

## INTERMOLECULAR DOMINO MICHAEL-[3+2] CYCLOADDITION THREE-COMPONENT COUPLING REACTIONS: A NEW SYNTHESIS OF 1, 5-DISUBSTITUTED TETRAZOLES

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### ABSTRACT

Intermolecular domino Michael-[3+2] cyclo addition reaction is described. Initial azide addition in a Michael fashion to acetylated Baylis-Hillman adducts and followed by reacted with *p*-toluene sulfonyl nitrile give multifunctional 1,5-disubstituted 1,2,3,4-tetrazoles.

**KEY WORDS:** Three-component coupling reaction, Baylis Hillman adducts, tetrazoles, *p*-toluene sulfonylnitrile

### INTRODUCTION

Carbon-carbon or carbon-hetero atom bond formation is of importance in organic synthesis with numerous interesting studies concerning reactivity, chemoselectivity and stereoselectivity.<sup>[1]</sup> Among all well-developed methodologies, the multicomponent reaction plays an important role due to its allowance of generation of an adduct in a single operation from three or more reactants with high atom economy and bond-forming efficiency.<sup>[2]</sup> Successful application of a multicomponent reaction highly relies on the good chemoselectivities in the presence of all the reactants.<sup>[3]</sup>

While exploring this multicomponent 'domino' reaction, we have discovered serendipitously that no additional catalyst is required for the domino Michael-[3+2] cycloaddition reaction.

Wherein acetylated Baylis-Hillman adducts<sup>[4]</sup> undergo a smooth, three component coupling with sodium azide and *p*-toluenesulfonylnitrile. The products thus formed drug like molecules with 1,5-disubstituted tetrazoles. These 1,5-disubstituted tetrazoles have shown interesting biological properties such as antibacterials<sup>[5]</sup>, cancer<sup>[6]</sup>, heartdiseases<sup>[7]</sup>, neurodegenerative<sup>8</sup> disease, lipophilic spacers and carboxylic acid surrogates.

## 2.0 MATERIALS AND METHODS

All reactions were performed under an atmosphere of N<sub>2</sub>, unless otherwise specified. All commercially available reagents were used without further purification including Ethanol solvent. Thin-layer chromatography was performed on 0.2 mm Merck 60F254 silica gel aluminum sheets, which were visualized with a vanillin/methanol/water/sulfuric acid mixture. ACROS 80-230 silica gel 60 was employed for column chromatography. A Perkin-Elmer RX-FTIR System was used to record IR spectra (neat of film). Bruker DPX 300, DRX 400 and DRX 500 spectrometers were employed for the NMR spectra (CDCl<sub>3</sub> solutions) using tetramethylsilane as internal reference for <sup>1</sup>H and CDCl<sub>3</sub> as an internal reference for <sup>13</sup>C. MS analyses were recorded on a GCMS-QP2010 Plus (Shimadzu) and HRMS analyses were recorded on a microTOF (Bruker).

## 2.1 EXPERIMENTAL

**General Procedure for the Synthesis of 1,5-disubstituted tetrazoles 1b-15b:** Acetylated benzaldehyde-methylacrylated adduct **4a** (200 mg, 0.854 mmol), *p*-toluene sulfonyl nitrile (185.6 mg, 1.025 mmol) and sodium azide (167 mg, 2.564 mmol) were suspended in Ethanol (10 mL) and the reaction mixture was refluxed for 0.5 h. After completion of the reaction (monitored by TLC), volatiles were removed on rotary evaporator and subsequent column chromatography over silica gel gave the 1,5-disubstituted tetrazoles with 87% yields.

**(E)-methyl 3-(4-fluorophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylate (1b):** mp 108.1-110.0°C. IR (KBr):  $\nu_{\max}$  3419.8, 2950.8, 1720.3, 1599.5, 1505.7, 1443.2, 1314.2, 1290.5, 1229.4, 1142.0, 1076.0, 827.5, 736.0, 586.2, 523.9 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.41 (s, 3H), 3.6 (s, 3H), 4.4 (s, 2H), 7.12-7.04 (m, 2H), 7.32-7.14 (m, 2H), 7.58-7.52 (m, 2H), 7.76-7.72 (m, 2H), 7.9 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  21.5, 52.3, 55.0, 115.7, 115.9, 120.7, 128.4, 129.5, 129.7, 131.3, 131.4, 136.2, 144.8, 144.9, 166.7; HRMS (ESI<sup>+</sup>): m/z calcd for C<sub>19</sub>H<sub>18</sub>FN<sub>4</sub>O<sub>4</sub>S: 417.1033; found: 417.1029;

