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Nitrile Oxide Cycloaddition Chemistry Using Benzotriazole as a Steric Auxiliary

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The relatively hindered 2,2-bis(benzotriazol-1-yl)acetonitrile oxide was prepared in situ from the precursor hydroximinoyl chloride, and was allowed to react with dipolarophiles to give rise to several isoxazoles. The benzotriazole substituents acted as steric auxiliaries to prevent unwanted dimerization of the nitrile oxide to the furoxan by-product.

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Introduction

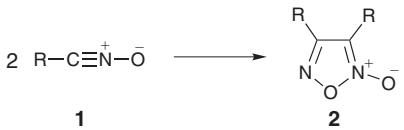
The 1,3-dipolar cycloaddition reaction of nitrile oxides **1** with carbon dipolarophiles is a versatile and powerful synthetic method to prepare Δ^2-isoxazolines and isoxazoles, which in turn, are useful precursors to β-hydroxy ketones, β-amino alcohols, 1,3-diols, and a range of other 1,3-disubstituted compounds.[1] Nitrile oxides also react with themselves in 1,3-cycloadditions to give dimeric furoxan products **2** (Scheme 1), and it is the comparative reactivity of the intended dipolarophile and the nitrile oxide itself that determines the extent of this competing side reaction.[2]

In general, alkylnitrile oxides are more prone to dimerization than arylnitrile oxides. In particular, alkylnitrile oxides with low degrees of substitution adjacent to the nitrile oxide give modest yields of cycloadducts in reactions with mono- and 1,1-disubstituted alkenes. When treated with 1,2-disubstituted and higher substituted alkenes, alkylnitrile oxides generally undergo dimerization in preference to the desired cycloaddition. This is the case even when the nitrile oxide is generated in situ in the presence of an excess of the alkene dipolarophile. The furoxans **2** formed by dimerization do not necessarily represent a dead end in nitrile oxide cycloaddition chemistry, however, as examples of thermolytic cycloreversion to nitrile oxides and subsequent cycloaddition reactions have been reported.[3,4] Unfortunately, these methods are not widely applicable because of the forcing conditions required for the cycloreversion.

When the alkylnitrile oxide is highly substituted, such as in 2,2-dimethylpropionitrile oxide **3** (Fig. 1), cycloaddition can occur in preference to dimerization, and this has been attributed to the greater steric bulk of the substituent R, which disfavours furoxan **2** formation. We have previously taken advantage of this phenomenon by exploiting the steric bulk of dithiane **4** to carry out cycloaddition reactions without competing dimerization.[5] The dithiane **4** can be considered as a masked analogue of propionitrile oxide, as the dithiane group can be removed by desulfurization following cycloaddition.

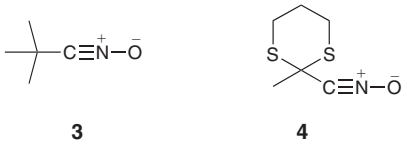
In such cases, dimerization was repressed by the bulky substituent, while cycloaddition reactions proceeded as desired. The dithiane was thus shown to be a useful steric auxiliary, albeit with limitations due to occasional problems associated with reaction at sulfur, and the modest yield of preparation. In addition, desulfurization of the final cycloadduct products to remove the steric auxiliary requires relatively harsh conditions, which can lead to unwanted side reactions.

The versatility of benzotriazole as a synthetic auxiliary has been extensively exploited, and reviews by Katritzky and co-workers attest to its prodigious synthetic utility.[6–8] Benzotriazole is inexpensive, easy to install, and mildly electron withdrawing, but has the ability to donate electrons depending on the nature of the substituent attached to the nitrogen.[8] It is also straightforward to remove or substitute, as the benzotriazolate anion is a reasonably stable leaving group. It was this versatility that we chose to exploit in an improved solution to the problem of dimerization of



1 **2**

Scheme 1.



3 **4**

Fig. 1. The structures of 2,2-dimethylpropionitrile oxide **3** and the dithiane **4**, in which cycloaddition can occur in preference to dimerization.

