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Three-component coupling of alkynes, Baylis–Hillman adducts and sodium azide: a new synthesis of substituted triazoles☆

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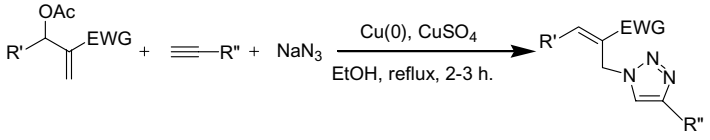
Abstract—A three-component coupling was used to prepare a series of 1,4-disubstituted-1,2,3-triazoles from the corresponding acetylated Baylis–Hillman adducts, sodium azide and terminal alkynes. This one-pot reaction further increases the efficacy of 'Click' synthesis and diversifies the preparation of multi-functional 1,4-disubstituted-1,2,3-triazoles.

1. Introduction

Multi-component coupling reactions have gained high prominence in the recent times,[1] especially for the synthesis of new chemical entities with diversity (diversity oriented organic synthesis).[2] 'Click' chemistry[3] has allowed the generation of large number of drug-like molecules with a triazole scaffold. These scaffolds have shown interesting biological properties such as antibacterial,[4] anti-HIV[5] and antiallergic.[6] Triazoles are also found in herbicides[7] and dyes.[8] Our group has been engaged in the development of new multi-component and one-pot reactions[9] under various conditions. To further extend our efforts towards this goal, we have developed a new 'Click-Multi-Component' (CMC) variant, wherein acetylated Baylis–Hillman adducts[10] undergo a smooth, three-component coupling with alkynes and sodium azide. The products thus formed, namely 1,4-disubstituted triazoles, provide diversity via various substitutions both in the triazole ring and alkyl side chain on N-1 of the triazole (Scheme 1).[11]

Initially, phenyl acetylene **1a**, furfuraldehyde–methyl acrylate adduct **1b** and sodium azide, with a catalytic amount of copper turnings and copper sulfate solution were heated in ethyl alcohol at reflux for 2 h to give highly diverse multi-functional **1c** in 92% yield after a simple work-up and isolation. Our mechanistic proposal for this transformation is shown in Scheme 2. Michael addition of azide onto the Baylis–Hillman adduct through a favourable six-membered transition state followed by [3+2] cycloaddition with the acetylene derivative would generate the observed products. We suggest that the acetylene group is activated through copper complex **I**.[12]

The scope of this triazole synthesis is revealed in the several examples shown in Table 1. 4-Methyl benzaldehyde-acrylonitrile Baylis–Hillman adduct **5b**, phenylacetylene **1a** and sodium azide also underwent the sequence to give **5c** in 90% yield. Other acetylated Baylis–Hillman adducts (entries **2b**, **3b**, **4b**, **6b**, **7b**) participated equally well in this one-pot procedure, with over 80% yields.



Scheme 1. One-pot synthesis of 1,4-disubstituted-1,2,3-triazoles.

Keywords: Multi-component coupling; Click synthesis; Triazoles; Baylis–Hillman adduct; Terminal alkynes.
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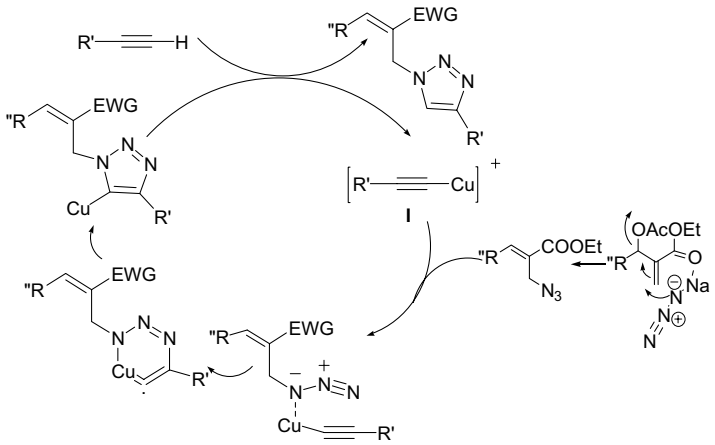


Scheme 2. Proposed catalytic cycle for the Cu(0)-catalyzed ligation followed by three-component coupling.

