

High Pressure Promoted Tandem [4+2]/[3+2] Cycloadditions On The Solid Phase

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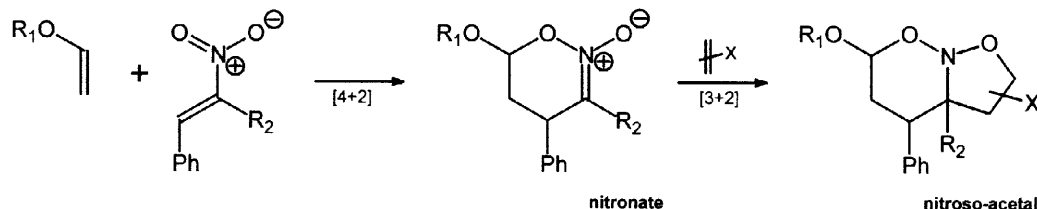
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Abstract

High pressure was applied to perform tandem [4+2]/[3+2] cycloadditions of enol ethers with nitrostyrenes and resin-bound acrylate. The scope of this tandem cycloaddition was studied by using building blocks with an increasing substitution pattern, resulting in the formation of highly substituted nitroso-acetals. To date, this is the first reported high pressure promoted cycloaddition reaction on a solid support. © 1998 Elsevier Science Ltd. All rights reserved.

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Tandem [4+2]/[3+2] cycloadditions of nitroalkenes, enol ethers and electron-poor alkenes seem very apt for application in combinatorial chemistry[1,2,3], as these multi-component reactions allow the synthesis of heterocyclic compounds with a large variety of substituents [4]. In this tandem cycloaddition reaction, which has been extensively studied by Denmark *et al.* [5,6], nitrostyrene reacts with an electron-rich alkene in an inverse electron demand Diels Alder reaction, thus forming a nitronate which is able to react with a third alkene, as shown in Scheme 1.

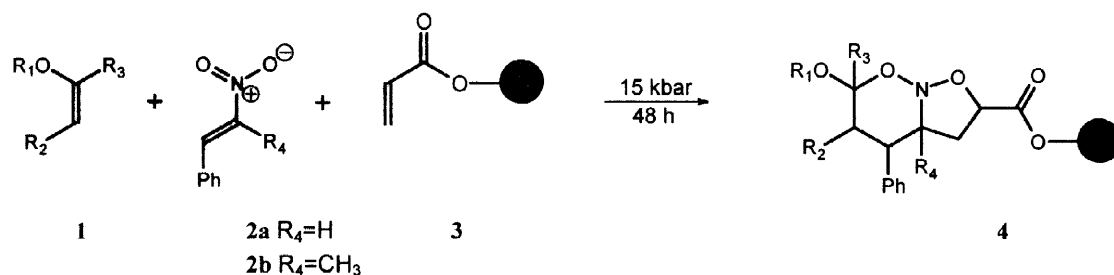


Scheme 1

In a previous paper [7], we showed that these tandem cycloaddition reactions are strongly accelerated by high pressure. Application of high pressure eliminates the need of Lewis acid

catalysts, which are normally used in an excess of more than one equivalent, as well as large excess of enol ethers [8]. As high pressure assists in overcoming steric hindrance, it allows the introduction of a large variety of substituents [9,10]. We also demonstrated that the reaction sequence described in Scheme 1, using methylacrylate as an electron-poor alkene in the [3+2] cycloaddition, proceeded as a one pot reaction.

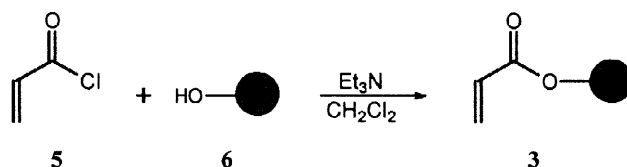
We now present our results on the high pressure promoted one pot three component tandem [4+2]/[3+2] cycloaddition of enol ethers, nitrostyrenes and resin-bound acrylate (Scheme 2).