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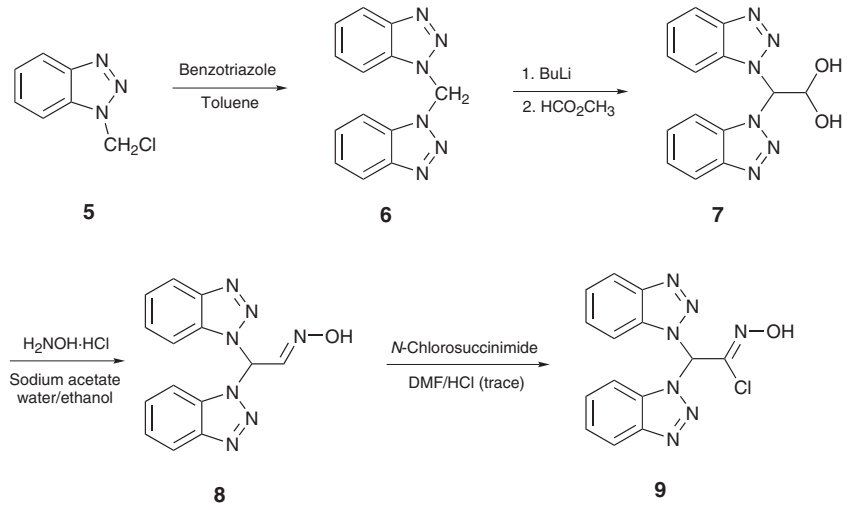
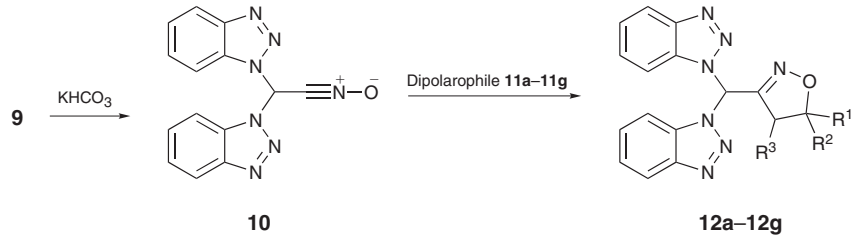


Scheme 2.



Scheme 3.

nitrile oxides—by temporarily introducing bulky benzotriazole substituents as steric auxiliaries. As an additional bonus, it was expected that the benzotriazole-substituted cycloaddition products thus formed would be flexibly amenable to further transformation if required.

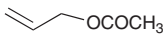
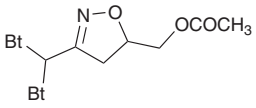
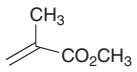
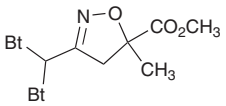
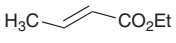
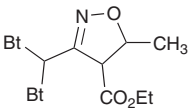
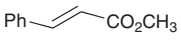
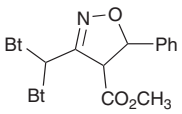
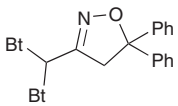
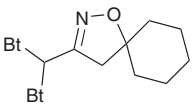
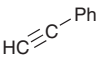
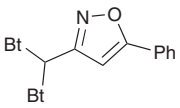
Results and Discussion

