

## ORIGINAL PAPER

Three-component one-pot reaction for the synthesis of  $\beta$ -amide ketones<sup>a</sup>Yan-Ping Luo\*, <sup>b</sup>Qiong Chen<sup>a</sup>Key Laboratory of Protection and Development Utilisation of Tropical Crop Germplasm Resources, Hainan University, Ministry of Education, HaiKou 570228, China<sup>b</sup>Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, China

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$\beta$ -amide ketones were synthesised by a three-component one-pot reaction of phenylacetylene, aldehydes, and amides in anhydrous acetonitrile containing trifluoroacetic acid and acetic acid in the presence of  $\text{AlCl}_3$  catalyst. The title compound structures were identified by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, MS, and elemental analysis.

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**Keywords:**  $\beta$ -amide ketones, one-pot reaction, synthesis

### Introduction

$\beta$ -Amide ketones exhibit excellent pharmacological activity (Kikuchi et al., 2005; Lee et al., 2010). Many methods are used to synthesise  $\beta$ -amide ketones, particularly by multi-component reactions (MCR), such as the Dakin–West reaction (Dakin & West, 1928), and four-component reactions of aldehydes, ketones, acyl chlorides, and acetonitrile in the presence of Brønsted acid or Lewis acid catalysts (Bahulayan et al., 2003; Khodaei et al., 2005; Pandey et al., 2005; Bhat et al., 2005; Rafiee et al., 2006). The development of new methods for the synthesis of  $\beta$ -amide ketones is of great significance for synthetic and medicinal chemistry.

In the literature, the three-component reactions of aldehydes, alkynes and amines provide access to propargylamines, whilst the three-component one-pot reactions involving aldehydes, alkynes, and urea or thiourea yield heterocyclic compounds (Sun et al., 2012; Samai, 2010 et al.; Du et al., 2008; Ramu et al., 2007). For example, Pan's group had synthesised 2-amino-1,3-oxazines *III* ( $\text{R}^2 = \text{NH}_2$ ) by using multi-component reactions (Fig. 1) (Huang et al., 2005).

In these reactions, only  $-\text{C}(\text{O})\text{NH}_2$  was involved in cyclisation. Due to the properties of amide situated between those of amine and urea, it was predicted that, by replacing urea with amides in the three-component reactions for the synthesis of oxazine derivatives, the diversity of the synthesis of oxazine heterocycles could be increased. However, when the aldehydes, alkynes, and amides were subjected to the conditions detailed in the literature (Huang, 2005), open-ring group *IV* products ( $\beta$ -amide ketones) were obtained smoothly; instead of the anticipated group *III* compounds (Fig. 1). Hence, this study describes the discovery of a new method to synthesise  $\beta$ -amide ketones from aldehydes, phenylacetylene, and amides.

### Experimental

All chemical reagents were commercially available and treated by standard methods prior to use. Solvents were dried routinely and redistilled.  $^1\text{H}$  NMR spectra were recorded on a Mercury-Plus 400 spectrometer (Varian, USA) in  $\text{CDCl}_3$  with TMS as the internal reference. MS spectra were determined using a Finnigan Trace MS organic mass spectrometer

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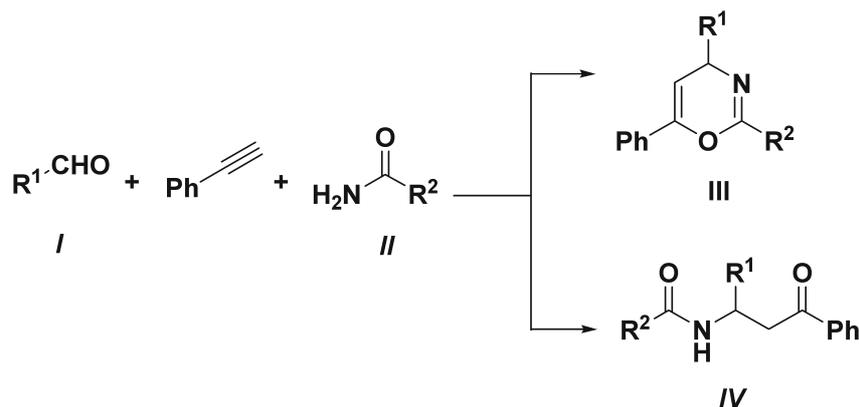


Fig. 1. Different products of three-component reactions.

