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# Copper-Catalyzed One-Pot Synthesis of 2-Alkylidene-1,2,3,4-tetrahydropyrimidines

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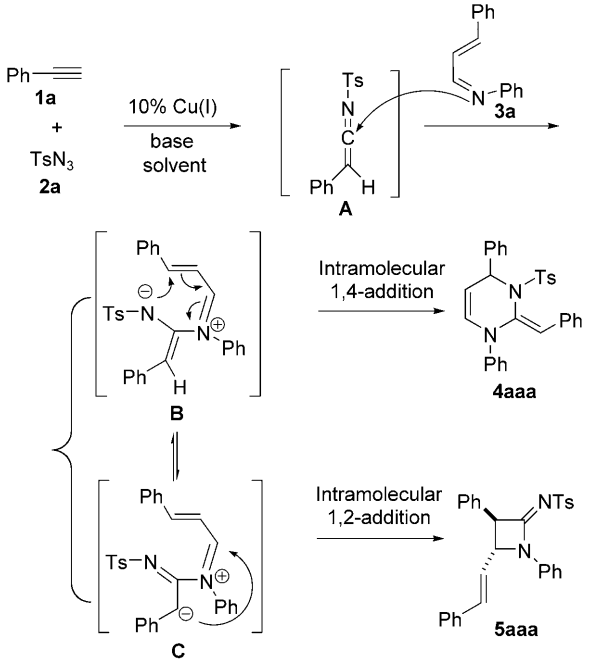
**Abstract:** A one-pot synthesis of *N*-sulfonyl-2-alkylidene-1,2,3,4-tetrahydropyrimidines *via* a highly selective and copper-catalyzed multicomponent reaction of sulfonyl azides, terminal alkynes and α,β-unsaturated imines has been developed. The α,β-unsaturated imine substrates could be generated from amines and α,β-unsaturated aldehydes in a one-pot process. The procedure is concise, general and efficient.

**Keywords:** ketenimines; multicomponent reactions; tandem reaction; tetrahydropyrimidines

Ketenimines are nitrogen-containing heterocumulenes, which can participate in a variety of organic reactions,[1] such as nucleophilic addition reactions,[2] radical addition reactions,[3] [2+2] and [4+2] cycloaddition reactions[4] and sigmatropic rearrangements.[5] Previously, we[6] and several other groups[7] developed the Cu-catalyzed three-component reactions of sulfonyl azides with terminal alkynes and a number of nucleophiles. The reactions involve a copper-catalyzed azide-alkyne cycloaddtion (CuAAC) and the generation of a ketenimine intermediate. Phosphoryl azides could also serve as a high-yielding type of azide to participate in the reaction.[8] These multicomponent reactions are versatile with regard to the substrate scope and the synthetic applicability. On the basis of these results, we anticipated that the ketenimine intermediate **A** (Scheme 1), which was *in situ* generated from terminal alkyne **1a** and sulfonyl azide **2a**, could react with α,β-unsaturated imine **3a** through a nucleophilic cyclization to give tetrahydropyrimidine **4aaa** and/or azetidin-2-imine **5aaa**, respectively. Since the formation of azetidin-2-imines *via* the reaction of the ketenimine intermediate with imines has been reported by Whiting and Fokin,[7e] we systematically optimized the reaction leading to the six-membered product and investigated the applicability of this method to a variety of terminal alkynes, sulfonyl azides and α,β-unsaturated imines. Herein, we report the details of this work.

