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# Practical synthesis of amides from alkynyl bromides, amines, and water

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ABSTRACT

A general and efficient method for the synthesis of a wide range of amides is described here. The reactions were conducted under convenient conditions and provided secondary and tertiary amides in moderate to excellent yields. A variety of amines and substituted alkynyl bromides were used to investigate the scope of the reactions.

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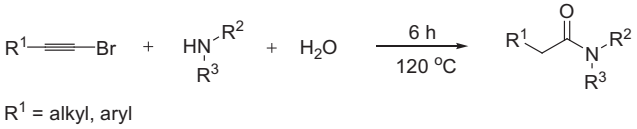
## 1. Introduction

Amides are one of the most important functional groups in polymers, natural products, and pharmaceuticals.[1] The prevalent chemical methods for simple amide synthesis rely on the reaction of carboxylic acids or their corresponding derivatives with amines.[2] Alternative methods, such as the variations of the Staudinger reaction,[3] the acid-promoted Schmidt reaction,[4] and transition-metal-catalyzed aminocarbonylation of aryl halides,[5] alkenes,[6] and alkynes[7] have been reported. Another attractive approaches including the direct amidation of alcohols and amines,[8] the oxidative amination of aldehydes to amides,[9] and the transition-metal-catalyzed rearrangement of ketoximes to amides[10] have been introduced. Very recently, Johnston and co-workers showed a non-conventional amide synthesis via iodonium-promoted nitroalkane-amine coupling[11] and our group reported an efficient method for the synthesis of amides via palladium-catalyzed C–C coupling of aryl halides with isocyanides.[12] On the other hand, terminal alkynes and haloalkynes are readily accessible materials and remarkable progress has been made through transition-metal-catalyzed reactions in the past decades. Recently, terminal alkynes were transformed to the corresponding amides[13] and haloalkynes were used to synthesize ynamides efficiently.[14] As part of our continuing project in the functionalization of haloalkynes,[15] here we present an efficient procedure for the amide synthesis from alkynyl bromides based on the multicomponent reaction employing water as one of the reacting species under very convenient conditions (Scheme 1).




$R^1$ = alkyl, aryl

**Scheme 1.** Multicomponent reaction leading to amides.

## 2. Results and discussion

The reaction of phenylethynyl bromide (**1a**) with a slight excess of diethylamine (**2a**, 1.5 equiv) was chosen as the model reaction. Initially, we added different transition metals in the reaction by assuming the reaction is a catalytic process (Table 1, entries 1–4). However, the control experiment results showed that the phenylethynyl bromide (**1a**) can be converted to the *N*,*N*-diethyl-2-phenylacetamide (**3aa**) without addition of any transition metals (Table 1, entry 5), which implies that it's a noncatalytic reaction. The reaction showed a strong solvent dependence. Among the solvents used, dioxane was proved appropriate and water is the solvent of choice (Table 1, entries 6–11). The lower temperature disfavored the reaction, and **3aa** was obtained in 80% yield after 3 h (Table 1, entries 12–14). After some attempts, we considered that the optimized reaction conditions are the following: **1a** (1 mmol) with amine (1.5 mmol) and water (2 mL) at 120 °C for 6 h (Table 1, entry 11).

With the optimized conditions in hand, we next focused on the generality of the reaction with regard to both coupling partners (Tables 2 and 3). The present approach for amide synthesis turned out to be quite general, phenylethynyl bromide and a wide range of amines underwent the coupling with water to furnish the corresponding amides in moderate to excellent yield (Table 2). In general, nearly all of the amines reacted smoothly with the exception of aniline, and the secondary amines could afford higher yields compared to the primary amines. The steric bulk of the amine had

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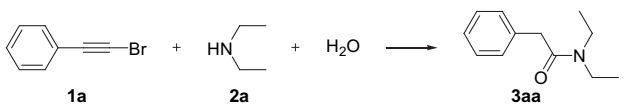
**Table 1**
Optimization of reaction conditions for the formation of amide[a]



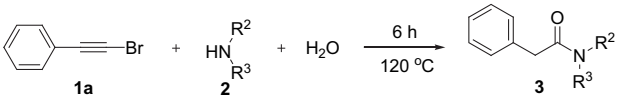

| Entry | Solvent | Catalyst | Yield (%)[b] |
|---|---|---|---|
| 1 | $CH_3CN$ | $Pd(OAc)_2$ | n.p. |
| 2 | $CH_3CN$ | CuI | 35 |
| 3 | $CH_3CN$ | $FeCl_3$ | 29 |
| 4 | $CH_3CN$ | $AgBF_4$ | n.p. |
| 5 | $CH_3CN$ | | 27 |
| 6 | HOAc | | n.p. |
| 7 | Toluene | | Trace |
| 8 | DMSO | | 36 |
| 9 | DMF | | 55 |
| 10 | 1,4-Dioxane | | 70 |
| 11 | Water | | 92 |
| 12[c] | Water | | Trace |
| 13[d] | Water | | 46 |
| 14[e] | Water | | 80 |

[a] Reaction conditions: phenylethynyl bromide (1.0 mmol), diethylamine (1.5 mmol), at 120 °C for 6 h.
[b] Isolated yield.
[c] Room temperature.
[d] 60 °C.
[e] 3 h.

some impact on the yield (Table 2, entry 3). The primary amines gave moderate to good yields (Table 2, entries 4–6). The standard conditions were compatible with allylic and benzylic amines (Table 2, entries 10, 11) as well as the heterocyclic amines (Table 2, entries 8, 9). Unfortunately, aniline is ineffective in the reaction conditions. Amazing, indoline could afford moderate yield (Table 2, entry 14). It is to be noted that the triethylamine could also produce the amide in good yield for prolonged reaction time (Table 2, entry 15).

