One-pot synthesis and crystal structure of an unusual amidine derived from heterocyclic ketene aminal derivative

Abstract: One-pot reaction of Meldrum’s acid (1) and heterocyclic ketene aminal (HKA, 2) in acetone affords an unusual amidine HKA derivative 4. The reaction catalysts were optimized and it was found that L-proline is the best catalyst for the one-pot reaction. The mechanism is discussed. The structure of compound 4 was determined by single crystal X-ray analysis.

Keywords: amidine; catalyst; crystal structure; heterocyclic ketene aminal (HKA); ketene aminals; synthesis.

Heterocyclic ketene aminals (HKAs) are versatile synths in organic chemistry [1]. Owing to the conjugation of the amino group and the electron-withdrawing group, the nucleophilicity of α-carbon is highly enhanced. As the amino group can serve as the second nucleophilic center, HKAs are often used to react with bis-electrophiles to construct fused heterocycles [2–6]. HKAs are reported to undergo aza-ene reaction, regiospecific alkylation, regiospecific acylation, regiospecific glycosylation, addition reaction with 1,3-dipolar reagents [1] and more recently the addition with allenic esters affording fused pyridones [4].

Multicomponent reactions (MCRs) are usually defined as one-pot reactions in which at least three starting materials react to form a product, incorporating essentially all of the atoms of the reactants [7]. Owing to their inherent character, MCRs have the capabilities to produce a large amount of highly complex molecules in a time- and cost-effective manner compared with linear synthesis, thus gaining importance in synthetic organic chemistry, especially in the pharmaceutical industry.

We have been interested in MCRs of HKAs and have previously developed an efficient synthesis of tetrahydropyridinone-fused 1,3-diazaheterocycles by a three-component reaction of HKAs, Meldrum’s acid and aldehydes [8] (Scheme 1). Both aromatic and aliphatic aldehydes work well in this reaction. We wondered whether ketones could also be used as starting materials. Thus, the feasibility of employing ketones in the reaction was investigated.

The one-pot reaction of Meldrum’s acid 1, HKA 2 and acetone in the presence of triethylamine as catalyst was studied. The reaction was carried out at 50–60°C and was monitored by thin layer chromatography. The reaction proceeded slowly and only after 6 days of reflux afforded the product 4 in 45% yield (Scheme 2). To improve the yield of 4, we optimized the reaction conditions and the results are shown in Table 1. It was found that the use of L-proline as a catalyst provides the best yield of 57% after 5 days of reflux.
Table 1 Reaction conditions for the synthesis of compound 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (amount)</th>
<th>Reaction time (days)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N (0.1 eq)</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>Morpholine (0.1 eq)</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>Morpholine/acetic acid (0.1 eq)</td>
<td>5</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>L-Proline (0.1 eq)</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>L-Proline (0.5 eq)</td>
<td>5</td>
<td>36</td>
</tr>
</tbody>
</table>

The structure of 4 was confirmed by IR, NMR, MS, elemental analysis and X-ray single crystal diffraction experiment. Interestingly, compound 4 exists exclusively as the amidine, but not in the enamine form. It is worth noting that in terms of amidine and enamine tautomerization, most HKA derivatives adopt the enamine form. For example, the structure of a similar enamine compound has been reported earlier by the Huang group [9].

The suggested mechanism of this one-pot reaction is depicted in Scheme 3; it is similar to the mechanism reported previously for the analogous reaction employing aldehydes [8]. The reaction starts with the condensation of Meldrum’s acid with acetone. The resulting alkylidene Meldrum’s acid A undergoes the aza-ene reaction with HKA 2 to form adduct B. The adduct B undergoes intramolecular cyclocondensation followed by decarboxylation to afford the final product 4.

The crystal structure of compound 4 is shown in Figure 1. The X-ray structural analysis is in agreement with the assignment of the structure from spectroscopic data. The bond length of N3-C7 is 1.271 Å, which is a typical value for a double bond and the bond length of C7-C11 is 1.513 Å, which is typical for a single bond. These results demonstrate that compound 4 in the solid state exists in the amidine form.

Experimental

NMR spectra were measured in CDCl₃ on a Bruker AV300 magnetic resonance spectrometer. IR spectrum was recorded on a JASCO FT/IR-480 spectrometer. Mass spectrum was recorded on an AEI MS-0 instrument. Elemental analysis was performed on a VarioEL III elementary analysis device. Melting point was measured on an X-4 melting point apparatus and is uncorrected. The substrate HKA 2 was prepared according to literature procedure [10].

9-Benzoyl-8,8-dimethyl-2,3,4,7,8,9-hexahydro-6H-pyrido[1,2-a]pyrimidin-6-one (4)

To a stirred solution of 404 mg (2.0 mmol) of compound 2 and 375 mg (2.6 mmol) of Meldrum’s acid in 20 mL of dried acetone was...
added a basic catalyst. The mixture was heated under reflux for 5 or 6 days (Table 1). Then the solvent was removed and the residue was chromatographed on silica gel using ethyl acetate as eluent to afford product 4: mp 144–145°C; IR (KBr): ν<sub>max</sub> 2954, 1683, 1628, 1289, 995 cm<sup>-1</sup>; 1H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.94 (s, 3H), 1.18 (s, 3H), 1.71–1.93 (m, 2H), 2.35 (dd, J = 1.5 Hz, 17.4 Hz, 1H), 2.98 (d, J = 17.4 Hz, 1H), 3.43 (t, J = 5.4 Hz, 2H), 3.77 (m, 2H), 4.46 (d, J = 0.6 Hz, 1H), 5.55 (m, 3H), 8.03–8.06 (m, 2H); 13<sup>C</sup> NMR (75 MHz, CDCl<sub>3</sub>): δ 20.8, 26.8, 28.9, 32.4, 39.6, 42.6, 45.3, 57.9, 128.8, 128.9, 133.6, 137.7, 150.2, 169.7, 198.7; MS (EI): m/z (%) 284 (M<sup>+</sup>, 3), 256 (21), 241 (100), 105 (17).

Crystal data for compound 4

C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>, monoclinic, space group P2<sub>1</sub>/c, a = 11.2812(8), b = 15.3887(6), c = 9.4273(6) Å, β = 111.535(8)<sup>°</sup>, V = 1522.36(15) Å<sup>3</sup>, Z = 4, T = 293 K, d<sub>calc</sub> = 1.261 g cm<sup>-3</sup>, µ (Mo Kα) = 0.082 mm<sup>-1</sup>, 5410 data collected up to θ<sub>max</sub> = 25.01 (R<sub>int</sub> = 0.0542, R<sub>ref</sub> = 0.0636); final R-indices for 2686 reflections with I > 2σ(I) and 192 refined parameters are: R<sub>1</sub> = 0.0542, wR<sub>2</sub> = 0.1780.

Crystallographic data for compound 4 have been deposited with the Cambridge Crystallographic Data Centre, Deposition No. CCDC 915516.

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References