Regiospecific synthesis of 1,4,5-trisubstituted 1,2,3-triazoles *via* enolate–azide cycloaddition between 1,3-dicarbonyl compounds and aryl azides

Ronald Nelson[a], Víctor Kesternich[a]*, Marcia Pérez-Fehrmann[a], Sally Jaldin[a], Laurence Marcourt[b] and Philippe Christen[b]

[a]*Departamento de Química, Facultad de Ciencias, Universidad Católica del Norte, Antofagasta, Chile*
[b]*School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland*

A cycloaddition reaction at room temperature between aryl azides and 1,3-dicarbonyl compounds in the presence of potassium carbonate in dimethylsulphoxide yielded 10 4-ethoxycarbonyl-1-aryl-5-methyl-1*H*-1,2,3-triazoles and seven other closely-related compounds. The 1,2,3-triazoles, nine of which are new, were obtained in good to high yields and only the 1,4-regioisomers were formed.

Keywords: 1,4,5-trisubstituted 1*H*-1,2,3-triazoles, regioselective synthesis of 1,2,3-triazole, enolate–azide cycloaddition, potassium carbonate-assisted synthesis

1*H*-1,2,3-Triazoles are five-membered nitrogen-containing heterocycles the derivatives of which have a wide range of biological activities. For example, they are known to be potent antibacterial,[1,2] antifungal,[3,4] antichagasic,[5,6] tuberculostatic,[7–12] antiviral,[13,14] antiplatelet,[15,16] anti-inflammatory,[17] and anticonvulsive agents[18] and some derivatives have antineoplastic and antiproliferative activity.[19–21]

One well-tried method of synthesis of 1,2,3-triazole rings is *via* the Huisgen reaction, the 1,3-dipolar cycloaddition between azides and alkynes.[22] However, this method requires long reaction times with high temperatures and generates mixtures of 1,4- and 1,5-disubstituted regioisomers.[23,24] An important contribution to this reaction was catalysis with copper using terminal alkynes,[25] but this method is not viable to obtain 1,2,3-trisubstituted 1,4,5-triazoles check script. Recently, the application of organocatalytic enamide–azide cycloadditions were reported for the synthesis of the 1,2,3-triazole moiety.[26–29]

The first report of a cycloaddition between an enolate and an aryl azide was by Kamalraj and coworkers[30] in 2008, who prepared 4-acetyl-1-aryl-5-methyl 1*H*-1,2,3-triazoles by reacting acetylacetone in EtOH at 75 °C with a series of aryl azides in the presence of K_2CO_3 (3 equiv.). In 2011, Danence and coworkers[31] reported a similar reaction between aryl azides and a wider group of 1,3-dicarbonyl compounds at 70 °C in DMSO catalysed by 5 mol% diethylamine. In 2013, Ahmadi and coworkers[32] also used aryl azides and a wider group of 1,3-dicarbonyl compounds at 30 °C in EtOH but catalysed by 15 mol% 1,1,3,3-tetramethylguanidine.

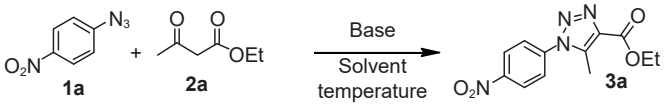
Herein, we report enolate-mediated [3+2] cycloaddition reactions conducted at room temperature between aryl azides and several types of 1,3-dicarbonyl compounds in the presence of a catalytic (10 mol%) or a stoichiometric amount of K_2CO_3 in DMSO which produce 4,5-disubstituted 1-aryl-1*H*-1,2,3-triazoles in high yields and absolute regioselectivities.

Results and discussion

To establish the appropriate reaction conditions for our planned enolate–azide cycloadditions, a set of experiments were undertaken with *p*-nitroazidobenzene (**1a**) and ethyl acetoacetate (**2a**) in the presence of base (Table 1). In the first experiment, we tested **1a** with ethyl acetoacetate (1.1 equiv.) in EtOH (0.5 M) using a stoichiometric amount of K_2CO_3 at reflux (entry 1).[30] Under these reaction conditions, the desired product **3a** was obtained in a modest yield after 2 h (49%, entry 1). Other solvents were used at room temperature (entries 2 and 3) and gave **3a** in good yield with DMSO as the solvent (85%, entry 3). A moderate or poor yield of **3a** was obtained using other bases such as Li_2CO_3, Na_2CO_3, $NaHCO_3$ and Cs_2CO_3 (entries 4–7). Gratifyingly, an excellent yield of product **3a** was obtained at 1.0 M dilution, even with only a catalytic amount of K_2CO_3 (10 mol%) (entries 8–10). Other bases, such as DBU and Et_3N, in a catalytic amount (10 mol%) were tested and gave 80 and 73% yields, respectively (entries 11 and 12).

