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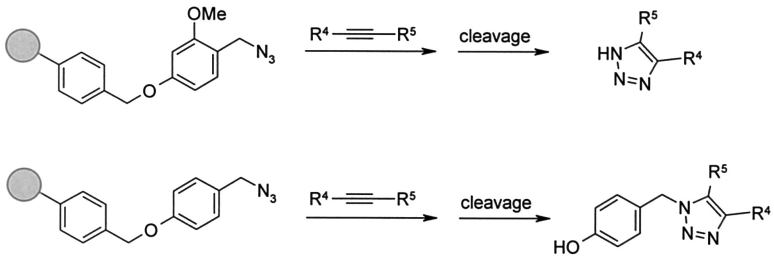

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Solid-Phase Synthesis of 1,2,3-Triazoles via 1,3-Dipolar Cycloaddition

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The solid-phase synthesis of 1,2,3-triazoles via 1,3-dipolar cycloaddition of polymer-bound azides to various alkynes is reported. Polymer-bound azides were synthesized from polymer-bound halides and sodium azide and reacted with alkynes to produce polymer-bound 1,2,3-triazoles. Cleavage of the triazoles was performed with trifluoroacetic acid. A traceless synthesis of 1,2,3-triazoles was developed using 2-methoxy-substituted resin (polymer-bound 4-hydroxy-2-methoxybenzyl alcohol). In addition, a synthesis of 4-hydroxybenzyl-substituted 1,2,3-triazoles from the bromo-Wang resin (4-(bromomethyl)phenoxymethyl polystyrene) was achieved.

Introduction

The synthesis of heterocycles is of great importance in pharmaceutical and medicinal chemistry. Combinatorial libraries of drug candidates can be constructed when the synthetic methods are developed on a solid phase. 1,3-Dipolar cycloaddition reactions are important in preparing five-membered heterocyclic rings, such as the 1,2,3-triazoles, which are known for their antibacterial,[1,2] β-lactamase inhibitory,[3] antiinflammatory,[4−6] antiviral,[7] anticonvulsant,[8] and muscarinic[9] activities. The synthesis of 1,2,3-triazoles from azides and various alkynes has been widely studied in solution phase.[10−12] However, there are only a few published reports on the solid-phase synthesis of 1,2,3-triazoles from polymer-bound azides,[13−16] alkynes,[16−18] or enamines.[19] Most reported solid-phase syntheses of 1,2,3-triazoles describe substituted 1,2,3-triazoles in which the triazoles are attached to resins with various linkers and the linker-derived functionalities accompany the triazoles when the triazoles are cleaved from the resin.

Finding an easy method to cleave the nitrogen−carbon bond in the solid-phase synthesis of nitrogen-containing heterocycles is essential. Recently, several reports have appeared on so-called "traceless" syntheses of nitrogen-containing heterocycles. The bond between the heterocycle and the resin has been cleaved with use of reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[20] and α-chloroethyl chloroformate (ACE-Cl);[21] linkers such as tetrahydropyranyl (THP)[22,23] and silyl;[24] and resins such as trityl type resins,[25] acid-labile Rink resin,[26] and 2-methoxy-4-alkoxybenzyl-substituted resin.[27,28]

We succeeded in cleaving the carbon−nitrogen bond between the resin and the triazole using 2-methoxy-substituted resin (polymer-bound 4-hydroxy-2-methoxybenzyl alcohol). A similar resin but without the 2-methoxy substituent (the Wang resin) gave 4-hydroxybenzyl-substituted 1,2,3-triazoles. This kind of cleavage is typical for the Wang resin, and there are reports in the literature of similar solid-phase syntheses of 4-hydroxybenzyl-substituted compounds in which competitive cleavage of the C−O bond of aryl benzyl ether occurs instead of other cleavages.[29,30]

We report here the details of our solid-phase syntheses of substituted 1,2,3-triazoles. A wide variety of 4- and 5-monosubstituted and disubstituted 1,2,3-triazoles were prepared, either in traceless manner from the 2-methoxy resin or from the Wang resin with the 4-hydroxybenzyl substituent at nitrogen.

Results and Discussion

Azide Chemistry. The polymer-bound azides **2** and **8** were synthesized from sodium azide and polymer-bound halides **1** and **7** (Schemes 1 and 3). The reaction took place when the halide-functionalized resin was heated with an excess of sodium azide in DMF. The appearance of the azide functionality was conveniently monitored by IR spectrometry. One reason for using the polymer-bound azide in the cycloaddition reaction was the explosive and toxic nature of sodium azide and the need to develop a safer medium for the synthesis of 1,2,3-triazoles. There are various commercially available halide-functionalized resins, and in our experiments, we found the bromo-Wang (4-(bromomethyl)-phenoxymethyl polystyrene) resin **1**, which is easily available in large amounts, suitable for the development of the solid-phase synthesis of 1,2,3-triazoles.

Cycloaddition Reaction. Azide acts as a 1,3-dipole in cycloaddition reaction with alkynes or enamines. It is known from earlier studies that the steric and electronic factors of alkynes affect the regiochemistry and reaction times of the cycloaddition reactions in 1,2,3-triazole synthesis.[4,31] In the solid-phase synthesis of 1,2,3-triazoles, alkynes with electron-withdrawing substituents, for example, ester groups, reacted in 5 h at 120 °C, whereas alkynes with electron-donating substituents reacted very poorly. Propargylamine, for ex-

