Use of Cyclic Allylic Bromides in the Zinc–Mediated Aqueous Barbier–Grignard Reaction

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Abstract: The zinc–mediated aqueous Barbier–Grignard reaction of cyclic allylic bromide substrates with various aldehydes and ketones to afford homoallylic alcohols was investigated. Aromatic aldehydes and ketones afforded adducts in good yields (66–90%) and with good diastereoselectivities. Non–aromatic aldehydes also reacted well under these conditions, but only poor yields were obtained with non–aromatic ketones. Regioselectivity was high when some substituted cyclic allylic bromides were investigated.

Keywords: Barbier–Grignard reaction, aqueous reactions, organozinc, homoallylic alcohols.

Introduction

The synthesis of homoallylic alcohols via the reaction of cyclic and acyclic allylic organometallic compounds with aldehydes and ketones is an important process in synthetic organic chemistry [1]. Unfortunately, however, the process typically requires the use of toxic and/or water–sensitive organometallic compounds. Recently a “greener” allylation method has been developed in which the reaction is carried out in aqueous media under Barbier–type conditions using allylic halides and metals such as zinc, tin, and indium [2]. The method is simple, avoids the handling of toxic and water-sensitive reagents, and generally affords good–to–high yields of products. In addition, examples of impressive regio–, diastereo–, and (more recently) enantioselectivities have also been reported [2,3]. While acyclic allylic halides have been subjected to detailed investigations in this regard, the reactivity of cyclic allylic halides—with only a few exceptions [4]—have escaped attention despite the fact that
the cycloalkenyl–substituted methanols generated from these reactions are of considerable synthetic importance [1b,5]. We have therefore undertaken a systematic study of the reactivity of a series of cyclic allylic bromides under Barbier–type conditions with the intention of determining the feasibility and scope of the method, as well as the regio– and diastereoselectivity of the process.

Results and Discussion

Addition of 2 equivalents of 3–bromocyclohexene (1b) as a solution in THF to a rapidly stirred mixture of zinc metal (2 eq) and benzaldehyde (1 equiv) in saturated aqueous NH₄Cl resulted in rapid consumption of the zinc metal in a mildly exothermic reaction. The addition product 2b (R = C₆H₅, R’ = H) was isolated in 87% yield (Table 1).

The ¹H-NMR spectra of both the crude and purified adduct suggested the presence of diastereomeric products. Gas chromatographic analysis indicated an 83:17 ratio of the erythro and threo isomers, respectively, identified by comparison of their ¹H- and ¹³C-NMR spectra with literature data [5a]. The major by-product from this reaction was a dimeric compound formed from Wurtz–type coupling of the starting bromide [6].

Bromide 1b reacted with substituted benzaldehydes to afford adducts in good yields and stereoselectivities (see Table 1). In all cases, erythro adducts were obtained as the predominant diastereomer as determined by comparison of their ¹H- and/or ¹³C-NMR spectra with those of the same or similar compounds [5a-b,7]. Reaction with the non–aromatic aldehydes heptaldehyde and isobutyraldehyde, however, afforded very low stereoselectivity although the mixtures of diastereomers were obtained in reasonable yield. The change in reactivity from aromatic to non–aromatic aldehydes was also marked by a change in diastereoselectivity from that favoring formation of erythro adducts to that favoring threo adducts. A reasonable yield of addition product was also obtained with the aromatic ketones acetophenone and benzophenone, and with good diastereoselectivity in the case of acetophenone [8]. However, the non–aromatic ketones 3-pentanone and acetone afforded only poor yields of adduct (12% and 28% yield, respectively) and were not further pursued.
Table 1. Reaction of Cyclic Allylic Bromides with Various Aldehydes and Ketones Under Aqueous Barbier–Type Conditions

| Cyclic Bromide | Substrate       | % Yield | Ratio of diastereomers erythro/threo c |
|---------------|----------------|---------|-------------------------------------|
| 1b            | benzaldehyde   | 87      | 83:17                               |
|               | tolualdehyde   | 90      | 87:13                               |
|               | 4-chlorobenzaldehyde | 90 | 85:15                               |
|               | n–heptaldehyde | 77      | 45:55                               |
|               | isobutyraldehyde | 72 | 34:66                               |
|               | acetophenone   | 83      | 90:10 d                             |
|               | benzophenone   | 66      |                                     |
| 1a            | tolualdehyde   | 82 e    | 80:20 f                             |
| 1c            | tolualdehyde   | 85      | 89:11                               |
| 1d            | tolualdehyde   | 85      | 87:13                               |

a Performed according to the General Procedure described in the Experimental.  
b Isolated yields.  
c Ratio determined by gas chromatography unless otherwise specified.  
d Ratio determined by 13C-NMR spectroscopy.  
e Reaction conducted at 0 °C.  
f Ratio determined by 1H-NMR spectroscopy.