As can be seen from Table 1, the best reaction conditions to obtain triazole **3a** used a catalytic amount of K_2CO_3 (10 mol%) in DMSO (1.0 M) at room temperature. We then applied these optimised conditions to the reaction between other aryl azides (**1a**–**k**) and other types of 1,3-dicarbonyl compounds (**2a**–**f**). The compatibility of several variants of **1** and **2** and the yields of the corresponding products **3** are presented in Table 2. We first evaluated the reactivity of ethyl acetoacetate (**2a**) towards different functionalised aryl azides (entries 1–10). In general, all of the evaluated aryl azides were obtained in good yields under catalytic and stoichiometric conditions (78–91% yields), except those with substitutions at positions 4-Me (**1e**), 3-Cl,4-$MeOC_6H_3$ (**1i**) and 3-Cl,4-FC_6H_3 (**1j**), which were obtained in 55–60% yields, which were only improved under stoichiometric

Table 1 Optimisation of the reaction conditions for the preparation of ethyl 5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate **3a** from 4-nitroazidobenzene **1a** and ethyl acetoacetate **2a**

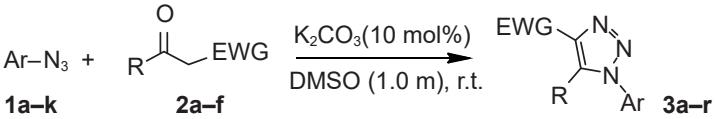


Entry[a]	Solvent	Molarity/ M	Base (equiv.)	Temp./°C	Time/h	Yield **3a**/%[b]
1	EtOH	0.5	K_2CO_3 (1)	79	2	49
2	DMF	0.5	K_2CO_3 (1)	23	6	Trace
3	DMSO	0.5	K_2CO_3 (1)	23	2	85
4	DMSO	0.5	Li_2CO_3 (1)	23	2	61
5	DMSO	0.5	Na_2CO_3 (1)	23	2	74
6	DMSO	0.5	$NaHCO_3$ (1)	23	6	28
7	DMSO	0.5	Cs_2CO_3 (1)	23	2	42
8	DMSO	1.0	K_2CO_3 (1)	23	0.5	94
9	DMSO	1.0	K_2CO_3 (0.5)	23	1	91
10	**DMSO**	**1.0**	**K_2CO_3 (0.1)**	**23**	**2**	**90**
11	DMSO	1.0	DBU (0.1)	23	12	80
12	DMSO	1.0	Et_3N (0.1)	23	24	73

[a]Reactions were performed using **1a** (1 equiv.) and ethyl acetoacetate **2a** (1.1 equiv.).
[b]Yields are given for isolated products.

* Correspondent. E-mail: vkestern@ucn.cl

Table 2 Yields of a series of 4,5-disubstituted 1-aryl-1*H*-1,2,3-triazole derivatives **3a–r** prepared from aryl azides **1a–k** and a series of 1,3-dicarbonyl compounds **2a–f**



