

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.

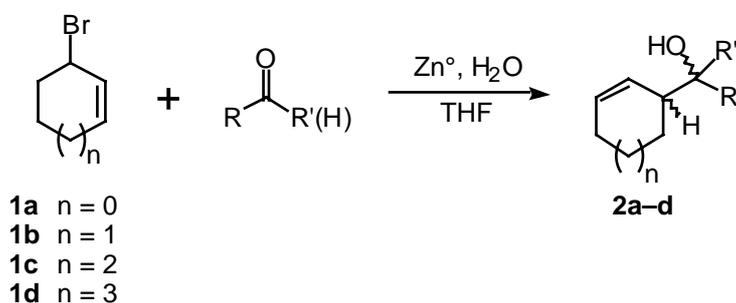
Introduction

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 NH_4Cl resulted in rapid consumption of the zinc metal in a mildly exothermic reaction. The addition product **2b** ($\text{R} = \text{C}_6\text{H}_5$, $\text{R}' = \text{H}$) 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 ^{13}C -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 ^{13}C -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^a

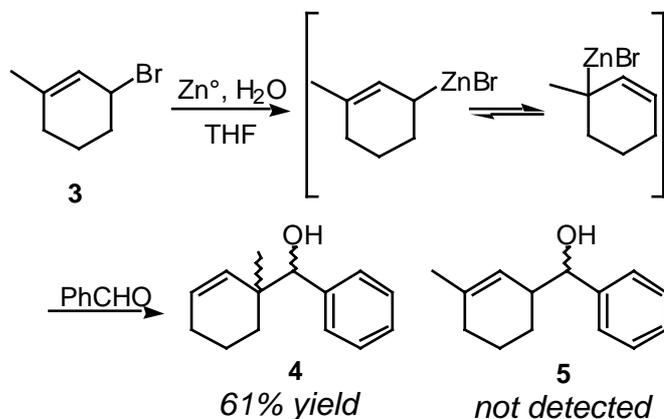
Cyclic Bromide	Substrate	% Yield ^b	Ratio of diastereomers <i>erythro/threo</i> ^c
1b	benzaldehyde	87	83:17
	tolualdehyde	90	87:13
	4-chlorobenzaldehyde	90	85:15
	<i>n</i> -heptaldehyde	77	45:55
	isobutyraldehyde	72	34:66
	acetophenone	83	90:10 ^d
	benzophenone	66	–
1a	tolualdehyde	82 ^e	80:20 ^f
1c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

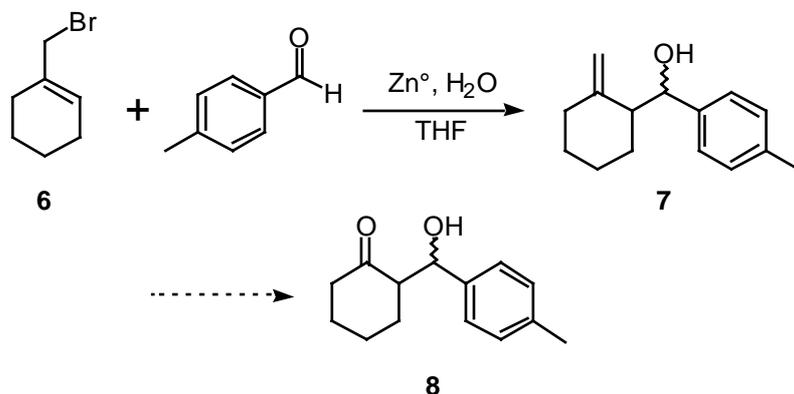
In order to determine the scope of the method, a series of cyclic allylic bromides (**1a–d**) that differed in ring size was investigated. Utilizing the same experimental protocol as was used with **1b**, with the exception that three equivalents of bromide and zinc were used rather than two, good yields 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 *erythro/threo* diastereomers, respectively, resulting from reaction at the more highly substituted allylic

site [7]. 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 toluanaldehyde 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 1H -NMR (δ 4.67) relative to that of the minor isomer (at δ 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 minor, 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.



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 ^{13}C -NMR spectra were recorded in CDCl_3 at 60 and 15 MHz, respectively. Gas chromatography was conducted using a $6' \times 1/8''$ 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 N_2 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 NH_4Cl solution (40 mL). The organic phase was separated, and the aqueous phase washed with diethyl ether ($2 \times 20\text{mL}$). The combined organic phases were dried over Na_2SO_4 , 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); ^{13}C -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 CH_2Cl_2 (2 mL), the phases were mixed, and the organic layer removed, dried over Na_2SO_4 filtered, and concentrated under reduced pressure to afford bromide **3** which was used directly in the zinc reactions;

$^1\text{H-NMR}$ δ 5.60 (br d, $J = 5$ Hz, 1H), 4.90 (br m, 1H), 2.1–1.5 (m, 6H), 1.65 (s, 3H); $^{13}\text{C-NMR}$ δ 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_2O (2 mL) followed by 10% H_2SO_4 (30 mL). The aqueous layer was separated and washed with ether (2×5 mL). The combined organics were dried over Na_2SO_4 , filtered and concentrated to afford 2.33 g (87% yield) of α -(2-cyclohexen-1-yl)methanol as a colorless liquid; $^1\text{H-NMR}$ δ 5.66 (br s, 1H), 3.93 (br s, 2H), 3.26 (br s, 1H, OH), 2.2–1.6 (m, 4H), 1.6–1.3 (m, 4H); $^{13}\text{C-NMR}$ δ 135.5, 120.3, 64.8, 23.6, 23.0, 20.6, 20.5; IR (neat) 3318, 2926, 1008 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 α -(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); $^1\text{H-NMR}$ δ 5.96 (br m, 1H), 3.93 (br s, 2H), 2.2–1.8 (m, 4H), 1.8–1.3 (m, 4H)

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_4Cl (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 (3×1 mL). The combined organics were dried over Na_2SO_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.

α -(2-Cycloocten-1-yl)-4-methylbenzenemethanol. Isolated as a colorless viscous liquid. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{O}$: C, 83.43; H, 9.63; Found: C, 83.01; H, 9.83; $^1\text{H-NMR}$ δ 7.09 (br s, 4H), 5.50–5.00 (m,

2H), 4.42 (d, $J = 7.2$ Hz, 1H) [4.36 (d, $J = 7.6$ Hz, 1H)], 3.20–2.5 (br m, 1H), 2.29 (s, 3H), 2.20–0.90 (m, 11H); $^{13}\text{C-NMR}$ δ 21.5, 25.9, 27.1, 27.2 [27.3], 29.7, 32.0 [32.9], 43.4 [44.2], 79.0, 126.1 (2C), 128.3 (2C), 129.2, 129.9, 136.3, 140.1; IR (neat) 3398, 3011, 2925, 2856, 1008 cm^{-1}

α -(2-Cyclohepten-1-yl)-4-methylbenzenemethanol. Isolated as a colorless viscous liquid. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: C, 83.28; H, 9.32; Found: C, 82.99; H, 9.59; $^1\text{H-NMR}$ δ 7.08 (br s, 4H), 5.80–5.50 (m, 2H), 4.45 (d, $J = 6.9$ Hz, 1H), 2.27 (s, 3H), 1.2–2.3 (10H); $^{13}\text{C-NMR}$ δ 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; IR (neat) 3392, 3020, 2853, 1037 cm^{-1}

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

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

References and Notes

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Sample Availability: Available from the authors.

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