LITHIATION OF *N*-SUBSTITUTED BENZOTRIAZOLES

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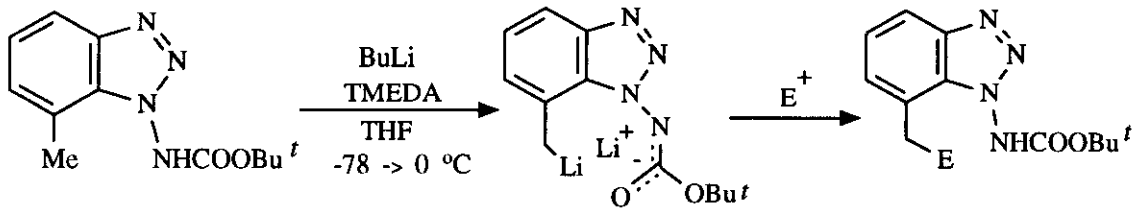
Abstract - The behavior on lithiation of seventeen *N*-substituted benzotriazoles was investigated. In seven cases, the *N*-substituent was either removed or no lithiation occurred, in six instances lithiation occurred in the *N*-substitutent and in the four remaining compounds lithiation occurred at the ring 7-position, albeit in low yield.

Heteroatom-assisted lithiation has become recognized as an increasingly important tool in the elaboration of carbocyclic-aromatic and heteroaromatic systems, and regioselective *ortho*-lithiation at an sp^2-hybridized ring carbon directed by a heteroatom containing substituent has been used for the functionalization of a great variety of compounds.[1] The common directing groups include nitrogen-containing (amino, amido, hydrazono, and heterocycles such as 2-oxazolinyl, 2-pyridinyl, 2-imidazolinyl, 2-pyrazolyl), oxygen-containing (alkoxide, ether, acetal, and ketal) and sulfur-containing (sulfide, sulfone, sulfonamide, and thioheterocycles) substituents.[1] Individual directing groups have different effects, which mainly depend on their electron-withdrawing ability and coordinative properties.

The generation and reaction of sp^2 carbanionic centers in the vicinity of heterocyclic nitrogen atoms was reviewed recently.[2] Direct deprotonation without the assistance of a facilitating group is often difficult to achieve due to charge repulsion of the heteroatomic lone pair, low acidity of the hydrogen to be abstracted, and undesired side reactions at other reactive sites in the molecule. Repulsion between the lone pair of electrons and the negative charge can significantly reduce thermodynamic stability. However, precoordination of the active lithiating agent to an *ortho*-directing group[3,4] bestows on such lithiations the advantages of an intramolecular reaction.[5-8] Formation of an organo-lithium product which is stabilized by the intramolecular interaction between lithium and the directing group also facilitates *ortho*-lithiation.

Although numerous investigations regarding the lithiation of 5-membered, 6-membered and polycyclic heterocycles, containing nitrogen, oxygen, and sulfur, have been carried out in recent years,[2] there have been no reports concerning lithiation of the benzotriazole ring. Recent work in our group has demonstrated that *N*-carboxylate[9,10] and other *N*-substituents, such as dialkylaminomethyl[11-13] and oxidomethyl[14,15] moieties, could simultaneously serve as efficient protection and activation groups for the *ortho*-lithiation of aromatic and heteroaromatic systems. During this same period, benzotriazole auxiliary methodology has blossomed.[16] As the preparations of *C*-substituted benzotriazoles are not trivial, we have now investigated the heteroatom-assisted lithiation of benzotriazole, and found that the reactivity and selectivity critically depend upon the presence of an *O*- or *N*-containing directing group in the substrate.

