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One-pot selective oxidation/olefination of primary alcohols using TEMPO–BAIB system and stabilized phosphorus ylides

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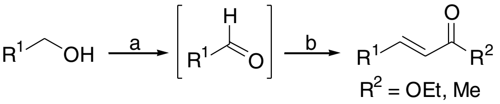
Abstract—A one-pot process for the synthesis of α,β-unsaturated esters from a variety of alcohols, obtained in good yields and diastereoselectivities, is described. The use of BAIB/TEMPO system at the oxidizing step authorizes the chemoselective homologation of primary alcohols in the presence of secondary ones.

In the course of synthetic studies towards a member of the amphidinolide family, we needed to transform an alcohol to a two-carbon homologated (*E*)-α,β-unsaturated ester via the classical oxidation–Wittig olefination sequence. The volatility of the aldehyde intermediate and its epimerizable character encouraged us to use a one-pot procedure, a modification of that developed by Ireland and Norbeck.[1] Although if the yield of the desired α,β-unsaturated ester was satisfying (80%), the large excess of the reagent (pyridine·SO_3) needed for the completion of the oxidation and the relatively low *E*/*Z* selectivity (6:1) of the Wittig reaction prompted us to develop a more efficient and practical protocol for this transformation.

Among the numerous oxidation methods of alcohols to aldehydes, our attention was drawn by the *N*-oxoammonium salt based oxidation described by Piancatelli and co-workers.[2] The oxidation system developed by these authors call for a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), which gives by disproportionation a oxoammonium salt and an hydroxylamine, in combination with bis(acetoxy)iodobenzene (BAIB) that regenerates TEMPO by oxidation of the hydroxylamine. This oxidative process is very attractive because of its mildness, commercially available reagents, compatibility with many functional and protecting groups[3] and high selectivity in the oxidation of primary alcohols in the presence of secondary ones.

Armed with this conviction, we developed a new one-pot procedure for the homologation of alcohols to α,β-unsaturated esters, depicted in Scheme 1. This method involves the rapid oxidation of alcohols in dichloromethane at room temperature using 1.15 equiv of BAIB in the presence of 0.1 equiv of TEMPO followed by the addition, at 0 °C, of 1.3 equiv of stabilized phosphoranes. Unsaturated esters were obtained in good yields and stereoselectivities (Tables 1 and 2).[4–6]

As already observed by others,[2,7] *N*-oxoammonium salt mediated oxidation of primary alcohols was rapid (1–3 h); the oxidation of diol **20** (Table 1, entry 11) and sugar derivatives **5** and **25** (Table 1, entry 3 and Table 2, entry 3) being slower (between 5 and 7 h). It is noticeable that the Wittig reaction proceeded with both high speed and trans-selectivity (>95:5 as determined by ^{1}H NMR) on most substrates. Acetic acid, formed during the oxidation step, may be responsible for this acceleration and enhancement of the *E*/*Z*



Scheme 1. Reagents and conditions: (a) $PhI(OAc)_2$, TEMPO cat., CH_2Cl_2, rt; (b) $Ph_3P{=}CH–COR^2$, 0 °C to rt.

Keywords: Bis(acetoxy)iodobenzene (BAIB); Olefination; Oxidation; 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO); Unsaturated esters.

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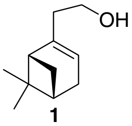
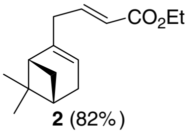
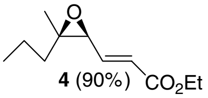
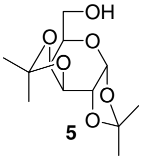
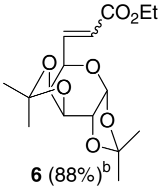
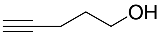
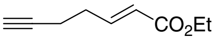
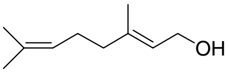
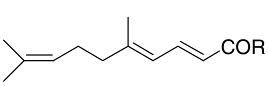
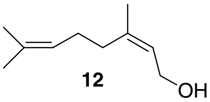
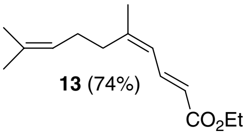
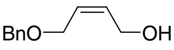
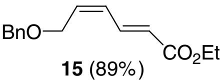
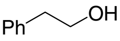
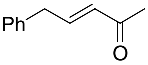
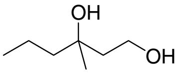
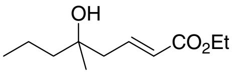
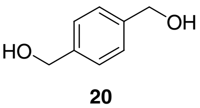
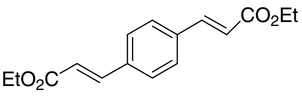
Table 1. One-pot BAIB/TEMPO oxidation–Wittig olefination of primary alcohols