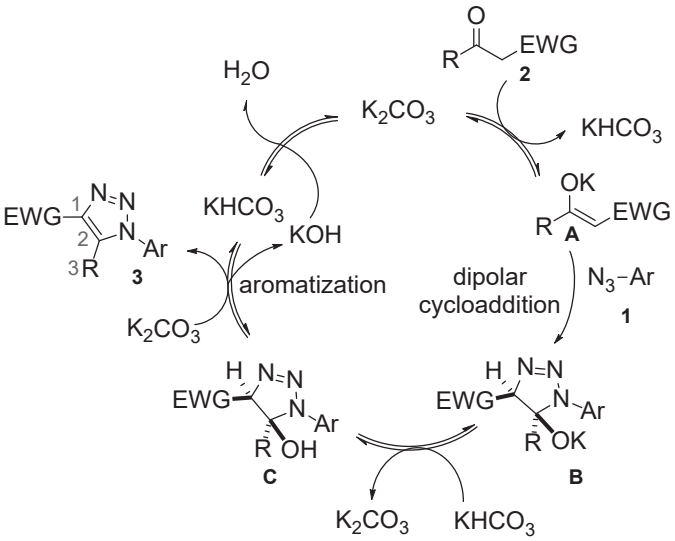
1a–k 2a–f 3a–r

	Ar–N_3		1,3-Dicarbonyl compounds			Time/h	Product	Yield/%[b]
Entry[a]	**1**	Ar	**2**	R	EWG		**3**	
1	**1b**	4-$MeOC_6H_4$	**2a**	Me	CO_2Et	2	**3b**	80/78[c]
2	**1c**	4-ClC_6H_4	**2a**	Me	CO_2Et	2.5	**3c**	78/78[c]
3	**1d**	4-BrC_6H_4	**2a**	Me	CO_2Et	1	**3d**	91/88[c]
4	**1e**	4-MeC_6H_4	**2a**	Me	CO_2Et	3	**3e**	60/68[c]
5	**1f**	3-$NO_2C_6H_4$	**2a**	Me	CO_2Et	1	**3f**	87/90[c]
6	**1g**	3,4-$Cl_2C_6H_3$	**2a**	Me	CO_2Et	2	**3g**	78[c]
7	**1h**	3,4-$Me_2C_6H_3$	**2a**	Me	CO_2Et	2	**3h**	83[c]
8	**1i**	3-Cl,4-$MeOC_6H_3$	**2a**	Me	CO_2Et	2	**3i**	55[c]
9	**1j**	3-Cl,4-FC_6H_3	**2a**	Me	CO_2Et	2	**3j**	56[c]
10[d]	**1k**	2-BrC_6H_4	**2a**	Me	CO_2Et	12	**3k**	–[e]
11	**1a**	4-$NO_2C_6H_4$	**2b**	Me	COMe	2	**3l**	90/88[c]
12	**1b**	4-$MeOC_6H_4$	**2b**	Me	COMe	3	**3m**	70/76[c]
13[d]	**1k**	2-BrC_6H_4	**2b**	Me	COMe	12	**3n**	46[c]
14	**1a**	4-$NO_2C_6H_4$	**2c**	Ph	COMe	2	**3o**	53
15	**1a**	4-$NO_2C_6H_4$	**2d**	Me	$CO_2(CH_2)_4C{\equiv}CH$	12	**3p**	75
16	**1a**	4-$NO_2C_6H_4$	**2e**	Me	$CON(CH_2CH_2)_2O$	12	**3q**	86
17	**1a**	4-$NO_2C_6H_4$	**2f**	Ph	CN	12	**3r**	62

[a]Reactions were performed using **1a** (1 equiv.) and ethyl acetoacetate **2a** (1.1 equiv.).
[b]Yields are given for isolated products.
[c]Reaction was performed using a stoichiometric amount of K_2CO_3 for 2 h.
[d]Reaction was performed at 40 °C.
[e]Product not detected.

conditions with 68% of **3e** (entries 4, 8 and 9). In the reaction with **1k**, the formation of a triazole was not detected (entry 10). Other 1,3-dicarbonyl compounds were evaluated successfully (entries 11–16). Good yields were achieved with a symmetrical 1,3-diketone **2b**, aryl azides containing an electron-withdrawing group or an electron-releasing group, **1a** (4-NO_2) or **1b** (4-MeO), and a catalytic amount of K_2CO_3, producing 90 and 70% yields for triazoles **3l** and **3m**, respectively (entries 11 and 12). Interestingly, aryl azide **1k** (inactive with ethyl acetoacetate, entry 10) under stoichiometric conditions yielded the corresponding acetyltriazole **3n** in 46% yield when reaction with **2b** was performed at 40 °C (entry 13). In addition, unsymmetrical 1,3-diketone **2c** was tested with **1a** and gave the desired product in 53% yield as a single regioisomer (entry 14). Furthermore, β-ketoester **2d** and β-ketoamide **2e** reacted with **1a** successfully to afford the corresponding products in 75 and 86% yields, respectively (entries 15 and 16). It was noted that no side reaction was observed between the alkyne group present in the alkyl chain of **2d** and the azide moiety. Finally, β-ketonitrile **2f** was tested under the optimised catalytic reaction conditions and gave a 62% yield of the corresponding cyanotriazole **3r** (entry 17).

Based on the results obtained in our study, and those obtained for other base-catalysed cycloadditions between aryl azides and 1,3-dicarbonyl compounds[30–32] and for organocatalytic enamide–azide cycloaddition reactions reported by Seus *et al.*[29] a plausible mechanism for the synthesis of 4,5-disubstituted 1-aryl-1*H*-1,2,3-triazoles (**3**) involves a catalytic cycle, as shown in Scheme 1. First, K_2CO_3 reacts with the active methylene of a 1,3-dicarbonyl compound (**2**) to produce the key intermediate, a stabilised potassium enolate **A**. Subsequently,



Scheme 1. Proposed reaction mechanism.

a 1,3-dipolar cycloaddition reaction of enolate **A** with the aryl azide (**1**) affords a potassium triazolate intermediate **B**, which is protonated to form intermediate **C**, regenerating K_2CO_3. Finally, product **3** is obtained by dehydration of intermediate **C**.

