Enantioselective Synthesis of Functionalized Pyrazoles by NHC-Catalyzed Reaction of Pyrazolones with \(\alpha,\beta\)-Unsaturated Aldehydes

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Supporting Information

ABSTRACT: The N-heterocyclic carbene (NHC)-organocatalyzed enantioselective annulation reaction of pyrazolones with \(\alpha,\beta\)-unsaturated aldehydes proceeding via the chiral \(\alpha,\beta\)-unsaturated acyl azolium intermediates under oxidative conditions is presented. The reaction afforded dihydropyranone-fused pyrazoles in moderate to good yields and good ee values under operationally simple and base-free conditions.

Pyrazoles and their derivatives are an important class of heterocycles because of the ubiquity of these motifs in pharmaceutically and agriculturally relevant molecules. Among the functionalized pyrazoles, pyrazolones and pyranopyrazolones possess important biological properties. For instance, phenazone A is an antipyretic and analgesic drug, the pyranopyrazol-6-one derivative B is known to have analgesic and anti-inflammatory activities, and the pyrazole derivative of type C exhibits antiplatelet activity (Figure 1). Moreover, the pyranopyrazole of the type D is known to possess fungicide activity, the trifluoromethylated analogue E has AMPA receptor activity enhancer property, and the spirocyclic derivative F has antibacterial activity. Because of the excellent biological properties, synthesis of the functionalized pyrazole scaffolds is of great importance in synthetic chemistry.

Pyrazolones are excellent nucleophiles in various carbon–carbon bond-forming reactions, especially the Michael addition reactions. They can exist either in the carbonyl form or in the aromatic pyrazole form due to tautomerism. However, in solution, the pyrazolone form predominates. In spite of the widespread utility of pyrazolones as nucleophiles in organocatalysis, their application in N-heterocyclic carbene (NHC)-organocatalyzed transformations, to the best of our knowledge, is unknown. Notably, Scheidt and co-workers recently demonstrated the NHC-catalyzed reaction of enals with imidazolidinones leading to the enantioselective synthesis of imidazole-fused pyranones proceeding via a formal \([4 + 2]\) annulation. Moreover, Ye and co-workers disclosed the NHC-catalyzed enantioselective \([4 + 2]\) annulation of \(\alpha\)-chloroaldehydes with pyrazole-fused oxodienes. Herein, we report the NHC-catalyzed reaction of pyrazolones with \(\alpha,\beta\)-unsaturated aldehydes under oxidative conditions, and the reaction resulted in the enantioselective synthesis of dihydropyranone-fused pyrazoles in moderate to good yields and good ee values under mild conditions. The underlying principle was to generate the chiral \(\alpha,\beta\)-unsaturated acyl azoliums by the reaction of enals with NHCs under oxidative conditions pioneered by Studer and co-workers followed by subsequent reaction with pyrazolones.

The present studies were initiated by treating pyrazolone 1a with cinnamaldehyde 2a under the NHC-catalyzed conditions. After a brief survey of NHC precatalysts, bases, and solvents, we were delighted to find that the reaction of 1a with 2a in the presence of the oxidant 5 and the NHC generated from the chiral

Figure 1. Biologically active functionalized pyrazoles.
triazolium salt $\text{4}^{16}$ using Na$_2$CO$_3$ as the base resulted in the enantioselective synthesis of dihydropyranone-fused pyrazole $\text{3a}$ in 54% yield (based on $^1$H NMR spectroscopy) and excellent 98:2 er (Table 1, entry 1). The generation of chiral $\alpha$-$\beta$-pyrazolones moiety (Scheme 2). Pyrazolones with electron-rich and electron-donating groups at the $\alpha$-$\beta$-unsaturated aldehydes afforded the expected dihydropyranone-fused pyrazoles in good yields and er values ($3\text{a}$–$\text{f}$). Additionally, substitution at the meta-position as well as ortho-position of $\beta$-aryl ring of $\text{2}$ as well as disubstitution resulted in the smooth conversion to the product in good yield and good enantioselectivity ($3\text{g}$–$\text{i}$). Moreover, $\beta$-furyl enal underwent efficient annulation with pyrazolones furnishing the desired product $\text{3j}$ in 75% yield and 91:9 er. Notably, the er value of $\text{3j}$ was improved to >99.9:0.1 upon single crystalization in 2-propanol. The structure of $\text{3j}$ was further confirmed by single-crystal X-ray analysis.$^{24}$ Gratifyingly, various linear aliphatic $\alpha$-$\beta$-unsaturated aldehydes afforded the expected dihydropyranone-fused pyrazoles in good yields and er values ($3\text{k}$–$\text{m}$). Furthermore, extended conjugation at the $\beta$-position of enal did not affect the outcome of the reaction, and the target vinyl dihydropyranopyrazole was obtained in good yield and moderate er values ($3\text{n}$, $3\text{o}$).

