Tandem oxa-Michael addition–S_N2' substitution of 4-chlorobut-2-yn-1-ol with nitroalkenes: a total allylic 1,3-strain-controlled diastereoselective synthesis of 3-vinylidenetetrahydrofurans

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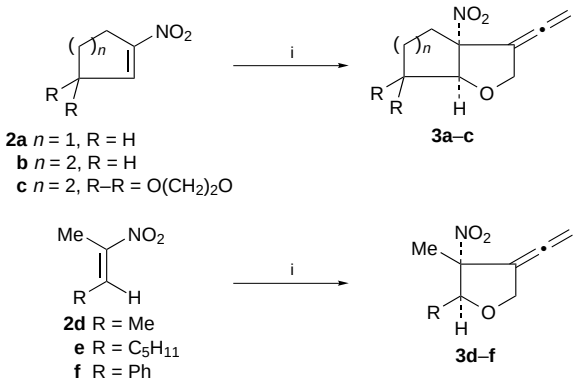
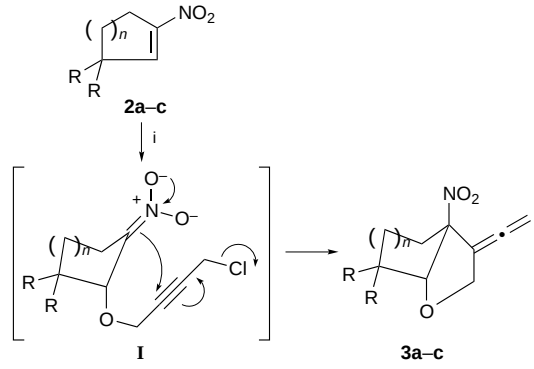
Bu^{t}OK-promoted reaction of 4-chlorobut-2-yn-1-ol 1 with nitroalkenes 2 affords 3-vinylidenetetrahydrofurans 3 in good yields with total diastereoselectivity.

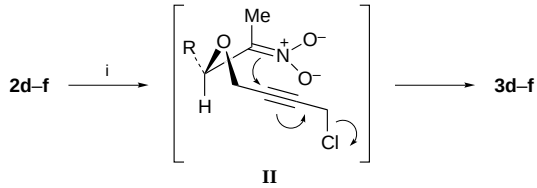
The tetrahydrofuran ring is present in a number of biologically significant natural products[1] and the synthesis of tetrahydrofurans bearing unsaturated substituents is of great interest for further transformations. Among these substituents, the allenyl functionality has received very little attention. In a recent report,[2] we disclosed a radical-mediated carbocyclisation of bromoalkynyloxiranes which gave vinylidenetetrahydrofurans. Very recently,[3] oxa-Michael initiated tandem conjugate reactions of 1-nitrocyclohexene with 4-hydroxybut-2-ynoates were shown to afford alkylidenetetrahydrofurans. Provided the oxa-Michael addition is followed by an S_N2' substitution, this tandem reaction should constitute an alternative route to vinylidenetetrahydrofurans.



Scheme 1 *Reagents and conditions*: i, **2** (1 equiv.), THF, Bu^{t}OK (1.5 equiv.), **1** ($ClCH_2C{\equiv}CCH_2OH$, 1.5 equiv.), 0 °C, 10 min, then room temp., 15–30 min, 70–78%



Scheme 2 *Reagents and conditions*: i, see Scheme 1



Scheme 3 *Reagents and conditions*: i, see Scheme 1

We present here our preliminary results on the oxa-Michael–S_N2' substitution of 4-chlorobut-2-yn-1-ol **1** with nitroalkenes **2a**–**f**. Nitroalkenes **2a**–**f**† (Scheme 1) were reacted at 0 °C in THF with **1**, in the presence of Bu^{t}OK. After 10 min the mixture was warmed to room temperature, where it was maintained until completion of the reaction (10–30 min). Vinylidenetetrahydrofurans **3a**–**f** were isolated‡ as the sole products (70–78% yield) after flash chromatography on silica gel.

According to the known reactivity of nitroalkenes with oxygen nucleophiles,[4] the oxa-Michael addition first affords nitronate **I** which then undergoes S_N2' substitution to provide the allenyl moiety[5] (Scheme 2). Bicyclic adducts **3a**–**c** are *cis* ring-fused.

Interestingly, acyclic (*E*)-nitro alkenes **2d**–**f**§ afford, under the same reaction conditions, vinylidenetetrahydrofurans **3d**–**f** in a totally diastereoselective way.¶ We assume that this is due to allylic 1,3-strain, which allows only one conformation **II** for the transition state and thereby leads to the *trans* stereoselectivity observed in the intramolecular cyclisation into vinylidenetetrahydrofurans **3d**–**f** (Scheme 3). Indeed, due to the allylic 1,3-strain effect,[4b,6] excellent diastereoselectivities have been reported for the kinetically controlled protonation of nitrones bearing substituents which differ in steric hindrance[7] and for intermolecular nitrone cycloadditions when a stereogenic centre is present at C-2.[8] However, allylic 1,3-strain does not play a significant role in Michael additions to nitroalkenes bearing a stereogenic centre at C-3, which proceed with remarkable 1,2-asymmetric induction due to steric and stereoelectronic control.[9]

In conclusion, the tandem oxa-Michael addition–intramolecular S_N2' substitution of nitroalkenes constitutes an efficient and stereocontrolled procedure for the preparation of synthetically valuable and relatively unknown vinylidenetetrahydrofurans.

Footnotes

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† Prepared by literature procedures: **2a**–**c** (ref. 10); **2d**–**f** [refs. 11, 12(*b*)].

‡ Satisfactory analytical and spectral data were obtained for all compounds. *Selected data* for **3b**: ν_{max}/cm^{-1} 2950, 2870, 1985, 1965, 1550, 1365, 1080, 1040; δ_H (400 MHz, $CDCl_3$) 1.64–1.99 (m, 4 H), 2.12–2.40 (m, 4 H), 4.49 (dt, *J* 12, 4.2 Hz, (1 H), 4.58 (dt, *J* 12, 4.8 Hz, 1 H), 4.67 (dd, *J* 9, 6 Hz, 1 H), 5.18 and 5.22 (ddd, *J* 11.9, 4.8, 4.2 Hz, 2 H); δ_C (100.61 MHz, $CDCl_3$) 201.6, 100.6, 97.5, 82.8, 81.2, 66.2, 30.7, 27.7, 22.1, 21.6; *m/z* 196 (M + 1), 149 (6%), 99 (12), 87 (30), 81 (100), 69 (24).

§ (*E*)-Stereochemistry for **2d**–**f** was assigned by comparison of ^1H NMR spectra with previously reported data (ref. 12).

¶ *Selected data* for **3e**: δ_H (400 MHz, $CDCl_3$) 0.87 (t, *J* 6.9 Hz, 3 H), 1.28–1.32 (m, 6 H), 1.44–1.50 (m, 2 H), 1.62 (s, 3 H), 4.43 (m, 1 H), 4.45 (dt, *J* 11.8, 3.7 Hz, 1 H), 4.55 (dt, *J* 11.8, 4.9 Hz, 1 H), 5.15 (dd, *J* 4.9, 3.7 Hz, 2 H); δ_C (100.61 MHz, $CDCl_3$) 200.8, 104.6, 96.3, 86.1, 83.0, 67.3, 31.7, 29.7, 25.4, 22.5, 18.9, 14.0; by using a NOESY 2D correlation experiment, NOE interactions detected between the Me at C-4 and the CH_2 at C-5 allowed the assignment of *trans* stereochemistry to **3e**.

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