All of the compounds were characterised by IR, ^{1}H NMR, ^{13}C NMR and high-resolution electrospray-ionisation mass spectrometry (HRESIMS) methods. In general, the IR spectra of all compounds showed a C=O stretching band in the 1612–1722 cm^{-1} range as well as an N=N stretching band of the triazole ring in the 1516–1598 cm^{-1} range. For compound **3r**,

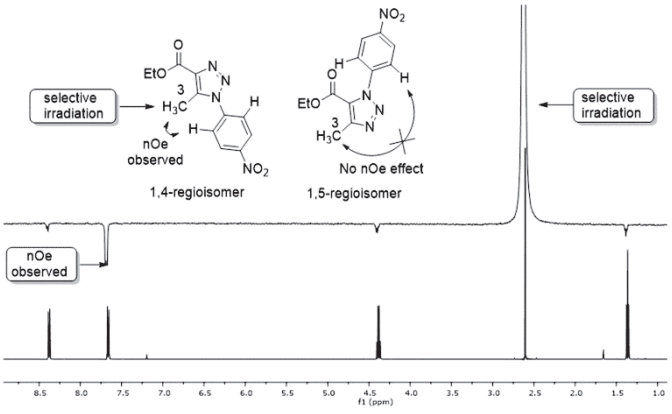


Fig. 1 ^{1}H NMR spectrum and selective irradiation at 2.67 ppm (1D-nOe) for compound **3a**.

no C=O band was seen but a C≡N stretching band was seen at 2240 cm^{-1}. In the ^{1}H NMR spectra, the most characteristic signal was a singlet in the range δ_H = 2.41–2.69 due to the protons from the methyl group (except **3o** and **3r**, R = Ph). In the ^{13}C NMR spectra, C=O signals were seen at δ_C = 160.8–194.3 and, for **3r**, δ_C = 111.5 corresponding to C≡N. In addition, a chemical shift was seen at δ_C = 136.5–144.3 and 137.5–139.9, corresponding to C_1 and C_2, respectively. The regioselectivity of **3** was established by measurement of nuclear Overhauser effects (nOe) spectra. As an example, for compound **3a**, when H_3 was selectively irradiated at 2.67 ppm, an nOe effect was observed with the *ortho* proton of the aromatic ring indicative of a 1,4-regioisomer (Fig. 1).

Experimental

Melting points were determined on a Kofler-type apparatus and are uncorrected. The IR spectra were taken on a PerkinElmer 200 spectrophotometer as KBr pellets. NMR spectra were obtained in DMSO-d_6 or $CDCl_3$ with a Varian Unity Inova 500 MHz spectrometer equipped with a 5 μL microflow probe from Protasis. Chemical shifts were reported in parts per million (δ) using the residual solvent signals (DMSO-d_6: δ_H 2.50, δ_C 39.5) ($CDCl_3$; δ_H H 7.26, δ_C C 77.2) as the internal standards for the ^{1}H and ^{13}C NMR spectra and coupling constants (*J*) in Hz. UHPLC-TOFMS spectra were recorded on a Micromass-LCT Premier Time-of-Flight ESI spectrometer with an Acquity UHPLC (ultra-high performance liquid chromatography) interface system. TLC was performed on Al Si gel Merck 60 F_{254}, and the TLC plates were visualised by spraying them with phosphomolybdic acid reagent and heating. The starting materials and reagents were acquired commercially from Sigma Aldrich or Merck.

All the functionalised aryl azides (**1a**–**k**) were prepared according to previously published procedures.[30] Amide **2e** was prepared from ethyl acetoacetate (**2a**) and morpholine with a catalytic amount of DMAP in 76% yield, according to previously published procedures.[33] Cyanoacetophenone (**2f**) was prepared from 2-bromoacetophenone and NaCN in 87% yield, according to previously published procedures.[34]

Synthesis of hex-5-yn-1-yl 3-oxobutanoate; general procedure (**2d**)

