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Benzotriazol-1-yl-sulfonyl Azide for Diazotransfer and Preparation of Azidoacylbenzotriazoles

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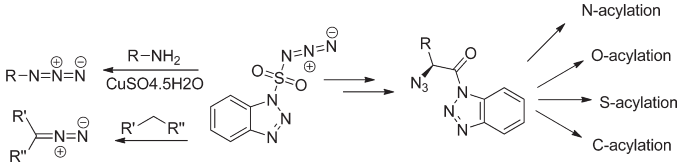

Benzotriazol-1-yl-sulfonyl azide, a new crystalline, stable, and easily available diazotransfer reagent provides *N*-(α-azidoacyl)benzotriazoles convenient for N-, O-, C- and S-acylations. The efficient syntheses of various amides, azido protected peptides, esters, ketones and thioesters is reported together with a wide range of azides (including α-azido acids from α- amino acids in partially aqueous conditions) and diazo compounds.

Introduction

The choice of an appropriate amino protecting group depends on its stability and the conditions that can be tolerated for its removal. Activation of the carboxyl group depends on the degree of activation and the nature of the selectivity required together with convenience in preparation and use. We now report that *N*-(α-azidoacyl)benzotriazoles are efficient agents for N-, O-, S-, and C- acylations that introduce azide as a masked amino group.[1,2a]

Organic azides[2b,3a] have been utilized (i) as building blocks,[3] exemplified by the synthesis of natural products,[4] (ii) in photoaffinity labeling,[5] (iii) as drugs, such as anti-HIV medication (AZT),[6] and (iv) as masked amines such as in the synthesis of oseltamivir phosphate Tamiflu.[3a,7]

Azides as "protected" amines have found application for sensitive substrates such as oligosaccharides, aminoglycoside antibiotics,[3] glycosoaminoglycans,[8] and peptidonucleic acids (PNA)[9] and in solid-phase peptide synthesis.[10]

Azides can be prepared by (i) classical nucleophilic displacement with azide anion;[11] however such reactions at the sp^3 carbon may cause inversion, epimerization,[12] or concurrent

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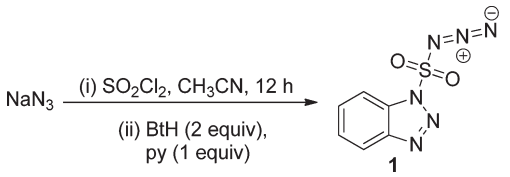
elimination and when performed in solvents such as DMF and DMSO can hinder isolation of the azide product; (ii) reactions of aryldiazonium salts with inorganic azides;[13] (iii) catalyzed displacement by sodium azide with aryl and vinyl boronic acids,[14] or (iv) catalyzed displacement by sodium azide with aryl halides.[15]

The alternative preparation of azides from amines by diazo transfer[16a] avoids epimerization, inversion, and elimination. An ideal diazotransfer reagent should be crystalline (for ease of purification, handling[16b] and stability), nonexplosive, easily prepared, and of general applicability for diazotransfer. *p*-Tosyl azide, the classical diazotransfer reagent, melts at 21−22 °C,[17a] and requires relatively harsh conditions that limit its use.[17b] Suggested replacements include (i) mesyl azide,[18] an oil needing distillation at 56 °C (0.5 mm. Hg); (ii) polystyrene-supported benzenesulfonyl azide,[19] a safe-to-handle but insoluble resin; (iii) oligomer-bound benzenesulfonyl azide,[20] which is insoluble in most organic solvents, lacks long-term stability, and needs to be utilized within 1−2 weeks; (iv) imidazole-1-sulfonyl azide,[16] a colorless oil used as crystalline hydrochloride salt; and (v) the most commonly used "diazo-transfer reagent" of amines to azides, trifluoromethanesulfonyl azide (TfN_3),[7,16,17b,21] prepared from sodium azide and trifluoromethanesulfonic anhydride, which has a poor shelf life and must be used in situ as a solution because of its explosive nature. Thus, the synthesis of an improved diazotransfer reagent is of considerable interest. We have prepared benzotriazol-1-sulfonyl azide, **1**, convenient for converting α-amino acids into α-azido acids (see later).