Table 3 summarizes the results of coupling reaction of a variety of alkynyl bromides to amines. In general, the aromatic alkynyl bromides with either an electron-donating or electron-withdrawing group on the benzene ring were able to generate the corresponding products in good yields (Table 3, entries 1–14). The chain amine (diethylamine) and the cyclo amine (morpholine) could afford the products in satisfactory yields. For the *para*-electron-rich substituted aromatic 1-bromoalkynes, the coupling yields gradually decreased from methyl to methoxy group (Table 3, entries 1, 4–6). Clearly, electronic effect plays an important role. Interestingly, substitutions with opposite nature at the *ortho*-position of aromatic ring had no impact on the yields (Table 3, entries 1–3, 7–9). It should be pointed out that the carbon–halogen bonds tolerated the substrate reactivity and the halogen-containing products were afforded smoothly (Table 3, entries 7–12). 3,5-Bis(trifluoromethyl) substituted phenylethynyl bromide gave excellent yield (Table 3, entry 14). Gratifying, the standard conditions were compatible with bromoalkyne attached to the alkyl group,

**Table 2**
Scope of amines for the formation of amides[a]



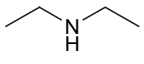
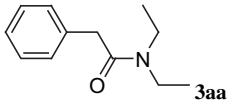
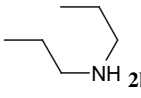
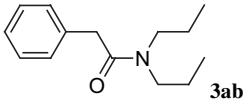
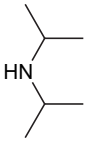
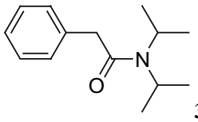
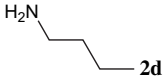
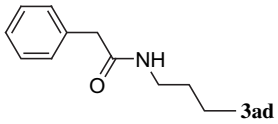
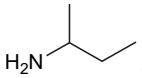
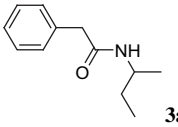
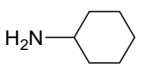
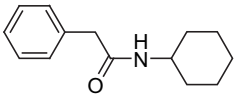
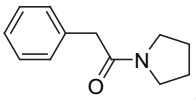
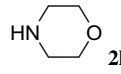
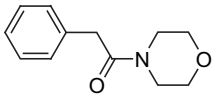
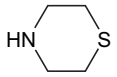
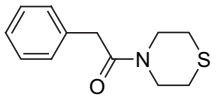
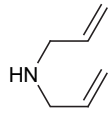
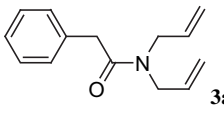
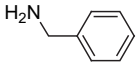
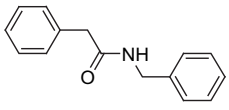
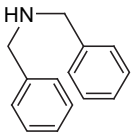
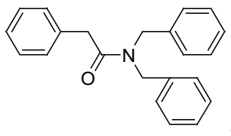
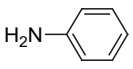
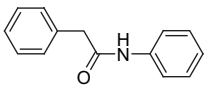
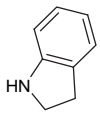
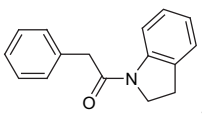
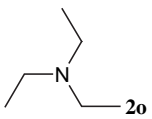
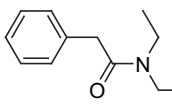
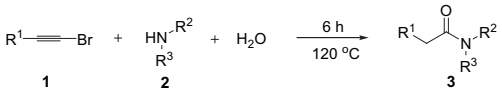

| Entry | Amine | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  **2a** |  **3aa** | 92 |
| 2 |  **2b** |  **3ab** | 88 |
| 3 |  **2c** |  **3ac** | 75 |
| 4 |  **2d** |  **3ad** | 52 |
| 5 |  **2e** |  **3ae** | 40 |
| 6 |  **2f** |  **3af** | 80 |
| 7 |  **2g** |  **3ag** | 91 |

