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

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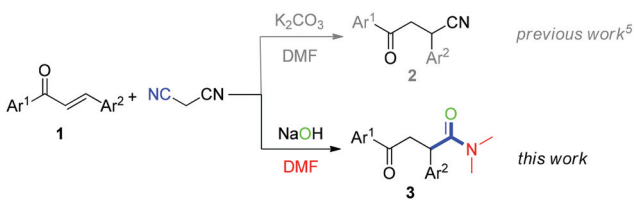
An efficient synthesis of γ-ketoamides was developed by the one-pot multicomponent reaction of chalcones, malononitrile and DMF (as both the reactant and solvent) in the presence of NaOH (3.0 equiv.). The reaction features high atom economy, easily available starting materials, operational simplicity,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

Introduction

4-Oxobutanamides[1] 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 malononitrile[4] with K_2CO_3 as the base, affording 4-oxo-butanenitrile derivatives,[5] in which malononitrile is used as an organic cyanide source[6] (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.



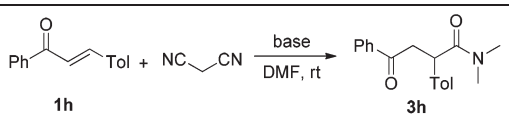
Scheme 1

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 K_2CO_3 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[a]



Entry	Base (3.3 equiv.)	Time (h)	Yield[b] (%)
1	K_2CO_3	72	26
2	**NaOH**	**48**	**92**
3	*t*-BuOK	48	88
4	Piperidine	72	n.d.
5	DABCO	72	n.d.
6	DBU	72	n.d.

[a] Reactions were carried out with **1h** (1.0 mmol) and malononitrile (1.1 equiv.) in DMF (4.0 mL) at rt. [b] Isolated yield. n.d. = not detected.

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

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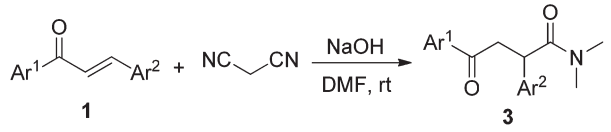
Table 2 Scope of substrates[a]



Entry	Ar^1	Ar^2	3	Yield[b] (%)
1	Ph	Ph	**3a**	84
2	4-MeC_6H_4	Ph	**3b**	91
3	4-$MeOC_6H_4$	Ph	**3c**	92
4	4-ClC_6H_4	Ph	**3d**	71
5	2-Naphthyl	Ph	**3e**	78
6	2-Furyl	Ph	**3f**	84
7	2-Thienyl	Ph	**3g**	89
8	Ph	4-MeC_6H_4	**3h**	92
9	Ph	4-$MeOC_6H_4$	**3i**	86
10	Ph	2-$MeOC_6H_4$	**3j**	87
11	Ph	4-$Me_2NC_6H_4$	**3k**	63
12	Ph	3,4-O_2CH_2Ph	**3l**	78
13	Ph	4-FC_6H_4	**3m**	79
14	Ph	4-ClC_6H_4	**3n**	72
15	Ph	2-ClC_6H_4	**3o**	71
16	Ph	4-BrC_6H_4	**3p**	73
17	Ph	3-$NO_2C_6H_4$	**3q**	68
18	Ph	1-Naphthyl	**3r**	74
19	Ph	2-Furyl	**3s**	67
20	Ph	2-Thienyl	**3t**	83

[a] Reactions were carried out with **1** (1.0 mmol), malononitrile (1.1 equiv.), NaOH (3.3 equiv.) in DMF (4.0 mL) at rt for 48 h. [b] Isolated yield.

the enone substrates **1** was investigated. Substituent Ar^1 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 Ar^2 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

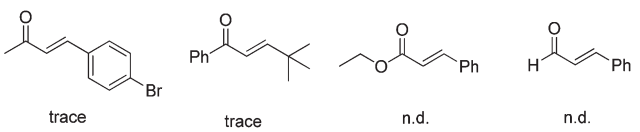


Fig. 1 Further exploration on the substrate scope.

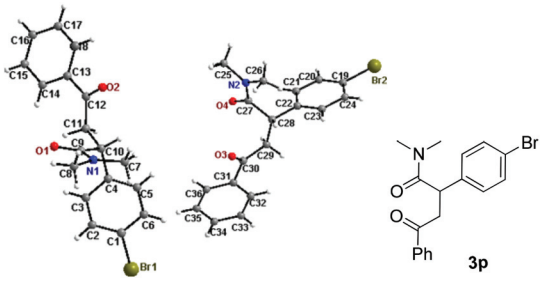
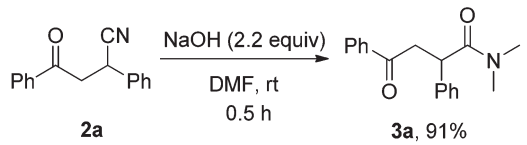
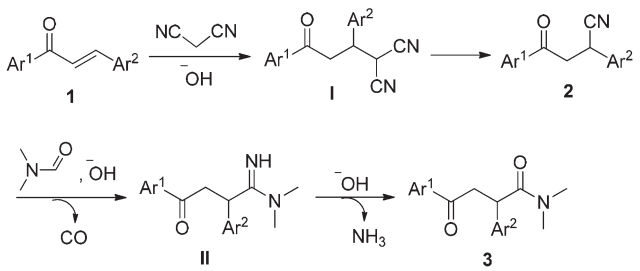


Fig. 2 X-ray crystal structure of **3p**.



Scheme 2 Control experiment.



Scheme 3 Plausible mechanism for the formation of γ-ketoamides.

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 4-oxobutanamides **3** was tentatively proposed in Scheme 3. Cyanated intermediate **2**[5,9] is generated first, which further reacts with dimethylamine[10] 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.

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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. ^{1}H NMR (500 MHz, $CDCl_3$): 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), 7.53 (t, J = 7.5 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.0, 36.0, 37.2, 43.7, 44.5, 127.7, 128.1, 128.4, 129.7, 133.0, 136.2, 136.6, 136.8, 172.4, 198.8; HRMS (ESI-TOF): calcd for $C_{19}H_{21}NO_2$ 296.1651 (M + H$^+$), found 296.1659.

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 F was based on 13 527 observed reflections ($I > 0.00\sigma(I)$) 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 R_w = 0.226. Crystal data for **3p** $C_{18}H_{18}BrNO_2$: M_r = 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) Å^3, Z = 8, D_c = 1.442 g cm^{-3}, F(000) = 1472.0, μ(Mo Kα) = 0.95 cm^{-3}.

Acknowledgements

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