Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 3755–3759
Tetrahedron Letters

Reaction of allylic and benzylic alcohols and esters with PPh_3/I_2: one-pot synthesis of β,γ-unsaturated compounds

E. J. Alvarez-Manzaneda,[a,*] R. Chahboun,[a] E. Cabrera Torres,[a] E. Alvarez,[a] R. Alvarez-Manzaneda,[b] A. Haidour[a] and J. M. Ramos López[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Biotecnología, Universidad de Granada, 18071 Granada, Spain*
[b]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Almería, 04120 Almería, Spain*

Received 22 December 2004; revised 15 March 2005; accepted 21 March 2005
Available online 6 April 2005

Abstract—The treatment of tertiary and secondary allylic alcohols containing a terminal double bond, and their acetyl derivatives, with triphenylphosphine and iodine under mild conditions leads regiospecifically and in high stereoselectivity to the corresponding primary allylic iodides, which can react 'in situ' with diverse nucleophiles. Primary allylic alcohols and benzyl alcohols and acetates are also transformed into the corresponding iodides under these conditions.

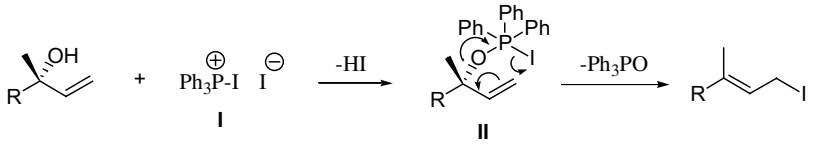
1. Introduction

Allylic halides are versatile starting materials that are widely used in synthetic organic chemistry. They are usually prepared from the corresponding allylic alcohols by the action of a great variety of reagents. Chlorides have been prepared utilizing chlorohydric acid,[1] thionyl chloride,[2] titanium(IV) chloride,[3] *N*-chlorosuccinimide[4] or chloromethylsilanes.[5] Bromides are frequently synthesized using phosphorous tribromide[6] or bromohydric acid.[7] Some examples of preparation of iodides have also been reported utilizing P_2I_4,[8] magnesium iodide[9] or trimethylsilyl iodide.[10]

Allylic iodides are particularly interesting synthetic intermediates. Their high reactivity makes them very useful reagents, but this feature frequently becomes an important drawback due to rapid decomposition during storage. Because of this it would be advisable to prepare allylic iodides under reaction conditions which enable further synthesis in the same reaction vessel.

Continuing our research into the development of new synthetic methodologies and the utilization of the triphenylphosphine–iodine system,[11] we studied the behaviour of allylic alcohols against this reagent.

Our investigation started with tertiary alcohols having a terminal double bond, which are an important type of allylic alcohols due to their presence in the structure of many natural products. Linalool (**1a**), *trans*-nerolidol (**2a**), geranyl–linalool (**3a**) and alcohols **4a** and **5a** were treated with triphenylphosphine and iodine in dichloromethane affording in good yields the corresponding *E*-allyl iodides **12**–**16**, which were characterized by ^{1}H NMR after immediate flash column chromatography,



Scheme 1.

Keywords: Allylic alcohols; Allylic esters; Benzylic alcohols; Benzylic esters; Allyl iodides; Triphenylphosphine; Iodine.
* Corresponding author. Tel./fax: +34 958 24 80 89; e-mail: eamr@ugr.es

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.132

Table 1. Reaction of allylic and benzylic alcohols and acetates with PPh_3–I_2 and some nucleophiles