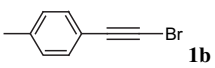
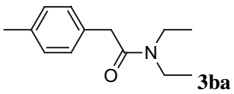
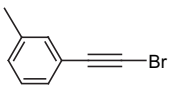
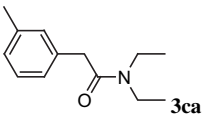
**Table 2** (*continued*)

| Entry | Amine | Product | Yield (%)[b] |
|---|---|---|---|
| 8 |  **2h** |  **3ah** | 82 |
| 9 |  **2i** |  **3ai** | 94 |
| 10 |  **2j** |  **3aj** | 90 |
| 11 |  **2k** |  **3ak** | 73 |
| 12 |  **2l** |  **3al** | 70 |
| 13 |  **2m** |  **3am** | n.p. |
| 14 |  **2n** |  **3an** | 55 |
| 15[c] |  **2o** |  **3aa** | 75 |

[a] Reaction conditions: phenylethynyl bromide (1.0 mmol), amine (1.5 mmol), and water (2.0 mL) at 120 °C for 6 h.
[b] Isolated yield.
[c] Triethylamine was used and reacted for 15 h.

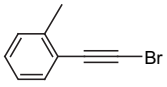
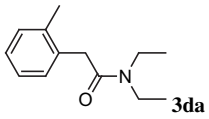
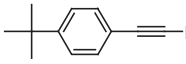
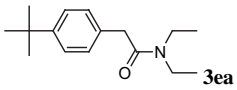
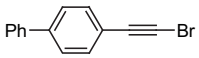
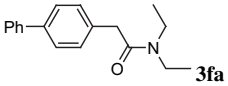
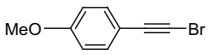
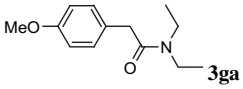
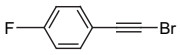
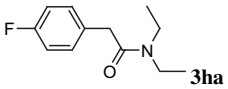
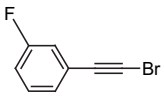
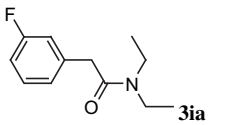
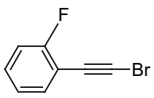
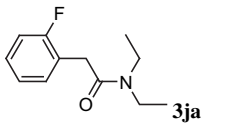
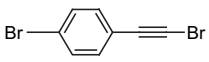
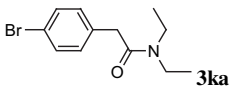
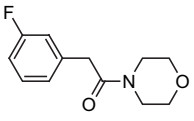
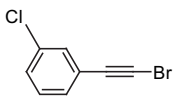
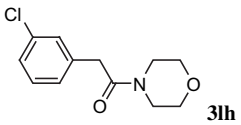
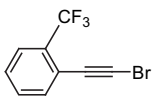
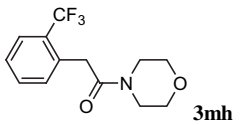
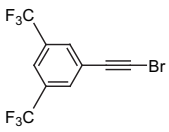
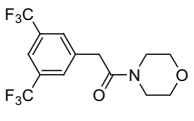
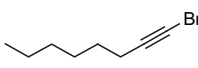
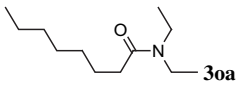
**Table 3**
Scope of alkynyl bromides for the formation of amides[a]




| Entry | Alkynyl bromide | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  **1b** |  **3ba** | 90 |
| 2 |  **1c** |  **3ca** | 88 |

(*continued on next page*)

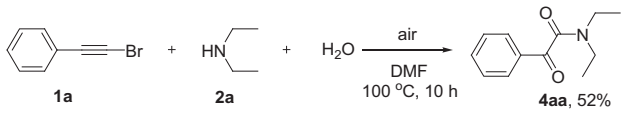
**Table 3** (*continued*)

| Entry | Alkynyl bromide | Product | Yield (%)[b] |
|---|---|---|---|
| 3 |  **1d** |  **3da** | 91 |
| 4 |  **1e** |  **3ea** | 83 |
| 5 |  **1f** |  **3fa** | 63 |
| 6 |  **1g** |  **3ga** | 60 |
| 7 |  **1h** |  **3ha** | 91 |
| 8 |  **1i** |  **3ia** | 92 |
| 9 |  **1j** |  **3ja** | 92 |
| 10 |  **1k** |  **3ka** | 94 |
| 11 | **1i** |  **3ih** | 90 |
| 12 |  **1l** |  **3lh** | 94 |
| 13 |  **1m** |  **3mh** | 96 |
| 14 |  **1n** |  **3nh** | 95 |
| 15 |  **1o** |  **3oa** | 72 |

[a] Reaction conditions: alkynyl bromide (1.0 mmol), amine (1.5 mmol), and water (2.0 mL) at 120 °C for 6 h.
[b] Isolated yield.

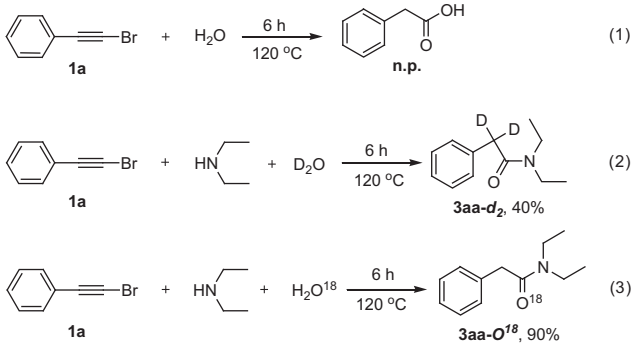
and the coupling of 1-bromooct-1-yne with diethylamine gave amide in 72% yield (Table 3, entry 15).

