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Intramolecular cyclization of 1-nitroalkenyl radicals generated by one-electron oxidation of *aci*-nitro anions with CAN: stereoselective formation of 3,4-functionalized tetrahydrofurans

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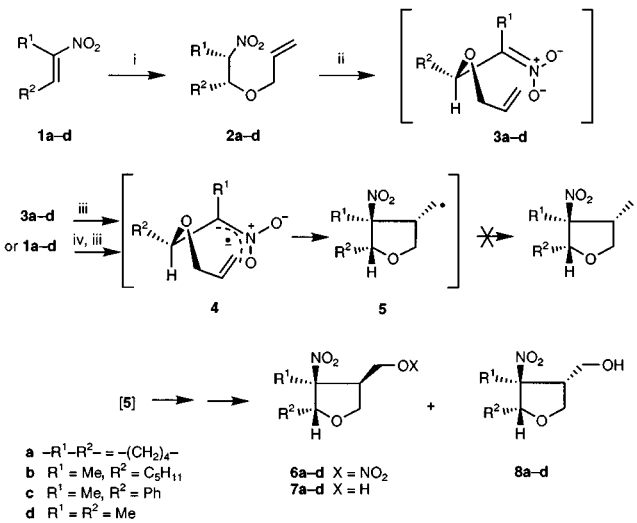
Upon one-electron oxidation by ammonium hexanitratocerate(IV) (CAN), *aci*-nitro anions 3a-d resulting from oxa-Michael addition of allylic alcohol to α,β-disubstituted nitroalkenes 1a-d undergo stereoselective radical cyclization into 3-nitro-4-nitrooxymethyltetrahydrofurans 6a-d and 3-nitro-4-hydroxymethyltetrahydrofurans 7,8a-d.

One-electron oxidation of carbanions is one of the simplest methods for generation of carbon-centered radicals. However, so-generated radicals usually afford self-condensation products,[1] and intermolecular[2] carbon–carbon bond forming reactions have only occasionally been disclosed in the literature.

Recently, ammonium hexanitratocerate(IV) (CAN) was found to be an efficient one-electron oxidant of *aci*-nitro anions to provide 1-nitroalkyl radicals which add intermolecularly to electron-rich olefins;[3] moreover, secondary 1-nitroalkenyl radicals undergo intramolecular cyclization to afford isoxazoles, provided the olefinic moiety is appropriately substituted.[4]

The failure of tertiary α-nitroalkyl radicals to cyclise, except in particular cases in which the yields of cyclized products are not satisfactory,[5] prompted us to study the reactivity of readily available α-substituted β-allyloxynitronates **3** upon oxidation with CAN.

α-Substituted β-allyloxy nitro compounds **2a**–**d**, obtained in 85–90% yield by oxa-Michael addition of allylic alcohol[6] to nitroalkenes **1a**–**d**, were reacted with NaH to afford *aci*-nitro anions **3a-d** (Scheme 1); addition of **3a**–**d** to a solution of CAN (3 equiv.) in THF at −78 °C generated radical anion intermediates **4** resulting in the stereoselective formation of *exo* nitronitrates **6a-d**† (45–60%) along with nitro alcohols **7,8a**–**d** (5–8%, **7**:**8** = 5:1).‡§ Alternatively, the same product mixture could be obtained directly from **1a-d**, in a one-pot process. According to previous reports,[4,5] reduction by solvent of alkyl radicals **5** resulting from direct 5-*exo* cyclization was not observed; indeed, a further transformation occurs, and the transformation into nitronitrates **6** which constitute the major products of the reaction could be related to a ligand transfer reaction in the presence of CAN.[7]