Entry	Substrate	Conditions[a]	Product (isolated yield)
1	 **1**	(1) 3 h, rt; (2) 1 h, 0 °C	 **2** (82%)
2	 **3**	(1) 2 h, rt; (2) 1 h, 0 °C	 **4** (90%)
3	 **5**	(1) 5 h, rt; (2) 30 min, 0 °C	 **6** (88%)[b]
4	 **7**	(1) 3 h, rt; (2) 1 h, rt	 **8** (85%)
5	 **9**	(1) 90 min, rt; (2) 16 h, rt	 **10** R = OEt (85%)
6		(1) 90 min, rt; (2) 72 h, rt	**11** R = Me (57%)
7	 **12**	(1) 1 h, rt; (2) 16 h, rt	 **13** (74%)
8	 **14**	(1) 3 h, rt; (2) 1 h, rt	 **15** (89%)
9	 **16**	(1) 3 h, rt; (2) 2 h, rt	 **17** (90%)
10	 **18**	(1) 4 h, rt; (2) 1 h, 0 °C	 **19** (75%)
11	 **20**	(1) 7 h, rt; (2) 1 h, rt	 **21** (86%)[c]

[a] Reaction conditions: (1) BAIB (1.15 equiv), TEMPO (0.1 equiv), CH_2Cl_2; (2) $Ph_3P{=}CH{-}COR$ (R = OEt, Me) (1.3 equiv), multiply by 2 for diol **20**.

[b] *E*/*Z* ratio: 3/1.

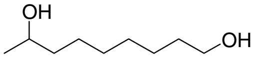
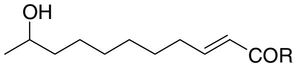
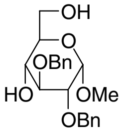
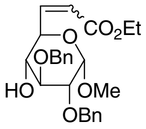
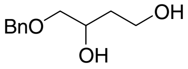
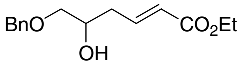
[c] *EE*/*ZZ* ratio: 16/1.

selectivity.[8,9] Other features of this one-pot process are that either epimerization at C-2 carbon of the epoxy alcohol **3** (Table 1, entry 2) or migration of the double bond of the homoallylic alcohol **1** did not occur under the reaction conditions.

During the oxidation/olefination of nerol (Table 1, entry 7), some *E*/*Z* isomerization at the C4–C5 trisubstituted double bond happened.[10] Contrary to the smooth reaction of 2-phenylethanal with 1-triphenylphosphoranylidene-2-propanone, leading exclusively to the (*E*)-unsaturated ketone **17** in quantitative yield (Table 1, entry 9), geranial reacted sluggishly with this phosphorane giving the conjugated diene **11** in only a modest yield (Table 1, entry 6).

We next turned our attention to the selective oxidation/olefination of primary alcohols in the presence of

Table 2. Chemoselective oxidation/olefination of primary alcohols in the presence of secondary ones

Entry	Substrate	Conditions[a]	Product (isolated yield)
1	 **22**	(1) 2 h, rt; (2) 1 h, rt	 **23** R = OEt (87%)
2		(1) 2 h, rt; (2) 3 h, rt	**24** R = Me (69%)
3	 **25**	(1) 6 h, rt; (2) 30 min, 0 °C	 **26** (68%)[b]
4	 **27**	(1) 3 h, rt; (2) 1 h, rt	 **28** (50%)

[a] Reaction conditions: (1) BAIB (1.15 equiv), TEMPO (0.1 equiv), CH_2Cl_2; (2) $Ph_3P{=}CH–COR$ (1.3 equiv).

[b] E/Z ratio: 1/2.

secondary ones (Table 2). Under the same reaction conditions as described above, 1,8-nonanediol **22** was transformed to the mono-(*E*)-unsaturated ester **23** in a rewarding 87% yield (entry 1), thus demonstrating the excellent chemoselectivity of our procedure. Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **25** gave **26** in good yield but with a low selectivity in favour of the *Z* isomer (entry 3). In the case of 1,3-diol **27**, the ester **28** was obtained in a moderate yield due to the formation of several minor products at the oxidation stage (entry 4).

