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Nitrous acid elimination from 4-alkyl-5-formyl-4-nitrocyclohex-1-enes: synthesis of mono and bicyclic benzene and dihydrobenzene derivatives

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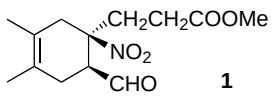
Abstract—Elimination of nitrous acid from 4-alkyl-5-formyl-4-nitrocyclohex-1-enes, by treatment with silica gel or potassium carbonate, is described. Whereas in the former case the product consisted in a mixture of the starting material, 2-alkyl-4,5-dimethylcyclohexa-1,4-diene-1-carbaldehyde and 2-alkyl-4,5-dimethylbenzaldehyde, reaction with potassium carbonate at 60°C yielded exclusively aromatic compounds. Furthermore, when a ketone function was present in the γ-position of the alkyl chain at C-4, the alkaline medium promoted an intramolecular aldol condensation, being obtained bicyclic products. PM3 calculations have been made to justify the result of the cyclization.

The 4-nitrocyclohexene derivatives constitute an useful class of compounds that are generally obtained by Diels–Alder reaction between buta-1,3-dienes and α-nitroalkenes,[1] their synthetic utility being a consequence of both their availability and reactivity. For example, they are intermediates in the preparation of *cis*-1,2-aminoalcohols,[1b] enantiomerically pure cyclic β-amino acids,[1c] natural alkaloids,[1a,d] sesquiterpenes as (±)-α- and -β-biotol[1f] and (±)-chamigrene,[1g] the aglycon of the antitumor antibiotic calicheamicin γ_1,[1i] the A-ring of 9-azasteroids,[1j] etc.



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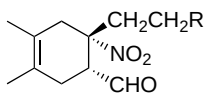

2, R = COOMe
3, R = COMe
4, R = CN

In previous papers,[2] we reported on the synthesis of a variety of chiral 5-glyco-4-nitrocyclohex-1-enes, that were prepared by Diels–Alder reactions between buta-1,3-diene, 2-methyl-, or 2,3-dimethylbuta-1,3-diene and sugar derived α-nitroalkenes. More recently, we have described[3] stereoselective Michael reaction additions between electron-deficient alkenes and some of those chiral 4-nitrocyclohexenes, thus leading to a series of adducts that were used for the enantioselective synthesis of 4-alkyl-5-formyl-4-nitrocyclohex-1-enes **1** and **2**. Now, by using the same procedure, but starting from the corresponding Michael adducts with methyl vinyl ketone and acrylonitrile, nitroaldehy-des **3** (85%) and **4** (69%) have been obtained.

Since to our knowledge there is no previous data about the reactivity of nitrocyclohexenes with a similar substitution pattern, we wish to present here our preliminary results on the reactions of compounds **1**–**4** with either silica gel[4] or potassium carbonate in methanol–water. Thus, we have observed that when either pure **1** or **2** were subjected to thin-layer chromatography (silica gel Merck 60 GF_{254}) with hexane–ethyl acetate 4:1 as the eluent, each one of these enantiomeric products was resolved as two spots with R_f values of 0.52 and 0.42, being the second much more intense. After separation by preparative thin-layer chromatography, the band of lower mobility contained the starting compounds **1** or **2**, whereas the band with R_f 0.52 consisted in a 4:1 mixture of 1,4-cyclohexadiene **5**[5] and aromatic **6**.[5] Furthermore, when either mixtures with (**1** or **2**)+**5**+**6**, or each one of the pure nitroaldehydes **1**, **2** or **4** were treated with potassium carbonate for 5 h in methanol at

Keywords: nitro compounds; aromatic compounds; cyclohexenes; 1,4-cyclohexadienes; indenes; intramolecular cyclization.

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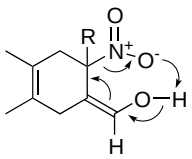
60°C, there was complete transformation into their corresponding aromatic derivatives **6** or **7**[5] (Scheme 1).