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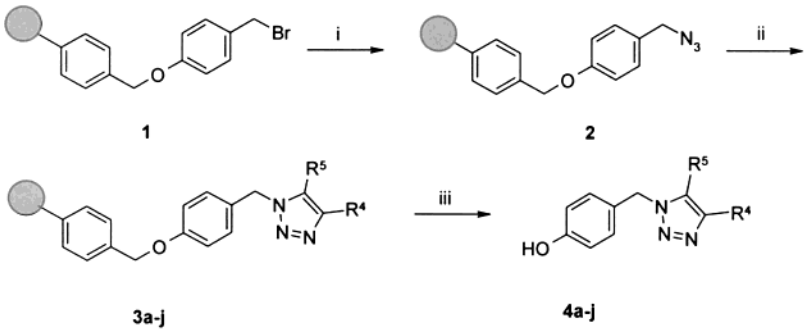
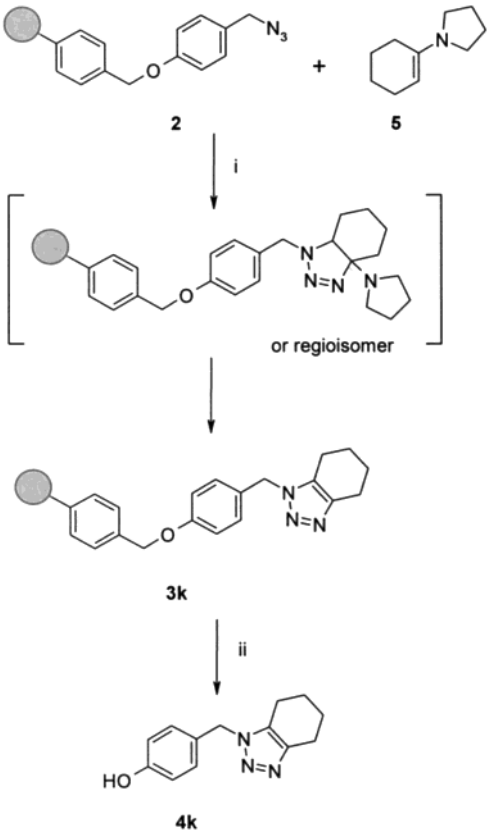
Scheme 1.[a] Synthesis of 1,2,3-Triazoles **4a**−**j** from the Wang Resin



[a] Reagents and conditions: (i) NaN_3 (3−5 equiv), DMF, 70 °C, ∼15 h; (ii) alkyne (5−15 equiv), DMF, 80−120 °C, 5−111 h; (iii) TFA−DCM 4:1 or TFA−H_2O 9:1, rt, 1 h to overnight.

Scheme 2.[a] Synthesis of 1,2,3-Triazole **4k** from Enamine **5**



[a] Reagents and conditions: (i) polymer-bound azide **2** and enamine **5** (10 equiv), DMF, 120 °C, 3 h; (ii) TFA−DCM 4:1, rt, 1 h.

ample, did not react properly after 6 days of heating at 80 °C. We monitored the reactions of the polymer-bound azide by IR spectrometry, and the disappearance of the characteristic strong peak of azide at ∼2100 cm^{-1} was taken to indicate a successful reaction.

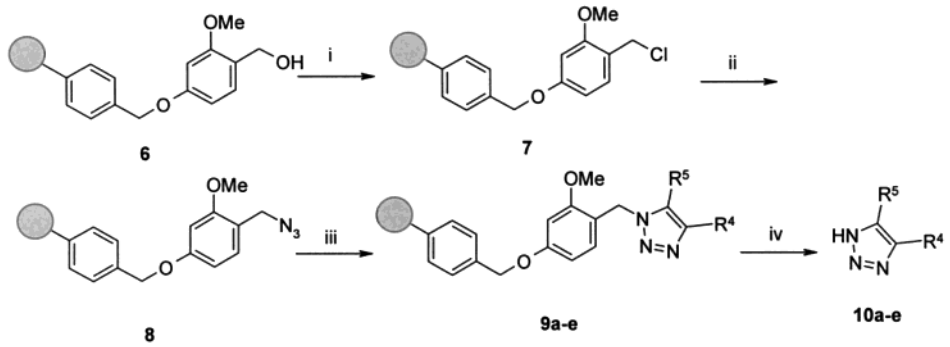
Decarboxylation[7] of the carboxyl group took place in the cycloaddition reaction. Propiolic acid acted as a synthetic equivalent of acetylene and yielded the unsubstituted 1,2,3-triazole **4d** (Table 1). The missing carbonyl peak in the IR spectrum of the polymer-bound triazole confirmed that the decarboxylation had occurred during the cycloaddition reaction. Phenylpropiolic acid decarboxylated, as well, and gave the same products **4e** and **4f** with the polymer-bound azide **2** as did phenylacetylene. The unsubstituted 1,2,3-triazole was also obtained when (trimethylsilyl)acetylene[3,32] was used as alkyne in the cycloaddition reaction. However, the desilylation was not complete, and we obtained a mixture of unsubstituted and trimethylsilyl-substituted triazoles **4d** and **4j**.

Enamines are also known to react with azides to produce 1,2,3-triazolines, which aromatize to 1,2,3-triazoles.[33−35] We studied the reactions of some enamines with polymer-bound azide and obtained aromatized 4-hydroxybenzyl-substituted 1,2,3-triazole **4k** from the reaction between 1-(pyrrolidino)-1-cyclohexene **5** and polymer-bound azide **2** (Scheme 2). 1-Pyrrolidino-1-cyclopentene reacted in the cycloaddition reaction, too, but the cleaved product was a complex mixture. Ethyl-3-(1-pyrrolidino)acrylate did not react in the cycloaddition reaction, even when heated overnight at 120 °C.

Cleavage. The cleavages of the polymer-bound 1,2,3-triazoles **3** and **9** were performed in trifluoroacetic acid (TFA). We found that a second treatment of the resin with TFA increased the yield of the crude product and therefore applied successive cleavage treatments with TFA. Either TFA−DCM 4:1 or TFA−H_2O 9:1 was used in the cleavage procedure; TFA−H_2O 1:1 was not strong enough for the cleavage of 1,2,3-triazoles. Some of the residual resins were analyzed by IR spectrometry after the cleavage procedure. Despite the three TFA treatments and moderate yields of the cleaved 1,2,3-triazoles, the spectra of the residual resins still showed peaks typical of 1,2,3-triazoles, especially traces of the various carbonyl functionalities, in addition to the TFA ester peak at ∼1780 cm^{-1}.