**(E)-methyl 3-(3-nitrophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylate (2b):** mp 125.4-127.4°C. IR (KBr):  $\nu_{\max}$  3422.2, 2951.1, 1720.6, 1596.2, 1521.5, 1455.4, 1442.0, 1346.2, 1309.5, 1268.9, 1220.8, 1165.1, 1145.6, 1084.5, 965.6, 814.4, 730.4, 674.0, 517.8  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.40 (s, 3H), 3.7(s, 3H), 4.40 (s, 2H), 7.31-7.29 (m, 2H), 7.59-7.50 (m, 1H), 7.75-7.70 (m, 2H), 7.90-7.89 (m, 1H), 7.99 (s, 1H), 8.21(s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.5, 52.7, 54.5, 123.7, 123.9, 128.4, 129.7, 129.8, 134.6, 135.2, 135.8, 142.9, 145.1, 148.2, 166.1; HRMS ( $\text{ESI}^+$ ): m/z calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_5\text{O}_6\text{S}$ : 444.0978; found: 444.0975;

**(E)-methyl 3-(3-fluorophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylate (3b):** mp 110.9-112.4°C. IR (KBr):  $\nu_{\max}$  3414.8, 2925.6, 1712.2, 1623.5, 1580.2, 1436.4, 1310.2, 1289.8, 1245.9, 1228.1, 1140.3, 1084.7, 945.7, 889.2, 802.9, 728.1, 704.0, 608.2, 561.7  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.39 (s, 3H), 3.65 (s, 3H), 4.41 (s, 2H), 7.08-7.02 (m, 2H), 7.36-7.22 (m, 4H), 7.72-7.68 (m, 2H), 7.85 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.4, 52.4, 54.7, 115.7, 115.7, 116.1, 116.3, 122.3, 124.5, 124.6, 128.4, 129.6, 130.2, 135.6, 135.9, 144.3, 144.8, 166.5; HRMS ( $\text{ESI}^+$ ): m/z calcd for  $\text{C}_{19}\text{H}_{18}\text{FN}_4\text{O}_4\text{S}$ : 417.1033; found: 417.1030;

**(E)-methyl 3-phenyl-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylate (4b):** mp 123.4-125.6°C. IR (KBr):  $\nu_{\max}$  3417.3, 3058.4, 2950.6, 1716.0, 1623.3, 1593.4, 1494.2, 1436.4, 1399.0, 1315.4, 1270.8, 1203.5, 1133.5, 1082.5, 982.0, 899.4, 820.2, 763.7, 733.3, 588.6, 512.8  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.40 (s, 3H), 3.60 (s,3H), 4.45 (s, 2H), 7.5-7.29 (m, 7H), 7.77-7.3 (m, 2H), 7.93 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.5, 52.3, 55.0, 121.0, 128.5, 128.6, 129.1, 129.5, 133.6, 136.2, 144.6, 146.1, 166.9, HRMS ( $\text{ESI}^+$ ): m/z calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_4\text{O}_4\text{S}$ : 399.1127; found: 399.1125;

**(E)-methyl 3-(4-methoxyphenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylate (5b):** mp 110.0-114.0°C. IR (KBr):  $\nu_{\max}$  3408.3, 2935.8, 1716.8, 1616.3, 1598.3, 1509.5, 1458.1, 1435.8, 1313.1, 1282.5, 1174.7, 1133.2, 1084.5, 1022.2, 904.5, 831.8, 814.7, 719.3, 591.9, 541.9, 509.9  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.40 (s, 3H), 3.56 (s, 3H), 3.87 (s, 3H), 4.42 (s, 2H), 6.93-6.90 (m, 2H), 7.31-7.29 (m, 2H), 7.59-7.58 (m, 2H), 7.78-7.69 (m, 2H), 7.9(s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.5, 52.1, 55.3, 55.4, 114.1, 118.1, 126.2, 128.5, 129.5, 131.5, 136.5, 144.6, 146.0, 161.0, 167.2; HRMS ( $\text{ESI}^+$ ): m/z calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_4\text{O}_5\text{S}$ : 429.1233; found: 429.1229;