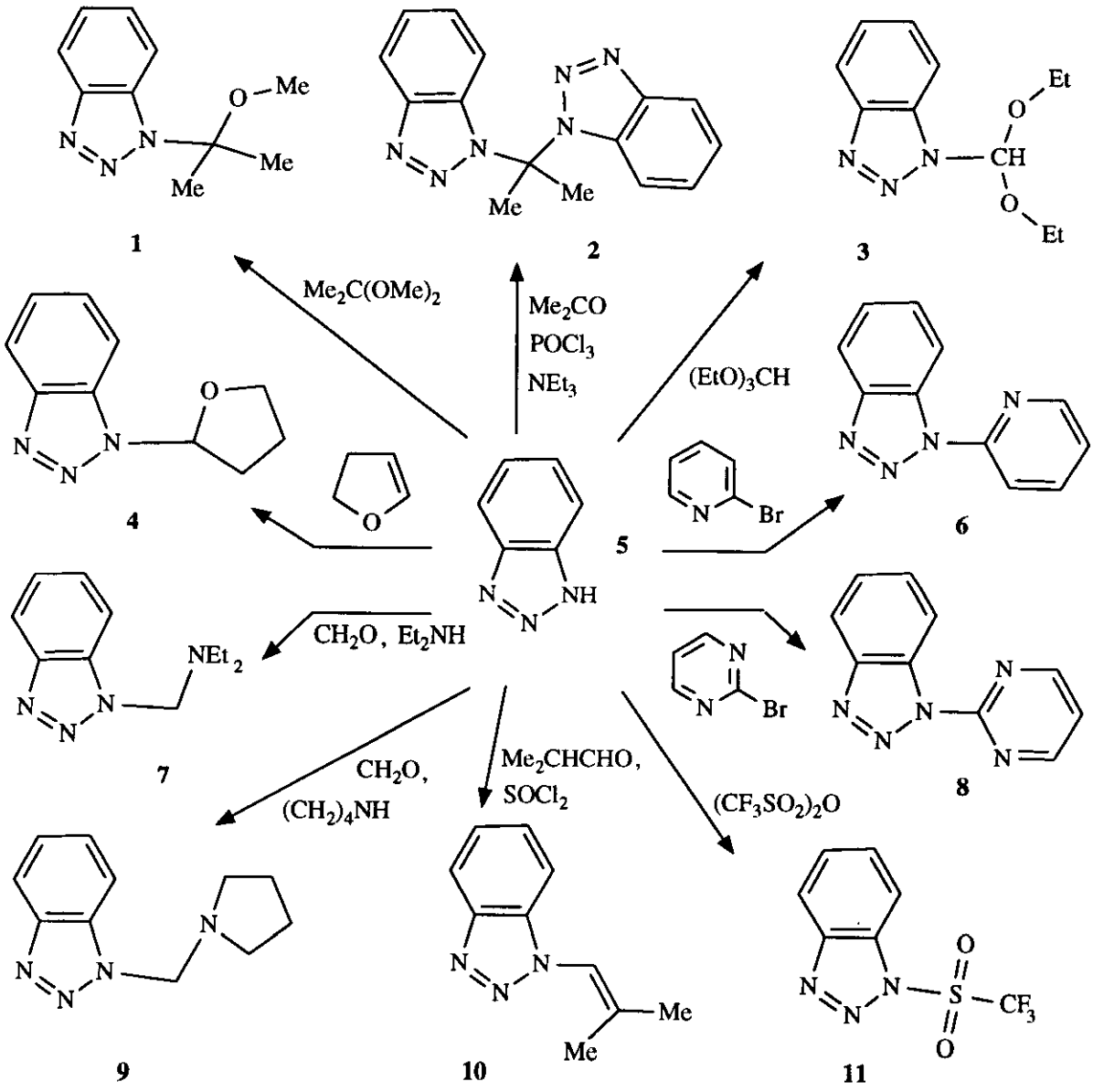


Scheme 1

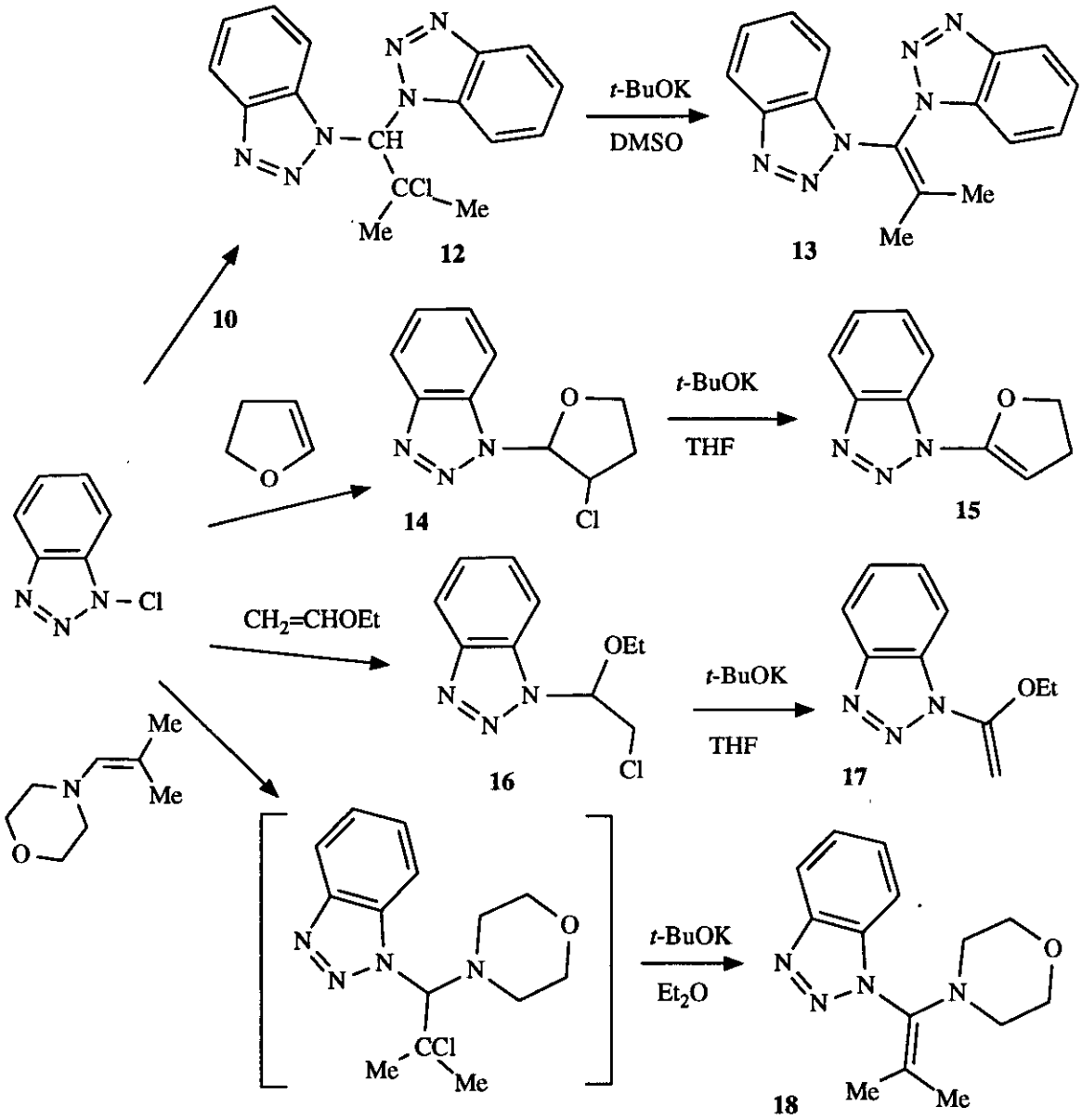
The benzo ring in benzotriazole is strongly deactivated towards electrophilic substitution by the electron-withdrawing nitrogen atoms and consequently very few examples of the elaboration of the benzo ring have been reported. Electrophilic substitutions such as alkylation and acetylation, which occur easily in many heterocyclic compounds, are rarely observed, although chlorination of benzotriazole and 2-methylbenzotriazole by aquaregia results in the formation of 4,5,6,7-tetrachlorobenzotriazole[17] (87%). In contrast, *N*-alkylations and *N*-acylations of benzotriazoles are facile.[18,19] Moreover, 1-substituted benzotriazoles undergo further alkylation with alkyl sulfates or halides to yield 1,3-disubstituted benzotriazolium cations[20,21] demonstrating that the benzo ring is inactive towards alkylation. The rearrangement of 5-hydroxy-1-hydroxymethylbenzotriazole into 5-hydroxy-4-hydroxymethylbenzotriazole is attributed to activation by the hydroxy group.[22] Recently, Birkett *et al.*[23] reported the facile deprotonation of the methyl group in 1-amino-*N*-*tert*-butoxycarbonyl-7-methylbenzotriazole as shown in Scheme 1. However, no mention was made regarding the lithiation of a benzotriazole ring carbon atom. Evidently, such benzyl-like deprotonation proceeds more readily.

RESULTS AND DISCUSSION

(i) **Preparation of the benzotriazoles (1-4, 6-9, 11, 13, 15, 17-19, 21a, 26, 28) studied for lithiation behavior.** Most of the compounds examined were easily prepared in one step reactions from unsubstituted benzotriazole (Scheme 2). Generally, the syntheses involved benzotriazole addition to available carbonyl compounds or suitable derivatives. Thus, compound *(1)* was prepared by refluxing benzotriazole with an



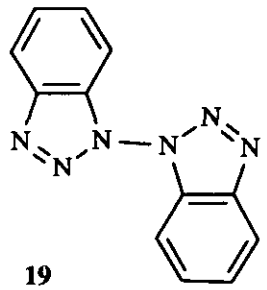
Scheme 2. Preparation of some starting materials.



