. 1 H and 13 C NMR spectra were determined on a

 Table 4. Synthesis of flavones through selective deallylation of allyl phenyl ether by molecular iodine (10 mol%) in PEG-400

Entry	Product (4a-e)	Time (min)	Temperature (°C)	Yield (%) ^a
a		20	60	92
b		20	60	91
с	H ₃ C	45	100	86
d	H ₃ C	45	100	87
e		20	60	90

^aIsolated yields of the products.



Figure 1. Plausible reaction pathway for synthesis of flavone.

Varian Mercury 300-MHz Fourier transform (FT) spectrometer. Mass spectra were obtained on Shimazdu-QP 5050 GC-MS spectrometer. IR spectra (KBr) were recorded on a Shimadzu FT-IR DR-8001 spectrophotometer. The purity of the compounds was assessed by thin-layer chromatography (TLC) on silica gel 60 F254.

General Procedure for Synthesis of Flavones (4a)

A mixture of 2'-allyloxy chalcones **3** (1 mmol) and iodine (20 mol%) in PEG-400 (10 mL) was stirred at 60 °C for 30–45 min. The reaction mixture was poured in a cold solution of sodium thiosulfate and extracted by ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 , evaporated under vacuum, and purified by column chromatography. The corresponding product was obtained in 86–92% yield.

6-Chloro-2-(3-methoxy-4-allyloxyphenyl)-4H-chromen-4-one (4a)

IR (KBr): 3648, 3078, 1702, 1645, 1612, 1564, 1445, 1348, 1296, 1245, 1132, 1064, 1005, 929, 864, 818, 756 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.12 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 2.7, 2.4 Hz, 1H), 7.49 (d, J = 12.6 Hz, 1H), 7.32 (s, 1H), 6.96 (d, J = 1.4 Hz, 1H), 6.73–6.70 (m, 1H), 6.10–6.13 (m, 1H), 5.88–5.89 (m, 1H), 5.46 (dd, J = 3.3, 10.5 Hz, 2H), 4.69 (d, J = 5.4 Hz, 2H), 3.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 180.75, 163.36, 154.85, 154.17, 151.04, 149.33, 133.54, 132.13, 124.88, 124.61, 123.63, 119.77, 119.52, 118.54, 112.61, 108.89, 106.07, 72.68, 56.05; MS(m/z): 342 (M+ion). Anal. calcd. for C₁₉H₁₅ClO₄: C, 66.58; H, 4.41; Cl, 10.34. Found: C, 66.63; H, 4.52; Cl, 10.37.

CONCLUSION

In conclusion, a simple and metal-free deallylation of allyl phenyl ethers to corresponding phenols using 20 mol% of iodine in polyethylene glycol-400 has been reported. The present method does not involve any hazardous organic solvent. The solvent was reusable for a number of times without appreciable loss of activity. Therefore,

this procedure could be classified as green protocol. The present methodology is applied for the synthesis of flavones occurring in natural products and drugs.

SUPPORTING INFORMATION

Full experimental detail and ¹H and ¹³C NMR spectra of all synthesized compounds can be found via the Supplementary Content section of this article's webpage.

ACKNOWLEDGMENTS

V. T. H. thanks the Counsil of Scientific and Industrial Research, New Delhi, India, for the award of a fellowship.

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