Organic LETTERS

Letter

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Base-Free and Catalyst-Free Synthesis of Functionalized Dihydrobenzoxazoles via Vinylogous Carbonate to Carbamate Rearrangement

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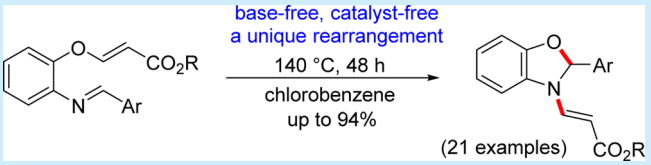
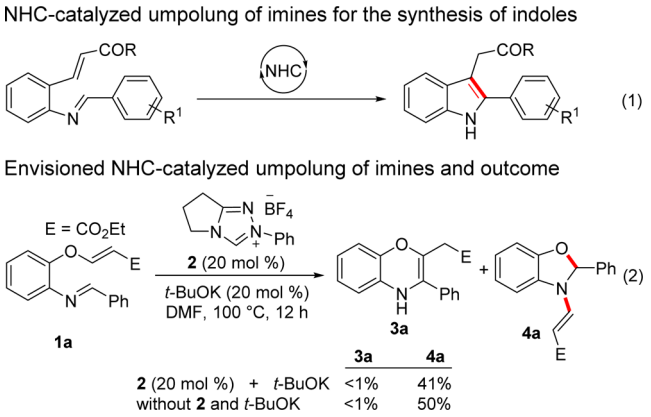
Supporting Information

ABSTRACT: An unexpected, catalyst-free, and base-free intramolecular cyclization of *N*-aryloxyacrylate aldimines, under thermal conditions leading to the synthesis of functionalized dihydrobenzoxazoles, is reported. The reaction features a unique rearrangement of vinylogous carbonates to vinylogous carbamates resulting in a new carbon−oxygen and carbon−nitrogen bond construction. The reaction tolerates a broad range of functional groups and the desired products are formed in moderate to good yields.



In an effort to expand the scope of N-heterocyclic carbene (NHC)-organocatalyzed transformations[1] beyond the umpolung of aldehydes[2] and Michael acceptors,[3] we have recently reported the NHC-catalyzed umpolung of aldimines for the synthesis of 2,3-disubstituted indoles (Scheme 1, eq 1).[4,5] As a part of this program to extend the substrate scope of NHC-catalyzed umpolung of imines, we envisaged that the NHC-catalyzed umpolung of *N*-aryloxyacrylate aldimine **1a** using the NHC generated from the triazolium salt **2** and using KO-*t*-Bu as the base could result in the formation of the benzoxazine derivative **3a**. Interestingly, this reaction did not afford the expected product **3a** but instead resulted in the formation of the dihydrobenzoxazole derivative **4a** in 41% yield (Scheme 1, eq 2). To our surprise, when the reaction was performed in the absence of **2** and KO-*t*-Bu, **4a** was formed in 50% yield. The benzoxazole derivative **4a** was possibly formed by the intramolecular nucleophilic addition of imine onto the vinylogous carbonate followed by a unique vinylogous carbonate to carbamate rearrangement. Herein, we report this base- and catalyst-free annulation of *N*-aryloxyacrylate aldimines to dihydrobenzoxazole derivatives.

Scheme 1. Reported and Envisioned NHC-Catalyzed Umpolung of Imines



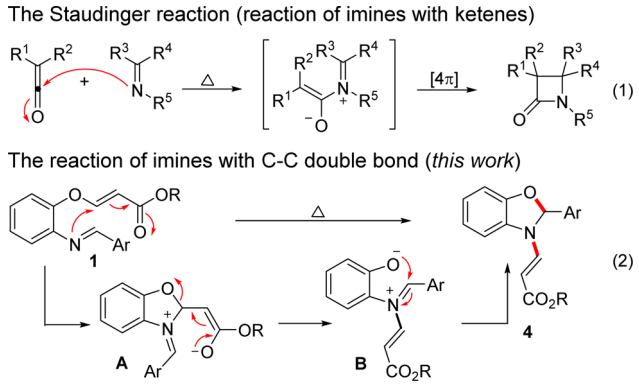
The nucleophilic reactivity of imines using the nitrogen center for the construction of carbon−nitrogen bonds is a convenient method for the synthesis of nitrogen heterocycles. Discovered in 1907, the Staudinger reaction employs the imines as nucleophiles (via the nitrogen center) to couple with ketenes for the synthesis of β-lactams.[6] Notably, recent experimental and computational studies on the mechanism of this reaction reveal that the addition of imines to ketenes is not concerted but stepwise (Scheme 2, eq 1).[7−9] Moreover, the imines having an α-hydrogen are nucleophilic via the carbon center, and this mode of reactivity is well-known in enamine catalysis.[10] The observed reactivity of imines in the present case prompted us to investigate this further. It is reasonable to believe that the imine **1** undergoes intramolecular nucleophilic attack on the carbon−carbon double bond generating the enolate **A**, which undergoes the carbon−oxygen bond-rupture to form the zwitterion **B** (Scheme 2, eq 2). Intramolecular cyclization of **B** could result in the formation of the dihydrobenzoxazole derivative **4**. It may be noted in this context that although the conjugate addition of carbon-centered nucleophiles to vinylogous carbonates is known, the related oxa- and aza-conjugate addition has received only scant attention.[11,12]