Scheme 3. Preparation of starting materials (continued).

excess of 2,2-dimethoxypropane.[24] The same reaction, carried out with an excess of benzotriazole, led to the disubstituted derivative (**2**); although, it was easier to prepare (**2**) from acetone (see Experimental). The reaction with triethyl orthoformate afforded *N*-substituted benzotriazole (**3**) bearing two ethoxyl groups as potential ligands for coordination in the following lithiation. Electrophilic addition of benzotriazole to the double bond of 2,3-dihydrofuran led to the preparation of **4**.[25] Mannich reactions of benzotriazole afforded aminals (**7**)[26] and (**9**).[26] Compounds (**6**)[27] and (**8**), previously unknown, were prepared by nucleophilic

substitution of the 2-bromo derivatives of pyridine and pyrimidine, respectively. Alkene (**10**), a precursor of enamine (**13**), was prepared in a one-pot reaction involving three steps: 1) benzotriazole addition to isobutyraldehyde, 2) chlorination of the intermediate and 3) elimination of HCl. The trifluoromethanesulfonyl group was introduced to benzotriazole by reaction with the corresponding anhydride to give compound (**11**). Somewhat longer sequences were usually required for the introduction of alkenyl substituents to benzotriazole and typically proceeded *via* the addition of 1-chlorobenzotriazole to various alkenes followed by the elimination of hydrogen chloride (Scheme 3). Compounds (**13**, **15**, **17** and **18**) were prepared in this manner from enamines or enol ethers. Bisbenzotriazole (**19**) was synthesized by diazotization of azoaniline according to the literature procedure.[28] Our attempts to prepare **19** from benzotriazole or 1-chlorobenzotriazole were unsuccessful. The preparation of starting materials (**21a**, **26** and **28**), themselves the products of lithiation, will be discussed in the following section.



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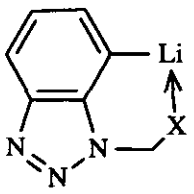

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(ii) **Lithiation.** We now examine the attempted lithiation of the seventeen diversely *N*-substituted benzotriazoles prepared as described above. In each case the compound was treated with butyllithium at -78 °C followed by an electrophile. Five different results were noted:

(a) In the case of (1-methoxy-1-methylethyl)benzotriazole (**1**), the starting material was recovered unchanged.

(b) In six cases (compounds **3**, **4**, **7**, **9**, **11** and **19**) the *N*-substituent was removed during the lithiation or work-up, and benzotriazole was recovered.

(c) In five *N*-substituted benzotriazoles (**6**, **13**, **15**, **17** and **21a**) lithiation took place in the *N*-substituent, with subsequent replacement by the electrophile (see Schemes 4, 5 and 6).

(d) In one instance (compound **8**) the *N*-substituent underwent nucleophilic substitution by the lithiating agent (Scheme 4).

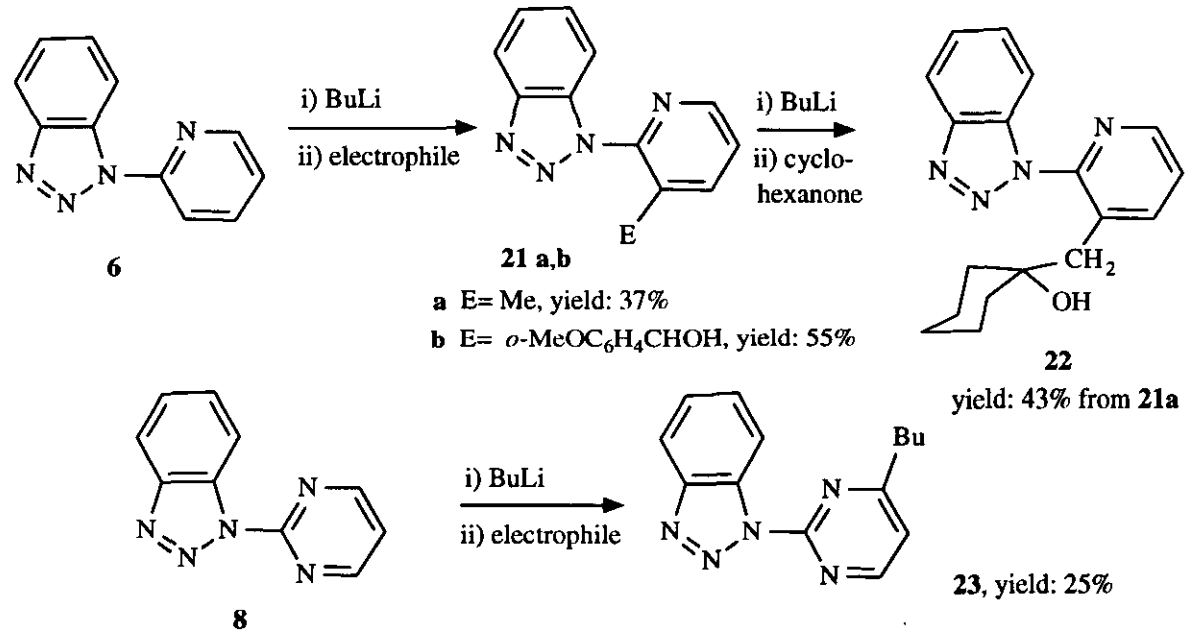
(e) In the case of the four compounds (**2**, **18**, **26** and **28**), the desired reaction indeed occurred, and electrophiles were introduced into the 7-position of the benzotriazole ring (see Schemes 5 and 6).

