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

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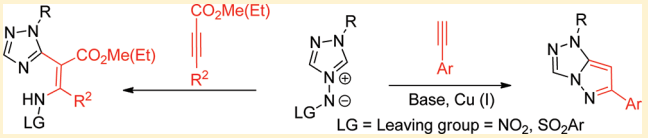
Supporting Information

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.



The 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 toxicity[7] and antitumor agents.[8]

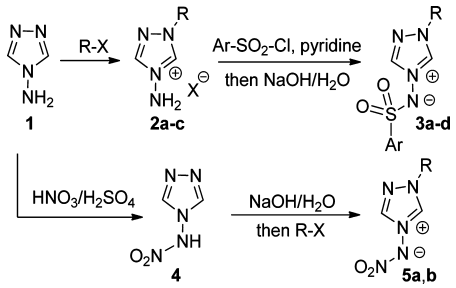
The limited synthetic methods for such systems fall into three groups: (i) starting from substituted pyrazolo derivatives such as 3-amino,[9,10] 3-hydrazino,[1,11−16] 3-hydroxy[10] or 3-diazonium salts,[17,18] (ii) cyclic condensations of 4-amino-5-thioxo-1,2,4-triazoles,[19] 3,4-diamino-1,2,4-triazoles,[20,21] 3-methylthio-1,2,4-triazolium salts[22] or 4-amino-1,2,4-triazolium salts[23] 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 nitration[28] followed by reaction with the corresponding alkyl halides[29] (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 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% Cu_2Br_2 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).

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



entry	R	X	Ar	product	yield (%)
1	Bn	Br	–	**2a**	>99
2	Me	I	–	**2b**	>99
3	Bu^n	Br	–	**2c**	>99
4	Bn	–	4-Me-C_6H_4	**3a**	94
5	Me	–	4-Me-C_6H_4	**3b**	83
6	Bu^n	–	4-Me-C_6H_4	**3c**	88
7	Bu^n	–	4-NO_2−C_6H_4	**3d**	91
8	–	–	–	**4**	63
9	Bn	–	–	**5a**	57
10	Me	–	–	**5b**	93

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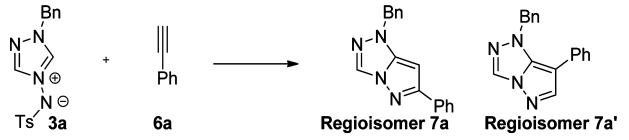
Table 2. Optimization of Reaction Conditions

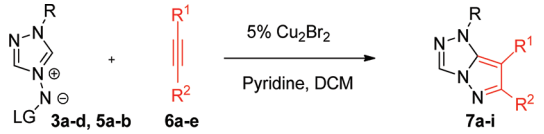


entry	solvent	T (°C)/time (h)	catalyst	base	7a	7a′
1	CH_2Cl_2	25/24	–	–	0	0
2	CH_2Cl_2	40/24	–	–	0	0
3	THF	60/24	–	Et_3N	0	0
4[a]	CH_2Cl_2	25/24	5% Cu_2Br_2	pyridine	62	0
5	CH_2Cl_2	25/24	5% Cu_2Br_2	–	30	0
6	CH_2Cl_2	25/24	20% Cu_2Br_2	pyridine	20	0
7	CH_2Cl_2	25/24	5% Cu_2Br_2	Et_3N	45	0
8	CH_2Cl_2	25/24	1% Cu_2Br_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–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.

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



entry	substrates		R	LG	R^1	R^2	product	yield (%)
1	**3a**	**6a**	Bn	Ts	H	Ph	**7a**	62
2	**3a**	**6b**	Bn	Ts	H	4-MeO-Ph	**7b**	65
3	**5a**	**6a**	Bn	NO_2	H	Ph	**7a**	72
4	**5a**	**6b**	Bn	NO_2	H	4-MeO-Ph	**7b**	69
5	**3b**	**6a**	Me	Ts	H	Ph	**7c**	54
6	**3b**	**6b**	Me	Ts	H	4-MeO-Ph	**7d**	57
7	**5b**	**6a**	Me	NO_2	H	Ph	**7c**	62
8	**5b**	**6b**	Me	NO_2	H	4-MeO-Ph	**7d**	73
9	**3c**	**6a**	Bu^n	Ts	H	Ph	**7e**	75
10	**3c**	**6b**	Bu^n	Ts	H	4-MeO-Ph	**7f**	71
11	**3d**	**6a**	Bu^n	Ns	H	Ph	**7e**	78
12	**3d**	**6b**	Bu^n	Ns	H	4-MeO-Ph	**7f**	70
13	**3c**	**6c**	Bu^n	Ts	H	4-Me-Ph	**7g**	68
14	**3d**	**6c**	Bu^n	Ns	H	4-Me-Ph	**7g**	77
15	**3a**	**6d**	Bn	Ts	Ph	Ph	**7h**	0
16	**3a**	**6e**	Bn	Ts	Me	Ph	**7i**	0