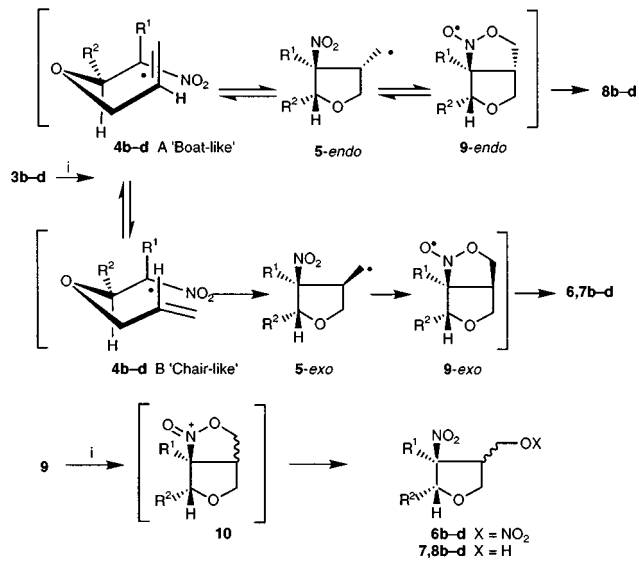


Scheme 1 *Reagents and conditions*: i, Bu^{t}OK (1.5 equiv.), Bu^{t}OH–benzene (0.5:1), then allylic alcohol, then H$^+$, 85–90%; ii, Na, H, THF; iii, CAN, THF, −78 °C, then 0.1 M $Na_2S_2O_3$, 45–60%; iv, NaH, THF, then allylic alcohol, 60% (**6a**), 58% (**6b**), 52% (**6c**), 45% (**6d**), 6% [(**7** + **8**)**a**], 7% [(**7** + **8**)**b**], 8% [(**7** + **8**)**c**], 5% [(**7** + **8**)**d**].

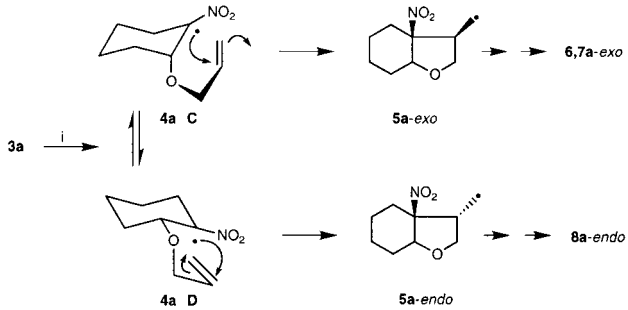
The relative *cis* stereochemistry for R^1 and R^2 in acyclic compounds **6**–**8** arises from favored conformation **B** required by allylic 1,3-strain (Scheme 2) during the intramolecular *C*-alkylation; [8] the Beckwith transition state model[9] invoked to account for these selective transformations has previously been proposed for radical cyclisations of α-nitroalkyl radicals.[10]

Moreover, the isolation of *endo* nitro alcohols **8** as minor products indicates that the observed stereochemistry is also consistent with a reversible tandem cyclisation,¶ leading to a persistent *cis*-fused bicyclic nitroxyl radical **9**-*exo*,‖ which could act as a driving force for this stereoselective cyclisation to occur; oxidation of nitroxyl radical **9** with a second molecule of CAN affords cation **10** which is then neutralized by ligand exchange with CAN[7] (Scheme 2).

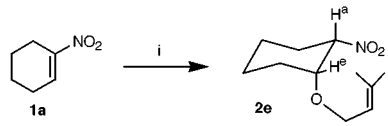
Selective formation of bicyclo compound **6a** is well-interpreted by using the '*cis*-decalin' model for cyclization of cyclohexyl radicals (Scheme 3).[11] This model predicts that *exo* product should result from conformation **C** in which the allyloxy substituent is axial, while cyclisation of **D**, with an equatorial substituent, should provide *endo* product. Indeed NMR data of 1-nitro-2-dimethylallyloxycyclohexane **2e** indicates that, even at room temperature, only the conformation with an axial dimethylallyloxy group is observed**†† (Scheme



Scheme 2 *Reagents and conditions*: i, CAN, THF, −78 °C.



Scheme 3 *Reagents and conditions*: i, CAN, THF, −78 °C.

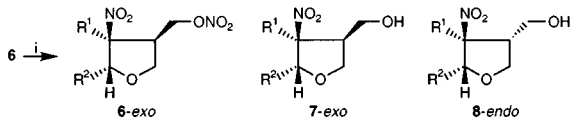


Scheme 4 *Reagents and conditions*: i, NaH, THF, then 3-methylbut-2-en-1-ol, then H^+, 12%.

4); this fact could argue for the high selectivities obtained at low temperature.

Therefore, although an intramolecular [3+2][12] cycloaddition of radical **4** could account for a totally stereoselective formation of *exo*-nitronitrates **6** through the bicyclic intermediate **9**-*exo* (Scheme 2), the proposal of a prior 5-*exo*-*trig* radical cyclization is better supported by the selectivities obtained in these transformations.