We now turn to the effects of the various *N*-substituents and attempt to rationalize the results. As described previously, *N*-carboxylate is an efficient directing group for the facilitation of β-lithiation in some heterocyclic systems such as indole[9] and phenothiazine,[10] but it failed as a simultaneous protecting and coordinating group for others,[2] including benzotriazole. Our objective, then, was to find suitable alternative ligands. According to well-established rules, the ability of substituents to direct lithiation is based both on their electron-withdrawing and coordinative properties which must be combined to achieve the best results.[1] In our case, electron-withdrawing substituents introduced into the benzotriazole 1-position seemed unlikely to further increase the acidity of the aromatic protons. It is probable that the inductive effect would be small compared to that already existing and induced by the nitrogen π-system. Indeed, electron-withdrawing substituents could cause instability towards nucleophilic attack by the lithiating agent. This is likely to be the reason for the failure of lithiation in the case of 1-trifluoromethanesulfonylbenzotriazole (**11**). Therefore, in our strategy we focussed on the coordinative properties of the director substituent. The substituents we chose for examination were attached so that the ligand heteroatom could form a six-membered ring transition state (**20**). Another factor to be considered concerns the possibility of competitive lithiation at the substituent. We have recently found that benzotriazole itself can serve as a good directing group for the β-lithiation of a vinyl ether (**17**).[29] The same lithiation result was observed for dihydrofuran (**15**) (Scheme 6). Consequently, the number of appropriate substituents is restricted by excluding those containing *beta*-protons relative to the benzotriazole ring.

Compounds (**3**, **4**, **7** and **9**) contained promising nitrogen and oxygen directing groups, but upon treatment with BuLi reverted to benzotriazole. Possibly, deprotonation took place preferentially in the methine (methylene) group of the substituent, and the anion thus formed was not sufficiently stable to undergo further lithiation at the 7-position. Compound (**1**) contains no α-protons in the substituent, and is thus stable to attack by base. Nevertheless, no lithiation occurred in this case as indicated by recovery of the starting material after treatment with BuLi followed by cyclohexanone.

Pyridine nitrogen, a common director, was expected to facilitate the lithiation of 2-pyridinylbenzotriazole (**6**). Treatment of **6** with BuLi in THF at -78 °C, followed by quenching with electrophiles, gave the pyridine ring lithiated products (**21a,b**) rather than the desired benzotriazole ring lithiated product (Scheme 4). Evidently, the proton in the pyridine ring 3-position of **6** is more acidic than that of the 7-position in benzotriazole. The