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 ^{13}C NMR and HRMS spectral data, it was identified as **8a** (Table 4). Similarly, the reaction with DMAD **6g** and ethyl but-2-ynoate **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**.

Scheme 1. Proposed Mechanism for the Cu(I) Mediated Regioselective Synthesis of Pyrazolo[5,1-*c*]-1,2,4-triazoles

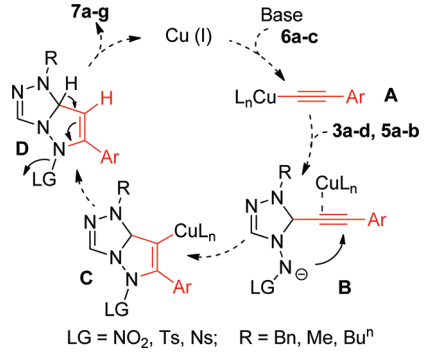
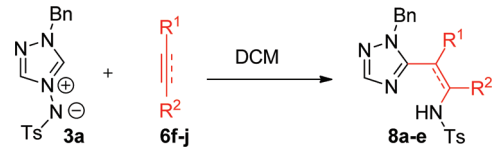
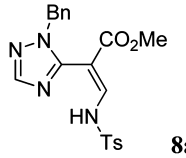
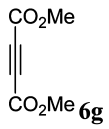
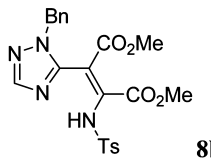
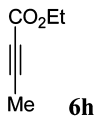
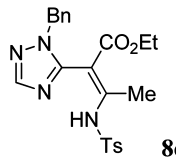
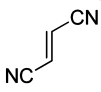


Table 4. Reactions of 1,2,4-Triazolium *N*-Imides with Propiolates



entry	substrate	product	yield (%)
1	 **6f**	 **8a**	>99
2	 **6g**	 **8b**	>99
3	 **6h**	 **8c**	98
4	 **6i**	**8d**	0
5	 **6j**	**8e**	0

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).

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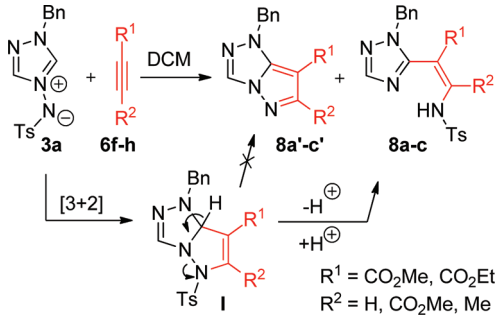
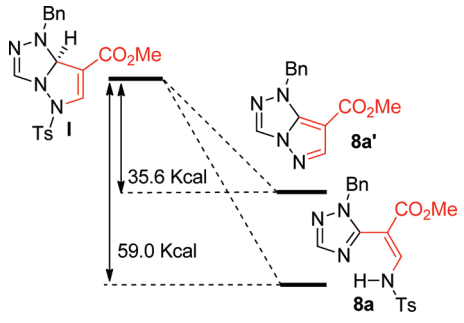
Scheme 2. Proposed Mechanism for the Reactions of 1,2,4-Triazolium *N*-Imides with Propiolates



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 gamma-aromatic 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**.

