

Short communication

Thiourea-catalyzed dearomatizing [4+2] cycloadditions of 3-nitroindole



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ABSTRACT

We have developed two efficient thiourea promoted dearomatizing processes involving the cycloadditions of 3-nitroindoles. The C2=C3 double bond of the heteroarene can be involved as electron-poor 2 π dienophile in [4+2] cycloadditions. While the uncatalyzed process requires harsh conditions, the organocatalyzed reaction takes place at room temperature and atmospheric pressure. The C2=C3–N=O motif of the heteroarene can also react as an electron-poor 4 π heterodiene in [4+2] / [3+2] cycloadditions cascades, under high pressure. In contrast to Lewis acid activation, thiourea promotion thus proves efficient even under unconventional activation conditions and in the presence of acid sensitive reactants such as enol ethers.

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Dearomatization processes involving cycloadditions are crucial chemical transformations that allow generation of elaborated polycyclic structures from easily available raw materials. The possible involvement of indoles in dearomatizing Diels–Alder reactions has been reported for some time. The intrinsic electron-rich character of this heteroarene mainly leads to the implication of vinylindoles as electron-rich dienic partners in Normal Electron Demand (NED) processes[1]. Indoles also react as enriched dienophiles in Inverse Electron Demand (IED) reaction with electron-poor dienes[2]. The involvement of electron-poor indoles in [4+2] cycloadditions is more scarcely described. However, provided that the heterocycle bears sufficiently electron-withdrawing substituents, the C2=C3 double bond of indoles has been shown to react as an electron-deficient dienophile with external enriched dienes [3, 4]. Considering the powerful electron-withdrawing effect of the nitro group, nitroindoles have been exploited for these cycloadditions. Thus, the dienophilic character of nitroindoles **1** has been evidenced in the presence of the electron-rich 1-methoxy-3-trimethylsilyloxybutadiene (Danishefsky diene) (**2**) under thermal or high pressure activation[4]. The thermal cycloaddition leads, after loss of nitrous acid, to the efficient formation of hydroxycarbazoles (Scheme 1)[5].

In addition to their possible involvement as dienophiles, electron-poor indoles can also react as (hetero)diene in IED cycloaddition processes [6,7]. We have shown that 3-nitroindoles can be involved as electron-poor heterodienes in [4+2] / [3+2] cascades[7]. In this sequence, the C2=C3–N=O moiety first reacts as a heterodiene with

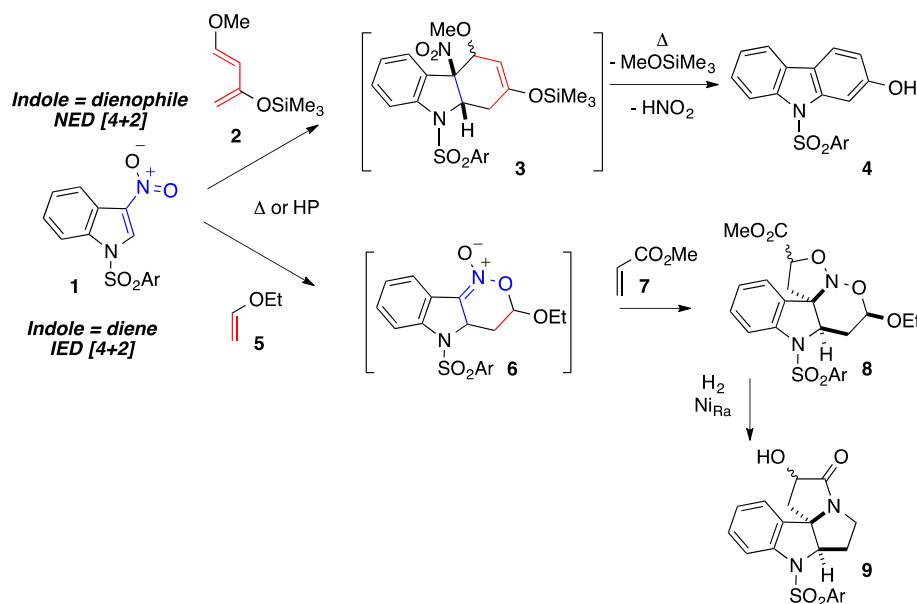
an electron-rich dienophilic component such as a vinyl ether **5**, to lead to the formation of nitronate **6** (Scheme 1). This intermediate behaves as an electron-rich 1,3-dipole, interacting with acrylate **7** to generate a nitrosoketal cycloadduct **8**. Its reduction into the tetracyclic indolopyrrolizidone **9**, featuring a tetrasubstituted center at the ring junction, illustrates the synthetic interest of the method to access indole derivatives with innovative structures.

From readily available starting materials, both these [4+2] processes thus allow the efficient generation of elaborated nitrogenated polycyclic motifs common to many indole alkaloids. The cycloadducts thereby generated constitute interesting scaffolds for molecular diversity.