Regiochemistry. When we used monosubstituted or unsymmetrically substituted alkynes in 1,2,3-triazole synthesis, we obtained from the Wang resin either a mixture of two regioisomers or one main regioisomer with 4-hydroxybenzyl substituent at nitrogen. The regiochemistry of the cycloaddition reaction has been studied fairly well, and the typical regiochemistry has been determined for several alkynes. The results that we obtained were consistent with the results reported for benzylic azides[36−38] with ethyl propiolate, phenylacetylene, or ethyl phenylpropiolate and for other azides[4,34,39,40] with methyl or ethyl propiolate, (trimethylsilyl)acetylene, phenylacetylene, or ethyl phenylpropiolate. Methyl and ethyl propiolate reacted regioselectively and gave 4-substituted regioisomers **4b** and **4c** as main products. (Trimethylsilyl)acetylene gave the 4-substituted regioisomer **4j**, possibly because of steric reasons[3,4] (Figure 1). Phenyl-substituted acetylenes did not react regioselec-

Scheme 3. Synthesis of 1,2,3-Triazoles **10a**−**e** from the 2-Methoxy Resin[a,b]



[a] Reagents and conditions: (i) $SOCl_2$ (10 equiv), PhMe, 65−70 °C, 1 h; (ii) NaN_3 (3−5 equiv), DMF, 70 °C, ∼15 h; (iii) alkyne (5 equiv), DMF, 120 °C, 5−91 h; (iv) TFA−DCM 4:1 or TFA−H_2O 9:1, rt, 1 h to overnight. [b]Only one tautomeric structure of 1,2,3-triazole **10** is presented.

Table 1. N-Substituted 1,2,3-Triazoles **4** from the Wang Resin

compd	R^4	R^5	yield (%)[a]	purity (%)[b]
4a	CO_2Me	CO_2Me	23	92
4b	CO_2Me	H	44	>97
4c	CO_2Et	H	57	>97
4d	H	H	58	>98
4e	Ph	H	57,[c] 56[d]	>98
4f	H	Ph		90
4g	CHO	Ph	20	96
4h	CO_2Et	Ph	31	>98
4i	CH_2OH	CH_2OH	46	95
4j	$SiMe_3$	H	17	−[e]
4k	$-(CH_2)_4-$		42	>98

[a] Based on the original loading of the resin. [b] Evaluated on the basis of the analytical results. [c] Mixture of regioisomers from phenylacetylene. [d] Mixture of regioisomers from phenylpropiolic acid. [e] Decomposed during storage.

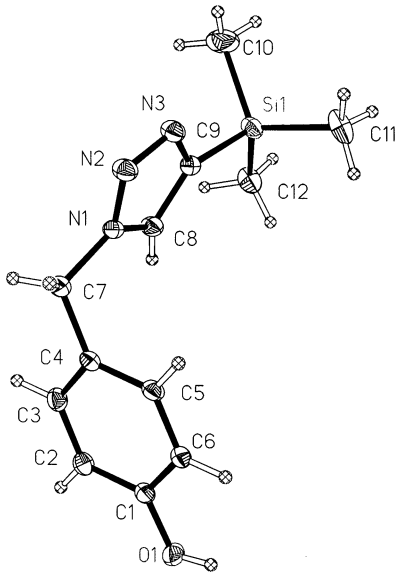


Figure 1. View of the molecule **4j**. Thermal ellipsoids have been drawn at 30% probability level.

tively, and we obtained mixtures of regioisomers. Phenylacetylene and phenylpropiolic acid gave ∼1:1 mixtures of 4- and 5-phenyl-substituted regioisomers **4e** and **4f**. Phenylpropargyl aldehyde and ethyl phenylpropiolate gave 5-phenyl-substituted regioisomers **4g** and **4h** as the main isolated products, and the amounts of isolated 5-phenyl-substituted regioisomers were ∼60% of the total of the material obtained after chromatographic purification.

The regiochemistry has often been assigned on the basis of ^{1}H NMR data, and typically, the H-5 proton in 4-substituted 1,2,3-triazoles is shifted downfield relative to the H-4 proton in 5-substituted 1,2,3-triazoles.[17,32] This is what we observed. Two-dimensional NMR data (gHMQC and gHMBC) of the regioisomers gave further proof of the regiochemistry because we could see the couplings between the benzylic CH_2 protons and the nearest C-5 carbon of the triazole ring. The regiochemistry was confirmed by determination of the X-ray crystal structures of the purified N-substituted 1,2,3-triazoles (**4b**, **4c**, **4e**, **4g**, **4h**, and **4j**).

LC−MS Analysis of the Crude Products. In an analysis of some unpurified crude products by LC−MS, we found that cleavage of both the carbon−oxygen bond and the carbon−nitrogen bond occurs when the Wang-resin-bound triazole **3** is treated with trifluoroacetic acid. In addition to 4-hydroxybenzyl-substituted 1,2,3-triazoles **4**, we also obtained N-unsubstituted triazoles **10** as side products. The 1,2,3-triazole prepared from dimethyl acetylenedicarboxylate was actually cleaved so that approximately equal amounts of N-substituted (**4a**) and N-unsubstituted (**10a**) 1,2,3-triazoles were obtained (Table 2). LC−MS also gave further information about the regiochemistry of methyl and ethyl propiolates, and we could detect the 5-substituted regioisomers and N-unsubstituted triazoles as side products in addition to the isolated main products **4b** and **4c.** The crude products of the triazoles prepared from phenylacetylene and phenylpropiolic acid were also compared. After the decarboxylation, the regioisomers **4e** and **4f** were formed in equal amounts for both alkynes, according to UV spectra. The ^{1}H NMR analyses of the purified fractions of phenyl-substituted triazoles confirmed these data. Furthermore, we could detect a small amount of carboxyl-substituted 1,2,3-triazole in the crude product of the 1,2,3-triazole that was prepared from phenylpropiolic acid. The calculated values were based on the atomic mass unit (amu) intensities of the main mass peaks, because the sensitivity of the UV detector was not sufficient to detect the impurities. It should be noted that these results are only approximate because of the probable differences in the degradation behavior.