At the outset, the optimization of reaction conditions for this annulation reaction has been investigated. Treatment of the

Received: September 1, 2017

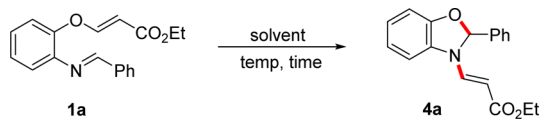
DOI: 10.1021/acs.orglett.7b02733
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Nucleophilic Reactivity of Imines via the N Center



aldimine **1a** in DMF for 12 h at 100 °C resulted in the formation of the dihydrobenzoxazole derivative **4a** in 50% yield (Table 1, entry 1). When the reaction was carried out in

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	time (h)	yield of **4a** (%)[b]
1	DMF	100	12	50
2	toluene	100	24	38
4	DMSO	140	48	<5
4	CH_3CN	140	36	55
5	chlorobenzene	100	24	62
6	*chlorobenzene*	*140*	*48*	*83*
7	chlorobenzene	140	60	74
8	chlorobenzene	140	36	77

[a]See the Supporting Information for the experimental details. [b]Isolated yield on a 0.5 mmol scale.

toluene, the yield of **4a** was dropped to 38%, whereas the reaction did not work at all when performed in DMSO (Table 1, entries 2 and 3). The use of CH_3CN furnished **4a** in 55% yield (Table 1, entry 4). Interestingly, the use of chlorobenzene as solvent at 100 °C improved the yield of **4a** to 62% (Table 1, entry 5). Increasing the reaction temperature to 140 °C enhanced the yield of **4a** to 83% (Table 1, entry 6). The reaction time of 48 h was found to be optimal and heating the reaction mixture for 60 and 36 h was not found to be beneficial (Table 1, entries 7 and 8).[13]

The compound **4a** was characterized using standard spectroscopic analysis. Finally, the structure of **4a** was confirmed, and the configuration of the vinylogous carbamate was found to be *trans* using single-crystal X-ray analysis (Figure 1).[14]

With the optimized reaction conditions in hand, we evaluated the substrate scope of this reaction (Scheme 3). A series of aldimines derived from aldehydes having electron-releasing and -withdrawing groups at the 4-position of the ring underwent smooth vinylogous carbonate to carbamate rearrangement leading to the synthesis of dihydrobenzoxazoles in 26–90% yield (**4a–h**). As expected, with strongly electron-withdrawing groups at the 4-position (CF_3 and NO_2), the yields of **4** are only moderate because of the reduced

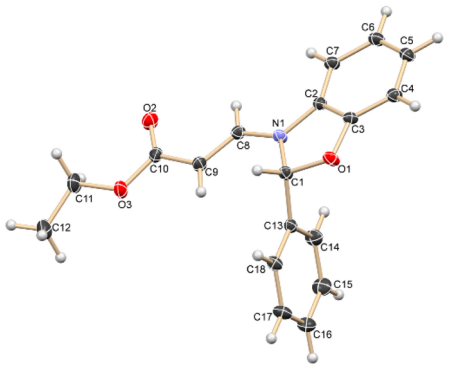
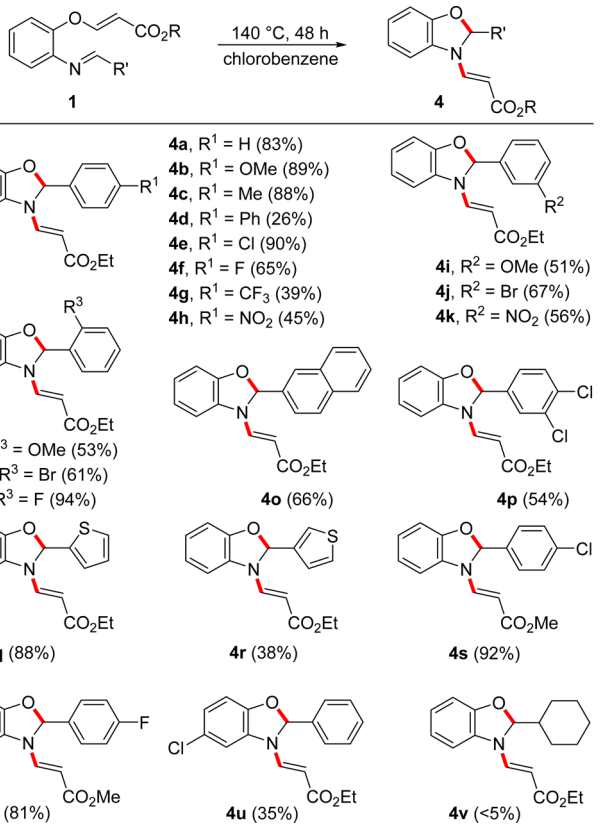