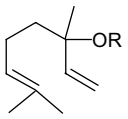
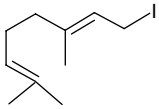
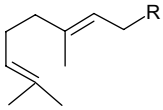
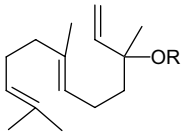
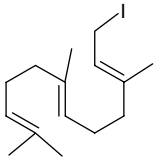
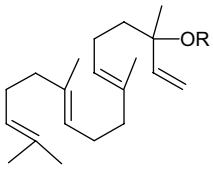
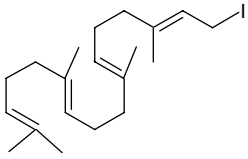
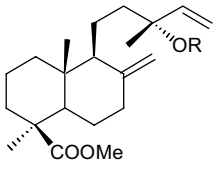
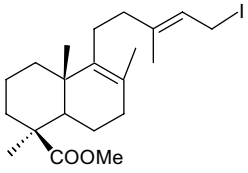
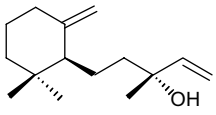
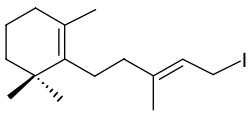
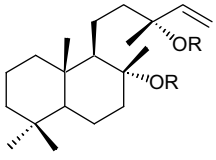
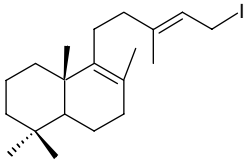
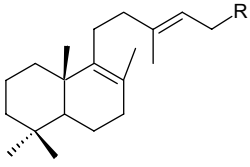
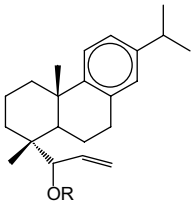
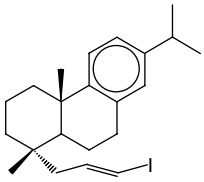
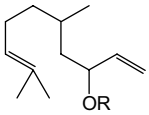
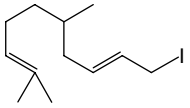
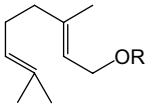
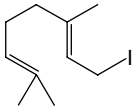
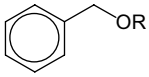
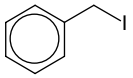
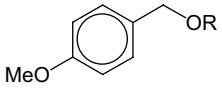
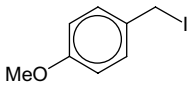
Entry	Substrate	Time	Iodide (%)	Nucleophile	Time	Product (%)
1						
	1a R: H	0.5 h	**12** (90)	$NaSO_2Ph$	12 h	**23a** R: SO_2Ph (84)
	1b R: Ac	13 h	(94)	NaCN	24 h	**23b** R: CN (86)
				NaN_3	22 h	**23c** R: N_3 (82)
				K phthalimide	10 h	**23d** R: N-phthal (88)
2						
	2a R: H	1.0 h	**13** (94)			
	2b R: Ac	13 h	(96)			
3						
	3a R: H	1.0 h	**14** (92)			
	3b R: Ac	11 h	(94)			
4						
	4a R: H	1.5 h	**15** (95)			
	4b R: Ac	14 h	(97)			
5						
	5a R: H	1.0 h	**16** (96)			
	5b R: Ac	10 h	(98)			
6						
	6a R: H	8 h	Complex mixture	$NaSO_2Ph$	12 h	**24a** R: SO_2Ph (78)[14]
	6b R: Ac		**17** (92)[14]	NaCN	24 h	**24b** R: CN (73)[14]
				NaN_3	22 h	**24c** R: N_3 (75)[14]
				K phthalimide	10 h	**24d** R: N-phthal (85)[14]

Table 1 (*continued*)

