JOC Note

An Unexpected N-Heterocyclic Carbene-Catalyzed Annulation of Enals and Nitroso Compounds†

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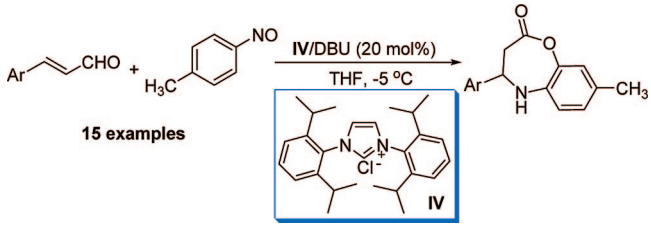

The N-heterocyclic carbene (NHC)-catalyzed annulation of enals with nitroso compounds in the presence of DBU in THF has been described. Unexpected seven-membered 4-azalactones were formed according to a process involving a 1,2-Bamberger-type rearrangement.

The carbon−nitrogen bond-forming reactions play an outstanding role in chemical transformations.[1] To date, the discovery of new catalytic methods for carbon−nitrogen bond formation still remains a challenge in the continuing development of efficient, sustainable chemical processes. In the past decade, the inversion of the classical reactivity (Umpolung) has provided unusual synthetic avenues for target molecules.[2] N-Heterocyclic carbenes (NHCs), due to their unique electronic characteristics, not only promote development of new organometallic processes,[3] but also act as Umpolung catalysts in organocatalytic reactions,[4] and as reagents in multicomponent coupling reactions.[5] The polarity reversal of carbonyl units generates carbonyl or acyl anions which represent a useful class of d^1-nucleophiles. Addition reactions involving this kind of acyl anions are called a^1-d^1 Umpolung which can be found in benzoin condensation[6] and the Stetter reaction.[7]

In contrast to the a^1-d^1 Umpolung, the NHC-catalytic Umpolung of α,β-unsaturated aldehydes generates d^3-nucleophiles which show homoenolate reactivity, and thus constitute an a^3-d^3 Umpolung. The first applications of the homoenolate intermediate involving the formation of γ-butyrolactones by the reaction of enals and aldehydes were reported by Glorius and Bode simultaneously.[8] Employing a similar strategy, Bode described NHC-catalyzed γ-lactam formation via direct annulation of enals and imine.[9] Scheidt disclosed the NHC-catalyzed amination of the d^3-nucleophiles with diazene to afford pyrazolidinones as a single regioisomer.[10] The formal [3+3] homoenolate cycloaddition with 1,3-dipoles such as azomethine imine and nitrone delivering bicyclic pyridazinone products and γ-amino ester derivatives respectively was also reported by Scheidt.[11] Ying reported the NHC-catalytic reaction of direct amidation of aldehyde with nitroso compounds for the synthesis of *N*-arylhydroxamic acids. They also reported NHC-catalyzed addition of α,β-unsaturated aldehydes to nitrosobenzene followed by an acid-catalyzed esterification of the intermediate

† Dedicated to Professor Dr. Richard A. Lerner on the occasion of his 70th birthday.

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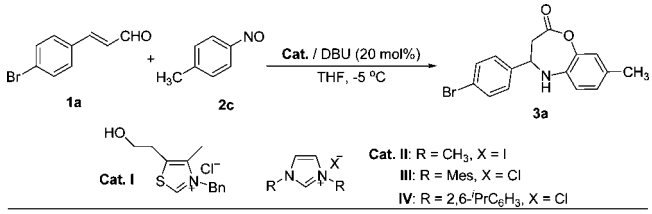
TABLE 1. Optimization of Annulation of Enal 1a and 4-Nitrosotoluene 2c[a]



entry	catalyst	solvent	base	yield[b] (%)
1	I	THF	DBU	ND[c]
2	II	THF	DBU	ND
3	III	THF	DBU	30
4	IV	THF	DBU	68
5	IV	DCM	*t*-BuOK	56
6	IV	DCM	DBU	42
7	IV	THF	*t*-BuOK	51
8	IV	toluene	DBU	53
9	IV	Et_2O	DBU	55
10[d]	IV	THF	DBU	42
11[e]	IV	THF	DBU	41

