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Multicomponent Domino [4+2]/[3+2] Cycloadditions of Nitroheteroaromatics: An Efficient Synthesis of Fused Nitrogenated Polycycles

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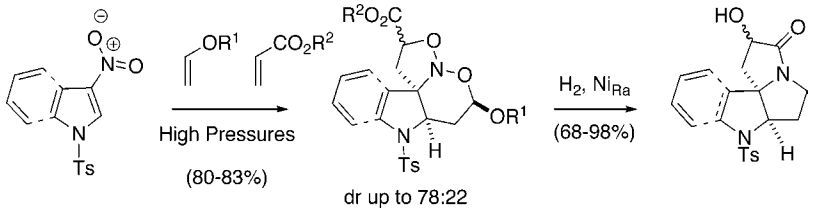
ABSTRACT

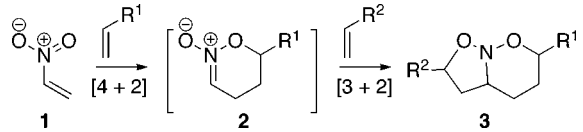


Activation by high pressure allows 3-nitroindole and 3-nitropyrrole derivatives to behave as electron-poor heterodienes in multicomponent domino [4+2]/[3+2] cycloaddition processes. The primary [4+2] inverse demand cycloaddition appears to be completely *endo* selective, while the subsequent [3+2] process shows a total facial selectivity, setting the stereochemistry at ring junction, and an *endo*/*exo* selectivity depending on the nature of the heterocycle. In two operations, a polycyclic diamine featuring a quaternary center at ring junction is efficiently generated.

Over the years, domino processes have emerged as efficient tools for the rapid generation of complex compounds in few synthetic steps.[1] In this context, [4+2]/[3+2] cycloadditions of nitroalkenes proved very useful for the synthesis of various nitrogen-containing compounds.[2] In this process, nitroalkene **1** first acts as heterodiene, in an inverse demand [4+2] cycloaddition, to generate intermediate nitronate **2** that undergoes a subsequent [3+2] cycloaddition leading to a nitrosoacetal derivative, of type **3** (Scheme 1). Such compounds provide useful synthetic intermediates, giving an easy access to nitrogenated motifs, after cleavage of the N−O bonds for instance.[2]

Denmark et al. have reported many elegant syntheses of polynuclear heterocycles involving intramolecular domino [4+2]/[3+2] cycloadditions of nitroalkenes.[2,3] The structural diversity of the reported sequences derives not only from the different possibilities for the attachment of the various components (dienophile and dipolarophile) to the nitroalkene, but also from the length of the tethers. Multicomponent intermolecular processes involving nitrostyrenes were studied by Scheeren et al., who showed the positive impact of high pressures on these cycloadditions.[4] The implication of nitro-substituted heterocycles in domino cycloadditions is, however, scarcely described in the literature. Nitrooxazoles and

Scheme 1



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(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (e) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329. (g) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564. (h) Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933−1952.

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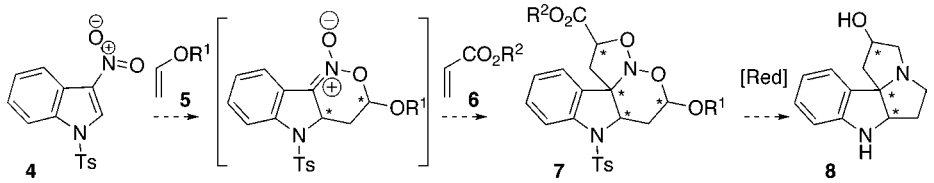
Scheme 2

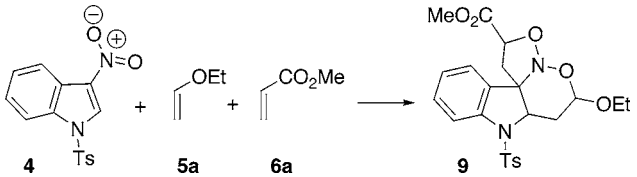


nitroisooxazoles were found to efficiently react as heterodienes with ethyl vinyl ether in homodomino processes, while the multicomponent reaction led to a 2:3 mixture of homodomino and heterodomino nitrosoacetals, thus limiting the practical development of these reactions.[5]