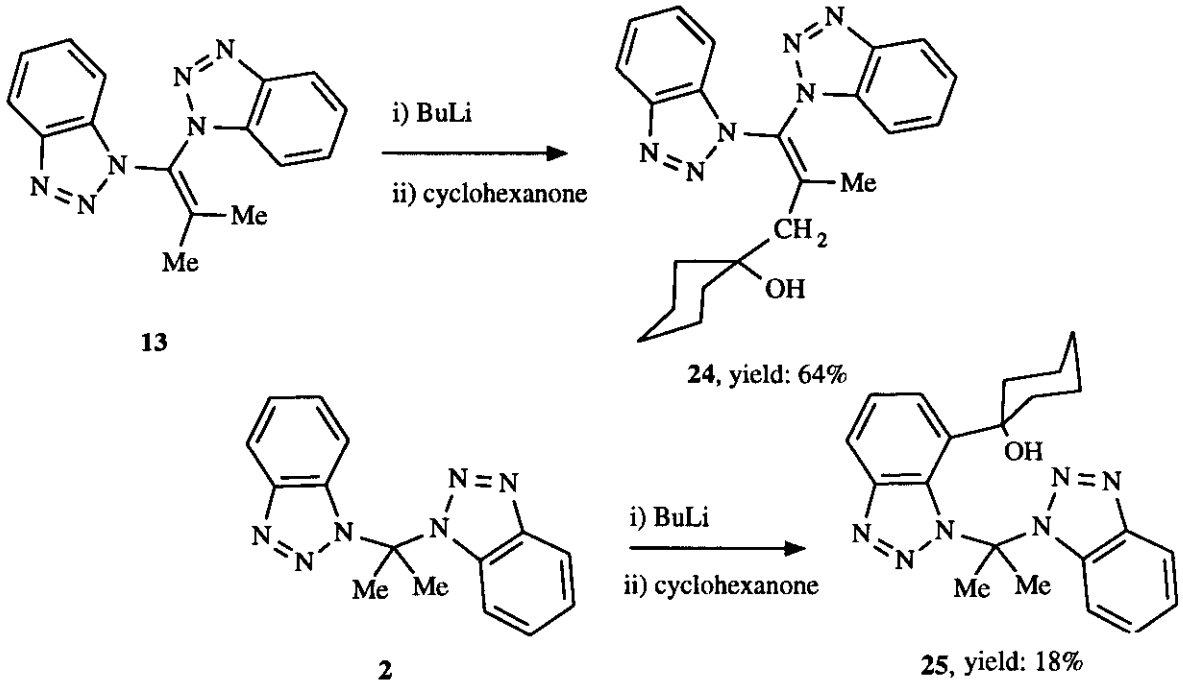
alternative five-membered ring intermediate was thus favored in the reaction, demonstrating the directing ability of the benzotriazole group. To avoid this undesired reaction, compound (**21a**), in which the pyridine ring 3-position is now blocked by a methyl substituent, was used as the substrate. However, treatment of **21a** with BuLi followed by quenching with cyclohexanone afforded the methyl lithiated product (**22**) in 43% yield. This indicates that either a benzylic-like proton in a pyridine ring is more acidic, or the anion formed in this case is more stable than that of the 7-position in the benzotriazole ring. In order to further investigate the behavior of such a bis-heterocyclic system, the second *ortho*-position of **6** was blocked by nitrogen, as represented by 2-pyrimidinylbenzotriazole (**8**) (Scheme 4). Unexpectedly, when **8** was treated with BuLi, the proton in the 4-position of the pyrimidine ring was displaced by the butyl group of the lithiating agent, evidently *via* a nucleophilic addition mechanism, to give compound (**23**) as the major product (Scheme 4). No evidence of benzotriazole ring lithiation was detected.



Scheme 4. Lithiation of pyridine and pyrimidine substituted benzotriazoles.

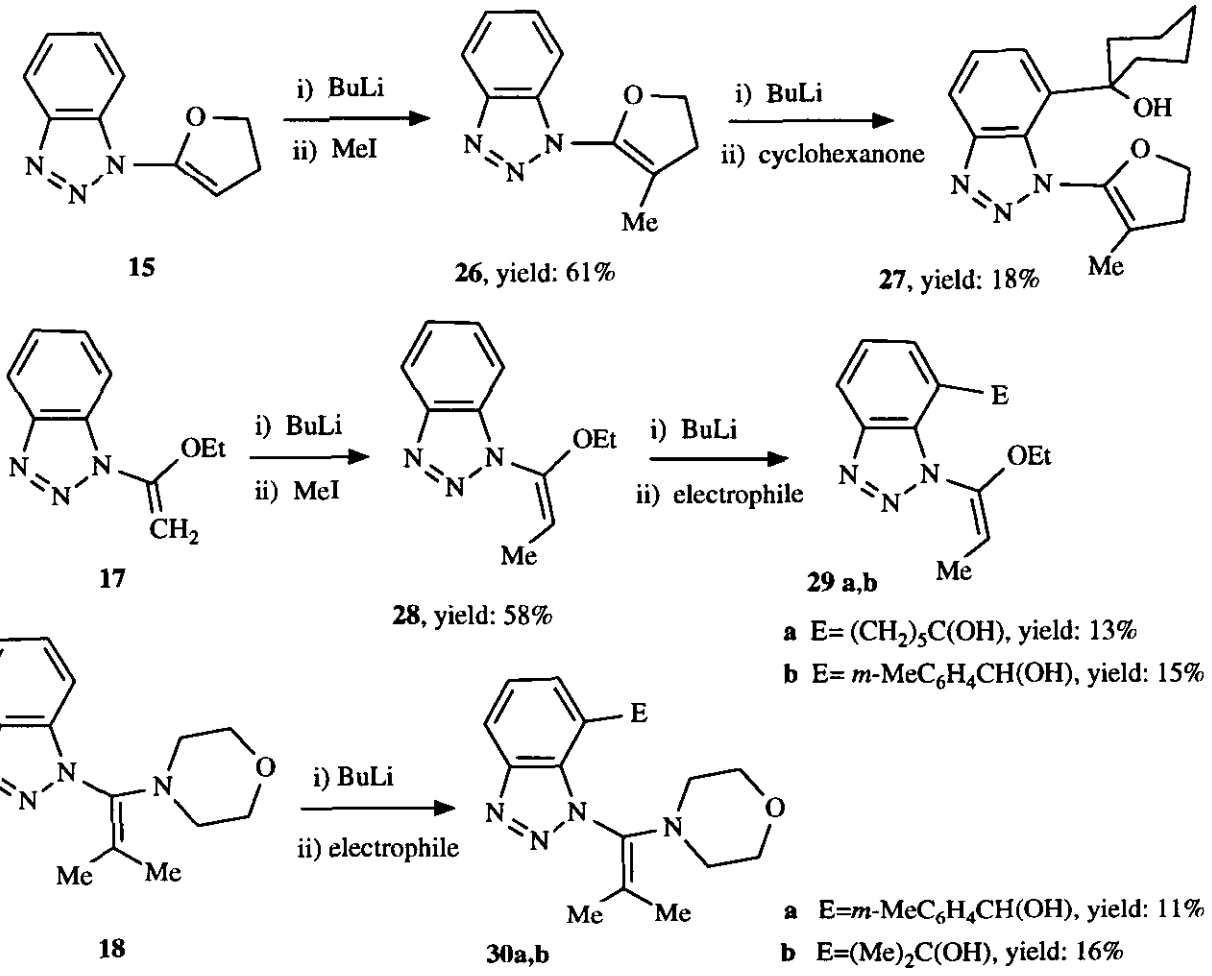
We attempted to exploit the favorable coordinating ability of one benzotriazole ring in the lithiation of another for substrates (**2**, **13**, and **19**). Treatment of **13** with BuLi in THF at -78 °C and subsequent reaction with cyclohexanone gave **24** in 64% yield (Scheme 5), indicating the more facile lithiation of allylic protons conjugated with two electron-withdrawing groups. The attempted lithiation of bisbenzotriazole (**19**) under the same conditions was unsuccessful and yielded benzotriazole. However, when the bis-benzotriazolyl substituted