**(E)-methyl 3-(4-nitrophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylate (6b):** mp 178-183°C. IR (KBr):  $\nu_{\max}$  3422.8, 2928.3, 1721.6, 1626.5, 1593.73, 1512.7, 1429.0, 1342.5, 1273.5, 1206.2, 1135.2, 1084.8, 974.2, 903.1, 840.4, 730.4, 582.9, 512.9  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.44 (s, 3H), 3.65 (s, 3H), 4.39 (s, 2H), 7.30 (d,  $J = 8.4$  Hz, 2H), 7.69 (dd,  $J = 8.1, 16.8$  Hz, 4 H), 7.96 (s, 1H), 8.23 (d,  $J = 8.7$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.6, 52.7, 54.8, 123.8, 124.3, 128.4, 129.7, 129.8, 136.1, 140.0, 143.2, 145.2, 148.0, 166.0; HRMS (ESI<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_5\text{O}_6\text{S}$ : 444.0978; found: 444.0973;

**(E)-methyl 2-((5-tosyl-1H-tetrazol-1-yl)methyl)hex-2-enoate (7b):** mp 52-56 °C. IR (KBr):  $\nu_{\max}$  3658.6, 2963.9, 2873.9, 1719.0, 1643.0, 1596.6, 1456.7, 1436.9, 1319.2, 1135.8, 1086.9, 1067.6, 911.2, 817.1, 746.7, 729.8, 574.8, 512.9  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.92 (t,  $J = 7.2$  Hz, 3H), 1.45 (q,  $J = 7.2, 15.2$  Hz, 2H), 2.18 (q,  $J = 7.2, 15.2$  Hz, 2H), 2.43 (s, 3H), 3.50 (s, 3H), 4.22 (s, 2H), 7.11 (t,  $J = 7.2$  Hz, 1H), 7.32 (d,  $J = 7.6$  Hz, 2H), 7.73 (d,  $J = 8.8$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.7, 21.5, 31.3, 51.9, 54.0, 120.6, 128.6, 129.5, 135.9, 144.6, 151.5, 166.0; HRMS (ESI<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{16}\text{H}_{21}\text{N}_4\text{O}_4\text{S}$ : 365.1284; found: 365.1280;

**(Z)-3-(4-nitrophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylonitrile (8b):** mp 146-150 °C. IR (KBr):  $\nu_{\max}$  3431.4, 2981.5, 2933.1, 2212.7, 1596.4, 1522.6, 1352.0, 1298.8, 1257.5, 1143.1, 1086.3, 919.0, 811.8, 756.3, 744.9, 644.5, 594.6, 547.3, 512.3  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.49 (s, 3H), 4.08 (s, 2H), 7.13 (s, 1H), 7.48-7.41 (m, 2H), 7.95-7.79 (m, 4H), 8.23-8.35 (m, 2H),  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 61.1, 102.9, 116.1, 124.2, 128.6, 129.9, 130.3, 134.5, 138.0, 146.2, 148.8; HRMS (ESI<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_6\text{O}_4\text{S}$ : 411.0875; found: 411.0872;

**(Z)-3-(4-fluorophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylonitrile (9b):** mp 155-159°C. IR (KBr):  $\nu_{\max}$  3435.0, 2990.2, 2938.2, 2211.1, 1599.0, 1510.5, 1292.0, 1242.3, 1143.1, 1086.2, 923.2, 831.8, 755.0, 634.7, 610.2, 509.6  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.43 (s, 3H), 4.06 (s, 2H), 7.19-7.02 (m, 3H), 7.43-7.38 (m, 2H), 7.93-7.65 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 61.2, 97.7, 116.2, 116.4, 117.0, 128.7, 130.1, 131.5, 134.6, 145.8, 150.2; HRMS (ESI<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{15}\text{FN}_5\text{O}_2\text{S}$ : 384.0930; found: 384.0928;