We also investigated the variation on the 4-unsubstituted pyrazolones moiety (Scheme 2). Pyrazolones with electron-rich and electron-poor substituents on the para-position of the S-aryl ring readily afforded the desired pyrazoles in good yield and er values ($3\text{p}$–$\text{r}$). Moreover, methoxy substitution at the ortho- and meta-positions of the S-aryl ring were tolerated ($3\text{s}$,$\text{t}$). In addition, alkyl substitution at the S-position of $\text{1}$ also furnished the expected products ($3\text{u}$,$\text{v}$). It may be noted that the 5-tert-butyl-substituted pyrazolone afforded the product $\text{3u}$ in 75% yield but in moderate er of 87:13. Moreover, it was found that the tert-butyl group at the 2-position of pyrazolone $\text{1}$ was found to be crucial for good reactivity and selectivity.

When the NHC-catalyzed reaction of pyrazolone $\text{1a}$ was carried out using a $\beta$-$\beta$-substituted enal (citril, $\text{2p}$), the expected pyranone-fused pyrazole $\text{3w}$ was isolated in a high yield of 93% and a poor er of 62:38 (eq 1). The er value was not improved when the reaction was carried out at low temperature and in different solvents. The high reactivity in this case is an indication

### Table 1. Optimization of the Reaction Conditions$^{4*}$

<table>
<thead>
<tr>
<th>entry</th>
<th>variation of the standard conditions$^{4*}$</th>
<th>yield of $\text{3a}$ (%)</th>
<th>er of $\text{3a}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>54</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>mesitylene instead of toluene</td>
<td>50</td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td>xylene instead of toluene</td>
<td>49</td>
<td>98:2</td>
</tr>
<tr>
<td>4</td>
<td>THF instead of toluene</td>
<td>45</td>
<td>92:7</td>
</tr>
<tr>
<td>5</td>
<td>DABCO instead of Na$_2$CO$_3$</td>
<td>54</td>
<td>97:4</td>
</tr>
<tr>
<td>6</td>
<td>DMAP instead of Na$_2$CO$_3$</td>
<td>55</td>
<td>97:3</td>
</tr>
<tr>
<td>7</td>
<td>DIPEA instead of Na$_2$CO$_3$</td>
<td>63</td>
<td>96:5</td>
</tr>
<tr>
<td>8</td>
<td>Li$_2$CO$_3$ instead of Na$_2$CO$_3$</td>
<td>65</td>
<td>97:3</td>
</tr>
<tr>
<td>9</td>
<td>no base</td>
<td>55</td>
<td>98:2</td>
</tr>
<tr>
<td>10</td>
<td>no base, 1.5 equiv of $\text{1a}$</td>
<td>82 (81)</td>
<td>98:2</td>
</tr>
</tbody>
</table>

$^{4*}$Standard conditions: $\text{1a}$ (0.125 mmol), $\text{2a}$ (0.125 mmol), $\text{4}$ (5.0 mol %), Na$_2$CO$_3$ (10.0 mol %), $\text{5}$ (1.0 equiv), toluene (2.0 mL), 25 °C and 12 h. $^\circ$Yields were determined by $^1$H NMR analysis of crude products. $^\u200b$Determined by HPLC analysis on a chiral column.

unsaturated aldehydes from oxidized substrates such as ynal$^{17}$ and 2-bromoaldehydes$^{18}$ (with a view to avoid the use of stoichiometric oxidant $\text{5}$) was tested but resulted in poor conversion to $\text{3a}$ (not shown in Table 1). The solvent optimization studies revealed that nonpolar solvents such as mesitylene and xylene resulted in comparable selectivity but with poor yield (entries 2 and 3), whereas THF resulted in reduced selectivity and yield (entry 4). An extensive base screening revealed that bases like DABCO, DMAP, DIPEA, and Li$_2$CO$_3$ furnished the desired product in similar yields and selectivities as compared to Na$_2$CO$_3$ (entries 5–8). Surprisingly, the reaction afforded the product $\text{3a}$ in the same yield and selectivity in the absence of base (entry 9).$^{19}$ In this case, it is reasonable to believe that the chloride counterion in $\text{4}$ acts as a base in generating traces of free NHC, which immediately reacts with $\text{2a}$ to begin the catalytic cycle.$^{20,21}$ Finally, increasing the amount of pyrazolone $\text{1a}$ to 1.5 equiv improved the yield of $\text{3a}$ to 82% with 98:2 er (entry 10).$^{25}$ It is important to note in this context that the condensation product between $\text{1a}$ and $\text{2a}$ was not observed under the optimized conditions.$^{23}$