Exhaustive studies of the reaction conditions for the synthesis of **4aaa** from terminal alkyne **1a**, sulfonyl azide **2a** and α,β-unsaturated imine **3a** showed that CuCl (Table 1, entry 1), CuBr (Table 1, entry 2), and CuI (Table 1, entries 3–14) could catalyze the reaction to result in a mixture of the six-membered product **4aaa** and the four-membered product **5aaa**,




**Scheme 1.** Copper-catalyzed three-component reaction of alkyne **1a**, sulfonyl azide **2a** and imine **3a**.

**Table 1.** Screening of the reaction conditions.[a]

| Entry | Cu(I) | Base/equiv. | Solvent | Reaction temperature | Reaction time [h] | Yield [%][b] | |
|---|---|---|---|---|---|---|---|
| | | | | | | **4aaa** | **5aaa** |
| 1 | CuCl | TEA/2 | toluene | r.t. | 3 | 75 | 19 |
| 2 | CuBr | TEA/2 | toluene | r.t. | 3 | 82 | 10 |
| 3 | CuI | TEA/2 | toluene | r.t. | 3 | 63 | 27 |
| 5 | CuI | TEA/2 | $CH_2Cl_2$ | reflux | 3 | 49 | 46 |
| 6 | CuI | TEA/2 | $CH_3CN$ | reflux | 2 | trace | 81 |
| 7 | CuI | TEA/1.2 | hexane | r.t. | 12 | 43 | 40 |
| 8 | CuI | TEA/2 | THF | reflux | 3 | 55 | 38 |
| 9 | CuI | Py/2 | $CH_3CN$ | r.t. | 12 | 65 | 23 |
| 12 | CuI | $K_2CO_3$/2 | $CH_3CN$ | r.t. | 3 | 45 | 46 |
| 13 | CuI | TMEDA/2 | $CHCl_3$ | r.t. | 3 | 34 | 57 |
| 14 | CuI | TEA/2 | $CH_3CN$ | 0 °C | 12 | 52 | 34 |
| 15 | CuBr | TEA/1 | toluene | r.t. | 5 | 75 | 15 |
| 16 | CuBr | TEA/4 | toluene | r.t. | 2 | 72 | 13 |
| 17 | CuBr | TEA/2 | $CHCl_3$ | r.t. | 3 | 67 | 17 |
| 18 | CuBr | TEA/2 | $CH_3NO_2$ | r.t. | 3 | trace | trace |
| 19 | CuBr | TEA/2 | $CH_3CN$ | r.t. | 3 | 18 | 48 |

[a] *Reaction conditions:* **1a** (1 mmol), **2a** (1 mmol), **3a** (1.05 mmol), copper catalyst (0.1 mmol), base, solvent (2 mL), $N_2$.
[b] Isolated yield.

but only CuBr gave the best selectivity for the formation of the six-membered product (Table 1, entry 2). Prolonging the reaction time (Table 1, entry 15) or increasing the amount of base additive (Table 1, entry 16) led to a lower selectivity. Toluene was found to be the best solvent as compared with other solvents, such as $CHCl_3$ (Table 1, entry 17), $CH_3NO_2$ (Table 1, entry 18), and $CH_3CN$ (Table 1, entry 19).

With the optimized reaction conditions in hand, we next explored the protocol with a variety of terminal alkynes, sulfonyl azides and imines (Table 2). In all cases, the three-component reaction furnished 2-alkylidene-1,2,3,4-tetrahydropyrimidines **4** as the major (Table 2, entries 1–6 and 27) or sole products (Table 2, entries 7–26 and 28–35). In several cases, we also isolated azetidin-2-imines **5**, generally with high *trans* selectivity (Table 2, entries 1–6 and 27). Both aryl (Table 2, entries 1–30 and 35) and aliphatic alkynes (Table 2, entries 31 and 32) afforded the desired products in good to excellent yields (60–96%), whereas 2-ethynylpyridine (**1g**) gave the corresponding pyrimidines **4gaa** and **4gab** in lower yields (Table 2, entries 33 and 34).

It is noteworthy that the resulting 2-alkylidene-1,2,3,4-tetrahydropyrimidines **4** are not stable in solution state, especially under acidic conditions, to yield azetidin-2-imines **5**.[9] For example, the six-membered product **4aaa** could be converted to the four-membered product **5aaa** in 43% conversion by stirring in chloroform at room temperature for 2 days.