[a] Unless other specified, all of the reactions were carried out with **1a** (0.15 mmol, 1.5 equiv) and **2c** (0.10 mmol, 1.0 equiv) in the presence of 20 mol % of catalyst and base in solvent (0.5 mL) at −5 °C. [b] Isolated yields. [c] Not detected. [d] At room temperature (23 °C). [e] The ratio of **1a** and **2c** is 1.0:1.1.

leading to the N-PMP protected β-amino acid esters via 1,4-Bamberger-type rearrangement.[12]

Herein we report a NHC-catalyzed *annulation* of enals and 4-nitrosotoluene to afford unexpected seven-membered 4-azalactone derivatives by way of the intramolecular 1,2-Bamberger-type rearrangement.

Our studies began with an initial experiment of 4-bromocinnamaldehyde (**1a**) and 4-nitrosotoluene (**2c**) catalyzed by a NHC catalyst generated from imidazolium salts **III**. To our surprise, an unexpected seven-membered 4-azalactone **3a** was isolated. We then investigated the NHC-catalyzed enal-nitroso annulation by using different imidazolium and thiazolium salts. Thiazolium catalyst **I** did not afford the desired product; only trace amounts of undesired direct amidation products and azoxytoluene were observed (Table 1, entry 1). While bisalkyl imidazolium salts **II** proved to be unreactive (Table 1, entry 2), the N-heterocyclic carbenes generated in situ from bisarylimidazolium salts **IV** exhibited high catalytic activity toward 4-azalactone formation (Table 1, entry 4). And we were very pleased to find that the benzoin condensation, Stetter reaction, and homo addition of aldehyde to the Umpoled enal were sufficiently suppressed due to the high reactivity of the nitroso compounds.

Hence, we chose **IV** as the most promising catalyst to optimize the conditions. Further optimization of the reaction conditions revealed that the reaction temperature and ratio of reactants played critical roles in the reaction. Optimized reaction conditions were found when 1.5 equiv of 4-bromocinnamaldehyde (**1a**) and nitrosobenzene were added to catalyst **IV** and DBU at −5 °C in 0.2 M THF. This gave **3a** in 68% yield.

Under the optimized reaction conditions, we investigated the reaction of other nitroso compounds such as nitrosobenzene (**2a**) and 2-nitrosotoluene (**2b**). Our results are summarized in Table 2. The best yield (68%) was obtained when 4-nitrosotoluene

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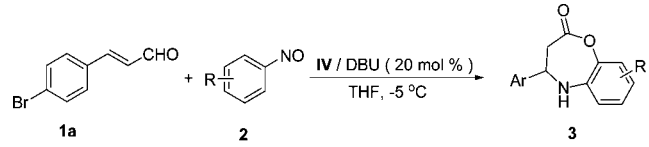
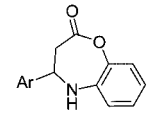
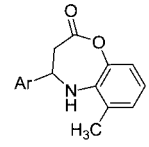
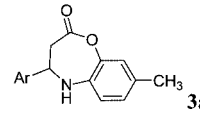
TABLE 2. NHC-Catalytic Annulation of Enal 1a and Nitroso Compounds[a]



entry	R	3	yield (%)[b]
1	H	 **3aa**	48
2	2-CH_3	 **3ab**	53
3	4-CH_3	 **3a**	68

[a] Unless otherwise specified, all of the reactions were carried out with **1a** (0.15 mmol, 1.5 equiv) and **2** (0.10 mmol, 1.0 equiv) in the presence of 20 mol % of catalyst and base in solvent (0.5 mL) at −5 °C. [b] Isolated yields.

was used (Table 2, entry 3). Annulation of 4-bromocinnamaldehyde with nitrosobenzene (**2a**) and 2-nitrosotoluene (**2b**) afforded the corresponding seven-membered 4-azalactones **3aa** and **3ab** in yields of 53% and 48%, respectively (Table 2, entries 1 and 2) and the X-ray crystal structure of **3ab** was shown in the Supporting Information. The more electron donating substituted nitroso compounds, for example, 4-methoxylnitrosobenzene, cannot proceed with reaction and just the starting enal was recovered due to the rapid formation of azoxy(methoxybenzene). The electron withdrawing substituted nitroso compounds such as 4-chloronitrosobenzene cannot give any of the product due to their poor reactivity.

