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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Mieczyslaw Makosza & Karol Grela (1996) A Mild and Simple Zinc-Promoted Barbier-Type Allylation of Aldehydes in Liquid Ammonia, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:15, 2935-2940, DOI: <u>10.1080/00397919608005230</u>

To link to this article: http://dx.doi.org/10.1080/00397919608005230

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A MILD AND SIMPLE ZINC-PROMOTED BARBIER-TYPE ALLYLATION OF ALDEHYDES IN LIQUID AMMONIA

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ABSTRACT: The Barbier reaction of allylic bromides and carbonyl compounds can be carried out in liquid ammonia using commercial zinc powder.

Substituted homoallylic alcohols are important intermediates in synthesis of natural products and there is a continuous interest in simple methods of preparation of these compounds.¹ Usually they are prepared *via* the Barbier reaction of allylic halides and carbonyl compounds with zinc powder. Such reactions are typically carried out in anhydrous organic solvents in oxygen-free atmosphere.¹ Recently, there has been considerable interest in performing organometallic reactions in aqueous media.²

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It was shown by Luche³ that the Barbier type reaction can be carried out in a mixture of organic solvent with water, particularly when the metal surface was activated with ultrasound or ammonium salts.

During our studies on reductive generation of active zinc we have observed that benzaldehyde reacts with allyl bromide in the presence of active zinc in liquid ammonia.⁴ This surprising observation and potential advantages of liquid ammonia as the reaction medium prompted us to study the synthetic utility of the Barbier type allylation of carbonyl compounds with commercial zinc powder in liquid ammonia. Using model reaction of benzaldehyde (1a) with allyl bromide we have studied effect of ratio of the reagents and additives (NH₄Cl, NH₄OCOMe, NH₄OCOPh, Et₃N×HCl) on this reaction (Scheme 1).



Additive	Molar Equivalent (mol) ^{b)}			Material Balance (Yield %) ^{C)}			
	Zn	Allyl Bromide	Additive	<u>1a</u>	<u>2a</u>	3	<u>4</u>
NH ₄ CI	1.5	1.5	15	77	23	_	-
NHACI	2.5	1.5	5	6	41	47	6
NH ₄ OCOMe	1.5	1.5	1	37	55	8	-
None	1.5	1.5	-	4	96	-	-

Allylation of Benzaldehyde (1a) under Various Conditions (Selected Examples)^{a)}

^{a)} Reaction of 5 mmol benzaldehyde (**1a**) in 30 mL of liquid ammonia. ^{b)} Per one equivalent of **1a**. ^{c)} GC yields

Scheme 1

Contrary to the reported examples in which the reaction in protic (aqueous) medium was promoted with ammonium salts added,³ these additives exert negative

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effect on the reaction course in liquid ammonia. Due to high acidity of ammonium salts in liquid ammonia zinc undergoes rapid dissolution even in low temperature of boiling ammonia⁵ thus the formation of the intermediate organozinc reagent is limited. On the basis of a number of preliminary experiments we have found that the optimal conditions are: ratio aldehyde / halide / zinc as 1 / 1.5 / 1.5 in boiling ammonia (-33°C) without other additives. Under such conditions the reaction of aromatic aldehydes and cinnamic aldehyde with allylic bromides proceeds smoothly to give the corresponding homoallylic alcohols in moderate to high yields. Somewhat lower yields gave the reaction with aliphatic aldehydes and with ketones (Table 1). Allylic chlorides are much less reactive.

Although it appears that experimental procedures for reactions in liquid ammonia are inconvenient and create difficulties in handling this opinion is groundless. We would like to emphasize that contrary to such common opinion this procedure is very simple and convenient. The ammonia can be simply condensed in the reaction flask by cooling with dry ice - acetone, during the reaction temperature is kept constant at -33°C (boiling ammonia) and under this conditions the reaction mixture is protected against atmospheric oxygen. Isolation of the product is also very simple. Upon evaporation of ammonia the residue is washed with ethyl ether to give a solution of organic products and insoluble zinc bromide ammonate $(ZnBr_2 \times 2NH_3)$,⁶ which can be filtered-off.

This procedure is also advantageous in large scale operations because ammonia can be readily recovered whereas troublesome aqueous treatment of the reaction mixture necessary in conventional procedure³ is avoided. From an industrial viewpoint, the use of liquid ammonia is more desirable because of the low cost as well as its availability and facile recycling.

Entry	Carbonyl Compound <u>1</u>	Allyl Bromide	Product <u>2</u>	Yield (%) ^{a)}
a	Ho	<i>∕∕</i> Br	HO	83 (96)
b	CI H	Br	HO CI	61 (69)
C	H CI CI	<i>∕∕∕</i> Br	HO	49 (54)
d	H O O	<i>∕∕∕</i> Br	HO) 78 (89)
е	H O	₩ ₩ ₩ Br	HO	75 (86)
f	∕~∕~¢°	<i>∳</i> ∕∕Br	ОН	(37)
g	o	<i>∕∕</i> Br	HO	(42)
h		<i>⊳</i> , Br	HO	(25)

Table 1

^{a)} Yields od isolated pure products. GC yields are shown in parentheses.

