Efficient Functional Group Transformations on a Cyclic Nitroalkene System

Jih Ru Hwu* and Naelong Wang

Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218, U.S.A.

Single-pot nitroalkene → cyanoaldehyde transformation, α-methoxy oxime formation, α- and β-alkylations of β-sulphenylated nitro compound, generation of β-sulphenylated silyl nitronate, and sequential Michael addition and Nef reaction have been accomplished in good to excellent yields.

Double functional group transformations in a 'single-pot,' although difficult to accomplish owing to their complexity, can have significantly synthetic benefits.[1] Recently we have developed methods to convert nitroalkenes into cyanoaldehydes and other important classes of compounds. Herein we illustrate this chemistry using 1-nitrocyclohexene (**1**) as an example[2] (see Scheme 1).

Alkoxylation of (**1**) with potassium methoxide (1.5 equiv.) in 1,2-dimethoxyethane (DME) at room temperature for 2 h[3] followed by addition of triethyloxonium tetrafluoroborate (1.5 equiv.) gave a brown solution which was further refluxed for 7 h. Treatment of the mixture with thionyl chloride (2.0 equiv.) *in situ* provided the ω-cyanoaldehyde (**2**) in 77% isolated yield after normal aqueous work-up. Use of phosphorus pentachloride (2.0 equiv.) in carbon tetrachloride also gave the desired product (**2**) although the yield was lower (55%). When we employed tetrahydrofuran (THF) as the solvent, the tailing of the THF–BF_3 complex in silica gel chromatography caused purification problem.

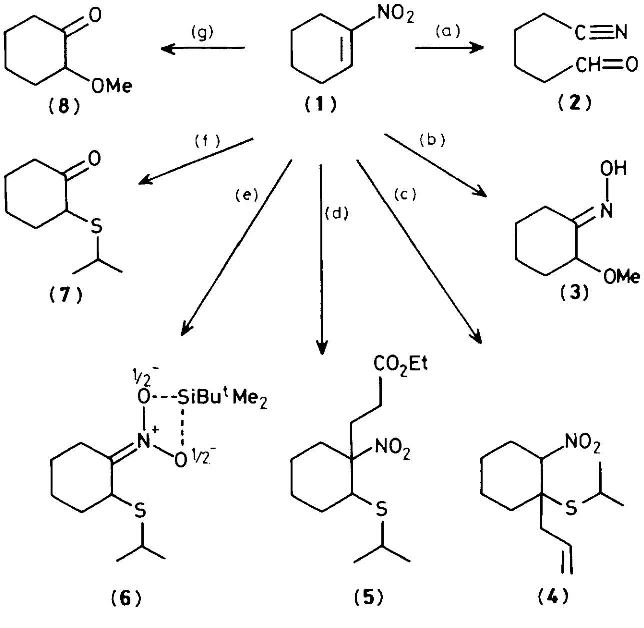
The mechanism depicted in Scheme 2 illustrates our initial design and accounts for the double functional group transformation.[4] When applying the same procedure described above but without adding thionyl chloride, we were able to isolate the intermediate α-methoxy oxime (**3**) along with its *Z*-isomer in an overall 91% yield. Use of methylene chloride, a low b.p. solvent, for this reaction made the decomposition of ethyl nitronate (**9**) sluggish.[5]

We observed two spots on t.l.c. with equal intensity and similar R_f values (0.12 and 0.17, 1:4 EtOAc–hexanes as eluant) before the reaction of (**1**) to give (**3**) was worked up. The component with the higher R_f value was partly converted into the one with the lower value during purification. N.m.r. analysis showed that the ratio of these two components was 2:5. Upon treatment with aqueous hydrochloric acid, the component with the lower R_f value underwent a second-order Beckmann rearrangement much faster than the other.[6] Therefore we assigned the compound with the lower R_f value as the *E*-oxime [*i.e.* (**3**)].

Thiolation of (**1**) with lithium isopropyl sulphide (1.5 equiv.) in THF gave the nitronate (**10**).[3] This intermediate possesses four reacting centres that provide different functionalization possibilities: (a) the C-1 carbon for Michael† acceptors;[7] (b) the C-2 acidic proton being removed followed by *C*-alkylation;[8] (c) the $C{=}N^+$ double bond for the Nef reaction;[9] (d) the O-centre for silylation.[10] The resulting silyl nitronate can be extensively used for a variety of reactions,[11] such as 1,3-dipolar cycloaddition[12] and the Henry reaction.[13]

We abstracted the C-2 acidic proton of (**10**) *in situ* with n-butyl-lithium (1.3 equiv.) in hexamethylphosphoramide (HMPA) at −78 °C and injected allyl bromide (1.8 equiv.) to give the alkenyl nitro sulphide (**4**) in 51% isolated yield. This strategy provides a synthetic route to nitro compounds containing an α-sulphenylated, quaternary carbon centre from nitroalkenes. On the other hand, treatment of (**10**) with ethyl acrylate (3.5 equiv.) in THF at −4 °C produced the Michael adduct (**5**) in 71% yield. Furthermore, reaction of (**10**) with t-butyldimethylsilyl chloride (2.0 equiv.) in THF afforded the silyl nitronate (**6**) in 96% yield, determined by n.m.r. spectroscopy. This compound gradually decomposed upon heating *in vacuo*, consistent with a previous report.[10]

