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Green H_2O-Promoted Solvent-Free Synthesis of Enaminocarbonyl Compounds with High Stereoselectivity from Electron-Deficient Terminal Alkynes

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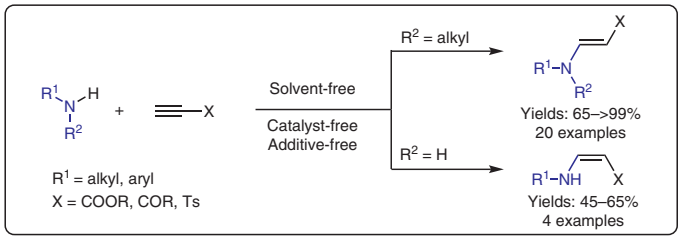

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Abstract A green H_2O-promoted solvent-free hydroamination of electron-deficient terminal alkynes with amines has been developed. All secondary amines, including aliphatic and aromatic amines, gave the corresponding (*E*)-enamines in good to excellent yields, whereas primary aromatic amines afforded *Z*-configured products in moderate yields. Propiolates, propyn-1-ones, propynamides, and 1-(ethynylsulfonyl)-4-methylbenzene were explored in this Michael addition.

Key words green chemistry, water catalysis, hydroamination, alkynes, enamines

Enaminocarbonyl compounds are widely used in syntheses of various heterocycles,[1] including indoles,[1c–e] pyrroles,[1f–h] quinolines,[1i] and pyridines,[1j,k] to give bioactive compounds and natural products[2] such as alkaloids,[2a,b] peptides,[2c] or amino acids,[2d,e] as well as their derivatives.[2f,g] Therefore, extensive efforts have been devoted to the exploration of new methods for synthesizing enaminocarbonyl compounds. At present, enaminocarbonyl compounds are mainly synthesized by direct condensation of 1,3-dicarbonyl compounds with amines or their derivatives.[1c,3] However, there these protocols have several disadvantages; for example, neat β-keto esters or 1,3-diketones are usually needed as precursors, and certain catalysts are required. Recently, due to their almost complete atom-efficiency, hydroaminations of alkynes with nitrogen-containing reagents have been used to prepare a range of enamines.[1f,4] Among such methods, a solvent-free copper-catalyzed method[4e] and a water-promoted hydroamination[4a] show several unique advantages (Figure 1). Inspired by these protocols, and on the basis of our experience of functionalization of unsaturated C–C bonds,[5] we considered that a green and general method for synthesizing enaminocarbonyl compounds with good stereoselectivity, a broad substrate range, and mild reaction conditions without a solvent or catalyst would be highly desirable.

