Preliminary Communication

Zheng-Jun Quan*, Miao-Miao Wang, Liang-Jie Yang, Yu-Xia Da, Zhang Zhang and Xi-Cun Wang*

One-pot three-component synthesis of substituted 2-(1,2,3-triazol-1-yl)pyrimidines from pyrimidin-2-yl sulfonates, sodium azide and active methylene ketones

Abstract: New 2-(1,2,3-triazol-1-yl)pyrimidines were synthesized in good yields by the three-component reaction of pyrimidin-2-yl sulfonates, sodium azide and active methylene ketones in the presence of K_2CO_3 at room temperature. This procedure eliminates the need to handle organic azides in the synthesis of analogous compounds.

Keywords: methylene ketones; pyrimidines; pyrimidin-2-yl sulfonates; three-component reaction; 1,2,3-triazoles.

***Corresponding authors: Zheng-Jun Quan and Xi-Cun Wang,** Key Laboratory of Eco-Environment-Related Polymer Materials, Ministry of Education, China, Gansu 730070, P.R. China; and Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Anning East Road 967#, Lanzhou, Gansu 730070, P.R. China,
e-mail: quanzhengjun@hotmail.com; wangxicun@nwnu.edu.cn
Miao-Miao Wang, Liang-Jie Yang, Yu-Xia Da and Zhang Zhang: Key Laboratory of Eco-Environment-Related Polymer Materials, Ministry of Education, China, Gansu 730070, P.R. China; and Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Anning East Road 967#, Lanzhou, Gansu 730070, P.R. China

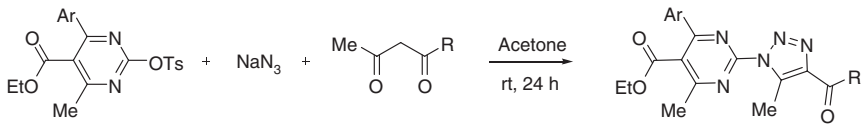
Introduction

Since the copper(I)-catalyzed azide-alkyne cycloaddition was reported independently by the groups of Sharpless and Meldal, the synthesis of 1,4- and 1,5-disubstituted 1,2,3-triazoles have attracted a great deal of attention due to their potential biological activities [1]. In recent years, 1,4,5-trisubstituted 1,2,3-triazoles have found important applications in medicinal chemistry [2–5]. A few methods for the synthesis of fully substituted 1,2,3-triazoles have been described [6]. One of the most attractive approaches to the synthesis of these compounds is the direct Pd- or Cu-catalyzed arylation of 1,4-disubstituted triazoles with aryl halides [7–12]. Transition metal-catalyzed reactions for the chemoselective and regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from organic azides and alkyl iodides or bromides have also been developed [13–16]. Another access to these compounds is the highly regioselective 1,3-dipolar cycloaddition between an azide and an enamine [17]. 1,4,5-Trisubstituted 1,2,3-triazoles can also be obtained by treatment of aryl azides with ketones in the presence of amines [18–20].

In our previous reports [21, 22], we have described an efficient protocol for the synthesis of C2-substituted pyrimidines by cross-coupling reaction of readily available pyrimidin-2-yl sulfonates with N-, S-, O- and C-nucleophiles. In this work, the synthesis of polysubstituted 2-(1,2,3-triazol-1-yl)pyrimidines by the reaction of pyrimidin-2-yl sulfonates, sodium azide and active methylene ketones is described.

Conditions for the three-component reaction were explored using pyrimidin-2-yl sulfonate (**1a**), NaN_3 and ethyl acetoacetate (**2a**) as the substrates (Scheme 1) and various base catalysts. In the presence of Et_3N and Et_2NH in acetone, product **3a** was obtained in only 10% and 17% yield, respectively. By contrast, in the presence of inorganic bases, namely K_2CO_3, K_3PO_4, NaOH and KOH in acetone product **3a** was obtained in the respective yields of 81%, 53%, 19% and 54%. The yields were also significantly affected by solvents. For example, the reactions conducted in acetonitrile, ethanol, DMF and DMSO in the presence of K_2CO_3 delivered **3a** in the respective yields of 54%, 15%, 60% and 66%. Traces of **3a** were obtained for the reaction conducted in dichloromethane. The best result was obtained when the reaction was conducted in acetone in the presence of 1.2 equivalent amounts of K_2CO_3.