The most convenient precursors to nitrile oxides are the corresponding hydroximoyl chlorides, which eliminate HCl upon treatment with mild bases such as triethylamine and carbonate.[9] The synthesis of the bisbenzotriazole hydroximoyl chloride **9** proceeded as follows (Scheme 2). Bis(benzotriazol-1-yl)methane **6** was prepared by a modification of the procedures reported in the literature.[10–12] Nucleophilic displacement of 1-chloromethylbenzotriazole **5** with an excess of the weakly acidic benzotriazole in hot toluene gave bis(benzotriazol-1-yl)methane **6**, along with a trace of the corresponding benzotriazol-2-yl isomer. Benzotriazole is a mildly electron withdrawing substituent and, hence, bis(benzotriazol-1-yl)methane can be deprotonated with base. As such, treatment of **6** with butyllithium followed by methyl formate led to 2,2-bis(benzotriazol-1-yl)acetaldehyde, which was isolated as the stable hydrate **7**. The more usual formylating agent, dimethylformamide (DMF), did not lead to the desired product, presumably due to steric hindrance around the lithium bisbenzotriazole complex.[13] Evidence for hydrate formation included a strong infrared absorption at 3250 cm^{-1} and a weak absorption at 1720 cm^{-1}, while the ^{1}H NMR and ^{13}C NMR spectra were devoid of resonances typically associated with aldehydes. Treatment of the hydrate **7** with ethanol readily formed a hemiacetal, which could also be isolated as a stable solid. Aldehyde and ketone hydrates are commonly observed when α-halogenated (compare chloral hydrate and hexafluoroacetone). In this case, the electron-withdrawing nature of the two benzotriazole substituents probably stabilizes the hydrate **7**, relative to the corresponding aldehyde. The aldehyde hydrate **7** was then treated with hydroxylamine hydrochloride under standard conditions[14] to give the aldoxime derivative **8**. Treatment of this aldoxime with *N*-chlorosuccinimide in DMF, again under standard conditions,[15] gave the hydroximoyl chloride **9** in high yield, as a stable white solid.

The cycloaddition precursor bis(benzotriazol-1-yl)-acetonitrile oxide **10** was not isolated but rather generated in situ by treating the hydroximoyl chloride **9** with potassium bicarbonate in wet ethyl acetate, in the presence of the appropriate substituted alkenes.[16] Cycloaddition took place with a range of dipolarophile alkenes to give the corresponding 3-[bis(benzotriazol-1-yl)methyl] substituted Δ^2-isoxazolines (Scheme 3). In keeping with the general reactivity of nitrile oxides, the more highly substituted, especially 1,2-disubstituted, dipolarophiles gave lower yields compared to monosubstituted dipolarophiles. However, there was still quite some variability in yield, presumably due to competing steric and electronic effects.

Nitrile oxide cycloaddition reactions with unsymmetrical dipolarophiles can proceed to give a mixture of two regioisomers, although with monosubstituted dipolarophiles the product is usually exclusively the 5-substituted

Table 1. Cycloaddition reactions between nitrile oxide 10 and selected dipolarophiles 11a–11g

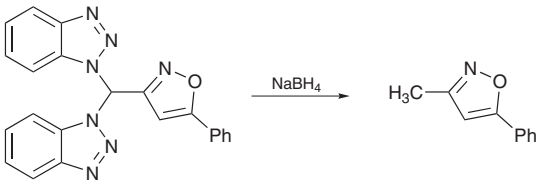
Entry	Dipolarophile **11a–11g**	Cycloadducts **12a–12g**[A]	Yield[B] [%]
a			77
b			70
c			61
d			42
e			26
f			51
g			48

[A] Bt = Benzotriazol-1-yl. [B] Isolated and purified yield.

isoxazolines.[1] In reactions with bis(benzotriazol-1-yl)-acetonitrile oxide **10** (Table 1), only a single regioisomer was detected for each case, except entries **c** and **d** where a trace of another isomer (not isolated) was detected by gas chromatography mass spectrometry (GC-MS). The regiochemistry of the cycloaddition can be determined by NMR spectroscopy of the product, as the chemical shift of the H4 protons on isoxazolines is significantly upfield (approx. 1 ppm) from the H5 proton chemical shift.[17,18]

No evidence of dimerization to the furoxan could be detected in any of these reactions. Indeed, the nitrile oxide **10**, generated in situ without the presence of a dipolarophile, completely resisted dimerization. Even under forcing conditions of heat or extended reaction periods, the nitrile oxide started to break down hydrolytically rather than dimerize, with benzotriazole being the only isolatable product.

