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Synthesis of functionalized nitrocyclohexene derivatives from 2-nitrocycloalkanones, via anionic domino reactions

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Abstract—The reaction of various 2-nitrocycloalkanones, at room temperature, with acrolein and in the presence of methanolic solution of potassium carbonate, affords functionalized nitrocyclohexene derivatives, via an anionic domino reaction. © 2001 Elsevier Science Ltd. All rights reserved.

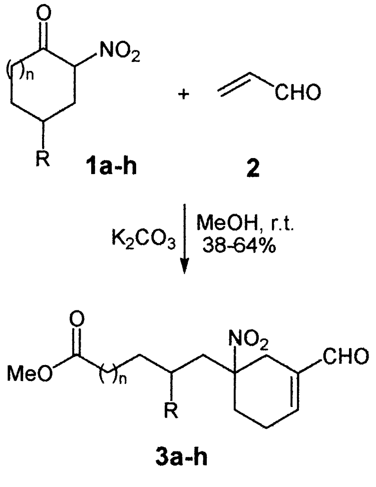
Nitrocyclohexene derivatives are useful building blocks of relevant practical interest that provide an efficient entry to important frameworks.[1] The classical approach for their synthesis is the Diels–Alder cycloaddition between the appropriate conjugated nitroalkenes and 1,3-dienes. However, although a wide range of the title compounds can be obtained by this method, problems with the preparation of starting materials and/or of regioselectivity are often a serious drawback.[2]

The synthesis of complex molecules is traditionally performed by a chain of separate reaction steps, each step requiring its own conditions, reagents, solvent, and catalyst. After each reaction is complete the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Now, environmental and economic pressures are forcing the chemical community to search for more efficient ways of performing chemical transformations.[3] These new issues can be addressed by the development of new synthetic methods that, bringing together simple components, generate complex structures in one pot, much the same way as nature does. Though the origins of this type of process can be dated back to the Robinson–Schopf synthesis of tropinone,[4] it was only recently that terms like 'multicomponent reactions'[5] and 'domino reactions'[6] became familiar and, in this context, anionic domino transformations appear of great attraction.[7]

α-Nitroketones are of particular interest in the formation of carbanions under basic conditions[8] and, additionally, cyclic ones are prone to ring cleavage through a nucleophilic retro-Claisen condensation.[9]

Some years ago we found that the Michael addition of 2-nitrocycloalkanones to conjugated enones, followed by reductive reaction, affords spiroketals via in situ 'ring-cleavage/ring-closure'.[10] Later, we reported the one-pot preparation of functionalized 1,4-dicarbonyl derivatives, by conjugate addition of α-nitrocycloalkanones to the appropriate enones, in MeOH/Ph_3P, then in situ oxidation ($KMnO_4$) of the mixture.[11]

In continuation with the above studies, we have now found that cyclic 2-nitroketones **1a–h** and acrolein **2** can be conveniently employed as precursors for the synthesis of functionalized nitrocyclohexenes **3**, via an anionic domino reaction (Scheme 1). The reaction of **1** with two equivalents of **2** proceeds, at



Scheme 1.

Keywords: nitrocyclohexenes; domino reactions; 2-nitrocycloalkanones; potassium carbonate; acrolein.

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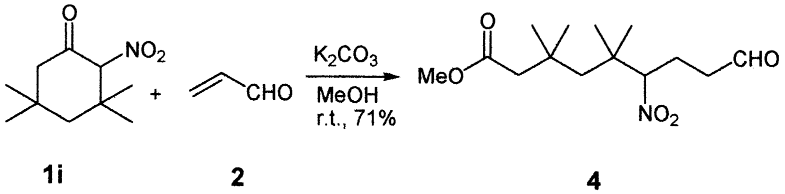
Table 1. Preparation of cyclohexenes **3**

1, **3**	*n*	R	Yield (%)[a] of **3**
a	0	H	64
b	1	H	53
c	1	Me	51[b]
d	1	*t*-Bu	55[c]
e	2	H	50
f	5	H	38
g	6	H	49
h	10	H	53

[a] Isolated yield.

[b] As 3:2 diastereomeric mixture.

[c] As 2:1 diastereomeric mixture.



Scheme 2.

room temperature, in a methanolic solution of potassium carbonate, affording compound **3** in a one-pot sequence.