This is a further example of the use of liquid ammonia as medium for organic synthesis purposes. Although the preliminary results are limited to the aromatic aldehydes and allylic bromides, further applications in synthesis are under development.

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EXPERIMENTAL

¹H NMR spectra were recorded with Varian GEMINI-200 spectrometer (200 MHz). Chemical shifts values are given in δ [ppm] units relative to TMS. IR spectra were recorded with a Perkin-Elmer FTIR 1640 spectrophotometer; v_{max} in cm⁻¹. GC analyses were performed on Shimadzu GC-14A chromatograph. GC-MS analyses were performed with Hewlett Packard HP 5972A MSD unit. Aldehydes, allylic bromides and tetrahydrofuran were distilled before use. Technical grade ammonia was purified by passing it throught a column of granular potassium hydroxide. Zinc powder (Fluka) was used as received.

LARGER SCALE REACTION OF BENZALDEHYDE (1a) AND ALLYL BROMIDE

A 500 mL round-bottom flask equipped with a magnetic stirrer, dropping funel and dry-ice condenser protected by a drying tube filled with granular KOH was charged with zinc powder (5.0 g, 0.076 mol) and liquid ammonia (250 mL) was condensed. Then a solution of benzaldehyde (5.31 g, 0.05 mol) and allyl bromide (9.2 g, 0.075 mol) in THF (15 mL) was added dropwise during 15 min. After stirring for additional 30 min. the solid ammonium bromide (7.4 g, 0.076 mmol) was added and ammonia was evaporated. To the resulting mixture ethyl ether (100 mL) was added, the inorganic material was filtered-off and washed with ethyl ether (5×25 mL). The solvent was evaporated and the residue was purified by distillation *in vacuo* to give 1-phenylbut-3-en-1-ol (**2a**), yield 6.15 g (83%): b.p. 68/0.8 Torr (ref.⁷ 111-112/13 Torr).

GENERAL PROCEDURE FOR PREPARATION OF HOMOALLYLIC ALCOHOLS 2a-2e.

To the stirred suspension of zinc powder (0.49 g, 7.65 mmol) in liquid ammonia (30 mL) a solution of carbonyl compound (5.0 mmol) and allylic bromide (7.5 mmol) in THF (2.5 mL) was added in one portion. After stirring for 30 min. the solid ammonium bromide (1.5 g, 15.3 mmol) was added and ammonia was evaporated to dryness. To the residue ethyl ether (50 mL) was added, the inorganic solid was filtered-off and washed with ethyl ether (5×10 mL). The filtrate was washed with aqueous sodium bisulphite (5×10 mL), water (20 mL), and dried over magnesium sulphate. The solvent was removed *in vacuo* and the crude product was purified by distillation or flash chromatography (silica gel, hexan - ethyl acetate: 1 / 0 to $1 / 3 \nu/\nu$).

1-(4-Chlorophenyl)-but-3-en-1-ol (**2b**)⁸: IR (neat) 3397, 1641; ¹H NMR (CDCl₃) 2.03 (s, 1H), 2.36-2.59 (m, 2H), 4.73 (m, 1H), 5.16 (m, 2H), 5.69-5.90 (m, 1H), 7.29-7.34 (m, 4H); MS (m/z, rel. int. %) 182 (0.1 M⁺⁺), 164 (0.1 $[M-H_2O]^{++}$), 141 (100), 113 (22), 77 (78).

1-(2-Chlorophenyl)-but-3-en-1-ol (2c)⁸: IR (neat) 3387, 1640; ¹H NMR (CDCl₃) 2.06 (s, 1H), 2.36-2.60 (m, 2H), 4.72 (m, 1H), 5.16 (m, 2H), 5.68-5.89 (m, 1H), 7.29-7.34 (m, 4H); MS (m/z, rel. int. %) 164 (0.1 [M-H₂O]⁺⁺), 141 (89), 113 (25), 77 (100).

1-Phenylhexa-1,5-dien-3-ol (**2d**)⁹: IR (neat) 3383, 1641; ¹H NMR (CDCl₃) 1.79 (s, 1H), 2.30-2.53 (m, 2H), 4.37 (m, 1H), 5.12-5.25 (m, 2H), 5.76-5.97 (m, 1H), 6.19-6.30 (m, 1H), 6.58-

6.65 (m, 1H), 7.20-7.42 (m, 5H); MS (m/z, rel. int. %) 156 (0.1 $[M-H_2O]^{++}$), 133 (54), 115 (33), 77 (33) 55 (100).

2-Methyl-1-phenylbut-3-en-1-ol (2e): b.p. 54/0.2 Torr (ref.¹⁰ 110/4 Torr). Mixture of diastereoisomers. The *threo: erythro* ratio was determined to be 52:48 by ¹H NMR.⁸

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(Received in The Netherlands 09 February 1996)