We also investigated the possibility for the one-pot sequential synthesis of 2-alkylidene-1,2,3,4-tetrahydropyrimidines **4** from amines **6** and α,β-unsaturated aldehydes **7** as the starting materials. It was found that when primary amines **6** were coupled with α,β-unsaturated aldehydes **7** in the presence of CuBr and 4 Å molecular sieves for 30 min, the resulting α,β-unsaturated imines could react with alkynes **1** and $TsN_3$ in a one-pot procedure to yield the desired products **4**. Except in the case of $R^4$ = Me (Table 3, entry 9), the sequential procedure gave moderate to good yields (Table 3, entries 1–8, 10 and 11), which are comparable to those obtained directly from α,β-unsaturated imines (Table 2).

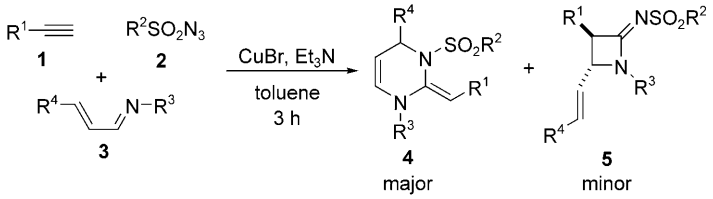
All products were well characterized by $^1$H NMR and $^{13}$C NMR spectroscopy as well as high-resolution mass spectrometry. The *trans* configuration of azetidin-2-imines **5** was assigned on the basis of the coupling constants between 3-H and 4-H, which were 1.0–2.4 Hz in agreement with the literature.[7e] The structures of compounds **4aaa** (Figure 1) and **5aaa** were confirmed by single-crystal X-ray analysis.[10]

The pyrimidine moiety is one of the most widespread heterocycles in biologically occurring compounds, such as nucleic acids and vitamin B1, and is an important constituent of numerous drug molecules in many therapeutic areas. Consequently, the synthesis of pyrimidine derivatives and pyrimidine-containing libraries has attracted much attention in the last decades.[11] The presented three-component reaction provides an efficient and versatile method for the synthesis of 2-alkylidene-1,2,3,4-tetrahydropyrimidines, a new class of pyrimidine derivatives.

In conclusion, we have developed a copper-catalyzed three-component reaction of sulfonyl azides, terminal alkynes and α,β-unsaturated imines, furnishing a new class of pyrimidine derivatives *N*-sulfonyl-2-alkylidene-1,2,3,4-tetrahydro-pyrimidines. The method