Various pyrimidin-2-yl sulfonates (**1**) were allowed to react with NaN_3 and ethyl acetoacetate (**2a**) under optimized conditions (Scheme 1). In general, good yields were



1a: Ar = Ph
1b: Ar = 4-MeC_6H_4
1c: Ar = 4-MeOC_6H_4
1d: Ar = 4-ClC_6H_4
1e: Ar = 4-FC_6H_4
2a: R = EtO
2b: R = MeO
2c: R = Me

3a: Ar = Ph; R = EtO
3b: Ar = 4-MeC_6H_4; R = EtO
3c: Ar = 4-MeOC_6H_4; R = EtO
3d: Ar = 4-ClC_6H_4; R = EtO
3e: Ar = 4-FC_6H_4; R = EtO
3f: Ar = Ph; R = MeO
3g: Ar = 4-MeC_6H_4; R = MeO
3h: Ar = 4-ClC_6H_4; R = MeO
3i: Ar = 4-FC_6H_4; R = MeO
3j: Ar = Ph; R = Me
3k: Ar = 4-MeC_6H_4; R = Me
3l: Ar = 4-MeOC_6H_4; R = Me
3m: Ar = 4-ClC_6H_4; R = Me
3n: Ar = 4-FC_6H_4; R = Me

Scheme 1

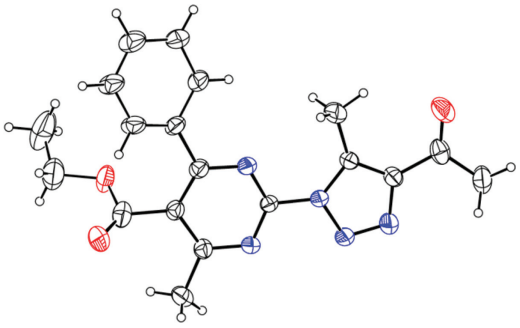


Figure 1 The single crystal X-ray crystallographic structure of product **3j**.

obtained under the standard reaction conditions. Methyl acetoacetate (**2b**) and pentane-2,4-dione (**2c**) were also used to further explore the scope of the synthesis of the triazolylpyrimidines. As expected, the desired products **3f–n** were obtained smoothly in good to excellent yields (Scheme 1; see Supplementary material online). The structures of all products are fully consistent with their spectral data and that for **3j** was unambiguously assigned by using X-ray diffraction analysis (Figure 1). Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. CCDC 944956 for **3j**. Copies of this information can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Experimental details

Melting points were determined on an XT-4 electrothermal micromelting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) spectra and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Varian Mercury plus-400 instrument. IR spectra were recorded using KBr pellets on Nicolet Avatar 360 spectrophotometer. Electron-impact mass spectra were recorded at 70 eV on a TRACE DSQ instrument. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. X-Ray diffraction data were recorded using a Rigaku Mercury CCDC area detector with graphite monochromated Mo Kα radiation. Column chromatography was performed on silica gel (300–400 mesh). Commercially available reagents were used without further purification.

General procedure for the synthesis of 2-(1,2,3-triazol-1-yl)pyrimidines 3a–n

A mixture of a pyrimidin-2-yl sulfonate (**1**, 0.5 mmol), NaN_3 (1.0 mmol), a methylene ketone (**2**, 1.0 mmol), K_2CO_3 (1.2 mmol) and acetone (5 mL) was stirred at room temperature for 24 h. After complete consumption of the starting material, as evidenced by TLC analysis, the mixture was quenched with saturated NH_4Cl aqueous solution (5 mL) and extracted with diethyl ether (2 × 10 mL). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (5:1) to provide product **3**.

Ethyl 2-[4-(ethoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]-4-methyl-6-phenylpyrimidine-5-carboxylate (3a) Yellow oil; yield 81%; ^{1}H NMR: δ 7.74 (q, *J* = 8.0 Hz, 2H, ArH), 7.55–7.50 (m, 3H, ArH), 4.48 (q, *J* = 8.0 Hz, 2H, CH_2), 4.28 (q, *J* = 8.0 Hz, 2H, CH_2), 2.98 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 1.45 (t, *J* = 8.0 Hz, 3H, CH_3), 1.13 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 168.8, 166.9, 165.6, 161.6, 154.2, 140.6, 137.3, 136.2, 131.1, 128.8, 128.5, 125.4, 62.4, 61.2, 22.8, 14.4, 13.7, 11.5; IR: 2980, 1722, 1542, 1428, 1251, 1089 cm^{-1}; EI-MS: m/z 395 (M^+). Anal. Calcd for $C_{20}H_{21}N_5O_4$: C, 60.75; H, 5.35; N, 17.71. Found: C, 60.90; H, 5.40; N, 17.62.

