Efficient Synthesis of 3,5-Functionalized Isoxazoles and Isoxazolines *via* 1,3-Dipolar Cycloaddition Reactions of 1-Propargyl- and 1-Allylbenzotriazoles

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3-Aryl-5-(benzotriazol-1-ylmethyl)- **10a-f** and 3-*p*-methoxyphenyl-5-(α-benzotriazol-1-yl-α-ethoxymethyl)-isoxazole (**13**) were prepared in high yields by 1,3-dipolar cycloadditions of 1-propargylbenzotriazole (**5**) and (α-ethoxypropargyl)benzotriazole (**8**), respectively, with nitrile oxides **3a-f** (prepared *in situ* from benzohydroximoyl chlorides **2a-f**). The benzotriazol-1-ylmethyl moiety was further elaborated by sequential lithiation and reaction with aldehydes, alkyl halides and Michael acceptors. Similar 1,3-cycloadditions using 1-allylbenzotriazole (**6**) and 1-(α-ethoxyallyl)benzotriazole (**7**) afforded 3,5-substituted isoxazolines **11b,f** and **12** in excellent yields.

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Introduction.

Isoxazoles and isoxazolines are important synthons and synthetic intermediates [1,2] and they are often used as masked β-diketones and β-aminoenones [3]. Biologically active 3,5-substituted isoxazole derivatives include muscimol [4], dihydromuscimol [5], cycloserine and many others [2]. Amongst numerous synthetic methods for the preparation of isoxazoles, many utilize 1,3-cycloadditions of electron rich olefins or acetylenes with nitrile oxides [6,7,8].

Benzotriazole is a versatile synthetic auxiliary [9]. Substitution at the 5-position of the isoxazole ring with a 2-(benzotriazol-1-ylmethyl) moiety should allow for side chain elaboration. This was previously demonstrated for many similar Bt-CH_2-heterocycle and Bt-CH(R)-heterocycle systems including polysubstituted pyrroles [10], indoles [11] and thiophenes [12]. Specific utility of the benzotriazol-1-ylmethyl moiety was demonstrated by benzannulation [13] and $ZnBr_2$-mediated carbon insertion [14]. Removal of the benzotriazole moiety has also been achieved by nucleophilic displacement, acid hydrolysis and reductive cleavage [9]. 4-(Benzotriazol-1-ylmethyl)-3-phenylisoxazoles were previously synthesized by the regiospecific 1,3-dipolar cycloaddition of electron rich benzotriazol-1-ylpropenes with benzonitrile oxide, and subsequent elimination [15]. However, no further transformations of benzotriazol-1-ylmethylisoxazoles were reported.

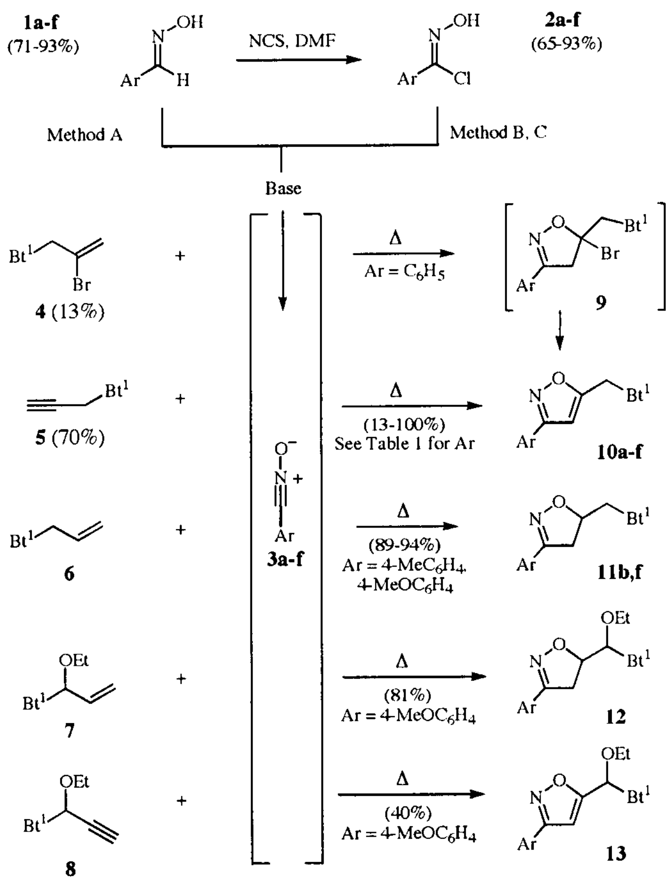
We now report convenient syntheses of polysubstituted isoxazoles **10a-f, 13** and isoxazolines **11b,f, 12** from 1-propargyl- and 1-allylbenzotriazoles **4-8** using 1,3-dipolar cycloadditions with nitrile oxides **3a-f**. Further functionalization of the benzotriazol-1-ylmethyl moiety is described, including examples of lithiation, alkylation and benzotriazole displacement.

Results and Discussion.

