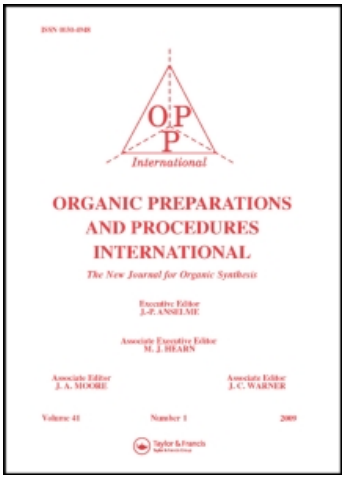

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A FACILE AND EFFICIENT ZINC-PROMOTED ALLYLATION OF CARBONYL COMPOUNDS

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10. Compounds **1a,b** were obtained as 80-90% of the keto tautomers by ^{1}H NMR spectra. These selectivities were measured from the signals of the acidic methylene H_{16} and those due to the vinylic hydrogens of the corresponding enol forms.

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A FACILE AND EFFICIENT ZINC-PROMOTED ALLYLATION OF CARBONYL COMPOUNDS

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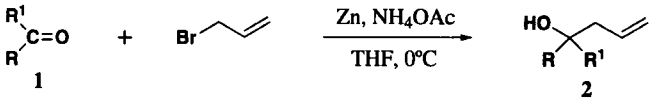
The synthesis of homoallylic alcohols by allylation of carbonyl compounds is an important process[1] because these alcohols can be easily converted into many essential functional groups for natural product synthesis.[2] By the use of a variety of metals such as manganese,[3] tin,[4] and zinc,[5] different homoallylic alcohols are generally prepared *via* the Barbier-type reaction of allylic halides and carbonyl compounds with metal powder. Such reactions are typically performed in anhydrous organic solvents under an inert atmosphere.[5a-5f] The feasibility of performing organometallic reactions in an aqueous media has been of considerable recent interest.[5g-5k] Luche has demonstrated that the Barbier-type reaction could be performed in a mixture of organic solvent with water, particularly when the metal surface was activated by ultrasound[5k] or with ammonium salts. The present work describes a study of the Barbier-type reaction of allyl bromide and carbonyl compounds in the presence of zinc powder and ammonium chloride in an aqueous media.



1 2

a) R = C_6H_5, R^1 = H b) R = C_5H_{11}, R^1 = H c) R = *p*-$MeOC_6H_4$, R^1 = H
d) R = CH_3, R^1 = C_4H_9 e) R = R^1 = $(CH_2)_5$ f) R = CH_3, R^1 = C_6H_5
g) R = CH_3, R^1 = 2-furyl h) R = CH_3, R^1 = 2-pyridyl i) R = R^1 = C_6H_5

Although aldehydes reacted completely, several ketones (acetophenone, 2-hexanone, benzophenone and 2-acetylfuran) were not consumed entirely. The results indicate a clean and smooth reaction of allyl bromide with aldehydes and ketones in the presence of ammonium acetate (crystal) and commercial zinc powder in tetrahydrofuran to produce the corresponding homoallylic alcohol in excellent yields. To our knowledge, the reaction of allyl bromide with carbonyl compounds under these conditions has never been described. The reaction of benzyl bromide with benzaldehyde in the presence of ammonium acetate and zinc in THF did not give the expected 1,2-diphenylethanol. The Table summarizes the yields and the time required for the reaction of carbonyl compounds with allyl bromide in the presence of zinc and ammonium acetate or ammonium chloride (crystal) in tetrahydrofuran. When ammonium acetate was used, the reaction was complete almost as soon as the allyl bromide was added. To prevent the above reaction from becoming too vigorous, the reaction solution was cooled in an ice-bath. When ammonium chloride was used, the reaction was completed after stirring for several hours at room temperature. All reagents in the above reactions were used as purchased and no further treatment was necessary. This procedure is also successful in large-scale operations. A 0.5-mole scale reaction of benzaldehyde and allyl bromide was performed and gave a 94% yield. During synthesis of natural and non-natural products, mild conditions are always preferred in key bond-forming steps. This study not only overcame the problems that some ketones could not be consumed completely in aqueous media. However, although anhydrous solvent and inert atmosphere conditions are not essential in the reaction of allyl bromide with carbonyl compounds in tetrahydrofuran, the use of ammonium acetate in THF is clearly a better choice of reagents than is ammonium chloride in water.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded at 300 MHz on Bruker AVANCE DPX-300 spectrometer. Chemical shifts are reported in using $CDCl_3$ (δ 7.26) as standard and coupling constants value *J* are given in Hz. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer Version 2. Zinc powder (325 mesh) was purchased from Strem Chemicals and used without further activation.