Traceless Synthesis of 1,2,3-Triazoles. We found the 2-methoxy-substituted resin **6** (Scheme 3) very valuable in

Table 2. Percentages of Cleaved N-Substituted (**4**) and N-Unsubstituted (**10**) 1,2,3-Triazoles in Crude Products from the Wang Resin

entry	alkyne	R^4	R^5	% (**4**)[a]	% (**10**)[a]
1[b]	dimethyl acetylenedicarboxylate	CO_2Me	CO_2Me	60 (**4a**)	40 (**10a**)
2[c]	dimethyl acetylenedicarboxylate	CO_2Me	CO_2Me	50 (**4a**)	50 (**10a**)
3	methyl propiolate	CO_2Me	H	70 (**4b**)	10 (**10b**)
		H	CO_2Me	20[d]	
4	ethyl propiolate	CO_2Et	H	70 (**4c**)	10[d]
		H	CO_2Et	20[d]	
5[e]	phenylpropiolic acid	Ph	H	40[f] (**4e**)	10 (**10c**)
		H	Ph	45[f] (**4f**)	
6	phenylacetylene	Ph	H	50[f] (**4e**)	10 (**10c**)
		H	Ph	40[f] (**4f**)	

[a] Based on the amu intensities of the main mass peaks. [b] Cleavage with TFA−DCM 4:1. [c] Cleavage with TFA−H_2O 9:1. [d] Side product based on the MS data. [e] Additionally, 5% of Ph/COOH-substituted compound **4** detected. [f] Because of the insufficient separation, the ratios of the regioisomers are based on the peak heights of the UV spectra.

Table 3. N-Unsubstituted 1,2,3-Triazoles **10** from the 2-Methoxy Resin

compd	R^4	R^5	yield (%)[a]	purity (%)[b]
10a	CO_2Me	CO_2Me	42[c], 21[d]	90
10b	CO_2Me	H	28	>95
10c	Ph	H	17	>95
10d	CHO	Ph	10	94
10e	CO_2Et	Ph	29	>98

[a] Based on the original loading of the resin. [b] Evaluated on the basis of analytical results. [c] Cleaved with TFA−DCM 4:1. [d] Cleaved with TFA−H_2O 9:1.

our efforts to develop a traceless 1,2,3-triazole cleavage without the attached 4-hydroxybenzyl linker. Owing to the presence of the 2-methoxy substituent in the resin, the cleavage of the triazoles differed from that of the Wang resin, and we obtained N-unsubstituted triazoles **10** (Table 3). The 2-methoxy-substituted resin was not commercially available as a halide, so the polymer-bound alcohol was first chlorinated with thionyl chloride. The subsequent preparation of the azide and the cycloaddition reactions were similar to the reactions that were performed on the Wang resin. The cleavage of the polymer-bound triazole **9** took place smoothly with trifluoroacetic acid, and we obtained N-unsubstituted 1,2,3-triazoles. A comparison of the two cleavage methods showed that both TFA−DCM 4:1 and TFA−H_2O 9:1 gave N-unsubstituted 1,2,3-triazoles. Treatment with glacial acetic acid at 100 °C did not give any extra cleavage.[27] LC−MS of the crude product of **10a** showed no 2-methoxy-4-hydroxybenzyl-substituted 1,2,3-triazole, and this was an indication that the linker of the resin had not accompanied the product.

Conclusions

The cycloaddition reaction of various dipolarophilic alkynes to polymer-bound azide was studied. Comparison was made of two resins differing in the presence and the absence of the 2-methoxy group. A new method to synthesize 1,2,3-triazoles in a traceless manner on solid support was developed, and N-unsubstituted 1,2,3-triazoles were synthesized. In addition, N-substituted 1,2,3-triazoles were synthesized from the Wang resin. Our studies of 1,3-dipolar cycloadditions on solid supports will be continued with the aim of developing an efficient methodology for preparing a variety of nitrogen-containing heterocyclic compounds.

Experimental Section

The resins were purchased from Novabiochem (4-(bromomethyl)phenoxymethyl polystyrene **1**, 100−200 mesh, Catalog no. 01-64-0186) and Sigma-Aldrich (4-hydroxy-2-methoxybenzyl alcohol, polymer bound **6**, 50−90 mesh, Catalog no. 54,073-0). The polymer matrix of both resins was polystyrene cross-linked with 1% divinylbenzene. Thin-layer chromatography was performed with Merck TLC aluminum sheets, silica gel 60 F_{254}. Column chromatography was performed with Merck silica gel 60 (0.040−0.063 mm). Melting points were measured with a Bibby Stuart Scientific SMP3 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on either Varian Unity 500 or Varian Mercury 300 Plus spectrometers. Chemical shifts (δ) are given in ppm relative to NMR solvent signals (DMSO-d_6 2.5 and 39.51 ppm, CD_3OD 3.31 and 49.15 ppm). IR spectra of the products were recorded on a Perkin-Elmer FT-IR spectrometer 1725X with KBr technique. LC−MS analyses were performed with an HP1100 instrument with UV detector wavelength of 220 nm and Merck Chromolith SpeedROD RP-18 (50 × 4.6 mm) column and an API 3000 triple quadrupole LC/MS/MS mass spectrometer with TurboIonSpray ion source. The mobile phase was a gradient of 5 mM NH_4OAc buffer solution (pH 5) and MeOH. Elemental analyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ. Crystal structures were determined at the Department of Chemistry, University of Helsinki. Crystal data were collected with a Nonius KappaCCD area-detector diffractometer at 173(2) K using graphite monochromatized MoKα radiation, 0.71073 Å: COLLECT.[41] Multiscan absorption corrections were made: SADABS.[42] Solutions were made by direct methods and refinement on F^2: SHELX97.[43] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were refined on calculated positions isotropically (riding model). The displacement factors of H atoms were 1.2 × (1.5 × for methyl hydrogens) to that of the host atom. Publication material: SHELX97.[43] Graphics: SHELXTL (Sheldrick,1990).[44]