Synthesis of 3-Aryl-5-(benzotriazol-1-ylmethyl)isoxazoles **10a-f & 13** and 3-aryl-5-(benzotriazol-1-ylmethyl)-isoxazolines **11b,f & 12.**

1,3-Dipolar cycloadditions of propargylbenzotriazole (**5**) with benzonitrile oxide (**3a**) (obtained *in situ* from benzohydroximoyl chloride (**2a**) using triethylamine as a base in dichloromethane, tetrahydrofuran or ethyl acetate) at 20° or reflux, gave 3-phenyl-5-(benzotriazol-1-ylmethyl)isoxazole

Scheme 1



Method A: 1 step, **1a,b,e,f** + NCS, $KHCO_3$ & **5,6,7** or **8** in EtOAc, Δ
Method B: Et_3N, THF or DCM or EtOAc, Δ
Method C: $KHCO_3$, EtOAc, Δ

(**10a**) in 27-45% yield (Method B, Scheme 1, Table 1). As reported previously [16], we found that the use of potassium bicarbonate to generate the nitrile oxides *in situ* from **1a-f** led to substantial yield improvements for 3-aryl-5-(benzotriazol-1-ylmethyl)isoxazoles **10a-f** (Method C, Scheme 1, Table 1). The excess potassium bicarbonate and potassium chloride were removed easily by filtration. Furthermore, a one-pot reaction provided almost quantitative yields of isoxazoles **10a** (100%), **10b** (94%), and **10f** (95%) after 24-36 hours reflux of oximes **1a, 1b** and **1f**, propargylbenzotriazole (**5**), *N*-chlorosuccinimide and potassium bicarbonate (Method A, Scheme 1, Table 1).

Table 1

Preparation of 3-Aryl-5-(benzotriazol-1-ylmethyl)isoxazoles **10a-f** & **13** and 3-Aryl-5-(benzotriazol-1-ylmethyl)isoxazolines **11b,f** & **12** *via* 1,3-Cycloaddition Reactions

Entry	Ar	Solvent	Base	Time(h)	Yield %
10a	C_6H_5	EtOAc	$KHCO_3$	24	100[a]
		THF	Et_3N	18	45
		EtOAc	Et_3N	18	27
10b	4-$CH_3C_6H_4$	EtOAc	$KHCO_3$	36	94[a]
		DCM	Et_3N	17.5	35
10c	2-ClC_6H_4	EtOAc	$KHCO_3$	18	84
10d	3-$NO_2C_6H_4$	EtOAc	$KHCO_3$	14	52
		EtOAc	$KHCO_3$	20	13[a]
10e	3-$CH_3OC_6H_4$	EtOAc	$KHCO_3$	15	67
10f	4-$CH_3OC_6H_4$	EtOAc	$KHCO_3$	23	95[a]
		EtOAc	$KHCO_3$	12	72
11b	4-$CH_3C_6H_4$	EtOAc	$KHCO_3$	21	100[a]
		EtOAc	$KHCO_3$	36	89
11f	4-$CH_3OC_6H_4$	EtOAc	$KHCO_3$	18	94
12	4-$CH_3OC_6H_4$	EtOAc	$KHCO_3$	18	81 [a]
13	4-$CH_3OC_6H_4$	EtOAc	$KHCO_3$	20	40 [a]

[a] one-step procedure.

1,3-Cycloaddition reactions of nitrile oxides **3a-b** succeeded with 1-allylbenzotriazoles **4, 6** and **7**. 1-Allylbenzotriazole (**6**) and benzohydroximoyl chlorides **2b,f** afforded isoxazolines **11b** (89%) and **11f** (94%) using the two-step method (Method C, Scheme 1, Table 1). Isoxazoline **11b** was also synthesized quantitatively from oxime **1b** using the more efficient one-step method (Method A, Scheme 1, Table 1). 1-(2-Bromo-2-propenyl)-1*H*-1,2,3-benzotriazole (**4**) reacted with **2a** under the conditions of method B, to give isoxazole **10a** (58%) after column chromatography which was used to remove traces of **4** and intermediate isoxazoline **9** (Scheme 2). The presence of **9** was deduced from the ^1H nmr spectrum of the crude reaction mixture.

5-(α-Ethoxy-α-benzotriazol-1-ylmethyl)isoxazoline (**12**) was synthesized from (α-ethoxyallyl)benzotriazole (**7**) using the one pot reaction with *N*-chlorosuccinimide and potassium bicarbonate (81%) (Method A, Scheme 1, Table 1). Similarly, isoxazole **13** was synthesized from (α-ethoxypropargyl)-benzotriazole (**8**) (40%) (Method A, Scheme 1, Table 1). However, the less electron rich nitrile oxides derived from benzaldehyde and 4-methylbenzaldehyde did not react smoothly with **7**, affording only trace quantities of isoxazoline and mainly decomposition products.

Synthetic Manipulation of the Attached Benzotriazol-1-ylmethyl Groups.