Table 1. Synthesis of triazoles through three-component coupling

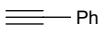
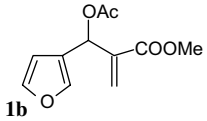
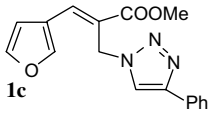
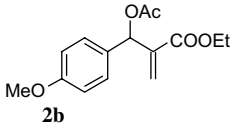
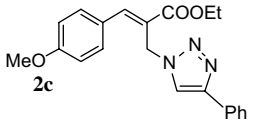
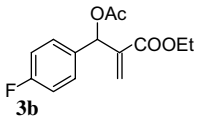
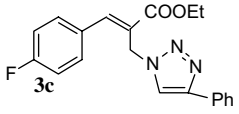
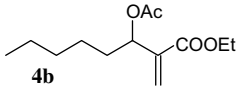
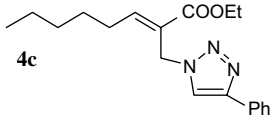
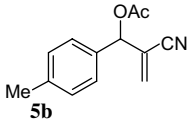
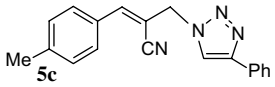
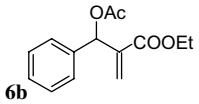
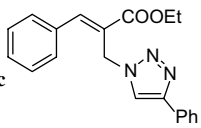
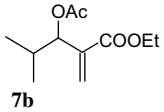
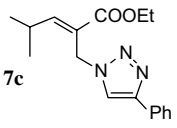
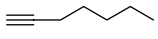
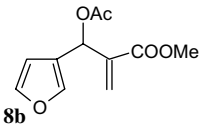
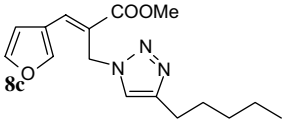
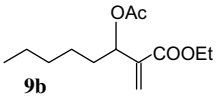
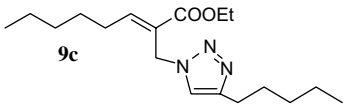
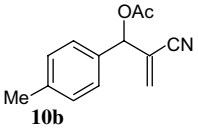
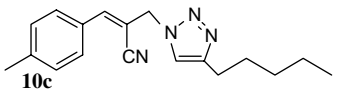
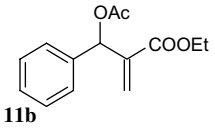
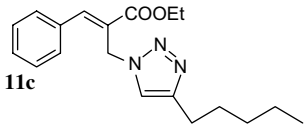
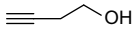
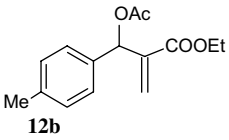
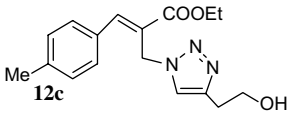
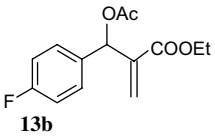
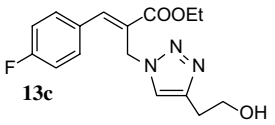
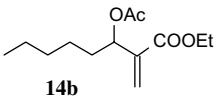
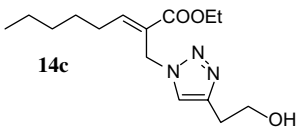
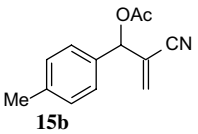
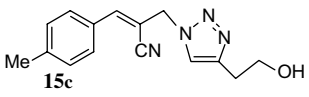
Entry	Alkyne	Baylis–Hillman adduct	Product[a]	Stereochemistry[b]	Yield[c] (%)
1	 **1a**	 **1b**	 **1c**	*E*	92
2		 **2b**	 **2c**	*E*	85
3		 **3b**	 **3c**	*E*	76
4		 **4b**	 **4c**	*E*	89
5		 **5b**	 **5c**	*Z*	90
6		 **6b**	 **6c**	*E*	87
7		 **7b**	 **7c**	*E*	84