In α-azido acyl groups the azide both masks the amine functionality and strongly activates the carboxyl moiety,[22] thus facilitating the formation of peptide bonds.[23] The small size of the azide unit in comparison to, e.g., Boc or Fmoc may assist in hindered coupling. The azide group is stable under both acidic and basic conditions and toward osmium-[3a,24] and ruthenium-catalyzed dihydroxylation or alkylation.[3a,25]

SCHEME 1. Synthesis of Benzotriazol-1-sulfonyl Azide 1



Choice of activation for an α-azido acid is important: (i) acyl halides tend to be over-activated[26,27] and require base for neutralizing the hydrogen halide formed;[2a] (ii) acid anhydrides easily form imides with ammonia and primary amines; (iii) esters are frequently under-activated and require basic catalysts and/or high pressure,[26,27] By contrast *N*-acylbenzotriazoles are efficient neutral acylating agents and form amide bonds at ambient temperatures with unprotected amino acids in aqueous/organic solvents resisting side reactions in the preparation of N-terminal protected peptides.[23,28] Thus *N*-(protected-α-aminoacyl)benzotriazoles have enabled fast preparations of biologically relevant peptides and peptide conjugates in high yields and purity, under mild reaction conditions, with full retention of the original chirality.[29]

Results and Discussion

Preparation and Characterization of Benzotriazol-1-yl-sulfonyl Azide 1. We react chlorosulfonyl azide, prepared *in situ* from sodium azide and sulfuryl chloride, with benzotriazole (2 equiv) and pyridine (1 equiv) in MeCN to give benzotriazol-1-yl-sulfonyl azide **1** (70%, obtained after aqueous workup) as a white crystalline solid (mp 85.3−88.3 °C) requiring no further purification (Scheme 1). The reagent **1** as a dry solid has a long shelf life at room temperature and could be utilized 6 weeks after its preparation. (Caution: appropriate safety measures must always be taken at all times because azides are high energy compounds). Reagent **1** is soluble in many organic solvents as well as in partially aqueous conditions (e.g., MeCN, CH_2Cl_2, MeOH, EtOAc, MeCN/H_2O (1:1)).

The detailed molecular structure of benzotriazol-1-yl-sulfonyl azide **1** was established by X-ray diffraction analysis (see Supporting Information).

Thermogravimetric analysis (TGA) shows that 64 wt % of **1** is lost around 112 °C. Differential scanning calorimetry (DSC) shows that **1** is stable below 95 °C melting and resolidifying (see Figure 1, which shows 2 cycles of heating to 95 °C and cooling to −100 °C). The heats of fusion (166.7 J/g for cycle 1 and 163.8 J/g for cycle 2) and heats of freezing (114.1 J/g for cycle 1 and 101.4 J/g for cycle 2) show that there is negligible material loss (see Supporting Information).

Preparation of Azides by the Reaction of Benzotriazole-1-sulfonyl Azide 1 with Primary Amines. Benzotriazol-1-yl-sulfonyl azide **1** converted amine compounds **2a**−**f** into the corresponding azides **3a**−**f** (in 47−85% yields, average 64%), without requiring a base. In a typical reaction, benzotriazol-1-yl-sulfonyl azide **1**

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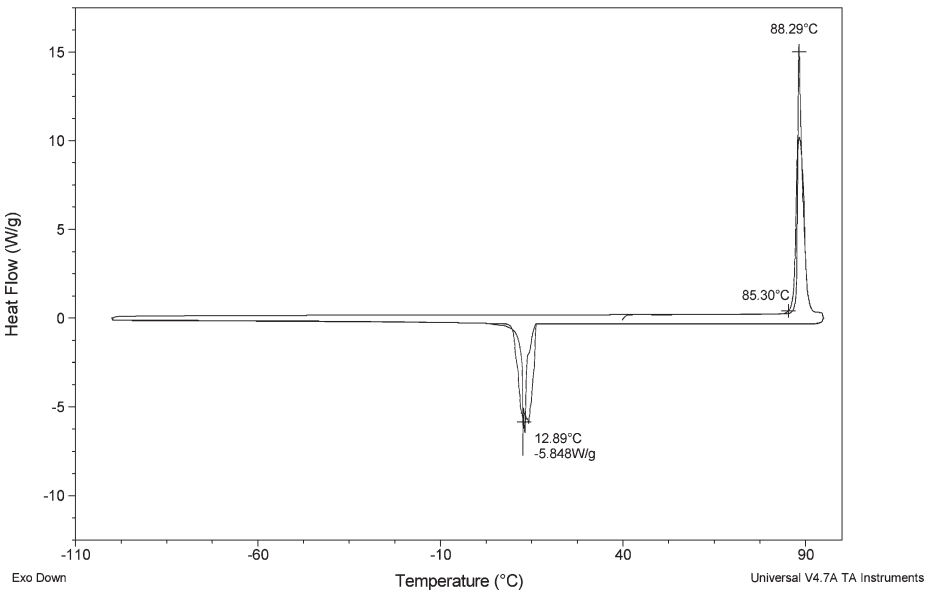
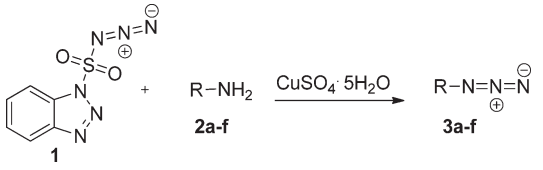
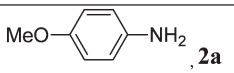
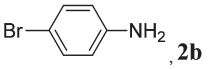
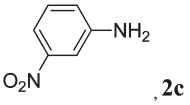
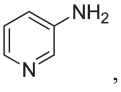
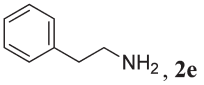
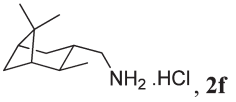


FIGURE 1. Differential scanning calorimetry of **1** (heats of fusion and freezing are recorded in Supporting Information).