**Table 2.** Three-component synthesis of 2-alkylidene-1,2,3,4-tetrahydropyrimidines **4**.[a]




| Entry | $R^1$ | $R^2$ | $R^3/R^4$ | Product/Yield [%][b] | |
|---|---|---|---|---|---|
| | | | | **4** | **5** |
| 1 | Ph (**1a**) | 4-$MeC_6H_4$ (**2a**) | Ph/Ph (**3a**) | **4aaa**/82 | **5aaa**/10 |
| 2 | **1a** | **2a** | 4-$MeOC_6H_4$/Ph (**3b**) | **4aab**/93 | **5aab**/4 |
| 3 | **1a** | **2a** | Ph/4-$MeOC_6H_4$ (**3c**) | **4aac**/87 | **5aac**/9 |
| 4 | **1a** | **2a** | 4-$BrC_6H_4$/Ph (**3d**) | **4aad**/83 | **5aad**/7 |
| 5 | **1a** | **2a** | Ph/4-$BrC_6H_4$ (**3e**) | **4aae**/81 | **5aae**/12 |
| 6 | **1a** | **2a** | 4-$MeC_6H_4$/Ph (**3f**) | **4aaf**/83 | **5aaf**/8 |
| 7 | **1a** | **2a** | 4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**3g**) | **4aag**/90 | – |
| 8 | **1a** | **2a** | Ph/4-$NO_2C_6H_4$ (**3h**) | **4aah**/79 | – |
| 9 | **1a** | **2a** | 4-$MeOC_6H_4$/4-$NO_2C_6H_4$ (**3i**) | **4aai**/96 | – |
| 10 | **1a** | **2a** | 3-$MeC_6H_4$/Ph (**3j**) | **4aaj**/70 | – |
| 11 | **1a** | **2a** | 4-$MeOC_6H_4$/2-$MeOC_6H_4$ (**3k**) | **4aak**/68 | – |
| 12 | **1a** | Me (**2b**) | **3a** | **4aba**/60[c] | – |
| 13 | **1a** | 4-$AcNHC_6H_4$ (**2c**) | **3a** | **4aca**/89 | – |
| 14 | **1a** | 4-$ClC_6H_4$ (**2d**) | **3a** | **4ada**/82 | – |
| 15 | **1a** | 4-$NO_2C_6H_4$ (**2e**) | **3a** | **4aea**/86 | – |
| 16 | **1a** | Ph (**2f**) | **3a** | **4afa**/73 | – |
| 17 | **1a** | **2f** | **3c** | **4afc**/88 | – |
| 18 | **1a** | **2f** | **3e** | **4afe**/82 | – |
| 19 | **1a** | **2f** | **3i** | **4afi**/86 | – |
| 20 | **1a** | **2c** | **3b** | **4acb**/93 | – |
| 21 | **1a** | **2e** | **3b** | **4aeb**/91 | – |
| 22 | **1a** | **2b** | **3c** | **4abc**/75[c] | – |
| 23 | **1a** | **2d** | **3c** | **4adc**/72 | – |
| 24 | 4-$EtC_6H_4$ (**1b**) | **2a** | **3c** | **4bac**/93 | – |
| 25 | **1b** | **2a** | **3b** | **4bab**/96 | – |
| 26 | **1b** | **2a** | **3a** | **4baa**/85 | – |
| 27 | 4-$MeOC_6H_4$ (**1c**) | **2a** | **3a** | **4caa**/65 | **5caa**/28 |
| 28 | **1c** | **2a** | **3b** | **4cab**/89 | – |
| 29 | 4-$MeC_6H_4$ (**1d**) | **2a** | **3a** | **4daa**/79 | – |
| 30 | **1d** | **2a** | **3c** | **4dac**/93 | – |
| 31 | *n*-Bu (**1e**) | **2a** | **3a** | **4eaa**/79 | – |
| 32 | *n*-$C_8H_{17}$ (**1f**) | **2a** | **3a** | **4faa**/73 | – |
| 33 | 2-Py (**1g**) | **2a** | **3a** | **4gaa**/43[d] | – |
| 34 | **1g** | **2a** | **3b** | **4gab**/43[d] | – |
| 35 | **1b** | **2d** | **3i** | **4bdi**/83 | – |

[a] *Reaction conditions:* **1** (1 mmol), **2** (1 mmol), **3** (1.05 mmol), CuBr (0.1 mmol), TEA (2 mmol), PhMe (3 mL), $N_2$, room temperature, 3 h.
[b] Isolated yield.
[c] Yield after 8 h.
[d] Yield after 6 h.

is concise, general, highly selective, and efficient. The substrates are readily available and the imine substrates could be generated in a one-pot sequential process. It is expected that the presented method will find its applications in the area of the synthesis of pyrimidine heterocycles.

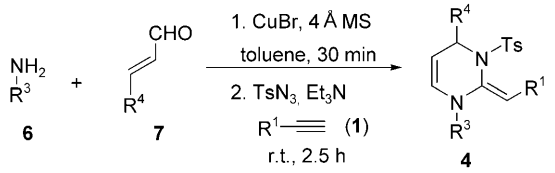
# Experimental Section

### General Procedure for the Three-Component Synthesis of Pyrimidines 4

To a mixture of CuBr (14 mg, 0.1 mmol), alkynes **1** (1 mmol), azides **2** (1 mmol), and α,β-unsaturated imines **3**

