Copper-Catalyzed Alkyne Cycloaddition on Electron Deficient Azides *via* Tetrazolo[1,5-*a*]pyrimidines

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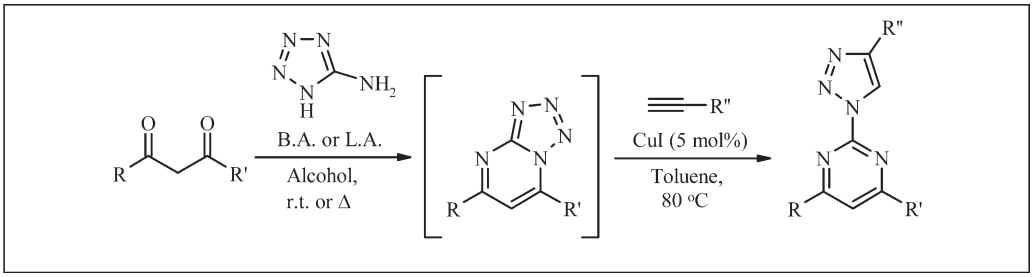

Tetrazolo[1,5-*a*]pyrimidines are capable of serving as masked azides in copper-catalyzed Huisgen cyclization with a variety of terminal alkynes, providing a simple protocol for the generation of novel 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidines.

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INTRODUCTION

In recent years, the application of transition metals to promote 1,3-dipolar cycloaddition between organic azides and alkynes has effected a revitalization of the field pioneered by Huisgen *et al.* in the 1960s [1]. This surge of attention has been brought about by reports from the research groups of Meldal and Sharpless, independently demonstrating how the catalytic presence of copper(I) facilitates a remarkable enhancement of reactivity and regioselectivity, in the case of terminal alkynes acting as the dipolarophile [2,3].

The intrinsic affinity of organic azides toward terminal alkynes, realized in the established protocol, has prompted Sharpless to coin the term ''Click Chemistry'' [4]. However, despite the many merits publicized to endorse copper-catalyzed azide-alkyne cycloaddition (CuAAC) [5,6], there is a notable absence of examples involving electron deficient 1,3-dipoles.

In the instance of electron deficient hetaryl azides, the authors of this article have only come across a handful of articles entailing CuAAC [7–9]. The obvious reason is the ability of the appended heterocycle to disperse negative charge residing on the azide, thereby disrupting its innate dipolar nature and hampering the concomitant cycloaddition.

The reactivity can be improved through the introduction of electron donating substituents on the heterocyclic moiety, enabling the CuAAC to take place under non-forcing conditions [7,8]. Conversely, the absence of any mitigating functionality may result in a sluggish reaction that demands elevated temperature and auxiliary reagent to bring about conversion [9,10].

Observing the facile reaction between β-diketones **1** and 5-aminotetrazole **2** as an entry to 2-azidopyrimidines **4**, we wanted to explore their ability to undergo alkyne cycloaddition within the context of copper(I) catalysis [11].

RESULTS AND DISCUSSION

The electron deficient 1,3-dipoles, projected as the investigative starting point for CuAAC, were synthesized by performing cyclodehydration on the appropriate β-diketone **1** with 5-aminotetrazole **2**, capitalizing on the tautomeric equilibrium existing between tetrazolo[1,5-*a*]-pyrimidine **3** and 2-azidopyrimidine **4** (Scheme 1). It was found that the presence of either Brönsted or Lewis acid in refluxing alcoholic solvent advanced cyclodehydration, allowing the prerequisite azides to be isolated in high purity by simple filtration upon cooling of the reaction media (Table 1).

The coexistence of **3** and **4**, through valence tautomery, seems to be an inherent feature of fused tetrazoles. However, the directional preference of the equilibrium is subject to several factors, including phase, solvent, temperature, and pH [12].

Scheme 1

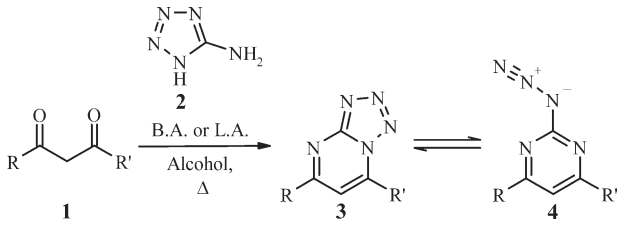

Table 1

Synthesis of 2-azidopyrimidines **4**.[a]