Synthetic manipulations utilizing the deprotonation of α-benzotriazol-1-ylmethyl isoxazoles **10b,c,f** are shown in Scheme 2. Alkylation of lithiated **10c** with *p*-tolualdehyde gave alkene **15** in a 92% yield, *via* intermediate alcohol **14**. Treatment of **10f** with lithium diisopropyl amide at -78° followed by addition of 1.1 equivalent of benzyl bromide afforded **16** in a 76% yield after purification by column chromatography or recrystallization (Scheme 2). Refluxing **16** in tetrahydrofuran/*t*-butyl alcohol in the presence of excess potassium *t*-butoxide afforded exclusively the *trans* olefin **17** in 83% yield. Such transformation should provide a convenient route to styrylisoxazoles. The *trans* stereochemistry of **17** was assigned by the 16 Hz coupling constant observed for the olefinic protons.

Allylation of **10b** was also successful. Lithiation with lithium diisopropyl amide and subsequent addition of allyl bromide gave **18** (90%). Lithiation of **10f** with butyllithium followed by conjugate addition of chalcone

Scheme 2

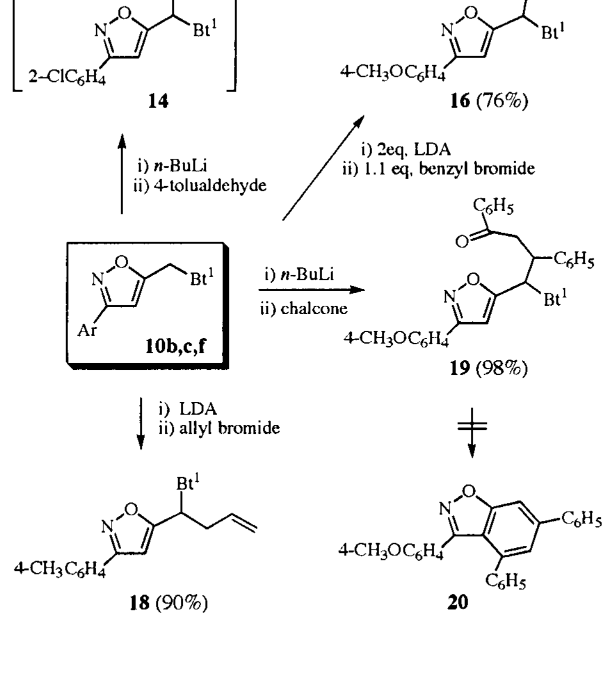


Table 2

^{1}H nmr Data for Isoxazoles **10a-f** & **13** and Isoxazolines **11a,f** & **12** in $CDCl_3$ [a]