(Finnigan, USA), and signals were given in  $m/z$ . Elementary analyses were performed on a Vario EL III elementary analysis instrument (Elementar, Germany). Melting points were measured using a Buchi B-545 melting point apparatus (Buchi, Switzerland) and are uncorrected.

#### General procedure for synthesis of title compounds (IVa–IVq)

A solution of benzaldehyde (1 mmol), phenylacetylene 0.11g (1.1 mmol), and acetamide or benzamide (1.5 mmol) in anhydrous acetonitrile (6 mL) containing AcOH (1 mL), and trifluoroacetic acid (3 mL) in the presence of 5 mole %  $AlCl_3$  catalyst was refluxed until the reaction was completed, as indicated by TLC analysis. The reaction mixture was diluted with water; the resulting solid was collected by filtration and directly subjected to silica gel column chromatography using petroleum ether–ethyl acetate ( $\varphi_r = 5 : 1$ ) as eluent to give the title compounds IVa–IVq.

#### X-ray diffraction

Orthorhombic blocks of IVc (0.20 mm  $\times$  0.20 mm  $\times$  0.10 mm) were mounted on a quartz fibre with protection oil. Cell dimensions and intensities were measured at (297  $\pm$  2) K on a Bruker SMART CCD area-detector diffractometer (Bruker, Germany) with graphite-monochromated  $MoK_\alpha$  radiation ( $\lambda = 0.71073$  Å);  $\theta_{max} = 26.00^\circ$ ; 24483 measured reflections; 2952 independent reflections ( $R_{int} = 0.0352$ ) of which 2471 had  $|F_o| > 2|F_c|$ . Data were corrected for Lorentz and polarisation effects and for absorption ( $T_{min} = 0.9804$ ;  $T_{max} = 0.9901$ ). The structure was solved by direct methods using SHELXS-97 software (Sheldrick, 1997); all other calculations were performed with Bruker SAINT System and Bruker SMART programs, Bruker (2003). Full-matrix least-squares refinement based on  $F^2$  using the weight of  $1/[\sigma^2(F_o^2) + (0.0668P)^2 + 0.7878P]$  gave the final values of  $R = 0.0490$ ,  $\omega R = 0.1300$ , and  $GOF(F) = 1.067$

for 209 variables and 2952 contributing reflections. Maximum shift/error = 0.000, max/min residual electron density = 0.212/−0.192  $e \text{ \AA}^{-3}$ . Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

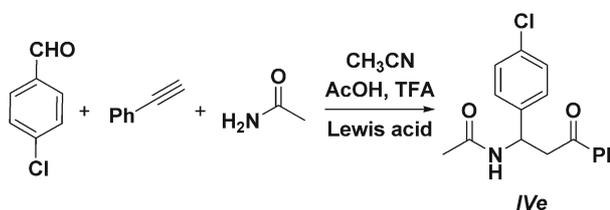
Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-869792.

#### Results and discussion

In accordance with the conditions detailed in the literature (Huang et al., 2005), 4-chlorobenzaldehyde reacted with phenylacetylene and acetamide to yield 18 %  $\beta$ -amide ketones, and no other products were isolated. Various other solvent systems, such as toluene, THF, 1,4-dioxane, DMF,  $CH_3CN$ , and AcOH were employed; however, according to thin layer chromatographic (TLC) analysis, the reactions did not pro-

Table 1. Effect of Lewis acids on reaction; solvent system used:  $CH_3CN$ –AcOH–TFA ( $\varphi_r = 6 : 1 : 3$ )

Entry	Lewis acid	Isolated yield/%
1	$CuBr_2$	38
2	$ZnCl_2$	50
3	$NiCl_2$	34
4	$BaCl_2$	43
5	$InCl_3$	41
6	$AlCl_3$	56
7	$TiCl_4$	55