TABLE 1. Synthesis of Azides from Primary Aromatic Amines Utilizing 1



entry	substrate **2**	product	time (h)	yield (%)
1	 **2a**	**3a**	7	70
2	 **2b**	**3b**	12	75
3	 **2c**	**3c**	10	57
4	 **2d**	**3d**	8	47
5	 **2e**	**3e**	12	85
6[α]	 **2f**	**3f**	7	51

[α]Et_3N (1 equiv) was required.

reacted with an amine in methanol at room temperature in the presence of copper(II) sulfate (Table 1). The reaction of benzotriazol-1-yl-sulfonyl azide **1** with 4-methoxyphenylamine **2a** without catalyst gave 4-methoxyphenyl azide **3a** (57%) after 24 h.

Preparation of α-Azido Acids by the Reaction of Benzotriazole-1-sulfonyl Azide 1 with Amino Acids. Benzotriazol-1-yl-sulfonyl azide **1** reacted with free amino acids **4a**−**e**, (**4a** + **4a**′) at 20 °C in aqueous CH_3CN in the presence of Et_3N and copper(II) sulfate to give corresponding α-azido acids **5a**−**e**, (**5a** + **5a**′) in good yield (60−87%, average 70%) (Table 2). HPLC analysis [chirobiotic T column (250 mm × 4.6 mm), detection at 254 nm, flow rate 0.5 mL/min, MeOH] on **5a**

SCHEME 2. Proposed Mechanism for the Formation of Diazo Compounds 12

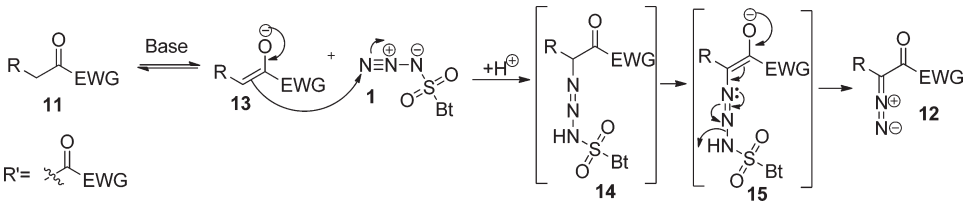
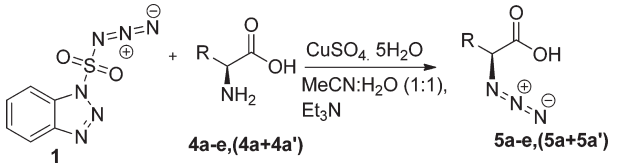
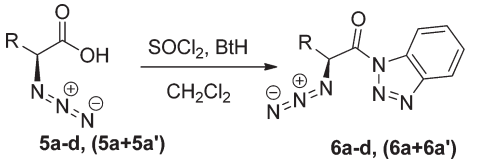


TABLE 2. Synthesis of α-Azido Acids from α-Amino Acids Utilizing 1



entry	substrate	product	time (h)	yield (%)
1	L-Phe, **4a**	**5a**	12	65
2	L-Leu, **4b**	**5b**	12	65
3	L-Ala, **4c**	**5c**	12	60
4	DL-Phe, (**4a** + **4a′**)	(**5a** + **5a′**)	12	65
5	L-Val, **4d**	**5d**	12	87
6	$(L\text{-Cys})_2$, **4e**	**5e**	12	77

TABLE 3. Synthesis of *N*-(α-Azidoacyl)benzotriazoles 6 from α-Azido Acids



α-azido acids, **5**	product	yield (%)	mp (°C)
N_3-L-Phe, **5a**	**6a**	98	66.1−68.3
N_3-L-Leu, **5d**	**6b**	96	47.3−49.0
N_3-L-Ala, **5c**	**6c**	65	77.0−77.9
N_3-DL-Phe, (**5a** + **5a′**)	(**6a** + **6a′**)	98	oil
N_3-L-Val, **5d**	**6d**	72	oil

(single peak, retention time 7.2 min) and (**5a** + **5a′**) (two equal peaks, retention times 6.7 and 7.2 min) confirmed that product **5a** is enantiomerically pure.

