Cu(I)-Catalyzed Regioselective Synthesis of Pyrazolo[5,1-c]-1,2,4triazoles

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Supporting Information

ABSTRACT: Cycloadditions of terminal alkynes to 1,2,4-triazolium *N*-imides in the presence of base and Cu(I) afford pyrazolo[5,1-c]-1,2,4-triazoles regioselectively. The scope of alkynes, the influence of the electronic nature of the leaving group, and variations in the 1-alkyl substituent were examined. Quantum chemical calculations were employed to explain the distinct reactivity of the propiolates.

T he diverse applications of pyrazoloazines and pyrazoloazoles with bridgehead nitrogen have aroused interest in their synthesis. The pyrazolo[5,1-c]-1,2,4-triazole scaffold endows unique properties, and such compounds have been studied as azo dyes,^{1,2} inkjets and color filters,³ photographic materials,^{4,5} electrophotographic toners,⁶ antibacterial agents with reduced human toxicity⁷ and antitumor agents.⁸

The limited synthetic methods for such systems fall into three groups: (i) starting from substituted pyrazolo derivatives such as 3-amino,^{9,10} 3-hydrazino,^{1,11–16} 3-hydroxy¹⁰ or 3-diazonium salts,^{17,18} (ii) cyclic condensations of 4-amino-5-thioxo-1,2,4-triazoles,¹⁹ 3,4-diamino-1,2,4-triazoles,^{20,21} 3-meth-ylthio-1,2,4-triazolium salts²² or 4-amino-1,2,4-triazolium salts²³ and (iii) ring contraction of [1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazines.^{24,25}

Our continuing interest in the chemistry of heterocyclic compounds derived from 4-amino-1,2,4-triazole prompted a study that has resulted in a novel, efficient process for the regioselective preparation of pyrazolo[5,1-c]-1,2,4-triazole derivatives. Herein, we report a one-pot, Cu(I)-catalyzed synthesis of the pyrazolo[5,1-c]-1,2,4-triazole moiety, starting from 1,2,4-triazolium *N*-imides and terminal alkynes. We found no literature reports of such reactions and have now examined the scope of alkyne substrates together with the effect of variations in the 1-alkyl substituent and the nature of the leaving group on the course of the reactions.

1,2,4-Triazolium *N*-imides **3a**–**d** and **5a,b** were prepared in 83–94% yield via a two-step procedure. Sulfonimids **3a**–**d** were prepared by the reaction of 4-amino-1,2,4-triazolium salts with the corresponding arylsulfonyl chlorides.^{26,27} In the case of *N*-nitroimides **5a,b**, we first generated 1,2,4-triazolium *N*-nitroimide **4** by nitration²⁸ followed by reaction with the corresponding alkyl halides²⁹ (Table 1).

Substrate 3a underwent a one-pot, Cu(I)-catalyzed reaction with phenylacetylene 6a under basic conditions to give 7a. We then investigated the effects of various parameters to optimize



	$ \begin{bmatrix} N-N \\ N \\ NH_2 \\ 1 \\ HNO_3 \end{bmatrix} $		Ar-SO ₂ -Cl, py H ₂ X ^O then NaOH/H ta-c N-N N N N N N N N N N N N N N	ridine $N \rightarrow N$ $H_2O \rightarrow S$ $3a$ - Ar $N \rightarrow N$ Ar $N \rightarrow N$ $N \oplus O_2N$ $5a,b$	d
entry	R	Х	Ar	product	yield (%)
1	Bn	Br	-	2a	>99
2	Me	Ι	_	2b	>99
3	Bu^n	Br	_	2c	>99
4	Bn	-	4-Me-C ₆ H ₄	3a	94
5	Me	-	4-Me-C ₆ H ₄	3b	83
6	Bu^n	-	4-Me-C ₆ H ₄	3c	88
7	Bu^n	-	$4 - NO_2 - C_6 H_4$	3d	91
8	-	-	-	4	63
9	Bn	-	-	5a	57
10	Me	-	-	5b	93

Table 1. Synthesis of 1,2,4-Triazoliun N-Imides

the conditions and study the regiochemical outcome of the reaction (Table 2). The reaction of (1-benzyl-1*H*-1,2,4-triazol-4-ium-4-yl)(tosyl)amide **3a** with phenylacetylene **6a** in the presence of 5 mol% Cu₂Br₂ and pyridine (3 equiv) at room temperature gave 1-benzyl-6-phenyl-1*H*-pyrazolo[5,1-c][1,2,4]-triazole **7a** as a single regioisomer in 62% yield. In the absence of catalyst or base, there was either no conversion or a reduced yield. An increase of catalyst loading had a deleterious effect (Table 2).

