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A novel domino (4+2)/(4+2)/(3+2) cycloaddition reaction leading to highly functionalized polycyclic nitroso acetals

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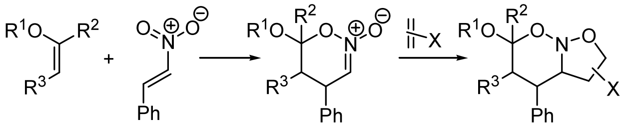
Abstract—2-Methoxybuta-1,3-diene reacts under high pressure conditions in a one-pot domino (4+2)/(4+2)/(3+2) cycloaddition reaction with a dienophile, β-nitrostyrene and a dipolarophile to give tri, tetra and pentacyclic nitroso acetals. In this novel domino reaction up to six bonds and up to eight stereogenic centers are created in one step in good yield and good stereoselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

With the advent of combinatorial chemistry, multicomponent reactions have received much scientific interest, because they allow for the rapid preparation of complex and highly functionalized products from simple precursors in a single operation.[1]

In this report, a novel high pressure promoted[2] four component domino (4+2)/(4+2)/(3+2) cycloaddition reaction starting with a Diels–Alder reaction of 2-methoxybuta-1,3-diene is described. To our knowledge, this is the first example of a multicomponent reaction involving three successive cycloaddition reactions.

In our research group, it was demonstrated that the (4+2)/(3+2) cycloaddition reaction of enol ethers, nitrostyrenes, and electron-rich or electron-poor olefins leading to nitroso acetals[3] is strongly promoted by high pressure (12–15 kbar) (Scheme 1).[4] Using high pressure, no Lewis acid catalyst is needed which enables a one-pot domino (4+2)/(3+2) procedure since quenching of the catalyst from the (4+2) cycloadduct prior to the (3+2) cycloaddition is unnecessary.[4] The domino (4+2)/(3+2) cycloaddition reaction leads in a straightforward way to nitroso acetals which have been shown to be versatile intermediates for the synthesis of polycyclic alkaloids.[5]



Scheme 1.

It was reasoned that the three component domino (4+2)/(3+2) reaction can also be performed by generating an enol ether in situ by a Diels–Alder reaction between a 2-alkoxybuta-1,3-diene and a dienophile. The enol ether that is generated can then react further with a nitroalkene and a dipolarophile to give an overall one-pot four component domino (4+2)/(4+2)/(3+2) cycloaddition reaction.

To test this concept, it was decided to react 2-methoxybuta-1,3-diene (**1**) with an excess of β-nitrostyrene (**2**). β-Nitrostyrene was selected since it can react as a dienophile (in a Diels–Alder reaction), as a heterodiene (in an inverse electron demand Diels–Alder reaction) and as a dipolarophile (in a 1,3-dipolar cycloaddition).

In order to determine the appropriate reaction conditions for the domino (4+2)/(4+2)/(3+2) cycloaddition, it was first performed in a stepwise fashion. Cyclic enol ether **3** was prepared via a high-pressure promoted Diels–Alder reaction of β-nitrostyrene (**2**) and 2-methoxybuta-1,3-diene (**1**). The cycloaddition proceeded with complete regioselectivity and gave cycloadduct **3** in 72% isolated yield after 18 h at 12

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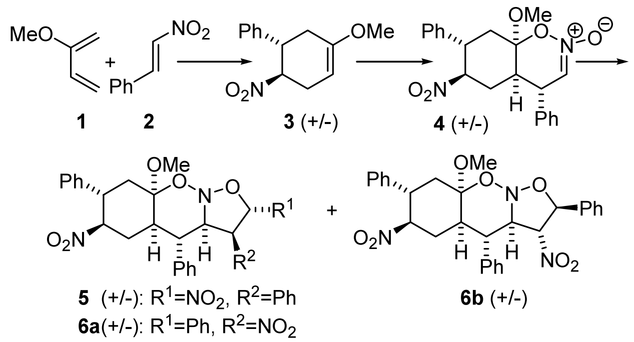


Scheme 2.