In order to determine the scope of the method, a series of cyclic allylic bromides (1a–d) that differed in ring size was investigated. Utilizing the same experimental protocol as was used with 1b, with the exception that three equivalents of bromide and zinc were used rather than two, good yields of addition products were obtained with tolualdehyde as substrate in all cases (Table 1). The stereoselectivity of the process was found to be nearly independent of the size of the bromide ring. The reactivity of bromide 1a towards hydrolysis under the aqueous reaction conditions required conducting the reaction at 0 °C rather than the usual room temperature to limit competing formation of 2–cyclopenten–1–ol.

Reaction of bromide 3 with benzaldehyde could have conceivably afforded adduct 4 or regioisomer 5 by way of the two possible isomeric organometallic intermediates (see below). We found, however, that standard reaction conditions yielded only adduct 4 in 61% yield as a 90:10 mixture of erythrol/threo diastereomers, respectively, resulting from reaction at the more highly substituted allylic
This finding is in agreement with those previously reported for acyclic allylic bromides in which reaction was also generally observed to occur at the more substituted allylic position [2].

Similarly, reaction of bromide 6 with tolualdehyde afforded adduct 7 as the sole product in 82% yield as a 91:9 mixture of diastereomers [9]. The major diastereomer of 7 is tentatively assigned the erythro configuration based on two observations: 1) the chemical shift of the carbinol proton of the major diastereomer was found at lower field in the $^1$H-NMR ($\delta$ 4.67) relative to that of the minor isomer (at $\delta$ 4.52) as was observed for the erythro isomers of the other aromatic adducts 2a–d, and 2) the GC retention time of the major isomer was shorter than that of the major, and it was observed in all cases examined by us that the erythro isomer consistently eluted from a carbowax GC column prior to that of the threo isomer. Given the potential for conversion of compound 7 to ketone 8 via oxidative cleavage of the exocyclic double bond, this reaction presents itself as a possible aqueous-based synthetic alternative to the conventional aldol reaction. Studies directed towards the exploitation of this potential route are underway in our labs.

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Conclusions

Cyclic allylic bromides behave admirably in the zinc-mediated aqueous Barbier-Grignard reaction towards aromatic and non-aromatic aldehydes, as well as towards aromatic ketones to afford good yields of the corresponding homoallylic alcohols. Good diastereoselectivities were observed for aromatic aldehyde and ketone substrates.

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Experimental

General

Unless otherwise indicated, reagents were obtained from commercial suppliers, and used without further purification. Column chromatography was conducted on Merck grade 60 (230–400 mesh) silica gel. 1H- and 13C-NMR spectra were recorded in CDCl3 at 60 and 15 MHz, respectively. Gas chromatography was conducted using a 6’ × 1/8” stainless steel column packed with 10% carbowax 20M on 80/100 Chromosorb W AW. Bromides 1a and 1c–1d were synthesized via standard allylic bromination of the corresponding alkenes utilizing N–bromosuccinimide followed by distillation at reduced pressure [10].

3–Bromo–1–methylcyclohexene (3) [11].

A solution of 2–cyclohexenone (5.16 g, 0.0538 mol) in diethyl ether (5 mL) was added dropwise via syringe at 0 °C under N2 to a stirring solution of a 1.4 M MeLi solution (45 mL, 1.4 mol, 1.2 equiv) in diethyl ether. The resulting solution was stirred for 30 minutes and then quenched with saturated aqueous. NH4Cl solution (40 mL). The organic phase was separated, and the aqueous phase washed with diethyl ether (2 × 20mL). The combined organic phases were dried over Na2SO4, filtered, and concentrated. Column chromatography afforded 1–methyl–2–cyclohexen–1–ol as a colorless oil: 1H-NMR δ 6.63 (br s, 2H), 2.10–1.90 (m, 3H), 1.63 (br m, 4H), 1.27 (s, 3H); 13C-NMR δ 133.8, 128.4, 68.4, 38.6, 30.3, 25.9, 20.5; IR (neat) 3361, 3019, 2935, 1125 cm⁻¹.