Entry	H4	H5	H1'	Bt and Aryl Resonances	Other Resonances
10a	6.49 (s)	-	6.01 (s)	7.38-7.48 (m, 4H), 7.51 (t, 7.6, 1H), 7.62 (d, 8.2, 1H), 7.68-7.74 (m, 2H), 8.07 (d, 8.3, 1H)	
10b	6.46 (s)	-	6.00 (s)	7.22 (d, 8.4, 2H), 7.41 (t, 7.7, 1H), 7.53 (t, 7.7, 1H), 7.59-7.65 (m, 3H), 8.10 (d, 8.7, 1H)	2.37 (s) Me
10c	6.71 (s)	-	6.04 (s)	7.28-7.50 (m, 4H), 7.53 (t, 7.6, 1H), 7.65 (d, 8.9, 2H), 8.09 (d, 8.3, 1H)	
10d [b]	7.38 (s)	-	6.39 (s)	7.48 (t, 7.5, 1H), 7.64 (t, 8.0, 1H), 7.81 (t, 8.0, 1H), 7.98, (d, 8.3, 1H), 8.11 (d, 8.2, 1H), 8.33 (t, 8.8, 2H), 8.63 (s, 1H)	
10e	6.47 (s)	-	6.01 (s)	6.97 (d, 8.1, 1H), 7.25-7.34 (m, 3H), 7.41 (t, 7.7, 1H), 7.54 (t, 7.5, 1H), 7.62 (d, 8.2, 1H), 8.10 (d, 8.3, 1H)	3.82 (s) MeO
10f	6.43 (s)	-	5.99 (s)	6.92 (d, 8.6, 2H), 7.40 (t, 7.6, 1H), 7.52 (t, 7.6, 1H), 7.64 (t, 8.2, 3 H), 8.08 (d, 8.3, 1H)	3.82 (s) MeO
11b	3.36 (dd, 7.2, 17.1) 3.50 (dd, 10.5, 17.1)	5.20-5.30 (m)	4.86 (dd, 5.4, 14.7) 4.93 (dd, 5.1, 14.7)	7.15 (d, 7.8, 2H), 7.36 (t, 7.7, 1H), 7.44 (d, 8.1, 2H), 7.50 (t, 7.7, 1H), 7.73 (d, 8.4, 1H), 8.03 (d, 8.4, 1H)	2.35 (s) Me
11f	3.34 (dd, 7.2, 17.1) 3.48 (dd, 10.2, 16.8)	5.21-5.24 (m)	4.84 (dd, 5.7, 14.7) 4.93 (dd, 4.8, 14.7)	6.85 (d, 8.6, 2H), 7.37 (t, 7.8, 1H), 7.50 (d, 6.8, 3H) 7.74 (d, 8.0, 1H), 8.02 (d, 8.4, 1H)	3.80 (s) MeO
12	3.60 (d, 8.4)	5.30-5.40 (m)	6.03 (d, 5.7)	6.90 (d, 8.7, 2H), 7.39 (t, 7.7, 1H), 7.54 (t, 8.3, 3H), 7.83 (d, 8.4, 1H), 8.08 (d, 8. 1, 1H)	3.82 (s) MeO, 1.18 (t, 6.9), 3.37-3.62 (m) EtO
13	6.74 (s)	-	7.30 (s)	6.96 (d, 7.8, 2H), 7.38-7.49 (m, 2H), 7.59 (d, 7.8, 1H), 7.73 (d, 7.5, 2H), 8.11 (d, 8.4, 1H)	1.26 (t, 6.9) & 3.46-3.58 & 3.77-3.82 (m) EtO, 3.85 (s) MeO
15	6.14 (s)	-		6.66 (d, 8.1, 2H), 6.92 (d, 8.1, 2H), 7.24-7.43 (m, 6H), 7.67-7.71 (m, 1H), 8.14-8.22 (m, 1H)	2.22 (s) Me, 7.83 (s) alkene
16	6.50 (s)	-	6.29-6.34 (m)	6.93 (d, 8.7, 2H), 7.03-7.06 (m, 2H), 7.13-7.17 (m, 3H), 7.31-7.48 (m, 3H), 7.67 (d, 9.0, 2H), 8.04 (d, 7.97, 1H)	3.83 (s) MeO, 3.90-3.94 (m) Ph-CH_2
17	6.50 (s)	-	6.95-7.00 (d, 16.4)	6.96-7.00 (d, 8.8, 2H), 7.30-7.41 (m, 3H), 7.52 (d, 6.8, 2H), 7.76 (d, 8.8, 2H)	3.84 (s) MeO, 7.33-7.39 (d, 16.5) alkene
18	6.50 (s)	-	6.19-6.25 (m)	7.21 (d, 8.1, 2H), 7.38 (t, 7.7, 1H), 7.49 (t, 7.5, 1H), 7.61 (t, 7.2, 3H), 8.11 (d, 8.1, 1H)	2.36 (s) Me, 3.32-3.45 (m) & 5.01-5.15 (dd, 10.2, 16.8) & 5.64-5.78 (m) allyl
19[c]	6.48 (s) & 6.81 (s)	-	6.55-6.65 (dd, 9.3, 10.5)	6.87-8.07 (m, 18H)	3.81 & 3.83 (2xs) MeO, 4.86-4.94, (m, 1H), >CH-Ph, 3.16-3.70 (m, 2H) CH_2

[a] chemical shifts in (ppm) and coupling constants in (Hz); [b] carried out using DMSO-d_6. [c] Both diasteromers present in a 1:1 ratio.

afforded product **19** in a 98% yield. However, attempted electrophilic cyclization of adduct **19** under a variety of conditions with Brönsted and Lewis acids failed to give benzisoxazole **20** (Scheme 2). Reaction with cyclopentyl- and allylmagnesium bromide did not effect nucleophilic displacement of the benzotriazole group in **10f**.

Surprisingly, unlike in reference [17], the (α-ethoxy-α–benzotriazol-1-ylmethyl) moiety of isoxazoline **12** did not hydrolyze even in concentrated hydrochloric acid at 100°.

^{1}H and ^{13}C nmr data.

The 3,5-substituted isoxazoles **10a-f** and **13** show characteristic ^{1}H and ^{13}C nmr spectra (Table 2). The C-4 proton resonances were found between 6.4-6.7 ppm for all isoxazoles other than that for 1-[3-(3-nitrophenyl)-5-isoxazolyl]-1*H*-1,2,3-benzotriazole (**10d**) which was found at 7.4 ppm. The 2-(benzotriazol-1-ylmethyl) CH_2 resonances were observed between 6.0-6.5 ppm for all products. These data agree with literature values [1]. The ^{13}C nmr spectra exhibited the expected resonances at *ca.* 100 ppm (C-4) and two signals at 160-170 ppm (C-3, C-5) in addition to those expected for the benzotriazole moiety [1].

The isoxazolines showed characteristic ^{1}H nmr resonances as reported in the literature with multiplets at 5.2-5.4 ppm for the C-5 protons and 3.3-3.8 ppm for the C-4 protons [1]. The ^{13}C nmr signals were present at *ca.* 40, 80 and 155 ppm for the C-3, C-4 and C-5 carbons respectively [1]. The nmr data and also spectroscopic information for the analogous 4-(benzotriazol-1-lylmethyl)isoxazole confirm the isoxazolines as 5-substituted [15].

Conclusions.

