

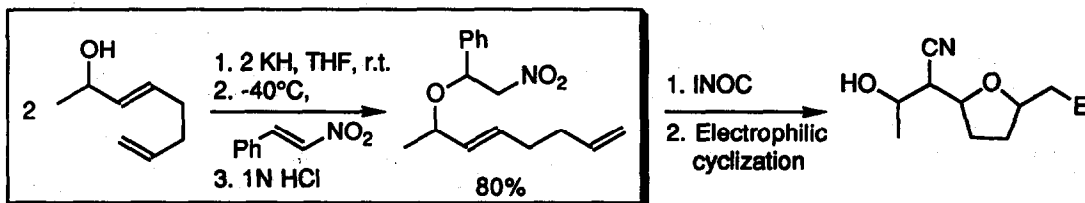
Lithium, Potassium, and Sodium Alkoxides: Donors in the Michael Addition Reaction of α -Nitroolefins.

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Abstract: Michael addition of potassio- or sodioalkoxides to α -nitroolefins provides essentially pure β -nitroethers (1-10) in 78-100% isolated yield.

Our interest in the tandem 1,3-dipolar nitrile oxide-olefin cycloaddition/electrophilic isoxazoline-olefin cyclization protocol^{1,2} has confronted us with the troublesome nature of preparing β -nitroethers from nitroalkenes and alkoxides. The literature suggests that this Michael addition delivers β -nitroethers in only poor to moderate yield.³ Indeed, we found that under optimized conditions excess lithioalkoxide (6 equiv.; generated from the corresponding alcohol and *n*-BuLi) reacts with a THF/TMEDA (1.5:1) solution of the nitroolefin (0.50 M) at room temperature to deliver the target β -nitroether in only low to moderate yield (13-49%). As reported previously,^{3,4} Michael addition of lithioalkoxides to nitroolefins produces complex reaction mixtures in which a large portion of the starting nitroolefin is lost to competing Michael addition of the intermediate nitronate; entries 1, 2, and 4 (Scheme 2) establish that this unwanted competition is problematic even when a large excess (6 eq.) of lithioalkoxide is employed. In contrast, under the conditions reported below, potassio- and sodioalkoxides deliver essentially pure β -nitroethers in far superior yields (70-96%) with only two equivalents of alkoxide (Schemes 1 and 2). TLC analysis at the end of nitroolefin addition showed only β -nitroether product and starting alcohol; di- and trimerization products were not detected. Sodium hydride and potassium hydride generated alkoxides performed equally well in this Michael addition.

Scheme 1

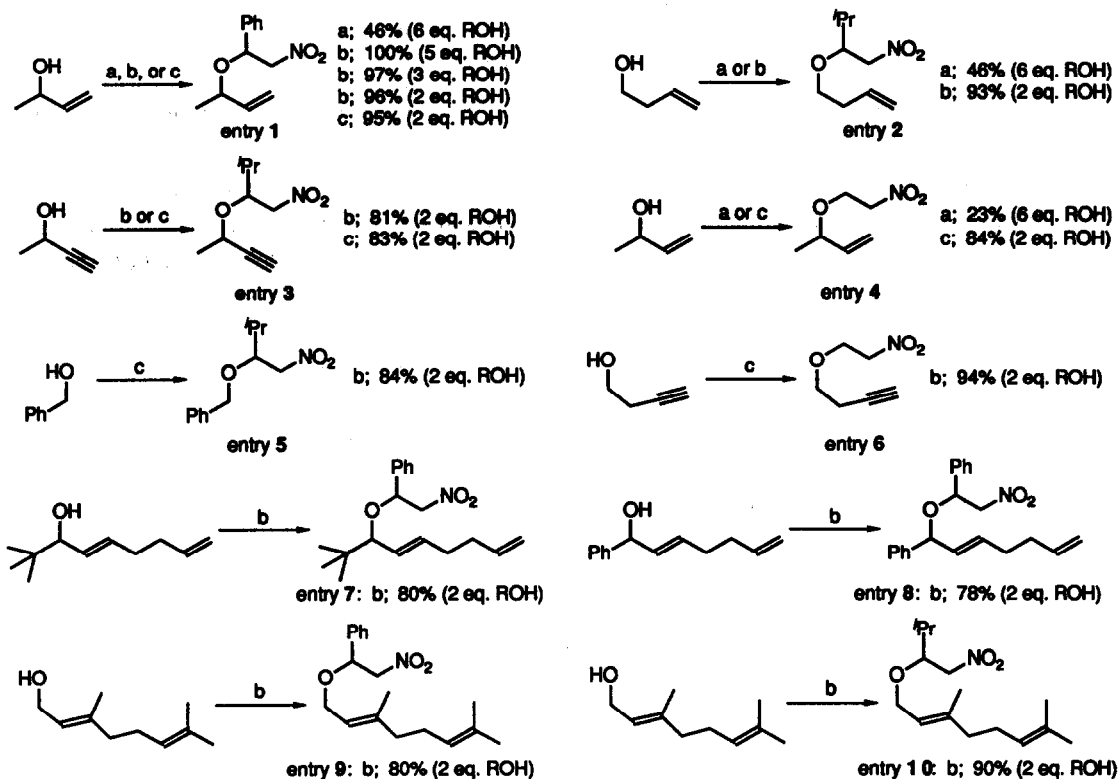


While a variety of nitroolefins have been employed in this procedure, only nitrostyrene⁵, 3-methyl-1-nitrobutene⁶, and nitroethylene⁷ examples are presented here (Scheme 2). Even nitroethylene, which is well known for its tendencies to decompose or polymerize quickly, reacted cleanly with the sodio- and potassioalkoxides under the following reaction conditions:

General procedure for the formation of β -nitroethers. Oil-covered potassium hydride (35%, 2.0 mmol) was placed in a 1-necked 50 mL flask and washed with dry hexane (5 x 10 mL). After the remaining hexane was removed by evaporation with a dry stream of N₂, dry THF (25 mL) was added followed by the dropwise addition of the appropriate alcohol (2.0 mmol). The resulting mixture was stirred at room temperature for 1h, cooled to -40°C, and treated with a THF (5 mL) solution of nitroolefin (1.0 mmol) at the rate of 0.1 mL/min. When addition was complete, the reaction was warmed to 0°C and quenched by

addition of 1N HCl (10 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic layers were then washed with 5% aq. NaHCO₃, water, and brine, dried over Na₂SO₄, and filtered. Solvent removal under reduced pressure gave the nitroether as a clear, colorless oil (when the starting alcohol is non-volatile, it is removed by flash column chromatography on silica gel).

Scheme 2: a → (i) n-BuLi, THF, TMEDA, r.t.; (ii) nitroolefin; (iii) 1N HCl. b → (i) KH, THF, r.t.; (ii) nitroolefin, -40°C; (iii) 1N HCl; c → (i) NaH, THF, r.t.; (ii) nitroolefin, -40°C; (iii) 1N HCl.



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- (a) Ranganathan, D. *J. Org. Chem.* 1980, 45, 1185. (b) Noland, W.E. *Org. Syn.* 1961, 41, 67. (c) Nitroethylene (1 mmol in 5 mL THF) was slowly added while protected from light.