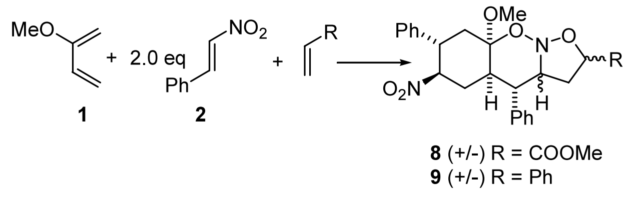
kbar. Next, the cycloadduct **3** was reacted further as an enol ether in the high-pressure promoted domino (4+2)/(3+2) cycloaddition with two equivalents of β-nitrostyrene. At 15 kbar and 50°C, complete conversion of enol ether **3** was observed after 18 h. It was observed that the 1,3-dipolar cycloaddition did not proceed with complete regioselectivity since two regioisomers (**5**/**6**: 0.2/0.8) of the tricyclic nitroso acetals were formed.

After the sequential formation of the nitroso acetals **5** and **6** from the enol ether **3**, the (4+2)/(4+2)/(3+2) cycloaddition was performed in a domino one-pot fashion (Scheme 2). A mixture of 3 equiv. of β-nitrostyrene (**2**) and one equivalent of 2-methoxybuta-1,3-diene (**1**) afforded the nitroso acetals **5** and **6**. At 15 kbar and 50°C, the conversion of the starting compounds was complete within 18 h. ^{1}H NMR analysis of the crude reaction mixture showed the formation of **5**, **6a**, and **6b** in ratio of 0.2/0.6/0.2, respectively.

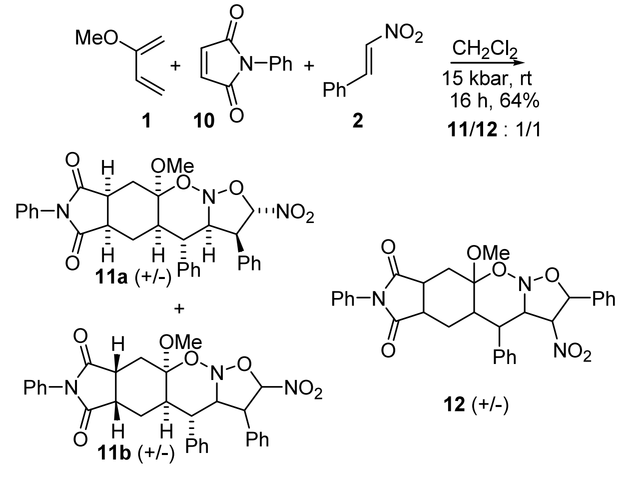
To investigate further the scope of the reaction, the (4+2)/(4+2)/(3+2) cycloaddition between 2-methoxybuta-1,3-diene and two equivalents of β-nitrostyrene was performed in the presence of other dipolarophiles (Scheme 3). As determined by NMR, a mixture of four diastereoisomers was obtained when methyl acrylate was used as the dipolarophile. When styrene was used as the dipolarophile, a mixture of three diastereoisomers was formed.

After it had been shown that different dipolarophiles could be used in the domino (4+2)/(4+2)/(3+2) cycloaddition reaction, it was investigated whether a dienophile other than β-nitrostyrene could be used in the first (4+2) cycloaddition step.

It was reasoned that for this purpose a dienophile that is more reactive than β-nitrostyrene in the first (4+2) cycloaddition was required. A competition experiment, in which an equimolar mixture of 2-methoxybuta-1,3-diene, β-nitrostyrene, and *N*-phenylmaleimide (**10**) was stirred at room temperature, showed that *N*-phenylmaleimide was more reactive than β-nitrostyrene with 2-methoxybuta-1,3-diene.