In summary, 3-aryl-5-(benzotriazol-1-ylmethyl)isoxazoles **10a-f, 13** and 3-aryl-5-(benzotriazol-1-ylmethyl)isoxazolines **11b,f, 12** were prepared in good to excellent yields as crystalline solids *via* 1,3-cycloaddition reactions with

1-propargyl- and 1-allylbenzotriazoles, respectively. Further syntheses of polysubstituted isoxazoles were demonstrated utilizing the facile deprotonation of the benzotriazol-1-ylmethyl side chain followed by reaction with electrophiles. A convenient route to the synthesis of styrylisoxazole derivatives exemplified by **17** was developed by base promoted elimination of benzotriazole from **16**.

EXPERIMENTAL

Preparation of Starting Materials.

1-Propargylbenzotriazole (**5**) and 1-allylbenzotriazole (**6**) were prepared by the methods used previously [18], although for **5** the method was improved by using NaH in DMF to generate the benzotriazole anion.

(α-Ethoxyallyl)benzotriazole (**7**) [19] and (α-ethoxypropargyl)benzotriazole (**8**) [20] were prepared in high yield from the corresponding acetals using previously reported methods.

The benzaldoximes were prepared using a standard procedure in which **1a-f** were obtained in excellent yields (71-93%) following extractive work-up and were used without further purification.

Benzohydroximoyl chlorides **2a-f** were prepared by the chlorination of benzaldoximes using *N*-chlorosuccinimide in *N,N*-dimethylformamide [21,22] in good to excellent yields (65-92%). In some cases, the benzohydroximoyl chlorides formed were not completely pure, but this did not effect the 1,3-cycloaddition reactions providing an excess was used.

Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H nmr spectra were recorded on a Varian Gemini-300 MHz spectrometer using tetramethylsilane as the internal standard. The ^{13}C nmr spectra were recorded at 75 MHz on the same instrument with the solvent ($CDCl_3$) peak as the internal reference. The gcms instrument used was Hewlett Packard 5890 series 11 gas chromatograph coupled to a 5972 mass selective detector. Elemental analyses (C, H, N) were carried out on a Carlo Erba-1106 instrument. Column chromatography was carried out on MCB silica gel (230-400 mesh).

1-(2-Bromo-2-propenyl)-1*H*-1,2,3-benzotriazole (**4**).

A solution of benzotriazole (40 mmoles, 4.76 g) and sodium hydroxide (40 mmoles) in water (0.5 ml) and ethanol (16 ml) was stirred at 20° until all the solids had dissolved. To this solution was added (2,3)-dibromo-1-propene (80%) (50 mmoles) dropwise over 30 minutes. Following 24 hours stirring at this temperature the solvent was removed *in vacuo* and the remaining solution extracted into ether (3 x 30 ml). The combined organic extracts were washed with 6 *N* hydrochloric acid (4 x 50 ml) and then washed with ether. The aqueous extracts were combined and basified with solid sodium carbonate and extracted into ether, dried over magnesium sulfate and concentrated *in vacuo* to give the Bt^1 isomer as white microcrystals following crystallization from carbon tetrachloride and hexanes (13%).

^{1}H nmr ($CDCl_3$): δ 5.50 (s, 2H), 5.68 (s, 1H), 5.71 (s, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.52-7.55 (m, 2H), 8.10 (d, *J* = 8.3 Hz, 1H); ^{13}C nmr ($CDCl_3$): δ 55.5, 109.5, 120.2, 124.2, 125.0, 127.9, 133.0, 146.0; (EI^+) hrms for $C_9H_9N_3Br$ Calcd. 237.9979; Found 237.9985.

1-Propargylbenzotriazole (**5**).

To a suspension of NaH (95%) (0.152 mole) in dry *N,N*-dimethylformamide (50 ml) was added a solution of benzotriazole (0.167 mole) in *N,N*-dimethylformamide (20 ml) dropwise at 0°. After 20 minutes at this temperature the mixture was warmed to room temperature for another 20 minutes. The reaction mixture was cooled to 0° and propargylbromide (0.182 mol) was added dropwise and allowed to reach room temperature. Following 2 hours at this temperature, the mixture was quenched with saturated sodium bicarbonate (20 ml) and extracted into ether (3 x 20 ml). The combined organic extracts were washed with sodium bicarbonate (20 ml) and water (3 x 20 ml), dried over magnesium sulfate, and solvent removed *in vacuo* to yield a brown oil. This oil was crystallized from carbon tetrachloride and washed with cold hexanes to yield 1-propargyl benzotriazole (**5**) as brown microcrystals (70%), mp 72° [18].

^{1}H nmr ($CDCl_3$): δ 2.50 (s, 2H), 5.47 (s, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H). ^{13}C nmr ($CDCl_3$): δ 38.0, 75.1, 109.8, 120.2, 124.2, 127.7, 132.4, 141.0, 146.3.

General Procedures for the Preparation of Isoxazoles **10a-f**.

Method A (One step method).