In the course of a program focusing on the use of electron-poor indole derivatives in [4+2] cycloadditions,[6] we became interested in the implication of this common aromatic heterocycle in domino [4+2]/[3+2] processes. The aromaticity of the substrate would presumably deactivate the whole process, but bears the advantage of involving easily accessible starting materials to lead to partially dearomatized polycycles featuring a quaternary center at ring junction (Scheme 2). In the first [4+2] cycloaddition reaction, the nitroalkenic part should react through its LUMO as electron-poor heterodiene and should thus better interact with an electron-rich dienophile in an inverse demand [4+2] cycloaddition. The higher reactivity of 3-substituted indole derivatives, when compared to 2-substituted ones as electron-poor dienophiles in normal electron demand [4π+2π] cycloadditions,[6,7] led us to consider the 3-nitroindole derivative **4**, bearing a tosyl group on the nitrogen atom, for this study.[8] Alkyl vinyl ethers were chosen as model electron-rich dienophiles. In contrast, the nitronate dipole intermediate involved in the second [3+2] cycloaddition should better react through its HOMO with an electron-deficient dipolarophile such as an acrylate. The respective reactivities of the two alkene species thus allow us to envision a multicomponent domino process to generate nitrosoacetals **7**.[4] After cleavage of the N−O bonds by reduction,[2−4] such derivatives would thus lead to nitrogenated tetracyclic structures **8** and find a bearing in the access to both biologically active compounds and new ligands useful in the context of asymmetric synthesis (Scheme 2).

Reacting indole **4** with ethyl vinyl ether and methyl acrylate in dichloromethane at room temperature led to the formation of the expected nitrosoacetal **9** (Table 1, entry 1).

Table 1. Cycloadditions between Indole **4**, Ethyl Vinyl Ether **5a**, and Methylacrylate **6a**



entry	reaction conditions	convn[a] (%)	yield (%)	dr[b]
1	DCM, rt,[c] 168 h	42	20	50/50/0/0
2	$Cu(OTf)_2$,[d] DCM, rt,[c] 168 h	0		
3	$SnCl_4$,[d] DCM, rt,[c] 168 h	0		
4	DCM, 42 °C, 168 h	53	29	50/50/0/0
5	toluene, 110 °C, 60 h	100	83	45/45/5/5
6	120 W,[e] Toluene, 130 °C, 1 h	100	75	35/35/15/15
7	1.2 GPa, THF, rt,[c] 24 h	100	83	55/45/0/0

[a] Percent conversion. [b] Diastereomeric ratio. [c] Room temperature. [d] 10 mol %. [e] Microwave irradiation.

No homodomino nitrosoacetal was found to have formed on the basis of the crude NMR spectra. The conversion was

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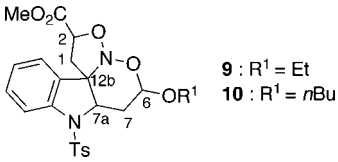
far from complete, even after one week, and the isolated yield proved low. This result nevertheless pointed out the feasibility of the above multicomponent domino reaction. Thus, the electron demand of the two sequential cycloadditions is sufficiently different to allow a selective domino process. The possible Lewis acid catalysis of such cycloadditions has been reported by Denmark.[3] In our case, however, catalysis by copper(II) triflate or tin(IV) tetrachloride induced polymerization of the dienophile/dipolarophile and no reaction occurred (entries 2 and 3). Heating the reaction mixture at reflux of dichloromethane allowed the conversion and yield to be increased, while still remaining unsatisfactory (entry 4). The use of a higher boiling point solvent such as toluene proved more beneficial, leading to a complete conversion after 60 h (entry 5). Nitrosoacetals **9** were isolated in good yield as a 45:45:5:5 diastereomeric mixture. Microwaves have been shown to constitute a powerful activation method for both [4+2] and [3+2] cycloadditions.[9] In our case, it indeed induced a significant reduction of the reaction time to 1 h but simultaneously decreased the stereoselectivity of the process (entry 6). Finally, hyperbaric activation proved the most efficient method for this reaction, limiting the degradation of the medium and allowing the reaction to proceed completely in 24 h at room temperature (entry 7). The expected cycloadduct **9** was isolated in 83% yield as a 55:45 mixture of diastereomers. The partially dearomatized cycloadducts thus obtained appeared to be quite stable compounds and the diastereomers were easily separated by chromatography on silica.