The details of the interconversion of an amine into an azide are not well established. The mechanism for diazo-transfer has been proposed involving a tetrazene intermediate. The mechanism incorporates a divalent metal ion that complexes with the amine. The amine in this complex is then thought to attack the electrophilic azide.[16a]

Preparation of *N*-(α-Azidoacyl)benzotriazoles. *N*-(α-Azidoacyl)benzotriazoles **6a**−**d**, (**6a** + **6a′**) were prepared in good yields (65−98%) by the treatment of the corresponding α-azido acids **5a**−**d**, (**5a** + **5a′**) with 1.2 equiv of thionyl chloride and 2 equiv of benzotriazole in methylene chloride (Table 3).

N-Acylation. The reliability of *N*-(α-azidoacyl)benzotriazoles as acylating agents was tested on a variety of *N*-nucleophiles to provide amides **8a**−**k** in 62−87% yields (Table 4). The azide demonstrated its functional group tolerance as a protecting group in *N*-acylation of aromatic, aliphatic amines and free amino acids (including free cysteine), nucleobases, nucleosides, and sulfonamides. HPLC analysis [chiracel OD-H column (250 mm × 4.6 mm), detection at 254 nm, flow rate 0.5 mL/min, hexane/isopropyl alcohol (90:10)] on **8a** (single peak, retention time 50.8 min) and **8g** (two equal peaks, retention times 47.6 and 51.4 min) confirmed that product **8a** is enantiomerically pure (Figure 2) (this was also confirmed with a co-injection).

Entries 9 and 10 (Table 4) were performed without added base with the objective of forming *S*-acylated products according to a reported literature method by our group where *S*-acylation was performed on aryl *N*-acylbenzotriazoles.[30] It is expected that *S*-acylation occurs first giving the thioester product, followed by S- to N-shift to provide the amide linkage. Interestingly, in this case ligation occurs spontaneously providing the *N*-acylated dipeptides containing free thiol in the absence of base.

O-, S-, and C-Acylation. Similarly, the reactivity of *N*-(α-azidoacyl)benzotriazoles **6a**−**c**, (**6a** + **6a′**) was tested against a variety of O-, S-, and C- nucleophiles (Table 5). As expected, azide as a protecting group is well tolerated, and *N*-(α-azidoacyl)benzotriazoles **6** could be used in the acylation of phenols, alcohols (including sterols), thiols, and stabilized enolates (Table 5).

Preparation of Diazo Compounds by the Reaction of Benzotriazole-1-sulfonyl Azide 1 with Activated Methylene Substrates. Diazo compounds are versatile synthetic building blocks[31] with rich transition-metal-catalyzed chemistry.[32] Thus, carbene insertion into C−H bonds has increased in importance since its discovery by Meerwein and Werner.[33] We utilized benzotriazol-1-yl-sulfonyl azide **1** in the preparation of diazo compounds **12a,b** containing activated methylene groups, and the results are summarized in Table 6. In general, yields and reaction times compare favorably with those reported in the literature using the most recent diazo-transfer reagent, imidazole-1-sulfonyl azide hydrochloride.[16]

We believe that the formation of diazo compounds from activated CH_2 groups via diazotransfer occurs through a nucleophilic attack of an intermediate enolate **13** onto benzotriazol-1-yl-sulfonyl azide **1**, followed by proton transfer to give intermediate **14**. In the presence of base, intermediate **15** is formed, which is converted to the desired diazo product **12** (Scheme 2).

Conclusions

Benzotriazol-1-yl-sulfonyl azide **1** is a new, stable, and safe to handle crystalline diazotransfer reagent with a long shelf

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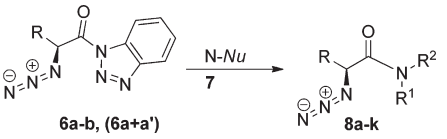
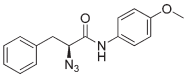
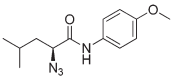
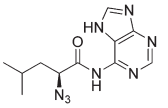
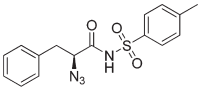
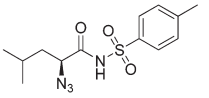
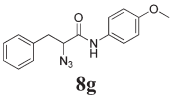
(33) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.

