Nickel-Catalyzed Oxidative Cyclotrimerization of α-Amino Ketones: Selective Synthesis of Pyrazoles

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Abstract: A new strategy for the synthesis of 3-methylene-2,3-dihydro-1H-pyrazoles is presented by Ni-catalyzed oxidative cyclotrimerization of α-amino ketones. This unprecedented method allows three α-amino ketones to undergo sequential multiple deprotonations and deamination through two C–C bonds and one N–N bond formation cascade.

Key words: nickel, oxidation, cyclotrimerization, α-amino ketones, pyrazoles

The functionalization of α-amino carbonyl compounds is one of the most important tasks for biochemists or synthetic chemists because the α-amino carbonyl motif is a ubiquitous structural component of multitudinous natural products and biomolecules.1,2 Despite the impressive progress in the field, the functionalization of α-amino carbonyl compounds remains challenging due to the presence of some highly reactive functional groups in them, such as an active α-C–H bond, a free N–H bond and a carbonyl group, often resulting in some competing reactions. To our knowledge, however, a method using the three functional groups for constructing new chemical bonds in one reaction has not been established.

Pyrazoles are important structural units found in numerous pharmaceuticals, agricultural chemicals and functional materials as well as valuable synthetic intermediates in organic synthesis.3 Many elegant methods have been developed for their synthesis,4–8 including, (i) the cyclocondensation of hydrazines with 1,3-dielectrophiles (1,3-dicarbonyl compounds or α,β-unsaturated aldehydes and ketones),5 (ii) the intermolecular 1,3-dipolar cycloaddition of diazoalkanes and nitrilimines with unsaturated compounds (such as alkenes or alkynes), and (iii) the introduction of substituents onto a pre-existing aromatic ring (often onto the nitrogen atom).7 However, these methods suffer from the poor reactivity, somewhat limited substrate scope, and the potential hazardousness and deamination of the substrates; moreover, regio- and chemoselectivity are usually unsatisfactory in many cases. Therefore, the development of new strategies for the synthesis of functionalized pyrazoles is highly desirable. Herein we report a novel route to prepare pyrazoles by Ni-catalyzed oxidative cyclotrimerization of α-amino arylketones wherein sequential multiple C–H bonds cleavage, deamination and carbonyl isomerization take place to simultaneously form three C–C bonds and one N–N bond (Scheme 1).8,9

Our investigation began with the reaction of 1-phenyl-2-(phenylamino)ethanone (1a) to optimize the reaction conditions (Table 1). Gratifyingly, substrate 1a could undergo cyclotrimerization with NiCl2 in CH2ClCH2Cl at 80 °C, providing the desired product 2a in 28% yield (entry 1). Encouraged by the results a number of other Ni catalysts were examined (entries 2–6). Extensive screening revealed that (C5H5)Ni(II)Cl(PPh3) displayed the highest catalytic reactivity (entry 5). It is noteworthy that Ni(PPh3)3, a zerovalent Ni catalyst, also effected the reaction (entry 6). Interestingly, benzoic acid was found to favor the reaction: The yield of 2a was enhanced to 75% when one equivalent PhCO2H was added (entry 7). In light of the results, a series of other organic acids were subsequently evaluated (entries 8–11). While 4-cyanobenzoic acid could improve the reaction, the other acids, 4-methoxybenzoic acid, AcOH and PivOH, lowered the yield slightly. Gratifyingly, good yield was still achieved under O2 atmosphere (entry 12). However, substrate 1a was found to be inert under argon atmosphere (entries 13 and 14) as well as in the absence of Ni catalysts (entry 15).

Scheme 1 Synthesis of pyrazoles
The structure of 2a was unambiguously confirmed by the single-crystal X-ray diffraction analysis. As shown in Scheme 2, the above cyclotrimerization protocol was found to be applicable to a diverse range of α-amino arylketones 1 in the presence of (C₅H₅)Ni(II)Cl(PPh₃), PhCO₂H and air. Initially, a variety of 2-(substituted arylamino)-1-phenylethanones were investigated under the optimal conditions (products 2b–g): several substituents, such as Me, MeO, Cl and F, on the aryl ring of the arylamino moiety were tolerated well. Methyl-substituted substrates 1b–d, for instance, were successfully cyclotrimerized in moderate yields, and the reactive order was found to be para > meta > ortho (products 2b–d). Importantly, functional groups F and Cl were compatible with the optimal conditions, thereby facilitating additional modifications at the halogenated positions (products 2f, 2g, 2j, 2m, 2r and 2s). It is noteworthy that 2-amino-1-p-tolylenethanones 1b–k with an aryl group, such as Ph, 4-MeOC₆H₄, 4-ClC₆H₄ or 2,3-dihydro-1H-inden-5-yl group, on the amino moiety successfully underwent the cyclotrimerization in the presence of (C₅H₅)Ni(II)Cl(PPh₃), PhCO₂H and air (products 2h–k).