The flexibility of using benzotriazole as a steric auxiliary was demonstrated by the ease of removal under mild reducing conditions. Hence, when the bis(benzotriazol-1-yl)methyl substituted isoxazole **12g** was treated with sodium borohydride in ethanol, the benzotriazole auxiliaries were cleanly removed to give the corresponding methyl isoxazole **13** (Scheme 4), which was identical to that previously



12g **13**

Scheme 4.

reported.[19,20] By comparison, acetonitrile oxide itself has a short half life, and the precursor acetohydroximinoyl chloride is unstable.[21] It is expected that such mild removal of benzotriazole would also proceed readily with other substituted isoxazolines and isoxazoles. As benzotriazole substituents can also be displaced by a variety of nucleophiles (such as amines, Grignard reagents, thiolate anions),[22] the use of benzotriazole-substituted acetonitrile oxide in dipolar cycloaddition reactions represents a highly versatile synthesis of substituted 3-methyl isoxazoles and Δ^2-isoxazolines.

Conclusions

Bis(benzotriazol-1-yl)acetonitrile oxide **10** is a convenient synthon for acetonitrile oxide derivatives. It undergoes nitrile oxide cycloaddition reactions without the common concomitant problem of dimerization to furoxans. It will be possible to elaborate the resulting bisbenzotriazolmethyl-isoxazoles or -Δ^2-isoxazolines to give a flexible range of isoxazole or Δ^2-isoxazoline derivatives.

Experimental

Melting points were measured (uncorrected) on an Electrothermal apparatus, and microanalyses were performed by the Campbell Microanalytical Laboratory, University of Otago. Infrared spectra were recorded on a Perkin Elmer 783 instrument. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or a Bruker WM 200 instrument with $SiMe_4$ as the internal standard. ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer at 50.3 MHz. Low-resolution mass spectra were obtained with a Finnigan 3300 instrument, or a JEOL JMS-DX 303 instrument, as chemical ionization spectra with methane as the reagent gas, or using APCI techniques on a Micromass LC/MS platform. High-resolution mass spectra were recorded on a Micron-SS 77OF instrument or as electrospray (ES) on a Bruker Bio Apex FT mass spectrometer.

Column chromatography was carried out using silica gel 60 (Merck, Art. 9385, 230-400#). Analytical thin-layer chromatography (TLC) was performed on aluminium sheets precoated with silica 60 (Merck, Art 5567). Spots were visualized with a UV lamp, iodine vapour, bromocresol green solution, or with 2,4-dinitrophenylhydrazine.

1,1-Bis(benzotriazol-1-yl)methane ***6***

1-(Chloromethyl)benzotriazole **5** (20.10 g, 0.12 mol) was mixed with benzotriazole (28.40 g, 0.24 mol) in toluene (200 mL) and the stirred mixture was heated to reflux for 24 h during which time a white precipitate formed. The reaction mixture was cooled and the precipitate was collected. The solid was triturated with hot water and recrystallized from ethanol to yield 1,1-bis(benzotriazol-1-yl)methane **6** (20.7 g, 69%), mp 191–193°C (lit.[9] 192–193°C) as a white powder. δ_H 7.33–7.56 (m, 4H, ArH), 7.42 (s, 2H, Bt_2CH_2), 7.86 (d, 2H, *J* 8, ArH), 8.03 (d, 2H, *J* 8, ArH). δ_C 146.3, 132.1, 128.7, 124.8, 120.1, 109.8, 58.0. *m/z* 251 (10%, $MH^{+\bullet}$), 132 (100), 118 (100).