According to what we have reported previously for closely related *cis*- or *trans*-5-formyl-4-nitrocyclohexenes,[2b] the formation of compounds **5**–**7** could be explained through a nitrous acid elimination by a mechanism involving a cyclic transition state **8**, which would arise from the enolic form promoted by the silica gel or the base; then, oxidation of the resulting 1,4-cyclohexadiene would yield the aromatic compound. On the other hand, noteworthy is the resemblance between **5** and compounds **9** or **10**, which have been described[6] as components in oral or parentheral antineoplastic drugs.



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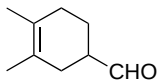

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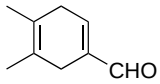

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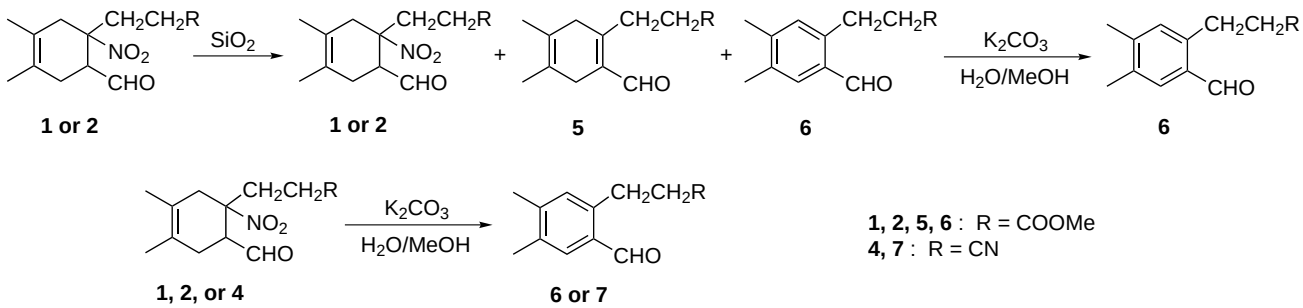
In contrast to nitroaldehydes **1**, **2** or **4**, treatment of a methanolic solution of (4*S*,5*R*)-5-formyl-4-nitro-(3-oxobutyl)cyclohex-1-ene (**3**) with aqueous potassium carbonate led, after 1 h at room temperature, to a clean mixture (Scheme 2) in which the only detected products (^{1}H and ^{13}C NMR) were 2-acetyl-4,7-dihydro-5,6-dimethylindene (**11**), 2-acetyl-5,6-dimethylindene (**12**)[7] and 5,6-dihydro-2,3-dimethyl-benzocyclohept-8-en-7-one (**13**) (relative ratio **11**:**12**:**13**, 85:15:1). From this mixture, the two major components could be isolated pure by preparative thin-layer chromatography,[8] whereas the minor one had to be studied from fractions in which its NMR signals were clearly distinguishable. Furthermore, when either methanolic solutions of pure compound **11** or mixtures **11**–**13** were heated for 5 h at 60°C with aqueous potassium carbonate, there was complete conversion of these to indene **12**, together with a small amount (1–2%) of benzocycloheptenone **13**.

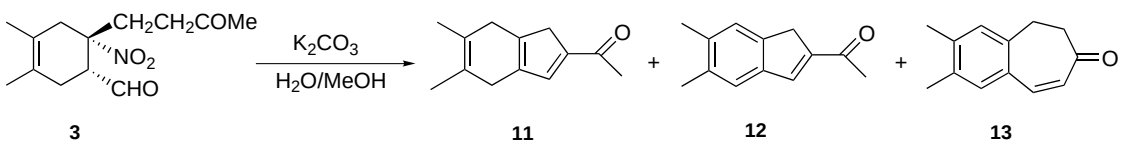
Indene derivatives are interesting products that have been used in the preparation of structural analogues of several biologically active substances,[9a,b] and as chiral auxiliaries in asymmetric synthesis.[9c]

Structures of bicyclic **11**–**13** were supported by their ^{1}H and ^{13}C NMR data;[10] thus, only one olefinic proton was observed for **11**, whereas for **12** appeared three and for **13** were four; furthermore, in this last compound was absent the singlet attributable to methyl acetyl group, which appeared instead at $\delta \approx 2.4$ in the ^{1}H NMR spectra of **11** and **12**. Concerning ^{13}C NMR spectra, DEPT experiments showed the presence of three methylene groups in the case of **11**, one for **12**, and two for **13**.

