Double Michael Addition in the Synthesis of Tertiary Allylic Nitro Compounds

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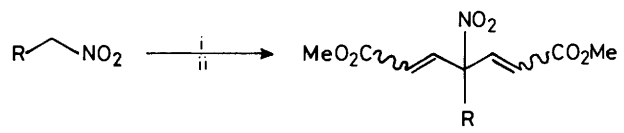
Tertiary allylic nitro compounds have been synthesized in good yields by the double Michael addition of primary nitroalkanes to electron-deficient acetylenes and alkenes in the presence of potassium fluoride and tetrabutylammonium chloride in dimethyl sulphoxide.

Tertiary allylic nitro compounds are versatile synthetic intermediates. The nitro group can be readily replaced by nucleophiles such as amines,[1] enolates,[1-3] lithium dialkylcuprates,[4] sulphinates,[5] and thiolates.[5] The nitro group can also be reduced to an amine [6] or replaced by hydride.[7] The applicability of tertiary allylic nitro compounds in synthesis is nevertheless limited because only a few general methods exist for their preparation. The method reported by Tanikaga *et al.* involves the use of nitroalkanes and phenyl vinyl sulphoxide as the starting materials,[8] and the procedure requires two steps and high reaction temperature (180 °C). Ono *et al.* developed another method, in which nitroalkenes react with aldehydes or electron-deficient olefins;[9] preparation of the starting nitroalkenes usually requires two steps or more.[10] We now report a simple method for the synthesis of tertiary allylic nitro compounds by the double Michael addition of primary nitroalkanes to electron-deficient acetylenes and alkenes.

The double Michael addition is known to occur between primary nitroalkanes and 2 equiv. of electron-deficient olefins.[11] Primary nitroalkanes can also react sequentially with two different C=C double bonds in the same molecule.[12-14] However, to the best of our knowledge, the double Michael addition between primary nitroalkanes and acetylenes is unprecedented.‡,§

We found that nitroalkanes (**1**) and (**2**) individually reacted with an excess of methyl propiolate, in the presence of potassium fluoride (KF) and the phase-transfer catalyst tetrabutylammonium chloride (Bu_4NCl), to give the double Michael adducts (**3**) and (**4**), respectively (Scheme 1). In a typical experiment, a mixture of the nitroalkane (1.0 equiv.), KF (5.0 equiv.), Bu_4NCl (1.0 equiv.), and dimethyl sulphoxide (DMSO; 1.0M) was stirred at room temperature for 30 min.

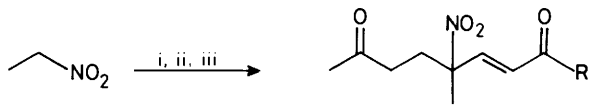


(**1**) R = Me (**3**) R = Me
(**2**) R = $(CH_2)_2CO_2Me$ (**4**) R = $(CH_2)_2CO_2Me$

Scheme 1. *Reagents:* i, KF, Bu_4NCl; ii, $HC{\equiv}CCO_2Me$

Methyl propiolate (3.0—3.5 equiv.) was then added over 30 min and stirring was continued for an additional hour. Accordingly, nitroethane (**1**) gave the adduct (**3**) in 75% yield and methyl 4-nitrobutyrate (**2**) gave the adduct (**4**) in 53% yield; both (**3**) and (**4**) were obtained as a mixture of regioisomers.

We next explored the possibility that a primary nitro compound could react with 1 equiv. of an acetylene and then with a second Michael acceptor *in situ* (Scheme 2). A solution of



(**5**) R = OMe
(**6**) R = Me

Scheme 2. *Reagents:* i, KF, Bu_4NCl; ii, $HC{\equiv}CCOR$ (R = OMe or Me); iii, $H_2C{=}CHCOMe$

nitroethane (1.0 equiv.), KF (5.0 equiv.), Bu_4NCl (1.0 equiv.), and DMSO (1.0M) was stirred at room temperature for 30 min, after which methyl propiolate (1.0 equiv.) was added over 2 h; stirring was continued for an additional hour. Methyl vinyl ketone (2.0 equiv.) was then added and the reaction was stirred for a further 2 h. Aqueous work-up and purification of the reaction mixture by chromatography gave the double Michael adduct (**5**) as the only enedione in 60% yield. We identified (**5**) as the *E*-isomer on the basis of the coupling constant (J = 16.1 Hz) of the olefinic protons.¶ By the same procedure, Michael acceptors but-3-yn-2-one (1.0 equiv.) and methyl vinyl ketone (2.0 equiv.) were added in sequence to nitroethane (1.0 equiv.) to give the allylic nitro compound (**6**) as the pure *E*-isomer in 52% yield.

We found that electron-deficient alkenes with an alkyl substituent at either the α- or the β-position were also suitable Michael acceptors (Scheme 3). Thus, treatment of nitroethane (1.0 equiv.) sequentially with ethyl methacrylate (1.0 equiv.), and methyl propiolate (1.0 equiv.) in the presence of KF (5.0 equiv.), Bu_4NCl (1.0 equiv.), and DMSO (1.0M) afforded a 41% yield of adduct (**7**),‖ as a 2:3 mixture of diastereoisomers. In addition, use of cyclohex-2-enone (1.0 equiv.) and methyl

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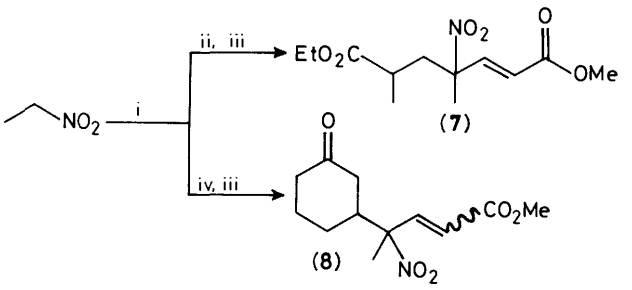
‡ A search of *Chemical Abstracts* from 1907—1987 revealed no relevant reports.
§ Battersby *et al.* reported the Michael addition of the secondary nitro compound, diphenylnitropropane, to 1 equiv. of methyl propiolate.[15]

¶ For *Z*-isomers of this type, we found that J = 12.6 Hz.
‖ The n.m.r. spectrum of (**7**) indicated that only the *E*-isomer was obtained. Compound (**7**) was unstable to g.c. conditions.



Scheme 3. *Reagents:* i, KF, Bu_4NCl; ii, $H_2C{=}CMeCO_2Et$; iii, $HC{\equiv}CCO_2Me$; iv, cyclohex-2-enone

propiolate (1.0 equiv.) as Michael acceptors gave the adduct (**8**) in 50% yield.

It is difficult to add secondary nitronates to alkenes that contain an electron-withdrawing group and an alkyl group at either the α- or the β-position.[16,17] Thus, such alkenes must be used as the first Michael acceptor in the newly developed double addition procedure. Also after the addition of such alkenes to nitroethane, the reaction mixture must be stirred for 24 h before the addition of the second Michael acceptor.

In conclusion, a new method was developed for the synthesis of tertiary allylic nitro compounds. These compounds can be obtained in good yields by the double Michael addition of primary nitroalkanes to electron-deficient acetylenes and alkenes in the presence of KF, Bu_4NCl, and DMSO. Because primary nitroalkanes are readily available and the nitro group can be easily converted into various functionalities, the new method should be valuable in organic synthesis. Further work is in progress to synthesize biologically active natural products by use of this method.

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