Entry	Compound	R	R′	Method[c]	Solvent	Time (h)	Yield (%)[d]	DSC: Exotherm (J/g)[e]	DSC: Peak interval (°C)
1	**4a**	Me	H[b]	A	EtOH	n.d.	n.d.	1457	138–224
2	**4a**	Me	H[b]	B	EtOH	3	17		
3	**4b**	Me	Me	A	EtOH	4	42	1578	163–273
4	**4b**	Me	Me	B	EtOH	3	98		
5	**4c**	Ph	Me	A	EtOH	2	84	1188	193–269
6	**4c**	Ph	Me	B	EtOH	72	43		
7	**4d**	Ph	Ph	A	MeOH	48	23	851	169–272
8	**4d**	Ph	Ph	B	EtOH	n.d.	0		
9	**4e**	Ph	CO_2Me	A	EtOH	48	35	1145	181–298
10	**4e**	Ph	CO_2Me	B	EtOH	n.d.	n.d.		

[a] The reactions were run with equimolar proportions of diketone **1** and aminotetrazole **2**.
[b] The corresponding dimethyl acetal **1a** was used.
[c] Method A: 10 mol % of conc. HCl (aq) in refluxing solvent. Method B: Preincubated solution of 10 mol % $CuCl_2$ and 10 mol % Vitamin C at ambient temperature.
[d] Isolated yield.
[e] The measured exotherms are >800 J/g, the compounds should thus be treated as potentially explosive. We strongly advise to take safety precautions, as e.g. described in *Bretherick's Handbook of Reactive Chemical Hazards* [14].

When applying single-crystal diffraction technique on a select cyclodehydration product, subsequent X-ray analysis clearly demonstrated that the compound preferred the azido-tautomer in the solid state (Fig. 1) [13].

Considering the generally high nitrogen content manifest in 2-azidopyrimidines **4**, the prepared compounds were submitted to differential scanning calorimetry (DSC) for the purpose of establishing safety margins (Table 1). Based on the relative thermal stability and yield, **4c** was subsequently selected as the candidate dipole to be tested in CuAAC (Scheme 2).

In accordance with the precognized conditions published by Sharpless and coworkers [3], cycloaddition was initially attempted utilizing an *in situ* generated Cu(I)-catalyst and a polar solvent. However, no product formation was observed and the reaction remained unresponsive to alteration of temperature as well as electronic modulation of the dipolarophile **5** (Table 2; entry 1,2).

Surprisingly, when the catalytic constellation was interchanged and Cu(I) instead was added directly, reaction proceeded at elevated temperatures. Furthermore, it became evident that the nature of the alkyne substituent dramatically affected the rate. Thus, with an aryl appendage, cycloaddition occurred only reluctantly, while the ester counterpart participated readily (Table 2; entry 3,4).

To encourage swifter conversion, it was in turn opted to perform the CuAAC in a nonpolar solvent. Seeing the ability to delocalize charge within its interior, the pyrimidine featured in **4c** effectively acts as an electronic

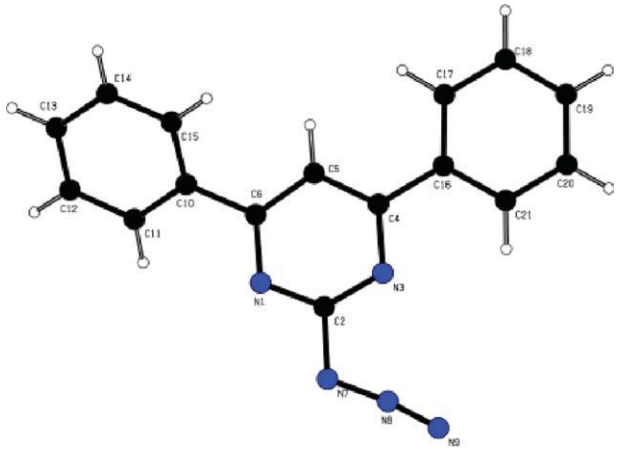

Figure 1. Crystal structure of compound **4d** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 2

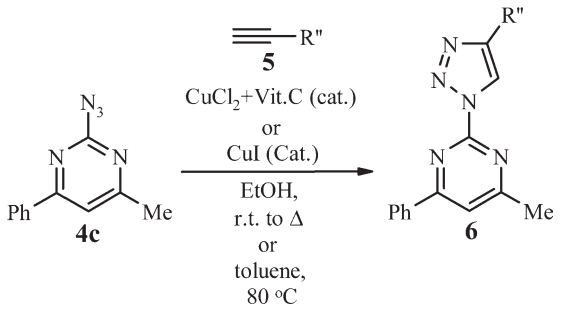

Table 2

Synthesis of 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidines **6**.[a]

