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Synthesis of Alkyl Nitronates via Mitsunobu Condensation

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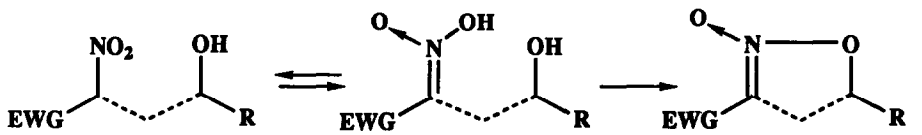
Key words: Nitronate; Nitronic ester; Mitsunobu; 2-Isoxazoline-2-oxide; 5,6-dihydro-4H-oxazine-2-oxide

Summary: Nitroalkanes bearing electron-withdrawing or unsaturated substituents at the α-carbon experience exclusive intra- and intermolecular O-alkylation by alcohols under Mitsunobu condensation conditions furnishing good to excellent yields of alkyl nitronates; in contrast, 1-phenylsulphonyl-1-nitro-3-propanol affords mainly the corresponding cyclopropane.

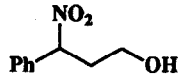
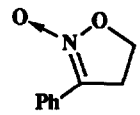
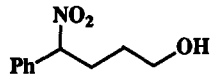
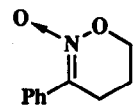
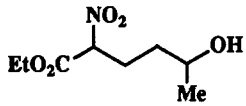
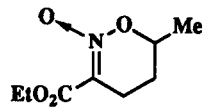
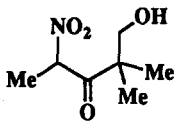
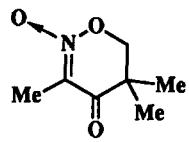
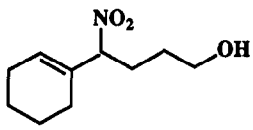
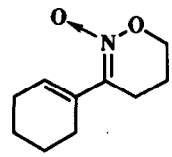
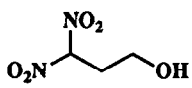
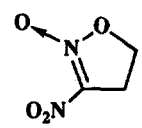
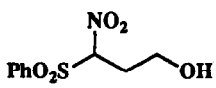
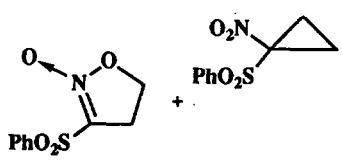
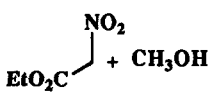
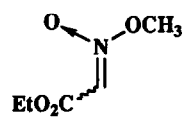
Alkyl nitronates, i.e., esters of nitronic acid, have been confirmed as reactive 1,3-dipoles in cycloadditions with alkenes, alkynes, and heterodipolarophiles.[1] Although not as extensively studied as the structurally related nitrones, several investigators have recently exploited the unique properties of nitronates, especially the more robust cyclic species, for the stereo- and regioselective construction of highly functionalized molecules.[2] These studies have also highlighted the need for efficient and specific methodology for generating alkyl nitronates, which are commonly prepared[3] by O-alkylation of the parent nitroalkane under basic conditions. Herein, we report that aliphatic nitro compounds bearing electron-withdrawing or unsaturated substituents on the α-carbon experience intra- or intermolecular O-alkylation by alcohols under the influence of a preformed complex of diethyl azodicarboxylate (DEAD) and triphenylphosphine affording good to excellent yields of alkyl nitronates[4] (eq 1). The reaction[5] proceeds rapidly at ambient temperature under essentially neutral conditions in benzene or THF. Competitive C-alkylation of the ambident nitronic acid generally is not observed (*vide infra*).[5]



nitro nitronic acid alkyl nitronate (eq 1)

Some representative condensations are summarized in the Table. Utilizing the standard procedure, 1-nitro-1-phenyl-3-propanol (entry 1) was almost quantitatively transformed into the chromatographically more polar 3-phenyl-2-isoxazoline-2-oxide[6], mp 117-118.5°C (EtOH). Its identity was confirmed by trimethyl phosphite deoxygenation[2a] to give 3-phenyl-2-isoxazoline, mp 65-66°C (lit.[7] mp 66°C). The six-membered heterocycles 5,6-dihydro-3-phenyl-4H-1,2-oxazine-2-oxide,[8] mp 77-78°C (EtOH), and its 6-methyl homologue were obtained similarly in good yield from primary and secondary δ-nitroalkanols (entries 2 and 3, respectively).

Table. Synthesis of Alkyl Nitronates via Mitsunobu Condensation

Entry	Substrate(s)	Product(s)	Yield,[a] %
1			98
2			93
3			94
4			94
5			81
6			98
7			82 15
8			82 (1:2 c / t)[b]

[a]Isolated yield of chromatographically and spectrally homogeneous material. [b]Ratio determined by ^{1}H NMR.

Moderately hindered alcohols such as the neopentyl-like example in entry 4 are also suitable substrates, but more crowded or tertiary alcohols are unreactive in keeping with other Mitsunobu displacements.[9]

Even a simple olefin was sufficient to favor nitronate formation (entry 5). However, the nature of the α-substituent can have a profound influence. Whereas the dinitro-activated methylene in entry 6 smoothly cyclized to the known 3-nitro-2-isoxazoline-2-oxide, mp 96.5-97.5°C (lit.[10] mp 96.5°C), replacement of a nitro by phenylsulfonyl unexpectedly gave rise to the corresponding cyclopropane[5] as the principal product (entry 7). The basis of this differential reactivity is unclear[11]; we speculate it may be a consequence of arrested rehybridization[12] of the nitronate anion from sp^3 to sp^2, thus retaining more electron density on carbon.

Intermolecular coupling of ethyl nitroacetate with methanol (2 equiv) gave a mixture of *cis*- and *trans*-nitronate[13] (entry 8). This contrasts sharply with the usual preferential C-alkylation of alkyl nitroacetate anions by alkyl halides in aprotic solvents.[3] In the case of acyclic nitronates, improved yields were obtained by dropwise addition of DEAD to a stirring solution of the nitroalkane, alcohol, and Ph_3P.

General Procedure. DEAD (2 mmol) is added dropwise to a stirring solution of PPh_3 (2 mmol) in anhydrous benzene (20 ml) at ambient temperature under an inert atmosphere. After 15 min, the nitroalkanol (1 mmol) in benzene (10ml) is added to the resultant deep red, homogeneous solution. Following complete consumption of the reactant (1 h), the solvent is removed *in vacuo* and the residue purified by SiO_2 column chromatography to give alkyl nitronate in 81-98% yield (Table 1).

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