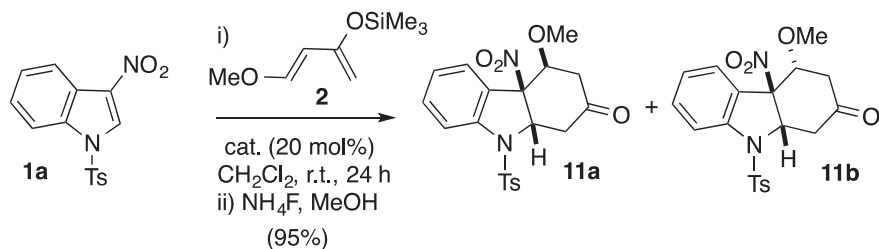
Due to the aromatic character of the indole partner, high energy barriers have to be overcome in these cycloadditions, requiring harsh thermal activation and prolonged heating[8] or high pressure conditions[4b,7a, 9]. An efficient activation of these [4+2] reactions by potentially chiral catalysts would thus highly enhance the applicability and the scope of these methodologies. The acid sensitivity of electron-rich species such as silyloxydienes or vinyl ethers has, however, precluded the use of common Lewis acids until now.

Thioureas have become key activators, allowing powerful catalytic enantioselective processes, even in the presence of acid sensitive substrates[10]. Their hydrogen bonding with the nitro groups of nitroalkenes has been shown to be remarkably efficient, in particular for conjugate addition reactions. We have thus envisaged to activate [4+2] cycloadditions involving 3-nitroarenes and electron-rich species by thiourea catalysis. The non-covalent interaction between the organocatalyst and the nitroarene should lead to a significant decrease in the LUMO energy of the aromatic partner. The cycloaddition

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Scheme 1. Reactivity of 3-nitroindole **1** towards electron-rich diene **2**[4] or dienophile **5**[7].



Scheme 2. Catalyzed reaction of nitroindole **1a** with diene **2**.

processes should thus proceed under milder conditions and be more compatible with sensitive substrates or cycloadducts, prone to rearomatization in the present case.

1. Nitroindole as electron-poor dienophile

In the presence of 20 mol% of the achiral Schreiner's thiourea **10**[11], we were pleased to note that the reaction of *N*-toluenesulfonyl-3-nitroindole **1a** and diene **2** could proceed at room temperature and ambient pressure. The NED cycloaddition was achieved in 24 h, leading, after NH₄F hydrolysis, to the formation of the dearomatized compounds **11a** and **11b** as a 67:33 mixture of cis/trans diastereomers (Scheme 2, Table 1, entry 1)[12]. As expected, the process, involving an enriched polarized diene bearing two oxy substituents with synergistic effects, proved to be totally regioselective. These mild thermal conditions prevented the rearomatization of the cycloadducts and allowed isolation of the corresponding tricyclic compound in 95% yield. This result highlights the efficiency of the thiourea catalysis that now allows the dearomatizing cycloaddition to take place in mild conditions, at room temperature and atmospheric pressure, even with acid sensitive substrates such as Danishefsky diene.

While high pressure activation leads to a 1:1 mixture of diastereomers, a slight enrichment in the cis diastereomer **11a**, arising from a preferred approach of the diene on the NO₂ side of the dienophile, is observed when thiourea **10** is employed[13].

The activation capability of thiourea **10** was evaluated by B3LYP/6-31+G** DFT calculations[14]. Comparison of the LUMO energy levels of *N*-methylsulfonyl-3-nitroindole (**1b**) computed as *N*-sulfonyl-3-nitroindole model and its complex with **10** indeed indicated a significant

energy decrease, from -2.78 eV to -4.00 eV, pointing the finger at a possible efficient reaction promotion (Fig. 1). In addition, the calculated O–H distances, of 2.08 Å, proved to be in the range of strong hydrogen bonds[15]. Moreover, this proximity between the substrates is encouraging for the development of an enantioselective process with chiral catalysts.

We next examined the stereoselectivity of the cycloaddition process with chiral thiourea catalysts (Fig. 2). Takemoto catalyst **12** and other cyclohexanediamine derived thioureas **13–14** were first considered[16]. Their influence on the course of the reaction was evidenced by the slight modifications observed in the diastereomeric ratios (Table 1, compare entries 1 and 2), without, however, inducing any enantioselectivity. Bis-thiourea **17**[17] led to a better endo/exo selectivity, but, here again, the catalyst did not allow facial differentiation (Table 1, entry 5). Due to

Table 1
Catalyzed cycloaddition of nitroindole **1a** with diene **2**.

Entry	Catalyst	d.r. ^a (e.e.) ^b
1	10	63:37
2	12	31(0):69(0)
3	13	62(2):38(2)
4	14	50(0):50(4)
5	17	28(4):72(4)
6	18	55(10):45(8)
7	19	50(2):50(0)
8	21	64(0):36(0)
9	22	33(0):67(0)
10	23	44(2):56(0)

^a Cis/trans ratio: determined by ¹H NMR on crude reaction mixtures.

^b Determined by HPLC analysis (Chiralcel AD(–)–heptane/*i*PrOH).

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