Table 1 (*continued*)

Entry	Alkyne	Baylis–Hillman adduct	Product[a]	Stereochemistry[b]	Yield[c] (%)
8	 **8a**	 **8b**	 **8c**	*E*	91
9		 **9b**	 **9c**	*E*	85
10		 **10b**	 **10c**	*Z*	87
11		 **11b**	 **11c**	*E*	73
12	 **12a**	 **12b**	 **12c**	*E*	85
13		 **13b**	 **13c**	*E*	72
14		 **14b**	 **14c**	*E*	81
15		 **15b**	 **15c**	*Z*	86

[a] All products were characterized by ^{1}H NMR and mass spectral data.

[b] The exclusive (*E*) and (*Z*) stereochemistry was assigned on the basis of NMR experiments, which clearly showed NOE cross-peaks between the methylene protons and R′-group protons and the absence of an effect between these protons and the vinylic protons for the compounds with (*E*) stereochemistry whereas the opposite effects were observed for the compounds with (*Z*) stereochemistry.

[c] Yield refers to the isolated pure products after column chromatography.

Two other alkynes, 1-heptyne **8a** and homopropargyl alcohol **12a**, were also subjected to this three-component coupling, with variety of acetylated Baylis–Hillman adducts (entries **8b**–**15b**) and sodium azide, without any difficulty to realize the corresponding triazoles[13] in good yields.

In conclusion, it has been demonstrated that acetylated Baylis–Hillman adducts undergo smooth three-component coupling with sodium azide and terminal alkynes in one pot to furnish the diverse multi-functional 1,4-disubstituted triazoles. The operational simplicity of this method and the high yields of the products make it attractive not only for the large scale synthesis of this class of potentially biologically active molecules, but also for the synthesis of screening libraries for drug discovery.[14]

2. Typical experimental procedure

Acetylated furfuraldehyde–methyl acrylate adduct **1b** (100 mg, 0.44 mmol), phenylacetylene **1a** (0.073 mL, 0.66 mmol) and sodium azide (43 mg, 0.66 mmol) were suspended in ethanol (2 mL). To this was added copper turnings (10 mg) and copper sulfate solution (1 M, 200 μL) and the reaction mixture was refluxed for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite. Volatiles were removed on a rotary evaporator and subsequent column chromatography over silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) gave the triazole **1c** in 92% yield.