**Table 3.** One-pot sequential synthesis of 2-alkylidene-1,2,3,4-tetrahydropyrimidines.[a]




| Entry | $R^1$ | $R^3$ | $R^4$ | Product/Yield [%][b] |
|---|---|---|---|---|
| 1 | Ph (**1a**) | Ph (**6a**) | Ph (**7a**) | **4aaa**/75[c] |
| 2 | **1a** | 4-$MeOC_6H_4$ (**6b**) | **7a** | **4aab**/72 |
| 3 | **1a** | **6a** | 4-$NO_2C_6H_4$ (**7b**) | **4aah**/88 |
| 4 | **1a** | **6b** | **7b** | **4aai**/75 |
| 5 | 4-$EtC_6H_4$ (**1b**) | **6a** | **7a** | **4baa**/79 |
| 6 | 4-$MeOC_6H_4$ (**1c**) | **6b** | **7a** | **4cab**/62 |
| 7 | 4-$MeC_6H_4$ (**1d**) | **6a** | **7a** | **4daa**/68 |
| 8 | *n*-Bu (**1e**) | **6a** | 4-$MeOC_6H_4$ (**7c**) | **4a**/61 |
| 9 | **1a** | **6b** | Me (**7d**) | **4b**/35 |
| 10 | **1a** | 3-$MeC_6H_4$ (**6c**) | **7a** | **4aaj**/49 |
| 11 | **1a** | **6b** | 2-$MeOC_6H_4$ (**7e**) | **4aak**/43 |

[a] *Reaction conditions:* (1) CuBr (0.1 mmol), 4 Å molecular sieves (0.2 g), **6** (1.05 mmol), **7** (1.05 mmol), PhMe (2 mL), room temperature, $N_2$, 0.5 h; (2) **1** (1 mmol), $TsN_3$ (1 mmol), TEA (2 mmol), PhMe (3 mL), room temperature, 2.5 h.
[b] Isolated yield.
[c] **5aaa** was also isolated in 15% yield.

(1.05 mmol) in toluene (2 mL) was added TEA (2 mmol) in toluene (1 mL) under an $N_2$ atmosphere. The mixture was then stirred at room temperature for 3 h. After completion of the reaction, which was monitored by TLC, the mixture was evaporated under vacuum. The residue was subjected to silica gel column chromatography with petroleum ether (Pet)/ethyl acetate (EA) as eluent (containing 0.5% v/v TEA). The products were recrystalized from hexane/EA or Pet/EA.