2,2-Bis(benzotriazol-1-yl)-1,1-dihydroxyethane **7**

A solution of the bisbenzotriazolemethane **6** (6.25 g, 25 mmol) in anhydrous tetrahydrofuran (200 mL) was stirred under argon and cooled to –70°C (dry ice/ethanol). *n*-Butyllithium in hexane (1.6 M, 17.5 mL, 28 mmol) was added dropwise. During the addition, a dark coloured solution developed. The mixture was stirred at −70°C for 1.5 h after which time methyl formate (1.64 g, 27 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise. The mixture was stirred at −70°C for 2 h, allowed to warm to room temperature, and then stirred for a further 16 h. The reaction mixture was treated with saturated aqueous ammonium chloride (50 mL) and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a white glassy solid (6.5 g). This material was subjected to flash column chromatography (silica, 1/4 dichloromethane/ethyl acetate elution) to afford a waxy solid. Recrystallization (acetone/hexane) afforded the *dihydroxyethane* **7** (2.52 g, 34%) as a white powder, mp 143.5–147.5°C. (Found: $[M + Na]^+$ 319.091. $C_{14}H_{12}N_6O_2Na$ requires $[M + Na]^+$ 319.092.) ν_{max} (KBr)/cm^{-1} 3600–2450br, 1750–1710br, 1625, 1600, 1505, 1460, 1320, 1300, 1250, 1180s, 1150–1080, 960, 850, 840, 800, 790, 760. δ_H 6.70 (q, 1H, *J* 7, $Bt_2CHCH(OH)_2$), 7.10 (d, 2H, *J* 6, $Bt_2CHCH(OH)_2$, exchangeable with D_2O), 7.45 (t, 2H, *J* 7, ArH), 7.65 (t, 2H, *J* 7, ArH), 7.75 (d, 1H, *J* 7.5, $Bt_2CHCH(OH)_2$), 8.12 (d, 2H, *J* 8, ArH), 8.25 (d, 2H, *J* 8, ArH). δ_C 145.1, 132.7, 128.5, 124.8, 119.5, 111.0, 88.0, 72.9. *m/z* 279 (18%, $[MH - H_2O]^+$), 249 (76), 221 (30), 160 (100), 132 (55), 120 (20).

2,2-Bis(benzotriazol-1-yl)-1-(hydroxyimino)ethane ***8***

The dihydroxyethane **7** (6.16 g, 19 mmol) was mixed with hydroxylamine hydrochloride (2.64 g, 38 mmol) and sodium acetate trihydrate (5.17 g, 38 mmol) in water (75 mL). Ethanol (90 mL) was added to the stirred suspension. The mixture was heated to 75°C for 5 h after which time the mixture was concentrated under reduced pressure. The resulting solid was partitioned between dichloromethane (100 mL) and water (100 mL), and the dichloromethane was separated and retained. The aqueous layer was extracted with dichloromethane (2 × 70 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a glassy solid. Trituration with hot hexane yielded the *oxime* **8** as an unseparated mixture of *E*- and *Z*-isomers (5.17 g, 93%) as a white powder, mp 89–93°C. (Found: C 57.4, H 3.5, N 33.3%; $M^{+\bullet}$ 293.102. $C_{14}H_{11}N_7O$ requires C 57.3, H 3.8, N 33.4%; $M^{+\bullet}$ 293.103.) δ_H 7.32–7.55 (m, 4H, ArH), 7.89 (d, 2H, *J* 8, ArH), 7.93–8.00 (m, 2H, ArH), 8.38 (d, 1H, *J* 2, $Bt_2CHCH{=}NOH$), 8.76 (d, 0.05H, *J* 2, $Bt_2CHCH{=}NOH$, isomer 1) and 8.88 (d, 0.95H, *J* 2, $Bt_2CHCH{=}NOH$, isomer 2). δ_C 145.8, 145.7, 141.6, 139.7, 131.5, 128.9, 125.1, 120.0, 110.1, 110.0, 69.3, 63.3. *m/z* 293 (7%, $M^{+\bullet}$), 175 (100), 120 (52), 104 (37), 93 (35).

2,2-Bis(benzotriazol-1-yl)-1-chloro-1-(hydroxyimino)-ethane ***9***

A stirred solution of the oxime **8** (1.46 g, 5 mmol) in dimethylformamide (6 mL) was maintained under argon. *N*-Chlorosuccinimide (136 mg, 0.75 mmol) was added followed by HCl gas (5 mL) by syringe to catalyze the reaction. The HCl gas was obtained from the head-space of a reagent bottle of concentrated hydrochloric acid. The reaction mixture was warmed to 35°C and *N*-chlorosuccinimide (770 mg, 4.25 mmol) was added as several portions, the reaction temperature being maintained at 35°C during the addition. The reaction mixture was allowed to cool to room temperature where it was maintained for 16 h and then added to ice/water (80 mL). An off-white precipitate formed which was collected and washed with water. The solid was triturated with water to yield the *title compound* **9** as a white powder (1.64 g, 100%). An analytical sample was crystallized from ethyl acetate/hexane to yield colourless crystals, mp 127.5–128.5°C (dec.). (Found: C 51.6, H 3.0, Cl 10.7, N 29.7%. $C_{14}H_{10}ClN_7O$ requires C 51.3, H 3.1, Cl 10.8, N 29.9%.) δ_H 7.20 (t, 2H, *J* 6, ArH), 7.34 (t, 2H, *J* 6, ArH), 7.65 (d, 2H, *J* 10, ArH), 7.86 (d, 2H, *J* 10, ArH), 8.61 (s, 1H, $Bt_2CHC(Cl){=}NOH$), 12.35 (s, 1H, NOH). δ_C 146.0, 132.6, 130.5, 129.3, 125.5, 120.2, 111.1, 72.6.