The β-ketoester was prepared using methodology described by Yadav *et al*.[35] Triphenylphosphine (0.4 mmol) was added to a stirred mixture of ethyl acetoacetate (506 μL, 521 mg, 4.0 mmol) and hex-5-yn-1-ol (441 μL, 393 mg, 4.0 mmol) in dry toluene (20 mL, 0.2 M). The resulting reaction mixture was refluxed for 18 h. After complete conversion of the substrate, the reaction mixture was directly adsorbed onto silica gel (60–120 mesh) and eluted with 5–20% ethyl acetate in hexane gave **2d** as a colourless oil in an 80% yield. IR (cm^{-1}) ν: 3298 (C_{sp}–H), 2950, 2865 (C_{sp^3}–H), 2111 (C≡C), 1738 (C=O), 1714 (C=O ester); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.17 (t, *J* = 6.5 Hz, 2H), 3.45 (s, 2H), 2.27 (s, 3H), 2.23 (td, *J* = 7.0, 2.7 Hz, 2H), 1.96 (s, 1H), 1.84–1.72 (m, 2H), 1.69–1.51 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 200.3 (C=O), 166.9 (C=O), 89.4 (CH), 83.5 (C, C≡CH), 68.8 (C, C≡CH), 64.5 (CH2), 63.1 (CH2), 49.8 (CH2), 29.9 (CH3), 27.3 (CH2), 24.6 (CH2), 17.7 (CH2); HRESIMS *m/z* for $C_{10}H_{14}O_3Na$ $[M + Na]^+$ calcd 205.0841; found: 205.0808.

*Synthesis of 4,5-disubstituted 1-aryl 1*H*-1,2,3-triazoles; general procedure* (**3a**–**r**)

Catalytic K_2CO_3 (100 mg, 0.724 mmol) or stoichiometric K_2CO_3 (1.0 g, 7.24 mmol) were added to a solution of phenylazide **1a**–**k** (7.24 mmol) with a β-ketoester, an amide or a nitrile **2a**–**f** (7.96 mmol, 1.1 equiv.) in DMSO (7.2 mL, 1.0 M). The resulting reaction mixture was stirred at room temperature for the appropriate amount of time (Table 2). The progress of the reaction was monitored by TLC. Then, cold water (30 mL) was added to give a precipitate that was filtered off and washed successively with cold water and then vacuum dried. The products were purified by crystallisation with EtOH or other solvents.

*Ethyl 5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate* (**3a**): Yellow crystals (AcOEt); m.p.: 178–180 °C (lit.[32] 181–184 °C); IR (cm^{-1}) ν: 3120, 3099, 3080 (C_{Ar}–H), 2977, 2937, 2870 (C_{sp^3}–H), 1721 (C=O), 1597 (C_{Ar}–C_{Ar}), 1566 (N=N), 1533, 1346 (Ar–NO_2), 1249 (CO–O), 980 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.44 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 1H), 2.67 (s, 1H), 1.43 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.4 (C=O), 148.3 (C), 140.3 (C), 138.9 (C), 137.5 (C), 126.0 (CH), 125.3 (CH), 61.5 (CH_2), 14.4 (CH_3), 10.3 (CH_3); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.48 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 160.9 (C=O), 147.9 (C), 139.9 (C), 139.8 (C), 136.2 (C), 126.6 (CH), 125.1 (CH), 60.6 (CH_2), 14.2 (CH_3), 9.8 (CH_3); HRESIMS *m/z* for $C_{12}H_{13}N_4O_4$ $[M + H]^+$ calcd 277.0937; found: 277.0909.

*Ethyl 1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate* (**3b**): White crystals (THF); m.p.: 140–142 °C (lit.[32] 137–139 °C). IR (cm^{-1}) ν: 3086, 3004 (C_{Ar}–H), 1709 (C=O), 1564 (N=N), 1247 (CO–O), 982 (N–N=N); ^{1}H NMR (500 MHz. $CDCl_3$) δ (ppm): 7.32 (d, *J* = 5.4 Hz, 2H), 7.02 (d, *J* = 5.1 Hz, 2H), 4.43 (q, *J* = 6.2 Hz, 2H), 3.85 (s, 3H), 2.52 (s, 3H), 1.41 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.8 (C=O), 160.7 (C), 139.1 (C), 136.5 (C), 128.2 (C), 126.9 (CH), 114.8 (CH), 61.1 (CH_2), 55.8 (CH_3), 14.5 (CH_3), 10.1 (CH_3); HRESIMS *m/z* for $C_{13}H_{16}N_3O_3$ $[M + H]^+$ calcd 262.1192; found: 262.1152.

