

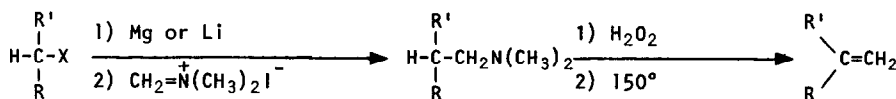
ADDITION OF GRIGNARD AND LITHIUM REAGENTS TO ESCHENMOSER'S  
SALT. A CONVENIENT SYNTHESIS OF TERMINAL OLEFINS.<sup>1</sup>

John L. Roberts, Peter S. Borromeo, and C. Dale Poulter\*<sup>2,3</sup>  
Department of Chemistry, University of Utah  
Salt Lake City, Utah 84112

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Terminal double bonds are common functional groups which are found in many synthetically useful intermediates and naturally occurring compounds. Although there are several methods for construction of an unsaturated methylene group,<sup>4</sup> few of the procedures are operationally simple or proceed in high yield. Pyrolysis of amine oxides is an excellent method for introducing this moiety.<sup>4a</sup> However, the approach suffers from a major limitation. In most synthetic sequences, it is desirable to add the carbon that will become the methylene portion of the double bond to a simpler fragment. The manipulations required to construct the desired amine oxide functionality reduce the efficiency (yield and time) of the procedure to the point where it is not competitive with moderate yield one-pot approaches such as the Wittig reaction.<sup>4b</sup> In this communication we describe a direct method for introducing the dimethylaminomethyl moiety. Subsequent oxidation and elimination afford olefins with terminal methylenes in high yield.

Our approach to the construction of the dimethylaminomethyl functional group involves



addition of a carbon nucleophile (Grignard or lithium reagent) to Eschenmoser's salt.<sup>5</sup> In a typical experiment, a dry, nitrogen-filled flask was charged with dimethyl(methylene)ammonium iodide<sup>5,6</sup> (ca. 10% excess) and anhydrous ether (ca. 5 ml/mmol of salt). A solution of the appropriate organometallic reagent (1-2M in ether) was added via syringe to the stirred suspension at a rate which maintained a gentle reflux.<sup>7</sup> When addition was complete, the resulting mixture was vigorously stirred for one hour at room temperature. Work-up involved careful addition of water until the suspended salts just dissolved, followed by vigorous stirring for

30 min. The ether layer was separated from the aqueous layer, and the latter extracted three times with ether. The combined ether layers were washed with saturated brine and dried over anhydrous magnesium sulfate before solvent was removed at reduced pressure.<sup>8</sup> Gpc analysis on a 500' x 0.03" open tubular column (Carbowax 20M) showed no products other than the desired amine (>95%). For the oxidation, the amine was dissolved in methanol (1 ml/mmol of amine), and one equivalent of 30% hydrogen peroxide was added. The progress of the reaction was monitored by the alcoholic phenolphthalein test,<sup>4a</sup> and additional one equivalent portions of 30% hydrogen peroxide were added periodically. Excess peroxide was quenched (to a negative potassium iodide test) with a catalytic amount of platinum oxide, the solution filtered, and solvent removed at reduced pressure. The residue was heated to ca. 160° with stirring, and olefin was trapped at -78°. After the reaction was complete, water was added to the trap, and the product was worked-up in the usual way.<sup>4a</sup>

The results for four representative alkyl halides are listed in Table I. All of the amines, amine oxides, and olefins gave satisfactory IR and NMR spectra. Each reported yield represents an isolated yield of pure material, and some losses inevitably occurred during purification when working on a 1-15 mmol scale. The overall yields are higher than shown in the Table when

TABLE I. YIELDS

Organometallic Reagent	Yield of Amine (%)	Yield, Isolated as methyl iodide salt (%)	Yield of Olefin via Amine Oxide (%)	Overall Yield from Halide
n-Octylmagnesium bromide <sup>a</sup>	91 <sup>c,d</sup>	90-95 <sup>h,i</sup>	87	78-83
Cyclohexylmagnesium bromide <sup>a</sup>	--	92-95 <sup>h,j</sup>	(88) <sup>p</sup>	81-84
Benzylmagnesium chloride <sup>a</sup>	85 <sup>c,f</sup>	----- <sup>l</sup>	83	70
n-Butyllithium <sup>b</sup>	--	84 <sup>n</sup>	--	--

a) Stock solutions of Grignard reagent were prepared in diethyl ether. R. Lespieau and M. Bourguet, *Org. Syn.*, Coll. Vol. 1, (Second Ed.), 186 (1941) and F.S. Prout, R.J. Hartman, E.P.Y. Huang, C.J. Korpics and G.R. Tichelaar, *Org. Syn.*, Coll. Vol. IV, 93 (1963). Excess magnesium was used to insure complete reaction, and the ether solutions of the Grignard reagents were filtered through a Schlenk filter before storage. G.l.c. analysis of hydrolyzed aliquots showed no starting halide and only traces (<5%) of other impurities, presumably from coupling during Grignard formation. Molarity of the Grignard solutions were determined by the procedure of Watson and Eastham; S.C. Watson and J.F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967). b) Commercial product from Alfa Ventron, 2.4M in hexane. c) From experiments carried out on a 10-15 mmol scale. d) bp 97°, 20 mm (lit.<sup>e</sup> 209°, 741 mm). e) H. King and T. Work, *J. Chem. Soc.*, 403 (1942). f) bp 85°, 12 mm (lit.<sup>g</sup> 98°, 22 mm). g) R.N. Icke, B.B. Wisegarver and G.A. Alles, *Org. Syn.*, Coll. Vol. III, 723 (1955). h) From experiments carried out on a 1-5 mmol scale. i) mp 180-181.5° (lit.<sup>e</sup> 170°) j) mp 227-227.5° (lit.<sup>k</sup> 226.5-227.5°), k) O. Wallach, *Ann.*, **353**, 284 (1907). l) mp 228-229° (lit.<sup>m</sup> 229°). m) T. Kato, T. Morikawa, and Y. Suzuki, *J. Pharm. Soc. Japan*, **72**, 1177 (1952); *Chemical Abstracts*, **47**, 7433f (1953). n) mp 222-224° (lit.<sup>o</sup> 222-223°). o) R. Willstätter and E. Waser, *Ber.*, **43**, 1176 (1910). p) Ref. 4.

the amines are oxidized, and the resulting amine oxides pyrolyzed without attempting to purify the intermediates. It should also be emphasized that Eschenmoser's salt can be prepared in large batches and stored until needed; thereby, eliminating the need to freshly prepare one of the reagents. The only limiting factor in using the iminium salt approach appears to be preparation of the organometallic reagent.<sup>9</sup>

The synthesis of methylene-containing olefins via the amine oxide route now nicely complements the Wittig reaction in convenience and yield. Also, the procedure is apparently useful with a variety of carbon nucleophiles<sup>12</sup> such as ketone,<sup>14</sup> ester,<sup>14</sup> and lactone<sup>14,15</sup> enolates in the preparation of Mannich intermediates that can be converted into the corresponding  $\alpha$ -methylene derivatives.

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