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13. Spectroscopic data for the new typical products. Compound **1c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.81–7.63 (m, 4H), 7.43–7.19 (m, 3H), 7.06 (d, $J = 3.71$ Hz, 1H), 6.57 (dd, $J = 2.23$, 3.71 Hz, 1H), 5.68 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.27, 149.70, 147.40, 147.35, 146.30, 130.74, 128.64, 127.85, 125.59, 119.97, 119.62, 119.33, 112.70, 52.48, 46.63. IR (KBr) ν 2952, 2365, 1707, 1636, 1436, 1255, 1212, 762 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{16}N_3O_3$ M^+ 310.1191, found 310.1193. Compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.98 (s, 1H), 7.88–7.77 (m, 4H), 7.43–7.34 (m, 5H), 5.37 (s, 2H), 4.31 (q, $J = 6.79$ Hz, 2H), 1.38 (t, $J = 6.79$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.61, 165.21, 147.46, 144.41, 132.07, 131.96, 128.76, 128.06, 125.64, 125.12, 120.84, 116.25, 115.96, 61.61, 46.72, 14.16. IR (KBr) ν 2923, 1704, 1507, 1225, 769 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{19}FN_3O_2$ M^+ 352.1461, found 352.1461. Compound **4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.78 (d, $J = 7.55$ Hz, 2H), 7.36 (m, 2H), 7.25 (m, 1H), 7.1 (t, $J = 8.3$ Hz, 1H), 5.24 (s, 2H), 4.23 (q, $J = 6.79$ Hz, 2H), 2.52 (q, $J = 7.55$ Hz, 2H), 1.51–1.47 (m, 2H), 1.35–1.30 (m, 7H), 0.90 (t, $J = 6.79$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.29, 150.58, 147.43, 130.68, 128.64, 127.88, 126.02, 125.56, 119.91, 61.15, 45.35, 31.39, 28.94, 28.01, 22.31, 14.11, 13.81. IR (KBr) ν 2925, 1704, 1221, 770 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{26}N_3O_2$ M^+ 328.2025, found 328.2023. Compound **6c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.96 (s, 1H), 7.81 (d, $J = 7.55$ Hz, 2H), 7.73 (d, $J = 6.79$ Hz, 2H), 7.78–7.24 (m, 6H), 5.39 (s, 2H), 4.29 (q, $J = 6.79$ Hz, 2H), 1.35 (t, $J = 6.79$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.69, 145.71, 133.55, 130.57, 129.90, 129.70, 128.90, 128.74, 128.02, 126.00, 125.60, 125.22, 120.72, 61.57, 46.84, 14.15. IR (KBr) ν 3430, 1706, 1252, 763, 695 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{20}N_3O_2$ M^+ 334.1555, found 334.1543. Compound **7c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.79 (d, $J = 6.79$ Hz, 2H), 7.43–7.18 (m, 3H), 7.86 (d, $J = 10.17$ Hz, 1H), 5.24 (s, 2H), 4.23 (q, $J = 7.63$ Hz, 2H), 3.16 (m, 1H), 1.33 (t, $J = 7.63$ Hz, 3H), 1.09 (d, $J = 5.93$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.58, 156.33, 130.66, 128.75, 127.99, 126.01, 125.59, 123.80, 120.13, 61.26, 45.49, 29.68, 28.49, 21.85, 14.17. IR (KBr) ν 3427, 2965, 1707, 1462, 1221, 771 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{22}N_3O_2$ M^+ 300.1712, found 300.1717. Compound **9c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.07 (t, $J = 7.55$ Hz, 1H), 5.16 (s, 2H), 4.22 (q, $J = 6.79$ Hz, 2H), 2.64 (t, $J = 7.55$ Hz, 2H), 2.47 (m, 2H), 1.64 (m, 2H), 1.46 (m, 2H), 1.39–1.21 (m, 14H), 0.89 (t, $J = 6.79$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.34, 150.37, 148.19, 126.23, 120.73, 61.09, 45.15, 31.39, 29.64, 29.06, 28.91, 28.04, 25.63, 22.34, 14.13, 14.05, 13.93, 13.84. IR (KBr) ν 3426, 2927, 1709, 1459, 1260, 773 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{32}N_3O_2$ M^+ 322.2494, found 322.2493. Compound **14c**: ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.08 (t, $J = 7.55$ Hz, 1H), 5.17 (s, 2H), 4.21 (q, $J = 6.79$ Hz, 2H), 3.88 (t, $J = 6.04$ Hz, 2H), 2.87 (t, $J = 6.04$ Hz, 2H), 2.48 (q, $J = 7.55$ Hz, 2H), 1.73 (br s, 1H), 1.57–1.41 (m, 2H), 1.40–1.23 (m, 7H), 0.90 (t, $J = 6.79$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.26, 150.52, 145.43, 126.02, 121.77, 45.23, 31.36, 31.07, 29.61, 29.29, 28.94, 28.56, 27.98, 26.59, 22.31. IR (KBr) ν 3370, 2360, 1696, 1219, 1053 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{26}N_3O_3$ M^+ 296.1974, found 296.1964.

14. This reaction was performed in a parallel synthesizer (CORUSEL stirring hot plate RR 98072) to synthesize a 24 compound library whose biological data will be published elsewhere.