Annulation of 4-bromocinnamaldehyde with nitrosobenzene (**2a**) and 2-nitrosotoluene (**2b**) afforded the corresponding seven-membered cyclic 4-azalactones **3aa** and **3ab** in yields of 53% and 48%, respectively (Table 2, entries 1 and 2).

It was observed that a variety of functionalized α,β-unsaturated aldehydes and 4-nitrosotoluene gave the respective substituted 4-azalactones in moderate to good yields under our reaction conditions. It was discovered that enal substrates with an electron-withdrawing substituent on the aromatic ring provide better results. Highest yield was obtained with 4-nitrocinnamaldehyde (Table 3, entry 7). It appeared that the position of the substituents on the aromatic rings also has an effect on the result (Table 3, entries 1, 4, and 5). We noticed that para-substituted α,β-unsaturated aldehydes gave higher yields than ortho- or meta-substituted α,β-unsaturated aldehydes. For example, 2-bromocinnamaldehyde gave a lower yield. Even the naphthyl, hetero aryl groups also participated in this process to give the expected products in good yields (Table 3, entries 9−11).

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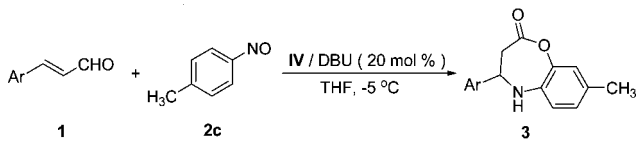
TABLE 3. NHC-Catalytic Annulation of Enals and 4-Nitrosotoluene[a]

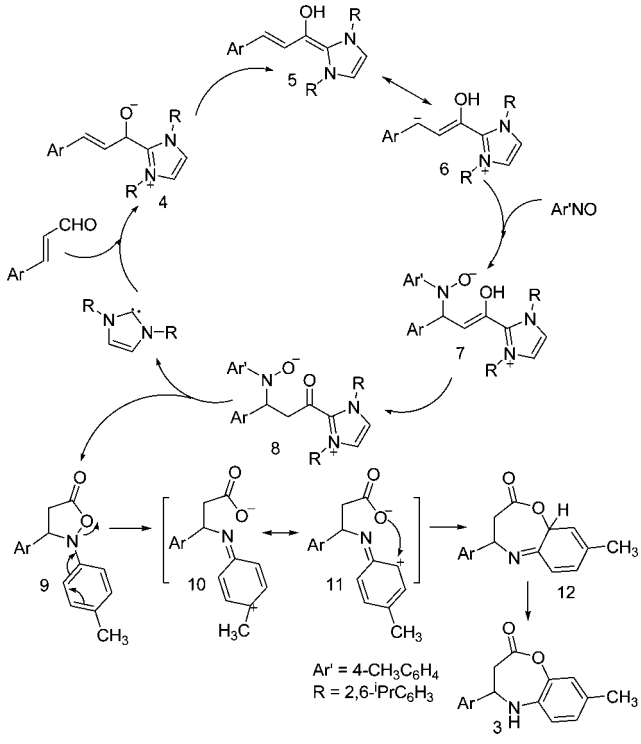


1 2c 3

entry	Ar	3	yield (%)[b]
1	4-BrC_6H_4	**3a**	68
2	4-ClC_6H_4	**3b**	69
3	4-FC_6H_4	**3c**	66
4	3-BrC_6H_4	**3d**	58
5	2-BrC_6H_4	**3e**	50
6	4-$CF_3C_6H_4$	**3f**	76
7	4- $O_2NC_6H_4$	**3g**	81
8[c]	2- $O_2NC_6H_4$	**3h**	71
9	1-naphthyl	**3i**	60
10	2-thienyl	**3j**	65
11	2-furyl	**3k**	64
12	C_6H_5	***3l***	55
13	4-$CH_3C_6H_4$	**3m**	45

[a] All of the reactions were carried out with **1a** (0.15 mmol, 1.5 equiv) and **2** (0.10 mmol, 1.0 equiv) in the presence of 20 mol % of **III** and DBU at −5 °C in THF (0.5 mL). [b] Isolated yields. [c] The reaction was carried out in 0.1 M THF.