We also found that the α-ketoamides could be readily achieved from bromophenylacetylene and diethylamine in DMF solvent in 52% yield. Jiao and Zhang[16] have reported a Cu-catalyzed oxidative amidation–diketonization reaction of terminal alkynes and offered a valuable mechanistic insight into the transformation, however, only the aromatic amines could afford the corresponding products (Scheme 2).



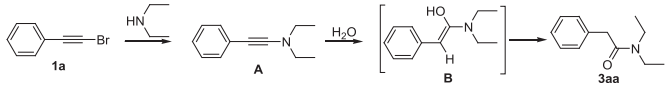

**Scheme 2.** The formation of α-ketoamides.

To elucidate the mechanism, controlled experiments were conducted (Scheme 3). We found there was no reaction of phenylethynyl bromide with water under the reaction conditions (Scheme 3, Eq. 1). Moreover, we also found that compound **1a** could transform to **3aa-*d*$_2$** and **3aa-*O*$^{18}$** in the presence of $D_2O$ or $H_2O^{18}$ (Scheme 3, Eqs. 2 and 3). The controlled experiments suggested that the alkynyl bromide reacted with amine first and the oxygen atom came from water.




**Scheme 3.** Controlled experiments.

Consequently, the possible mechanisms were proposed (Scheme 4). In the first step, the alkynyl bromide reacts with diethylamine to afford the ynamine,[17] and then the oxygen atom of water attacks the triple bond and forms the intermediate **B**, which is then subsequently converted to the amide.




**Scheme 4.** Possible reaction mechanisms.

## 3. Conclusions

In conclusion, we have presented a general and facile procedure for the synthesis of amides, which provides a valuable complement to the traditional methods. Although the alkynyl bromides mainly derived from terminal alkynes, the diverse substrate scope, transition-metal-free method, water as the sole solvent combined with an operationally simple procedure make this a useful methodology. Further utilization of this procedure will continue in our laboratory.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.24 and 77.0 ppm, respectively, chloroform is a solvent with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Bruker Vector 22 spectrometer. Mass spectra were recorded on a Shimadzu GC–MS-QP5050A spectrometer at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter: 0.25 mm, length: 30 m). Elemental analyses were performed with a Vario EL elemental analyzer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF254) and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

### 4.2. General procedure for the synthesis of amides (3aa–oa and 4aa)

The mixture of 1-bromoalkyne (1 mmol) and amine (1.5 mmol) in water (2 mL) was stirred at 120 °C for 6 h in a 25 mL schlenk tube. Water (8 mL) was added after completion of the reaction, the aqueous solution was extracted with diethyl ether (3×5 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography to give the pure sample.

*4.2.1. N,N-Diethyl-2-phenylacetamide (**3aa**).* IR (KBr): 2973, 2932, 1642, 1456, 1375, 1256, 1130, 848, 726. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.27–7.32 (m, 2H), 7.20–7.25 (m, 3H), 3.69 (s, 2H), 3.35–3.40 (m, 2H), 3.25–3.31 (m, 2H), 1.05–1.13 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.1, 135.5, 128.6, 128.6, 126.6, 42.3, 40.8, 40.1, 14.1, 12.9. MS (EI) *m*/*z*: 44, 65, 72, 91, 100, 191. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.05; H, 9.03; N, 7.40.

*4.2.2. 2-Phenyl-N,N-dipropylacetamide (**3ab**).* IR (KBr): 2971, 1643, 1552, 1376, 1131, 847, 686. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.28–7.32 (m, 2H), 7.22–7.26 (m, 3H) 3.69 (s, 2H), 3.26–3.30 (m, 2H), 3.15–3.19 (m, 2H), 1.47–1.58 (m, 4H), 0.84–0.88 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.6, 135.6, 128.7, 128.5, 126.6, 49.9, 47.5, 40.9, 22.1 20.8, 11.3, 11.2. MS (EI) *m*/*z*: 43, 65, 72, 86, 91, 128, 219. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.45; H, 9.72; N, 6.46.

*4.2.3. N,N-Diisopropyl-2-phenylacetamide (**3ac**).* IR (KBr): 2982, 1644, 1556, 1371, 1260, 1170, 745. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.28–7.32 (m, 2H), 7.22–7.25 (m, 3H), 3.92–3.98 (m, 1H), 3.69 (s, 2H), 3.36 (s, 1H), 1.40 (d, *J*=6.8 Hz, 6H), 1.00 (d, *J*=6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.9, 135.7, 128.6, 128.4, 126.5, 49.4, 45.8, 43.4, 20.5, 20.4. MS (EI) *m*/*z*: 43, 66, 86, 91, 128, 176, 219. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.42; H, 9.73; N, 6.34.