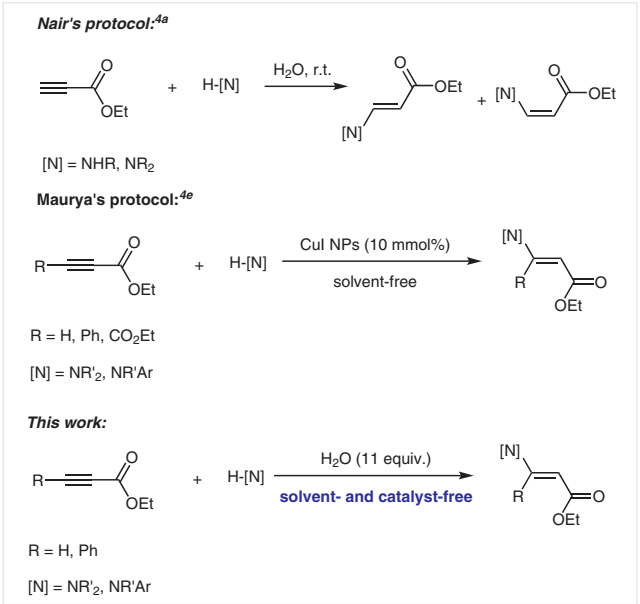

Figure 1 Hydroaminations of electron-deficient alkynes

In Nair's protocol,[4a] water was used as solvent, giving the *E*-adducts in almost quantitative yield. Maurya's solvent-free approach with a CuI catalyst[4e] again led to near quantitative formation of the *E*- adducts (Figure 1). These results encouraged us to examine to the reaction of less-reactive *N*-methylaniline with ethyl propiolate in the absence of a solvent or any other additive at room temperature. Unfortunately, none of the desired product **3a** was detected after stirring for one hour at room temperature (Table 1, entry 1). However, raising the reaction temperature to 80 °C

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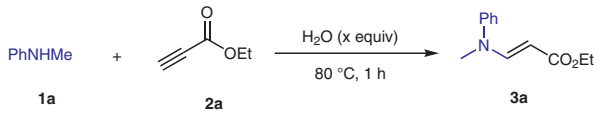
resulted in a 60% yield of **3a** (entry 2). On the basis of the hypothesis that dispersion of the reactants in water might benefit the reaction, we added 0.44 equivalents of water to the reaction mixture, which improved the yield to 72% (entry 3). By changing the amount of H_2O from 0.44 equivalents to 11 equivalents, the yield of **3a** was improved from 72 to 94% (entries 3–7). Further increases in the amount of water from 11 to 25 equivalents had little influence on the yield (entries 7–9). Therefore, 11 equivalents of H_2O was chosen as the optimal amount for this reaction. Next, the reaction temperature was investigated. Raising or lowering the temperature reduced the yield (entries 7 and 10–12). Finally, the optimal conditions were chosen to be a mixture of the propiolate (1 equiv) and an aniline or aromatic N-heterocycle (1.2 equiv) with 11 equivalents of water under stirring at 80 °C for one hour. In contrast, for aliphatic amines, the reactions need to be performed in a water bath at room temperature for only 10 minutes.

Table 1 Optimization of the Reaction Conditions[a]

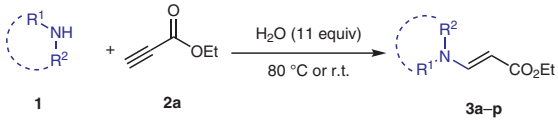


Entry	Temp (°C)	H_2O (equiv)	Yield[b] (%)
1	rt	0	trace
2	80	0	60
3	80	0.44	72
4	80	1	78
5	80	2.2	89
6	80	5	90
7	80	11	94
8	80	25	93
9	80	55	91
10	40	11	63
11	60	11	83
12	100	11	68

[a] Reaction conditions: ethyl propiolate (0.5 mmol), *N*-methylaniline (0.6 mmol, 1.2 equiv), H_2O, 1 h under air.
[b] Isolated yield.

With the optimal reaction conditions in hand, we examined the reactions of various amines, including aliphatic amines, aryl amines, and N-containing aromatic compounds with ethyl propiolate (**2a**). Most of the amines formed the corresponding 3-aminopropenoates **3** in good yields (65–99%; Table 2). In general, anilines, including primary and secondary anilines, reacted smoothly to afford the corresponding products **3a–i** in yields of 26–99% (Table 2; entries 1–9). In particular, secondary anilines, including highly sterically hindered *N*-isopropylaniline, gave the corresponding products **3a–d** in good to excellent yields of 78–99% (entries 1–4). As expected, weakly nucleophilic primary anilines gave products **3e–i** with a *Z*-configuration in low to moderate yields of 26–65% (entries 5–9). The decreased nucleophilicity of 3,4-dicholoroaniline as a result of the presence of the two chloro substituents resulted in the corresponding product **3g** being obtained in only 26% yield, even when the reaction time was prolonged to 12 hours (entry 7), whereas 4-chloroaniline afforded the corresponding product **3f** in 65% yield (entry 6).[6] Due to its poor stability, product **3h** was obtained in only 47% yield, even though the strongly nucleophilic 4-methoxyaniline was used (entry 8).[7] 1-Naphthylamine gave product **3i** in a moderate 42% yield (entry 9). Furthermore, N-containing heterocyclic compounds, including 1*H*-benzo[*d*]imidazole, and 1*H*-imidazole, gave the corresponding products without *E*/*Z* selectivity in yields of 89 and 97% yields, respectively (see Supporting Information, Figure S2).[8] Unfortunately, indole and carbazole did not afford the desired products under the standard conditions, presumably because of the lower nucleophilicities of their NH groups.

