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Copper-Catalyzed Four-Component Reaction of Baylis–Hillman Adducts with Alkynes, Sulfonyl Azides and Alcohols

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Abstract: 4-(Alkoxycarbonyl)-pent-4-enimidates were regioselectively synthesized *via* a copper-catalyzed four-component reaction of Baylis–Hillman adducts with terminal alkynes, sulfonyl azides and alcohols. The procedure is concise, general and efficient. The resulting pentenimidates could be further transformed to 3-methylene-2,3-dihydroindene-1-imidates.

Keywords: Baylis–Hillman adducts; cascade reactions; copper; imidates; ketenimines; multicomponent reactions

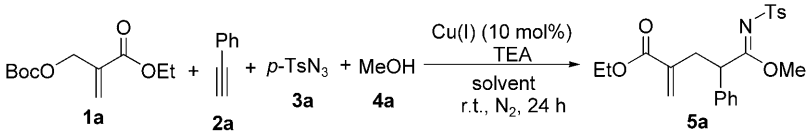
Ketenimine, as an active intermediate, has attracted much attention in organic synthesis due to its reactivity and diverse chemistry.[1] Based on the *in situ* formation of ketenimine *via* copper-catalyzed azide-alkyne cycloaddition (CuAAC),[2] Chang,[3] our group[4] and others[5] developed a series of three-component reactions (3-CRs) based on sulfonyl or phosphoryl azides, terminal alkynes and various nucleophiles. The reactions were conducted in a single step with both economic and ecological values and were proved to process through a ketenimine intermediate. Using this strategy, a number of interesting products, such as functionalized amidines, imidates, iminocoumarins, iminodihydrocoumarins, iminodihydroquinolines, benzimidazoles, tetrahydropyrimidines and pyrroles were efficiently constructed. However, to the best of our knowledge, there were only two published examples of four-component reactions (4-CRs) on the basis of formation of ketenimine *via* CuAAC, which furnished α-aryl-β-hydroxyimidates[6] and γ-nitroimidates[7] in one pot, respectively.

Baylis–Hillman adducts, containing a minimum of three chemospecific functional groups, which are hydroxy/amino, alkene, and electron-withdrawing groups, are important precursors for the synthesis of various complicated molecules and biologically active products.[8] Upon the conversion of the hydroxy to a better leaving group, such as their *tert*-butyl carbonates (**1a**), Baylis–Hillman adducts become more pratical and easily to undergo allylic substitution with different nucleophiles,[9] which makes Baylis–Hillman chemistry more valuable.

Attracted by the versatile ketenimine intermediate and Baylis–Hillman chemistry, we designed a new reaction, using Baylis–Hillman adducts **1**, terminal alkynes **2**, sulfonyl azides **3**, and alcohols **4** as substrates for a cascade, four-component process. The reaction was promoted by copper (I) and occurred smoothly. It regioselectively afforded 4-(alkoxycarbonyl)-pent-4-enimidates **5** in a single step.

In our initial investigation, the *tert*-butyl carbonate of Baylis–Hillman adduct (**1a**), phenylacetylene (**2a**), *p*-toluenesulfonyl azide (**3a**), and methanol (**4a**) were selected as starting materials for optimizing the reaction condition (Table 1). The reaction occurred smoothly in dichloroethane (DCE), chloroform and acetonitrile, respectively (Table 1, entries 1–3). The reaction in THF or toluene only afforded the three-component product, which was not associated with **1a** (Table 1, entries 4 and 5). Starting materials **1a**, **2a** and **3a** remained unreacted when dimethyl sulfoxide (DMSO) or *N*,*N*-dimethylformamide (DMF) was used as solvent (Table 1, entries 6 and 7). Besides the solvent effect on this 4-CR reaction, the base also functioned as a major factor. In the case of pyridine, only a trace amount of four-components adduct **5a** was detected on TLC (Table 1, entry 8). Potassium carbonate did not trigger the reaction at all (Table 1, entry 9). DBU worked for the reaction, but its effi-

Table 1. Optimization of conditions for four-component reactions.[a]