A portion of the 1–methyl–2–cyclohexen–1–ol (0.79 g, 7 mmol) was added dropwise with stirring to concentrated HBr (2.9 mL). A second layer formed immediately. To the mixture was added CH2Cl2 (2 mL), the phases were mixed, and the organic layer removed, dried over Na2SO4 filtered, and concentrated under reduced pressure to afford bromide 3 which was used directly in the zinc reactions;
\[ ^1\text{H-NMR} \delta 5.60 \text{ (br d, } J = 5 \text{ Hz, } 1\text{H}), 4.90 \text{ (br m, } 1\text{H}), 2.1–1.5 \text{ (m, } 6\text{H}), 1.65 \text{ (s, } 3\text{H}); ^{13}\text{C-NMR} \delta 139.1, 123.5, 50.5, 32.1, 29.5, 23.4, 18.5. \]

1-(Bromomethyl)cyclohexene (6) [12].

A solution of 1-cyclohexene-1-carboxylic acid (2.86 g, 0.024 mol) in ether (30 mL) was added dropwise to a stirring mixture of LiAlH\(_4\) (1.08 g, 0.029 mol) in anhydrous ether (40 mL) in a 100 mL RBF fitted with a reflux condenser. After full addition, the mixture was stirred for an additional 15 min, and then quenched with H\(_2\)O (2 mL) followed by 10% H\(_2\)SO\(_4\) (30 mL). The aqueous layer was separated and washed with ether (2 \(\times\) 5 mL). The combined organics were dried over Na\(_2\)SO\(_4\), filtered and concentrated to afford 2.33 g (87% yield) of \(\alpha\)-(2-cyclohexen-1-yl)methanol as a colorless liquid; \[ ^1\text{H-NMR} \delta 5.66 \text{ (br s, } 1\text{H}), 3.93 \text{ (br s, } 2\text{H}), 3.26 \text{ (br s, } 1\text{H, } \text{OH}), 2.2–1.6 \text{ (m, } 4\text{H}), 1.6–1.3 \text{ (m, } 4\text{H}); ^{13}\text{C-NMR} \delta 135.5, 120.3, 64.8, 23.6, 23.0, 20.6, 20.5; \text{IR (neat) } 3318, 2926, 1008 \text{ cm}^{-1} \]

Bromine (1.2 mL, 0.023 mol) was added to a stirring solution of triphenylphosphine (6.0 g, 0.023 mol) in dry acetonitrile (30 mL) at 0 °C. The resulting mixture was stirred while a solution of \(\alpha\)-(2-cyclohexen-1-yl)methanol (2.33 g, 0.021 mol) in acetonitrile (3 mL) was added. The reaction mixture was stirred for 10 minutes, and the acetonitrile was removed via rotary evaporation. The crude product was loaded onto a silica gel column and eluted with a 5:1 hexane/ethyl acetate solvent mixture. The fractions containing the product were concentrated to afford 2.87 g (79% yield) of 6. Final purification was effected via vacuum distillation (b.p. 73 °C at 2 mm Hg); \[ ^1\text{H-NMR} \delta 5.96\text{(br m, } 1\text{H}), 3.93 \text{ (br s, } 2\text{H}), 2.2–1.8 \text{ (m, } 4\text{H}), 1.8–1.3 \text{ (m, } 4\text{H)} \]

**General Procedure for the Reaction of Cyclic Allylic Bromides with Aldehydes and Ketones.**

A solution of the cyclic bromide (2 or 3 mmol) in THF (2 mL) was added dropwise to a rapidly stirring mixture of aldehyde or ketone (1 mmol), saturated aqueous NH\(_4\)Cl (1 mL) and zinc metal (2 or 3 mmol, see text). An immediate reaction was observed to take place with loss of the zinc metal. The mixture was stirred 3 h, filtered to remove excess zinc and precipitated salts, and the organic layer separated. The aqueous layer was washed with ether (3 \(\times\) 1 mL). The combined organics were dried over Na\(_2\)SO\(_4\), filtered, and concentrated. Reaction products were purified by column chromatography (SiO\(_2\)), eluting with a suitable hexane/ethyl acetate solvent mixture. The results are summarized in Table 1.

**NOTE:** For the compounds below, the *erythro* and *threo* diastereomers were inseparable by column chromatography. Data is provided for the major (*erythro*) isomer, but where distinct differences were discernable, information for the *threo* isomer is included in square brackets (i.e., [ ] ) immediately following the corresponding data for the *erythro* isomer.

