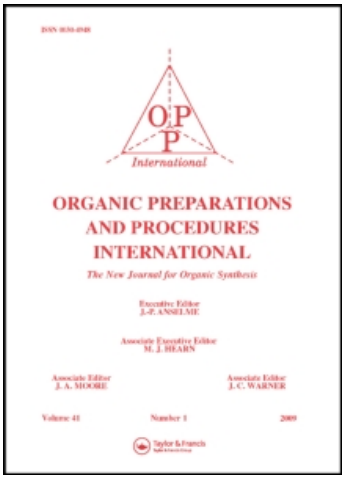

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A PRACTICAL SYNTHESIS OF 3-BUTYN-1-OL

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OPPI BRIEFS

A PRACTICAL SYNTHESIS OF 3-BUTYN-1-OL

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(01/10/06)

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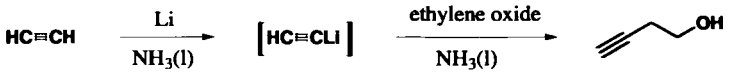
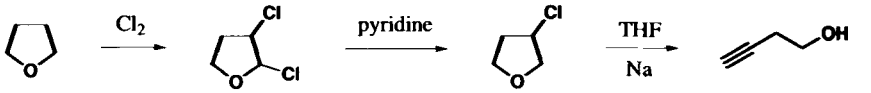
3-Butyn-1-ol is an important intermediate for the preparation of a number of natural products and for the synthesis of *fexofenadine*,[1,2] a selective HI-histamine receptor antagonist widely used as an antihistamine. As part of our research program, we required an efficient method to prepare 3-butyn-1-ol. Though it is a simple and small molecule, a review of the literature, including patents, indicated the absence of an easily-performed synthesis. A summary of the main known procedures[3-6] is shown in *Schemes 1* and *2*.

Since lithium acetylide is much less reactive towards ethylene oxide than most other polar organometallic derivatives,[7] its hydroxyalkylation in common organic solvents such as tetrahydrofuran or ether proceeds sluggishly; thus anhydrous liquid ammonia must be used as the most practical solvent to carry out the reaction which still required long times at low temperatures (*Scheme 1*).



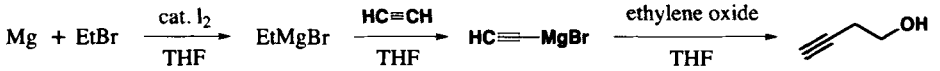
Scheme 1

Although all the reactions in *Scheme 2* may be carried out at room temperature, the use of pyridine and of sodium coupled with the lengthy sequence restricts its further development; in



Scheme 2

addition, the overall yield is low. We now report an efficient one-pot synthesis of 3-butyn-1-ol from ethynyl Grignard reagent and ethylene oxide with the advantages of easy operation, good yield and facile recovery of the solvent (*Scheme 3*).



Scheme 3

We began our investigation by following the conditions described[8] for the preparation of *n*-hexyl alcohol from ethylene oxide and *n*-butylmagnesium bromide. However, there was very little conversion when ethynyl Grignard reagent was used instead of *n*-butylmagnesium bromide to perform the reaction with ethylene oxide. Upon further investigation, it was found that the reaction temperature is the key factor and the yield of the desired alcohol increased to 75% when the reaction was carried out at 40°C; the major by-product was 2-bromoethanol, which can be destroyed by addition of aqueous sodium hydroxide easily.[9]

EXPERIMENTAL SECTION

Melting and boiling points are uncorrected. The purity of products was established on a Fuli GC-9790 gas chromatograph with FID, SE-30 capillary column (3.2 mm x 30 m). ^{1}H-NMR spectra were recorded on a Bruker 400 (400 MHz) instrument using $CDCl_3$ as the solvent with TMS as internal standard. Infrared spectra were obtained on an IR-408 instrument. All chemicals were reagent grade available commercially. Elemental analyses were performed on a Flash EA1112 instrument.

3-Butyn-1-ol.- In a 1 L round-bottomed flask, fitted with a stirrer, a separatory funnel, and a reflux condenser carrying a calcium chloride tube, was placed 13 g (0.54 mol) of magnesium turnings. A small crystal of iodine and a solution of 2 mL (2.42 g) of ethyl bromide in 400 mL of anhydrous tetrahydrofuran were added. As soon as the reaction started, the remainder of the ethyl bromide (54.5 g, 0.5 mol) in 100 mL of anhydrous tetrahydrofuran solution was added dropwise at such a rate that the mixture boiled continuously. The mixture was stirred for another 0.5 h and then cooled to −10°C. The separatory funnel was replaced by a fritted gas tube and ethyne (39.0 g, 1.5 mol) was bubbled for about 0.5 h (measured by weight difference from a small cylinder), while the temperature was kept below 10°C to give a pale purple solution. The temperature was then raised to 35-40°C and a solution of ethylene oxide (66.0 g, 1.5 mol) in 200 mL of anhydrous tetrahydrofuran, was added over 6-7 h. When the addition was complete, the mixture was stirred for another 2 h at 40°C. Evaporation of tetrahydrofuran gave a pale yellow solid which was treated with 1M hydrobromic acid. The mixture was extracted with ether (100 mL x 3) and the combined ethereal extract was shaken with 2M sodium hydroxide (100 mL) to remove 2-bromoethanol, and dried over $MgSO_4$. Evaporation of the solvent gave a liquid which was fractionally distilled to afford 26.2 g (75%) of a colorless oil, bp. 125-126°C, *lit.*[4] bp. 128-129°C in better than 95% purity by glc.

^{1}H NMR ($CDCl_3$): δ 2.05 (1 H, t, J = 2.8Hz), 2.46 (2 H, dd, J = 6.4, 2.8Hz), 2.55 (1 H, b), 3.73 (2 H, t, J = 6.4Hz).

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SYNTHESIS OF INDOLOSULFONYLUREAS, POTENT ACETOLACTATE SYNTHASE INHIBITORS

Submitted by (01/17/06)

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Sulfonylurea is one of the four classes of herbicides which inhibit *acetolactate synthase* (ALS), a key enzyme in the biosynthesis of branched-chain amino acids in plants.[1] However, a common problem is that sulfonylureas sometimes harm the plants or the next stubble crops