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Table 2. Optimization of Reaction Conditions

BI N ⁻ N U N N Ts 3	n + ₽ ⊖ \$a	 Ph► 6a	Regioisomer	₽ N-N N `Ph 1 7a Regio	n Ph N Disomer	7a'	
entry	solvent	T (°C)/time (h)	catalyst	base	7a	7a'	
1	CH_2Cl_2	25/24	-	-	0	0	
2	CH_2Cl_2	40/24	-	-	0	0	
3	THF	60/24	-	Et ₃ N	0	0	
4 ^{<i>a</i>}	CH_2Cl_2	25/24	$5\% Cu_2Br_2$	pyridine	62	0	
5	CH_2Cl_2	25/24	$5\% Cu_2Br_2$	-	30	0	
6	CH_2Cl_2	25/24	$20\%\ Cu_2Br_2$	pyridine	20	0	
7	CH_2Cl_2	25/24	5% Cu ₂ Br ₂	Et ₃ N	45	0	
8	CH_2Cl_2	25/24	1% Cu ₂ Br ₂	pyridine	25	0	
9	CH_2Cl_2	25/24	10% CuOAc	pyridine	<5	0	
10	CH_2Cl_2	25/24	10% AgOTf	pyridine	<15	0	
11	CH_2Cl_2	40/5	$5\% Cu_2Br_2$	pyridine	26	0	
12	THF	60/24	$5\% Cu_2Br_2$	pyridine	<15	0	
^a Optimized conditions.							

Using the optimized conditions, we examined the scope of this transformation (Table 3). 1,2,4-Triazol-1-ium-amides 3a-

Table 3. Synthesis of Pyrazolo[5,1-c]-1,2,4-triazoles

	R N ^{-N}			5%	% Cu ₂ Br ₂	Ň		
	[∟] Nຶ⊕ N⊝ LG 3a	-d, 5a-b	R ² 6a-e	Py	ridine, DC	M	⁻ N _N 7a-i	
entry	subst	rates	R	LG	\mathbb{R}^1	R ²	product	yield (%)
1	3a	6a	Bn	Ts	Н	Ph	7a	62
2	3a	6b	Bn	Ts	Н	4-MeO-Ph	7b	65
3	5a	6a	Bn	NO_2	Н	Ph	7a	72
4	5a	6b	Bn	NO_2	Н	4-MeO-Ph	7b	69
5	3b	6a	Me	Ts	Н	Ph	7c	54
6	3b	6b	Me	Ts	Н	4-MeO-Ph	7d	57
7	5b	6a	Me	NO_2	Н	Ph	7c	62
8	5b	6b	Me	NO_2	Н	4-MeO-Ph	7d	73
9	3c	6a	Bu^n	Ts	Н	Ph	7e	75
10	3c	6b	Bu ⁿ	Ts	Н	4-MeO-Ph	7f	71
11	3d	6a	Bu^n	Ns	Н	Ph	7e	78
12	3d	6b	Bu ⁿ	Ns	Н	4-MeO-Ph	7f	70
13	3c	6c	Bu^n	Ts	Н	4-Me-Ph	7 g	68
14	3d	6c	Bu^n	Ns	Н	4-Me-Ph	7 g	77
15	3a	6d	Bn	Ts	Ph	Ph	7h	0
16	3a	6e	Bn	Ts	Me	Ph	7i	0

d, **5a**,b were reacted with terminal or disubstituted alkynes 6a-e. While terminal alkynes 6a-c gave desired products 7a-g in 62-78% yields, attempts to use disubstituted aromatic alkynes **6d**,e resulted in recovery of starting materials.

On the basis of these results, we propose that the copper(I)catalyzed formation of intermediate **D** is followed by a double bond migration and elimination either of NO_2 or the arylsulfonyl moiety (Scheme 1).