1-(*p*-Anisyl)-3-buten-1-ol (2c). Typical Procedure.- Allyl bromide (1.8 g, 15 mmol) was added at 0° to a stirred suspension of *p*-anisaldehyde (0.68 g, 5 mmol), zinc powder (0.98 g, 15 mmol), and NH_4OAc (1.2 g, 15 mmol) in THF (20 mL). After one min, the reaction mixture became white suspension, and the reaction was quenched by addition of 20 mL of saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate (20 mL x 3). The combined extract was dried over $MgSO_4$ and evaporated to a crude product which was purified by elution through a column of silica gel using ethyl acetate:hexane (1:19) as the eluent to produce 0.89 g (100 %) of 1-(*p*-anisyl)-3-buten-1-ol, bp. 106-107°/0.1 torr, *lit.*[6c] bp. 90-95°/0.1 torr.

TABLE. Homoallylic Alcohols from Carbonyl Compounds and Allyl Bromide[a]

Cmpd	Yield (%)	bp (°C/mm)	*lit.* (°C/mm)	Salt	Time (min.)	^{1}H NMR (δ)
2a	85 99	79-80 (0.95)	94-98 (2)[6a]	NH_4Oac NH_4Cl	1 120	2.40 (1H, s), 2.47 (2H, dd, *J* = 7.3, 7.6), 4.71 (1H, t, *J* = 6.5), 5.16 (2H, dd, *J* = 9.4, 8.2), 5.79 (1H, m), 7.26-7.40, (5H, m)
2b	82 87	66-68 (3.9)	88-90 (15)[6b]	NH_4OAc NH_4Cl	1 30	0.85 (3H, t, *J* = 6.5), 1.20-1.50 (8H, m), 1.97 (1H, s), 2.05-2.15 (1H, m), 2.21-2.29 (1H, m), 3.60 (1H, m), 5.06 (1H, s), 5.10 (1H, d, *J* = 4.1), 5.72-5.86 (1H, m)
2c	100 100	106-107 (0.1)	90-95 (0.1)[6c]	NH_4OAc NH_4Cl	1 120	2.49 (2H, t, *J* = 6.8), 3.79 (3H, s), 4.66 (1H, t, *J* = 6.5), 5.10 (1H, d, *J* = 2.0), 5.15 (1H, d, *J* = 10.2 Hz), 5.72-5.86, (1H, m), 6.88 (2H, d, *J* = 8.6 Hz), 7.26 (2H, d, *J* = 8.6 Hz)
2d	82 97	62-63 (6.9)	68-70 (12.8)[6d]	NH_4OAc NH_4Cl	1 150	0.88 (3H, t, *J* = 6.9), 1.12 (3H, s), 1.26-1.44 (6H, m), 1.70 (1H, s), 2.17 (2H, d, *J* = 7.5), 5.05 (1H, d, *J* = 10.2), 5.10 (1H, d, *J* = 2.5), 5.75-5.89 (1H, m)
2e	95 98	54-55 (1.6)	62-64 (3)[6e]	NH_4OAc NH_4Cl	1 120	1.20-1.62 (10H, m), 1.65 (1H, s), 2.17 (2H, d, *J* = 7.5), 5.05 (1H, d, *J* = 16.6), 5.09 (1H, d, *J* = 7.7), 5.78-5.92 (1H, m)
2f	100 93	94-95 (6.5)	95-97 (7)[6f]	NH_4OAc NH_4Cl	1 510	1.56 (3H, s), 2.11 (1H, s), 2.48-2.55 (1H, dd, *J* = 8.3, 8.3), 2.67-2.74 (1H, dd, *J* = 6.4, 6.4), 5.12 (1H, s), 5.15 (1H, d, *J* = 7.4), 5.59-5.70 (1H, m), 7.23-7.47 (5H, m)
2g[b]	79 83	69-70 (5.6)	---- ----	NH_4OAc NH_4Cl	1 600	1.52 (3H, s), 2.51 (1H, dd, *J* = 7.9, 7.8), 2.55 (1H, dd, *J* = 6.8, 6.8), 5.09 (1H, s), 5.13 (1H, d, *J* = 3.7), 5.60-5.71 (1H, m), 6.18 (1H, d, *J* = 3.2), 6.30 (1H, m), 7.34 (1H, s)
2h[c]	92 92	70-72 (0.7)	---- ----	NH_4OAc NH_4Cl	1 510	1.51 (3H, s), 2.55 (2H, d, *J* = 6.8), 4.95 (1H, s), 5.00 (1H, s), 5.59-5.73 (1H, m), 7.14 (1H, dd, *J* = 5.8, 5.0), 7.33 (1H, d, *J* = 8.0), 7.67 (1H, td, *J* = 8.5, 1.6), 8.49 (1H, d, *J* = 4.7)
2i	100 98	129-130 (0.1)	142-146 (0.3)[6g]	NH_4OAc NH_4Cl	1 30	3.10 (2H, d, *J* = 7.0), 5.20 (1H, d, *J* = 16.3), 5.25 (1H, d, *J* = 22.6), 5.61-5.75 (1H, m), 7.23 (2H, t, *J* = 7.2), 7.33 (4H, t, *J* = 7.6), 7.46 (4H, d, *J* = 7.9)