We next set out to examine the effect of substituents on the aryl group of the 1-arylethanone moiety under the optimal conditions (products 21–s). The results disclosed that a number of substituents, including MeO, Cl, CN, and CF₃, displayed reactivity for the reaction, but the electron-donating groups were superior to the electron-withdrawing groups (products 21–o). Using substrates with the electron-withdrawing groups, however, the selectivity was

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**Table 1** Screening Optimal Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ni]</th>
<th>Additive</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl₂</td>
<td>–</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>NiBr₂</td>
<td>–</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>NiCl₂(dppe)₂</td>
<td>–</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂(PCy₃)₂</td>
<td>–</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>–</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>Ni(PPh₃)₄</td>
<td>–</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>PhCO₂H</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>p-MeO₆C₄H₄CO₂H</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>p-CNC₆H₄CO₂H</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>AcOH</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>PyrOH</td>
<td>43</td>
</tr>
<tr>
<td>12b</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>PhCO₂H</td>
<td>74</td>
</tr>
<tr>
<td>13c</td>
<td>(C₅H₅)Ni(II)Cl(PPh₃)</td>
<td>PhCO₂H</td>
<td>trace</td>
</tr>
<tr>
<td>14c</td>
<td>Ni(PPh₃)₄</td>
<td>PhCO₂H</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>–</td>
<td>PhCO₂H</td>
<td>0</td>
</tr>
</tbody>
</table>

| a | Reaction conditions: 1a (0.3 mmol), [Ni] (5 mol%), additive (1 equiv) and 1,2-dichloroethane (2 mL) at 80 °C for 12 h under air atmosphere. (C₅H₅)Ni(II)Cl(PPh₃) = [chloro(cyclopentadienyl)(triphenylphosphine)nickel(II)]. Aniline (3a) was observed by GC–MS analysis. b The reaction was carried out under O₂ atmosphere. c The reaction was carried out under argon atmosphere.

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shifted toward dimerization as the major reaction. For example, treatment of substrate 1a with a CN group with \((C_5H_5)Ni(II)Cl(PPh_3)\), PhCO_2H and air provided the corresponding dimerization product 4n in 55% yield. We are pleased to disclose that naphthalen-1-ylketone (1p) underwent the cyclotrimerization smoothly to offer the desired product 2p in 65% yield. Notably, heterocycle-containing substrate, 2-(phenylamino)-1-(thiophen-2-yl)ethanone (1q), was also suitable for the reaction, thereby making this methodology more useful for the preparation of pharmaceuticals and natural products. The reaction of diCl-substituted substrate 1r also proceeded smoothly, albeit in 30% yield (product 2r). In the presence of \((C_5H_5)Ni(II)Cl(PPh_3)\), PhCOOH and air, substrate 1s with a Me group and a F group in different aryl rings furnished the desired product 2s in moderate yield. However, ethyl 2-(phenylamino)acetate (1t), 2-aminophenylethanone (1u) and 1-(phenylamino)propan-2-one (1v) resulted in no detectable cyclotrimerization products.

The obtained pyrazole 2a was employed to synthesize diheterocycle 5a (equation 1 in Scheme 3). In the presence of KBH_4, \((Z)-3\)-benzylidene-1,2,4,6-tetraphenyl-2,3,4,6-tetrahydro-1H-furo[3,4-c]pyrazole (5a) was prepared in 59% yield, which is a structural unit found in some bioactive molecules.

During the reaction of substrate 1a, imine 6a as a side-product was observed by in situ GC–MS analysis. Indeed, imine 6a could be cyclotrimerized leading to product 2a in the presence of Ni catalyst, such as \((C_5H_5)Ni(II)Cl(PPh_3)\), Ni(cod)$_2$ or Ni(Ph$_3$)$_4$, albeit with lower activity of the latter two Ni catalysts (equation 2 in Scheme 3), suggesting that this present cyclotrimerization reaction may proceed via the first generation of an imine intermediate 6a.

Notably, the results in Table 1 also disclosed that without either air or Ni catalysts the cyclotrimerization reaction of substrate 1a could not take place even in the presence of PhCO_2H (entries 13 and 14 in Table 1). These suggest that Ni complex is the real catalyst, and PhCO_2H is only used to promote the reaction.