To a solution of 1-propargylbenzotriazole (**5**) (1 equivalent, 4 mmoles) and oximes **1a, b, d, f** (4.4 mmoles) in ethyl. acetate (20 ml) was added potassium carbonate (20 mmoles), *N*-chlorosuccinimide (4.8 mmoles) and a few drops of water. This mixture was refluxed for 18-36 hours and following cooling to 20° was filtered. The solvent was removed *in vacuo* and the residue extracted into ether (3 x 20 ml). The combined organic layers were washed with water and brine, dried over magnesium sulfate and solvent removed *in vacuo* to yield the desired isoxazoles **10a, b, d, f**.

Method B.

To a solution of 1-propargylbenzotriazole (**5**) (8 mmoles) and benzohydroximoyl chloride **2a-b** (8-8.4 mmoles) in dichloromethane, tetrahydrofuran or ethyl acetate (20 ml) was added triethylamine (12 mmoles). The mixture was heated under reflux for 18 hours, cooled to 20°, quenched with water (20 ml) and the product extracted into ether or dichloromethane (3 x 20 ml). The combined organic layers were washed with water and brine, dried over magnesium sulfate and solvent removed *in vacuo* to afford the desired products **10a-b** which were further purified by recrystallization from an appropriate solvent.

Method C.

To a solution of 1-propargylbenzotriazole (**5**) (4 mmoles) and benzohydroximoyl chloride **2a-f** (4 mmoles) in ethyl acetate (20 ml) was added potassium carbonate (20 mmoles) and a few drops of water. The mixture was heated under reflux for 12-36 hours, cooled to 20°, filtered and the solvent was removed *in vacuo*. The product was extracted into ether or dichloromethane (3 x 20 ml). The combined organic layers were washed with water (2 x 20 ml) and brine (2 x 20 ml), dried over magnesium sulfate and the solvent removed *in vacuo* to yield the desired isoxazoles **10a-f**.

1-[3-Phenyl-5-isoxazolyl)methyl]-1*H*-1,2,3-benzotriazole (**10a**).

The compound was recrystallized from methanol to yield white needles, mp 125°. See Table 2 for ^{1}H nmr; ^{13}C nmr

($CDCl_3$): δ 43.5, 101.8, 109.3, 120.2, 124.4, 126.7, 128.1, 128.2, 128.9, 130.3, 132.7, 146.1, 162.8, 165.8.

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.38; H, 4.30; N, 20.32.

1-{[3-(4-Methylphenyl)-5-isoxazolyl]methyl}-1*H*-1,2,3-benzotriazole (**10b**).

This compound was recrystallized from methanol to yield white needles, mp 130°. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 21.4, 43.5, 101.8, 109.3, 120.2, 124.4, 125.3, 126.6, 128.1, 129.6, 132.7, 140.5, 146.1, 162.8, 165.6.

Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 69.87; H, 4.78; N, 19.18.

1-{[3-(2-Chlorobenzyl)-5-isoxazolyl]methyl}-1*H*-1,2,3-benzotriazole (**10c**).

This compound was recrystallized from hexanes/chloroform to give white microcrystals, mp 143-146°. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 43.4, 105.2, 109.3, 120.2, 124.3, 127.1, 127.4, 128.1, 130.4, 130.8, 131.1, 132.6, 132.7, 146.1, 161.4, 164.9.

Anal. Calcd. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.89; H, 3.49; N, 18.04.

1-{[3-(3-Nitrophenyl)-5-isoxazolyl]methyl}-1*H*-1,2,3-benzotriazole (**10d**).

This compound was recrystallized from chloroform to give white microcrystals, mp 184-188°. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 42.8, 102.6, 110.6, 119.4, 121.3, 124.5, 125.1, 128.0, 129.6, 130.9, 132.8, 133.0, 145.8, 148.4, 160.9, 167.9.

Anal. Calcd. for $C_{16}H_{11}N_5O_3$: C, 59.81 H, 3.45; N, 21.80. Found: C, 59.58; H, 3.35; N, 21.67.

1-{[3-(3-Methoxyphenyl)-5-isoxazolyl]methyl}-1*H*-1,2,3-benzotriazole (**10e**).

This compound was recrystallized from methanol to give pale yellow needles, mp 117-119°. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 43.5, 55.3, 102.0, 109.3, 111.6, 116.5, 119.2, 120.2, 124.4, 128.2, 129.4, 130.0, 132.7, 146.1, 159.9, 162.7, 165.8.

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.33; H, 4.70; N, 18.27.

1-{[3-(4-Methoxyphenyl)-5-isoxazolyl]methyl}-1*H*-1,2,3-benzotriazole (**10f**).

This compound was recrystallized from methanol to give pale yellow needles, mp 110-111°. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 43.4, 55.3, 101.6, 109.3, 114.3, 120.1, 120.6, 124.3, 128.1, 132.7, 146.1, 161.2, 162.0, 165.5.

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.38; H, 4.58; N, 18.15.

General Procedure for Preparation of 3-Aryl-5-(benzotriazol-1-ylmethyl) Isoxazolines **11b,f**.