*Ethyl 1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate* (**3c**): White crystals (THF); m.p.: 168–170 °C (lit.[34] 155–158 °C); IR (cm^{-1}) ν: 3096, 3066 (C_{Ar}–H), 1716 (C=O), 1560 (N=N), 1223 (CO–O), 1026 (Ar–Cl), 981 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.54 (d, *J* = 6.9 Hz, 2H), 7.40 (d, *J* = 7.3 Hz, 2H), 4.44 (q, *J* = 6.5 Hz, 2H), 2.58 (s, 3H), 1.43 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.7 (C=O), 139.0 (C), 137.0 (C), 136.4 (C), 134.0 (C), 130.1 (CH), 126.8 (CH), 61.3 (CH_2), 14.5 (CH_3), 10.2 (CH_3); HRESIMS *m/z* for $C_{12}H_{13}ClN_3O_2$ $[M + H]^+$ calcd 266.0696; found: 266.0680.

*Ethyl 1-(4-bromophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate* (**3d**): White crystals (THF); m.p.: 176–178 °C; IR (cm^{-1}) ν: 3099, 3067 (C_{Ar}–H), 1717 (C=O), 1562 (N=N), 1248 (CO–O), 981 (N–N=N), 840 (Ar–Br); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.67 (d, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 4.41 (q, *J* = 6.7 Hz, 2H), 2.55 (s, 3H), 1.39 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.5 (C=O), 138.8 (C), 136.9 (C), 134.4 (C), 133.0 (CH), 126.9 (CH), 124.2 (C), 61.2 (CH_2), 14.4 (CH_3), 10.1 (CH_3); HRESIMS *m/z* for $C_{12}H_{13}BrN_3O_2$ $[M + H]^+$ calcd 310.0191; found: 310.0159.

*Ethyl 5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazole-4-carboxylate* (**3e**): White crystals (Et_2O); m.p.: 136–138 °C (lit.[32] 136–138 °C); IR (cm^{-1}) ν: 3065, 3059 (C_{Ar}–H); 1710 (C=O), 1564 (N=N), 1247 (CO–O), 983 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35 (d, *J* = 6.8 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 2H), 4.46 (q, *J* = 5.7 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 1.44 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm):

161.9 (C=O), 140.5 (C), 139.0 (C), 136.8 (C), 133.0 (C), 130.3 (CH), 125.4 (CH), 61.3 (CH_2), 21.4 (CH_3), 14.6 (CH_3), 10.3 (CH_3); HRESIMS *m/z* for $C_{13}H_{16}N_3O_2$ $[M + H]^+$ calcd 246.1243; found: 246.1222.

*Ethyl 5-methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate* (**3f**): Yellow solid; m.p.: 146–148 °C (lit.[32] 144–146 °C); IR (cm^{-1}) ν: 3095, 3002 (C_{Ar}–H), 1732 (C=O), 1590 (N=N), 1534, 1351 (Ar–NO_2), 1217 (CO–O), 973 (N–N=N), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.41 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.35 (t, *J* = 1.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 8.0 Hz, 1H), 4.44 (q, *J*=7.1 Hz, 2H), 2.65 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.4 (C=O), 148.8 (C), 139.0 (C), 137.3 (C), 136.4 (C), 131.1 (CH), 131.0 (CH), 124.8 (CH), 120.4 (CH), 61.4 (CH_2), 14.4 (CH_3), 10.2 (CH_3); HRESIMS *m/z* for $C_{12}H_{13}N_4O_4$ $[M + H]^+$ calcd 277.0937; found: 277.0897.

*Ethyl 1-(3,4-dichlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate* (**3g**): Pale orange solid; m.p.: 118–120 °C; IR (cm^{-1}) ν: 3101, 3092 (C_{Ar}–H), 1732 (C=O), 1577 (N=N), 1216 (CO–O), 1028 (Ar–Cl), 975 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (d, *J* = 8.1 Hz, 1H), 7.57 (s, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 2.55 (s, 3H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.3 (C=O), 138.8 (C), 136.9 (C), 134.6 (C), 134.5 (C), 133.8 (C), 131.4 (CH), 127.2 (CH), 124.4 (CH), 61.2 (CH_2), 14.3 (CH_3), 10.0 (CH_3); HRESIMS *m/z* for $C_{12}H_{12}Cl_2N_3O_2$ $[M + H]^+$ calcd 300.0307; found: 300.0279.

*Ethyl 1-(3,4-dimethylphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate* (**3h**): White solid; m.p.: 118–120 °C; IR (cm^{-1}) ν: 3085, 3055 (C_{Ar}–H), 1710 (C=O), 1564 (N=N), 1248 (CO–O), 985 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.26 (d, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.53 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.9 (C=O), 139.0 (C), 138.9 (C), 138.4 (C), 136.5 (C), 133.1 (C), 130.6 (CH), 126.4 (CH), 122.6 (CH), 61.1 (CH_2), 19.9 (CH_3), 19.6 (CH_3), 14.4 (CH_3), 10.1 (CH_3); HRESIMS *m/z* for $C_{14}H_{18}N_3O_2$ $[M + H]^+$ calcd 260.1399; found: 260.1399.

