Multicomponent reaction of chalcones, malononitrile and DMF leading to γ-ketoamides†

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An efficient synthesis of γ-ketoamides was developed by the one-pot multicomponent reaction of chalcones, malononitrile and DMF (as both the reactant and solvent) in the presence of NaOH (3.0 equiv.). The reaction features high atom economy, easily available starting materials, operational simplicity, and good tolerance with diverse functional groups.

Introduction

4-Oxobutanamides1 constitute the core structure of quite a lot of naturally occurring and unnatural compounds, which display important pharmacological and biological properties.2,3 In this context, development of convenient and efficient methods toward such types of products is of great significance. Recently, we reported the reaction of chalcones and malononitrile4 with K2CO3 as the base, affording 4-oxo-butanenitrile derivatives,5 in which malononitrile is used as an organic cyanide source6 (Scheme 1). In continuation of this research, we found that, in the presence of excess base and under otherwise identical conditions, 4-oxobutanamides could be assembled via a multicomponent process. Multicomponent reactions (MCRs) have been refined in recent years as powerful and useful tools in synthetic chemistry and have attracted increasing attention due to the advantages of greater efficiency, atom economy and structural complexity.7 On one hand, the present result further demonstrates the feasibility and validity of using malononitrile as an organic cyanide source in organic transformation. On the other hand, the multicomponent protocol provides a new and efficient entry to γ-ketoamide derivatives.

Results and discussion

Initially, the model reaction of chalcone 1h with malononitrile was examined under basic conditions (Table 1). For the reaction system in DMF with 3.3 equiv. of K2CO3 as the base, N,N-dimethyl-4-oxo-2,4-diphenylbutanamide (3h) was isolated in 26% yield after 72 h (entry 1). To our delight, when NaOH (3.3 equiv.) was used as the base, the product 3h was obtained in 92% yield within 48 h (entry 2). However, a stronger base like t-BuOK gave slightly lower yield (entry 3). By comparison, in the case of using organic bases such as piperidine, DABCO and DBU, no target product was observed (entries 4–6).

With the optimal conditions established above (Table 1, entry 1), a range of reactions was carried out with various substrates 1 and malononitrile in the presence of NaOH (3.3 equiv.) in DMF (Table 2). The scope of the substitutes on

Table 1  Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (3.3 equiv.)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K2CO3</td>
<td>72</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>48</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK</td>
<td>48</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Piperidine</td>
<td>72</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>DABCO</td>
<td>72</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>DBU</td>
<td>72</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

† Electronic supplementary information (ESI) available. CCDC 996425 (3p). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00971a

‡Reagents were carried out with 1h (1.0 mmol) and malononitrile (1.1 equiv.) in DMF (4.0 mL) at rt. a Isolated yield. n.d. = not detected.
the enone substrates 1 was investigated. Substituent Ar1 may be phenyl (Table 2, entry 2), electron-rich aryls (Table 2, entries 1 and 3), electron-deficient aryl (Table 2, entry 4), 2-naphthyl (Table 2, entry 5) and heteroaryl (Table 2, entries 6 and 7). The Ar2 substituents include electron-rich aryls (Table 2, entries 8–12), halogen-substituted phenyl (Table 2, entries 13–16), 3-nitrophenyl (Table 2, entry 17), 1-naphthyl (Table 2, entry 18) and heteroaryl groups (Table 2, entries 19 and 20). The scope of the reaction was further explored in regard to α, β-unsaturated carbonyl compounds as the substrates (Fig. 1). Nevertheless, 4-(4-bromophenyl)-3-buten-2-one and 4,4-dimethyl-1-phenylpent-1-en-3-one gave only a trace amount of the target products. Ethyl cinnamate and cinnamaldehyde gave no desired products, when subjected to otherwise identical conditions. The structure of 3p was confirmed by X-ray single crystal diffraction (Fig. 2). All the above results indicated the efficiency of the reactions which could proceed smoothly to afford the corresponding γ-ketoamides in moderate to excellent yields (63–92%).