To a solution of 1-allylbenzotriazole (**6**) (3.2 mmoles) and benzohydroximoyl chloride **2b** or **2f** (3.2 mmoles) in ethyl acetate (20 ml) was added potassium carbonate (16.0 mmoles) and a few drops of water. The mixture was heated under reflux for 18-21 hours, cooled and filtered. The solvent was removed *in vacuo* and the residue extracted into ether or dichloromethane (3 x 20 ml). The combined organic layers were washed with water (20 ml) and brine (2 x 20 ml), dried over magnesium sulfate and solvent removed *in vacuo* to yield the desired isoxazolines (**11b,f**). Alternatively, the one step procedure without isolation of the benzohydroximoyl chlorides could be used as demonstrated by the isoxazole syntheses, Method A, Scheme 1.

1-{[3-(4-Methylbenzyl)-4,5-dihydro-5-isoxazolyl]methyl}-1*H*-1,2,3-benzotriazole (**11b**).

This compound was recrystallized from methanol to give white needles, mp 143-144°. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 21.4, 38.1, 50.7, 79.0, 110.2, 119.7, 124.1, 125.8, 126.6, 127.7, 129.4, 133.7, 140.7, 145.8, 156.6.

Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.16. Found: C, 69.82; H, 5.52; N, 19.25.

1-{[3-(4-Methoxybenzyl)-4,5-dihydro-5-isoxazolyl]methyl}-1*H*-1,2,3-benzotriazole (**11f**).

This compound was recrystallized from methanol to give pale yellow needles, mp 142-143°. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 38.1, 50.7, 55.2, 78.9, 110.2, 114.0, 119.6, 121.1, 124.0, 127.7, 128.2, 133.6, 145.8, 156.1, 161.2.

Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 66.22; H, 5.23; N, 18.17. Found: C, 65.81; H, 5.33; N, 17.98.

1-Ethoxy{[3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolyl]-methyl}-1*H*-1,2,3-benzotriazole (**12**).

To a solution of (α-ethoxyallyl)benzotriazole (**7**) [19] (3.0 mmoles) and oxime (2.7 mmoles) in ethyl acetate (30 ml) (including 2-3 drops of water) was added *N*-chlorosuccinimide (3.3 mmoles) and potassium carbonate (13.5 mmoles). The mixture was stirred and gently heated under reflux for 18 hours. The yellow solution was filtered and solvent removed *in vacuo*. The product was extracted into ether (3 x 20 ml) washed with water (2 x 20 ml) and brine (20 ml), dried over magnesium sulfate and the solvent removed *in vacuo* to afford the desired product. The compound was recrystallized from methanol/petroleum ether to give pale yellow microcrystals. Only one diastereomer was present (mp 118-120°), although from the crude nmr spectra, two diastereoisomers were clearly present. See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 14.5, 37.7, 55.2, 65.4, 80.0, 89.2, 110.9, 114.0, 119.9, 121.1, 124.2, 127.8, 128.2, 132.2, 146.2, 155.9, 161.1.

Anal. Calcd. for $C_{19}H_{20}N_4O_3$: N, 15.90. Found: N, 15.74.

1-Ethoxy[3-(4-methoxyphenyl)-5-isoxazolyl]methyl-1*H*-1,2,3-benzotriazole (**13**).

This was prepared using the same procedure as reported for isoxazoline **12** using (α-ethoxypropargyl)benzotriazole (**8**) [20] and was purified by chromatography using hexanes/ethyl acetate = 1:3 to afford a light yellow oil.

See Table 2 for ^1H nmr; ^{13}C nmr ($CDCl_3$): δ 14.6, 55.3, 65.5, 83.4, 101.7, 111.0, 114.3, 120.2, 120.6, 124.6, 128.2, 128.3, 129.3, 131.3, 146.8, 161.2, 162.0, 166.1.

(FAB) hrms for $C_{19}H_{19}N_4O_3$ calculated; 351.1457. Found; 351.1469.

Alkylation of 3-Aryl-5-(benzotriazol-1-ylmethyl)isoxazoles, General Procedure.

To a solution of isoxazole **10** (2.0 mmoles) in dry tetrahydrofuran (25 ml) at -78° under argon was added lithium di-isopropyl amide (2.4 mmoles). The mixture was maintained at -78° for 30 minutes and warmed to 20° for 5 minutes. After re-cooling to -78° the electrophile (2.2 mmoles) was added dropwise. The mixture was maintained at -78° for 1 hour before warming and leaving overnight at 20°. The reaction was quenched with water (10 ml) and extracted into ether (3 x 15 ml). The combined ether extracts were washed with water (2 x 15 ml) and brine (2 x 15 ml) and dried over magnesium sulfate and concentrated *in vacuo*. The crude products were purified by column chromatography.

1-{(*Z*)-1-[3-(2-Chlorophenyl)-5-isoxazolyl]-2-(4-methylphenyl)-ethenyl}-1*H*-1,2,3-benzotriazole (**15**).