Entry	Substrate	Time	Iodide (%)	Nucleophile	Time	Product (%)
7						
	7a R: H	0.5 h	**18** (96)[14]			
	7b R: Ac	3 days	(90)			
8						
	8a R: H	1.0 h	**19** (92)			
	8b R: Ac	3 days	(87)			
9						
	9a R: H	2.0 h	**20** (88)			
	9b R: Ac	3 days	(Starting material)			
10						
	10a R: H	1.0 h	**21** (90)			
	10b R: Ac	3 days	(86)			
11						
	11a R: H	1.0 h	**22** (98)			
	11b R: Ac	2 days	(92)			

as the main stereoisomers. Compounds **1a**–**3a**, which consist of a 1:1 mixture of epimers, gave a *E*/*Z* mixture of allyl iodides in an approximate 4:1 ratio. Compounds **4a**–**5a**, which are pure diastereoisomers, gave exclusively the *E* derivative, with simultaneous exocyclic double bond isomerization. Sclareol (**6a**), under the same reaction conditions, led to a complex mixture. This reaction does not take place under Corey's iodination conditions (triphenylphosphine–iodine–imidazole in acetonitrile–water).[12]

In view of the parallelism observed in the behaviour of tertiary alcohols and their acetyl derivatives against the PPh_3–I_2 system,[11] tertiary allyl acetates were also investigated. Compounds **1b**–**5b**, having the same stereochemistry as related alcohols **1a**–**5a**, afforded similar results. It should be emphasized that whereas sclareol (**6a**) gave a complex mixture, its diacetyl derivative **6b** was converted into the *E*-allyl iodide **17**; the related bromide was converted into (+)-subersic acid,[13] thus the conversion of **6b** into **17** enables a very short synthesis of the above mentioned terpenic acid from (−)-sclareol (**6a**).

Secondary and primary allylic alcohols, as well as their acetyl derivatives, were also investigated. The secondary alcohols **7a**–**8a**, which consist of a mixture of epimers, led to the corresponding *E*-ally iodides **18**–**19** in good yields; the acetyl derivatives **7b**–**8b** gave similar results after prolonged reaction time. The primary alcohol **9a** was also transformed into iodide **20**; however, its acetyl derivative **9b** remained unaltered after 3 days under the same reaction conditions.

A possible mechanism consistent with these results is depicted in Scheme 1. The rearranged iodide could be formed through the intermediate **II**, which results from nucleophilic attack of the hydroxyl group on the phosphonium iodide **I**. In the case of acetyl derivatives, the complexation of carbonyl oxygen with the phosphonium iodide would allow the departure of the acetate group

previous to the nucleophilic attack of iodide anion; this process is favoured when substitution on the carbon bearing the oxygenated group is increased, which explains the high reactivity of tertiary esters and the lack of reactivity of primary derivatives.

The above allyl iodides can be reacted 'in situ' with some nucleophiles, by adding a solution of these in dimethylsulfoxide, affording the corresponding β,γ-unsaturated compounds. Iodides **12** and **17** and sodium benzenesulfinate, sodium cyanide, sodium azide and potassium phthalimide, as nucleophiles, were essayed.

The triphenylphosphine–iodine system was also essayed with benzyl alcohols and acetates (entries 10 and 11), which also afforded the corresponding iodides. As can be seen in Table 1, acetates required prolonged reaction times.

2. Experimental

2.1. Synthesis of allyl iodides

To a solution of PPh_3 (3.3 mmol) in CH_2Cl_2 (10 mL), resublimed iodine (3.3 mmol) was added and the mixture was stirred at room temperature for 5 min. Then, a solution of alcohol/acetate (3.2 mmol) in CH_2Cl_2 (5 mL) was added and the mixture was further stirred for the specified time. Then, it was diluted with ether (15 mL) and successively washed with aq 5% $NaHCO_3$ and brine, dried over anhyd Na_2SO_4 and evaporated to give a crude which, after flash chromatography (hexane), afforded the corresponding iodide.

2.2. 'In situ' reaction with nucleophiles

DMSO (3 mL) was added to the above reaction mixture under stirring, and then a solution of the nucleophilic reagent (4.8 mmol) in DMSO (5 mL). The stirring was continued at room temperature for the specified time, and then the mixture was diluted with ether (20 mL) and washed with H_2O (6×10 mL) and brine (2×10 mL). The organic phase was dried and evaporated to give a crude, which after column chromatography gave the β,γ-unsaturated compound.