*Ethyl 1-(3-chloro-4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate* (**3i**): Pale purple solid; m.p.: 120–121 °C; IR (cm^{-1}) ν: 3073 (C_{Ar}–H), 1725 (C=O), 1582 (N=N), 1214 (CO–O), 1019 (Ar–Cl), 977 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43 (s, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 3.93 (s, 3H), 2.51 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.6 (C=O), 156.3 (C), 139.0 (C), 136.6 (C), 128.3 (C), 127.3 (CH), 125.0 (CH), 123.4 (C), 112.2 (CH), 61.1 (CH_2), 56.6 (CH_3), 14.4 (CH_3), 9.9 (CH_3); HRESIMS *m/z* for $C_{13}H_{15}ClN_3O_3$ $[M + H]^+$ calcd 296.0802; found: 296.0810.

*1-(3-Chloro-4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate* (**3j**): Colourless crystals (toluene); m.p.: 98–99 °C; IR (cm^{-1}) ν: 3084, 3010 (C_{Ar}–H), 1722 (C=O), 1562 (N=N), 1255 (CO–O), 1026 (Ar–Cl), 974 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.51 (dd, *J* = 6.2, 2.0 Hz, 1H), 7.33 (m, 1H), 7.30 (t, *J* = 8.5 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.3 (C=O), 158.7 (d, *J* = 253.8 Hz, C), 138.9 (C), 136.7 (C), 131.8 (d, *J* = 2.5 Hz, C), 127.9 (CH), 125.4 (d, *J* = 7.8 Hz, CH), 122.4 (d, *J* = 19.1 Hz, C), 117.6 (d, *J* = 22.7 Hz, CH), 61.1 (CH_2), 14.2 (CH_3), 9.9 (CH_3); HRESIMS *m/z* for $C_{12}H_{12}ClFN_3O_2$ $[M + H]^+$ calcd 284.0602; found: 284.0604.

*1-(5-Methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)ethanone* (**3l**): White crystals (THF); m.p.: 139–40 °C (lit.[30] 148 °C); IR (cm^{-1}) ν: 3077, 3004 (C_{Ar}–H); 2852 (C_{sp3}–H), 1681 (C=O), 1598 (N=N), 1598 (C_{Ar}–C_{Ar}), 951 (N–N=N), 1518–1344 (Ar–NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.38 (d, *J* = 8.15 *Hz*, 2H), 7.88 (d, *J* = 8.14 *Hz*, 2H), 3.23 (s, 3H), 2.55 (s, 3H); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.47 (d, *J* = 8.9 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 2.64 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 193.2 (C=O), 147.9 (C), 143.1 (C), 139.8 (C), 138.2 (C), 126.5 (CH), 125.1 (CH), 27.6 (CH_3), 9.8 (CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 193.2 (C=O), 147.9 (C), 143.1 (C), 139.9 (C), 138.2 (C), 126.5 (CH), 125.1 (CH), 27.6 (CH_3), 9.8 (CH_3); HRESIMS *m/z* for $C_{11}H_{11}N_4O_3$ $[M + H]^+$ for 247.0831; found: 247.0828.

*1-(1-(4-Methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone* (**3m**): White crystals (THF); m.p.: 120–122 °C (lit.[30,36] 120 °C); IR (cm^{-1}) ν: 3050 (C_{Ar}–H), 1688 (C=O), 1517 (N=N), 950 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.35 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 2.75 (s, 3H), 2.55 (s, 3H); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.53 (d, *J* = 8.9 Hz, 2H), 7.16 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 2.62 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 194.6 (C=0), 160.8 (C), 143.7 (C), 137.7 (C), 128.3 (C), 126.8 (CH), 114.9 (CH), 55.8 (CH_3), 28.0 (CH_3), 10.2 (CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 193.3 (C=O), 160.2 (C), 142.6 (C), 137.7 (C), 127.7 (C), 126.9 (CH), 114.8 (CH), 55.6 (CH_3), 27.5 (CH_3), 9.6 (CH_3); HRESIMS *m/z* for $C_{12}H_{14}N_3O_2$ $[M + H]^+$ calcd 232.1086; found: 232.1085.