Ethyl 2-[4-(ethoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (3b) White solid; mp 36–37°C; yield 70%; ^{1}H NMR: δ 7.65 (d, *J* = 8.0 Hz, 2H, ArH), 7.30 (d, *J* = 8.0 Hz, 2H, ArH), 4.48 (q, *J* = 8.0 Hz, 2H, CH_2), 4.31 (q, *J* = 8.0 Hz, 2H, CH_2), 2.97 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 1.45 (t, *J* = 8.0 Hz, 3H, CH_3), 1.19 (t, *J* = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 168.6, 167.2, 165.4, 161.6, 154.2, 141.7, 140.5, 137.2, 133.3, 129.7, 128.5, 125.2, 62.4, 61.2, 22.8, 21.5, 14.4, 13.7, 11.5; IR: 1722, 1578, 1542, 1425, 1251, 1089 cm^{-1}; EI-MS: m/z 409 (M^+). Anal. Calcd for $C_{21}H_{23}N_5O_4$: C, 61.60; H, 5.66; N, 17.10. Found: C, 61.72; H, 5.60; N, 17.19.

Ethyl 2-[4-(ethoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate(3c) Yellow solid; mp 85–86°C; yield 78%; ^{1}H NMR: δ 7.75 (d, *J* = 8.0 Hz, 2H, ArH),

7.01 (d, J = 8.0 Hz, 2H, ArH), 4.49 (q, J = 8.0 Hz, 2H, CH_2), 4.34 (q, J = 8.0 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 1.46 (t, J = 8.0 Hz, 3H, CH_3), 1.23 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 168.4, 167.4, 164.7, 162.2, 161.7, 154.1, 140.5, 137.2, 130.4, 128.4, 124.7, 114.3, 62.4, 61.2, 55.5, 22.8, 14.4, 13.8, 11.5; IR: 2980, 1722, 1542, 1428, 1254, 1089 cm^{-1}; EI-MS: m/z 425 (M^+). Anal. Calcd for $C_{21}H_{23}N_5O_5$: C, 59.29; H, 5.45; N, 16.46. Found: C, 59.17; H, 5.51; N, 16.54.

Ethyl 4-(4-chlorophenyl)-2-(4-(ethoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl)-6-methylpyrimidine-5-carboxylate (3d) Yellow oil; yield 76%; ^{1}H NMR: δ 7.68 (t, J = 8.0 Hz, 2H, ArH), 7.47 (t, J = 8.0 Hz, 2H, ArH), 4.45 (q, J = 8.0 Hz, 2H, CH_2), 4.29 (q, J = 8.0 Hz, 2H, CH_2), 2.95 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 1.42 (t, J = 8.0 Hz, 3H, CH_3), 1.17 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 169.0, 166.7, 164.3, 161.5, 154.2, 140.5, 137.6, 137.3, 134.6, 129.9, 129.1, 125.3, 62.6, 61.2, 22.9, 14.3, 13.7, 11.5; IR: 2980, 1722, 1542, 1428, 1248, 1089 cm^{-1}; EI-MS: m/z 429 (M^+). Anal. Calcd for $C_{20}H_{20}ClN_5O_4$: C, 55.88; H, 4.69; N, 16.29. Found: C, 55.61; H, 4.74; N, 16.20.

Ethyl 2-[4-(ethoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (3e) Yellow oil; yield 78%; ^{1}H NMR: δ 7.73–7.70 (m, 2H, ArH), 7.17–7.13 (m, 2H, ArH), 4.43 (q, J = 8.0 Hz, 2H, CH_2), 4.26 (q, J = 8.0 Hz, 2H, CH_2), 2.93 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 1.39 (t, J = 8.0 Hz, 3H, CH_3), 1.14 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 168.8, 166.8, 165.7, 164.3, 163.2, 161.5, 154.1, 140.5, 137.2, 132.3, 130.8, 125.2, 116.1, 115.9, 62.5, 61.2, 14.3, 13.7, 11.4; IR: 2980, 1722, 1542, 1431, 1251, 1092 cm^{-1}; EI-MS: m/z 413 (M^+). Anal. Calcd for $C_{20}H_{20}FN_5O_4$: C, 58.11; H, 4.88; N, 16.94. Found: C, 58.24; H, 4.83; N, 17.03.