alkane (**2**) was treated with BuLi at -78 °C, followed by trapping with cyclohexanone, the expected lithiated product (**25**) was obtained (Scheme 5), albeit in low yield (18%). Some starting material (**2**) was recovered from the reaction mixture, but no other products were isolated or detected by GCms.



Scheme 5. Lithiation of compounds containing two benzotriazole groups.

We have found that an ethoxyl group cross-conjugated with benzotriazole nitrogen also enables successful lithiation at the benzotriazole C-7. Thus, treatment of **28** with BuLi, followed by quenching with electrophiles, gave the expected *ortho*-lithiated products (**29**) (Scheme 6), albeit also in low yields (13%-15%). No products derived from lithiation of the olefin or the allylic carbon were detected and substantial starting compound (**28**) was recovered. The result obtained warrants attention in view of the fact that the methoxyl group of **1** did not facilitate *ortho*-lithiation. Cross conjugation of a ligand with the benzotriazole group through a double bond generally seems to favor stabilization of the transition state (**20**). Accordingly, the expected benzotriazole *ortho*-lithiation occurred when the morpholino (**18**) or dihydrofuran derivatives (**26**) were treated consecutively with BuLi and an electrophile (Scheme 6). The fact that the allylic protons of **18** are less acidic compared to those of **13**, reverses the lithiation selectivity. The use of alternative lithiating agents (*tert*-BuLi, LDA), extended reaction times, and higher temperatures all failed to improve the yields of the benzotriazole ring lithiated derivatives (**25**), (**27**), (**29**), and (**30**).



Scheme 6. Lithiation of benzotriazole facilitated by enoxy and enamino groups.

The structures of the products obtained upon quenching with electrophiles were confirmed by ^{1}H, and ^{13}C nmr spectra and elemental analyses, or in some cases by high resolution mass spectra. For derivatives (**25**, **27**, **29**, and **30**) the typical two doublet and two triplet peaks of the *N*-substituted starting compounds were replaced by two doublets and one triplet (sometimes a multiplet). In addition, the characteristic nmr signals of the electrophile attached to the benzotriazole ring could be clearly seen from both the ^{13}C and ^{1}H nmr spectra.

In summary, benzotriazole rings can undergo heteroatom-assisted lithiation in certain cases, although with difficulty and in low yield. The reactivity and selectivity critically depends upon the presence of oxygen or nitrogen containing directing groups.

EXPERIMENTAL

General. Melting points were determined on a Kofler hot stage apparatus without correction. ^{1}H and ^{13}C nmr spectra were recorded on a Varian 300 MHz spectrometer using TMS as the internal reference for ^{1}H spectra and the solvent $CDCl_3$ or DMSO-d_6 for ^{13}C spectra. Elemental analyses were performed on a Carlo Erba-1106 instrument, and high resolution mass spectra were measured on an AEL MS-30 mass spectrometer. Column chromatography was carried out on MCB silica gel (230-400 mesh).