Attempts to synthesize the pyrazolo-1,2,4-triazole moiety by a Cu(I)-catalyzed one-pot reaction using methyl propiolate **6f** resulted in the regioselective formation of a compound that contained the *N*-tosyl moiety. On the basis of ¹H and ¹³C NMR





and HRMS spectral data, it was identified as **8a** (Table 4). Similarly, the reaction with DMAD **6g** and ethyl but-2-ynoate

Table 4. Reactions of 1,2,4-Triazolium N-Imides with Propiolates



6h furnished compounds **8b**,**c** in 98–99% yields (Table 4). No catalyst was needed for these reactions, but ethyl acrylate **6i** and fumaronitrile **6j** failed to react as dipolarophiles (Table 4). This outcome is probably the result of extended conjugation between the nitrogen lone pair and ester moiety in intermediate I (Scheme 2), which clearly would be absent in the analogous intermediates from **6i** and **6j**.

We propose that a [3 + 2] dipolar cycloaddition of **3a** with **6f-h** is followed by a ring-opening rearrangement to regenerate the aromatic 1,2,4-triazole unit,³⁰⁻³² thus producing ring-opened products **8a-c** (Scheme 2).

Scheme 2. Proposed Mechanism for the Reactions of 1,2,4-Triazolium N-Imides with Propiolates



To rationalize the different regiochemistry dependent on the acetylene reactant used (phenylacetylene or methyl propiolate) and gain further insight into this process, we employed theory and computations. Table 3 and Table 4 demonstrate that phenylacetylene adds to 3a-d and 5a,b in a "head-to-tail" fashion, considering the 1,2,4-triazole ring and the phenyl ring as the heads in 3a and 6a, respectively. Unlike phenylacetylene, methyl propiolate 6f adds "head-to-head" to 3a. These two terminal acetylenes differ mainly in the nature of the substituent. Methoxycarbonyl is the stronger electron-withdrawing group, as measured by a larger residual negative charge remaining on the acetylenic moiety. Molecular structures of the substrate 3a and the reactants 6a and 6f were optimized using the Firefly/GAMESS quantum chemical software. Geometry optimization and SCF energy calculations were done at the HF/6-31G* level of theory. Mulliken population analysis (atomic charges) and dipole moments were calculated at the same level of theory. Atomic charge distributions, starting from the terminal hydrogen atom, are as follows: 0.297 (H), -0.548 (C1), 0.165 (C2) and 0.314 (H), -0.474 (C1), 0.158 (C2) for the acetylenic units of 6a and 6f, respectively. Summing up the charges gives residual negative charges on the acetylenic units as -0.086 and -0.002 for 6a and 6f, respectively. The gammaaromatic system of the carbmethoxy group withdraws a significant amount of electron density from the acetylenic unit, thus making 6f a better dipolarophile. Dipole moment orientation can be another factor of regioselectivity: dipole moments of the substrate 3a and dipolarophile 6a interact beneficially only if 3a and 6a are oriented "head-to-tail" with respect to each other, otherwise a strong dipole repulsion occurs. In 6f, the dipole moment direction is different, which affords more beneficial orientations with the 1,3-dipole.

For the reaction of **3a** with **6f**, assuming the intermediate I as shown in Scheme 3, we can calculate relative energies (taken as





differences of total electronic energies) of the two reaction pathways: one leading to the isolated regioisomer 8a and the other leading to the hypothetical cyclic structure 8a'. The energy outcome of pathway I-8a can be evaluated directly by making a comparison of the total energies of the intermediate I and the final product 8a, because I and 8a have the same number of nuclei and electrons. These pathways are displayed in Scheme 3. It is seen that the total energy of product 8a lies 59.00 kcal/mol lower than the intermediate I. As for the hypothetical pathway I-8a', it can only be estimated as an isodesmic reaction involving two disjoint products: cyclic structure 8a' and toluenesulfinic acid. The reaction enthalpy of this isodesmic reaction was calculated to be -35.6 kcal/mol, which means that pathway I-8a' is 23.4 kcal/mol less energetically favorable than pathway I-8a. Another factor that can contribute to the higher stability of 8a is an intramolecular hydrogen bond found between the ring nitrogen and the hydrogen atom of the NH-Ts moiety in the optimized structure of 8a (Scheme 3). The quantum chemical calculations and theoretical reasoning are illustrative enough to demonstrate the preference to form the ring-opened product 8a as well as to explain the different regiochemistry of phenylacetylenes 6a-c and propiolates 6f-h.