Cycloaddition Reactions Between Alkenes ***a–f*** *and Bis(benzotriazol-1-yl)acetonitrile Oxide* ***10****, Generated In Situ from 2,2-Bis(benzotriazol-1-yl)-1-chloro-1-(hydroxyimino)ethane* ***9***

To a solution of 2,2-bis(benzotriazol-1-yl)-1-chloro-1-(hydroxyimino)-ethane **9** (328 mg, 1 mmol) in ethyl acetate (10 mL) was added the appropriate alkene **11a**–**11f** (1.1 mmol). Potassium bicarbonate (1 g) was added followed by water (2–3 drops) and the mixture was stirred at room temperature for 16 h. The mixture was filtered to remove insoluble solids. The solids were washed with dichloromethane and the combined washings and ethyl acetate filtrate were concentrated under reduced pressure. The residue was partitioned between dichloromethane (40 mL) and water (40 mL), and the dichloromethane was separated and retained. The aqueous layer was extracted with dichloromethane (2 × 30 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield the crude product.

3-[Bis(benzotriazol-1-yl)methyl]-Δ^2*-isoxazolin-5-ylmethyl Acetate* ***12a***

The crude material was purified by column chromatography (silica, dichloromethane/ethyl acetate, 9/1) to yield the Δ^2*-isoxazoline acetate* **12a** as a white glassy solid (300 mg, 77%). (Found: C 58.2, H 4.3, N 25.2%; $MH^{+\bullet}$ 392.148. $C_{19}H_{17}N_7O_3$ requires C 58.3, H 4.4, N 25.1%; $MH^{+\bullet}$ 392.147.) δ_H 2.09 (s, 3H, $COCH_3$), 3.28 (dd, 1H, *J* 18, 7, isox. H4), 3.54 (dd, 1H, *J* 18, 10, isox. H4), 4.21–4.39 (m, 2H, CH_2OCOMe), 5.08–5.20 (m, 1H, isox. H5), 7.32–7.52 (m, 4H, ArH), 7.58 (d, 2H, *J* 10, ArH), 8.03 (d, 2H, *J* 10, ArH), 8.60 (s, 1H, Bt_2CH). δ_C 170.8, 151.7, 146.3, 131.9, 129.1, 125.2, 120.4, 110.1, 80.3, 67.8, 64.5, 37.7, 20.7. *m/z* 392 (10%, $MH^{+\bullet}$), 364 (12), 336 (25), 273 (100), 247 (93), 185 (87), 148 (81), 120 (53).

Methyl 3-[Bis(benzotriazol-1-yl)methyl]-5-methyl-Δ^2*-isoxazoline-5-carboxylate* ***12b***

The crude material was purified by column chromatography (silica, dichloromethane/ethyl acetate, 9/1) to yield the Δ^2*-isoxazoline carboxylate* **12b** as a white glassy solid (271 mg, 70%). (Found: C 58.5, H 4.4, N 25.2%; $[M + Na]^+$ 414.129. $C_{19}H_{17}N_7O_3$ requires C 58.3, H 4.4, N 25.1%; $[M + Na]^+$ 414.129.) δ_H 1.76 (s, 3H, isox. 5-CH_3), 3.38 (d, 1H, *J* 17, isox. H4), 3.79 (s, 3H, OCH_3), 3.85 (d, 1H, *J* 17, isox. H4), 7.30–7.51 (m, 4H, ArH), 7.59–7.64 (m, 2H, ArH), 8.00–8.06 (m, 2H, ArH), 8.57 (s, 1H, Bt_2CH). δ_C 171.7, 151.9, 146.3, 132.0, 129.2, 125.3, 120.6, 110.2, 88.3, 67.9, 53.5, 45.4, 23.6. *m/z* 414 (32%, $[M + Na]^+$), 392 (26%, $M^{+\bullet}$), 273 (100), 139 (55), 120 (45).