In order to elucidate the possible mechanism for the reaction, a control experiment was carried out (Scheme 2). Starting from separately isolated intermediate, 4-oxo-2,4-diphenylbutanenitrile (2a), product 3a could be obtained in 91% yield with NaOH (2.2 equiv.) as the base and DMF as the solvent in 0.5 h.8

Although the exact mechanism was still unclear, a plausible mechanism for the formation of γ-ketoamides was tentatively proposed in Scheme 3. Cyanated intermediate 5,9 is generated first, which further reacts with dimethylamine10 liberated in situ from DMF under a strong alkaline environment,11 to give almidine intermediate II.12 Hydrolysis of the intermediate II delivers the final γ-ketoamide product 3.13

**Conclusion**

In summary, we have developed a convenient and efficient method for the synthesis of functionalized 4-oxobutanamides from simple α,β-unsaturated enones and malononitrile in DMF. The one-pot multicomponent reaction features readily available starting materials, broad substrate scope, mild conditions and high efficiency. Ongoing studies are focused on applying this reaction to more complex molecules as well as gaining detailed insights into the reaction mechanism.
Experimental

General procedure for the preparation of 3. Synthesis of 3h

General procedure for the preparation of 3 (3h as an example): to a mixture of (E)-1-phenyl-3-(p-tolyl)prop-2-en-1-one 1h (1 mmol, 0.2221 g) in 4 mL of DMF was added NaOH (3.3 mmol, 0.1320 g). The reaction mixture was stirred at room temperature for 48 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel (eluent, petroleum ether–ethyl acetate = 5 : 1). Product 3h was obtained as a pale yellow oil in 92% yield.

N,N-Dimethyl-4-oxo-4-phenyl-2-(p-tolyl)butanamide (3h)

Pale yellow oil. 1H NMR (500 MHz, CDCl3): δ = 2.34 (s, 3H), 2.95 (s, 3H), 3.03 (s, 3H), 3.05 (d, J = 3.5 Hz, 1H), 4.08–4.14 (m, 1H), 4.49–4.52 (m, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H); 13C NMR (CDCl3, 125 MHz): δ = 21.0, 36.0, 37.2, 43.7, 44.5, 127.7, 128.1, 129.7, 133.0, 135.2, 136.8, 136.9, 138.2, 147.4, 198.8; HRMS (ESI-TOF): calcd for C19H21NO2 320.1592, found 320.1594.

X-ray crystallographic analysis of compound 3p

A colorless block crystal having approximate dimensions of 0.80 × 0.50 × 0.30 mm was mounted on a glass fiber. All measurements were made on a CCD area detector with graphite-monochromated Mo Kα radiation. The structure was solved by Patterson methods (SHELXL-97) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F2 was based on 13 527 observed reflections (I > 0.00σ(I)) and 8387 variable parameters and converged (largest parameter shift was 0.001 times its esd) with unweighted and weighted agreement factors of R = 0.079 and Rw = 0.226. Crystal data for 3p C18H18BrNO2: Mw = 360.23, triclinic, space group P21/c, a = 17.4725(10) Å, b = 8.0638(4) Å, c = 24.9462(14) Å, α = 90°, β = 109.224(1)°, γ = 90°, V = 3318.8(3) Å3, Z = 8, Dc = 1.442 g cm−3, F(000) = 1472.0, μ(Mo Kα) = 0.95 cm−1.

Acknowledgements

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Notes and references


8 The 48 h reaction time was chosen to maintain general reaction conditions for all substrates (Table 2), while the control reaction (Scheme 2) finished within 0.5 h. The result might indicate that the formation of cyanated intermediate 2 is the rate-limiting step.


In an isolated reaction of pre-formed dimethylamine (which is derived from the treatment of DMF with NaOH) with compound 2a in polar solvents such as DMSO or MeOH, unidentified products were observed.