General Treatment of Sodium Azide. *Caution: Sodium azide is toxic and forms explosive compounds with heavy metals and dichloromethane. It also liberates toxic hydrazoic acid gas in acidic conditions.* Before disposal, the sodium azide waste was treated with an excess of a 20% solution of

sodium nitrite, acidified with a 30% solution of sulfuric acid, and neutralized with a solution of sodium hydroxide.[45]

General Preparation of Polymer-Bound 4-Hydroxy-2-methoxybenzyl Chloride 7. Polymer-bound 4-hydroxy-2-methoxybenzyl alcohol **6** (5.09 g, 0.4 mmol/g) was chlorinated with thionyl chloride (1.5 mL, 10 equiv) in toluene (40 mL) at 65−70 °C for 1 h. The resin was filtered and washed with toluene (3 × 10 mL), DMF (3 × 10 mL), THF (3 × 10 mL), and DCM (3 × 10 mL) and dried.

General Preparation of Polymer-Bound Azides 2 and 8. 4-(Bromomethyl)phenoxymethyl polystyrene **1** (1.2 mmol/g) or polymer-bound 4-hydroxy-2-methoxybenzyl chloride **7** (0.4 mmol/g) was treated with sodium azide (3−5 equiv) in DMF (∼5 mL/g resin) at 70 °C for ∼15 h. The resin was filtered; washed with DMF (2×), water (2×), DMF−water (2×), MeOH (3×), THF (3×), and DCM (3×); and dried. The filtered DMF−water mixture was treated like the sodium azide waste (see above) before disposal. IR (KBr, cm^{-1}): ∼2100.

General Preparation of Polymer-Bound 1,2,3-Triazoles 3 and 9. 4-(Azidomethyl)phenoxymethyl polystyrene **2** (1.2 mmol/g) or polymer-bound 4-hydroxy-2-methoxybenzyl azide **8** (0.4 mmol/g) was treated with various alkynes or enamines (5−15 equiv) in DMF (∼5 mL/g resin) at 80−120 °C for 3 h to 5 days. The resin was filtered; washed with DMF (3×), MeOH (3×), THF (3×), and DCM (3×); and dried.

General Cleavage of 1,2,3-Triazoles 4 and 10. The polymer-bound 1,2,3-triazoles **3** (1.2 mmol/g) and **9** (0.4 mmol/g) were treated one to three times with TFA−DCM 4:1 (1 h to overnight, room temperature) or TFA−H_2O 9:1 (1 h to overnight, room temperature). The filtrate was evaporated and dried in vacuo. The crude product was purified by column chromatography and dried in vacuo to constant weight.

1-(4-Hydroxybenzyl)-1*H*-[1,2,3]triazole-4,5-dicarboxylic Acid Dimethyl Ester 4a. Resin **2** (1.071 g, 1.2 mmol/g) was treated with dimethyl acetylenedicarboxylate (790 μL, 5 equiv) at 120 °C for 5 h. Triazole **3a** (560 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (3 × 5 mL, 2 × 1 h and overnight), and 170.8 mg of crude product was obtained after evaporation. The column chromatography of 168.3 mg (eluent hexanes−EtOAc 1:1, R_f value 0.22) yielded 44.3 mg (23%) of **4a**, mp 162−164 °C. ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.58 (s, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 5.65 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 160.0, 158.5, 157.5, 138.8, 130.1, 129.5, 124.6, 115.4, 53.5, 52.9, 52.4. IR (KBr, cm^{-1}): 1733, 1467, 1355, 1247, 1069. LC−MS: $[M + H]^+$, m/z 292. Calcd for $C_{13}H_{13}N_3O_5$: C 53.61%, H 4.50%, N 14.43%. Found: C 54.77%, H 4.13%, N 13.63%.

1-(4-Hydroxybenzyl)-1*H*-[1,2,3]triazole-4-carboxylic Acid Methyl Ester 4b. Resin **2** (816 mg, 1.2 mmol/g) was treated with methyl propiolate (435 μL, 5 equiv) at 120 °C for 5 h. Triazole **3b** (868 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (3 × 5 mL, 2 × 1 h and overnight), and 212.9 mg of crude product was obtained after evaporation. The column chromatography of 193.9 mg (eluent hexanes−EtOAc 1:1, R_f value 0.13) yielded 98.2 mg (44%) of **4b**, mp 171−173 °C. ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.56 (s, 1H), 8.80 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 5.51 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 160.6, 157.4, 138.6, 129.6, 128.7, 125.5, 115.4, 52.8, 51.6. IR (KBr, cm^{-1}): 3131, 1729, 1522, 1235, 1061. LC−MS: $[M + H]^+$, m/z 234. Calcd for $C_{11}H_{11}N_3O_3$: C 56.65%, H 4.75%, N 18.02%. Found: C 56.48%, H 4.51%, N 17.86%.

1-(4-Hydroxybenzyl)-1*H*-[1,2,3]triazole-4-carboxylic Acid Ethyl Ester 4c. Resin **2** (808 mg, 1.2 mmol/g) was treated with ethyl propiolate (490 μL, 5 equiv) at 120 °C for 5 h. Triazole **3c** (852 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (3 × 5 mL, 2 × 1 h and overnight), and 210.9 mg of crude product was obtained after evaporation. The column chromatography of 203.8 mg (eluent hexanes−EtOAc 1:1, R_f value 0.18) yielded 140.1 mg (57%) of **4c**, mp 153−154 °C. ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.57 (s, 1H), 8.78 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 5.50 (s, 2H), 4.28 (q, J = 7 Hz, 2H), 1.28 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 160.1, 157.4, 138.9, 129.6, 128.6, 125.5, 115.4, 60.4, 52.8, 14.1. IR (KBr, cm^{-1}): 3136, 1729, 1520, 1235, 1060. LC−MS: $[M + H]^+$, m/z 248. Calcd for $C_{12}H_{13}N_3O_3$: C 58.29%, H 5.30%, N 16.99%. Found: C 58.37%, H 5.10%, N 16.98%.