Entry	Cu(I)	Solvent	MeOH (equiv.)	Base/equiv.	Yield [%][b]
1	CuI	DCE	1.2	TEA/1.2	81
2	CuI	CH_3CN	1.2	TEA/1.2	71
3	CuI	$CHCl_3$	1.2	TEA/1.2	51
4	CuI	THF	1.2	TEA/1.2	trace[c]
5	CuI	toluene	1.2	TEA/1.2	trace[c]
6	CuI	DMSO	1.2	TEA/1.2	none[d]
7	CuI	DMF	1.2	TEA/1.2	none[d]
8	CuI	DCE	1.2	Py/1.2	trace[c]
9	CuI	DCE	1.2	K_2CO_3/1.2	none[d]
10	CuI	DCE	1.2	DBU/1.2	31
11	CuI	DCE	1.2	TEA/3	52
12	CuI	DCE	5	TEA/3	43
13	CuI	DCE	5	TEA/5	42
14	CuI	DCE	5	TEA/1.2	68
15	CuBr	DCE	1.2	TEA/1.2	74
16	CuCN	DCE	1.2	TEA/1.2	32
17	CuCl	DCE	1.2	TEA/1.2	78

[a] *Reaction conditions:* **1a** (1 mmol), **2a** (1.2 mmol), **3a** (1.2 mmol), Cu(I) (0.1 mmol), solvent, room temperature, under N_2, 24 h.
[b] Isolated yield.
[c] Major 3-CR product and reactant **1a**.
[d] All of the reactants remained unchanged.

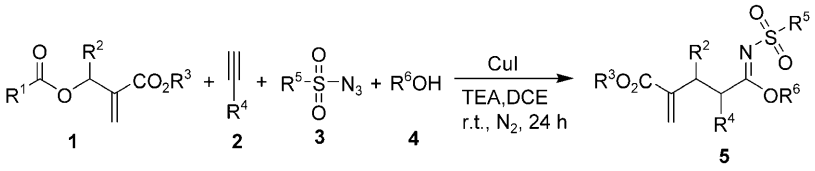
ciency was not comparable to that of triethylamine (TEA) (Table 1, entry 1 and 10). An equivalent amount of TEA to methanol was important for achieving high efficiency (Table 1, entries 1 and 11–14). Among the different sources of copper (I), CuI presented the most efficiency for this transformation (Table 1, entries 1 and 15–17). Thus, the optimized reaction conditions were established. We selected DCE as solvent, TEA as base, and CuI as catalyst, and performed the reaction under a nitrogen atmosphere at room temperature for 24 h.

With the optimized reaction conditions in hand, the scope of this transformation was further investigated with a variety of Baylis–Hillman adducts **1**, terminal alkynes **2**, sulfonyl azides **3** and alcohols **4** (Table 2). In all cases, the reactions proceeded smoothly and afforded the desired 4-CR products in moderate to high yields (35–81%). For Baylis–Hillman adducts **1**, the *tert*-butyl carbonate (BocO), as a better leaving group (Table 2, entry 1) and gave a much higher yield than the acetate group (AcO) (Table 2, entry 2). When methyl ester **1c** was used instead of ethyl ester **1a**, the isolated yields decreased significantly when methanol or ethanol was used as nucleophile (Table 2, entries 1 and 3, 7 and 8) , respectively. Steric hindrance in the allylic position of the Baylis–Hillman adducts **1d–f** slightly influenced the isolated yields, but without notable diastereoselectivity (Table 2, entries 4–6). Various terminal alkynes **2a–f** worked well for this reaction (Table 2, entries 8–13). Along with the formation of the normal 4-CR adduct **5l**, **6a** (Scheme 1) was also isolated in 11% yield when 2-pyridinylacetylene (**2f**) was employed (Table 2, entry 13). 4-Nitrophenylsulfonyl azide (**3c**) also worked for this transformation and generated **5n** and **6b** in yields of 42% and 14%, respectively (Table 2, entry 15).

It is noteworthy that a 3-CR product **7a** was isolated in 64% yield instead of the formation of the predicted 4-CR product when a secondary alcohol (for example, **4c**) was used as nucleophile (Scheme 2). Two similar cases occurred when aliphatic alkyne **2g** or aliphatic sulfonyl azide **3d** was used as the substrate (Scheme 2). In these cases, the Baylis–Hillman adduct **1a** failed to participate in the cascade process.