Stereochemical Implications. In the whole process, only 2 of the 8 possible diastereomer couples of **9** were formed. The significant NMR chemical shifts and coupling constants compiled in Table 2 suggest differences in the relative

Table 2. Selected ^{1}H NMR Chemical Shifts and Coupling Constants of **9** and **10**



9 : R^1 = Et
10 : R^1 = *n*Bu

		δ (ppm) (J (Hz))			
entry	^{1}H	**9a**[a]	**9b**[b]	**10a**[a]	**10b**[b]
1	7a	4.11 (5.3; 12.8)	4.14 (5.3; 12.8)	4.10 (5.3; 12.8)	4.13 (5.3; 12.8)
2	6	4.88 (6.6; 8.4)	4.84 (6.8; 8.7)	4.86 (6.6; 8.3)	4.83 (6.8; 8.7)
3	2	5.02 (5.7; 10.6)	4.73 (7.2; 9.0)	5.02 (5.7; 10.2)	4.73 (7.5; 9.0)

[a] First isomer eluted by chromatography. [b] Second isomer eluted by chromatography.

stereochemistry at carbon C_2 (compare entries 1−2 with 3 in Table 2).

The synthesis of tetracycle **10**, bearing an *n*-butyl group instead of the ethyl group on the 6-membered ring, led to similar results in terms of yield and de. Separation of the two diastereomers and crystallization of both compounds in a mixture of heptanes and ethyl acetate afforded materials suitable for X-ray diffraction analysis (Figure 1).

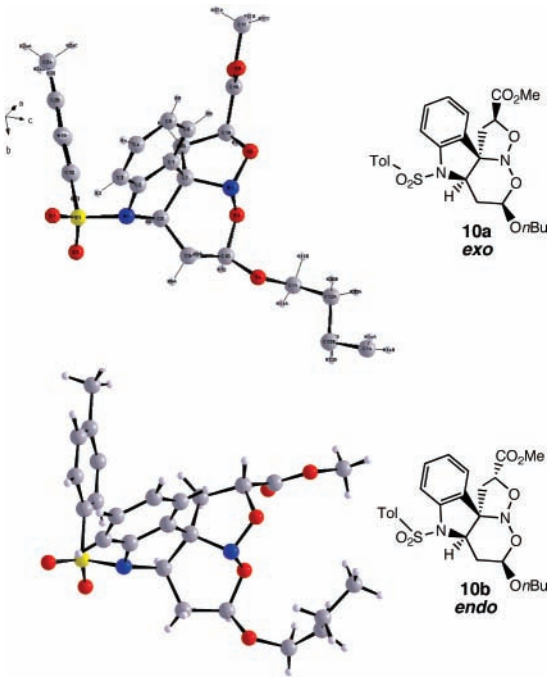


Figure 1. ORTEP for compounds **10a** and **10b**.

The collected data confirmed that the stereochemistry of the two diastereomers formed differs at the carbon bearing the methoxycarbonyl group. Thus, the observed relative configurations suggest a complete *endo* stereoselectivity for the primary [4+2] cycloaddition process, setting the relative stereochemistries of both C_{7a} at ring junction, and C_6 α to the alkoxy group. A complete facial differentiation for the subsequent [3+2] process, with an approach of the dipolarophile from the most accessible, bottom face (Figure 2),

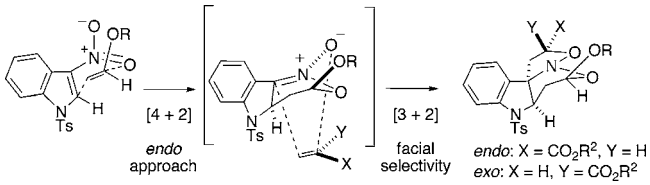


Figure 2. Proposed transition states for the [4+2]/[3+2] process.

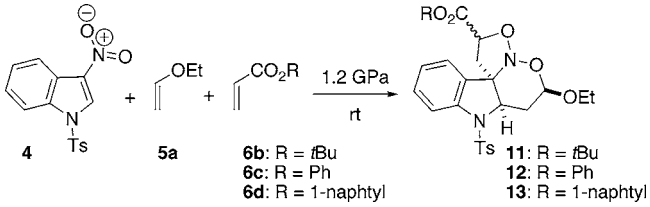
sets the relative stereochemistry of quaternary carbon C_{12b} at ring junction. This second cycloaddition, however, shows little or no selective *endo*/*exo* orientation of the acrylate. The whole domino process thus eventually leads to the formation

(9) Loupy, A. In *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002; pp 295−344.

of the two diastereomers having different relative configurations at carbon C_2.

