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3-Bromo-propenyl acetate in organic synthesis. The zinc-promoted α-hydroxyallylation of ketones

Marco Lombardo,* Stefano Morganti, Francesca d'Ambrosio and Claudio Trombini*

Dipartimento di Chimica 'G. Ciamician', Università di Bologna, via Selmi 2, I-40126 Bologna, Italy

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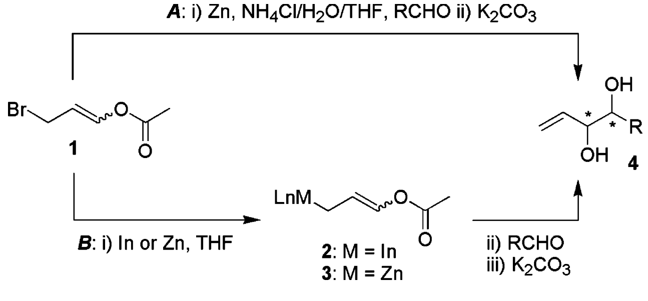
Abstract—3-Bromo-propenyl acetate easily undergoes oxidative addition by zinc, both under Barbier or Grignard conditions. The resulting acetoxyallylzinc species are reported to react efficiently with ketones, thus widening the scope of the 3-bromo-propenyl acetate route to homoallylic alcohols. Barbier conditions in water or a Grignard two-step protocol in the THF/DMSO binary solvent system are used, depending on the ketone reactivity. © 2003 Elsevier Science Ltd. All rights reserved.

The use of 3-halo-propenyl esters in organic synthesis as precursors of oxygen-functionalized allylic indium,[1,2] zinc[2–4] and chromium complexes,[5] has been recently reported.

In particular, as refers to indium and zinc complexes **2** and **3** (Scheme 1), prepared from 3-bromo-propenyl acetate (**1**), efficient acetoxyallylation reactions of aldehydes, affording alk-1-en-3,4-diols **4**, were developed under a variety of reaction conditions.

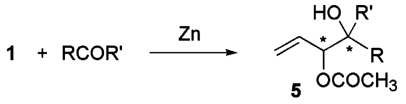
Pathway **A** corresponds to a typical one-pot Barbier reaction in NH_4Cl/H_2O, pathway **B** corresponds to a typical Grignard protocol involving the preliminary formation of the organometallic species in anhydrous THF, followed by the addition of the aldehyde. The final deprotected alk-1-en-3,4,diols **4** were obtained in pure forms after alkaline hydrolysis with methanolic K_2CO_3. The final alkaline hydrolysis is necessary to free **4** from a quite complex mixture of mono and diacetylated diols coming from intra and intermolecular acetate scrambling processes.



Scheme 1. Barbier (**A**) and Grignard (**B**) routes to alk-1-en-3,4-diols **4**.

Simple diastereoselectivity exhibited an abnormal trend since it was found to be mainly dependent on the aldehyde structure. In particular saturated aldehydes mainly afforded *anti*-**4**, while *syn*-**4** were formed starting from conjugated aldehydes.

In order to widen the scope of previously reported synthetic protocols, we inspected the reactivity of allylic zinc complexes **3** towards ketones, both in water and in organic solvents, in order to find an access to adducts **5** (Scheme 2).



Scheme 2. α-Hydroxyallylation of ketones promoted by zinc.

The interest for the α-hydroxyallylation of ketones is due to the limited number of synthetic options available to achieve this transformation. For example, THPO-substituted allylic boronates require critical conditions of pressure and temperature,[6] methoxy and silyloxy-substituted allylic stannanes afford very poor yields,[7] while acceptable results were recently obtained upon use of lithiated *t*-butyl allyl ether, in the presence of Et_3Al.[8]

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* Corresponding author. Tel.: +39 051 2099513; fax: +39 051 2099456; e-mail: marlom@ciam.unibo.it; trombini@ciam.unibo.it

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A first set of reactions was performed in NH_4Cl/H_2O according to a classical Barbier procedure (protocol **A**, Table 1, entries 1–8). Reactions in NH_4Cl/H_2O proceeded quite more slowly than in the case of aldehydes, not for intrinsic reactivity reasons but, simply, for the poorer solubility of ketones in the reaction medium. Indeed, addition of a small amount of THF (20% v/v) allowed us to get very high conversions in a reasonable reaction time (30 min) at room temperature. The results are collected in Table 1. Differently from aldehyde adducts, compounds **5** do not undergo acetyl transfer reactions and they are efficiently isolated by silica gel flash-chromatography in very good yields.[9] Determination of the *syn*/*anti* isomer mixture is carried out by NOE analysis of *cis* and *trans* 1,3-dioxolanes **7**,[10] obtained after alkaline hydrolysis of **5** to **6** (Scheme 3).[11]