In conclusion, a mild, efficient and regioselective one-pot Cu(I)-mediated synthesis of pyrazolo-1,2,4-triazoles has been developed. This transformation affords the products at room temperature under basic conditions. The different regioselectivity of phenylacetylenes and methyl propiolates again highlights the influence of substitution and electron density distribution in the dipolarophile. Electrostatic reasons cause phenylacetylenes to advantageously add to 1,2,4-triazolium *N*-imides to afford pyrazolo[5,1-c]-1,2,4-triazole bicyclic systems. The different reactivity of methyl propiolates (ring-opening) is explained by utilizing the formalism of model isodesmic reactions.

EXPERIMENTAL SECTION

Materials and Methods. All reactions were performed in singleneck round-bottom flasks fitted with rubber septa under positive pressure of nitrogen. Solvents were freshly distilled and degassed. Reaction progress was monitored by thin-layer chromatography (TLC) and visualized by UV light. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. NMR spectra were recorded in CDCl₃ or DMSO-*d*₆ with TMS for ¹H (300 MHz) and ¹³C (75 MHz) as an internal reference. 4-Amino-4H-1,2,4-triazole was purchased from Acros and used without further purification. Aryl acetylenes and propiolates were purchased from Sigma-Aldrich and used without further purification. Elemental analysis was performed on a Carlo Erba-1106 instrument.

General Method for the Preparation of 4-Amino-1,2,4triazolium Salts 2a-c. A mixture of 4H-1,2,4-triazol-4-amine (5.00 mmol) and alkyl halide (5.00 mmol, 15.00 mmol in the case of methyl iodide) in acetonitrile (10 mL) was stirred under reflux for 5 h (rt for 72 h in case of methyl iodide). The solvent and excess alkyl halide was removed under reduced pressure to give corresponding 1,2,4-triazolium salts 2a-c. For analytical purity, the residue was recrystallized from MeOH.

4-Amino-1-benzyl-1H-1,2,4-triazol-4-ium Bromide (2a). White crystals (1.26 g, >99%): mp 141.0–142.0 °C (lit.²³ mp 141.0–143.0 °C); ¹H NMR (DMSO- d_6) δ 10.57 (s, 1H), 9.25 (s, 1H), 7.48–7.40 (m, 5H), 7.07 (br s, 2H), 5.67 (s, 2H); ¹³C NMR (DMSO- d_6) δ 145.4, 142.6, 133.3, 128.7, 128.6, 54.6. Anal. Calcd. For C₉H₁₁N₄Br: C, 42.37; H, 4.35; N, 21.96. Found: C, 42.40; H, 4.27; N, 22.01.

4-Amino-1-methyl-4H-1,2,4-triazol-1-ium lodide (**2b**). Yellow crystals (1.12 g, >99%): mp 100.0–101.0 °C (lit.³³ mp 101.0 °C);

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¹H NMR (DMSO- d_6) δ 10.16 (s, 1H), 9.18 (s, 1H), 6.95 (br s, 2H), 4.07 (s, 3H); ¹³C NMR (DMSO- d_6) δ 144.9, 142.8, 39.0.

4-Amino-1-butyl-1H-1,2,4-triazol-4-ium Bromide (2c). Low melting solid (1.09 g, >99%): mp 46.0–47.0 °C (lit.³⁴ mp 47.5–49.0 °C); ¹H NMR (CDCl₃) δ 10.78 (s, 1H), 8.99 (s, 1H), 6.76 (br s, 2H), 4.48 (t, *J* = 7.2 Hz, 2H), 2.05–1.89 (m, 2H), 1.52–1.35 (m, 2H), 0.96 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃) δ 144.8, 142.6, 52.8, 30.7, 19.4, 13.5.