a) All product shows peaks between 3400-3350 (OH) and 3077-3030 (C=C) cm^{-1}. b) Compound **2g** has been reported (ref. 7) but was too unstable to be analyzed. c) Compound **2h** was too unstable to be analyzed; its *p*-nitrobenzoate ester, yellow solid, mp. 42°, was also too unstable to give correct elemental analysis datas. HRMS (FAB): Calcd for $C_{17}H_{17}N_2O_4$ ($M+H^+$) 313.1188. Found 313.1184.

1-Phenyl-3-buten-1-ol (2a). Large-scale Procedure.- Allyl bromide (72.6 g, 0.60 mmol) was slowly added at 0° to a stirred suspension of benzaldehyde (51.1 g, 0.50 mol), zinc powder (39.2 g, 0.60 mol), and NH_4OAc (42.4 g, 0.55 mol) in THF (500 mL). After stirring for 30 min, 500 mL of saturated $NaHCO_3$ aqueous solution was added and extracted with diethyl ether. The combined extract was dried over $MgSO_4$ and evaporated to produce a crude product, which was distilled to produce 69.8 g (94%) of 1-phenyl-3-buten-1-ol. bp. 79-80°/0.95 torr, *lit.*[6a] bp. 94-98°/2 torr.

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SYNTHESIS OF N-PROTECTED 1*H*-INDOLE-5-CARBOXYLIC ACIDS WITH ALDOSE REDUCTASE INHIBITORY POTENTIAL

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Indole carboxylic acids are useful building blocks for the preparation of bioactive compounds.[1-3] In these syntheses, selective functionalization of either the carboxylic acid or the indolyl-NH is often required. Based on the above considerations, the present work describes the preparation of 1-benzoyl- and 1-benzenesulfonyl-1*H*-indole-5-carboxylic acids (**4a** and **4b**). We consider these compounds as useful organic synthons and they contain important functionalities for a putative aldose reductase enzyme inhibitory activity.[4] Aldose reductase (ALR2) is implicated in chronic diabetic complications.[5]

Our initial attempt to synthesize these compounds involved a haloform reaction[6] of 1-benzoyl- or 1-benzenesulfonyl-5-acetylindoles. This route was selected because we had recently reported[7] a convenient two-step preparation of 5-acetylindole from indole. However, all attempts to isolate the desired carboxylic acids were unsuccessful, due to the extensive decomposition under these conditions. An alternative synthetic strategy involving the condensation of the commercially available 1*H*-indole-5-carboxylic acid (**1**) with O-benzyl-1,3-dicyclohexylisourea,[8-10] gave the corresponding benzyl ester **2** in excellent yield; no substitution on the heterocyclic ring was observed. In addition, this procedure gives better results than the previously reported Mitsunobu type esterification.[3] The introduction of the N-benzoyl- or the N-benzenesulfonyl-substituent was achieved under phase-