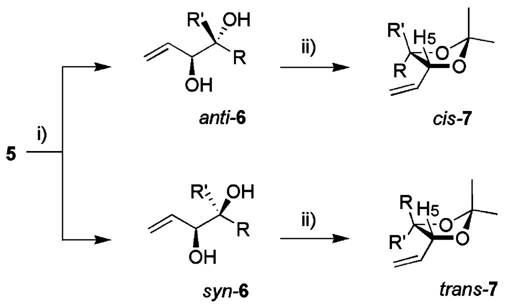
In analogy to conjugated aldehydes,[1–3] aromatic and α,β-unsaturated ketones (runs 1–4 and 7–9) favor the formation of *syn* adduct,[12] while a modest *anti* stereopreference is displayed by 2-octanone (run 6).[13]

Table 1. Acetoxyallylation of ketones under Barbier conditions in the NH_4Cl/H_2O/THF system

Run	Ketone	Protocol	**5** Yield (%)[a]	*syn*-**5**/*anti*-**5**[b]
1	Acetophenone	**A**	87	70:30
2	2-Acetonaphthone	**A**	98	70:30
3	4-Methoxy-acetophenone	**A**	98	80:20
4	Propiophenone	**A**	87	75:25
5	Cyclohexanone	**A**	87	–
6	2-Octanone	**A**	84	40:60
7	α-Ionone	**A**	98	70:30
8	Benzalacetone	**A**	65	70:30
9	Benzalacetone	**B**	83	85:15
10	Pinacolone	**A**	0	–
11	Pinacolone	**B**	35	35:65

[a] Isolated yield.

[b] Determined on the basis of GC–MS and ^1H NMR of the crude reaction mixture.



Scheme 3. *Reagents and conditions*: (i) K_2CO_3, H_2O/MeOH; (ii) $(MeO)_2CMe_2$, Amberlyst-15H.

Runs 8 and 10 show limitations of the above discussed Barbier protocol with less reactive ketones, either for electronic (benzalacetone) or steric reasons (pinacolone). In these cases, the great flexibility displayed by 3-halo-propenyl esters in tolerating a variety of reaction conditions, allowed us to identify an alternative successful reaction procedure based on a two-step Grignard protocol in an aprotic organic solvent mixture (protocol **B**). Thus, the organozinc species **3** is preformed in THF/DMSO 4:1, then in a second stage the ketone is added and is allowed to react with **3**.[14] Under these new conditions, the formerly unreactive pinacolone affords the desired adduct in 35% yield.

In conclusion, the above reported results represent a further extension of possible application of 3-halo propenyl esters in organic synthesis. In particular, a highly efficient and environmentally friendly synthesis of 4,4-disubstituted 3-acetoxy-alk-1-en-3-ols **5** is reported in aq. NH_4Cl. Hindered or less reactive ketones may be forced to react by adopting an alternative two-step protocol in THF/DMSO.

Acknowledgements

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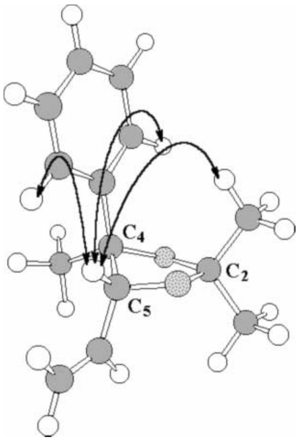
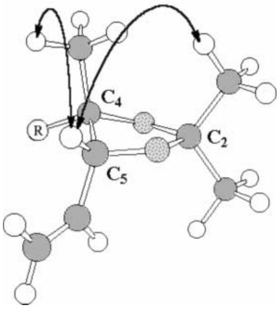
9. **Protocol A in NH_4Cl/THF: 1-Methyl-1-(2-naphthyl)-2-acetoxy-but-3-en-1-ol** (Table 1, entry 2). 3-Bromo-propenyl-acetate **1** (0.175 mL, 1.5 mmol) and zinc powder (0.1 g, 1.5 mmol) were added at rt to a solution of 2-acetonaphthone (0.086 g, 0.5 mmol) in 2.5 mL of satd aq. NH_4Cl/THF (4:1). The solution was vigorously stirred for 30 min at rt and aqueous layer was extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure. The title compound **5** was isolated by flash-chromatography on SiO_2 (cyclohexane/ethyl acetate 9/1) in 98% yield (0.132 g, 0.49 mmol) as a 70/30 mixture of *syn*/*anti* isomers. *syn*-**5**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.62 (3H, s), 1.92 (3H, s), 2.53 (1H, broad s), 5.40 (1H, dt, $J=1.4/10.2$ Hz), 5.68 (1H, dt, $J=1.0/7.0$ Hz), 5.91 (1H, ddd, $J=7.0/10.4/17.2$ Hz), 7.47–7.62 (3H, m), 7.82–7.99 (4H, m); ^{13}C