SCHEME 1. Proposed Mechanism



For this unusual reaction outcome, we proposed the following mechanism (Scheme 1). The addition of imidazolin-2-ylidene to α,β-unsaturated aldehyde form a zwitterionic structure **4**, which can tautomerize to the conjugated Breslow intermediate **5**. The intermediate **5** can give rise to a more reactive homoenolate **6**. This in turn attacks the 4-nitrosotoluene as a d^3-nucleophile under formation of intermediate **7**. The tautomerization of **7** to the acylimidazolium **8** is followed by an intramolecular attack of the amino-oxygen atom at the carbonyl unit, which regenerates the catalyst and forms the five-membered isoxazolidinone **9**. Isoxazolidinone **9** then undergoes 1,2-Bamberger-type rearrangement to its presumably more stable form **3** instead of the 1,4-Bamberger rearrangement reported by Ying.[12a,13] This could be ascribed to the blocking of the 4-position on the nitroso compound, the steric hindrance for the oxygen atom to attack 4-position, and the instability of the corresponding 1,4-Bamberger-type rearrangement product. Thus, the carboxylate nucleophile prefers to attack the 2-position of the imino quinone intermediate **11** during the Bamberger-type rearrangement. The carboxyl oxygen atom attacks the 2-position of the phenyl ring affording the very reactive intermediate **12**, which is followed by the tautomerization to the desired product **3**. The mechanism also provides a possible explanation to the failure of annulation reaction involving electron withdrawing substitutents on nitroso compounds such as 4-chloronitrosobenzene: the positive charge may not be efficiently stabilized by the electron withdrawing group and the absence of stabilizing group of nitrosobenzene results in a lower yield to the 1,2-Bamberger-type rearrangement product.

In summary, we have developed a concise annulation of enals and 4-nitrosotoluene catalyzed by N-heterocyclic carbene affording the unexpected seven-membered 4-azalactones in moderate to high yields (up to 81%) and electron-withdrawing substituents on the aromatic ring of α,β-unsaturated aldehydes favor the annulation reaction. The mechanism involves a 1,2-Bamberger-type rearrangement to the unexpected outcome. N-Heterocyclic carbenes as organocatalysts represent a mine for new discoveries in preparative chemistry.

Experimental Section

4-(4-Bromophenyl)-4,5-dihydro-8-methylbenzo[*b*][1,4]oxazepin-2(3*H*)-one (3a). To a solution of 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**IV**, 8.5 mg, 0.02 mmol, 0.2 equiv) in THF (0.5 mL) was added DBU (3 μL, 0.02 mmol, 0.2 equiv). After the mixture was stirred for 5 min, (*E*)-3-(4-bromophenyl)acrylaldehyde (**1a**, 0.15 mmol, 1.5 equiv) and 4-nitrosotoluene (**2c**, 0.1 mmol, 1.0 equiv) were added. The mixture was then stirred at −5 °C. After the reaction was complete, the purification by flashed column chromatography on neutral aluminum oxide (eluent: *n*-hexane/ethyl acetate = 10:1) afforded the seven-membered 4-azalactone product (**3a**, 68% yield): white solid (mp 120−122 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 6.95 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 4.93 (t, J = 6.4 Hz, 1H), 3.41 (br, 1H), 2.94 (dd, J = 6.2 Hz, J = 12.7 Hz, 1H), 2.81 (dd, J = 6.7 Hz, J = 12.7 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (Cq, CO), 145.0 (Cq), 141.8 (Cq), 134.2 (Cq), 132.6 (Cq), 132.2 (CH), 127.9 (CH), 126.9 (CH), 122.8 (CH), 122.4 (Cq), 120.9 (CH), 62.9 (CH), 39.1 (CH_2), 20.8 (CH_3). HRMS (ESI) calcd for $C_{16}H_{14}{}^{79}BrNO_2$ + H, *m*/*z* 332.0286, found 332.0278.

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Supporting Information Available: Experimental procedure, characterization spectra, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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