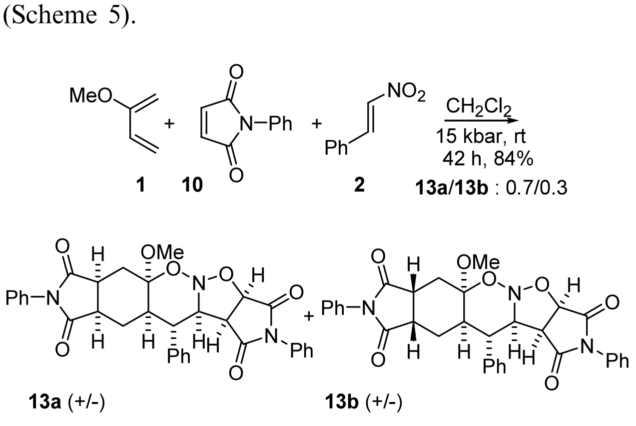
Scheme 3.



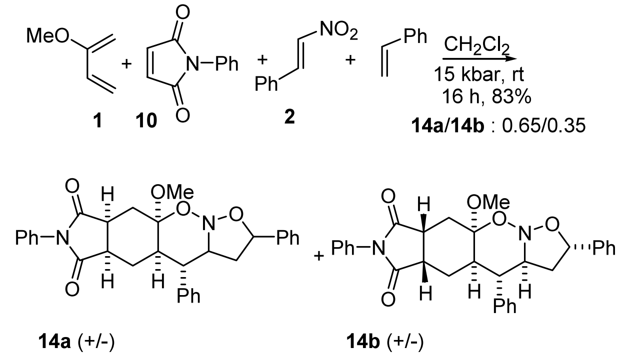
Scheme 4.

The high reactivity of *N*-phenylmaleimide was exploited in a one-pot high pressure promoted reaction between 2-methoxybuta-1,3-diene, two equivalents of β-nitrostyrene and 1 equiv. of *N*-phenylmaleimide (Scheme 4). After 16 h at 15 kbar, a mixture of two regioisomeric nitroso acetals, **11** and **12**, was obtained in a yield of 64% in a ratio of 1/1. In addition, it was found that both regioisomers consisted of two diastereomers in a ratio of 0.65/0.35. The configuration of one of the cycloadducts was determined using 2D NOESY NMR analysis.

Next, it was investigated whether *N*-phenylmaleimide could be used both as dienophile in the first (4+2) cycloaddition and as dipolarophile in the final (3+2) cycloaddition. Reacting a mixture of 2-methoxybuta-1,3-diene, one equivalent of β-nitrostyrene and 2 equiv. of *N*-phenylmaleimide at 15 kbar, at room temperature for 42 h resulted in the formation of two diastereomeric nitroso acetals, **13a** and **13b**, in a ratio of 0.7/0.3 (Scheme 5).



Scheme 5.



Scheme 6.

The configurations of **13a** and **13b** were unambiguously determined using 2D NOESY NMR analysis. The stereochemistry of **13a** was confirmed by X-ray structure analysis.[6]

Finally, the (4+2)/(4+2)/(3+2) cycloaddition was attempted using four different components (Scheme 6). In this reaction 2-methoxybuta-1,3-diene reacted as the diene, *N*-phenylmaleimide as the dienophile, β-nitrostyrene as the heterodiene, and styrene as the dipolarophile. Mixing these components at 15 kbar, at room temperature for 16 h yielded in 83% a mixture of two diastereomeric nitroso acetals, **14a** and **14b**. The stereochemistry of nitroso acetal **14b** was determined using X-ray crystallography.[6]

In conclusion, we have demonstrated that the domino (4+2)/(4+2)/(3+2) cycloaddition is a novel four component reaction. This reaction results in the formation of structurally diverse multicyclic nitroso acetals in good yield and in good stereoselectivity. Currently, we are further exploring the scope of the reaction and the application of this reaction in the synthesis of polycyclic alkaloids.

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6. Crystallographic data for the structures **13a** and **14b** have been deposited with the Cambridge Crystallography Data Centre as supplementary publication numbers CCDC 199579 and CCDC 199578, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).