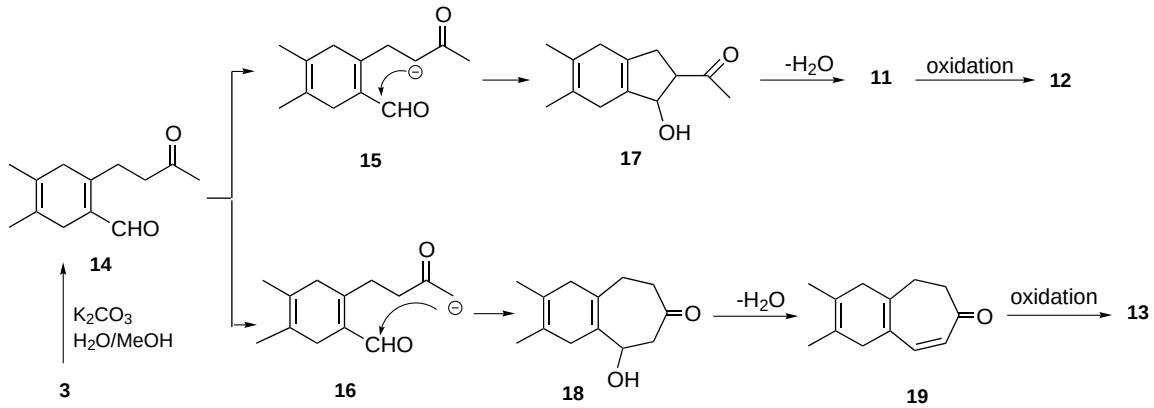
As shown in Scheme 3, formation of **11**–**13** could be justified by supposing that elimination of nitrous acid leading to cyclohexadiene **14** is followed by an intramolecular cyclization, due to a nucleophilic attack on the aldehyde carbon from either one or the other of carbanions **15** or **16**, generated at the adjacent carbons to the ketone function; then, elimination of water from **17** or **18** would produce **11** or **19** from which resulted, on oxidation, the aromatic compounds **12** or **13**, respectively. An alternative pathway, in which a cyclization step would occur previously to the elimination of nitrous acid has been discarded because, in this case, the reactive sites (i.e. the carbanion and the carbonyl group) would be too distant; in addition, we have not detected the presence of bicyclic compounds with nitro groups, that would be the intermediates if this pathway would operate.



Scheme 1.



Scheme 2.



Scheme 3.

The preponderance of the products **11** and **12** (cyclization 5-*exo*-*trig*[11]) on **13** (cyclization 7-*exo*-*trig*[11]) is consistent with the well known fact that intramolecular reactions leading to five-membered rings are much more faster than those leading to seven-membered rings;[12] furthermore, PM3 calculations by using the Gaussian 94W package[13] showed that secondary carbanion **15** is more stable than the primary one **16** by 9.37 kcal/mol. In the same sense, the hydroxycarbonyl intermediate **17** and the aromatic product **12** resulted 5.10 and 1.2 kcal/mol more stable than their respective isomers **18** and **13**.

In conclusion, we have demonstrated that when potassium carbonate reacts with 4-alkyl-5-formyl-4-nitrocyclohex-1-enes in which the alkyl group has a substituent that makes easy the formation of a carbanion (as it does the ketone function in **3**), loss of nitrous acid is followed by an aldol intramolecular reaction, thus leading to bicyclic products. On the contrary, if the functional group on the alkyl chain does not provide enough acidity to their α-hydrogens (for example, when it is a cyano or ester group, as in **2** or **4**), the intramolecular cyclization does not occur, and products as **5** or their corresponding aromatic derivatives as **6**, are obtained. The easy elimination of nitrous acid allows the access to mono or bicyclic aromatic or dihydroaromatic structures that would be difficult to synthesize by other methods.