In conclusion, allyl and benzyl alcohols and their acetyl derivatives react with triphenylphosphine and iodine under mild conditions affording in good yields the corresponding primary allylic and benzylic iodides, which can react 'in situ' with diverse nucleophiles. Primary allylic acetates did not react under these conditions. The described procedure constitutes a new methodology to synthesize allylic and benzylic iodides, and makes it possible to convert allylic alcohols or their acetyl derivatives into β,γ-unsaturated compounds.

Acknowledgements

Financial support was received from Ministerio de Ciencia y Tecnología (Project PPQ 2002-03308).

References and notes

1. Vani, P. V.; Chida, A. S.; Srinivasan, R.; Chandrasekharam, M.; Singh, A. K. *Synth. Commun.* **2001**, *31*, 219–224.
2. Jo, H.; Lee, J.; Kim, H.; Kim, S.; Kim, D. *Tetrahedron Lett.* **2003**, *44*, 7043–7044.
3. Takashi, T.; Furutani, A.; Seko, S.; PCT Int. Appl. 2000061530.
4. Xu, L.-H.; Kuendig, E. P. *Helv. Chim. Acta* **1994**, *77*, 1480–1484.
5. Labrouillere, M.; Le Roux, C.; Gaspard-Iloughmane, H.; Dubac, J. *Synlett* **1994**, 723–724.
6. Lambertin, F.; Taran, M.; Delmond, B. *Tetrahedron* **2002**, *58*, 6925–6930.
7. Borowiecki, L.; Welniak, M. *Pol. J. Chem.* **1989**, *63*, 149–156.
8. Lasne, M. C.; Cairon, P.; Villemin, D. *Synth. Commun.* **1990**, *20*(1), 41–44.
9. García Martínez, A.; Cruces Villalobos, A.; Oliver Ruiz, M. *Synthesis* **1988**, 58–60.
10. Kanai, T.; Irifune, S.; Ishii, Y.; Ogawa, M. *Synthesis* **1989**, 283–286.
11. (a) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* **2004**, *45*, 4453–4455; (b) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* **2005**, *46*, 1075–1077.
12. Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883–4886.
13. Basabe, P.; Diego, A.; Delgado, S.; Diez, D.; Marcos, I. S.; Urones, J. G. *Tetrahedron* **2003**, *59*, 9173–9177.
14. All new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data. Selected data:
Compound **17**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.53 (t, J = 8.3 Hz, 1H), 3.92 (d, J = 8.3 Hz, 2H), 1.66 (s, 3H), 1.54 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.4 (C-1), 19.1 (C-2), 41.8 (C-3), 33.2 (C-4), 51.9 (C-5), 19.1 (C-6), 37.1 (C-7), 126.3 (C-8), 143.4 (C-9), 39.1 (C-10), 26.4 (C-11), 33.7 (C-12), 139.9 (C-13), 121.3 (C-14), 4.3 (C-15), 20.2* (C-16), 19.6* (C-17), 33.4 (C-18), 21.7 (C-19), 15.9 (C-20). (*Interchangeable signals.)
Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07 (s, 3H), 1.21 (s, 3H), 1.25 (d, J = 6.9 Hz, 6H), 2.30 (d, J = 12.9 Hz, 1H), 2.85 (m, 3H), 3.89 (d, J = 9.7 Hz, 1H), 3.93 (d, J = 9.7 Hz, 1H), 5.53 (d, J = 15.5 Hz, 1H), 5.69 (dt, J = 15.5, 9.7 Hz, 1H), 6.88 (d, J = 1.1 Hz), 6.98 (dd, J = 8.2, 1.1 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.5[a] (C-1), 18.8 (C-2), 38.4[a] (C-3), 41.9[b] (C-4), 48.4 (C-5), 30.2[c] (C-6), 30.3[c] (C-7), 134.9 (C-8), 145.6 (C-9), 37.2[b] (C-10), 124.1[d] (C-11), 123.8[d] (C-12), 147.3 (C-13), 124.9[d] (C-14), 33.4 (C-15), 24.0[e] (C-16), 24.0[e] (C-17), 147.7 (C-18), 25.3[e] (C-19), 17.9 (C-20), 126.9 (C-1′), 7.7 (C-2′). ([a–e]Interchangeable signals.)
Compound **24a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.4 Hz, 1H), 7.48 (dd, J = 7.5, 7.4 Hz, 2H), 5.14 (t, J = 7.9 Hz, 1H), 3.76 (d, J = 7.9 Hz, 2H), 1.49 (s, 3H), 1.27 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H), 0.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 40.3 (C-1), 19.5 (C-2), 41.7 (C-3), 32.9 (C-4), 51.8 (C-5), 19.5 (C-6), 36.9 (C-7), 126.3 (C-8), 183.5 (C-9), 39.0 (C-10), 26.5 (C-11), 33.5 (C-12), 147.2 (C-13), 109.8 (C-14), 56.1 (C-15), 20.1* (C-16), 19.6* (C-17), 33.2 (C-18), 21.7 (C-19), 16.1 (C-20), 128.9 ($2 \times$ CH–SO_2Ph), 128.6 ($2 \times$ CH–SO_2Ph), 133.5 (CH–SO_2Ph), 139.7 (C–SO_2Ph). (*Interchangeable signals.)