NMR (50 MHz, $CDCl_3$) δ 20.8, 25.6, 75.7, 80.1, 119.9, 126.4, 124.0, 125.8, 125.9, 127.3, 127.6, 128.0, 132.0, 141.8, 169.7. *anti*-**5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.67 (3H, s), 1.91 (3H, s), 2.38 (1H, broad s), 5.12–5.26 (3H, m), 5.22 (1H, dt, J=1.4/7.0 Hz), 5.65 (1H, ddd, J=5.8/10.4/17.2 Hz), 7.45–7.62 (3H, m), 7.82–7.99 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0, 26.6, 75.4, 79.7, 118.8, 123.4, 124.0, 125.8, 125.9, 127.3, 127.6, 128.0, 132.0, 132.8, 141.2, 169.9.

10. In defining *syn* and *anti*-**5** and **6**, and *cis*- and *trans*-**7**, R corresponds to the higher priority substituent.
    When R is an aromatic ring, two regular trends were observed in ^{1}H NMR spectra, which may be useful to chemists working in this area. In particular (i) H5 is more shielded (0.2–0.3 ppm) in *trans*-**7** with respect to *cis*-**7**, and (ii) the vinyl group on C5 shows a CH proton more shielded (1.0–1.2 ppm) in *cis*-**7** with respect to the *trans* isomer.
11. **General procedure for the synthesis of diols 6. Synthesis of 1-(2-naphthyl)-but-3-en-1,2-diol**. Monoacetylated diol **5** (*syn*/*anti* 70/30) was dissolved in 2.5 mL of $MeOH/H_2O$ (9/1), K_2CO_3 (0.21 g, 1.5 mmol) was added and the heterogeneous mixture was vigorously stirred at rt for 2 h. MeOH was removed at reduced pressure, the aqueous layer was extracted with ether, the combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure. Product **6** was obtained as a 70/30 *syn*/*anti* mixture in 92% yield (0.1 g, 0.45 mmol) by flash-chromatography on SiO_2 (cyclohexane/ethyl acetate 8/2). *syn*-**6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60 (3H, s), 2.05 (1H, d, J=3.6 Hz), 2.53 (1H, s), 2.76 (1H, s), 4.40–4.46 (1H, m), 5.30 (1H, dt, J=1.4/10.2 Hz), 5.35 (1H, dt, J=1.6/17.2 Hz), 5.95 (1H, ddd, J=6.2/10.6/17.2 Hz), 7.42–7.62 (3H, m), 7.82–7.99 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 76.4, 75.3, 118.0, 123.7, 124.4, 125.9, 126.0, 127.4, 127.6, 127.8, 128.1, 132.9, 135.3, 142.4. *anti*-**6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.73 (3H, s), 2.07 (1H, d, J=5.8 Hz), 2.58 (1H, s), 4.36–4.37 (1H, m), 5.14 (1H, dt, J=1.4/10.8 Hz), 5.22 (1H, dt, J=1.4/16.8 Hz), 5.70 (1H, ddd, J=5.8/10.6/17.2 Hz), 7.47–7.62 (3H, m), 7.82–7.99 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.4, 76.4, 79.0, 117.4, 123.6, 124.1, 125.8, 126.0, 127.4, 127.6, 127.8, 128.1, 132.4, 136.1, 141.6.
    General procedure for the synthesis of dioxolanes 7. 2,2-Dimethyl-4-methyl-4-ethenyl-5-(2-naphthyl)-1,3-dioxolane. A catalytic amount of Amberlyst-15H (10–20 mg) was added to a solution of diol **6** (0.1g, 0.45 mmol) and 2,2-dimethoxy-propane (0.125 mL, 1 mmol) in anhydrous CH_2Cl_2 (1.5 mL). The reaction mixture is stirred for 2 h at rt, the resin was removed by filtration (Celite) and the organic layer was evaporated at reduced pressure. Acetonides **7** were isolated in quantitative yield by flash-chromatography on SiO_2 (cyclohexane). 4,5-*trans*-**7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (3H, s), 1.56 (3H, s), 1.66 (3H, s), 4.43 (1H, d, J=7.4 Hz), 5.37 (1H, dt, J=1.4/10.0 Hz), 5.39 (1H, dt, J=1.4/17.2 Hz), 6.07 (1H, ddd, J=7.4/10.8/17.4 Hz), 7.46–7.56 (3H, m), 7.81–7.93 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.2, 26.5, 28.6, 84.2, 85.3, 108.3, 120.2, 123.2, 123.3, 125.8, 126.0, 127.4, 127.8, 128.1, 132.5, 133.1, 142.2. 4,5-*cis*-**7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62 (3H, s), 1.77 (3H, s), 1.82 (3H, s), 4.61 (1H, d, J=7.0 Hz), 5.10 (1H, dd, J=2.9/9.5 Hz), 5.23 (1H, ddd, J=7.0/9.5/16.0 Hz), 5.37 (1H, dd, J=2.9/16.0 Hz), 7.37–7.56 (3H, m), 7.75–7.91 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 28.0, 28.5, 84.5, 87.6, 109.0, 119.1, 123.3, 125.1, 125.3, 125.8, 125.9, 127.0, 127.4, 127.5, 128.3, 134.7, 140.0.
12. NOE of *trans*-**7**: (i) R = aromatic, upon irradiation of H5, we observed a quite strong response (4–9%) from *ortho* aromatic protons and one methyl group on C2, but no response from methyl group on C4. (ii) R = alkenyl, upon irradiation of H5, we observed a quite strong response (5–6%) from H1' of alkenyl substituent on C4 and from one methyl group on C2, but no response from methyl group on C4.