The compound was prepared by the general alkylation procedure but using *n*-butyllithium. After 2 hours at -78°, *p*-tolualdehyde was added and, after 1 hour at -78°, the mixture was warmed to room temperature and allowed to stand for 18 hours. The crude product was obtained as yellow macroprisms (92%). A sample was purified further by recrystallization from carbon tetrachloride/hexanes, mp 159-160°. See Table 2 for ^{1}H nmr; ^{13}C nmr ($CDCl_3$): δ 21.3, 103.4, 107.5, 110.1, 120.2, 124.6, 127.0, 127.6, 128.6, 129.4, 129.7, 130.3, 130.9, 131.0, 132.1, 132.6, 132.8, 133.1, 140.8, 145.7, 161.8, 166.0. (EI$^+$) hrms for $C_{24}H_{18}N_4OCl$ (M^++1) calculated; 413.1169. Found; 413.1161.

1-{1-[3-(4-Methoxyphenyl)-5-isoxazolyl]-2-phenylethyl}-1*H*-1,2,3-benzotriazole (**16**).

The compound was purified by column chromatography using hexanes/ethyl acetate = 4:1 as eluent to yield a yellow oil which crystallized on standing (76%). A sample was further purified by recrystallization from carbon tetrachloride/methanol to yield white microcrystals, mp 178-179°. See Table 2 for ^{1}H nmr; ^{13}C nmr ($CDCl_3$): δ 39.7, 55.8, 58.2, 101.7, 109.9, 114.8, 120.6, 121.2, 124.7, 127.8, 128.3, 128.7, 129.2, 132.2, 135.7, 146.4, 161.6, 162.3, 169.0.

Anal. Calcd. for $C_{24}H_{20}N_4O_2$: N, 14.13. Found: N, 13.89.

1-{1-[3-(4-Methylphenyl)-5-isoxazolyl]-3-butenyl}-1*H*-1,2,3-benzotriazole (**18**).

The compound was purified by column chromatography using hexanes/ethyl acetate = 6:1 to yield a yellow oil which crystallized on standing, (90%). A sample was further purified by recrystallization from carbon tetrachloride to afford white microcrystals, mp 96-97°. See Table 2 for ^{1}H nmr; ^{13}C nmr ($CDCl_3$): δ 21.3, 36.8, 55.8, 101.1, 109.6, 120.0, 120.2, 124.2, 125.4, 126.6, 127.8, 129.6, 131.3, 132.4, 140.5, 146.1, 162.6, 168.7.

Anal. Calcd. for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.89; H, 5.67; N, 17.15.

4-(1*H*-1,2,3-Benzotriazol-1-yl)-4-[3-(4-methoxyphenyl)-5-isoxazolyl]-1,3-diphenyl-1-butanone (**19**).

To a solution of isoxazole (3.0 mmoles) in dry tetrahydrofuran (20 ml) was added *n*-butyllithium (3.3 mmoles) at -78°. The mixture was left stirring for 30 minutes and chalcone (3.3 mmoles) added in a solution of tetrahydrofuran (10 ml). The mixture was left ovenight at 20° and then quenched with water (15 ml). The product was extracted into ether (3 x 20 ml), washed with water (2 x 20 ml) and brine (2 x 20 ml) and dried over magnesium sulfate. Following solvent removal, yellow needles were obtained (98%). See Table 2 for ^{1}H nmr. This compound was present as a 1:1 mixture of diastereomers and had ^{13}C nmr ($CDCl_3$): δ 40.4, 41.5, 44.1, 44.7, 55.3, 60.0, 60.1, 102.5, 102.7, 109.7, 110.7, 114.2, 114.3, 119.9, 120.0, 120.6, 120.6, 123.9, 124.4, 127.4, 127.6, 127.8, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.5, 128.8, 132.5, 132.7, 133.2, 133.3, 136.3, 136.4, 138.4, 138.5, 145.5, 145.8, 161.1, 161.2, 161.9, 162.4, 167.1, 167.9, 196.5, 196.8 (all signals for both diastereomers).

Anal. Calcd. for $C_{32}H_{26}N_4O_3$: C, 74.69; H, 5.09. Found: C, 74.96; H, 5.30.

3-(4-Methoxyphenyl)-5-[(*E*)-2-phenylethenyl]isoxazole (**17**).

This isoxazole **16** (0.50 mmole) with potassium *t*-butoxide (1.0 mmole) in dry tetrahydrofuran (2 ml) and *t*-butanol (3 ml) were refluxed for 20 hours. After cooling, the reaction mixture was quenched with water (5 ml) and extracted with ether (3 x 10 ml). The combined extracts were washed with saturated potassium carbonate (3 x 10 ml) and water (3 x 10 ml) and dried over magnesium sulfate. The solvent was removed in *vacuo* to afford the expected compound as a yellow crystalline product (83%). A sample was further purified by recrystallization from carbon tetrachloride/hexanes to afford white microcrystals, mp 142-143°. See table 2 for ^{1}H nmr; ^{13}C nmr ($CDCl_3$): δ 55.3, 99.3, 113.1, 114.3, 121.6, 127.1, 128.1, 128.8, 129.1, 134.7, 135.6, 160.1, 161.2, 168.2.

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 5.41.

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