**Table 2.** Characterisation data of compounds *IVa–IVq*

Entry	Compound	R <sup>1</sup>	R <sup>2</sup>	$w_1(\text{calc.})/\%$ $w_1(\text{found})/\%$			Yield %	M.p. °C
				C	H	N		
1	<i>IVa</i>	C <sub>4</sub> H <sub>9</sub>	CH <sub>3</sub>	72.84	8.56	5.66	33	101–103
				72.73	8.67	5.59		
2	<i>IVb</i>	C <sub>5</sub> H <sub>11</sub>	CH <sub>3</sub>	73.53	8.87	5.36	26	86–88
				73.64	8.80	5.34		
3	<i>IVc</i>	2-F-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	71.56	5.65	4.91	48	105–107
				71.70	5.52	4.88		
4	<i>IVd</i>	2-Cl-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	67.66	5.34	4.64	59	140–142
				67.59	5.36	4.55		
5	<i>IVe</i>	4-Cl-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	67.66	5.34	4.64	56	154–155
				67.59	5.63	4.58		
6	<i>IVf</i>	2-Br-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	58.97	4.66	4.05	49	165–166
				58.97	4.78	4.18		
7	<i>IVg</i>	3-Br-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	58.97	4.66	4.05	50	114–116
				58.80	4.73	4.11		
8	<i>IVh</i>	4-Br-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	58.97	4.66	4.05	56	166–168
				58.84	4.49	4.12		
9	<i>IVi</i>	3-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	76.84	6.81	4.98	31	108–110
				76.67	6.59	5.03		
10	<i>IVj</i>	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	76.84	6.81	4.98	38	115–117
				76.71	6.63	5.05		
11	<i>IVk</i>	4-C <sub>2</sub> H <sub>5</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	77.26	7.17	4.74	29	103–105
				77.18	7.23	4.65		
12	<i>IVl</i>	3-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	72.71	6.44	4.71	37	116–118
				72.63	6.29	4.57		
13	<i>IVm</i>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	65.38	5.16	8.97	41	161–163
				65.22	5.31	8.76		
14	<i>IVn</i>	2-Thienyl	CH <sub>3</sub>	65.91	5.53	5.12	47	154–156
				65.74	5.49	5.22		
15	<i>IVo</i>	4-Oxochromen-3-yl	CH <sub>3</sub>	71.63	5.11	4.18	68	201–203
				71.49	4.98	4.03		
16	<i>IVp</i>	C <sub>6</sub> H <sub>5</sub>	Ph	80.22	5.81	4.25	25	160–161
				80.07	5.92	4.34		
17	<i>IVq</i>	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	Ph	80.44	6.16	4.08	36	177–178
				80.36	6.28	3.99		

ceed, while in trifluoroacetic acid (TFA) alone, evidence of reactions was observed by TLC analysis after 48 h, indicating that TFA played an important role in the three-component reactions. Next, we experimented with different ratios of THF–AcOH, and found that when the TFA–AcOH volume ratio was 3 : 1 the yield was increased to 49 %.

In the literature (Bahulayan et al., 2003; Khodaei et al., 2005; Pandey et al., 2005; Bhat et al., 2005; Rafiee et al., 2006), where aldehydes reacted with ketones, acyl chlorides and acetonitrile to yield  $\beta$ -acetamido ketones, Lewis acid catalyst played an important role, hence we considered using a Lewis acid

catalyst to improve the reaction yields. Various Lewis acid catalysts were screened (Table 1). In the presence of anhydrous aluminum chloride as the Lewis acid catalyst, the reaction yield was 56 % (Entry 6), but the yields were lower when other catalysts were used (Entries 1–5, 7).

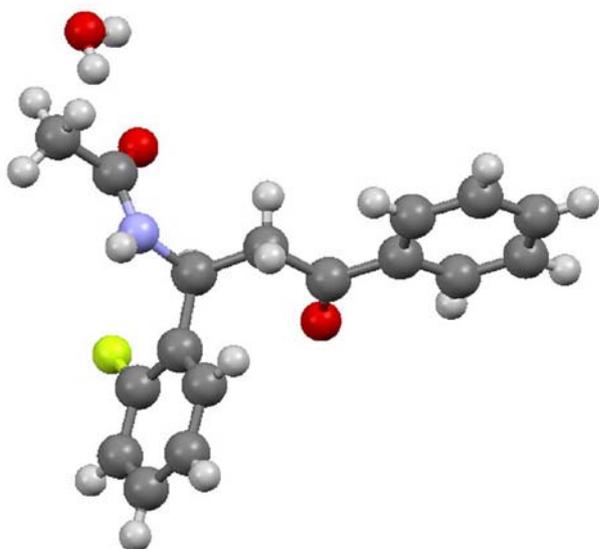
Various aldehydes, amides, and phenylacetylene with the AlCl<sub>3</sub> catalyst were investigated. The composition and properties of the corresponding products are summarised in Tables 2 and 3. For aliphatic aldehydes, the yields were lower (Entries 1–2); for aromatic aldehydes, the substituents on the aromatic ring affected the yields. When the substituents were electron-