Scheme 2

It is known that nitronates react much faster with electron-poor alkenes than with electron-rich alkenes [7,11]. The reaction of the nitronate, formed in situ, with the resin-bound acrylate is therefore expected to be faster than its reaction with the enol ether in solution. To study the scope of this one pot three component cycloaddition, reactions were performed with the non activated nitrostyrenes **2a** and **2b** [12], the mono-, di- and tri-substituted enol ethers (**1**) and the resin-bound acrylate (**3**), as presented in Scheme 2.

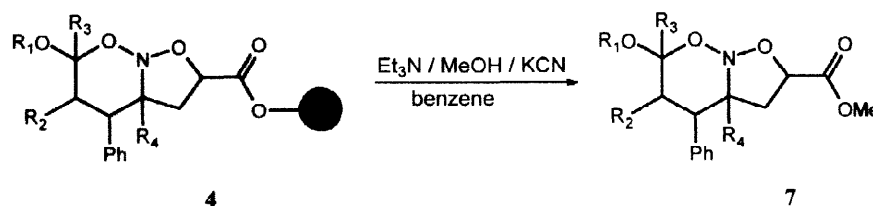
First the stability of the Wang resin under high pressure conditions was studied. Since no significant change was observed (swelling capacity, FT-IR analysis) after the application of a pressure of 15 kbar for 24 h, we started to investigate the tandem [4+2]/[3+2] cycloaddition under high pressure conditions with the dipolarophile (acrylate) attached to the resin. The acryloyl function was coupled to the resin by reacting acryloylchloride (**5**) under basic conditions with the hydroxybenzyl functionalized polystyrene resin (**6**) as demonstrated in Scheme 3.



Scheme 3

The enol ether and the nitrostyrene compounds were added to the acrylate functionalized Wang resin in a 2 fold excess and mixed in a teflon tube with CH_2Cl_2 as the solvent. The tandem cycloaddition was performed by applying a pressure of 15 kbar on the reaction mixture for 48 h at room temperature [13]. FT-IR analysis of the resin showed a C=O shift from 1721cm^{-1} to

1737 cm^{-1} , while the appearance of a new signal at 1563-1565 cm^{-1} (C-N bond vibration) in the case of **2a** [14] indicated a resin-bound tandem adduct. In order to determine the yield of this tandem cycloaddition, the products were cleaved from the resin by a transesterification reaction in a mixture of $\text{Et}_3\text{N}/\text{MeOH}/\text{benzene}$ (0.4/2/10 v/v/v) and a catalytic amount of KCN [15] (Scheme 4).



Scheme 4

The cycloadducts were isolated as mixtures of diastereomers. Yields (37-52%; not optimized) after a three step reaction sequence were reasonable, even in the case of higher substituted enol ethers and nitrostyrenes (Table 1).

Table 1. Nitroso-acetals prepared on the solid phase

Entry	R_1	R_2	R_3	R_4	product 7	c.y. ^a (%)
a	Et	H	H	H		33
b		$-\text{CH}_2\text{CH}_2-$	H	H		42
c	MeO^b	$-(\text{CH}_2)_4-$		H		52
d	Et	H	H	CH_3		44
e		$-\text{CH}_2\text{CH}_2-$	H	CH_3		38
f	MeO^b	$-(\text{CH}_2)_4-$		CH_3		37

^a Yields of purified cycloadducts based on initial loading level of the Wang Resin (1.22 mmol/g)

^b The enol ether is prepared from the corresponding dimethoxyacetal [16]

¹H-NMR analysis showed a complete regioselective outcome of both the [4+2] and [3+2] cycloadditions, which is in agreement with the results described earlier [7]. The relatively low

yield of entry **a** can be ascribed to a competing reaction between the nitronate and the low substituted enol ether.

Currently, we are exploring further variation in the substitution pattern of all reaction partners and conversions of nitroso-acetals **7** on the solid support towards fully substituted aryl-pyrrolidines and pyrrolizidines [17].