Solvolytic decomposition of nitrate esters in alkaline solution[13] accounts for the formation of nitro alcohols **7**-**8**; the isolation of *endo* nitro alcohol **8** as a minor compound could argue for the initial formation of *endo* nitro nitrate, transformation of which into **8** is quantitative under the reaction conditions, while the major *exo* nitro nitrate **6** is only partially converted into *exo* alcohol **7** (Scheme 5); indeed, when pure **6a** was reacted with NaH in 0.1 M $Na_2S_2O_3$ for 48 h, pure **7a** was isolated in 28% yield,‡‡ along with some remaining **6a**, while **8a** could not be detected by NMR. Thereby, the apparent total *exo* selectivity observed in the formation of nitro nitrates **6** should arise from the total transformation of the minor *endo* diastereomer into alcohol **8**.



Scheme 5 *Reagents and conditions*: i, NaH, THF.

In conclusion, although it has been previously believed that cyclization of α-nitroalkenyl radicals for synthetic purposes could only be useful if groups more nucleophilic than unactivated alkenes are present,[14] our results show that, in turn, α-nitroalkenyl radicals generated by one-electron oxidation of *aci*-nitro anions with CAN lead stereoselectively to bifunctionalized tetrahydrofurans bearing three contiguous stereogenic centers. Moreover, the scope of subsequent conversions of the nitro and nitrate ester groups[15] should expand the utility of this new strategy in organic synthesis.

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Notes and references

† *Selected data* for **6a**: υ/cm^{-1} 2945, 2903, 1639, 1540, 1282, 861; δ_H(400 MHz, $CDCl_3$) 1.30 (m, 1H), 1.42 (m, 1H), 1.51 (m, 2H), 1.82 (m, 2H), 1.95 (ddd, *J* 14.6, 10.9, 3.7, 1H), 2.50 (dt, *J* 14.6, 3.7, 1H), 2.75 (quin, *J* 7.9, 1H), 3.8 (dd, *J* 9.5, 6.4, 1H), 4.25 (dd, *J* 9.5, 8.3, 1H), 4.42 (dd, *J* 11.1, 7.7, 1H), 4.49 (t, *J* 4.5, 1H); δ_C(100 MHz, $CDCl_3$) 19.6, 21.2, 26.4, 30.9, 32.6, 44.4, 68.6, 71.0, 77.7, 92.7.

‡ *Selected data* for **7a**: υ/cm^{-1} 3427, 2941, 2868, 1538, 1055; δ_H(400 MHz, $CDCl_3$) 1.40 (m, 4H), 1.72 (m, 2H), 1.92 (m, 1H), 2.48 (m, 1H), 2.52 (quin, *J* 5.8, 1H), 3.64 (t, *J* 5.7, 2H), 3.84 (dd, *J* 9.3, 5.8, 1H), 4.18 (dd, *J* 9.2, 8.3, 1H), 4.50 (td, *J* 3.7, 1.0, 1H); δ_C(100 MHz, $CDCl_3$) 19.5, 21.4, 26.1, 33.5, 49.6, 61.5, 68.6, 79.4, 92.4.

§ *Selected data* for **8a**: δ_H(400 MHz, $CDCl_3$) 1.42 (m, 4H), 1.51 (m, 2H), 1.82 (m, 1H), 2,40 (m, 1H), 2.50 (m, 1H), 3.65 (m, 2H), 3.90 (dd, *J* 11.1, 7.9, 1H), 4.22 (dd, *J* 9.6, 9, 1H), 4.44 (t, br, *J* 3.3, 1H); δ_C(100 MHz, $CDCl_3$) 19.1, 21.0, 25.6, 26.1, 50.8, 60.0, 68.1, 79.4, 92.4.

¶ Although alkyl-substituted radicals undergo exothermic cyclizations which are not reversible, Julia and co-workers showed that cyclizations could be reversible in the presence of radical-stabilizing groups (ref. 16).

‖ The transient formation of cyclic nitroxide to account for a similar transformation of an *aci*-nitro anion of a norbornene derivative upon oxidation with $K_3Fe(CN)_6$ was previously reported (ref. 14).

** The low yield obtained in the preparation of **2e** (12%) resulted from a retro-Michael reaction, facilitated by the *trans* diaxial position of acidic hydrogen and the dimethylallyloxy substituent; attemps to generate the radical by oxidation of **3e** with CAN met with failure.

†† Assignement of the *axial* position for the dimethylallyloxy group resulted from an ^1H–^{13}C correlation experiment.

‡‡ Nevertheless, nitrate esters are easily transformed into the corresponding alcohols according to a known procedure (ref. 17).

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