Ethyl 2-(4-(methoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (3f) Yellow oil; yield 73%; ^{1}H NMR: δ 7.73–7.71 (m, 2H, ArH), 7.53–7.49 (m, 3H, ArH), 4.26 (q, J = 8.0 Hz, 2H, CH_2), 3.98 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 1.11 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 168.8, 166.9, 165.6, 161.9, 154.2, 140.8, 137.0, 136.2, 131.1, 128.8, 128.5, 125.4, 62.4, 52.1, 22.8, 13.6, 11.5; IR: 2950, 1722, 1578, 1542, 1437, 1251, 1092 cm^{-1}; EI-MS: m/z 381 (M^+). Anal. Calcd for $C_{19}H_{19}N_5O$: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.99; H, 4.96; N, 18.51.

Ethyl 2-[4-(methoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (3g) Yellow solid; mp 88–90°C; yield 90%; ^{1}H NMR: δ 7.63 (d, J = 8.0 Hz, 2H, ArH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 4.28 (q, J = 8.0 Hz, 2H, CH_2), 3.97 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 1.16 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 168.6, 167.1, 165.4, 161.9, 154.1, 141.7, 140.7, 136.9, 133.3, 129.6, 128.5, 125.2, 62.4, 52.1, 22.8, 21.5, 13.7, 11.5; IR: 2980, 1722, 1578, 1542, 1437, 1251, 1092 cm^{-1}; EI-MS: m/z 395 (M^+). Anal. Calcd for $C_{20}H_{21}N_5O$: C, 60.75; H, 5.35; N, 17.71. Found: C, 60.87; H, 5.31; N, 17.79.

Ethyl 4-(4-chlorophenyl)-2-(4-(methoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl)-6-methylpyrimidine-5-carboxylate (3h) Colorless oil; yield 62%; ^{1}H NMR: δ 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.48 (d, J = 8.0 Hz, 2H, ArH), 4.30 (q, J = 8.0 Hz, 2H, CH_2), 3.99 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 1.19 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 169.0, 166.7, 164.3, 161.9, 154.2, 140.7, 137.6, 137.1, 134.6, 129.9, 129.2, 125.3, 62.6, 52.1, 22.9, 13.7, 11.5; IR: 2974, 1725, 1578, 1542, 1434, 1251, 1092 cm^{-1}; EI-MS: m/z 415 (M^+). Anal. Calcd for $C_{19}H_{18}ClN_5O_4$: C, 54.88; H, 4.36; N, 16.84. Found: C, 54.75; H, 4.41; N, 16.92.

Ethyl 4-(4-fluorophenyl)-2-[4-(methoxycarbonyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]-6-methylpyrimidine-5-carboxylate (3i) Yellow oil; yield 77%; ^{1}H NMR: δ 7.75–7.72 (m, 2H, ArH), 7.19–7.15 (m, 2H, ArH), 4.28 (q, J = 8.0 Hz, 2H, CH_2), 3.97 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 1.15 (t, J = 8.0, 3H, CH_3); ^{13}C NMR: δ 168.9, 166.8, 165.8, 164.4, 163.2, 161.9, 154.1, 140.7, 137.0, 132.3 (d), 130.8 (d), 125.2, 116.2, 115.9, 62.5, 52.1, 22.8, 13.7, 11.4; IR: 2956, 1722, 1542, 1434, 1251, 1089 cm^{-1}; EI-MS: m/z 399 (M^+). Anal. Calcd for $C_{19}H_{18}FN_5O_4$: C, 57.14; H, 4.54; N, 17.54. Found: C, 57.26; H, 4.50; N, 17.44.