General Method for the Preparation of 1,2,4-Triazolium *N*-Imides 3a–d. Arylsulfonyl chloride (10.00 mmol) was added portionwise to a solution of corresponding 1,2,4-triazolium salt 2a-c (5.00 mmol) in pyridine (5 mL), and the mixture was stirred for 1 h at room temperature. After 1 h, EtOAc (70 mL) was added to the reaction mixture, which was washed with 10% NaOH solution (3 × 20 mL), dried over anhydrous sodium sulfate, and filtered, and the solvent was removed under reduced pressure to give corresponding 1,2,4-triazolium *N*-imide 3a–d. For analytical purity, the residue was recrystallized from MeOH.

(1-Benzyl-1H-1,2,4-triazol-4-ium-4-yl)(tosyl)amide (**3a**). White crystals (1.40 g, 85%): mp 170.0–172.0 °C (lit.²⁶ mp 171.0–173.0 °C); ¹H NMR (DMSO- d_6) δ 9.90 (s, 1H), 8.73 (s, 1H), 7.45–7.35 (m, 5H), 7.29–7.19 (m, 4H), 5.47 (s, 2H), 2.33 (s, 3H); ¹³C NMR (DMSO- d_6) δ 173.7, 145.6, 142.0, 140.5, 133.8, 129.1, 128.8, 128.6, 128.1, 126.3, 54.5, 20.8.

(1-Methyl-1H-1,2,4-triazol-4-ium-4-yl)(tosyl)amide (**3b**). White crystals (1.05 g, 83%): mp 203.0–204.0 °C; ¹H NMR (DMSO- d_6) δ 9.72 (s, 1H), 8.64 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 3.93 (s, 3H), 2.33 (s, 3H); ¹³C NMR (DMSO- d_6) δ 144.9, 142.1, 140.4, 140.1, 129.0, 126.3, 38.5, 20.8. Anal. Calcd. For C₁₀H₁₂N₄O₂S: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.82; H, 4.83; N, 22.27.

(1-Butyl-1H-1,2,4-triazol-4-ium-4-yl)(tosyl)amide (**3c**). White crystals (1.30 g, 88%): mp 178.0–180.0 °C; ¹H NMR (CDCl₃) δ 10.00 (s, 1H), 7.85 (s, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 4.35 (t, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.96–1.85 (m, 2H), 1.36–1.25 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃) δ 144.1, 142.5, 141.8, 138.9, 129.4, 127.0, 52.5, 30.8, 21.4, 19.3, 13.3. Anal. Calcd. For C₁₃H₁₈N₄O₂S: C, 53.04; H, 6.16; N, 19.03. Found: C, 53.21; H, 6.61; N, 19.16.

(1-Butyl-1H-1,2,4-triazol-4-ium-4-yl)((4-nitrophenyl)sulfonyl)amide (**3d**). White crystals (1.48 g, 91%): mp 198.0–200.0 °C; ¹H NMR (DMSO- d_6) δ 9.81 (s, 1H), 8.79 (s, 1H), 8.29 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 9.3 Hz, 2H), 4.23 (t, *J* = 6.9 Hz, 2H), 1.80–1.71 (m, 2H), 1.23–1.10 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (DMSO- d_6) δ 148.6, 148.5, 145.2, 141.9, 127.7, 124.1, 51.2, 29.9, 18.5, 13.0. Anal. Calcd. For C₁₂H₁₅N₅O₄S: C, 44.30; H, 4.65; N, 21.53. Found: C, 44.55; H, 4.98; N, 21.64.

N-(4*H*-1,2,4-*Triazol*-4-yl)*nitramide* (4). Concentrated nitric acid (70%, 50 mL) was added dropwise to a cooled (0 °C) solution of 4amino-1,2,4-triazole (1.68 g, 20.00 mmol) in sulfuric acid (90%, 50 mL). The resulting solution was stirred for 30 min and gradually warmed up to room temperature. The mixture was stirred for an additional 1 h and poured into ice water (200 mL). The precipitate was collected by filtration, washed with cold water, dried, and recrystallized from MeOH to afford *N*-(4*H*-1,2,4-triazol-4-yl)nitramide 4 as colorless needles (1.63 g, 63%): mp 175.0–176.0 °C (lit.²⁸ mp 175.0–176.0 °C); ¹H NMR (DMSO-*d*₆) δ 9.66 (s, 2H); ¹³C NMR (DMSO-*d*₆) δ 142.8. Anal. Calcd. For C₂H₃N₅O₂: C, 18.61; H, 2.34; N, 54.26. Found: C, 18.80; H, 2.22; N, 54.09.