TABLE 4. Synthesis of Amides from *N*-(α-Azidoacyl)benzotriazoles 6



entry	*N*-(α-azidoacyl)-benzotriazole, 6	*N*-Nu, 7	optimized reaction conditions	product, 8	yield (%) [m.p. (°C)]
1	N_3 - L-PheBt, **6a**	p-Anisidine, **7a**	MeCN, 12 h	 **8a**	79 [79-81]
2	N_3- L-LeuBt, **6b**	p-Anisidine, **7a**	MeCN, 12 h	 **8b**	84 [43-45]
3	N_3- L-LeuBt, **6b**	Adenine, **7b**	DMSO, 8 h	 **8c**	68 [187-188]
4	N_3- L-PheBt, **6a**	p-Toluene-sulfonamide, **7c**	Et_3N (1.1 equiv), MeCN, 12 h	 **8d**	79 [120-122]
5	N_3- L-LeuBt, **6b**	p-Toluene-sulfonamide,**7c**	Et_3N (1.1 equiv), MeCN, 8 h	 **8e**	77 [55-56]
6	N_3- DL-PheBt, (**6a+6a'**)	Cytidine, **7d**	DMF, 12 h	 **8f**	62 [glassy solid]
7	N_3- DL-PheBt, (**6a+6a'**)	p-Anisidine, **7a**	MeCN, 12 h	 **8g**	79 [oil]
8	N_3- DL-PheBt, **6a**	L-Leu, **7e**	H_2O:MeCN (1:1), Et_3N (2.5 equiv)	N_3- L-PheL-Leu **8h**	87 [oil]
9	N_3- L-PheBt, **6a**	L-Cys, **7f**	H_2O:MeCN (1:1)	N_3- L-PheL-Cys **8i**	80 [112-115]
10	N_3- L -LeuBt, **6b**	L-Cys, **7f**	H_2O:MeCN (1:1)	N_3- L-LeuL-Cys **8j**	83 [oil]
11	N_3- L -PheBt, **6a**	L-Ala, **7g**	H_2O:MeCN (1:1), Et_3N (2.5 equiv)	N_3- L-PheL-Ala **8k**	80 [48-50]

life and high solubility in organic and aqueous solvents, which allows convenient and efficient synthesis of a wide range of azides and diazo compounds, including *N*-(α-azidoacyl)-benzotriazoles, which are efficient N-, S-, C-, and O-acylating agents and enable facile preparation of azido-peptides.

Experimental Section

Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. The NMR spectra were recorded in $CDCl_3$, DMSO-d_6 with TMS for ^1H (300 MHz) and ^{13}C (75 MHz) as an internal reference. Silica was used as the stationary phase for column chromatography.

Benzotriazol-1-yl-sulfonyl Azide (1). Sulfuryl chloride (6.23 mL, 0.08 mol) was added portion-wise to a suspension of NaN_3 (5 g, 0.08 mol) in MeCN (25 mL) at 0 °C, and the mixture was stirred overnight at room temperature. Benzotriazole (18.35 g, 0.15 mol) was dissolved in pyridine (6.46 mL, 0.08 mol) and acetonitrile (10 mL), and the solution was added to the suspension at 0 °C. The resulting suspension was stirred for 10 h at room temperature. The unreacted solid was filtered, and the yellow-orange filtrate was evaporated and then diluted with ethyl acetate. The organic layer was then washed with a saturated solution of sodium carbonate to remove the excess of benzotriazole, dried over anhydrous $MgSO_4$, and filtered. The filtrate was dried under vacuum to give a light brown solid that was later used directly. Recrystallization using hexane/EtOAc 7:3 gave a white crystalline solid (12.5 g, 70%): mp 85.3−88.3 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 131.6, 126.9, 121.3, 112.1. Anal. Calcd for $C_6H_4N_6O_2S$: C, 32.14; H, 1.80; N, 37.48. Found: C, 32.18; H, 1.74; N, 37.27. NOTE: ^1H NMR on reagent **1** was performed after it had been stored in a closed clear glass vial at room temperature for a period of 6 weeks, showing its longevity.

