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A NEW, HIGHLY EFFICIENT SYNTHESIS OF CONJUGATED NITROCYCLOALKENES.

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Abstract: Sodium borohydride reduction of α-nitrocycloalkanones and successive dehydration of the obtained β-nitroalkanols, by acetylation and dehydroacetylation with basic alumina/DMAP, in refluxing dichloromethane, affords, in one-pot procedure, conjugated nitrocycloalkenes.

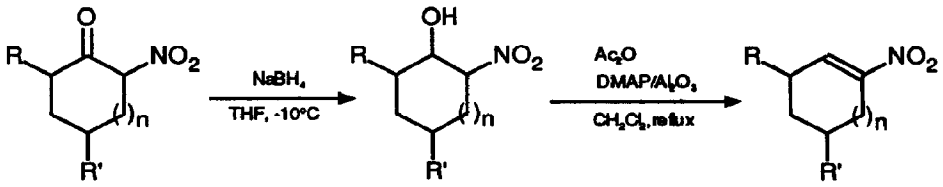
Conjugated nitrocycloalkenes are potentially versatile, synthetic intermediates for the stereoselective attachments of appendages and/or functional groups, for the extention of functionality to adjacent methylene groups, for annulation reactions,[1] and for transformation to a variety of polyfunctionalized molecules.[2]

Different approaches for the synthesis of nitrocycloalkenes have been developed starting from cycloalkenes,[3] cycloalkanones,[4] nitrocycloalkanes,[5] β-nitrocycloalkanols,[6] and 2-nitrocycloalkanones.[7] However, these procedures exhibit limitations such as the use of highly toxic reagents, very low temperatures, or have been reported to be efficient only for the preparation of nitrocyclohexenes, and/or show low yields.

In the course of the synthesis of certain natural products by nitro derivatives,[8] we felt in the need of converting the 2-nitro-15-methylcyclopentadecanol **2h**, obtained by chemoselective sodium borohydride reduction of the α-nitroketone **1h**, to the nitroalkene **3h** (Scheme 1).

For this dehydration we tested several reagents such as sodium hydride,[7] methanesulfonyl chloride,[9a] dicyclohexylcarbodiimide (DCC),[6] and basic alumina,[9b] but all these procedures gave unsatisfactory results.

After several trials, we found that a combination of DMAP[10] and basic alumina, provided the conversion of **2h** into **3h** in 78% yield. Our procedure was effected by acetylation of **2h** followed by elimination with basic alumina/DMAP, in refluxing dichloromethane, and with vigorous mechanical stirring.



1a-h **2a-h** **3a-h**

Scheme 1

In view of the synthetic utility of cyclic nitroalkenes, we have investigated the potential of our method for the conversion of different α-nitrocycloalkanones **1** to conjugated nitrocycloalkenes **3**, *via* nitrocycloalkanols **2** (Table 1).

The reduction of nitroketones **1** with sodium borohydride in large excess (5 equivalents) led to ring cleavage,[11] while with a stoichiometric amount or a small surplus (1.5 equivalents), we observed the formation of nitroalkanols **2**, and nitroalkenes **3** (due to the partial dehydration of **2**). We tested both absolute ethanol and dry THF as solvents for the reduction and found that the latter afforded the higher yields. In a one pot procedure, nitroalcohols **2** were then converted to **3** by acetylation, with acetic anhydride/DMAP, and dehydroacetylation, by basic alumina/DMAP, in refluxing dichloromethane.

Table 1. Products and Yields of Conversion of α-Nitrocycloalkanones to Conjugated Nitrocycloalkenes, *via* β-Nitroalkanols.

				Yield (%)[a]	
	n	R	R^1	(2)[b]	(3)
a	1	H	H	75 (2)	78
b	1	CH_3	H	65 (8)	60
c	1	H	$C(CH_3)_3$	75 (7)	55
d	2	H	H	60 (36)	88
e	3	H	H	60 (35)	60
f	7	H	H	66 (3)	88
g	10	H	H	65 (4)	90
h	10	CH_3	H	72 (20)	78

[a] Yields of pure, isolated compounds.
[b] In brackets, yields (%) of **3** obtained during the reduction of **1** to **2**.

Compared with the reported method for dehydration of β-nitrocyclohexanols to conjugated nitrocyclohexenes by sodium hydride,[7] our procedure provided the ring alkylated **2b,c** to **3b,c** in 60% and 55% yields, against 12% and 25% yields respectively.