Entry	Compound	R′′	Solvent	Temp.(°C)	Catalyst/Loading (mol%)	Time (h)	Yield[c]/Conversion[d] (%)
1	**6a**	Ph	EtOH	r.t. to δ	$CuCl_2$+Vit.C/10	1 Week	n.d./No
2	**6b**	CO_2Et	EtOH	r.t. to δ	$CuCl_2$+Vit.C/10	1 Week	n.d./No
3	**6a**	Ph	EtOH	δ	CuI/10	1 Week	n.d./Full
4	**6b**	CO_2Et	EtOH	δ	CuI/10	4	n.d./Full
5	**6a**	Ph	Toluene	80	CuI/5	2	64/Full
6	**6b**	CO_2Et	Toluene	80	CuI/5	2	77/Full
7	**6c**	*o*-Toluyl	Toluene	80	CuI/5	15[b]	56/Full
8	**6d**	*m*-Toluyl	Toluene	80	CuI/5	15[b]	70/Full
9	**6e**	*p*-Toluyl	Toluene	80	CuI/5	15[b]	67/Full
10	**6f**	*o*-Anisyl	Toluene	80	CuI/5	2	58/Full
11	**6g**	*m*-Anisyl	Toluene	80	CuI/5	2	73/Full
12	**6h**	*p*-Anisyl	Toluene	80	CuI/5	2	58/Full
13	**6i**	4-(Dimethylamino)phenyl	Toluene	80	CuI/5	24	71/Full
14	**6j**	6-Methoxynaphth-2-yl	Toluene	80	CuI/5	7	71/Full
15	**6k**	Benzyl	Toluene	80	CuI/5	2	72/Full
16	**6l**	Cyclopropyl	Toluene	80	CuI/5	3	91/Full
17	**6m**	Diethoxymethyl	Toluene	80	CuI/5	2	79/Full
18	**6n**	CO_2Me	Toluene	80	CuI/5	3	51/Full

[a] The reactions were performed on an 0.47 mmol scale with equimolar proportions of azide **4c** and alkyne **5**.
[b] The reaction was run overnight.
[c] Isolated yield after recrystallization.
[d] The reactions were monitored by HPLC and LC-MS.

sink, draining the azide of its latent reactivity. Running the CuAAC in a nonpolar solvent would thus *a priori* act as a counter, disfavoring charge separation and ensure a more well-behaved dipole. Gratifyingly, the choice solvent proved efficacious in bringing about the reaction: By changing from ethanol to toluene, rapid reaction was realized with both aryl and ester appended alkyne **5**. Additionally, the catalytic mediation of copper was underpinned on the account that 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidine **6** was the sole cyclized product observed. In contrast to the preceding literature [3], neither additional base nor the exclusion of oxygen was needed, as none of the reported by-products were formed.

Having established workable conditions, the generality of the CuAAC was tested by subjecting 2-azidopyrimi-dine **4c** to an ensemble of terminal alkynes **5**, exploring both electronic and steric effects (Table 2; entry 5–18). In the majority of cases, full conversion was realized smoothly within a couple of hours and at the latest after 24 h. The isolated yield of compound **6** varied between 51 and 91% after recrystallization, which was performed to remove the catalyst.

CONCLUSIONS

This article outlines a novel protocol for highly selective copper-catalyzed 1,3-dipolar cycloaddition between electron deficient hetaryl azides and a variety of terminal alkynes. Applied on 2-azidopyrimidines, the protocol allows smooth transformation to the corresponding 4′-substituted 2-triazolylpyrimidines in the absence of any auxiliary reagents.

EXPERIMENTAL

NMR spectra were recorded either on a Bruker DPX400 NMR spectrometer operating at 400 MHz for ^{1}H, and 101