**\(\alpha\)-(2-Cycloocten-1-yl)-4-methylbenzenemethanol.** Isolated as a colorless viscous liquid. Anal. Calcd for C\(_{16}\)H\(_{22}\)O: C, 83.43; H, 9.63; Found: C, 83.01; H, 9.83; \[ ^1\text{H-NMR} \delta 7.09 \text{ (br s, } 4\text{H}), 5.50-5.00 \text{ (m, } 6\text{H}) \]
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2H), 4.42 (d, \( J = 7.2 \text{ Hz}, 1H \)) [4.36 (d, \( J = 7.6 \text{ Hz}, 1H \))] , 3.20–2.5 (br m, 1H), 2.29 (s, 3H), 2.20–0.90 (m, 11H); \(^{13}\text{C}-\text{NMR} \delta 21.5, 25.9, 27.1, 27.2 \quad [27.3] \quad , 29.7, 32.0 \quad [32.9], 43.4 \quad [44.2], 79.0, 126.1 \quad (2C), 128.3 \quad (2C), 129.2, 129.9, 136.3, 140.1; \text{IR} \quad (\text{neat}) \quad 3398, 3011, 2925, 2856, 1008 \text{ cm}^{-1}

\(\alpha\)-(2-Cyclohepten-1-yl)-4-methylbenzenemethanol.\) Isolated as a colorless viscous liquid. Anal. Calcd for \(\text{C}_{15}\text{H}_{20}\text{O}: \text{C}, 83.28; \text{H}, 9.32; \text{Found: C}, 82.99; \text{H}, 9.59; \quad ^{1}\text{H}-\text{NMR} \quad \delta 7.08 \quad (br \quad s, \quad 4H), \quad 5.80-5.50 \quad (m, \quad 2H), \quad 4.45 \quad (d, \quad \text{J} = 6.9 \text{ Hz,} \quad 1H), \quad 2.27 \quad (s, \quad 3H), \quad 1.2-2.3 \quad (10H); \quad ^{13}\text{C}-\text{NMR} \quad \delta 139.5, 136.0, 133.0, 131.2, 128.1, 126.0, 76.9, 46.9, 30.3, 28.9, 28.7, 27.1, 21.4; \text{IR} \quad (\text{neat}) \quad 3392, 3020, 2853, 1037 \text{ cm}^{-1}

\(\alpha\)-(2-Cyclopenten-1-yl)-4-methylbenzenemethanol.\) Isolated as a colorless viscous liquid. Anal. Calcd for \(\text{C}_{13}\text{H}_{16}\text{O}: \text{C}, 82.94; \text{H}, 8.57; \text{Found: C}, 82.79; \text{H}, 8.85; \quad ^{1}\text{H}-\text{NMR} \quad \delta 7.15 \quad (br \quad s, \quad 4H), \quad 5.90-5.70 \quad (m, \quad 1H), \quad 5.45-5.20 \quad (m, \quad 1H), \quad 4.45 \quad (d, \quad J = 6.8 \text{ Hz,} \quad 1H) \quad [4.40 \quad (d, \quad J = 6.9 \text{ Hz,} \quad 1H)], \quad 3.30–2.70 \quad (br \quad m, \quad 1H), \quad 2.31 \quad (s, \quad 3H), \quad 2.50–1.53 \quad (m, \quad 5H); \quad ^{13}\text{C}-\text{NMR} \quad \delta 141.3, 137.4, 133.8, 132.2, 129.5, 127.0, 77.8 \quad [78.0], \quad 54.5 \quad [54.0], \quad 32.8, \quad 26.2 \quad [27.1], \quad 21.7; \text{IR} \quad (\text{neat}) \quad 3407, 3052, 2932, 1058 \text{ cm}^{-1}

\(\alpha\)-(2-Methylenecyclohexyl)-4-methylbenzenemethanol.\) Isolated as a white solid, m.p. 87.5–88°C. Anal. Calcd for \(\text{C}_{15}\text{H}_{20}\text{O}: \text{C}, 83.28; \text{H}, 9.32; \text{Found: C}, 83.07; \text{H}, 9.44; \quad ^{1}\text{H}-\text{NMR} \quad \delta 7.20 \quad (br \quad s, \quad 4H), \quad 4.953 \quad (br \quad s, \quad 2H), \quad 4.67 \quad (d, \quad J = 10.0 \text{ Hz,} \quad 1H) \quad [4.52 \quad (d, \quad J = 6.5 \text{ Hz,} \quad 1H)], \quad 3.30–2.70 \quad (br \quad m, \quad 1H), \quad 2.31 \quad (s, \quad 3H), \quad 2.50–1.53 \quad (m, \quad 5H); \quad ^{13}\text{C}-\text{NMR} \quad \delta 149.6, 139.5, 137.2, 128.9 \quad [128.6], \quad 126.9 \quad [126.1], \quad 110.7, \quad 72.7 \quad [73.1], \quad 51.8 \quad [50.4], \quad 32.7 \quad [34.9], \quad 29.1, \quad 28.1 \quad [27.2], \quad 22.2 \quad [23.5], \quad 21.0; \text{IR} \quad (\text{neat}) \quad 3407, 3071, 2937, 1038 \text{ cm}^{-1}

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