Figure 1. ORTEP diagram of **4a** drawn with 50% probability displacement ellipsoids.

Scheme 3. Substrate Scope of the Reaction[a]



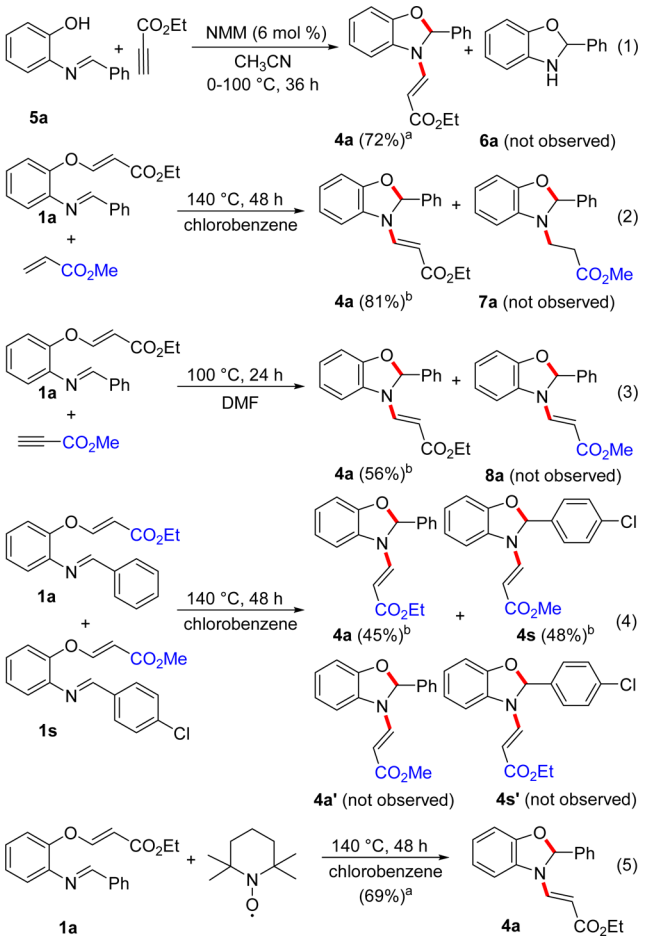
[a]Conditions: **1** (0.5 mmol) and chlorobenzene (2 mL) stirred at 140 °C for 48 h. Isolated yields of products are given.

nucleophilicity of the imines in these cases. Moreover, a variety of electronically dissimilar imines synthesized from aromatic aldehydes substituted at the 3-position and 2-position afforded the desired product in moderate to good yield (**4i–n**). In addition, the disubstituted aldehyde-derived imines as well as the imines synthesized from heterocyclic aldehydes furnished the expected products in moderate to good yields (**4o–r**). The reactions using the methyl ester instead of ethyl ester worked well (**4s,t**), and imines synthesized from 4-chloro 2-amino-phenol also resulted in the formation of the annulated product in moderate yield (**4u**). Disappointingly, the present annulation did not work with imines synthesized from aliphatic aldehydes (**4v**).[15,16]

DOI: 10.1021/acs.orglett.7b02733
Org. Lett. XXXX, XXX, XXX−XXX

A few experiments have been performed to gain insight into the mechanism of this transformation. Treatment of the imine **5a** with ethyl propiolate in the presence of catalytic amounts of *N*-methylmorpholine at 0 °C followed by heating at 100 °C in CH_3CN afforded the dihydrobenzoxazole **4a** in 72% yield without the formation of the dihydrobenzoxazole **6a** (Scheme 4, eq 1). This is equivalent of a one-pot reaction where the vinylogous carbonate **1a** was formed in situ. Since **6a** was not formed, this indicates that the reaction is not proceeding via the initial cyclization of **5a** followed by an aza-Michael addition to the ethyl propiolate. This also sheds light on the fact that a retro-Michael reaction of **1a** (generating the propiolate and phenoxide) followed by the cyclization is not operating in the present case.