(1-Benzyl-4H-1,2,4-triazol-1-ium-4-yl)(nitro)amide (5a). The mixture of sodium hydroxide (0.20 g, 5.0 mmol) and N-(4H-1,2,4-triazol-4-yl)nitramide 4 (0.65 g, 5.00 mmol) in water (10 mL) was stirred at room temperature for 1 h and evaporated to dryness under reduced pressure. The resulting white powder was dissolved in acetonitrile (10 mL). Benzyl bromide (0.86 g, 5.00 mmol) was added in one portion, and the resulting mixture refluxed for 12 h. After it was cooled to room temperature, excess solvent was removed under reduced pressure. The remaining solid was dissolved in EtOAc (50 mL), washed with water (3 \times 20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford corresponding N-nitroimide **5a** as white crystals (0.62 g, 57%): mp 164.0–165.0 °C (lit.³⁵ mp 164 °C); ¹H NMR (DMSO- d_6) δ 10.41 (s, 1H), 9.28 (s, 1H), 7.44–7.40 (m, 5H), 5.60 (s, 2H); ¹³C NMR (DMSO- d_6) δ 144.3, 141.5, 133.5, 128.9, 128.9, 128.7, 55.0.

(1-Methyl-1H-1,2,4-triazol-4-ium-4-yl)(nitro)amide (**5b**). A mixture of sodium hydroxide (0.08 g, 2.00 mmol) and N-(4H-1,2,4triazol-4-yl)nitramide 4 (0.26 g, 2.00 mmol) in water (10 mL) was stirred at room temperature for 1 h and evaporated to dryness under reduced pressure. The resulting white powder was dissolved in DMF (5 mL). Methyl iodide (0.71 g, 5.00 mmol) was added in one portion, and the mixture was stirred at room temperature for 12 h. The precipitate was removed by filtration, and the filtrate was diluted with Et₂O (100 mL). The resulting precipitate collected by filtration was dried and recrystallized from EtOH to give corresponding *N*nitroimide **5b** as white crystals (0.27 g, 93%): mp 169.0–170.0 °C (lit.³⁶ mp 169.0–170.0 °C); ¹H NMR (DMSO-d₆) δ 10.17 (s, 1H), 9.24 (s, 1H), 4.06 (s, 3H); ¹³C NMR (DMSO-d₆) δ 143.7, 141.6, 38.7.

General Method for the Preparation of Pyrazolo[5,1c][1,2,4]triazoles 7a–g. Copper(I) bromide (0.03 mmol) was added to the mixture of 1,2,4-triazolium *N*-imide (0.50 mmol), arylacetylene (0.50 mmol), and pyridine (1.50 mmol) in dichloromethane (2 mL), and the resulting mixture was stirred for 24 h. Solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography using EtOAc/hexanes (1:5) as eluent to afford corresponding pyrazolo[5,1-c][1,2,4]triazoles 7a–g.

1-Benzyl-6-phenyl-1H-pyrazolo[5,1-c][1,2,4]triazole (**7a**). White crystals (85 mg, 62%): mp 113.0–114.0 °C; ¹H NMR (CDCl₃) δ 8.25(s, 1H), 7.79(d, J = 6.9 Hz, 2H), 7.41–7.29(m, 8H), 5.70(s, 1H), 5.29(s, 2H); ¹³C NMR (CDCl₃) δ 160.1, 147.2, 134.5, 133.7, 129.0, 128.6, 128.5, 128.2, 128.0, 126.2, 75.1, 54.5. Anal. Calcd. For C₁₇H₁₄N₄: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.31; H, 5.09; N, 20.44.

1-Benzyl-6-(4-methoxyphenyl)-1H-pyrazolo[5,1-c][1,2,4]triazole (**7b**). White crystals (99 mg, 65%): mp 110.0–111.0 °C; ¹H NMR (CDCl₃) δ 8.23 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.38–7.31 (m, 5H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.62 (s, 1H), 5.27 (s, 2H), 3.83 (s, 3H); ¹³C NMR (CDCl₃) δ 159.9, 134.5, 129.9, 129.2, 128.9, 128.5, 128.1, 127.9, 127.4, 126.2, 114.0, 74.6, 55.3, 54.4; HRMS (+ESI-TOF) *m/z* for C₁₈H₁₇N₄O [M + H]⁺ calcd. 305.1397, found 305.1403.