MHz for ^{13}C equipped with a 4-nucleus probe-head with Z-gradients, or a Bruker Avance III 500 NMR spectrometer, operating at 500 MHz for ^{1}H and 126 MHz for ^{13}C equipped with a 5 mm TCI cryo probe-head with Z-gradients. Chemical shifts are given in ppm down- and upfield from TMS (0.00 ppm). DMSO-d_6 δ_H 2.49; δ_C 39.51 and $CDCl_3$ δ_H 7.27; δ_C 77.00 were used as reference signals. All experiments were performed at a sample temperature of 26°C ± 2°C. LC-MS analyses were performed on a LC-MS system consisting of a Waters Alliance 2795 HPLC, a Waters PDA 2996 diode array detector, a Sedex 75 ELS detector, and a ZQ 2000 single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. The capillary voltage was set to 3.3 kV and the cone voltage to 28 V, respectively. The mass spectrometer was scanned between *m/z* 100 and 700 with a scan time of 0.3 s. The diode array detector scanned from 200 to 400 nm. The temperature of the ELS detector was adjusted to 40°C, and the pressure was set to 1.9 bar. Separation was performed on an Gemini C18 3.0 × 50, 3 μm (Phenomenex) run at a flow rate of 1 mL/min. A linear gradient was applied starting at 100% A (A: 10 m*M* NH_4OAc in 5% CH_3CN) ending at 100% B (B: CH_3CN) in 4 min followed by 100% B until 5.5 min. The column oven temperature was set to 40°C. HPLC analyses were performed on an Agilent HP1100 system consisting of a G1322A Micro Vacuum Degasser, a G1311A Quaternary Pump, a G1367 Well-Plate Autosampler, a G1316A Thermostated Column Compartment and a G1315A Diode Array Detector. The diode array detector was scanned from 200 to 400 nm, step and peak width were set to 2 nm and 0.01 min, respectively. The column used was an Gemini C18, 3.0 mm × 50 mm, 3.0 μm, 110 Å run at a flow rate of 1.0 mL/min. The column oven temperature was set to 40°C. A linear gradient was applied, starting at 100% A (A: 10 m*M* NH_4OAc in 5% CH_3CN) and ending at 95% B (B: CH_3CN) after 6.5 min then 95% B for 0.5 min. High resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof micro mass spectrometer equipped with a LockSpray source and connected to an Acquity UPLC system with a PDA detector. All analyses were acquired using positive mode electrospray ionization (ESI+) in full scan, and Leucine Enkephalin (Sigma) was used as the lock mass (m/z 556.2771) at a concentration of 0.9 pmol/μL and a flow rate of 100 μL/min with a 1:10 split, ion source:waste. Cone Voltage was set to 54 to achieve ~200 counts for Leucine Enkephalin. Nitrogen was used as the nebulizing and desolvation gas, with the source operated at 120°C and the desolvation gas at 300°C. Capillary voltage was 3000 V, Cone voltage 30 V. Argon was used as the collision gas. Chromatographic separation for HRMS was achieved with a 2.3 min linear gradient from 95% A (A: 10 m*M* NH4OAc in MilliQ water + 5% MeCN) to 95% B (B: MeCN) over an ACQUITY UPLC BEH C18 1.7 μm, 2.1 mm × 50 mm column maintained at 65°C and run at a flow rate of 0.7 mL/min with a 1:5 split, ion source:waste. Analytes were diluted in H2O:ACN (50:50) until suitable concentration for the LC-MS analysis. DSC was performed in a Mettler Toledo DSC 820 equipped with a high-pressure gold-plated capsule in the temperature range of 30–500°C using a heating rate of 5 K/min.

2-Azido-4-methylpyrimidine (4a)

Method B. $CuCl_2$ (10.1 mg, 0.07 mmol) was dissolved in MeOH (2 mL), resulting in a green solution. Ascorbic acid (13.3 mg, 0.07 mmol) was added and the mixture was stirred for 5 min, to give a colorless solution. 4,4-Dimethoxybutan-2-one (**1a**) (100 mg, 0.76 mmol) and 1H-tetrazol-5-amine (**2**) (64.4 mg, 0.76 mmol) were added in sequence and the mixture was stirred at ambient temperature for 3 h. Saturated NH_4Cl (10 mL) was added and the resulting suspension was extracted with EtOAc (5 × 30 mL). The organic layers were dried with $NaSO_4$ and evaporated *in vacuo*. The crude material was washed with hot heptane, yielding the title compound as a pink solid after failed recrystallization with MeOH/H_2O. Yield: 19 mg, 17%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.93 (s, 3H), 7.48 (d, J = 4.3 Hz, 1H), 9.02 (d, J = 4.3 Hz, 1H). MS: (ES) *m/z* 136 [M+1].

2-Azido-4,6-dimethylpyrimidine (4b)

Method A. Pentane-2,4-dione (**1b**) (0.103 mL, 1.00 mmol) was dissolved in EtOH (2.5 mL) and hydrochloric acid, 37% (0.1 mL) to give a colorless solution. 1H-Tetrazol-5-amine (**2**) (85 mg, 1.00 mmol) was added and the resulting mixture refluxed for 4 h. The formed suspension was evaporated to dryness yielding a white solid, and the solid was redissolved in a minimal amount of hot EtOH. The title compound precipitated on cooling and was collected by suction filtration as a white solid. Yield: 63 mg, 42%.