Table 2 Scope of Amines[a]



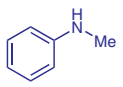
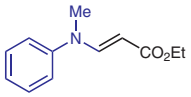
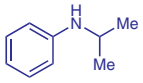
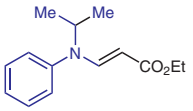
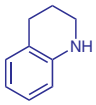
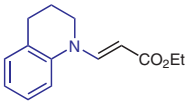
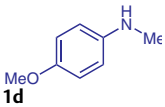
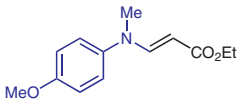
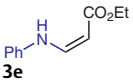
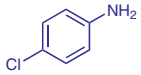
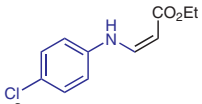
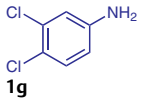
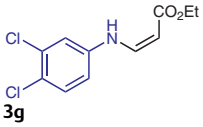
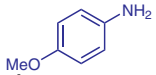
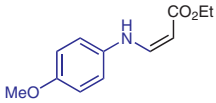
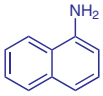
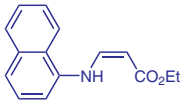
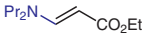
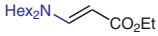
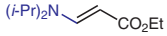
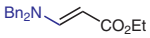
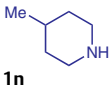
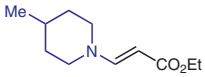
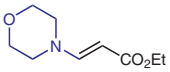
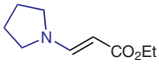
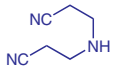
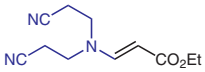
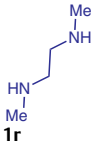
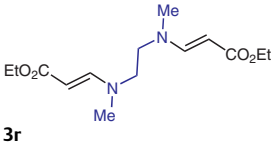
Entry	Amine **1**	Product **3**	Yield (%)
1	 **1a**	 **3a**	94
2[c]	 **1b**	 **3b**	65
3[c]	 **1c**	 **3c**	>99
4[d]	 **1d**	 **3d**	78
5	PhNH$_2$ **1e**	 **3e**	45
6[e]	 **1f**	 **3f**	65

Table 2 (continued)

Entry	Amine **1**	Product **3**	Yield (%)
7[e]	 **1g**	 **3g**	26
8	 **1h**	 **3h**	47[6]
9	 **1i**	 **3i**	42
10[f]	 **1j**	 **3j**	91
11[f]	 **1k**	 **3k**	>99
12[f]	 **1l**	 **3l**	77
13[f]	 **1m**	 **3m**	>99
14[f]	 **1n**	 **3n**	78
15[f]	 **1o**	 **3o**	99
16[f]	 **1p**	 **3p**	>99
17[f]	 **1q**	 **3q**	98
18[g]	 **1r**	 **3r**	93

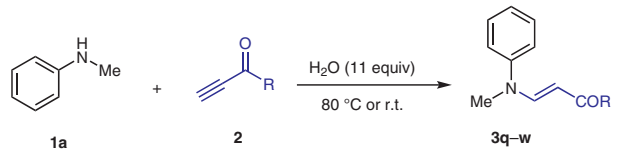
[a] Reaction conditions: ethyl propiolate (**2a**, 0.5 mmol, 1.0 equiv), amine **1** (0.6 mmol, 1.2 equiv), water (5 mmol, 11 equiv), 80 °C, 1 h, under air.
[b] Isolated yield.
[c] Reaction time 4 h.
[d] Stirred at r.t. for 1 h.
[e] Reaction time 12 h.
[f] Stirred at r.t. in a water bath for 10 min.
[g] 2 equiv ethyl propiolate.