**Table 3.** Spectral data of compounds *IVa–IVq*; spectra are given in the supplementary data, Figs. S1–S17

Compound	Spectral data
<i>IVa</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.46–7.97 (m, 5H, ArH), 6.33 (s, 1H, NH), 4.34 (d, <i>J</i> = 4.5 Hz, 1H, CH), 3.35 (dd, <i>J</i> = 17.1 Hz, <i>J</i> = 4.3 Hz, 1H, CH), 3.15 (dd, <i>J</i> = 17.1 Hz, <i>J</i> = 5.5 Hz, 1H, CH), 1.98 (s, 3H, CH <sub>3</sub> ), 1.73–1.49 (m, 2H, CH <sub>2</sub> ), 1.30 (d, <i>J</i> = 3.2 Hz, 4H, 2 × CH <sub>2</sub> ), 0.87 (t, <i>J</i> = 6.7 Hz, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 199.3, 169.6, 136.6, 133.3, 128.6, 127.9, 46.5, 41.9, 33.5, 28.5, 23.3, 22.3, 13.9 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 248 ([M – 1] <sup>+</sup> , 55), 105 (100), 91 (34), 77 (94)
<i>IVb</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.97–7.46 (m, 5H, ArH), 6.27 (s, 1H, NH), 4.34 (s, 1H, CH), 3.34 (dd, <i>J</i> = 17.0 Hz, <i>J</i> = 3.9 Hz, 1H, CH), 3.14 (dd, <i>J</i> = 17.0 Hz, <i>J</i> = 5.3 Hz, 1H, CH), 1.98 (s, 3H, CH <sub>3</sub> ), 1.76–1.52 (m, 2H, CH <sub>2</sub> ), 1.37–1.27 (m, 6H, 3 × CH <sub>2</sub> ), 0.86 (t, <i>J</i> = 6.3 Hz, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 199.3, 169.6, 136.6, 133.3, 128.5, 127.9, 46.5, 41.9, 33.7, 31.4, 26.0, 23.3, 22.4, 13.9 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 262 ([M + 1] <sup>+</sup> , 4), 105 (47), 77 (32), 43 (100)
<i>IVc</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.91–6.96 (m, 9H, ArH), 6.87 (m, 1H, NH), 5.54 (dd, <i>J</i> = 13.5 Hz, <i>J</i> = 5.7 Hz, 1H, CH), 3.75 (dd, <i>J</i> = 17.0 Hz, <i>J</i> = 5.0 Hz, 1H, CH), 3.42 (dd, <i>J</i> = 17.0 Hz, <i>J</i> = 6.0 Hz, 1H, CH), 2.03 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.3, 169.5, 163.1, 160.7, 136.4, 133.6, 128.7, 128.2, 128.1, 128.0, 115.5, 115.3, 49.3, 43.1, 23.3 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 285 ([M] <sup>+</sup> , 3), 242 (100), 179 (8), 138 (72), 124 (63), 105 (70)
<i>IVd</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.90–7.15 (m, 9H, ArH), 7.06 (s, 1H, NH), 5.82 (d, <i>J</i> = 6.2 Hz, 1H, CH), 3.76 (dd, <i>J</i> = 16.7 Hz, <i>J</i> = 5.7 Hz, 1H, CH), 3.46 (dd, <i>J</i> = 16.7 Hz, <i>J</i> = 5.4 Hz, 1H, CH), 2.04 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.7, 169.5, 138.0, 136.3, 133.6, 132.4, 129.8, 128.7, 128.2, 128.1, 126.9, 114.2, 47.7, 41.4, 23.3 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 302 ([M] <sup>+</sup> , 1), 266 (100), 207 (13), 154 (52), 145 (84), 105 (69)