**(Z)-3-(3-nitrophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylonitrile (10b):** mp 181-183°C. IR (KBr):  $\nu_{\max}$  3430.1, 2991.4, 2940.9, 2211.4, 1611.1, 1594.9, 1548.3, 1349.9, 1314.6, 1302.7, 1139.4, 1086.2, 939.4, 889.9, 824.1, 806.8, 756.5, 734.4, 672.9, 635.7, 617.4,

553.5, 514.9  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.49 (s, 3H), 4.06 (s, 2H), 7.19 (s, 1H), 7.42 (d,  $J = 8.4$  Hz, 2H), 7.66 (t,  $J = 8.0$  Hz, 1H), 7.81 (d,  $J = 8.0$  Hz, 2H), 8.14 (d,  $J = 8.0$  Hz, 1H), 8.32-8.30 (m, 1H), 8.39 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 61.0, 102.2, 116.1, 124.3, 125.6, 128.7, 130.2, 130.3, 133.8, 134.5, 146.2, 148.4, 148.7; HRMS ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_6\text{O}_4\text{S}$ : 411.0875; found: 411.0870;

**(Z)-3-(3-fluorophenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylonitrile (11b):** mp 130-133°C. IR (KBr):  $\nu_{\text{max}}$  3434.5, 2994.6, 2940.7, 2211.0, 1622.3, 1595.6, 1493.1, 1410.1, 1299.8, 1247.1, 1142.7, 1085.8, 942.9, 896.5, 783.0, 756.0, 681.5, 637.2, 532.2, 515.6  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.43 (s, 3H), 4.0 (s, 2H), 7.09 (s, 1H), 7.19-7.14 (m, 1H), 7.49-7.39 (m, 5H), 7.79 (d,  $J = 8.4$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 61.2, 99.8, 115.5, 115.8, 116.6, 118.4, 118.6, 125.1, 128.7, 130.2, 130.6, 130.7, 134.3, 134.4, 134.5, 145.9, 150.1, 161.4, 163.9; HRMS ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{15}\text{FN}_5\text{O}_2\text{S}$ : 384.0930; found: 384.0932;

**(Z)-3-(4-methoxyphenyl)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylonitrile (12b):** mp 130.8-133.5°C. IR (KBr):  $\nu_{\text{max}}$  3444.7, 2943.7, 2841.0, 2208.2, 1597.8, 1512.1, 1454.0, 1312.4, 1266.5, 1181.7, 1149.2, 1115.2, 1085.5, 1020.0, 917.2, 831.5, 818.0, 742.5, 639.7, 606.9, 539.3, 509.0  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.46 (s, 3H), 3.85 (s, 3H), 3.98 (s, 2H), 6.93 (d,  $J = 9.3$  Hz, 2H), 7.02 (s, 1H), 7.37 (d,  $J = 8.4$  Hz, 2H), 7.70 (d,  $J = 8.7$  Hz, 2H), 7.78 (d,  $J = 8.4$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 55.4, 61.4, 94.4, 114.3, 117.7, 125.3, 128.7, 130.0, 131.3, 134.6, 145.6, 151.1, 162.1; HRMS ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_5\text{O}_3\text{S}$ : 396.1130; found: 396.1128;

**(Z)-3-phenyl-2-((5-tosyl-1H-tetrazol-1-yl)methyl)acrylonitrile (13b):** mp 126.9-129.2 °C. IR (KBr):  $\nu_{\text{max}}$  3435.5, 2993.8, 2939.6, 2208.8, 1617.5, 1596.4, 1409.3, 1308.5, 1297.5, 1249.1, 1143.6, 1085.8, 948.0, 927.6, 817.5, 752.0, 688.0, 635.5, 616.9, 548.9, 516.3  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.47 (s, 3H), 4.0 (s, 2H), 7.11 (s, 1H), 7.45-7.37 (m, 5H), 7.72-7.68 (m, 2H), 7.79 (d,  $J = 8.7$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 61.3, 98.1, 109.9, 117.1, 128.7, 129.0, 129.2, 130.1, 131.5, 132.5, 134.6, 145.8, 151.7; HRMS ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_5\text{O}_2\text{S}$ : 366.1025; found: 366.1022;

**(Z)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)hex-2-enenitrile (14b):** mp 61.8-63.9 °C. IR (KBr):  $\nu_{\text{max}}$  3439.5, 2966.1, 2921.7, 2876.2, 2223.5, 1626.4, 1595.8, 1408.5, 1382.6, 1318.2, 1305.1, 1255.9, 1157.2, 1126.5, 1085.8, 925.6, 814.9, 799.0, 663.2, 634.0, 541.9  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300