Acknowledgement

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References and Notes

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- ¹² Without a Lewis acid catalyst, an additional activating electron withdrawing substituent on the nitrostyrene is required (in the [4+2] cycloaddition): Tohda Y, Yamawaki N, Matsui H, Kawashima T, Ariga M, Mori Y. *Bull. Chem. Soc. Jpn.* 1988;61:461-465.
- ¹³ Representative experimental procedure for high pressure promoted tandem cycloaddition: 750 mg of the resin-bound acrylate **3** was placed in a teflon tube with enol ether **1** (2 eq.) and nitrostyrene **2** (2 eq.). The teflon tube was placed in the high pressure apparatus (described in Aben RWM, Scheeren JW. *J. Org. Chem.* 1987;52:365-370) at a pressure of 15 kbar for 48 h at room temperature. After depressurizing, the reaction mixture was poured over a glassfilter, drained and the resin was washed with CH₂Cl₂ (3x 10 mL), MeOH (2x 10 mL) and CH₂Cl₂ (3x 10 mL). The resin was dried at 70°C under reduced pressure for 2 h. The increase in weight of the resin was a measure of the amount of cycloadduct formed on the resin. For less substituted enol ethers and nitrostyrenes good conversions were already achieved at lower pressures and shorter reaction times (12 kbar, 17 h). We have chosen the given standard conditions (15 kbar, 48 h) because of satisfactory conversions using more substituted reaction partners.
- ¹⁴ In the case of **2b** (entry d, e and f) the C-N signal is probably hidden under neighbouring frequencies of the resin.
- ¹⁵ Representative experimental procedure for cleavage reaction: A mixture of Et₃N (0.4 mL), MeOH (2.0 mL), benzene (10 mL) and was added to 800 mg of resin. After addition of 2-5 mg KCN, the mixture was refluxed for 48 h after which the solution was separated from the resin by filtration over a glassfilter. After washing the resin with CH₂Cl₂ (3x 10 mL), MeOH (2x 10 mL), H₂O/sat. NaHCO₃ solution (1/1 v/v), MeOH (2x 10 mL), and CH₂Cl₂ (3x 10 mL) the organic phase was separated from the water phase. The water phase was extracted with CH₂Cl₂. The combined organic layers were dried with brine and MgSO₄ and concentrated in vacuo. The products were purified by passage through a short path of silica (eluens EtOAc/hexane 1/4 and 1% Et₃N), isolated as colourless or light yellow coloured oils and analyzed by ¹H-NMR and mass spectroscopy.
7a MS (CI) m/z 308 (M + H⁺), HRMS calcd. for C₁₆H₂₁NO₅: 307.1420, found 307.1420 ± 0.0012;
7b MS (CI) m/z 306 (M + H⁺), HRMS calcd. for C₁₆H₁₉NO₅: 305.1263, found 305.1264 ± 0.0012;
7c MS (CI) m/z 348 (M + H⁺), HRMS calcd. for C₁₉H₂₅NO₅: 347.1733, found 347.1732 ± 0.0010;
7d MS (CI) m/z 322 (M + H⁺), HRMS calcd. for C₁₇H₂₃NO₅: 321.1576, found 321.1577 ± 0.0015;
7e MS (CI) m/z 320 (M + H⁺), HRMS calcd. for C₁₇H₂₁NO₅: 319.1420, found 307.1420 ± 0.0012;
7f MS (CI) m/z 362 (M + H⁺), HRMS calcd. for C₂₀H₂₇NO₅: 361.1889, found 361.1890 ± 0.0014.
- ¹⁶ Synthesis of 1-methoxy-1-cyclohexene is described in Houben Weil, E 15/Teil 1:268 Georg Thiemes Verlag Stuttgart-New York.
- ¹⁷ These compounds are studied in the framework of our research towards CNS active compounds related to serotonin and dopamin.