<i>IVe</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.90–7.25 (m, 9H, ArH), 7.07 (s, 1H, NH), 5.54 (dt, <i>J</i> = 8.0 Hz, <i>J</i> = 5.5 Hz, 1H, CH), 3.76 (dd, <i>J</i> = 17.2 Hz, <i>J</i> = 5.1 Hz, 1H, CH), 3.42 (dd, <i>J</i> = 17.2 Hz, <i>J</i> = 5.8 Hz, 1H, CH), 2.05 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.3, 169.6, 139.5, 136.3, 133.7, 133.1, 128.7, 128.6, 128.0, 127.9, 49.2, 42.9, 23.4 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 302 ([M] <sup>+</sup> , 26), 258 (100), 241 (21), 153 (78), 137 (65), 105 (81), 77 (88)
<i>IVf</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.91–7.10 (m, 9H, ArH), 7.08 (s, 1H, NH), 5.77 (d, <i>J</i> = 5.7 Hz, 1H, CH), 3.78 (dd, <i>J</i> = 16.6 Hz, <i>J</i> = 5.7 Hz, 1H, CH), 3.44 (dd, <i>J</i> = 16.6 Hz, <i>J</i> = 5.2 Hz, 1H, CH), 2.04 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.8, 169.32, 139.7, 136.4, 133.6, 133.2, 128.9, 128.7, 128.4, 128.2, 127.5, 122.7, 50.1, 41.4, 23.4 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 346 ([M] <sup>+</sup> , 1), 266 (29), 184 (22), 146 (94), 105 (100), 77 (68)
<i>IVg</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.91–7.15 (m, 9H, ArH), 6.96 (s, 1H, NH), 5.54 (s, 1H, CH), 3.73 (dd, 1H, <i>J</i> = 16.6 Hz, <i>J</i> = 5.7 Hz, CH), 3.43 (dd, 1H, <i>J</i> = 16.6 Hz, <i>J</i> = 5.2 Hz, CH), 2.04 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 197.8, 169.7, 143.5, 136.2, 133.6, 130.3, 130.1, 129.4, 128.6, 128.0, 125.2, 122.6, 49.1, 43.1, 23.2 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 346 ([M] <sup>+</sup> , 4), 302 (52), 105 (88), 77 (100)
<i>IVh</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.91–7.21 (m, 9H, ArH), 6.87 (s, 1H, NH), 5.52 (d, <i>J</i> = 7.5 Hz, 1H, CH), 3.75 (dd, <i>J</i> = 17.2 Hz, <i>J</i> = 4.8 Hz, 1H, CH), 3.42 (dd, <i>J</i> = 17.2 Hz, <i>J</i> = 5.8 Hz, 1H, CH), 2.04 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.3, 169.6, 140.0, 136.2, 133.7, 131.6, 128.7, 128.2, 128.0, 121.1, 49.1, 42.8, 23.4 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 347 ([M + 1] <sup>+</sup> , 6), 345 ([M – 1] <sup>+</sup> , 10), 304 (100), 302 (76), 105 (44)
<i>IVi</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.90–6.84 (m, 9H, ArH), 6.79 (s, 1H, NH), 5.51 (d, <i>J</i> = 6.7 Hz, 1H, CH), 3.69 (dd, <i>J</i> = 16.7 Hz, <i>J</i> = 5.4 Hz, 1H, CH), 3.40 (dd, <i>J</i> = 16.7 Hz, <i>J</i> = 6.1 Hz, 1H, CH), 2.30 (s, 3H, CH <sub>3</sub> ), 1.97 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.3, 169.4, 140.7, 138.2, 136.5, 133.3, 128.6, 128.4, 128.1, 128.0, 127.2, 123.3, 49.9, 43.3, 23.3, 21.4 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 281 ([M] <sup>+</sup> , 44), 238 (100), 207 (30), 134 (68), 120 (69), 105 (80)