For aliphatic secondary amines, most reactions were performed in a water bath for 10 minutes (Table 2, entries 10–18). All secondary aliphatic amines, including highly sterically hindered *N*,*N*-diisopropylamine, reacted efficiently with ethyl propiolate (**2a**) to give the corresponding products in good to excellent yields (77 to >99%). The linear dialkylamines dipropylamine and dihexylamine performed well, affording the desired products **3j** and **3k**, respectively, in yields of 91 and 99% (Table 2, entries 10 and 11). The sterically hindered *N*,*N*-diisopropylamine gave product **3l** in 77% yield (entry 12), whereas dibenzylamine gave the desired product **3m** in almost quantitative yield (>99%) (entry 13). When 4-methylpiperidine was used, the yield of **3n** was only 78% (entry 14), similar to that obtained from with *N*,*N*-diisopropylamine. Morpholine and pyrrolidine also performed well in this reaction, affording the corresponding products **3o** and **3p** quantitatively (entries 15 and 16). Di(2-cyanoethyl)amine similarly gave product **3q** in 98% yield (entry 17). Finally, *N*,*N*′-dimethylethane-1,2-diamine gave the (2*E*,2′*E*)-diacrylate **3r** in 93% yield (entry 18).

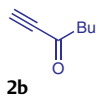
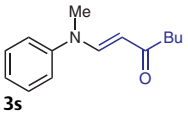
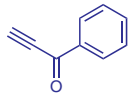
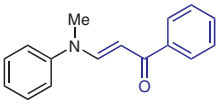
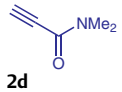
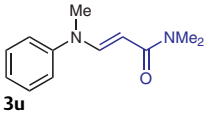
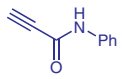
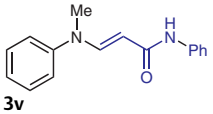
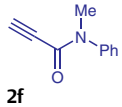
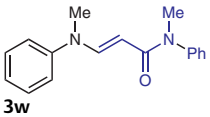
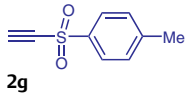
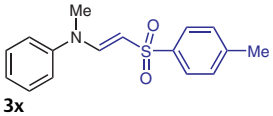
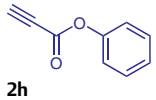
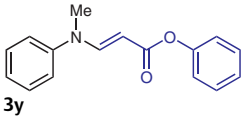
Next, we examined the effect of changing the alkyne component by using phenyl propiolate, propargyl ketones, various propiolamides, and 1-(ethynylsulfonyl)-4-methylbenzene in the reaction (Table 3). Hept-1-yn-3-one and 1-phenylprop-2-yn-1-one reacted smoothly to give corresponding products **3s** and **3t** in excellent yields of 85 and 91%, respectively (Table 3, entries 1 and 2). Due to differences in the stability and electron-deficiency of the products, the reaction was performed at 20 °C for one hour when hept-1-yn-3-one was used as substrate. When various propiolamides were applied in the reaction, the best results were achieved with soluble *N*,*N*-dimethylpropanamide, which gave product **3u** in >99% yield (entry 3). Compared with *N*,*N*-dimethylpropanamide, *N*-phenylpropanamide and *N*-phenyl-*N*-methylpropanamide, which were insoluble in the reaction mixture, gave **3v** and **3w** in lower yields (88% in each case; entries 4 and 5). To our satisfaction, 1-(ethynylsulfonyl)-4-methylbenzene also reacted well to give product **3x** in 93% yield after stirring for one hour at room temperature (entry 6). Finally, the lowest yield and the worst stereoselectivity were observed with phenyl propiolate, which gave product **3y** in 67% yield (entry 7).