1-(1-(2-Bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone (**3n**): White solid; m.p.: 110–111 °C; IR (cm^{-1}) ν: 3065, 3003 (C_{Ar}–H), 1679 (C=O), 1553 (N=N), 951 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.81–7.71 (m, 1H), 7.51 (td, *J* = 7.5, 1.7 Hz, 1H), 7.51–7.38 (m, 1H), 7.37 (dd, *J* = 7.3, 2.2 Hz, 1H), 2.73 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 194.3 (C=O), 143.2 (C), 139.1 (C), 134.6 (C), 133.9 (CH), 132.4 (CH), 129.2 (CH), 128.8 (CH), 121.5 (C), 27.9 (CH_3), 9.7 (CH_3); HRESIMS *m/z* for $C_{11}H_{10}BrN_3ONa$ $[M + Na]^+$ calcd 301.9899; found: 301.9902.

*1-(1-(4-Nitrophenyl)-5-phenyl-1*H*-1,2,3-triazol-4-yl)ethanone* (**3o**): White solid; m.p.: 172–174 °C; IR (cm^{-1}) ν: 3088, 3062 (C_{Ar}–H), 1687 (C=O), 1555 (N=N), 853 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.23 (d, *J* = 9.2 Hz, 2H), 7.47 (d, *J* = 9.3 Hz, 2H), 7.45–7.36 (m, 3H), 7.31–7.25 (m, 2H), 2.74 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 192.6 (C=O), 147.8 (C), 143.9 (C), 140.6 (C), 139.3 (C), 130.7 (CH), 130.2 (CH), 128.9 (CH), 125.7 (CH), 125.1 (C), 124.9 (CH), 28.5 (CH_3); HRESIMS *m/z* for $C_{16}H_{12}N_4O_3Na$ $[M + Na]^+$ calcd 331.0802; found: 331.0808.

*Hex-5-yn-1-yl 5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate* (**3p**): Yellow solid; m.p.: 137–139 °C; IR (cm^{-1}) ν: 3293 (C_{sp}–H), 3118, 3075 (C_{Ar}–H), 2953–2917 (C_{sp3}–H), 1719 (C=O), 1550 (N=N), 1210 (CO–O), 907 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.47 (d, *J* = 9.0 Hz, 2H), 7.73 (d, *J* = 9.0 Hz, 2H), 4.45 (t, *J* = 6.6 Hz, 2H), 2.69 (s, 3H), 2.29 (td, *J* = 7.0, 2.6 Hz, 2H), 2.05–1.89 (m, 3H), 1.80–1.63 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.4 (C=O), 148.3 (C), 140.3 (C), 138.9 (C), 137.4 (C), 126.0 (CH), 125.3 (CH), 83.8 (C, C≡CH), 68.9 (CH, C≡CH), 64.8 (CH_2), 27.8 (CH_2), 25.0 (CH_2), 18.2 (CH_2), 10.3 (CH_3); HRESIMS *m/z* for $C_{16}H_{16}N_4O_4Na$ $[M + Na]^+$ calcd 351.1064; found: 351.1062.

*(5-Methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(morpholino)methanone* (**3q**): Yellow solid; m.p.: 182–183 °C; IR (cm^{-1}) ν: 3118, 3088 (C_{Ar}–H), 2977, 2937 (C_{sp3}–H), 1612 (C=O), 1568 (N=N), 859 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.44 (d, *J* = 9.1 Hz, 2H), 7.72 (d, *J* = 9.0 Hz, 2H), 4.18–4.12 (m, 2H), 3.79 (s, 6H), 2.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 160.8 (C=O), 148.2 (C), 140.6 (C), 140.3 (C), 138.3 (C), 125.8 (CH), 125.3 (CH), 67.3 (CH_2), 67.0 (CH_2), 47.9 (CH_2), 42.9 (CH_2), 10.5 (CH_3); HRESIMS *m/z* for $C_{14}H_{16}N_5O_4$ $[M + H]^+$ calcd 318.1197; found: 318.1200.

*1-(4-Nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carbonitrile* (**3r**): Yellow solid; m.p.: 162–165 °C (lit.[31,32] 162–165 °C); IR (cm^{-1}) ν: 3088 (C_{Ar}–H), 2240 (C≡N), 1532 (N=N), 854 (N–N=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.32 (d, *J* = 9.2 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.55–7.46 (m, 3H), 7.38–7.32 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 148.3 (C), 143.5 (C), 139.9 (C), 131.8 (CH), 129.9 (CH), 129.0 (CH), 125.8 (CH), 125.3 (CH), 122.7 (C), 121.4 (C), 111.5 (C, C≡N); HRESIMS *m/z* for $C_{15}H_{10}N_5O_2$ $[M + H]^+$ calcd 292.0829; found: 292.0827.

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