*4.2.4. N-Butyl-2-phenylacetamide (**3ad**).* IR (KBr): 2960, 1646, 1550, 1344, 1257, 982, 700. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.26–7.30 (m, 2H), 7.20–7.24 (m, 3H), 6.55 (s, 1H), 3.48 (s, 2H), 3.12–3.17 (m, 2H), 1.35–1.42 (m, 2H), 1.19–1.29 (m, 2H), 0.85 (t, *J*=7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=171.4, 135.4, 129.2, 128.7, 126.9, 43.4, 39.4, 31.4, 20.0, 13.7. MS (EI) *m*/*z*: 57, 65, 92, 99, 149, 191. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.16; H, 8.92; N, 7.39.

*4.2.5. N-sec-Butyl-2-phenylacetamide (**3ae**).* IR (KBr): 2973, 1643, 1553, 1372, 1251, 974, 683. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.33–7.36 (m, 2H), 7.24–7.29 (m, 3H), 5.21 (s, 1H), 3.85–3.94 (m, 1H), 3.54 (s, 2H), 1.29–1.42 (m, 2H), 1.03 (d, *J*=6.8 Hz, 3H), 0.80 (t, *J*=7.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.3, 135.1, 129.3, 128.9, 127.2, 46.6, 44.0, 29.4, 20.3, 10.1. MS (EI) *m*/*z*: 44, 57, 65, 91, 162, 191. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.11; H, 9.03; N, 7.25.

*4.2.6. N-Cyclohexyl-2-phenylacetamide (**3af**).* IR (KBr): 3280, 3079, 2932, 2854, 1643, 1552, 1448, 1263, 1170. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.32–7.36 (m, 2H), 7.24–7.29 (m, 3H), 3.71–3.78 (m, 1H), 3.53 (s,

2H), 1.80–1.84 (m, 2H), 1.53–1.63 (m, 3H), 1.25–1.34 (m, 3H), 0.97–1.14 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.0, 135.1, 129.3, 128.9, 127.2, 48.1, 43.9, 32.8, 25.4, 24.7. MS (EI) *m*/*z*: 41, 55, 83, 92, 136, 217. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.15; H, 8.87; N, 6.53.

*4.2.7. 2-Phenyl-1-(pyrrolidin-1-yl)ethanone (**3ag**).* IR (KBr): 2970, 2874, 1643, 1426, 1340, 1296, 1190, 717. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.22–7.33 (m, 5H), 3.67 (s, 2H), 3.47 (s, 4H), 1.87 (d, *J*=13.2 Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.7, 134.8, 128.9, 128.6, 126.7, 46.9, 46.0, 42.1, 26.1, 24.3. MS (EI) *m*/*z*: 55, 91, 98, 189. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.01; H, 8.05; N, 7.34.

*4.2.8. 1-Morpholino-2-phenylethanone (**3ah**).* IR (KBr): 2855, 1645, 1455, 1362, 1270, 1114, 1038, 964, 729. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.30–7.33 (m, 2H), 7.22–7.27 (m, 3H), 3.72 (s, 2H), 3.63 (s, 4H), 3.47 (t, *J*=5.2 Hz, 2H), 3.42 (t, *J*=4.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.6, 134.7, 128.8, 128.5, 126.9, 66.7, 66.4, 46.5, 42.1, 40.8. MS (EI) *m*/*z*: 56, 70, 91, 114, 205. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.05; H, 7.43; N, 6.74.

*4.2.9. 2-Phenyl-1-thiomorpholinoethanone (**3ai**).* IR (KBr): 2912, 1642, 1494, 1423, 1367, 1292, 1185, 1030, 959, 727. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.28–7.33 (m, 2H), 7.22–7.25 (m, 3H), 3.87 (t, *J*=4.8 Hz, 2H), 3.72 (s, 2H), 3.68 (t, *J*=4.4 Hz, 2H), 2.56 (t, *J*=4.8 Hz, 2H), 2.28 (t, *J*=4.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.4, 134.8, 128.8, 128.5, 126.9, 48.8, 44.4, 41.2, 27.4, 27.2. MS (EI) *m*/*z*: 42, 56, 91, 118, 130, 221. Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.34; H, 6.77; N, 6.40.

*4.2.10. N,N-Diallyl-2-phenylacetamide (**3aj**).* IR (KBr): 3027, 2929, 1645, 1454, 1290, 978, 923, 746, 639. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.31–7.35 (m, 2H), 7.26–7.27 (m, 3H), 5.65–5.82 (m, 2H), 5.07–5.23 (m, 4H), 4.01 (d, *J*=5.6 Hz, 2H), 3.87 (d, *J*=4.8 Hz, 2H), 3.72 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=171.0, 135.1, 133.1, 132.8, 128.7, 128.6, 126.8, 117.3, 116.8, 49.4, 47.9, 40.7. MS (EI) *m*/*z*: 41, 56, 81, 91, 124, 174, 215. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.35; H, 7.90; N, 6.43.