Acknowledgements

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5. ^{1}H NMR (400 MHz, $CDCl_3$), **5**: 10.17 (s, 1H, CHO), 3.68 (s, 3H, Me-4′), 2.91 (t, 2H, H-1′a,1′b), 2.85–2.75 (m, 4H, H-3a,3b,6a,6b), 2.56 (t, 2H, H-2′a,2′b), 1.67 (s, 6H, Me-4,5); **6**: 10.12 (s, 1H, CHO), 7.55 (m, 1H, H-6), 7.08 (m, 1H, H-3), 3.66 (s, 3H, Me-4′), 3.28 (t, 2H, $J_{1',2'}=7.6$ Hz, H-1′a,1′b), 2.62 (t, 2H, H-2′a,2′b), 1.73 (s, 6H, Me-4,5); **7**: 9.99 (s, 1H, CHO), 7.54 (s, 1H, H-6), 7.13 (s, 1H, H-3), 3.26 (t, 2H, $J_{1'a,1'b}=7.1$ Hz, H-1′a,1′b), 2.69 (t, 2H, $J_{2'a,2'b}=7.1$ Hz, H-2′a,2′b), 2.33 (s, 6H, Me-4,5).
^{13}C NMR (100 MHz, $CDCl_3$), **5**: 189.9 (CHO), 172.5 (C-3′), 153.7 (C-4), 132.3 (C-5), 123.4, 120.6 (C-1,2), 51.8 (C-4′), 39.0 (C-1′), 33.2, 30.6 (C-3,6), 26.0 (C-2′), 18.0, 17.8 (Me-4,5); **6**: 192.4 (CHO), 173.2 (C-3′), 143.6, 140.3 (C-2,4), 135.4, 131.7 (C-1,5), 134.7, 132.6 (C-3,6), 51.6 (C-4′), 35.5 (C-1′), 27.6 (C-2′), 20.0, 19.1 (Me-4,5); **7**: 193.3 (CHO), 151.8 (C-2), 137.3 (C-6), 133.2 (C-3), 136.9, 136.5, 131.4, (C-1,4,5), 121.6 (C-3′), 28.9 (C-1′), 19.9, 19.3 (Me-4,5), 18.4 (C-2′).

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10. ^{1}H NMR (400 MHz, $CDCl_3$), **11**: 7.19 (brs, 1H, H-3), 3.21 (m, 2H, $J_{1,3} \approx J_{1,4} = 1.8$ Hz, H-1,1′), 2.98 (m, 2H, H-7,7′), 2.94 (m, 2H, H-4,4′), 2.37 (s, 3H, $COCH_3$), 1.73 (s, 6H, Me-5,6); **12**: 7.60 (brs, 1H, $J_{1,3} = 1.6$ Hz, H-3), 7.33 (s, 1H, H-7), 7.31 (s, 1H, H-4), 3.62 (brs, 2H, H-1,1′), 2.49 (s, 3H, $COCH_3$), 2.33 (s, 6H, Me-5,6); **13**: 7.13 (s, 1H, H-4), 7.08 (d, 1H, $J_{8,9} = 12.5$ Hz, H-9), 7.04 (s, 1H, H-1), 6.12 (d, 1H, H-8), 2.94 (m, 2H, H-5,5′), 2.73 (m, 2H, H-6,6′), 2.24 (s, 6H, Me-2,3).
^{13}C NMR (100 MHz, $CDCl_3$), **11**: 193.7 (CO), 146.2, 144.5, 144.4 (C-2,3,7a), 136.6 (C-3a), 123.0 (C-5,6), 41.1 (C-1), 33.8, 32.1 (C-4,7), 26.0 ($COCH_3$), 18.8 (Me-5,6); **12**: 195.6 (CO), 145.5, 143.0, 141.5, 140.8, 137.3, 135.4 (C-2,3,3a,5,6,7a), 125.7, 124.7 (C-4,7), 36.9 (C-1), 26.0 ($COCH_3$), 20.3, 19.9 (Me-5,6).
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