1-Methyl-6-phenyl-1H-pyrazolo[5,1-c][1,2,4]triazole (**7c**). Colorless crystals (61 mg, 62%): mp 140.0–141.0 °C; ¹H NMR (CDCl₃) δ 8.22 (s, 1H), 7.88–7.83 (m, 2H), 7.46–7.36 (m, 3H), 6.00 (s, 1H), 3.88 (s, 3H); ¹³C NMR (CDCl₃) δ 160.1, 133.7, 128.7, 128.6, 127.6, 126.2; HRMS (+ESI-TOF) *m*/*z* for C₁₁H₁₀N₄ [M + H]⁺ calcd. 199.0978, found 199.0986.

6-(4-Methoxyphenyl)-1-methyl-1H-pyrazolo[5,1-c][1,2,4]triazole (**7d**). White crystals (83 mg, 73%): mp 152.0–153.0 °C; ¹H NMR (CDCl₃) δ 8.22 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.91 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H); ¹³C NMR (CDCl₃) δ 160.1, 160.0, 148.0, 127.6, 127.4, 126.4, 114.1, 73.7, 55.3, 36.7; HRMS (+ESI-TOF) *m*/*z* for C₁₂H₁₂N₄O [M + H]⁺ calcd. 229. 1084, found 229.1092.

1-Butyl-6-phenyl-1H-pyrazolo[5,1-c][1,2,4]triazole (7e). Yelow solid (94 mg, 78%): mp 35.0–40.0 °C; ¹H NMR (CDCl₃) δ 8.21, (s, 1H), 7.88–7.84 (m, 2H), 7.46–7.38 (m, 2H), 7.38–7.32 (m, 1H), 5.99 (s, 2H), 4.12 (t, *J* = 7.2 Hz, 2H), 1.95–1.84 (m, 2H), 1.46–1.33 (m, 2H), 0.97 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃) δ 160.0, 147.3, 133.9, 128.7, 128.5, 127.4, 126.1, 74.3, 50.2, 30.7, 19.8, 13.6; HRMS (+APCI-TOF) *m/z* for C₁₄H₁₇N₄ [M + H]⁺ calcd. 241.1448, found 241.1447.

1-Butyl-6-(4-methoxyphenyl)-1H-pyrazolo[5,1-c][1,2,4]triazole (**7f**). Yelow solid (96 mg, 71%): mp 60.0–62.0 °C; ¹H NMR (CDCl₃) δ 8.19 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 5.91 (s, 1H), 4.10 (t, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.93–1.83 (m, 2H), 1.44–1.32 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃) δ 160.0, 147.4, 130.0, 129.6, 127.4, 126.5, 114.1, 73.8, 55.3, 50.2, 30.7, 19.8, 13.6; HRMS (+APCI-TOF) *m*/*z* for C₁₅H₁₉N₄O [M + H]⁺ calcd. 271.1553, found 271.1551.

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1-Butyl-6-(*p*-tolyl)-1H-pyrazolo[5,1-*c*][1,2,4]triazole (**7g**). Yellow solid (98 mg, 77%): mp 54.0–55.0 °C; ¹H NMR (CDCl₃) δ 8.20 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.96 (s, 1H), 4.12 (t, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.95–1.85 (m, 2H), 1.46–1.33 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃) δ 160.1, 147.3, 138.4, 131.0, 129.4, 127.4, 126.0, 50.2, 30.7, 21.3, 19.8, 13.6; HRMS (+ESI-TOF) *m*/*z* for C₁₅H₁₉N₄ [M + H]⁺ calcd. 255.1604, found 255.1607.