*4.2.11. N-Benzyl-2-phenylacetamide (**3ak**).* IR (KBr): 3289, 2924, 1641, 1550, 694. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.24–7.36 (m, 8H), 7.16 (d, *J*=6.8 Hz, 2H), 5.77 (s, 1H), 4.40 (d, *J*=5.6 Hz, 2H), 3.62 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=171.0, 138.1, 134.7, 129.4, 129.0, 128.6, 127.5, 127.4, 127.4, 43.8, 43.6. MS (EI) *m*/*z*: 51, 65, 77, 91, 104, 225. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.71; H, 6.78; N, 6.28.

*4.2.12. N,N-Dibenzyl-2-phenylacetamide (**3al**).* IR (KBr): 3030, 2925, 1644, 1494, 1448, 1359, 1203, 1078, 742. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.16–7.34 (m, 13H), 7.08 (d, *J*=7.2 Hz, 2H), 4.60 (s, 2H), 4.41 (s, 2H), 3.77 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=171.6, 137.3, 136.4, 135.0, 129.0, 128.8, 128.7, 128.6, 128.3, 127.7, 127.4, 126.9, 126.5, 50.2, 48.3, 41.0. MS (EI) *m*/*z*: 65, 91, 106, 132, 224, 315. Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.52; H, 6.77; N, 4.52.

*4.2.13. 1-(Indolin-1-yl)-2-phenylethanone (**3an**).* IR (KBr): 3032, 2963, 2913, 1664, 1597, 1480, 1456, 1337, 1210, 1076, 768, 733. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=8.26 (d, *J*=8.0 Hz, 1H), 7.25–7.35 (m, 5H), 7.13–7.19 (m, 2H), 6.97–7.01 (m, 1H), 4.03 (t, *J*=8.4 Hz, 2H), 3.79 (s, 2H), 3.13 (t, *J*=8.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.1, 143.0, 134.2, 131.1, 129.1, 128.7, 127.5, 127.0, 124.5, 123.7, 117.2, 48.2, 43.5, 28.0. MS (EI) *m*/*z*: 51, 65, 91, 119, 237. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.71; H, 6.43; N, 5.98.

*4.2.14. N,N-Diethyl-2-p-tolylacetamide (**3ba**).* IR (KBr): 2925, 1648, 1412, 1192, 1129, 924, 725, 698. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.12 (d, *J*=8.0 Hz, 2H), 7.08 (d, *J*=8.4 Hz, 2H), 3.62 (s, 2H), 3.33–3.38 (m, 2H), 3.23–3.29 (m, 2H), 2.29 (s, 3H), 1.04–1.11 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.3, 136.1, 132.3, 129.3, 128.5, 42.3, 40.5, 40.1, 21.0, 14.2, 12.9. MS (EI) *m*/*z*: 44, 72, 100, 105, 205. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.23; H, 9.28; N, 6.76.

*4.2.15. N,N-Diethyl-2-m-tolylacetamide (**3ca**).* IR (KBr): 2974, 1643, 1456, 1376, 1278, 1130, 1092, 764, 694. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.15–7.18 (m, 1H), 7.00–7.05 (m, 3H), 3.63 (s, 2H), 3.33–3.39 (m, 2H), 3.24–3.29 (m, 2H), 2.30 (s, 3H), 1.04–1.11 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.2, 138.2, 135.4, 129.4, 128.4, 127.4, 125.6, 42.3, 40.8, 40.1, 21.3, 14.2, 12.9. MS (EI) *m*/*z*: 44, 72, 91, 105, 205. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.92; H, 9.39; N, 6.89.

*4.2.16. N,N-Diethyl-2-o-tolylacetamide (**3da**).* IR (KBr): 2963, 1646, 1428, 1356, 1130, 931, 728. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.10–7.12 (m, 4H), 3.61 (s, 2H), 3.36–3.41 (m, 2H), 3.22–3.27 (m, 2H), 2.23 (s, 3H), 1.08–1.14 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.1, 136.3, 134.1, 130.1, 128.7, 126.8, 126.1, 42.3, 40.2, 38.4, 19.6, 14.1, 13.0. MS (EI) *m*/*z*: 44, 58, 72, 100, 105, 205. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.15; H, 9.30; N, 6.81.

*4.2.17. 2-(4-tert-Butylphenyl)-N,N-diethylacetamide (**3ea**).* IR (KBr): 2984, 1641, 1453, 1426, 1374, 1189, 1074, 768, 690. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.30 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 3.63 (s, 2H), 3.33–3.39 (m, 2H), 3.25–3.31 (m, 2H), 1.27 (s, 9H), 1.05–1.12 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.3, 149.4, 132.4, 128.3, 125.5, 42.3, 40.2, 40.2, 34.4, 31.3, 14.2, 12.9. MS (EI) *m*/*z*: 58, 72, 91, 100, 117, 159, 247. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.41; H, 10.25; N, 5.60.