After optimizing the reaction conditions, we examined the substrate scope of this NHC-catalyzed annulation reaction (Scheme 1). First, tolerance of this reaction with various $\alpha$-$\beta$-unsaturated aldehydes has been tested. The unsubstituted cinnamaldehyde worked well, and various electron-donating and -withdrawing groups at the para-position of the $\beta$-aryl ring were well tolerated, leading to synthesis of dihydropyranone pyrazolones in moderate to good yields and with good er values ($\text{3a}$–$\text{f}$). Additionally, substitution at the meta-position as well as ortho-position of $\beta$-aryl ring of $\text{2}$ as well as disubstitution resulted in the smooth conversion to the product in good yield and good enantioselectivity ($\text{3g}$–$\text{i}$).
of the probable 1,2-addition of 1a to the α,β-unsaturated acyl azolium intermediate formed from 2p and 4.25

The reaction of pyrazolones with α-substituted enals did not afford the expected dihydropyranone-fused pyrazoles under the present reaction conditions (Scheme 3). Moreover, the reactions performed using nucleophiles such as oxazolones26 and α-angelica lactone instead of pyrazolone was also unsuccessful.

A tentative mechanism for this NHC-catalyzed annulation reaction of enals and pyrazolones is shown in Scheme 4. Initially, the free NHC will be generated with the aid of the chloride counterion20,21 or using the pyrazolone 1, which upon nucleophilic 1,2-addition to enal 2 will generate the nucleophilic Breslow intermediate G.27 The enaminol G is subsequently transformed into the key α,β-unsaturated acyl chloride counterion3,21 or using the pyrazolone 1, which upon nucleophilic 1,2-addition to enal 2 will generate the nucleophilic Breslow intermediate G.27 The enaminol G is subsequently transformed into the key α,β-unsaturated acyl azolium intermediate H in the presence of oxidant 5. Nucleophilic addition of 1 to H can proceed in a 1,4-fashion13a,15b or in a 1,2-pathway.13m−o The 1,4-addition can directly generate the enol intermediate I. Considering the minor amount of 3-hydroxypryrazole form of 1 in solution, a 1,2-addition of 1 to H can also be invoked. This can generate the hemiacetal intermediate J, which can undergo a [3,3] sigmatropic rearrangement to furnish I. The intermediate I undergoes proton transfer generating the acyl azolium intermediate K, and an intramolecular acylation resulted in the formation of the desired product 3 with the release of free carbene.

In conclusion, we have developed a mild and base-free enantioselective annulation protocol for the NHC-catalyzed reaction of pyrazolones to enals. This reaction furnished diverse dihydropyranone-fused pyrazoles in good yield and selectivity with broad substrate scope. Given the pharmaceutical and agricultural importance of functionalized pyrazoles, the method presented herein is a feasible procedure for the synthesis of these compounds.

ASSOCIATED CONTENT

Supporting Information

Details on experimental procedures, characterization data of all compounds, HPLC data of dihydropyranone-fused pyrazoles, and single-crystal X-ray data of 3j. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) For recent reviews on NHC catalysis, see: (a) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. Nature 2014, 510, 485.

(11) It is also likely that the pyrazole 1a could act as a base to generate the free carbene in solution.

(13) It is also probable that the chloride ion could add to the αβ-unsaturated acylazolium in a hetero-Michael addition to generate a transient enolate. This enolate could then act as a base for generating free loadings of NH, which will immediately add to also be the starting carbonyl reactant.

(14) For details, see the Supporting Information.

(15) Simple mixing of 1a with 2a in THF at 25 °C resulted in the formation of the condensation products (trisubstituted pyrazolone) in 91% yield.

(16) CCDC-1029784 (3) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) For a report on the reaction of αβ-unsaturated acylazolium generated from related enals, see ref 15m.


(19) For the seminal report on this umpolung concept, see: Breslow, R. J. Am. Chem. Soc. 1958, 80, 3719.