Method B. $CuCl_2$ (13.4 mg, 0.01 mmol) was dissolved in EtOH (3 mL), resulting in a green solution. Ascorbic acid (17.6 mg, 0.01 mmol) was added and the mixture was stirred for 5 min to give a colorless, homogenous, mixture. Pentane-2,4-dione (**1b**) (0.103 mL, 1.00 mmol) and 1H-tetrazol-5-amine (**2**) (85 mg, 1.00 mmol) were added in sequence, and the resulting mixture was stirred at ambient temperature for 3 h. Saturated NH_4Cl (10 mL) was added and the resulting suspension was extracted with EtOAc (5 × 30 mL). The organic layers were dried with $NaSO_4$ and evaporated *in vacuo*, yielding the title compound as a white solid. Yield: 132 mg, 98%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (m, 3H), 2.86 (s, 3H), 7.39 (s, 1H). MS: (ES): *m/z* 150 [M+1], 148 [M–1].

2-Azido-4-methyl-6-phenylpyrimidine (4c)

Method A. 1-Phenylbutane-1,3-dione (**1c**) (100 mg, 0.62 mmol) was dissolved in EtOH (2.5 mL) and hydrochloric acid, 37% (0.06 mL) to give a colorless solution. 1H-Tetrazol-5-amine (**2**) (52.5 mg, 0.62 mmol) was added and the resulting mixture was refluxed for 2 h. The formed suspension was evaporated *in vacuo*, yielding a white solid. The solid was dissolved in hot EtOH and cooled to ambient temperature, followed by storage in the refrigerator overnight. The precipitated material was collected by suction filtration to yield the title compound as colorless, needle-like crystals. Yield: 111 mg, 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.97 (s, 3H), 7.6–7.7 (m, 3H), 8.18 (s, 1H), 8.3–8.4 (m, 2H). MS; ES *m/z* 212 [M+1].

Method B. $CuCl_2$ (4.2 mg, 0.03 mmol) was dissolved in EtOH (3 mL), resulting in a green solution. Ascorbic acid (17.6 mg, 0.03 mmol) was added, and the mixture was stirred for 5 min to give a colorless, homogenous mixture. 1-Phenylbutane-1,3-dione (**1c**) (100 mg, 0.62 mmol) and 1H-tetrazol-5-amine (**2**) (52 mg, 0.62 mmol) were added in sequence, and the resulting mixture was stirred at ambient temperature for 72 h. Saturated NH_4Cl (10 mL) was added and the resulting suspension was extracted with EtOAc (5 × 30 mL). The organic layers were dried with $NaSO_4$ and evaporated *in vacuo*. The crude material was recrystallized in MeOH/H_2O, yielding the titled compound as colorless, needle-like, crystals. Yield: 56 mg, 43%.

2-Azido-4,6-diphenylpyrimidine (4d)

Method A. 1,3-Diphenylpropane-1,3-dione (**1d**) (100 mg, 0.45 mmol) was dissolved in EtOH (2.5 mL) and hydrochloric acid 37% (0.04 mL, 0.48 mmol) to give a colorless solution. 1H-

Tetrazol-5-amine (**2**) (40 mg, 0.45 mmol) was added and the resulting mixture was refluxed for 48 h. The mixture was cooled to ambient temperature, followed by storage in the refrigerator overnight. The precipitated material was collected by suction filtration to yield the title compound as colorless, needle-like crystals. Yield: 27.8 mg, 23%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.5–7.8 (m, 6H), 8.3–8.5 (m, 5H). MS: (ES) *m*/*z* 274 [M+1].

Methyl 2-azido-6-phenylpyrimidine-4-carboxylate (4e)

Method A. Methyl 2,4-dioxo-4-phenylbutanoate (**1e**) (100 mg, 0.48 mmol) was dissolved in EtOH (3 mL) and hydrochloric acid 37% (0.04 mL, 0.48 mmol) to give a colorless mixture. 1H-Tetrazol-5-amine (**2**) (41.3 mg, 0.48 mmol) was added and the resulting mixture was refluxed for 48 h. The solution was cooled to ambient temperature, followed by storage in the refrigerator overnight. The precipitated material was collected by suction filtration to yield the title compound as colorless, needle-like crystals. Yield: 43.4 mg, 35%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.96 (s, 3H), 7.6–7.7 (m, 3H), 8.2–8.3 (m, 3H). MS: (ES) *m*/*z* 256 [M+1].

