Domino reactions

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Triethyl Phosphite Mediated Domino Reaction: Direct Conversion of ω-Nitroalkenes Into N-Heterocycles

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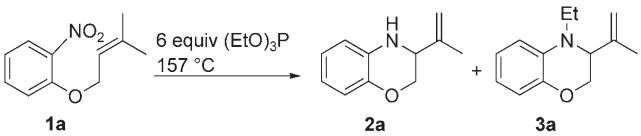
Dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 65th birthday

The development of new synthetic methods for N-heterocycles is an important topic of research in organic synthesis because of their potential application as pharmaceuticals.[1] So far, reductive cyclizations of nitro compounds[2] have been predominantly employed to construct indoles and related N-heteroaromatic compounds. The best known methods include the synthesis of indoles following the procedures of Leimgruber–Batcho,[3,4] Bartoli,[3,5] and Reissert,[3] the transition-metal-catalyzed reductive N-heteroannulation of *o*-nitrostyrenes,[6] and the Cadogan cyclization.[7] Still little is known about their application to the synthesis of saturated N-heterocycles. Another method for the reductive cyclization of aromatic nitro compounds is the transformation of ω-nitro ketones under reducing conditions.[8] In addition, the potential of the nitroso-ene reaction for the formation of C–N bonds has by no means been exhausted.[9] In particular, there is a lack of methods for the one-step generation of the nitroso group from easily accessible precursors. Furthermore, the primary product of the nitroso-ene reaction is a hydroxylamine instead of the much more interesting amine.

Our aim was to join the nitroso-ene reaction and two reduction reactions to create a novel domino process.[10] To this end, the nitro group of a ω-nitroalkene was first to be reduced to give the corresponding nitroso group which then, as the enophile, should undergo an intramolecular ene reaction with the alkene to produce the corresponding hydroxylamine. Final reduction of the NOH group would then deliver the cyclic amine.

Here we describe the reductive cyclization of ω-nitroalkenes to saturated N-heterocycles in a single step. As an example, we chose the transformation of allyl 2-nitrophenyl ethers **1** into substituted 3,4-dihydro-2*H*-1,4-benzoxazines **2**, since this structural element occurs in numerous biologically active compounds.[11] A further advantage of allyl 2-nitrophenyl ethers is that they are accessible from the most simple substrates in a single step and in high yields. After some preliminary experiments, which included Pd-catalyzed reactions with CO, we found that this novel domino process can best be accomplished with phosphites. For example, 3,3-dimethylallyl-2-nitrophenyl ether (**1a**) was heated with triethyl phosphite $(EtO)_3P$ to reflux for two hours to give 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**2a**) as the main product in 57% yield (Scheme 1). The N-ethyl derivative of **2a**, 4-ethyl-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazine (**3a**) was formed as a side product in 8% yield. Longer reaction times (12 h) decreased the yield of **2a** to 50%, but increased the yield of **3a** to 15%.



1a	2a	3a
2 h	57 %	8 %
12 h	50 %	15 %

Scheme 1. Domino reaction of **1a** with $(EtO)_3P$ under thermal conditions.

We assumed that **3a** is formed by the N-ethylation of **2a** with triethyl phosphate $(EtO)_3PO$, which was produced by oxidation of $(EtO)_3P$. This assumption was corroborated by the experimental finding that **2a** was recovered unchanged after heating in $(EtO)_3P$ (reflux, 8 h), whereas heating **2a** with $(EtO)_3PO$ (reflux, 6 h) gave **3a** in 70% yield. The formation of N-alkylated side products was also observed with other phosphites such as trimethyl and triisopropyl phosphite.

In addition, we investigated whether the new transformation could also be applied to allyl 2-nitrophenyl ethers that were substituted in their aromatic nucleus. The cyclization precursors **1b–k** were synthesized from the reaction of the corresponding substituted *o*-nitrophenols with prenyl bromide under standard conditions (K_2CO_3, acetone, reflux) in yields of 85–96%.

The precursors **1b–k** were heated with $(EtO)_3P$ (reflux, 1–3 h) to give the substituted 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines **2b–k** as the main products with yields of 52–64% (Table 1). Again, in about half the cyclizations, N-ethylation was observed as a side reaction to give the substituted 4-ethyl-3-isopropenyl-3,4-dihydro-2*H*-1,4-benzoxazines **3b**,**d**,**e**,**f**,**k** (yields of 1–6%).

As one of the well-known advantages of the use of microwaves (MW) is reaction acceleration,[12] we repeated the cyclization of **1a** under microwave conditions (300 W, 200 °C). Although the reaction time could be reduced from 2 h to 30 min it was not possible to suppress the formation of **3a** in

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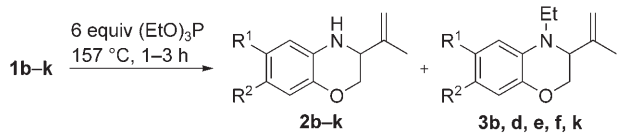
Table 1: Domino reaction of **1b–k** with $(EtO)_3P$ under thermal conditions.