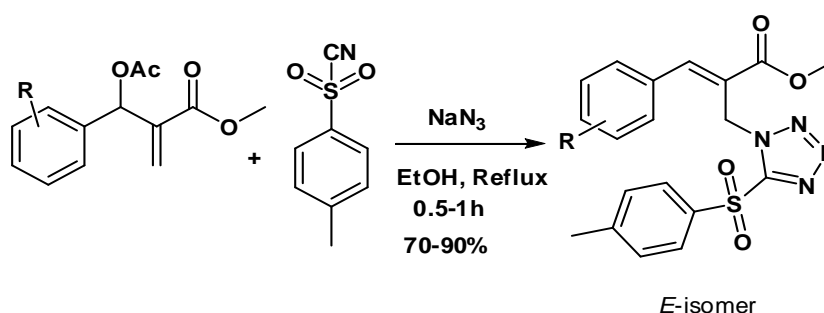
MHz, CDCl<sub>3</sub>):  $\delta$  0.93 (t, J = 7.2 Hz, 3H), 1.57-1.43 (m, 2H), 2.37 (q, J = 7.5, 15.0 Hz, 2H), 2.46 (s, 3H), 3.85 (s, 2H), 6.43 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  13.4, 21.2, 21.4, 21.6, 33.9, 59.6, 103.1, 115.5, 128.6, 130.0, 134.5, 145.6, 158.0; HRMS (ESI<sup>+</sup>): m/z calcd for C<sub>15</sub>H<sub>18</sub>N<sub>5</sub>O<sub>2</sub>S: 332.1181; found: 332.1179;

**(Z)-2-((5-tosyl-1H-tetrazol-1-yl)methyl)oct-2-enitrile (15b):** IR (KBr):  $\nu_{\max}$  3436.5, 2957.1, 2931.1, 2860.6, 2223.7, 1734.0, 1631.8, 1597.1, 1457.5, 1405.8, 1322.8, 1304.9, 1155.3, 1087.3, 896.4, 817.0, 752.3, 633.7, 545.5 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.90 (t, J = 6.4 Hz, 3H), 1.34-1.21 (m, 5H), 1.45-1.38 (m, 2H), 2.38 (q, J = 8.0, 15.6 Hz, 2H), 2.47 (s, 3H), 3.84 (s, 2H), 6.43 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  13.8, 21.6, 22.2, 27.6, 31.0, 32.0, 59.6, 102.9, 115.5, 128.6, 130.0, 134.5, 145.6, 158.2; HRMS (ESI<sup>+</sup>): m/z calcd for C<sub>17</sub>H<sub>22</sub>N<sub>5</sub>O<sub>2</sub>S: 360.1494; found: 360.1491;

### 3.0 RESULTS AND DISCUSSION

#### 3.1 Chemistry

The Baylis-Hillman acetates **1a-15a** were prepared according to standard methods<sup>9</sup> by treating the aldehyde components with the corresponding methyl acrylates/acrylonitrile to give the corresponding adducts in good yields. Initially, 4-fluorobenzaldehyde-methylacrylate adduct **1a** and Sodium azide and *p*-toluenesulfonylnitrile were heated in ethyl alcohol at reflux for 1h to give highly diverse multi functional **1b** in 82% yield and with complete *E*-selectivity (Scheme 1), after simple workup and isolation.