Based on the reaction condition survey and the substrate investigation, a plausible mechanistic pathway is presented in Scheme 3. A Michael donor **B** is assumed to be generated by the nucleophilic addition of alcohol **4a** to the reactive *N*-sulfonyl ketenimine intermediate **A**, which is formed *via* the copper-catalyzed reaction of alkyne **2** and sulfonyl azide **3** (CuAAC).[2–5] Simultaneously, the Baylis–Hillman adduct **1** undergoes an allylic nucleophilic substitution with TEA to form the Michael acceptor **D** by releas-

Table 2. Substrate scope for the four-component reaction.[a]

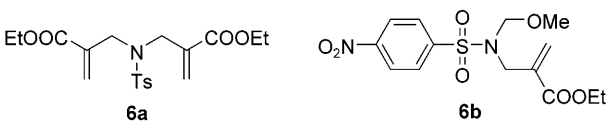


Entry	**1** (R^1/R^2/R^3)	**2** (R^4)	**3** (R^5)	**4** (R^6)	Product/Yield [%][b]
1	**1a** (*t*-BuO/H/Et)	**2a** (Ph)	**3a** (4-MeC_6H_4)	**4a** (Me)	**5a**/81
2	**1b** (Me/H/Et)	**2a**	**3a**	**4a**	**5a**/35
3	**1c** (*t*-BuO/H/Me)	**2a**	**3a**	**4a**	**5b**/52
4	**1d** (*t*-BuO/Ph/Et)	**2a**	**3a**	**4a**	**5c**/61[c,d]
5	**1e** (*t*-BuO/4-$NO_2C_6H_4$/Et)	**2a**	**3a**	**4a**	**5d**/68[c,e]
6	**1f** (*t*-BuO/Ph/Me)	**2a**	**3a**	**4a**	**5e**/51[c,f]
7	**1a**	**2a**	**3a**	**4b** (Et)	**5f**/58
8	**1c**	**2a**	**3a**	**4b**	**5g**/38
9	**1c**	**2b** (4-EtC_6H_4)	**3a**	**4a**	**5h**/57
10	**1a**	**2c** (3-MeC_6H_4)	**3a**	**4a**	**5i**/73
11	**1a**	**2d** (3-ClC_6H_4)	**3a**	**4a**	**5j**/64
12	**1a**	**2e** (2-BrC_6H_4)	**3a**	**4a**	**5k**/61
13	**1a**	**2f** (2-Py)	**3a**	**4a**	**5l**/56[g]
14	**1a**	**2a**	**3b** (Ph)	**4a**	**5m**/72
15	**1a**	**2a**	**3c** (4-$NO_2C_6H_4$)	**4a**	**5n**/42[h]

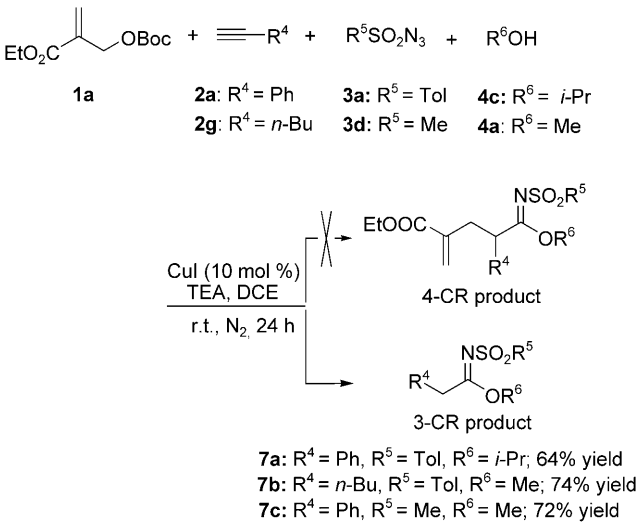
[a] *Reaction conditions:* **1** (1 mmol), **2** (1.2 mmol), **3** (1.2 mmol), **4** (1.2 mmol), CuI (0.1 mmol), TEA (1.2 mmol), DCE (2 mL), N_2, room temperature, 24 h.
[b] Isolated yield.
[c] Diastereomeric ratio (*syn*/*anti*) was determined by HPLC of the crude product.
[d] (*syn*/*anti*) 72:28.
[e] (*syn*/*anti*) 74:26.
[f] (*syn*/*anti*) 68:32.
[g] **6a** (Scheme 1) was also isolated in 11% yield.
[h] **6b** (Scheme 1) was also isolated in 14% yield.