General procedure for the synthesis of 4′-substituted 2-(1′,2′,3′-triazol-1′-yl)pyrimidines (6). Copper(I) iodide (9 mg, 0.05 mmol) was suspended in toluene (2 mL), whereupon the alkyne (**5**) (0.47 mmol) was added, followed by 2-azido-4-methyl-6-phenylpyrimidine (**4c**) (100 mg, 0.47 mmol) to yield a heterogeneous mixture. The resulting reaction mixture was heated to 80°C for the time specified (Table 2) and full conversion was observed according to HPLC. The volatiles were evaporated *in vacuo* to afford the crude as a solid. The solid was suspended/dissolved in a minimum of hot EtOH, and water was subsequently added until a turbid liquid phase was observed. Upon refrigeration/cooling precipitation ensued and the product was isolated and dried to give the yield specified.

4-Methyl-6-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrimidine (6a). Starting alkyne: Ethynylbenzene (**5a**). Reaction time: 2 h. Yield: 95 mg, 64%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.77 (s, 3H), 7.40 (t, J = 7.5 Hz, 2H), 7.65 (s, 1H), 8.01 (d, J = 7.8 Hz, 2H), 7.61–7.54 (m, J = 7.1 Hz, 3H), 7.49 (t, J = 7.5 Hz, 2H), 8.21 (dd, J = 6.8 Hz, 7.8 Hz, 2H), 8.94 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.6, 58.5, 115.5, 118.5, 126.1, 127.4, 128.5, 128.9, 129.1, 130.1, 131.8, 135.4, 147.9, 154.5, 166.0, 170.8. MS: (ES) *m*/*z* 314 [M+1]. HPLC: R_t= 4.6 min. HRMS: Found 314.1406, calc. for $C_{19}H_{16}N_5$: 314.1400.

Ethyl 1-(4-methyl-6-phenylpyrimidin-2-yl)-1H-1,2,3-triazole-4-carboxylate (6b). Starting alkyne: Ethyl propiolate (**5b**). Reaction time: 2 h. Yield: 112 mg, 90%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (t, J = 7.4 Hz, 3H), 2.76 (s, 3H), 4.50 (q, J = 7.4 Hz, 2H), 7.5–7.6 (m, 3H), 7.69 (s, 1H), 8.19 (dd, J = 7.2 Hz, 2H), 9.24 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.4, 24.6, 61.6, 116.1, 126.9, 127.4, 129.2, 132.0, 135.0, 140.3, 154.1, 160.6, 166.2, 171.1. MS: (ES) *m*/*z* 310 [M+1]. HPLC: R_t= 4.9 min. HRMS: Found 310.1305, calc. for $C_{16}H_{16}N_5O_2$: 310.1304.

4-Methyl-6-phenyl-2-(4-o-tolyl-1H-1,2,3-triazol-1-yl)pyrimidine (6c). Starting alkyne: 1-Ethynyl-2-methylbenzene (**5c**). Reaction time: Overnight. Yield: 88 mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H), 2.78 (s, 3H), 7.3–7.4 (m, 3H), 7.5–7.6 (m, 3H), 7.66 (s, 1H), 7.9 (m, 1H), 8.2–8.3 (m, 2H), 8.80 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.40, 24.6, 115.4, 120.6, 126.1, 127.4, 128.5, 129.1, 129.3, 129.5, 130.9, 131.7, 135.4, 136.0, 147.3, 154.6, 166.0, 170.8. MS: (ES) *m*/*z* 328 [M+1]. HPLC: R_t = 5.8 min. HRMS: Found 328.1570, calc. for $C_{20}H_{18}N_5$: 328.1562.

4-Methyl-6-phenyl-2-(4-m-tolyl-1H-1,2,3-triazol-1-yl)pyrimidine (6d). Starting alkyne: 1-Ethynyl-3-methylbenzene (**5d**). Reaction time: Overnight. Yield: 109 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.76 (s, 3H), 7.37 (t, J = 7.5 Hz 1H), 7.5–7.6 (m, 3H), 7.63 (s, 1H), 7.64 (s, 1H), 7.78 (d, J = 7.5 Hz 1H), 7.86 (s, 1H), 8.2–8.3 (m, 2H), 8.91 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.4, 24.6, 115.4, 118.5, 123.2, 126.7, 127.4, 128.7, 129.1, 129.3, 130.0, 131.7, 135.5, 138.6, 148.0, 154.5, 166.0, 170.8. MS: (ES) *m*/*z* 328 [M+1]. HPLC: R_t = 5.9 min. HRMS: Found 328.1569, calc. for $C_{20}H_{18}N_5$: 328.1562.