Attempts to epimerize the center α to the methoxycarbonyl substituent under basic conditions failed. The influence of the acrylate derivative on the diastereoselectivity of the sequence was then checked (Table 3). The use of a more

Table 3. Cycloadditions between Indole **4**, Ethyl Vinyl Ether **5a**, and Acrylate **6**

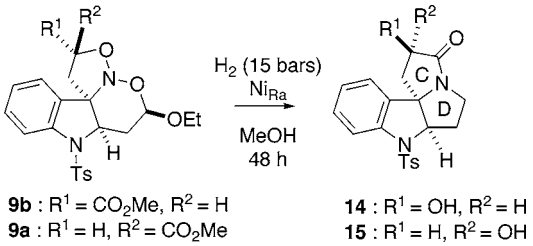


entry	R	reaction time (h)	yield (%)	*endo*/*exo* selectivity[b]
1	*t*Bu	24	83	60/40
2	Ph	45	92	66/34
3	1-naphtyl	24	99	78/22

sterically hindered dipolarophile led to a small enhancement of the *endo*/*exo* selectivity of the second [3+2] cycloadition process (entry 1). Specifically, acrylates bearing an aromatic ring proved more beneficial (entry 2) and allowed an increase of the ratio up to 78/22 with 1-naphthyl acrylate **6d** (entry 3).

Pivotal to the synthetic utility of this methodology is the ability to cleanly transform the obtained nitrosoacetals. Isomer **9b** was thus submitted to catalytic hydrogenation under 15 bar in the presence of Raney nickel for 48 h (Scheme 3). The expected pyrrolizidone **14** was isolated in

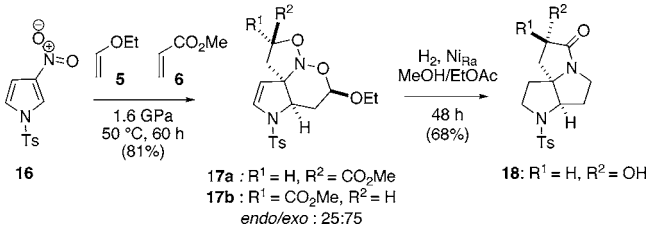
Scheme 3



98% yield with no loss of the stereochemical information (as shown by NOESY experiments). The product obtained here is thus the result of the sequential cleavage of two N−O bonds, formation and reduction of an imine derivative to generate ring D, and final lactamization to form ring C. Similarly, reduction of diastereomer **9a** resulted in the formation of diastereomeric tetracyclic lactam **15**.

Extending the above process to other ring systems was achieved with 3-nitropyrrole **16**. Thus, reacting **16** with ethyl vinyl ether and methyl acrylate at 1.2 GPa and room temperature for 24 h did not lead to the formation of the desired nitrosoacetal due to the higher aromaticity of this substrate. Compressing the reactants at 1.6 GPa and 50 °C for 60 h, however, induced a complete conversion of the starting material, and diastereomeric nitrosoacetals **17** were isolated in 81% yield (25/75 *endo*:*exo* diastereomeric ratio) (Scheme 4). Stereochemistry was assigned by comparison

Scheme 4



with the above data. With this smaller heterocycle, the stereoselectivity thus appears to be reverse. Major diastereomer **17a** was then subjected to reduction conditions and tricyclic diamine **18** was obtained in 68% isolated yield.

The results described in this paper establish the feasibility of multicomponent domino [4+2]/[3+2] cycloadditions from electron-poor nitroheteroaromatics. 3-Nitroindole **4** and 3-nitropyrrole **16** can be used to rapidly and efficiently generate tetracyclic dearomatized diamines featuring a quaternary center at ring junction. These hitherto undescribed structures would be difficult to prepare by other synthetic methods. Their structural similarities with numerous indolic alkaloids point the finger to potentially interesting biological properties. In addition, the rigid tetracyclic 1,2-diaminic moiety of these scaffolds makes them good candidates for the design and preparation of novel catalysts in the context of asymmetric synthesis. Further work is in progress in these laboratories to develop a completely stereoselective version of the process.

Supporting Information Available: Experimental procedure and complete characterization for compounds **9**−**15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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