Under our conditions the base is able to promote: (i) the conjugate addition between the activated cycloalkanones and acrolein, (ii) the ring cleavage of the Michael adduct, (iii) a further addition of another equivalent of acrolein and, finally, (iv) an intramolecular aldolization. The product **3** is obtained in moderate to respectable yields, regardless of the ring size of the cycloalkanones **1** (Table 1).

However, when 3,3,5,5-tetramethyl-2-nitrocyclohexanone **1i** is employed as starting material, the nitroderivate **4**, due to the first two steps of the domino sequence, is obtained as the sole product (Scheme 2).

This can be explained with the reduced acidity of the carbon bearing the nitro group (in the linear compound **4** compared with the cyclic one **1i**). That coupled with the relatively congested carbon site, prevents the conjugate addition of one more equivalent of acrolein.

We believe that our procedure offers an interesting alternative for the preparation of the title compounds because the starting materials are easily available, the reaction conditions are very simple, and no problems of regioselectivity are involved.

It is important to point out that the compounds **3** possess important functionalities which offer valuable opportunities for further elaborations. Additionally, these compounds can be also considered as polyfunctionalized α,β-unsaturated aldehydes, difficult to obtain by other ways.

1. Experimental

1.1. General

^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$ at 50 and 200 MHz, respectively, on a Varian Gemini instrument; *J* values are given in Hz. IR spectra were recorded with a Perkin–Elmer 257 spectrophotometer. Mass spectra were determined on a capillary GC/MS operating in the split mode with helium carrier gas and fitted with a mass-selective detector (MDS). The reactions were monitored by TLC or GC performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran Glass, stationary phase OV1. Microanalyses were performed using a Fisons model EA 1108. The products were purified by flash chromatography on Merck silica gel.

1.2. General procedure for the preparation of nitrocyclohexene derivatives 3

To a methanolic solution (3 ml) of 2-nitrocycloalkanone **1** (3.5 mmol) potassium carbonate (241 mg, 1.75 mmol) and acrolein **2** (392 mg, 7.0 mmol) were added. After stirring overnight at room temperature (TLC and GC), the solution was evaporated and, then diluted with Et_2O (20 ml). The organic phase was washed with water (2×5 ml), dried ($MgSO_4$), evaporated and the crude product was purified by flash chromatography (EtOAc/petrol ether) affording the pure compound **3**.

1.2.1. 3a. Oil. IR (neat) 1735, 1686, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50–2.10 (m, 6H), 2.33 (t, 2H, *J*=7.0 Hz), 2.40–2.50 (m, 3H), 3.30 (bd, 1H), 3.70 (s, 3H), 6.82 (bs, 1H), 9.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 192.6, 173.1, 148.5, 137.8, 88.8, 51.7, 38.9, 33.2, 30.4, 29.6, 23.6, 18.7; EI MS 209, 177, 176, 131, 91 (100%), 79, 77, 55, 41. Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.33; H, 6.77; N, 5.45.

1.2.2. 3b. Oil. IR (neat) 1735, 1685, 1648, 1536 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–1.50 (m, 2H), 1.50–1.70 (m, 2H), 1.70–2.10 (m, 4H), 2.29 (t, 2H, *J*=7.1 Hz), 2.40–2.80 (m, 3H), 3.28 (bd, 1H), 3.64 (s, 3H), 6.77 (bs, 1H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 192.5, 173.5, 148.3, 137.9, 89.0, 51.6, 39.7, 33.5, 30.7, 29.5, 24.5, 23.6, 22.8; EI MS 223, 204, 107, 91 (100%), 79, 41, 29. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.29. Found: C, 58.07; H, 7.04; N, 5.35.

1.2.3. 3c. Oil. IR (neat) 1733, 1685, 1649, 1536 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–0.90 (m, 1H), 0.90 (s, 3H), 1.40–1.70 (m, 6H), 2.27 (t, 2H, *J*=7.9 Hz), 2.40–2.80 (m, 3H), 3.28 (bd, 1H), 3.66 (s, 3H), 6.79 (bs, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) (3:2 diastereomeric mixture) δ 193.1, 193.0, 174.4, 174.3, 148.8, 148.7, 138.5, 138.4, 94.6, 92.0, 91.4, 91.2, 52.1 (2C), 47.2, 46.9, 33.2, 33.0, 31.9, 31.8, 31.3, 30.8, 28.4, 28.3, 21.3, 21.1, 21.0, 20.0; EI MS 252, 237, 184, 91, 79, 55 (100%), 41, 29. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 5.20. Found: C, 59.21; H, 7.44; N, 5.25.