<i>IVj</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.93–7.19 (m, 9H, ArH), 6.77 (s, 1H, NH), 5.53 (d, <i>J</i> = 6.7 Hz, 1H, CH), 3.76 (dd, <i>J</i> = 16.9 Hz, <i>J</i> = 3.0 Hz, 1H, CH), 3.43 (dd, <i>J</i> = 16.8 Hz, <i>J</i> = 6.1 Hz, 1H, CH), 2.30 (s, 3H, CH <sub>3</sub> ), 2.02 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 197.9, 169.5, 138.0, 136.7, 136.3, 133.1, 129.0, 128.4, 127.9, 126.3, 49.4, 43.5, 23.0, 20.8 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 281 ([M] <sup>+</sup> , 11), 238 (100)
<i>IVk</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.97–7.12 (m, 9H, ArH), 6.78 (d, <i>J</i> = 7.2 Hz, 1H, NH), 5.53 (d, <i>J</i> = 7.3 Hz, 1H, CH), 3.71 (dd, <i>J</i> = 16.7 Hz, <i>J</i> = 5.3 Hz, 1H, CH), 3.41 (dd, <i>J</i> = 16.8 Hz, <i>J</i> = 6.2 Hz, 1H, CH), 2.58 (q, <i>J</i> = 7.5 Hz, 2H, CH <sub>2</sub> ), 1.97 (s, 3H, CH <sub>3</sub> ), 1.18 (t, <i>J</i> = 7.6 Hz, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.4, 169.4, 143.3, 138.2, 136.5, 133.3, 128.6, 128.0, 126.4, 125.8, 49.7, 43.3, 28.3, 23.3, 15.4 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 296 ([M + 1] <sup>+</sup> , 9), 252 (54), 148 (36), 134 (44), 105 (100), 77 (73)
<i>IVl</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.91–6.75 (m, 10H, ArH, NH), 5.53 (d, <i>J</i> = 7.8 Hz, 1H, CH), 3.77 (s, 3H, OCH <sub>3</sub> ), 3.76–3.67 (m, 1H, CH), 3.42 (dd, <i>J</i> = 16.9 Hz, <i>J</i> = 6.0 Hz, 1H, CH), 2.03 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.3, 169.5, 159.6, 142.6, 136.5, 133.4, 129.6, 128.6, 128.0, 118.6, 112.6, 112.4, 55.1, 49.8, 43.2, 23.2 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 297 ([M] <sup>+</sup> , 50), 254 (100), 150 (60), 136 (59), 104 (93), 77 (76)
<i>IVm</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 8.18–7.46 (m, 9H, ArH), 7.04 (s, 1H, NH), 5.67 (s, 1H, CH), 3.83 (d, <i>J</i> = 15.5 Hz, 1H, CH), 3.51 (d, <i>J</i> = 15.8 Hz, 1H, CH), 2.09 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 197.7, 169.8, 148.7, 146.8, 135.9, 133.9, 128.8, 127.9, 127.3, 123.7, 49.0, 42.6, 23.3 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 312 ([M] <sup>+</sup> , 11), 298 (51), 283 (18), 269 (100), 252 (78), 105 (94)
<i>IVn</i>	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ: 7.94–6.78 (m, 9H, ArH, NH), 5.96–5.72 (m, 1H, CH), 3.78 (dd, <i>J</i> = 17.3 Hz, <i>J</i> = 4.5 Hz, 1H, CH), 3.48 (dd, <i>J</i> = 17.3 Hz, <i>J</i> = 5.8 Hz, 1H, CH), 1.99 (s, 3H, CH <sub>3</sub> ) <sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ: 198.1, 169.3, 144.7, 136.4, 133.5, 128.7, 128.0, 126.7, 124.4, 77.3, 77.0, 76.7, 45.8, 43.4, 23.2 MS, <i>m/z</i> ( <i>I<sub>r</sub></i> /%) : 274 ([M + 1] <sup>+</sup> , 2), 230 (17), 105 (100), 77 (83)