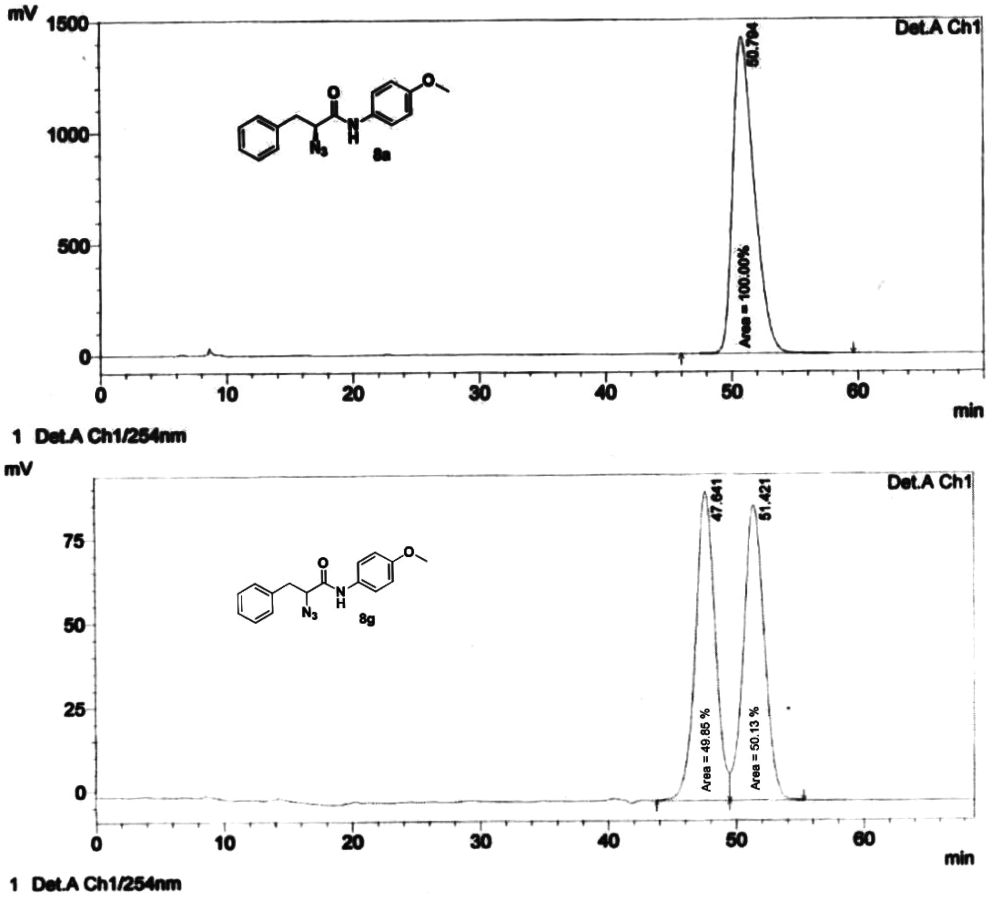


FIGURE 2. HPLC analysis for compounds **8a** and **8g**.

A moderate exothermic decomposition was noted when the hammer test was performed on **1**. [Caution: Although no trouble was noted when utilizing sodium azide, the *in situ* generated chlorosulfonyl azide, or any of the synthesized organic azides, appropriate safety measures must always be taken at all times because azides are high energy compounds.[3a,7,34]]

General Procedure for the Preparation of Azides, 3a−f. Benzotriazol-1-yl-sulfonyl azide **1** (0.50 g, 2.23 mmol) was added to the amine (2.23 mmol) in MeOH (20 mL). $CuSO_4 \cdot 5H_2O$ (2.5 mg, 10 μmol) was then added, and the mixture was stirred at room temperature for the specified time (Table 1). The mixture was concentrated, diluted with water (20 mL), and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification was performed *via* flash column chromatography to give the corresponding azide.

1-Azido-4-methoxybenzene (3a). 4-Methoxyaniline (275 mg, 2.23 mmol) was treated according to the above procedure [flash chromatography (hexane/EtOAc, 9:1)] to give 1-azido-4-methoxybenzene **3a**[1] as a pale yellow oil (233 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98−6.87 (m, 4H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 132.3, 120.0, 115.1, 55.6.

1-Azido-4-bromobenzene (3b). 4-Bromoaniline (384 mg, 2.23 mmol) was treated according to the above procedure [flash chromatography (hexane)] to give 1-azido-4-bromobenzene **3b**[2] as a pale yellow oil (332 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 6.92−6.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 132.7, 120.6, 117.7.

1-Azido-3-nitrobenzene (3c). 3-Nitroaniline (308 mg, 2.23 mmol) was treated according to the above procedure [flash chromatography (hexane/EtOAc, 9.8:0.2)] to give 1-azido-3-nitrobenzene **3c**[3] as a yellow solid (209 mg, 57%): mp 53.1−54.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.98 (m, 1H), 7.89 (t, J = 2.1 Hz, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.35 (dd, J = 1.8, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 130.6, 124.9, 119.7, 114.1.

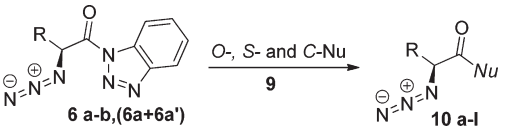
3-Azidopyridine (3d). Pyridin-3-amine (210 mg, 2.23 mmol) was treated according to the above procedure [flash chromatography (hexane)] to give 3-azidopyridine **3d**[4] as a pale yellow oil (126 mg, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41−8.35 (m, 2H), 7.38−7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 141.1, 137.0, 125.8, 124.0.