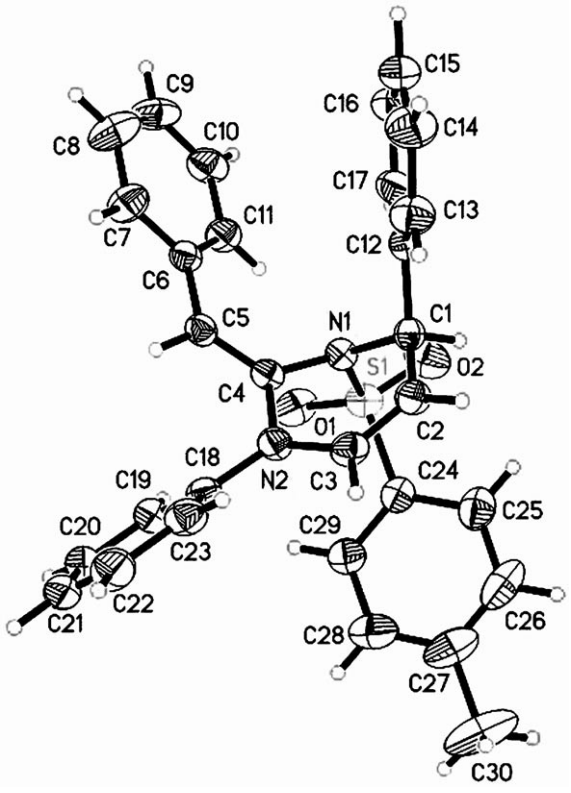



**Figure 1.** X-ray crystal structure of **4aaa**.

## General Procedure for the Sequential Synthesis of Pyrimidines 4

A mixture of CuBr (14 mg, 0.1 mmol), 4 Å molecular sieves (0.2 g), amines **6** (1.05 mmol), and α,β-unsaturated aldehydes **7** (1.05 mmol) in anhydrous toluene (2 mL) was stirred at room temperature under an $N_2$ atmosphere for 0.5 h. A solution of alkynes **1** (1 mmol) and $TsN_3$ (1 mmol) in toluene (1 mL) was added, following by addition of TEA (2 mmol) in toluene (1 mL). The mixture was then stirred at room temperature for an additional 2.5 h. After completion of the reaction, the mixture was filtered and washed with ethyl acetate. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography with Pet/EA as eluent (containing 0.5% v/v TEA).

**(*Z*)-2-Benzylidene-1,4-diphenyl-3-tosyl-1,2,3,4-tetrahydropyrimidine (4aaa):** colorless crystals; mp 135.2–136.1 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$ (d, $J = 8.4$ Hz, 2H), 7.44–7.34 (m, 6H), 7.24–7.18 (m, 3H), 7.17–7.14 (m, 3H), 7.00 (bs, 5H), 6.11 (d, $J = 8.4$ Hz, 1H), 5.92 (s, 1H), 5.63 (d, $J = 5.2$ Hz, 1H), 4.61 (dd, $J = 8.0$, 5.2 Hz, 1H), 2.35 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 143.8$, 143.7, 138.7, 136.1, 134.0, 131.4, 130.3, 129.7, 129.0, 128.7, 128.4, 128.2, 128.1, 127.6, 126.5, 125.1, 123.9, 116.3, 97.7, 58.4, 21.5; IR (KBr): $\nu = 3029$, 1649, 1595, 1492, 1341, 1297, 1162, 1145, 1087, 898, 750, 700, 566 cm$^{-1}$; MS (ESI): $m/z = 479.3$ ($[M+H]^+$); HR-MS (ESI): $m/z = 479.1765$, calcd. for $C_{30}H_{27}N_2O_2S$ $[M+H]^+$: 479.1788.

**(*Z*)-2-Pentylidene-1,4-diphenyl-3-tosyl-1,2,3,4-tetrahydropyrimidine (4eaa):** white solid; mp 95.4–95.6 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 7.84$ (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 7.0$ Hz, 2H), 7.35–7.30 (m, 4H), 7.27–7.25 (m, 1H), 7.21 (d, $J = 7.5$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.10 (t, 7.5 Hz, 1H), 6.06 (d, $J = 8.0$ Hz, 1H), 5.55 (d, $J = 5.5$ Hz, 1H), 5.04 (dd, $J = 8.0$, 6.5 Hz, 1H), 4.54 (dd, $J = 8.0$, 5.5 Hz, 1H), 2.35 (s, 3H), 1.92–1.89 (m, 2H), 0.91–0.86 (m, 2H), 0.81–0.75 (m, 1H), 0.63 (t, $J = 7.3$ Hz, 3H), 0.35–0.28 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 144.0$, 143.4, 140.0, 136.3, 130.3, 129.9, 129.4, 129.0, 128.6, 128.0, 127.7, 124.0, 122.5, 119.2, 96.5, 57.8, 31.1, 26.7, 22.2, 21.5, 13.8; IR (KBr): $\nu = 3061$, 2921, 2852, 1676, 1636, 1597, 1492, 1341, 1166, 1150, 1080, 1026, 937, 816, 703 cm$^{-1}$; MS (ESI): $m/z = 459.3$ ($[M+H]^+$); HR-MS (ESI): $m/z = 481.1932$, calcd. for $C_{28}H_{30}N_2O_2SNa$ $[M+Na]^+$: 481.1920.

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