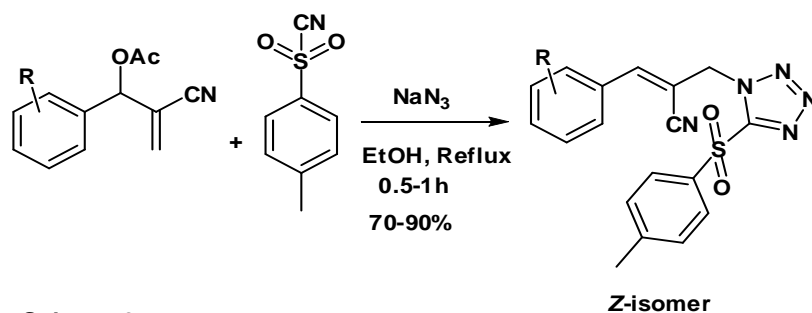


**Scheme 1: Synthesis of novel 1,5-disubstituted tetrazole derivatives 1b-7b (*E*-isomer)**

**Reaction conditions:** Aryl/alkyl methyl acrylate, *p*-toluene sulfonyl nitrile, ethanol, reflux, 1h.

The main advantages of this procedure are that it is very simple, and it gives very good yields. 3-nitrobenzaldehyde, 3-fluorobenzaldehyde, benzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde and n-butylaldehyde-methylacrylate adducts (Table-1, entries **2a-7a**), sodium azide and *p*-toluene sulfonyl nitrile were treated in Ethyl alcohol under heating conditions to afford the *E*-isomer of the 1,5-disubstituted tetrazoles in good yield (Table-1, entries **2b-7b**).

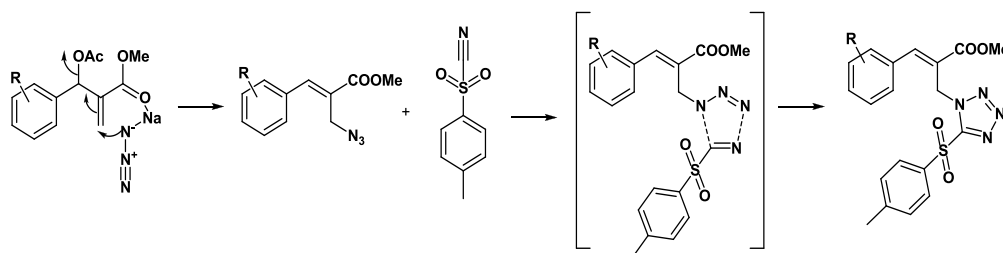
The scope of this 1,5-disubstituted tetrazoles synthesis is revealed in the several examples shown in table 1. 4-Nitro benzaldehyde-acrylonitrile Baylis-Hillman adduct **8a**, Sodium azide and *p*-toluene sulfonyl nitrile also underwent the sequence to give **8b** in 91% yield and with complete *Z*-selectivity (Scheme-2). Other acetylated Baylis-Hillman adducts (entries **9a, 10a, 11a, 12a, 13a, 14a** and **15a**) participated equally well in this one-pot procedure, with over 90% yields.



### Scheme 2: Synthesis of novel 1,5-disubstituted tetrazole derivatives **8b-15b** (*Z*-isomer)

**Reaction conditions:** Aryl/alkyl methyl acrylonitrile, *p*-toluene sulfonyl nitrile, ethanol, reflux, 1h.

Our Mechanistic proposal for this transformation is shown in Scheme-3. Michael addition of azide on to the Baylis-Hillman adducts and followed by [3+2] cycloaddition with the *p*-toluene sulfonyl nitrile would generate the observed products.