(E)-Methyl-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-3-(4methylphenylsulfonamido)acrylate (8a). Methyl propiolate 6f (0.17 g, 2.00 mmol) was added dropwise to a solution of (1-benzyl-1H-1,2,4triazol-4-ium-4-yl)(tosyl)amide 3a (0.66 g, 2.00 mmol) in DCM (5 mL) and stirred for 24 h at room temperature. After 24 h, the reaction mixture was concentrated under reduced pressure to afford pure (E)methyl-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-3-(4methylphenylsulfonamido)acrylate 8a as colorless microcrystals (0.85 g, >99%): mp 100.0–100.2 °C; ¹H NMR (DMSO-*d*₆) δ 8.32 (s, 1H), 8.08 (s, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 7.23-7.15 (m, 3H), 7.05 (d, J = 6.0 Hz, 2H), 5.09 (s, 2H), 3.54 (s, 3H), 2.38 (s, 3H); ¹³C NMR/DEPT-135° (DMSO-*d*₆) δ 165.1 (C), 148.3 (CH), 148.1 (C), 147.8 (CH), 143.2 (C), 137.9 (C), 134.9 (C), 129.7 (CH), 128.1 (CH), 127.6 (CH), 126.2 (CH), 92.1 (C), 52.2 (CH₂), 51.4 (CH₃), 20.9 (CH₃); HRMS (+ESI-TOF) m/z for C₂₀H₂₁N₄O₄S [M + H]⁺ calcd. 413.1278, found 413.1274.

Dimethyl-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-3-(4methylphenylsulfonamido)maleate (8b). Dimethyl but-2-ynedioate 6g (0.28 g, 2.00 mmol) was added dropwise to a solution of (1-benzyl-1H-1,2,4-triazol-4-ium-4-yl)(tosyl)amide 3a (0.66 g, 2.00 mmol) in DCM (5 mL) at -78 °C and stirred for 30 min. After 30 min, the reaction was allowed to warm up to room temperature and was left for additional 12 h. The reaction mixture was concentrated under reduced pressure to afford pure dimethyl2-(1-benzyl-1H-1,2,4-triazol-5-yl)-3-(4-methylphenylsulfonamido)maleate 8b as white solid (0.95 g, >99%): mp 45.0–47.0 °C; ¹H NMR (DMSO- d_6) δ 8.90 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.32-7.25 (m, 5H), 7.07-7.03 (m, 2H), 4.99 (s, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 2.34 (s, 3H); ¹³C NMR (DMSO d_6) δ 165.4, 163.9, 159.3, 149.7, 144.1, 141.5, 140.9, 133.7, 129.0, 128.5, 128.1, 128.0, 125.9, 81.8, 52.7, 52.1, 50.8, 20.8; HRMS (+ESI-TOF) m/z for $C_{22}H_{22}N_4O_6S$ $[M + H]^+$ calcd. 471.1333, found 471.1342. Anal. Calcd. For $C_{22}H_{22}N_4O_6S$: C, 56.16; H, 4.71; N, 11.91. Found: C, 56.01; H, 4.87; N, 11.41.

(E)-Ethyl-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-3-(4methylphenylsulfonamido)but-2-enoate (8c). Ethyl but-2-ynoate 6h (2.00 g, 2.0 mmol) was added dropwise to the solution of (1-benzyl-1H-1,2,4-triazol-4-ium-4-yl)(tosyl)amide 3a (0.66 g, 2.0 mmol) in DCM (5 mL) at room temperature over a period of 10 min. The resulting mixture was stirred under reflux for additional 12 h. After 12 h, the reaction was allowed to cool to room temperature and concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/hexanes) to afford pure (E)-ethyl 2-(1benzyl-1H-1,2,4-triazol-5-yl)-3-(4-methylphenylsulfonamido)but-2enoate 8c as white microcrystals (0.85 g, 98%): mp 128.0-130.0 °C; ¹H NMR (CDCl₃) δ 12.14 (s, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.34 (d. J = 8.4 Hz, 2H), 7.28-7.23 (m, 3H), 7.16-7.11 (m, 2H), 5.15–5.03 (m, 2H), 4.02 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.59 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃) δ 167.4, 157.3, 151.0, 149.6, 144.9, 136.9, 134.7, 130.1, 128.7, 128.3, 127.9, 127.4, 95.2, 61.3, 52.8, 21.6, 16.7, 13.9. Anal. Calcd. For C22H24N4O4S: C, 59.98; H, 5.49; N, 12.72. Found: C, 60.24; H, 5.74; N, 12.54.

ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C NMR spectra for **2a-c**, **3a-d**, **4**, **5a,b**, **7a-g**, and **8a-c** and Cartesian coordinates of key intermediate I. This material is available free of charge via the Internet at http:// pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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