Contrary to other methods, the success of this approach is independent of the ring size of the substrate as well as of the presence of alkyl groups as ring substituents, and the formation of conjugated nitroalkene is favoured even if the other isomer is expected by Saytzeff orientation (**2b,h** to **3b,h**). Moreover, since α-nitrocycloalkanones can be easily obtained by nitration of the corresponding ketone enol acetates or enol silyl ethers,[12] our process for the synthesis of cyclic nitroolefins is complementary to that in the literature, in which the starting materials are ketones or alkenes. In fact by our method, 4-*tert*-butylcyclohexanone yielded 1-nitro-5-*tert*-butylcyclohexene **3c**, whereas the vinyl stannate procedure[4] was reported to afford the 1-nitro-4-*tert*-butylcyclohexene. On the other hand, starting from 4-*tert*-butylcyclohexene, it has been reported[7] that a 1:1 mixture of the 1- and 2-vinyl nitro isomers were achieved.

In conclusion, the present methodology is simple, reliable, independent of ring size and gives high yields. It complements other reported procedures, and in general, could be preferred for the synthesis of this class of compounds.

Typical conditions for these reactions are the following: Sodium borohydride (15 mmol) was added, at 0 °C, to a THF solution of α-nitrocycloalkanone **1** (10 mmol). After stirring for 1-3 h, and usual work-up, the crude **2** was purified by flash chromatography (cyclohexane/EtOAc 7:3), or used as it is. The nitroalkanol **2** (5 mmol) was dissolved in diethyl ether, treated with acetic anhydride (75 mmol) and a catalytic amount of DMAP. After stirring for 3 h and evaporation of the solvent, the crude acetate was dissolved in dichloromethane, treated with DMAP (7.5 mmol)/basic alumina (1.5 g), and refluxed for 16-26 h (TLC). The alumina was then filtered off, the organic layer washed with water, dried, evaporated and purified by flash chromatography (cyclohexane/EtOAc 7:3), affording the pure **3**.[14]

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14. All compounds were characterized by spectroscopic methods: **3a**: ν_{max} neat/cm^{-1} 1650 and 1500; ^{1}H NMR δ ($CDCl_3$) 1.5-1.9 (4H, m), 2.3-2.4 (2H, m, $CH_2CH{=}CNO_2$), 2.5-2.7 (2H, m, CH_2CNO_2), 7.3-7.4 (1H, m, $CH{=}CNO_2$). **3b**: ν_{max} neat/cm^{-1} 1630 and 1500; ^{1}H NMR δ ($CDCl_3$) 1.13 (3H, d, *J* 6.6Hz, CH_3), 1.2-2 (7H, m), 7.17 (1H, m, $CH{=}CNO_2$). **3c**: ν_{max} neat/cm^{-1} 1600 and 1500; ^{1}H NMR δ ($CDCl_3$) 0.95 (9H, s, $3CH_3$), 1.4-2.6 (7H, m), 7.4-7.5 (1H, m, $CH{=}CNO_2$). **3d**: ν_{max} neat/cm^{-1} 1630 and 1505; ^{1}H NMR δ ($CDCl_3$) 1.5-1.8 (6H, m), 2.25-2.4 (2H, m, $CH_2CH{=}CNO_2$), 2.7-2.8 (2H, m, CH_2CNO_2), 7.3 (1H, t, *J* 6.8Hz, $CH{=}CNO_2$). **3e**: ν_{max} neat/cm^{-1} 1650 and 1505; ^{1}H NMR δ ($CDCl_3$) 1.5-1.8 (8H, m), 2.2-2.4 (2H, m, $CH_2CH{=}CNO_2$), 2.7-2.8 (2H, m, CH_2CNO_2), 7.3 (1H, t , *J* 8.8Hz, $CH{=}CNO_2$). **3f**: ν_{max} neat/cm^{-1} 1650 and 1505; ^{1}H NMR δ ($CDCl_3$) 1.2-1.8 (16H, m), 2.2-2.4 (2H, m, $CH_2CH{=}CNO_2$), 2.65 (2H, t, *J* 6.8Hz,CH_2CNO_2), 7.1 (1H, t, *J* 8.6Hz, $CH{=}CNO_2$). **3g**: ν_{max} neat/cm^{-1} 1650 and 1508; ^{1}H NMR δ ($CDCl_3$) 1.2-1.7 (22H, m), 2.2-2.3 (2H, m, $CH_2CH{=}CNO_2$), 2.6 (2H, t, *J* 6.8Hz, CH_2CNO_2), 7.1 (1H, t, *J* 8Hz, $CH{=}CNO_2$). **3h**: ν_{max} neat/cm^{-1} 1645 and 1510; ^{1}H NMR δ ($CDCl_3$) 1.05 (3H, d, *J* 7Hz, CH_3), 1.15-1.5 (22H, m), 2-2.75 (3H, m), 6.88 (1H, d, *J* 13Hz, $CH{=}CNO_2$).

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