In conclusion, we have shown that the BAIB/TEMPO system in combination with stabilized phosphoranes constitutes a mild and stereoselective one-pot method for the conversion of a variety of alcohols into their corresponding α,β-unsaturated esters. Our procedure has significant advantages over the existing ones such as its chemoselectivity (primary alcohols over secondary ones),[11,12] general applicability,[13] commercially available and safer reagents.[14]

Acknowledgements

The author thanks Mrs. Huynh Dong Doan and Alexandre Piou, for preliminary experiments.

References and notes

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2. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.
3. De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Synthesis* **1996**, 1153–1174.
4. *Representative experimental procedure* (Table 2, entry 1). To a stirred solution of 1,8-nonanediol **22** (0.15 g, 0.94 mmol) in CH_2Cl_2 (4 mL) were added bis(acetoxy)iodobenzene (0.346 g, 1.15 equiv) and 2,2,6,6-tetramethylpiperidinyloxy (0.015 g, 0.1 equiv). The yellow solution was stirred for 150 min, cooled to 0 °C and (carbethoxymethylene)triphenylphosphorane (0.423 g, 1.3 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solution was poured onto a column of silica gel and eluted with a mixture of ethyl acetate–petroleum ether (1:3) to give pure ethyl 10-hydroxyundec-2-enoate **23** (0.184 g, 87%) as an oil. IR (film): 3424, 1721, 1654 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): 1.16 (d, 3H, $J = 6.2$ Hz, Me), 1.23–1.40 (m, 15H, 5 CH_2, Me), 2.03 (br s, 1H, OH), 2.18 (br q, 2H, $J = 6.8$ Hz, CH_2–CH=CH), 3.77 (sextuplet, 1H, $J = 6.2$ Hz, C*H*OH), 4.16 (q, 2H, $J = 7.1$ Hz, Me), 5.79 (dt, 1H, $J = 15.64$ and 1.5 Hz, CH=C*H*–CO_2Et), 6.94 (tt, 1H, $J = 15.64$ and 6.9 Hz, C*H*=CH–CO_2Et). ^{13}C NMR: 14.3, 23.5, 25.6, 27.9, 29.1, 29.4, 32.1, 39.3, 60.1, 68.1, 121.3, 149.4, 166.8. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; O, 21.02. Found: C, 68.27; H, 10.71; O, 21.07.
5. In the presence of (carboethoxymethylene)triphenylphosphorane, the ability of the BAIB/TEMPO system to act as an oxidizing agent was inhibited (tested on compounds **1** and **16**).
6. All new compounds gave satisfactory physical and analytical data.
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9. For other examples of catalysis of the Wittig olefination by acids, see: benzoic acid catalysis: (a) Rüchardt, C.; Panse, P.; Eichler, S. *Chem. Ber.* **1967**, *100*, 1144–1164; Bose, A. K.; Manhas, M. S.; Ramer, R. M. *J. Chem. Soc. (C)* **1969**, 2728–2730; silica gel catalysis: (b) Patil, V. J.; Mävers, U. *Tetrahedron Lett.* **1996**, *67*, 1281–1284.
10. The presence of about 5–6% of compound **10** (Table 1, entry 7) was detected by ^{13}C NMR.
11. Swern oxidation used in this kind of one-pot process, developed by Ireland and Norbeck (Ref. 1) or pyridinium chlorochromate (PCC), have no selectivity on primary OH groups over secondary ones. For PCC, see: Bressette, A. R.; Glover, L. C. IV. *Synlett* **2004**, 738–740.
12. A chemoselective one-pot protocol for the C-2 homologation of carbohydrate-derived glycols, using SO_3·pyridine (5 equiv) as oxidant, has been very recently published.

However, the level of the chemoselectivity is very depending of the structure of the substrates. See: Pinacho Crisóstomo, F. R.; Carrillo, R.; Martin, T.; García-Tellado, F.; Martin, V. S. *J. Org. Chem.* **2005**, *70*, 10099–10101.

13. The two-step procedures employing oxidants such as MnO_2 or $BaMnO_4$ are only applicable to allylic, benzylic and propargylic alcohols. For MnO_2, see: Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815–3818. For $BaMnO_4$, see: Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 4489–4493.
14. Organo pentavalent iodine compounds such as Dess–Martin periodinane (DMP) and IBX, which have been used as patterns of stabilized ylides in the oxidation/homologation of alcohols, are potentially explosive. For IBX, see: (a) Crich, D.; Mo, X.-S. *Synlett* **1999**, 67–68; (b) Maiti, A.; Yadav, J. S. *Synth. Commun.* **2001**, *31*, 1499–1506, For DMP, see Ref. 8.