4-([1,2,3]Triazol-1-ylmethyl)phenol 4d. Resin **2** (880 mg, 1.2 mmol/g) was treated with propiolic acid (370 mg, 5 equiv) at 120 °C for 96 h. Triazole **3d** (848 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (3 × 5 mL, 2 × 1 h and overnight), and 241.8 mg of crude product was obtained after evaporation. The column chromatography of 208.8 mg (eluent EtOAc, R_f value 0.30) yielded 89.7 mg (58%) of **4d**, mp 177−178 °C (lit. 173−176 °C[37]). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.50 (s, 1H), 8.09 (s, 1H), 7.71 (s, 1H), 7.16 (d, J = 8 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 5.46 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 157.2, 133.3, 129.4, 126.2, 124.4, 115.3, 52.2. IR (KBr, cm^{-1}): 1518, 1271, 1241, 1116, 779. LC−MS: $[M + H]^+$, m/z 176. Calcd for $C_9H_9N_3O$: C 61.70%, H 5.18%, N 23.99%. Found: C 61.51%, H 5.13%, N 23.95%.

4-(4-Phenyl-[1,2,3]triazol-1-ylmethyl)phenol 4e and 4-(5-Phenyl-[1,2,3]triazol-1-ylmethyl)phenol 4f. Resin **2** (806 mg, 1.2 mmol/g) was treated with phenylpropiolic acid (707 mg, 5 equiv) at 120 °C for 96 h. Triazole **3e**−**f** (828 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (3 × 5 mL, 2 × 1 h and overnight), and 255.9 mg of crude product was obtained after evaporation. The column chromatography of 231.4 mg (eluent hexanes−EtOAc 2:1, R_f values 0.10 for **4e** and 0.06 for **4f**) yielded 127.5 mg (56%) of **4e** and **4f**. The amount of pure **4e** was 51.0 mg, the amount of **4f** (∼10% **4e**) was 12.5 mg, and the rest was obtained as a mixture of the two regioisomers. Resin **2** (831 mg, 1.2 mmol/g) was treated with phenylacetylene (550 μL, 5 equiv) at 120 °C for 96 h. Triazole **3e**−**f** (885 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (3 × 5 mL, 2 × 1 h and overnight), and 268.1 mg of crude product was obtained after evaporation. The column chromatography of 245.3 mg (eluent hexanes−EtOAc 2:1, R_f values 0.10 for **4e** and 0.06 for **4f**) yielded 140.2 mg (57%) of **4e** and **4f**. The amount of pure **4e** was 36.4 mg, and the rest was obtained as a mixture

of both regioisomers. **4e**: mp 222−223 °C (dec) (lit. 215−218 °C[6]). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.55 (s, 1H), 8.56 (s, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 5.49 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6, δ): 157.3, 146.5, 130.7, 129.5, 128.8, 127.7, 126.0, 125.1, 121.0, 115.4, 52.7. IR (KBr, cm^{-1}): 3140, 1519, 1246, 1088, 765. LC−MS [M + H]$^+$, m/z 252. Calcd for $C_{15}H_{13}N_3O$: C 71.70%, H 5.21%, N 16.72%. Found C 71.41%, H 5.26%, N 16.49%. **4f**: ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.45 (s. 1H), 7.91 (s, 1H), 7.48−7.44 (m, 5H), 6.82 (d, J = 8.5 Hz, 2H), 6.64 (d, J = 8.5 Hz, 2H), 5.53 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 157.0, 137.4, 133.1, 129.4, 129.0, 128.5, 128.5, 126.7, 126.2, 115.4, 50.9.

1-(4-Hydroxybenzyl)-5-phenyl-1*H*-[1,2,3]triazole-4-carbaldehyde 4g. Resin **2** (620 mg, 1.2 mmol/g) was treated with phenylpropargyl aldehyde (455 μL, 5 equiv) at 80 °C for 10 h. According to the IR spectrum of the isolated resin, the reaction was not complete. The treatment was repeated, and the reaction was continued at 120 °C for 68 h so that the azide peak disappeared. Triazole **3g** (674 mg, 1.2 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5 mL, 2 × 1 h and overnight), and 235.5 mg of crude product was obtained after evaporation. The column chromatography (eluent hexanes−EtOAc 2:1, R_f value 0.11) yielded 44.4 mg (20%) of **4g**, mp 139−140 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 9.91 (s, 1H), 9.51 (s, 1H), 7.59−7.49 (m, 5H), 6.80 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 5.47 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 184.2, 157.2, 143.1, 140.6, 130.4, 129.8, 129.0, 128.9, 125.1, 124.7, 115.4, 51.0. IR (KBr, cm^{-1}): 3153, 1708, 1517, 1273, 840. LC−MS: [M + H]$^+$, m/z 280. Calcd for $C_{16}H_{13}N_3O_2$: C 68.81%, H 4.69%, N 15.04%. Found C 68.58%, H 4.56%, N 15.05%.