*4.2.18. N,N-Diethyl-2-(4-biphenyl)acetamide (**3fa**).* IR (KBr): 3029, 2974, 2932, 1642, 1454, 1131, 756, 698. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.47–7.54 (m, 4H), 7.33–7.37 (m, 2H), 7.24–7.28 (m, 3H), 3.66 (s, 2H), 3.31–3.37 (m, 2H), 3.22–3.28 (m, 2H), 1.03–1.09 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.0, 140.8, 139.5, 134.6, 129.2, 128.7, 127.3, 127.2, 127.0, 42.4, 40.4, 40.2, 14.3, 13.0. MS (EI) *m*/*z*: 58, 72, 100, 152, 165, 194, 267. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.71; H, 7.96; N, 5.19.

*4.2.19. N,N-Diethyl-2-(4-methoxyphenyl)acetamide (**3ga**).* IR (KBr): 2973, 2934, 1640, 1512, 1459, 1247, 1119, 1033, 792. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.12 (d, *J*=8.4 Hz, 2H), 6.79 (d, *J*=8.4 Hz, 2H), 3.72 (s, 3H), 3.58 (s, 2H), 3.32–3.33 (m, 2H), 3.23–3.25 (m, 2H), 1.04–1.06 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=170.5, 158.3, 129.6, 127.4, 114.0, 55.2, 42.3, 40.1, 39.8, 14.2, 12.9. MS (EI) *m*/*z*: 44, 72, 78, 100, 121, 221. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.31; H, 8.73; N, 6.45.

*4.2.20. N,N-Diethyl-2-(4-fluorophenyl)acetamide (**3ha**).* IR (KBr): 2976, 2932, 1641, 1509, 1457, 1223, 1131, 795. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.15–7.18 (m, 2H), 6.91–6.96 (m, 2H), 3.60 (s, 2H), 3.30–3.36 (m, 2H), 3.22–3.28 (m, 2H), 1.04–1.08 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.9, 162.9, 160.5, 131.2, 131.1, 130.3, 130.2, 115.4, 115.2, 42.3, 40.2, 39.7, 14.2, 12.9. MS (EI) *m*/*z*: 44, 58, 72, 100, 109, 209. Anal. Calcd for $C_{12}H_{16}FNO$: C, 68.88; H, 7.71; N, 6.69. Found: C, 68.63; H, 7.76; N, 6.60.

*4.2.21. N,N-Diethyl-2-(3-fluorophenyl)acetamide (**3ia**).* IR (KBr): 2934, 2915, 1643, 1537, 1428, 1126, 1103, 794. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.24–7.29 (m, 1H), 6.97–7.04 (m, 2H), 6.90–6.94 (m, 1H), 3.69 (s, 2H), 3.36–3.41 (m, 2H), 3.27–3.32 (m, 2H), 1.12 (t, *J*=6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.5, 164.1, 161.6, 137.9, 137.8, 130.0, 129.9, 124.4, 115.8, 115.6, 113.7, 113.4, 42.3, 40.2, 40.2, 14.2, 12.8.

MS (EI) *m*/*z*: 44, 58, 72, 83, 100, 110, 209. Anal. Calcd for $C_{12}H_{16}FNO$: C, 68.88; H, 7.71; N, 6.69. Found: C, 68.71; H, 7.75; N, 6.74.

*4.2.22. N,N-Diethyl-2-(2-fluorophenyl)acetamide (**3ja**).* IR (KBr): 2938, 2917, 1645, 1513, 1426, 1255, 1203, 1138, 824. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.28–7.32 (m, 1H), 7.19–7.24 (m, 1H), 7.00–7.10 (m, 2H), 3.69 (s, 2H), 3.36–3.42 (m, 2H), 3.30–3.36 (m, 2H), 1.10–1.15 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.1, 161.8, 159.4, 131.0, 130.9, 128.5, 128.4, 124.1, 124.1, 122.8, 122.6, 115.2, 115.0, 42.2, 40.3, 33.2, 14.1, 12.9. MS (EI) *m*/*z*: 44, 58, 72, 100, 109, 209. Anal. Calcd for $C_{12}H_{16}FNO$: C, 68.88; H, 7.71; N, 6.69. Found: C, 68.96; H, 7.74; N, 6.63.

*4.2.23. 2-(4-Bromophenyl)-N,N-diethylacetamide (**3ka**).* IR (KBr): 2974, 2932, 1643, 1456, 1318, 1132, 1012, 797. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.34 (d, *J*=8.4 Hz, 2H), 7.05 (d, *J*=8.4 Hz, 2H), 3.54 (s, 2H), 7.27–7.32 (m, 2H), 7.18–7.23 (m, 2H), 1.03 (t, *J*=7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=169.4, 134.5, 131.5, 130.6, 120.5, 42.3, 40.2, 39.9, 14.2, 12.9. MS (EI) *m*/*z*: 44, 58, 72, 89, 100, 171, 269. Anal. Calcd for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97; N, 5.18. Found: C, 53.17; H, 6.04; N, 5.25.