Ethyl 3-[Bis(benzotriazol-1-yl)methyl]-5-methyl-Δ^2*-isoxazoline-4-carboxylate* ***12c***

The crude material was purified by column chromatography (silica, dichloromethane/ethyl acetate, 9/1) to yield the Δ^2*-isoxazoline carboxylate* **12c** as a glassy solid (247 mg, 61%). (Found: C 59.5, H 4.6, N 24.3%; $[M + Na]^+$ 428.145. $C_{20}H_{19}N_7O_3$ requires C 59.3, H 4.7, N 24.2%; $[M + Na]^+$ 428.145.) δ_H 1.09 (t, 3H, *J* 8, OCH_2CH_3), 1.64 (d, 3H, *J* 6.5, isox. 5-CH_3), 3.98–4.65 (m, 2H, OCH_2CH_3), 4.20 (d, 1H, *J* 8, isox. H4), 5.14–5.28 (m, 1H, isox. H5), 7.26–7.63 (m, 4H, ArH), 7.73–7.78 (m, 2H, ArH), 7.95–8.06 (m, 2H, ArH), 8.93 (s, 1H, Bt_2CH). δ_C 171.7, 148.8, 146.5, 132.3, 129.3, 125.4, 120.7, 110.7, 82.8, 67.7, 62.7, 59.4, 20.5, 14.0. *m/z* 405 (100%, $M^{+\bullet}$), 348 (44), 332 (30), 304 (70), 302 (95), 274 (30).

Methyl 3-[Bis(benzotriazol-1-yl)methyl]-5-phenyl-Δ^2*-isoxazoline-4-carboxylate* ***12d***

The crude material was purified by column chromatography (silica, dichloromethane/ethyl acetate, 9/1) to give a less polar fraction of unreacted methyl cinnamate and a more polar fraction of the Δ^2*-isoxazoline carboxylate* **12d** as a glassy solid (190 mg, 42%). (Found: C 63.4, H 4.1, N 21.2%; $[M + Na]^+$ 476.144. $C_{24}H_{19}N_7O_3$ requires C 63.6, H 4.2, N 21.6%; $[M + Na]^+$ 476.145.) δ_H 3.65 (s, 3H, OCH_3), 4.64 (d, 1H, *J* 10, isox. H4), 6.12 (d, 1H, isox. *J* 10, H5), 7.3–7.6 (m, 9H, ArH), 7.81 (t, 2H, *J* 8, ArH), 8.02 (d, 1H, *J* 8, ArH), 8.03 (d, 1H, *J* 8, ArH),

8.95 (s, 1H, Bt_2CH). δ_C 167.5, 148.1, 146.7, 138.1, 132.3, 131.7, 129.3, 129.2, 128.6, 125.3, 120.1, 111.9, 87.3, 67.9, 60.6, 53.5. *m/z* 452 (68%, $M^{+\bullet}$), 274 (26), 118 (100).

3-[Bis(benzotriazol-1-yl)methyl]-5,5-diphenyl-Δ^2-isoxazoline ***12e***

The crude material was purified by column chromatography (silica, dichloromethane/ethyl acetate, 9/1) to give the *Δ^2-isoxazoline* **12e** as a white powder (122 mg, 26%), mp 205–207.5°C. (Found: C 71.2, H 4.2, N 20.7%; $[M + Na]^+$ 494.170. $C_{28}H_{21}N_7O$ requires C 71.3, H 4.5, N 20.8%; $[M + Na]^+$ 494.171.) ν_{max} (KBr)/cm^{-1} 3441br, 3066, 1613, 1593, 1493, 1450, 1359, 1291, 1279, 1158, 1109, 1004, 928, 915. δ_H 4.05 (s, 2H, isox. H4), 7.30–7.50 (m, 14H, ArH), 7.65 (d, 2H, *J* 8, ArH), 8.00 (d, 2H, *J* 8, ArH), 8.57 (s, 1H, Bt_2CH). δ_C 151.4, 146.2, 142.8, 131.8, 128.9 (two overlapping signals), 128.1, 126.0, 125.0, 120.3, 110.3, 94.5, 67.9, 48.5. *m/z* 494 (32%, $[M + Na]^+$), 353 (45).