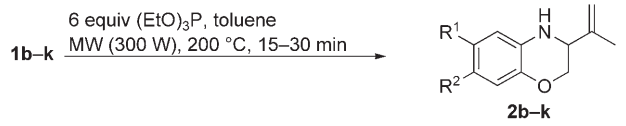
Entry	1	R^1	R^2	*t* [h]	Product **2** (yield [%])[a]	Product **3** (yield [%])[a]
1	**b**	Me	H	3	63	5
2	**c**	OMe	H	1	60	–
3	**d**	F	H	1	52	6
4	**e**	Cl	H	1	64	3
5	**f**	Br	H	1	55	2
6	**g**	CO_2Me	H	2	58	–
7	**h**	H	Me	1	57	–
8	**i**	H	F	2	58	–
9	**j**	H	CO_2Me	1.5	60	–
10	**k**	Cl	Me	1	60	1

[a] Yields refer to isolated, analytically pure product.

13% yield, along with **2a** in 47% yield. Finally, we examined the effect of solvents on the course of the reaction. Precursor **1a** was treated with $(EtO)_3P$ in toluene under both thermal (closed vial, 200°C, 3 h) and microwave conditions (closed vial, 300 W, 200°C, 30 min). Surprisingly, both conditions led to exclusive formation of **2a** in 45 and 55% yields, respectively. Similar results were obtained with solvents such as cumene and *o*-dichlorobenzene. As a result of the suppression of the side product **3a**, the higher yield of **2a**, and the shorter reaction time, the reductive cyclizations of **1b–k** were repeated under microwave conditions in toluene (Table 2). All cyclizations proceeded with complete selectivity within 15–30 min with formation of **2b–k** in yields of 57–65%. The results demonstrate that halide and ester functionalities are well tolerated in these transformations.

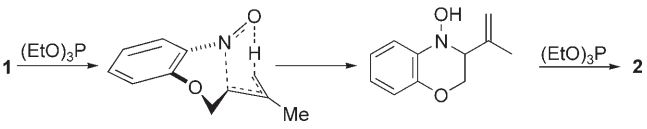
We considered both an intramolecular nitroso-ene reaction[9] and the reaction of a nitrene[13] as the reaction mechanism. In the case of a nitroso-ene reaction, the nitro group must be reduced to a nitroso group, which then reacts as an enophile intramolecularly with the 2-methylpropenyl group to form the hydroxylamine. Finally, the hydroxylamine would be reduced to give the amine **2** (Scheme 2).

Table 2: Domino reaction of **1b–k** with $(EtO)_3P$ in toluene under microwave conditions.



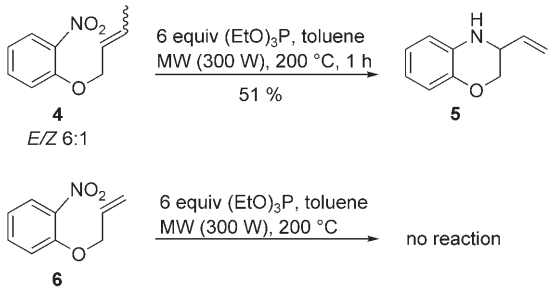
Entry	1	R^1	R^2	*t* [min]	Product **2** (yield [%])[a]
1	**b**	Me	H	20	57
2	**c**	OMe	H	30	58
3	**d**	F	H	15	60
4	**e**	Cl	H	20	63
5	**f**	Br	H	20	64
6	**g**	CO_2Me	H	20	60
7	**h**	H	Me	25	58
8	**i**	H	F	25	61
9	**j**	H	CO_2Me	25	60
10	**k**	Cl	Me	20	65

[a] Yields refer to isolated, analytically pure product.



Scheme 2. Potential reaction mechanism.

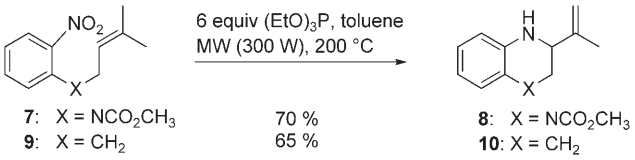
The finding that the 3-methylallyl ether **4** led to the formation of **5** in 51% yield, whereas the allyl ether **6** without any terminal methyl group does not react at all (Scheme 3)



Scheme 3. Investigations into the reaction mechanism.

supports both mechanisms. Even though we cannot make a definite statement about the mechanism, since both high yields of cyclization products **2** were achieved and the products that would be expected from nitrenes were not observed, we assume the nitroso-ene pathway is operating.

Notably the new reductive cyclization is not only an effective means to construct the 3,4-dihydro-2*H*-1,4-benzoxazine skeleton, but also may be extended to the one-step synthesis of 1,2,3,4-tetrahydroquinoxalines **8** and 1,2,3,4-tetrahydroquinolines **10** (Scheme 4).



Scheme 4. One-step synthesis of 1,2,3,4-tetrahydroquinoxaline (**8**) and 1,2,3,4-tetrahydroquinoline (**10**).

Here we describe the first domino reaction in which ω-nitroalkenes are converted into saturated N-heterocycles. The reductive cyclization reaction mediated by triethyl phosphite allows access to substituted 3,4-dihydro-2*H*-1,4-benzoxazines, 1,2,3,4-tetrahydroquinoxalines, and 1,2,3,4-tetrahydroquinolines. Investigations into the scope and mechanism of this reaction are ongoing.

Experimental Section

Cyclization of **1** under microwave conditions: Precursor **1** (1 mmol), $(EtO)_3P$ (6 mmol), and toluene (3 mL) were sealed in a septum reaction vial (10 mL) and irradiated with microwaves (Discover, CEM; 2450 MHz; 300 W; 200 °C; 15–30 min). After removal of $(EtO)_3P$ and $(EtO)_3PO$ (10^{-1} mbar), the residue was taken up in EtOAc (25 mL) washed with brine (3×20 mL). After drying over $MgSO_4$ and concentration in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 20:1).

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