13. NOE of *cis*-**7** (R = *n*-hexyl, R′ = methyl): upon irradiation of H4, we observed a quite strong response (4–8%) from methyl group on C4 and one of the methyl groups on C2, but no response from alkyl chain hydrogens was recorded.



14. **Protocol B in THF/DMSO. (*E*)-1-Phenyl-3-methyl-4-acetoxy-hexa-1,5-dien-3-ol** (Table 1, entry 9). Zinc powder (0.1 g, 1.5 mmol) was added at 0°C to a solution of 3-bromo-propenyl-acetate **1** (0.175 mL, 1.5 mmol) in 2.5 mL of THF/DMSO (4/1) and the reaction was stirred for 12 h, slowly raising temperature from 0 to 10–15°C. The ice bath was removed, (*E*)-4-phenyl-but-3-en-2-one (0.146 g, 1.0 mmol) was added and the reaction was stirred for 3 h at rt. The reaction was quenched with satd aq. NH_4Cl and the aqueous layer was extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated at reduced pressure. Purification by flash-chromatography on SiO_2, eluting with cyclohexane/ethyl acetate 95/5, afforded 0.175 g of *syn* (0.71 mmol, 71%) and 0.028 g of *anti* (0.11 mmol, 11%) isomers (*syn*/*anti*= 85/15). *syn*-**5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (3H, s), 2.09 (3H, s), 5.31 (1H, dt, J=0.8/17.6 Hz), 5.33 (1H,

dt, $J = 0.8/10.2$ Hz), 5.42 (1H, broad d, $J \sim 7.2$ Hz), 5.91 (1H, ddd, $J = 7.2/10.2/17.6$ Hz), 6.28 (1H, d, $J = 16.2$ Hz), 6.71 (1H, d, $J = 16.2$ Hz), 7.20–7.43 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 24.0, 74.2, 79.9, 120.0, 126.3, 127.4, 128.4, 128.9, 132.1, 132.9, 136.5, 170.0. *anti*-**5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (3H, s), 2.15 (3H, s), 5.26–5.44 (m, 3H), 5.91 (1H, ddd, $J = 6.2/10.3/16.8$ Hz), 6.27 (1H, d, $J = 16.2$ Hz), 6.69 (1H, d, $J = 16.2$ Hz), 7.20–7.43 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 26.8, 74.1, 79.8, 119.4, 126.5, 127.7, 128.5, 129.5, 131.9, 132.3, 136.6, 170.2.