(2-Azidoethyl)benzene (3e). 2-Phenylethanamine (270 mg, 2.23 mmol) was treated according to the above procedure [chromatography (hexane)] to give (2-azidoethyl)benzene **3e**[5] as colorless oil (279 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H), 3.52 (t, J = 7.4 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.6, 128.5, 126.7, 52.4, 35.3.

(1*S*,2*S*,3*S*,5*R*)-3-(Azidomethyl)-2,6,6-trimethylbicyclo[3.1.1]-heptanes (3f). (+)-3-Pinanemethylamine hydrochloride (454 mg, 2.23 mmol) and triethyl amine (1 equiv) were treated according to the above procedure [flash chromatography (hexane)] to give (1*S*,2*S*,3*S*,5*R*)-3-(azidomethyl)-2,6,6-trimethylbicyclo-[3.1.1]heptanes **3f** as a yellow oil (220 mg, 51%): $[\alpha]_D^{20}$ +6.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (dd, J = 5.7, 11.7 Hz, 1H), 3.18 (dd, J = 7.5, 11.7 Hz, 1H), 2.35−2.26 (m, 1H), 2.22−2.12 (m, 1H), 2.04−1.89 (m, 2H), 1.81−1.68 (m, 2H), 1.59−1.51 (m, 1H), 1.20 (s, 3H), 1.07 (dd, J = 1.5, 7.2 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.6, 47.7, 41.3, 40.5, 38.8, 36.5, 33.5, 32.2, 27.9, 22.9, 21.6; HRMS m/z for $C_{11}H_{20}N$ $[M - N_2 + H]^+$ calcd 166.1590, found 166.1593.

(34) Griffiths, J. *J. Chem. Soc. C* **1971**, *19*, 3191–3195.

TABLE 5. O-, S-, and C-Acylations Utilizing *N*-(α-Azidoacyl)benzotriazoles 6



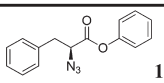
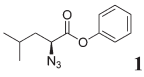
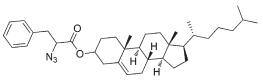
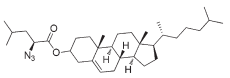
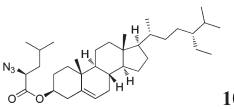
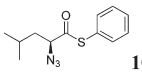
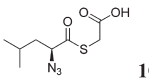
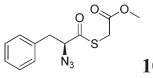
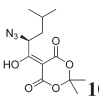
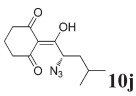
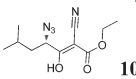
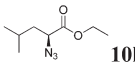
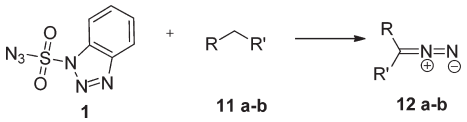
entry	*N*-(α-azidoacyl)-benzotriazole, 6	*Nu*, 9	optimized reaction conditions	product, 10	yield (%) [m.p. (°C)]
1	N_3- L-PheBt, **6a**	Phenol, **9a**	K_2CO_3 (2 equiv), MeCN,12 h	 **10a**	84 [oil]
2	N_3- L-LeuBt, **6b**	Phenol, **9a**	K_2CO_3(2 equiv), MeCN, 24 h	 **10b**	63 [oil]
3	N_3- DL - PheBt, **(6a+6a')**	Cholesterol, **9b**	THF, DMAP (cat.), 3 h	 **10c**	78 [56-58]
4	N_3- L -LeuBt, **6b**	Cholesterol, **9b**	$CHCl_3$, Et_3N (1 equiv), 72 h	 **10d**	61 [81-83]
5	N_3- L -LeuBt, **6b**	β-Sitosterol, **9c**	$CHCl_3$, Et_3N (1 equiv), 12h	 **10e**	70 [57-60]
6	N_3- L -LeuBt, **6b**	Thiophenol, **9d**	CH_2Cl_2, py (1 equiv), 18 h	 **10f**	72 [oil]
7	N_3- L -LeuBt, **6b**	2-Mercapto-acetic acid, **9e**	EtOAc, Et_3N (2 equiv), 18 h	 **10g**	82 [oil]
8	N_3- L -PheBt, **6a**	Methyl 2-mercapto-acetate, **9f**	EtOAc, Et_3N (1 equiv), 18 h	 **10h**	57 [oil]
9	N_3- L -LeuBt, **6b**	Meldrum's acid, **9g**	CH_3CN, Et_3N (1 equiv), 14 h	 **10i**	72 [oil]
10	N_3- L -LeuBt, **6b**	Cyclohexane-1,3-dione, **9h**	MeCN, Et_3N (1 equiv), 14 h	 **10j**	95 [oil]
11	N_3- L -LeuBt, **6b**	Ethyl 2-cyanoacetate, **9i**	CH_2Cl_2, Et_3N (1 equiv), 18 h	 **10k**	69 [oil]
12	N_3- L -LeuBt, **6b**	Ethanol, **9j**	EtOH, Et_3N (1 equiv), 12 h	 **10l**	95 [oil]