1-(4-Hydroxybenzyl)-5-phenyl-1*H*-[1,2,3]triazole-4-carboxylic Acid Ethyl Ester 4h. Resin **2** (628 mg, 1.2 mmol/g) was treated with ethyl phenylpropiolate (625 μL, 5 equiv) at 120 °C for 18 h. Triazole **3h** (750 mg, 1.2 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5 mL, 1 h, 2 h and overnight, and 250.4 mg of crude product was obtained after evaporation. The column chromatography (eluent hexanes−EtOAc 1:1, R_f value 0.24) yielded 89.2 mg (31%) of **4h**, mp 149−150 °C. ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.49 (s, 1H), 7.55−7.47 (m, 3H), 7.38−7.36 (m, 2H), 6.74 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 5.36 (s, 2H), 4.13 (q, J = 7 Hz, 2H), 1.09 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 160.3, 157.1, 140.7, 136.2, 129.9, 128.9, 128.3, 125.9, 125.2, 115.3, 60.2, 51.2, 13.8. IR (KBr, cm^{-1}): 1723, 1519, 1250, 1197, 1061. LC−MS [M + H]$^+$, m/z 324. Calcd for $C_{18}H_{17}N_3O_3$: C 66.86%, H 5.30%, N 13.00%. Found: C 66.67%, H 5.29%, N 12.92%.

4-{(4,5-Bis(hydroxymethyl)-[1,2,3]triazol-1-ylmethyl}-phenol 4i. Resin **2** (595 mg, 1.2 mmol/g) was treated with 2-butyne-1,4-diol (307 mg, 5 equiv) at 80−120 °C for 43 h. According to the IR spectrum of the isolated resin, the reaction was not complete. The treatment was repeated, and the reaction was continued at 120 °C for 68 h so that the azide peak disappeared. Triazole **3i** (599 mg, 1.2 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5 mL, 2 × 1h and overnight), and 213.2 mg of crude product was obtained after evaporation. The column chromatography (eluent DCM−MeOH from 9:1 to 8:2, R_f value, DCM−MeOH 9:1, 0.09) yielded 77.0 mg (46%) of **4i**, mp 158−159 °C (dec). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.48 (s, 1H), 7.11 (d, J = 8 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.44 (s, 2H), 5.40 (t, J = 5.5 Hz, 1H), 5.02 (t, J = 5.5 Hz, 1H), 4.54 (d, J = 5 Hz, 2H), 4.49 (d, J = 5.5 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 157.1, 145.0, 133.9, 129.3, 126.1, 115.3, 54.2, 50.8, 50.7. IR (KBr, cm^{-1}): 3235 (broad), 1519, 1233, 1027, 1005. LC−MS: [M + H]$^+$, m/z 236. Calcd for $C_{11}H_{13}N_3O_3$: C 56.16%, H 5.57%, N 17.86%. Found: C 55.97%, H 5.56%, N 17.04%.

4-(4-Trimethylsilyl-[1,2,3]triazol-1-ylmethyl)phenol 4j. Resin **2** (537 mg, 1.2 mmol/g) was treated with (trimethylsilyl)acetylene (3 × 450 μL, 3 × 5 equiv) at 120 °C for 3 × 24 h and at room temperature overnight. Triazole **3j** (560 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (5 mL, 1h), and 211 mg of crude product was obtained after evaporation. The column chromatography (eluent DCM−MeOH 9:1, R_f value 0.40) yielded 27.6 mg (17%) of pure **4j**, which partially decomposed to **4d** during storage, and 36.2 mg of 15:85 mixture of **4j** and unsubstituted **4d**. ^{1}H NMR (500 MHz, DMSO-d_6, δ): 9.53 (s, 1H), 8.11 (s, 1H), 7.18 (d, J = 8 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 5.44 (s, 2H), 0.23 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 157.3, 144.9, 130.2, 129.7, 126.3, 115.4, 52.1, −1.0. IR (KBr, cm^{-1}): 1674, 849. LC−MS: [M + H]$^+$, m/z 248.

4-(4,5,6,7-Tetrahydrobenzotriazol-1-ylmethyl)phenol 4k. Resin **2** (316 mg, 1.2 mmol/g) was treated with 1-pyrrolidino-1-cyclohexene **5** (585 μL, 10 equiv) at 120 °C for 3 h. Triazole **3k** (318 mg, 1.2 mmol/g) was cleaved with TFA−DCM 4:1 (5 mL, 1 h), and 126.4 mg of crude product was obtained after evaporation. The column chromatography (eluent DCM−MeOH 9:1, R_f value 0.34) yielded 36.9 mg (42%) of **4k**, mp 183 °C (dec). ^{1}H NMR (500 MHz, CD_3OD, δ): 7.07 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 5.36 (s, 2H), 2.65 (t, J = 5 Hz, 2H), 2.50 (t, J = 5.5 Hz, 2H), 1.78−1.77 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD, δ): 158.9, 144.8, 134.1, 130.4, 127.3, 116.8, 52.5, 23.7, 23.5, 22.7, 21.2. IR (KBr, cm^{-1}): 2934, 1516, 1272, 1240, 787. LC−MS: [M + H]$^+$, m/z 230. Calcd for $C_{13}H_{15}N_3O$: C 68.10%, H 6.59%, N 18.33%. Found: C 67.87%, H 6.38%, N 18.21%.

1*H*-[1,2,3]Triazole-4,5-dicarboxylic Acid Dimethyl Ester 10a. Resin **8** (1.880 g, 0.4 mmol/g) was treated with dimethyl acetylenedicarboxylate (460 μL, 5 equiv) at 120 °C for 5 h. Triazole **9a** (920 mg, 0.4 mmol/g) was cleaved with TFA−DCM 4:1 (3 × 5−10 mL, 2 × 1 h and overnight), and 83.7 mg of crude product was obtained after evaporation. The column chromatography of 82.0 mg (eluent DCM−MeOH 19:1, R_f value, DCM−MeOH 9:1, 0.12) yielded 28.1 mg (42%) of **10a**, mp ∼110 to 120 °C (lit. 130−131 °C[46]). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 3.85 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 160.9, 137.6, 52.5. IR (KBr, cm^{-1}): 3239, 1742, 1389, 1304, 1086. LC−MS: [M + H]$^+$, m/z 186. Calcd for $C_6H_7N_3O_4$: C 38.93%, H 3.81%, N 22.70%. Found: C 37.62%, H 3.47%, N 19.75%. Triazole **9a** (1.008 g, 0.4 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5−10