Scheme 3. Energy Diagram for the Formation of 8a



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 single-neck 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 $CDCl_3$ or DMSO-d_6 with TMS for ^{1}H (300 MHz) and ^{13}C (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-1,2,4-triazolium Salts 2a−c. A mixture of 4*H*-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); ^{1}H 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); ^{13}C NMR (DMSO-d_6) δ 145.4, 142.6, 133.3, 128.7, 128.6, 54.6. Anal. Calcd. For $C_9H_{11}N_4Br$: 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 Iodide (**2b**).* Yellow crystals (1.12 g, >99%): mp 100.0−101.0 °C (lit.[33] mp 101.0 °C);

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^{1}H NMR (DMSO-d_6) δ 10.16 (s, 1H), 9.18 (s, 1H), 6.95 (br s, 2H), 4.07 (s, 3H); ^{13}C 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); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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); ^{1}H 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); ^{13}C 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; ^{1}H 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); ^{13}C NMR (DMSO-d_6) δ 144.9, 142.1, 140.4, 140.1, 129.0, 126.3, 38.5, 20.8. Anal. Calcd. For $C_{10}H_{12}N_4O_2S$: 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{13}H_{18}N_4O_2S$: 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; ^{1}H 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); ^{13}C 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 $C_{12}H_{15}N_5O_4S$: C, 44.30; H, 4.65; N, 21.53. Found: C, 44.55; H, 4.98; N, 21.64.

*N-(4H-1,2,4-Triazol-4-yl)nitramide (**4**).* Concentrated nitric acid (70%, 50 mL) was added dropwise to a cooled (0 °C) solution of 4-amino-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); ^{1}H NMR (DMSO-d_6) δ 9.66 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 142.8. Anal. Calcd. For $C_2H_3N_5O_2$: 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*-(4*H*-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 × 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); ^{1}H NMR (DMSO-d_6) δ 10.41 (s, 1H), 9.28 (s, 1H), 7.44−7.40 (m, 5H), 5.60 (s, 2H); ^{13}C 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*-(4*H*-1,2,4-triazol-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 Et_2O (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); ^{1}H NMR (DMSO-d_6) δ 10.17 (s, 1H), 9.24 (s, 1H), 4.06 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 143.7, 141.6, 38.7.

General Method for the Preparation of Pyrazolo[5,1-*c*][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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{14}N_4$: 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{18}H_{17}N_4O$ $[M + H]^+$ 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) δ 160.1, 133.7, 128.7, 128.6, 127.6, 126.2; HRMS (+ESI-TOF) m/z for $C_{11}H_{10}N_4$ $[M + H]^+$ 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{12}H_{12}N_4O$ $[M + H]^+$ 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{14}H_{17}N_4$ $[M + H]^+$ 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{15}H_{19}N_4O$ $[M + H]^+$ 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; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{15}H_{19}N_4$ $[M + H]^+$ calcd. 255.1604, found 255.1607.

*(E)-Methyl-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-3-(4-methylphenylsulfonamido)acrylate (**8a**).* Methyl propiolate **6f** (0.17 g, 2.00 mmol) was added dropwise to a solution of (1-benzyl-1*H*-1,2,4-triazol-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-1*H*-1,2,4-triazol-5-yl)-3-(4-methylphenylsulfonamido)acrylate **8a** as colorless microcrystals (0.85 g, >99%): mp 100.0−100.2 °C; ^{1}H 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); ^{13}C 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 (CH_2), 51.4 (CH_3), 20.9 (CH_3); HRMS (+ESI-TOF) m/z for $C_{20}H_{21}N_4O_4S$ $[M + H]^+$ calcd. 413.1278, found 413.1274.

*Dimethyl-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-3-(4-methylphenylsulfonamido)maleate (**8b**).* Dimethyl but-2-ynedioate **6g** (0.28 g, 2.00 mmol) was added dropwise to a solution of (1-benzyl-1*H*-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-1*H*-1,2,4-triazol-5-yl)-3-(4-methylphenylsulfonamido)maleate **8b** as white solid (0.95 g, >99%): mp 45.0−47.0 °C; ^{1}H 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); ^{13}C 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-(4-methylphenylsulfonamido)but-2-enoate (**8c**).* Ethyl but-2-ynoate **6h** (2.00 g, 2.0 mmol) was added dropwise to the solution of (1-benzyl-1*H*-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-(1-benzyl-1*H*-1,2,4-triazol-5-yl)-3-(4-methylphenylsulfonamido)but-2-enoate **8c** as white microcrystals (0.85 g, 98%): mp 128.0−130.0 °C; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{22}H_{24}N_4O_4S$: C, 59.98; H, 5.49; N, 12.72. Found: C, 60.24; H, 5.74; N, 12.54.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C 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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