TABLE 6. Synthesis of Diazo Compounds Utilizing 1



product	R	R′	time [lit.][a] (h)	yield [lit.][a] (%)
12a	CN	CO_2Et	12 [9]	65 [61]
12b	SO_2Ph	CO_2Et	14 [48]	56 [-][b]

[a]Reaction with imidazole-1-sulfonyl azide. [b]No reaction was observed using imidazole-1-sulfonyl azide hydrochloride.[16]

***General* Procedure for the Preparation of α-Azido Acids, 5a−e (5a + 5a′).** The amino acid (4.46 mmol, 2 equiv) was dissolved in MeCN/H_2O (1:1, 20 mL) and triethyl amine (0.78 mL, 5.58 mmol). Benzotriazol-1-yl-sulfonyl azide **1** (0.50 g, 2.23 mmol) was added to the solution followed by $CuSO_4 \cdot 5H_2O$ (2.5 mg, 10 μmol), and the mixture stirred at room temperature for 12 h. The mixture was then acidified with 6 N HCl, concentrated, and then diluted with ethyl acetate. This was washed with 6 N HCl to remove benzotriazole. The organic layer was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the corresponding α-azido acid **5**.

(2*S*)-2-Azido-3-phenylpropanoic Acid (5a). L-Phenylalanine (736 mg, 4.46 mmol) was treated according to the above procedure to give (2*S*)-2-azido-3-phenylpropanoic acid **5a**[6] as a pale yellow oil (278 mg, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.38−7.27 (m, 5H), 4.15 (dd, *J* = 4.8, 9.0 Hz, 1H), 3.22 (d, *J* = 5.1 Hz, 1H), 3.08−3.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 135.6, 129.2, 128.8, 127.4, 63.1, 37.5.

(*S*)-2-Azido-4-methylpentanoic Acid (5b). L-Leucine (586 mg, 4.46 mmol) was treated according to the above procedure to give (*S*)-2-azido-4-methylpentanoic acid **5b**[7] as a pale yellow oil

(228 mg, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 3.88 (dd, J = 5.7, 9.0 Hz, 1H), 1.89−1.77 (m, 1H), 1.76−1.64 (m, 2H), 1.00−0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 60.0, 39.8, 25.0, 22.7, 21.4.

(*S*)-2-Azidopropanoic Acid (5c). L-Alanine (396 mg, 4.46 mmol) was treated according to the above procedure to give (*S*)-2-azidopropanoic acid **5c**[8] as a yellow oil (154 mg, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 1H), 4.03 (q, J = 7.1 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 57.0, 16.6.

2-Azido-3-phenylpropanoic Acid (5a + 5a′). D,L-Phenylalanine (736 mg, 4.46 mmol) was treated according to the above procedure to give 2-azido-3-phenylpropanoic acid (**5a** + **a′**)[7] as a pale yellow oil (278 mg, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.17 (dd, J = 5.0, 8.9 Hz, 1H), 3.25 (dd, J = 5.0, 14.0 Hz, 1H), 3.05 (dd, J = 8.9, 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 135.5 129.2, 128.8, 127.4, 63.0, 37.5.

(*S*)-2-Azido-3-methylbutanoic Acid (5d). L-Valine (523 mg, 4.46 mmol) was treated according to the above procedure to give (*S*)-2-azido-3-methylbutanoic acid **5d**[7] as a yellow oil (277 mg, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.8 (s, 1H), 3.76 (d, J = 5.7 Hz, 1H), 2.27−2.17 (m, 1H), 1.02 (dd, J = 6.9, 15 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 67.8, 30.8, 19.3, 17.6.

2-Azido-3-(((*R*)-2-azido-2-carboxyethyl)disulfanyl)propanoic Acid (5e). L-Cystine (268 mg, 1.12 mmol) was treated according to the above procedure to give 2-azido-3-(((*R*)-2-azido-2-carboxyethyl)disulfanyl)propanoic acid **5e** as an orange-brown oil (252 mg, 77%); $[\alpha]_D^{20}$ −37.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (bs, 2H), 4.43 (dd, J = 5.0, 7.1 Hz, 2H), 3.32 (dd, J = 5.0, 14.0 Hz, 2H), 3.03 (dd, J = 7.2, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 60.8, 39.9; HRMS m/z for $C_6H_8O_4N_6S_2Na$ $[M + Na]^+$ calcd 314.9941, found 314.9940.

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Supporting Information Available: X-ray analysis and thermo analytical measurements for **1**, experimental details, and ^{1}H and ^{13}C NMR for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.