On the basis of previous related reports,[9] water is considered to play a key role in promoting the protonation and deprotonation of the intermediate formed by Michael addition of the amines.[10] Subsequently, the thermodynamically favored *E*-type products are formed directly when secondary amines are used as nucleophilic coupling partners. When primary aromatic amines are used in the reaction, *Z*-type products are formed as a result of intramolecular hydrogen bonding between the NH group and the carbonyl oxygen.

Table 3 Scope of Alkynes[a]



1a 2 3q–w

Entry	Alkyne **2**	Product **3**	Yield[b] (%)
1[c]	 **2b**	 **3s**	85
2[d]	 **2c**	 **3t**	91
3	 **2d**	 **3u**	>99%
4	 **2e**	 **3v**	88
5	 **2f**	 **3w**	88
6[c]	 **2g**	 **3x**	93
7	 **2h**	 **3y**	67

[a] Reaction conditions: alkyne (0.5 mmol, 1.0 equiv), *N*-methylaniline (0.6 mmol, 1.2 equiv), H_2O (5 mmol, 11 equiv), 8 h, 80 °C, under air.
[b] Isolated yield.
[c] Stirred at r.t. for 1 h.
[d] Stirred at 80 °C for 1 h.

In conclusion, a simple, green, water-promoted, Michael addition has been developed. Various β-enamino esters and β-enaminones were synthesized stereoselectively in moderate to excellent yields (42 to >99%). (*Z*)-β-Enaminones were obtained from primary aromatic amines, whereas secondary amines gave (*E*)-β-enamino esters. We propose that water promotes the reaction, not only by improving the dispersion of the reactants, but also by assisting proton transfers in the formation of the intermediate and the product.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707968.

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(6) When the weakly nucleophilic *N*-methyl-*p*-nitroaniline was investigated as the aminating agent, none of the desired product was detected.

(7) When *p*-methoxyaniline was used, the desired product was formed in the first hour (TLC monitoring). On prolonging the reaction time, byproducts were detected and all the desired product was eventually consumed.

(8) The ratio of *Z*/*E* products from 1*H*-benzo[*d*]imidazole was about 29:50. The ratio of *Z*/*E* products from 1*H*-imidazole was about 50:21. The two ^{1}H NMR spectra are shown in Fig. S2 (Supporting Information).

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(10) When D_2O was used as additive in the reaction instead of H_2O, the ^{1}H NMR spectrum of the product (Figure S3; Supporting Information) showed that about half the double-bond protons were replaced by deuterium. However, as hydrogen exchange between both substrates and D_2O was found to occur, the degree of participation of H_2O/D_2O in protonation/deuteration could not be conclusively demonstrated by this experiment.

(11) **Ethyl (2*E*)-3-[Methyl(phenyl)amino]acrylate (3a); Typical Procedure**

Ethyl propiolate (0.5 mmol) was slowly added with stirring to a mixture of *N*-methylaniline (0.6 mmol) and distilled H_2O (0.1 mL) in a 2 mL vial, and the vial then sealed. The mixture was heated at 80 °C with stirring for 1 h. The reaction was then quenched with sat. brine (0.5 mL), and the mixture was cooled to r.t. and extracted with EtOAc (3 × 1 mL) by pipette in the same vial. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, PE–EtOAc (8:1)] to give a pale yellow oil; yield: 96.7 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 13.2 Hz, 1 H), 7.38–7.31 (m, 2 H), 7.15–7.08 (m, 3 H), 4.94 (d, *J* = 13.2 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.24 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3, 148.6, 146.7, 129.6, 124.3, 120.0, 90.5, 59.44, 36.7, 14.7. MS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$: 206.1; found: 206.1.