4-Methyl-6-phenyl-2-(4-p-tolyl-1H-1,2,3-triazol-1-yl)pyrimidine (6e). Starting alkyne: 1-Ethynyl-4-methylbenzene (**5e**). Reaction time: Overnight. Yield: 105 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.75 (s, 3H), 7.29 (d, J = 8.0 Hz, 3H), 7.5–7.6 (m, 3H), 7.63 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 8.2–8.3 (m, 2H), 8.86 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.3, 24.6, 115.4, 118.1, 126.00, 127.3, 127.4, 129.1, 129.5, 131.7, 135.5, 138.4, 148.0, 154.5, 166.0, 170.8. MS: (ES) *m*/*z* 328 [M+1]. HPLC: R_t = 5.9 min. HRMS: Found 328.1568, calc. for $C_{20}H_{18}N_5$: 328.1562.

2-(4-(2-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6f). Starting alkyne: 1-Ethynyl-2-methoxy-benzene (49). Reaction time: 2 h. Yield: 95 mg, 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (s, 3H), 4.03 (s, 3H), 7.04 (d, J = 8.4 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.2–7.4 (m, 1H), 7.6 (m, 3H), 7.64 (s, 1H), 8.2–8.3 (m, 2H), 8.5 (m, 1H), 9.10 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.5, 55.5, 110.7, 115.3, 118.9, 120.9, 121.7, 127.4, 128.2, 129.0, 129.2, 131.6, 135.5, 143.3, 154.7, 155.9, 165.9, 170.6. MS: (ES) *m*/*z* 344 [M+1]. HPLC: R_t = 5.7 min. HRMS: Found 344.1522, calc. for $C_{20}H_{18}N_5O$: 344.1511.

2-(4-(3-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6g). Starting alkyne: 1-Ethynyl-3-methoxy-benzene (**5g**). Reaction time: 2 h. Yield: 120 mg, 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 3H), 3.91 (s, 3H), 6.9–7.0 (m, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.5–7.6 (m, 5H), 7.64 (s, 1H), 8.2–8.3 (m, 2H), 8.91 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.6, 55.4, 111.1, 114.6, 115.5, 118.5, 118.7, 127.4, 129.1, 129.9, 131.4, 131.8, 135.4, 147.8, 154.4, 160.0, 166.0, 170.8. MS: (ES) *m*/*z* 344 [M+1]. HPLC: R_t= 5.6 min. HRMS: Found 344.1503, calc. for $C_{20}H_{18}N_5O$: 344.1511.

2-(4-(4-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6h). Starting alkyne: 1-Ethynyl-4-methoxy-benzene (**5h**). Reaction time: 2 h. Yield: 95 mg, 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 3H), 3.87 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.5–7.6 (m, 3H), 7.64 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 8.2–8.3 (m, 2 H), 8.84 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.6, 55.3, 114.2, 115.4, 117.6, 122.8, 127.2, 127.4, 128.2, 128.9, 129.1, 129.3, 131.3, 131.7, 132.4, 135.4, 147.8, 154.5, 159.8, 166.0, 170.8. MS: (ES) *m*/*z* 344 [M+1]. HPLC: R_t = 5.5 min. HRMS: Found 344.1504, calc. for $C_{20}H_{18}N_5O$: 344.1511.

N,N-Dimethyl-4-(1-(4-methyl-6-phenylpyrimidin-2-yl)-1H-1,2,3-triazol-4-yl)aniline (6i). Starting alkyne: 4-Ethynyl-*N,N*-dimethylbenzenamine (**5i**). Reaction time: 24 h. Yield: 120 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (s, 3H), 3.02 (s, 6H), 6.82 (d, J = 8.7 Hz, 2H), 7.5–7.6 (m, 3H), 7.62 (s, 1H), 7.87 (d, J = 8.7 Hz, 2H), 8.2–8.3 (m, 2H), 8.78 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.6, 40.5, 112.4, 115.2, 116.7, 127.1, 127.4, 129.1, 131.6, 135.6, 118.2, 148.4, 150.6, 154.6,

165.9, 170.7. MS: (ES) *m/z* 357 [M+1]. HPLC: R_t = 5.8 min. HRMS: Found 357.1823, calc. for $C_{21}H_{21}N_6$: 357.1828.

2-(4-(6-Methoxynaphthalen-2-yl)-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6j). Starting alkyne: 2-ethynyl-6-methoxynaphthalene (**5j**). Reaction time: 7 h. Yield: 133 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.31 (s, 3H), 3.90 (s, 3H), 7.1–7.3 (m, 3H), 7.3–7.4 (m, 1H), 7.6–7.7 (m, 3H), 7.94 (d, J = 8.9 Hz, 2H), 8.2–8.3 (m, 2H), 8.4–8.5 (m, 2H), 8.59 (bs, 1 H), 9.60 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.6, 55.3, 105.7, 115.5, 118.3, 119.3, 124.6, 124.9, 125.3, 127.36, 127.43, 128.9, 129.1, 129.8, 131.8, 134.5, 135.4, 148.1, 154.5, 158.0, 166.0, 170.8. MS: (ES) *m/z* 394 [M+1]. HPLC: R_t = 6.2 min. HRMS: Found 394.1660, calc. for $C_{24}H_{20}N_5O$: 394.1668.