Table 3. continued

Compound	Spectral data
<i>IVo</i>	$^1\text{H NMR}$ ( $\text{CDCl}_3$ ) $\delta$ : 8.23 (s, 1H, CH), 8.18–7.40 (m, 10H, ArH, NH), 5.56 (d, $J = 4.3$ Hz, 1H, CH), 3.83 (dd, $J = 17.6$ Hz, $J = 9.1$ Hz, 1H, CH), 3.55 (dd, $J = 17.6$ Hz, $J = 4.3$ Hz, 1H, CH), 2.03 (s, 3H, $\text{CH}_3$ ) $^{13}\text{C NMR}$ ( $\text{CDCl}_3$ ) $\delta$ : 197.5, 178.0, 169.3, 156.0, 155.3, 136.2, 133.9, 133.3, 128.5, 127.9, 125.2, 123.9, 121.7, 118.2, 45.0, 41.7, 23.3 MS, $m/z$ ( $I_r/\%$ ): 335 ( $[\text{M}]^+$ , 6), 292 (78), 215 (34), 188 (50), 174 (100), 105 (67)
<i>IVp</i>	$^1\text{H NMR}$ ( $\text{CDCl}_3$ ) $\delta$ : 7.93–7.23 (m, 16H, ArH, NH), 5.77 (d, $J = 7.9$ Hz, 1H, CH), 3.89 (dd, $J = 16.9$ Hz, $J = 4.9$ Hz, 1H, CH), 3.54 (dd, $J = 16.9$ Hz, $J = 5.9$ Hz, 1H, CH) MS, $m/z$ ( $I_r/\%$ ): 329 ( $[\text{M}]^+$ , 1), 224 (100), 105 (94)
<i>IVq</i>	$^1\text{H NMR}$ ( $\text{CDCl}_3$ ) $\delta$ : 7.93–7.10 (m, 10H, ArH, NH), 5.73–5.70 (m, 1H, CH), 3.85 (dd, $J = 16.9$ Hz, $J = 4.9$ Hz, 1H, CH), 3.49 (dd, $J = 16.9$ Hz, $J = 5.9$ Hz, 1H, CH), 2.29 (s, 3H, $\text{CH}_3$ ) $^{13}\text{C NMR}$ ( $\text{CDCl}_3$ ) $\delta$ : 199.0, 166.6, 137.8, 137.0, 136.5, 134.1, 133.5, 131.5, 129.3, 128.6, 128.5, 128.1, 127.0, 126.3, 50.0, 42.9, 21.0 MS, $m/z$ ( $I_r/\%$ ): 343 ( $[\text{M}]^+$ , 26), 237 (100), 207 (47), 117 (88), 104 (96), 77 (99)

Fig. 2. Crystal structure of compound *IVc*.

withdrawing groups, the yields were higher (Entries 3–8, 13–15); when the substituents were electron-donating groups, the yields were lower (Entries 9–12). For amides, the yields were higher for acetamide than for benzamide (Entries 16–17). The single-crystal structure of *IVc* was determined by X-ray crystallography as shown in Fig. 2.

A proposed reaction mechanism of three-component one-pot reaction is shown in Fig. 3. Aldehyde and amide reacted and the intermediate *V* was formed under the Lewis acid catalyst condition, followed by removal of a molecule of water from the intermediate *V* to generate intermediate *VI* (Akiyama et al., 2004; Dondoni et al., 2004; Kappe, 1997). Subsequently, the resulting intermediate *VI* underwent a hetero Diels–Alder cycloaddition with phenylacetylene, producing intermediate *VII* (Barluenga et al., 1995). Finally, a highly unstable intermediate *VII* was deprotonated to the open ring to form  $\beta$ -amido ketones *IV* upon the addition of water.

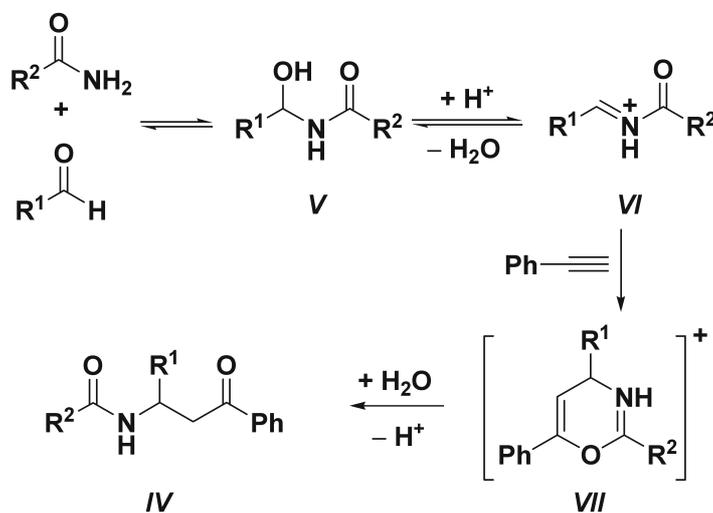


Fig. 3. Possible mechanism of three-component one-pot reaction.

## Conclusions

We successfully developed a novel three-component reaction for the synthesis of  $\beta$ -amide ketones in  $\text{AlCl}_3$  catalysis.

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## Supplementary data

Supplementary data associated with this article (Three-component one-pot reaction for the synthesis of  $\beta$ -amide ketones) can be found in the online version of this paper (DOI: 10.2478/s11696-013-0313-0).

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