ing the tertiary butyl alcohol and carbon dioxide.[9] Allylic nucleophilic substitution of Michael acceptor **D** with Michael donor **B** gives the desired 4-CR adduct **5** by giving off triethylamine *via* Pathway (a). When aliphatic alkyne **2g** or aliphatic azide **3d** is used as the substrate, the anion **B** is quickly protonated to afford the 3-CR product **7** *via* Pathway (b) due to the increased basicity of anion **B**. Tuning the electrophilicity of the Michael acceptor **1** to **D** is very important for this 4-CR reaction. As we can conclude from the isolated product, **8** was not observed in any cases because the Michael acceptor **1** was unable to be nucleophilically replaced by **B** *via* Pathway (c).

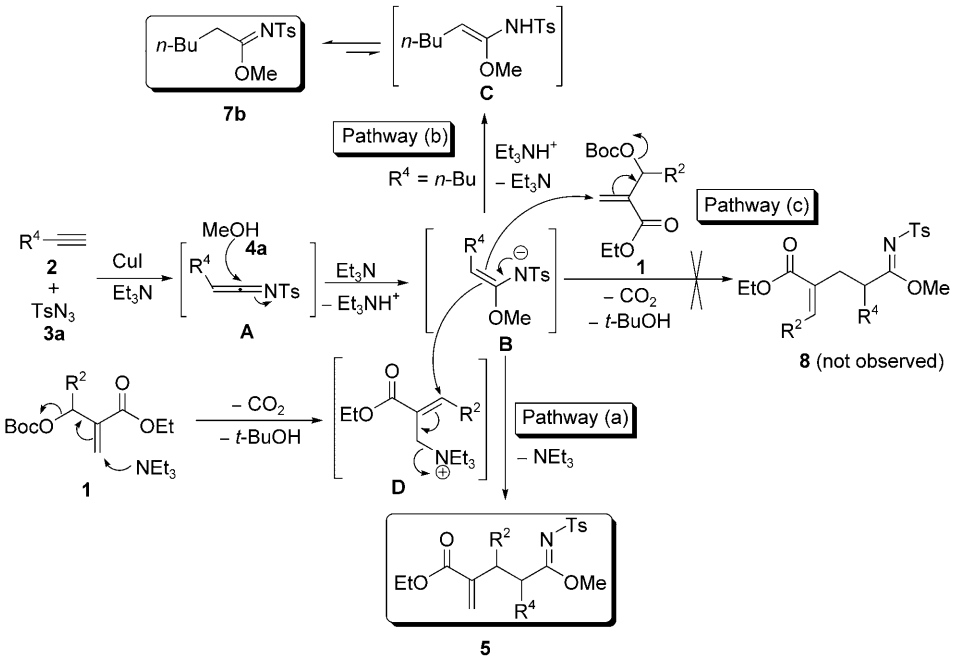
The formation of the side-products **6a** and **6b** is illustrated in the Supporting Information. Copper-catalyzed decomposition of azide **3** in the presence of methanol (**4a**) results in the formation of sulfoamide and formaldehyde.[10] Nucleophilic substitution of Michael acceptor **D** with deprotonated sulfonamide anion **E** generates allyl sulfonamide **F**. In the case of 2-pyridinylacetylene (**2f**), the further deprotonated



Scheme 1. Structures of the side-products **6a** and **6b**.



Scheme 2. Formation of three-component products **7**.