Oxidative cleavage of the $C{=}N^+$ double bonds in (**10**) with aqueous potassium permanganate in the presence of magnesium sulphate[14] provided the α-sulphenylated ketone (**7**) (81%). However use of hydrolytic techniques with various concentrations of aqueous sulphuric acid (0.01—4.5 M) for the Nef reaction[7] gave (**7**) in lower yields (<60%). Similarly, treatment of (**1**) with potassium methoxide (1.5 equiv.) in THF followed by addition of potassium permanganate and magnesium sulphate afforded the α-methoxy ketone (**8**) in 85% yield. Exposure of (**11**) to mineral acids yielded a large amount of starting material (**1**) *via* a retro Michael process. The successful combination of Michael and Nef reactions should provide a valuable route for preparation of α-sulphenylated and α-alkoxylated ketones.[15]



Scheme 1. *Reagents* (r.t. = room temperature): (a) i, KOMe (1.5 equiv.), DME, r.t., 2 h; ii, Et_3OBF_4 (1.5 equiv.), heat, 7 h; iii, $SOCl_2$ (2.0 equiv.), 0 °C, 0.5 h; iv, H_2O; 77%; (b) i, KOMe (1.5 equiv.), THF, r.t., 2 h; ii, Et_3OBF_4 (1.5 equiv.), heat, 4 h; iii, H_2O; 91%; (c) i, Pr^iSLi (1.5 equiv.), THF, r.t., 2 h, ii, Bu^nLi (1.3 equiv.), HMPA, −78 °C, 30 min; iii, $CH_2{=}CHCH_2Br$ (1.8 equiv.); −78 °C, 30 min, r.t., 14 h; 51%; (d) i, Pr^iSLi (1.5 equiv.), THF, r.t., 2 h; ii, $CH_2{=}CHCO_2Et$ (3.5 equiv.); −4 °C, 1 h; 71%; (e) i, Pr^iSLi (1.5 equiv.), THF, r.t., 2 h; ii, Bu^tMe_2SiCl (2.0 equiv.); −78 °C to r.t., 7 h; 96%; (f) i, Pr^iSLi (1.5 equiv.), THF, r.t., 2 h; ii, $KMnO_4$, $MgSO_4$, H_2O, 0 °C, 1 h; 81%; (g) i, KOMe (1.5 equiv.) THF, r.t. 2 h; iii, $KMnO_4$, $MgSO_4$, H_2O, 0 °C, 1 h; 85%.

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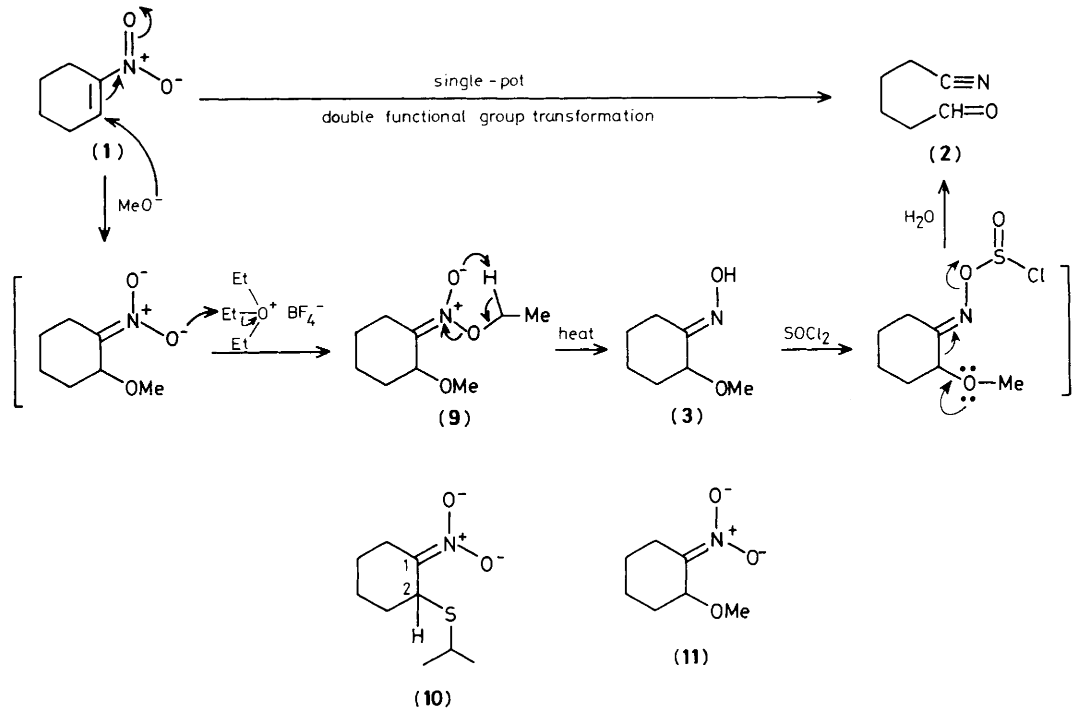
† We feel it appropriate to use the term 'Michael' in this context: see H. O. House, 'Modern Synthetic Reactions,' 2nd Edn., W. A. Benjamin, California, 1972, pp. 595—596, and references therein.



Scheme 2

A variety of conjugated nitroalkenes can be readily prepared by different procedures.[16] By adapting our recently developed alkoxylation and thiolation methods[3] followed by the strategies outlined in Scheme 1, we can efficiently convert a cyclic nitroalkene system into different classes of compounds. These single-pot, multiple functional group transformations should possess synthetic value.

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