Scheme 4. Studies toward the Mechanism of the Reaction*



*See the Supporting Information for details. [a]Isolated yield of **4a** [b]Yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

Moreover, when the reaction was performed under the optimized conditions in the presence of methyl acrylate, the product **4a** was formed in 81% yield and the formation of the related crossover product **7a** was not observed (Scheme 4, eq 2). This indicates that the vinylogous carbonate to carbamate rearrangement takes place in an intramolecular manner. This was also confirmed with the crossover experiment with methyl propiolate where the rearranged product **4a** was formed in 56% yield without the formation of the crossover product **8a** when the reaction was performed in DMF (Scheme 4, eq 3).

To gain insight into the intramolecular nature of this rearrangement, a crossover experiment was performed between substrates **1a** and **1s**. Mixing **1a** and **1s** under the present reaction conditions afforded the mixture of dihydrobenzoxazoles **4a** and **4s** in 45% and 48%, respectively (determined by ^{1}H NMR of the crude products).[13] The crossover products **4a′** and **4s′** are not formed under these conditions, indicating the intramolecular nature of the rearrangement (Scheme 4, eq 4). Moreover, to gain information on the possible involvement of radicals in the present annulation, an experiment was carried out in the presence of TEMPO (Scheme 4, eq 5). The formation of **4a** in 69% yield in the presence of TEMPO rules out the participation of radicals in this annulation reaction.

We also examined the kinetics of the present annulation reaction. It is interesting to note that only traces of **4a** was formed when quenched after 3 h (Figure 2). The reaction afforded 9% of **4a** after 6 h (determined by ^{1}H NMR of the crude products). At the end of 12 h, 28% of **4a** was formed.[13] The amount of **4a** formed increases with respect to time and at the end of 48 h, 83% of **4a** was formed. We also tried to get information on the unreacted imine **1a** at the given time. However, as part of the imine is breaking into the corresponding aldehyde and amine, we were not able to quantify the amount of imine recovered.

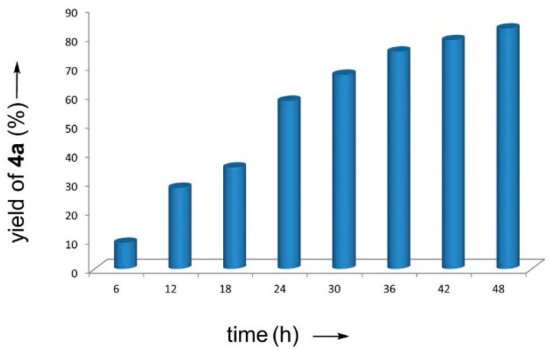


Figure 2. Kinetics of the reaction.

In conclusion, we have observed an unexpected intramolecular cyclization of *N*-aryloxyacrylate aldimines in an envisioned NHC-catalyzed umpolung of imines. This base- and catalyst-free reaction afforded dihydrobenzoxazoles in moderate to good yields and tolerates various functional groups. The reaction proceeds via a unique rearrangement involving vinylogous carbonates to vinylogous carbamates. Our preliminary mechanistic studies indicate that the vinylogous carbonate migration is intramolecular in nature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02733.

Details on experimental procedure, characterization, and NMR spectra of functionalized dihydrobenzoxazoles (PDF)

X-ray data of **4a** (CIF)

DOI: 10.1021/acs.orglett.7b02733
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Generous financial support by the Science and Engineering Research Board (SERB-DST), Government of India (Grant No. SR/S1/OC/12/2012), is kindly acknowledged. T.K.D. thanks CSIR and S.M. thanks UGC for senior research fellowships. We thank Dr. T. G. Ajithkumar and Dr. Udaya Kiran Marelli (both CSIR-NCL) for the excellent NMR support and Dr. B. Santhakumari (CSIR-NCL) for the HRMS data.

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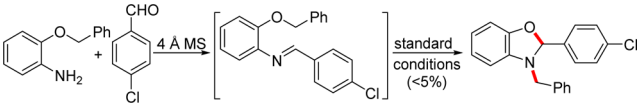
(13) For details, see the Supporting Information.

(14) CCDC 1568724 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For the details, see the Supporting Information.

(15) In an effort to extend this rearrangement to alkyl migration, we have synthesized the benzyl derivative and heated it under the optimized conditions. This reaction did not afford the rearranged product indicating that the present migration is limited to vinylogous carbonate to carbamate at present. For a related rearrangement, see: Fischer, G. W. *J. Prakt. Chem.* **1980**, *322*, 99.



(16) The attempted rearrangement of vinylogous thiocarbonate under the present conditions failed. Moreover, the present rearrangement is limited to vinylogous carbonates only, and the initial experiments using regular carbonates failed.

DOI: 10.1021/acs.orglett.7b02733
Org. Lett. XXXX, XXX, XXX−XXX