Consequently, two possible mechanisms outlined in Scheme 4 are proposed on the basis of the results described above and by the in situ HRMS analysis data (Schemes S1 and S2, and Figures S1 and S2 in Supporting Information). Initially, substrate 1a may proceed via two pathways, one is directly transferred into intermediate A with the aid of the Ni\(^{II}/[O]\) system, and the other includes the formation of imine 6a in the presence of Ni\(^{II}\) and air, followed by reaction of imine 6a with Ni\(^{II}\) and [O] to afford the intermediate A. Dimerization of the intermediate A with a molecule of imine 6a offers intermediate B, followed by a hydride shift which furnishes the intermediate C. Intermediate D is achieved by insertion of Ni into the C–N bond in intermediate C. The third molecule of imine 6a is used to react with intermediate D with the aid of acid, providing intermediate E. Isomerization of intermediate E affords intermediate F. Finally, reductive elimination and dehydroxylation reaction of intermediate F produces the desired product 2a. To rule out a radical process for the current reaction, a control experiment using a radical scavenger (TEMPO) was carried out: a sto-
The chemically active amount of TEMPO (1 equiv) had no effect on the reaction.

In summary, we have described a new route to polysubstituted 3-methylene-2,3-dihydro-1H-pyrazoles via Ni-catalyzed oxidative cyclotrimerization of α-amino carbonyl compounds, which utilizes three highly reactive functional groups, the active α-C-C bond, the free N-H bond and the carboxyl group, in α-amino carbonyl compounds to construct three new chemical bonds: two C–C bonds and one N–N bond. Importantly, this method employs accessible α-amino carbonyl compounds as the starting materials, which facilitates introduction of the α-amino carbonyl units into pyrazoles and makes the obtained pyrazole compounds more useful with some special complex bioactivities. Applications of this new Ni-catalyzed transformation in organic synthesis are currently underway in our laboratory.

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Supporting Information
This article is available online at http://www.thieme-connect.com/ejournals/toct/synlett.

Reference and Notes


Although few papers on the synthesis of tetrastubstituted pyrazoles from the Cu-mediated reaction of enamines with nitriles have been reported, Ni-catalyzed oxidative cyclotrimerization of α-amino arylketones is a promising route to access tetrasubstituted pyrazoles (11).

A typical experimental procedure for the Ni-catalyzed oxidative cyclotrimerization of α-amino arylketones is as follows (10).

1. To a Schlenk tube were added α-amino arylketones (0.3 mmol), (C5H5)Ni(II)Cl(PPh3) (5 mol%), PhCOOH (1 equiv) and DCE (CH2Cl2, 2 mL). Then the tube was sealed under air and stirred at 80 °C (the temperature of the heating bath) for the indicated time until complete consumption of the starting material as monitored by TLC and GC–MS analysis. After the reaction was finished, the reaction mixture was diluted with Et2O, filtered by a short crude silica gel column and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane–EtOAc) to afford the desired product 2.

(Z)-5-Benzylidene-1,2-diphenyl-2,5-dihydro-1H-pyrazole-3,4-diylbis(phenylmethanone) (2a): Yellow solid: 38.9 mg, 75% yield; mp 190.2–191.5 °C (uncorrected). 1H NMR (500 MHz, CDCl3): δ = 8.11 (d, J = 7.4 Hz, 1 H), 7.47 (t, J = 7.7 Hz, 1 H), 7.21–7.32 (m, 13 H), 7.09 (td, J = 7.3, 4.0 Hz, 7 H), 6.92–6.95 (m, 2 H), 6.59–6.62 (d, J = 8.5 Hz, 2 H). 13C NMR (125 MHz, CDCl3): δ = 191.9, 186.3, 144.0, 139.1, 138.7, 136.8, 132.6, 132.5, 131.4, 131.2, 130.9, 129.2, 128.7, 128.1, 127.9, 127.7, 127.5, 127.4, 127.0, 126.9, 126.8, 126.6, 125.3, 122.8, 120.0, 114.2. IR (neat): 1715, 1595, 1445, 1363, 1223, 958, 804, 736, 690 cm⁻¹. LRMS (EI, 70 eV): m/z (%) = 518 [M⁺] (100), 295 (94). HRMS (ESI): m/z [M + H⁺] calecd for C30H26NO2: 519.2067; found: 519.2089.

2. To our knowledge, only one paper has been reported on the formation of the N–N single bond oxidative strategy, in which 1.5–6 equiv of Cu(OAc)2 were used as both a Lewis acid activator and as an oxidizing agent, and also a Cu/air (2) strategy, in which 1.5–6 equiv of Cu(OAc)2 were used as both a Lewis acid activator and as an oxidizing agent, and two new bonds, a C–C bond and a C–N bond, were formed; see: Neumann, J. J.; Suri, M.; Glorius, F. Angew. Chem. Int. Ed. 2010, 49, 7790.