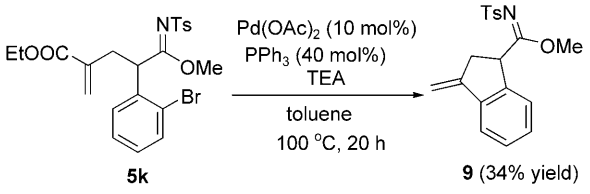


Scheme 3. Possible mechanism for the four-component reaction.

anion **H** nucleophilically attacks **D** to afford the side-product **6a**. When 4-nitrobenenesulfonyl azide (**3c**) is used, the increasing acidity of the sulfoamide **F**, due to the electron-withdrawing nature of the nitro group, makes the Mannich-type condensation possible and forms **6b** in a certain amount.

As an extension of this transformation, we tested the application of this cascade reaction in the synthesis of a complicated compound. Based on this consideration, **5k** was synthesized and tested for the palladium-catalyzed intramolecular coupling.[11] Instead of obtaining the normal Heck reaction product with a dihydronaphthlene substructure, a decarboxylative coupling process occurred and 3-methylene-2,3-dihydroindene-1-imidate **9** was obtained (Scheme 4).

In conclusion, we have developed a highly regioselective four-component reaction of Baylis–Hillman adducts with alkynes, sulfonyl azides and alcohols, which afforded 4-(alkoxycarbonyl)-pent-4-enimidates in a single step by nicely tuning the electrophilicity of Baylis–Hillman adducts. The products could be further transformed to potentially useful compounds, such as 3-methylene-2,3-dihydroindene-1-imidates. The scope, enantioselectivity and synthetic applications for this reaction are under investigation.



Scheme 4. Transformation of product **5k**.

Experimental Section

General Procedure for the Synthesis of Imidates 5

To a mixture of CuI (0.1 mmol), Baylis–Hillman adducts **1** (1 mmol), alkyne **2** (1.2 mmol) and azide **3** (1.2 mmol) in DCE (1 mL) were added TEA (1.2 mmol), alcohol **4** (1.2 mmol) in DCE (1 mL) under an N_2 atmosphere. The mixture was then stirred at ambient temperature for 24 h and then evaporated under vacuum. The residue was subjected to silica gel column chromatography with petroleum ether/ethyl acetate as eluent.

Procedure for the Synthesis of Indene 9

To a mixture of $Pd(OAc)_2$ (0.015 mmol) and PPh_3 (0.06 mmol) in toluene (1 mL) was added TEA (0.188 mmol) and **5k** (0.15 mmol) in toluene (1 mL) under an N_2 atmosphere. The mixture was then stirred at 100 °C for 20 h and then evaporated under vacuum. The residue was subjected to silica gel column chromatography with petroleum ether/ethyl acetate as eluent to afford pure **9**.

Data for compound 5a: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 7.2$ Hz, 2H), 7.32–7.21 (m, 5H), 6.21(s, 1H), 5.57 (s, 1H), 5.30–5.26 (m, 1H), 4.24 (q, $J = 14.4$, 7.2 Hz, 2H), 3.72 (s, 3H), 3.12–3.06 (m, 1H), 2.94–2.89 (m, 1H), 2.38 (s, 3H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.1$, 166.3, 143.0, 139.0, 137.3, 137.2, 129.1, 128.5, 127.5, 126.9, 126.5, 60.8, 55.5, 47.8, 35.4, 21.3, 14.0; IR: $\nu = 2983$, 1716, 1595, 1153, 1092, 814 cm^{-1}; MS (ESI): $m/z = 416.2$ ($[M+H]^+$); HR-MS (EI): $m/z = 415.1454$, calcd. for $C_{22}H_{25}NO_5S$: 415.1453.

Data for compound 9: White solid; mp: 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.35–7.26 (m, 4H), 7.26–7.23 (m, 1H), 5.52 (s, 1H), 5.36–5.33 (m, 1H), 5.09 (s, 1H), 3.65 (s, 3H), 3.24–3.18 (m, 1H), 3.03–2.97 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 176.5$, 147.6, 143.3, 141.2, 139.1, 129.4, 128.8, 128.0, 126.7, 125.5, 120.8, 103.8, 55.7, 46.4, 36.7, 21.5; IR (KBr): $\nu = 2923$, 1170, 913, 744, 666 cm^{-1}; MS (ESI): $m/z = 342.1$ ($[M+H]^+$); HR-MS (EI): $m/z =$ 341.1100, calcd. for $C_{19}H_{19}NO_3S$: 341.1086.

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