2-(4-Benzyl-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6k). Starting alkyne: Prop-2-ynylbenzene (**5k**). Reaction time: 2 h. Yield: 112 mg, 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (s, 3H), 4.24 (s, 2H), 7.2-7.3 (m, 1H), 7.34 (d, J = 4.6 Hz, 4H), 7.5–7.6 (m, 3H), 7.60 (s, 1H), 8.13 (dd, J = 8.2 Hz, 7.2 Hz, 2H), 8.35 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.5, 32.2, 115.4, 120.7, 126.6, 127.4, 128.6, 128.8, 129.0, 131.7, 135.4, 138.7, 148.0, 154.5, 165.9, 170.7. MS: (ES) *m/z* 328 [M+1]. HPLC: R_t= 4.6 min. HRMS: Found 328.1552, calc. for $C_{20}H_{18}N_5$: 328.1562.

2-(4-Cyclopropyl-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6l). Starting alkyne: Ethynylcyclopropane (**5l**). Reaction time: 3 h. Yield: 119 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9–1.0 (m, 4H), 2.1–2.2 (m, 1H), 2.73 (s, 1H), 7.5–7.6 (m, 3H), 7.61 (s, 1H), 8.1–8.2 (m, 2H), 8.36 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 6.78, 7.89, 24.6, 115.2, 118.5, 127.4, 129.1, 131.7, 135.5, 154.5, 165.9, 170.7. MS: (ES) *m/z* 277 [M+1]. HPLC: R_t= 4.9 min. HRMS: Found 278.1409, calc. for $C_{16}H_{16}N_5$: 278.1406.

2-(4-Diethoxymethyl-1H-1,2,3-triazol-1-yl)-4-methyl-6-phenylpyrimidine (6m). Starting alkyne: 3,3-Diethoxyprop-1-yne (**43**). Reaction time: 2 h. Yield: 127 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.1 Hz, 6H), 2.81 (bs, 3H), 3.6–3.8 (m, 4H), 5.87 (s, 1H), 7.5–7.6 (m, 3H), 7.66 (s, 1H), 8.1–8.2 (m, 2H), 8.76 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.2, 24.7, 61.6, 96.5, 115.7, 121.4, 127.4, 129.1, 131.8, 135.3, 147.5, 166.0, 170.8. MS: (ES) *m/z* 278 [M–61]. HPLC: R_t = 4.9 min. HRMS: Found 294.1351, calc. for $C_{16}H_{16}N_5O$: 294.1354 (The parent ion could not be observed. The observed mass corresponds to $[M+H^+ - C_2H_6O]$.)

Methyl 1-(4-methyl-6-phenylpyrimidin-2-yl)-1H-1,2,3-triazole-4-carboxylate (6n). Starting alkyne: Methyl propiolate (**37**). Reaction time: 3 h. Yield: 77 mg, 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (s, 3H), 4.03 (s, 3H), 7.69 (s, 1H), 7.5–7.6 (m, 3H), 8.1–8.2 (m, 2H), 9.26 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.6, 52.4, 116.1, 127.0, 127.4, 129.2, 132.0, 135.0, 140.1, 154.1, 161.0, 166.2, 171.1. MS: (ES) *m/z* 296 [M+1]. HPLC: R_t = 4.5 min. HRMS: Found 296.1137, calc. for $C_{15}H_{14}N_5O_2$: 296.1147.

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[13] Compound **4d**, C_{16} H_{11} N_5 (M_r = 273.30), Colorless, Rod, Monoclinic space group P $2_1/c$, Z = 4, a = 11.437(1) Å, b = 16.761(1) Å, c = 7.030(1) Å, α = 90°, β = 94.435(2)°, γ = 90°, V = 1343.6(2) Å^3, Mo $K\alpha$ radiation, θ = 1.0–27.5°, 6126 measured reflections, T = 200(2) K on Bruker-Nonius KappaCCD diffractometer. The structure was solved using direct methods SIR97 (Altomare *et al*., 1999). Program used to refine structure: SHELXL97 (Sheldrick, 1997). Molecular graphics: PLATON (Spek, 2003). The final $R[F^2 > 2\sigma(F^2)]$ = 0.0567 and $wR = [w = 1/[\sigma^2(F_o^2) + (0.0730P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$.

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