1.2.4. 3d. Oil. IR (neat) 1736, 1686, 1649, 1537 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9H), 1.30–1.40 (m, 1H), 1.10–1.50 (m, 2H), 1.60–2.10 (m, 4H), 2.31 (t, 2H, J=7.1 Hz), 2.40–2.80 (m, 3H), 3.30–3.40 (m, 1H), 3.67 (s, 3H), 6.78 (bs, 1H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (2:1 diastereomeric mixture) 192.9, 192.7, 174.2 (2C), 149.0, 148.7, 138.4, 138.3, 89.8, 89.3, 52.1, 52.0, 43.8, 43.5, 43.1, 42.7, 35.0, 34.9 (3C), 32.1, 31.4, 30.3, 30.2, 28.3, 28.2, 27.8 (6C), 24.3, 24.2; EI MS 246, 218, 189, 91 (100%), 57, 41, 29. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.82; H, 8.34; N, 4.35.

1.2.5. 3e. Oil. IR (neat) 1737, 1682, 1650, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–1.40 (m, 4H), 1.50–1.70 (m, 2H), 1.70–2.10 (m, 4H), 2.28 (t, 2H, J=7.2 Hz), 2.40–2.60 (m, 3H), 3.29 (bd, 1H), 3.65 (s, 3H), 6.79 (bs, 1H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 192.6, 174.0, 148.4, 138.0, 89.1, 51.5, 39.9, 33.7, 30.7, 29.5, 28.7, 24.5, 23.6, 22.9; EI MS 252, 237, 203, 144, 107, 91 (100%), 79, 55, 41, 29. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.44; H, 7.40; N, 4.99.

1.2.6. 3f. Oil. IR (neat) 1738, 1680, 1649, 1537 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–1.40 (m, 10H), 1.5–2.1 (m, 6H), 2.31 (t, 2H, J=7.2 Hz), 2.4–2.6 (m, 3H), 3.33 (m, 1H), 3.65 (s, 3H), 6.80 (bs, 1H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 192.5, 173.9, 148.3, 138.0, 89.0, 51.6, 39.5, 33.9, 33.7, 30.8, 29.6, 29.3, 29.1, 28.2, 24.4, 23.3, 22.8; EI MS 279, 278, 131, 91 (100%), 79, 55, 41, 29. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.84; H, 8.37; N, 4.23.

1.2.7. 3g. Oil. IR (neat) 1737, 1682, 1649, 1537 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–1.40 (m, 12H), 1.5–2.1 (m, 6H), 2.30 (t, 2H, J=7.1 Hz), 2.4–2.6 (m, 3H), 3.34 (m, 1H), 3.65 (s, 3H), 6.79 (bs, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 192.7, 173.6, 148.3, 137.9, 88.9, 51.7, 40.3, 34.8, 31.1, 30.1, 29.6 (2C), 29.4 (2C), 28.8, 24.8, 23.9, 23.2; EI MS 292, 274, 258, 131, 120, 107, 91 (100%), 79, 55, 41, 29. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.54; H, 8.67; N, 4.19.

1.2.8. 3h. Waxy solid. IR (neat) 1736, 1686, 1648, 1539 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–1.30 (m, 20H), 1.50–2.00 (m, 6H), 2.30 (t, 2H, J=7.1 Hz), 2.40–2.60 (m, 3H), 3.30–3.40 (m, 1H), 3.66 (s, 3H), 6.80 (bs, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 193.1, 174.9, 148.9, 138.6, 89.7, 51.9, 40.7, 34.6, 31.3, 30.0 (5H), 29.9 (2C), 29.7 (2C), 29.6, 25.4, 24.1, 23.7; EI MS 346, 314, 119, 105, 91 (100%), 74, 55, 41, 29. Anal. Calcd for $C_{22}H_{37}NO_5$: C, 66.80; H, 9.43; N, 3.54. Found: C, 66.89; H, 9.51, N, 3.49.

1.2.9. 4. Oil. IR (neat) 1731, 1666, 1547 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00–1.60 (m, 14H), 2.20–2.30 (m, 2H), 2.31 (s, 2H), 2.40–2.60 (m, 2H), 3.66 (s, 3H), 4.30–4.40 (m, 1H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 200.2, 172.7, 98.4, 51.8, 48.5, 47.6, 40.9, 39.9, 35.1, 30.0 (2C), 25.8, 24.8, 21.2; EI MS 223, 115, 97, 83, 73 (100%), 55, 41, 29. Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.61; H, 8.64, N, 4.79.

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