3-[Bis(benzotriazol-1-yl)methyl]-1,2-oxazaspiro[4,5]-dec-2-ene ***12f***

The crude material was purified by column chromatography (silica gel, dichloromethane/ethyl acetate, 9/1) to yield the *oxazaspiro[4,5]-dec-2-ene* **12f** as a white powder (196 mg, 51%), mp 180–182°C. (Found: C 65.4, H 5.3, N 25.5%; $[M + Na]^+$ 410.170. $C_{21}H_{21}N_7O$ requires C 65.1, H 5.5, N 25.3%; $[M + Na]^+$ 410.171.) δ_H 1.32–1.60 (br m, 6H, cyclohexyl), 1.60–2.02 (m, 4H, cyclohexyl), 3.09 (s, 2H, isox. H4), 7.32–7.49 (m, 4H, ArH), 7.63 (d, 2H, *J* 8, ArH), 8.03 (d, 2H, *J* 8, ArH), 8.51 (s, 1H, Bt_2CH). δ_C 150.9, 146.2, 131.9, 128.9, 125.0, 120.2, 110.3, 90.2, 68.2, 45.3, 36.2, 24.8, 23.2. *m/z* 410 (100%, $[M + Na]^+$).

3-[Bis(benzotriazol-1-yl)methyl]-5-phenylisoxazole ***12g***

To a solution of the chlorooxime **9** (327 mg, 1 mmol) in ethyl acetate (10 mL) containing phenylacetylene (150 mg, 1.5 mmol) was added potassium bicarbonate (1 g, 10 mmol) followed by water (2–3 drops). The mixture was stirred at room temperature for 16 h and then filtered, the filtrate was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a brown viscous oil (400 mg). The crude material was purified by column chromatography (silica, dichloromethane/ethyl acetate, 9/1) to give a light-brown semi-solid, which recrystallized from acetone/hexane to give the *phenylisoxazole* **12g** as fluffy needles (190 mg, 48%), mp 146–148°C. (Found: C 67.4, H 3.6, N 24.8%; $[M + Na]^+$ 416.124. $C_{22}H_{15}N_7O$ requires C 67.2, H 3.8, N 24.9%; $[M + Na]^+$ 416.124.) δ_H 6.86 (s, 1H, isox. H4), 7.36–7.55 (m, 7H, ArH), 7.78–7.82 (m, 4H, ArH), 8.06 (d, 2H, *J* 8, ArH), 9.01 (s, 1H, Bt_2CH). δ_C 172.0, 157.9, 146.4, 132.0, 131.0, 129.2, 129.1, 126.5, 126.1, 125.1, 120.5, 110.4, 99.9, 66.8. *m/z* 393 (20%, $M^{+\bullet}$), 336 (100), 144 (55), 118 (100).

3-Methyl-5-phenyl Isoxazole ***13***

A mixture of the phenylisoxazole **12g** (394 mg, 1 mmol) and $NaBH_4$ (160 mg, 4 mmol) was stirred in anhydrous ethanol (15 mL) at 25°C overnight. The reaction mixture was quenched with water and extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography with hexane/EtOAc (2/1) as an eluent to give the *title compound* as a white solid, mp 65°C (lit.[20] 65°C). δ_H 7.72 (d, 2H, ArH), 7.41 (m, 3H, ArH), 6.46 (s, 1H, CH), 2.35 (s, 3H, CH_3). δ_C 157.9, 148.0, 136.4, 129.0, 128.0, 126.3, 98.4, 15.3.

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