Ethyl 2-[4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl]-4-methyl-6-phenylpyrimidine-5-carboxylate (3j) Yellow solid; mp 94–96°C; yield 83%; ^{1}H NMR: δ 7.75–7.73 (m, 2H, ArH), 7.55–7.50 (m, 3H, ArH), 4.28 (q, J = 8.0 Hz, 2H, CH_2), 2.97 (s, 3H, CH_3), 2.78 (s, 6H, CH_3), 1.13 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 194.5, 168.8, 166.9, 165.6, 154.2, 143.8, 139.1, 136.2, 131.1, 128.8, 128.5, 125.4, 62.5, 28.4, 22.8, 13.7, 11.5; IR: 2980, 1725, 1686, 1569, 1542, 1425, 1248, 1083 cm^{-1}; EI-MS: m/z 365 (M^+). Anal. Calcd for $C_{19}H_{19}N_5O_3$: C, 62.46; H, 5.24; N, 19.17. Found: C, 62.32; H, 5.27; N, 19.26.

Ethyl 2-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (3k) Yellow oil; yield 68%; ^{1}H NMR: δ 7.64 (d, J = 8.0 Hz, 2H, ArH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 4.29 (q, J = 8.0 Hz, 2H, CH_2), 2.95 (s, 3H, CH_3), 2.74 (d, J = 8.0 Hz, 6H, CH_3), 2.41 (s, 3H, CH_3), 1.17 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 194.4, 168.5, 167.1, 165.4, 154.2, 143.8, 141.7, 139.0, 133.3, 129.5, 128.5, 125.1, 62.4, 28.3, 22.8, 21.4, 13.7, 11.4; IR: 2980, 1725, 1686, 1569, 1542, 1425, 1248, 1080 cm^{-1}; EI-MS: m/z 379 (M^+). Anal. Calcd for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.20; H, 5.64; N, 18.61.

Ethyl 2-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (3l) Yellow solid; mp 128–130°C; yield 70%; ^{1}H NMR: δ 7.74 (d, J = 8.0 Hz, 2H, ArH), 6.99 (d, J = 8.0 Hz, 2H, ArH), 4.32 (q, J = 8.0 Hz, 2H, CH_2), 3.87 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 1.21 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 194.5, 168.4, 167.4, 164.7, 162.2, 154.1, 143.8, 138.9, 130.4, 128.4, 124.6, 114.3, 62.4, 55.5, 28.3, 22.7, 13.8, 11.4; IR: 2974, 1722, 1686, 1569, 1542, 1425, 1251, 1080 cm^{-1}; EI-MS: m/z 395 (M^+). Anal. Calcd for $C_{20}H_{21}N_5O$: C, 60.75; H, 5.35; N, 17.71. Found: C, 60.90; H, 5.41; N, 17.63.

Ethyl 2-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (3m) Yellow oil; yield 65%; ^{1}H NMR: δ 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.48 (d, J = 8.0 Hz, 2H, ArH), 4.31 (q, J = 8.0 Hz, 2H, CH_2), 2.95 (s, 3H, CH_3), 2.73 (t, J = 8.0 Hz, 6H, CH_3), 1.20 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 194.4, 168.9, 166.7, 164.3, 154.2, 143.9, 139.0, 137.6, 134.6, 129.9, 129.1, 125.3, 62.59, 28.3, 22.8, 13.7, 11.4; IR: 2974, 1725, 1686, 1542, 1428, 1245, 1083 cm^{-1}; EI-MS: m/z 399 (M^+). Anal. Calcd for $C_{19}H_{18}ClN_5O_3$: C, 57.07; H, 4.54; N, 17.52. Found: C, 57.18; H, 4.58; N, 17.59.

Ethyl 2-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (3n) Yellow oil; yield 72%; ^{1}H NMR: δ 7.77 (q, J = 8.0 Hz, 2H, ArH), 7.20 (t, J = 8.0 Hz, 2H, ArH), 4.31 (q, J = 8.0 Hz, 2H, CH_2), 2.96 (s, 3H, CH_3), 2.77 (d, J = 8.0 Hz, 6H, CH_3), 1.19 (t, J = 8.0 Hz, 3H, CH_3); ^{13}C NMR: δ 194.5, 168.9, 166.9, 165.8, 164.4, 163.3, 154.2, 143.9, 139.0, 132.3 (d), 130.8 (d), 125.2, 116.2, 115.9, 62.6, 22.9, 13.8, 11.5; IR: 2980, 1722, 1686, 1542, 1425, 1245, 1083 cm^{-1}; EI-MS: m/z 383 (M^+). Anal. Calcd for $C_{19}H_{18}FN_5O_3$: C, 59.52; H, 4.73; N, 18.27. Found: C, 59.41; H, 4.79; N, 18.35.

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