Scheme 3: Proposed mechanism for three-component coupling



**Table 1:** Synthesis of 1,5-disubstituted tetrazoles through domino reaction

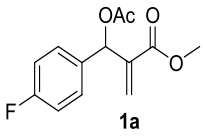
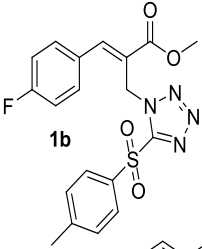
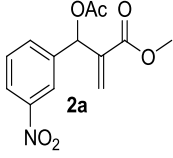
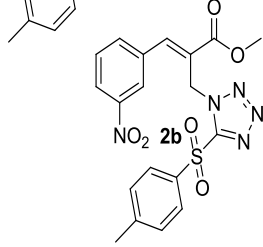
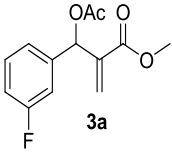
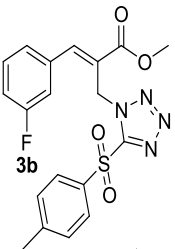
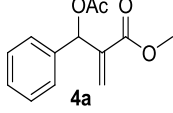
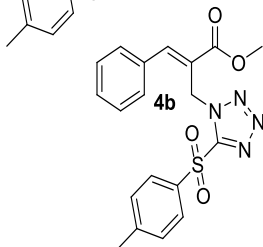
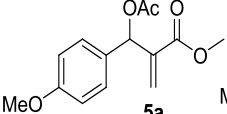
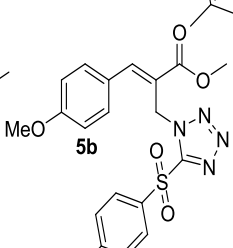
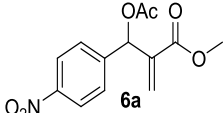
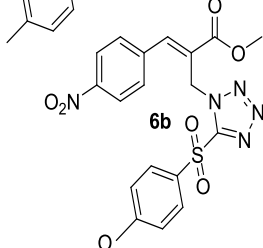
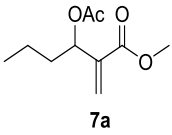
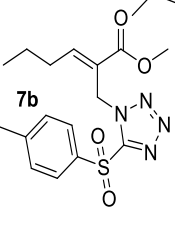
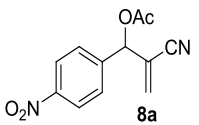
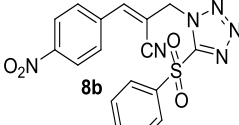
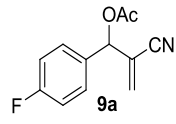
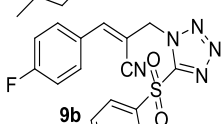
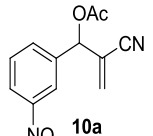
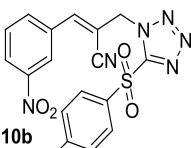
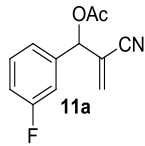
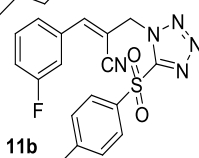
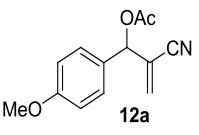
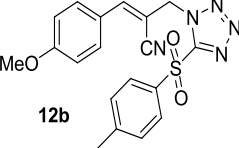
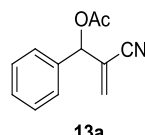
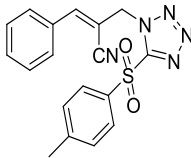
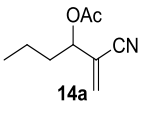
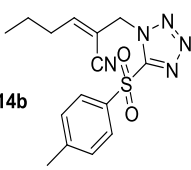
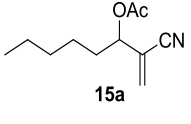
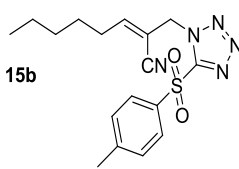
Entry	Baylis-Hillman adduct	Product <sup>a</sup>	Stereochemistry <sup>b</sup>	Time	Yield <sup>c</sup> (%)
1			<i>E</i>	1h	82
2			<i>E</i>	1h	80
3			<i>E</i>	1h	98
4			<i>E</i>	0.5 h	87
5			<i>E</i>	0.5 h	98
6			<i>E</i>	0.5 h	88
7			<i>E</i>	0.5 h	98



Table 1:(Continued)

Entry	Baylis-Hillman adduct	Product <sup>a</sup>	Stereochemistry <sup>b</sup>	Time	Yield <sup>c</sup> (%)
8			Z	0.5 h	91
9			Z	0.5 h	96
10			Z	0.5 h	86
11			Z	0.5 h	90
12			Z	1 h	94
13			Z	0.5 h	88
14			Z	0.5 h	91
15			Z	0.5 h	93

<sup>a</sup> All products were characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and HRMS spectral data.

<sup>b</sup> The exclusive (E) and (Z) stereochemistry was assigned on the basis of NMR experiments.

<sup>c</sup> Yield refers to the isolated pure products after column chromatography.

#### 4. CONCLUSION

In conclusion it has been demonstrated that acetylated Baylis-Hillman adducts undergo smooth three-component coupling with sodium azide and *p*-toluene sulfonyl cyanide in one pot to furnish the diverse multifunctional 1,5-disubstituted tetrazoles.

## 5. ACKNOWLEDGEMENT

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## 6. CONFLICT OF INTEREST

“The author(s) declare(s) that there is no conflict of interest regarding publication of this article”.

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