Compound **24b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.16 (t, J = 6.8 Hz, 1H), 3.02 (d, J = 6.8 Hz, 2H), 1.68 (s, 3H), 1.54 (s, 3H), 0.92 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H). ^{13}C NMR($CDCl_3$, 75 MHz): δ 39.9 (C-1), 19.1 (C-2), 41.8 (C-3), 33.0 (C-4), 51.9 (C-5), 19.1 (C-6), 37.0 (C-7), 126.3 (C-8), 139.8 (C-9), 39.2 (C-10), 26.5 (C-11), 33.6 (C-12), 143.2 (C-13), 111.0 (C-14), 16.2 (C-15), 20.0* (C-16), 19.6* (C-17), 33.2 (C-18), 21.7 (C-19), 16.5 (C-20), 122.6 (C–CN).
Compound **24c**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.23 (t, J = 7.4 Hz, 1H), 3.68 (d, J = 7.4 Hz, 2H), 1.61 (s, 3H), 1.48 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H), 0.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 40.3 (C-1), 19.1 (C-2), 41.8 (C-3), 33.0 (C-4), 51.9 (C-5), 19.1 (C-6), 37.1 (C-7), 132.0 (C-8), 140.1 (C-9), 39.1 (C-10), 26.9 (C-11), 33.7 (C-12), 144.2 (C-13), 116.3 (C-14), 48.1 (C-15), 20.1* (C-16), 19.5* (C-17), 33.3 (C-18), 21.8 (C-19), 16.5 (C-20). (*Interchangeable signals.)
Compound **24d**: ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 783 (s, 4H), 5.18 (t, J = 7.0 Hz, 1H), 4.23 (d, J = 7.0 Hz, 2H), 1.85 (s, 3H), 1.52 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (CD_3COCD_3, 100 MHz): δ 37.6 (C-1), 19.6 (C-2), 40.8 (C-3), 33.6 (C-4), 52.6 (C-5), 19.7 (C-6), 37.6 (C-7), 126.5 (C-8), 141.3 (C-9), 39.6 (C-10), 27.4 (C-11), 36.1 (C-12), 140.7 (C-13), 118.9 (C-14), 42.4 (C-15), 23.4* (C-16), 20.4* (C-17), 33.6 (C-18), 21.9 (C-19), 16.4 (C-20), 169.2 (C-CO), 168.3 (C-CO), 133.9 (C), 133.1 (C), 134.9 ($2 \times$ CH), 123.6 ($2 \times$ CH). (*Interchangeable signals.)