mL, 2 × 1 h and overnight), and 49.1 mg of crude product was obtained after evaporation. The column chromatography (eluent DCM−MeOH from 19:1 to 9:1, R_f value, DCM−MeOH 9:1, 0.12) yielded 15.5 mg (21%) of **10a**, mp 123−124 °C (lit. 130−131 °C[46]). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 3.87 (s, 6H). LC−MS: $[M + H]^+$, *m/z* 186. Triazole **3a** (621 mg, 1.2 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5 mL, 2 × 1 h and overnight), and 150 mg of crude product was obtained after evaporation. The column chromatography (eluent DCM−MeOH 19:1, R_f value, DCM−MeOH 9:1, 0.12) yielded 24.2 mg (18%) of **10a**, mp 124−126 °C (lit. 130−131 °C[46]). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 3.87 (s, 6H). LC−MS: $[M + H]^+$, *m/z* 186.

1*H*-[1,2,3]Triazole-4-carboxylic Acid Methyl Ester 10b. Resin **8** (1.012 g, 0.4 mmol/g) was treated with methyl propiolate (180 μL, 5 equiv) at 120 °C for 5 h. Triazole **9b** (1.007 g, 0.4 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5−10 mL, 2 × 1 h and overnight), and 44.8 mg of crude product was obtained after evaporation. The column chromatography (eluent hexanes−EtOAc 1:1, R_f value 0.18) yielded 14.4 mg (28%) of **10b**, mp 140−141 °C (lit. 145 °C[46]). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 8.55 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 161.1, 137.9, 131.4, 51.7. IR (KBr, cm^{-1}): 3143, 1703, 1349, 1217, 1026. LC−MS: $[M + H]^+$, *m/z* 128. Calcd for $C_4H_5N_3O_2$: C 37.80%, H 3.97%, N 33.06%. Found: C 38.64%, H 3.78%, N 32.32%.

4-Phenyl-1*H*-[1,2,3]triazole 10c. Resin **8** (1.002 g, 0.4 mmol/g) was treated with phenylacetylene (220 μL, 5 equiv) at 120 °C for 91 h. Triazole **9c** (0.979 g, 0.4 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5−10 mL, 2 × 1 h and overnight), and 65.4 mg of crude product was obtained after evaporation. The column chromatography (eluent hexanes−EtOAc 2:1, R_f value 0.20) yielded 9.4 mg (17%) of **10c**, mp 146 °C (lit. 148 °C[46]). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 8.34 (s, 1H), 7.86 (d, J = 7 Hz, 2H), 7.46 (t, J = 8 Hz, 2H), 7.35 (t, J = 7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 129.0, 128.1, 125.6. IR (KBr, cm^{-1}): 3161, 2964, 2873, 767, 695. LC−MS: $[M + H]^+$, *m/z* 146. Calcd for $C_8H_7N_3$: C 66.19%, H 4.86%, N 28.95%. Found: C 66.62%, H 4.64%, N 28.00%.

5-Phenyl-1*H*-[1,2,3]triazole-4-carbaldehyde 10d. Resin **8** (1.028 g, 0.4 mmol/g) was treated with phenylpropargyl aldehyde (250 μL, 5 equiv) at 120 °C for 91 h. Triazole **9d** (1.050 g, 0.4 mmol/g) was cleaved with TFA−H_2O 9:1 (3 × 5−10 mL, 2 × 1 h and overnight), and 31.3 mg of crude product was obtained after evaporation. The column chromatography (eluent hexanes−EtOAc 2:1, R_f value 0.11) yielded 7.3 mg (10%) of **10d**, mp 181−182 °C (dec) (lit. 189−189.5 °C[46]). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 10.17 (s, 1H), 7.96 (d, J = 6.5 Hz, 2H), 7.54−7.53 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 185.0, 129.8, 128.7, 128.5. IR (KBr, cm^{-1}): 3436, 1697, 1480, 776, 695. LC−MS: $[M + H]^+$, *m/z* 174. Calcd for $C_9H_7N_3O$: C 62.42%, H 4.07%, N 24.26%. Found: C 62.71%, H 4.30%, N 22.03%.

5-Phenyl-1*H*-[1,2,3]triazole-4-carboxylic Acid Ethyl Ester 10e. Resin **8** (1.00 g, 0.4 mmol/g) was treated with ethyl phenylpropiolate (330 μL, 5 equiv) at 120 °C for 20 h. Triazole **9e** (1.05 g, 0.4 mmol/g) was cleaved with TFA−H_2O 9:1 (2 × 3−5 mL, 1 h and overnight), and 165.8 mg of crude product was obtained after evaporation. The column chromatography (eluent DCM−MeOH 9:1, R_f value 0.41) yielded 35.9 mg (39%) of **10e**. The purified product was washed three times with hexane, yield 26.6 mg (29%), mp 92−93 °C (lit. 91−92 °C[46]). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.78−7.74 (m, 2H), 7.51−7.46 (m, 3H), 4.29 (q, J = 7 Hz, 2H), 1.25 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 160.9, 129.3, 129.1, 128.2, 60.7, 14.0. IR (KBr, cm^{-1}): 1718, 1484, 1245, 1180, 765. LC−MS: $[M + H]^+$, *m/z* 218. Calcd for $C_{11}H_{11}N_3O_2$: C 60.82%, H 5.10%, N 19.34%. Found: C 60.55%, H 4.98%, N 18.97%.

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Supporting Information Available. Crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

Abbreviations

Ac, acetyl; amu, atomic mass unit; DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; gHMBC, gradient heteronuclear multiple bond correlation gHMQC; gradient heteronuclear multiple quantum coherence; Ph, phenyl; rt, room temperature; TLC, thin-layer chromatography.

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