*4.2.24. 2-(3-Fluorophenyl)-1-morpholinoethanone (**3ih**).* IR (KBr): 2976, 2934, 1644, 1589, 1453, 1264, 1137, 776, 735, 684. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.24–7.29 (m, 1H), 6.91–7.00 (m, 3H), 3.69 (s, 2H), 3.62 (s, 4H), 3.50 (d, *J*=3.6 Hz, 2H), 3.42 (d, *J*=3.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.9, 164.1, 161.6, 137.2, 137.1, 130.2, 130.1, 124.3, 124.3, 115.7, 115.5, 114.0, 113.7, 66.7, 66.4, 46.4, 42.1, 40.2. MS (EI) *m*/*z*: 56, 70, 83, 109, 114, 223. Anal. Calcd for $C_{12}H_{14}FNO_2$: C, 64.56; H, 6.32; N, 6.27. Found: C, 64.34; H, 6.39; N, 6.34.

*4.2.25. 2-(3-Chlorophenyl)-1-morpholinoethanone (**3lh**).* IR (KBr): 2964, 2920, 2856, 1644, 1573, 1432, 1230, 1115, 1073, 766, 683. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.18–7.25 (m, 3H), 7.08 (d, *J*=6.8 Hz, 1H), 3.65 (s, 2H), 3.60 (s, 4H), 3.49 (t, *J*=4.4 Hz, 2H), 3.39 (t, *J*=4.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.9, 136.7, 134.4, 129.9, 128.8, 127.1, 126.9, 66.7, 66.4, 46.4, 42.1, 40.1. MS (EI) *m*/*z*: 42, 70, 89, 114, 125, 239. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.91; H, 5.96; N, 5.93.

*4.2.26. 2-(2-(Trifluoromethyl)phenyl)-1-morpholinoethanone (**3mh**).* IR (KBr): 2967, 2922, 2858, 1648, 1427, 1314, 1160, 1109, 962, 770, 727. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.59 (d, *J*=8.0 Hz, 1H), 7.43–7.47 (m, 1H), 7.29–7.32 (m, 2H), 3.80 (s, 2H), 3.60 (s, 4H), 3.53 (t, *J*=4.4 Hz, 2H), 3.38 (t, *J*=4.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=168.6, 133.4, 133.4, 131.9, 131.5, 128.8, 128.5, 128.2, 127.9, 127.1, 126.1, 126.1, 126.0, 126.0, 125.7, 123.0, 120.3, 66.7, 66.4, 46.1, 42.2, 36.9. MS (EI) *m*/*z*: 56, 70, 109, 114, 159, 204, 273. Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.31; H, 5.10; N, 5.21.

*4.2.27. 2-(3,5-Bis(trifluoromethyl)phenyl)-1-morpholinoethanone (**3nh**).* IR (KBr): 2924, 2858, 1649, 1437, 1376, 1280, 1173, 1129, 1038, 898. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.75 (s, 1H), 7.66 (s, 2H), 3.78 (s, 2H), 3.60–3.64 (m, 6H), 3.48 (t, *J*=4.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=167.8, 137.2, 132.2, 131.9, 131.5, 131.2, 129.6, 129.5, 127.3, 124.5, 121.8, 121.1, 121.0, 121.0, 121.0, 120.9, 119.1, 66.7, 66.4, 46.2, 42.3, 39.3. MS (EI) *m*/*z*: 56, 70, 86, 114, 177, 227, 341. Anal. Calcd for $C_{14}H_{13}F_6NO_2$: C, 49.27; H, 3.84; N, 4.10. Found: C, 49.13; H, 3.88; N, 4.14.

*4.2.28. N,N-Diethyloctanamide (**3oa**).* IR (KBr): 2927, 1730, 1647, 1459, 1376, 1266, 1146, 1098, 791. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=3.29–3.32 (m, 2H), 3.24–3.29 (m, 2H), 2.24 (t, *J*=8.0 Hz, 2H), 1.54–1.62 (m, 2H), 1.20–1.26 (m, 8H), 1.11 (t, *J*=6.4 Hz, 3H), 1.05 (t, *J*=6.4 Hz, 3H), 0.82 (t, *J*=6.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=172.5, 42.0, 40.0, 33.1, 31.7, 29.4, 29.1, 25.5, 22.5, 14.3, 14.0, 13.0. MS (EI) *m*/*z*: 58, 86, 112, 156, 184, 199. Anal. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03. Found: C, 72.13; H, 12.70; N, 7.11.

*4.2.29. N,N-Diethyl-2-oxo-2-phenylacetamide (**4aa**).* IR (KBr): 2977, 2933, 1681, 1640, 1446, 1228, 1144, 721. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.89–7.91 (m, 2H), 7.58–7.62 (m, 1H), 7.45–7.49 (m, 2H), 3.50–3.56 (m, 2H), 3.18–3.23 (m, 2H), 1.25 (t, *J*=6.4 Hz, 3H), 1.12 (t, *J*=6.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=191.6, 166.7, 134.5, 133.2, 129.6, 128.9, 42.1, 38.8, 14.1, 12.8. MS (EI) *m*/*z*: 44, 51, 72, 77, 100, 105, 205. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.04; H, 7.42; N, 6.91.

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