Compounds **1**, oil, yield 71%, (lit.,[24] oil, yield 88%); **4**, oil, yield 98%, (lit.,[25] oil, yield 100%); **6**, mp 108-110 °C, yield 91%, (lit.,[27] mp 108-110 °C, yield 99%); **7**, bp 120-124 °C/0.65 mm Hg, yield 96%, (lit.,[26] bp 120-124 °C/0.65 mm Hg, yield 96%); **9**, mp 75-78 °C, yield 98%, (lit.,[26] mp 75-78 °C, yield 98%); **10**, mp 68-69 °C, yield 29%, (lit.,[30] mp 69-71 °C, yield 29%); **16**, mp 49-51 °C, yield 67%, (lit.,[29] mp 49-51 °C, yield 67%); **17**, oil, yield 92%, (lit.,[29] oil, yield 92%); **19**, mp 232 °C (decomp.), yield 84%, (lit.,[28] mp 233 °C (decomp.), yield 63%); **28**, oil, yield 58%, (lit.,[29] oil, yield 58%) were prepared according to the literature procedures.

2,2-Di(benzotriazol-1-yl)propane (2): A solution of benzotriazole (1.19 g, 10 mmol), acetone (0.73 ml, 10 mmol), $POCl_3$ (1.0 ml, 10 mmol), and triethylamine (2.8 ml, 20 mmol) in acetonitrile (5 ml) was stirred at room temperature for 48 h. The reaction mixture was poured into ice water (50 ml) and extracted with toluene (50 ml). The extract was subsequently washed with water (50 ml), 5% $NaHCO_3$ (50 ml), and water (50 ml) then dried over $MgSO_4$. The solvent was removed in vacuo, and the residue separated by column chromatography (silica gel, toluene/ethyl acetate 5:1) to give compound **2** (0.69 g, 50%) as the second fraction, mp 138 °C. ^{1}H Nmr ($CDCl_3$): δ 2.74 (s, 6H), 6.71 (dd, 2H, J=8.3, 1.0), 7.16 (ddd, 2H, J=8.3, 7.0, 1.1), 7.26 (ddd, 2H, J=8.3, 7.0, 1.0), 8.05 (d, 2H, J=8.3). ^{13}C Nmr($CDCl_3$): δ 27.3, 78.7, 109.9, 120.0, 124.2, 127.9, 130.1, 146.6. Anal. Calcd for $C_{15}H_{14}N_6$: C, 64.72; H 5.07; N, 30.21. Found: C, 64.60; H, 5.22; N, 29.79.

(Benzotriazol-1-yl)diethoxymethane (3): A solution of triethyl orthoformate (4.08 g, 27.5 mmol) and benzotriazole (3.30 g, 27.7 mmol) in 3M Company Performance Fluid 5070 (bp 80 °C, 30 ml) was refluxed for 10 h with a reverse Dean-Stark apparatus. Ethanol was collected in the Dean-Stark apparatus and the reaction mixture was transferred to a separatory funnel. Performance Fluid was separated to yield pure product (5.46 g, 90%) as an oil. ^{1}H Nmr ($CDCl_3$): δ 1.25 (t, 6H, J=7.1), 3.57 (m, 2H), 3.80 (m, 2H), 6.79 (s, 1H), 7.39 (dt, 1H, J=7.9, 1.2), 7.50 (dt, 1H, J=8.2, 1.3), 7.91 (d, 1H, J=8.1), 8.07 (d, 1H, J=8.2). ^{13}C Nmr ($CDCl_3$): δ 14.6, 63.0, 105.8, 112.2, 119.6, 124.4, 127.7, 130.8, 146.4. Anal. Calcd for $C_{11}H_{15}N_3O_2$: M^+=221.1164. Hrms found: M^+=221.1145.

2-(Benzotriazol-1-yl)pyrimidine (8): A mixture of 2-bromopyrimidine (4.77 g, 30 mmol) and benzotriazole (7.14 g, 60 mmol) was refluxed in dry toluene (50 ml) for 8 h. After cooling, ether (200 ml) was added and the reaction mixture treated with 10% NaOH (3 × 50 ml) and water (3 × 50 ml). The organic solvent was evaporated and the residue crystallized from ethyl acetate to yield 4.5 g of product (76%), mp 164-165 °C. ^{1}H Nmr ($CDCl_3$): δ 7.36 (t, 1H, J=4.9), 7.45 (m, 1H), 7.60 (m, 1H), 8.13 (dd, 1H, J=8.3, 0.7), 8.53 (d, 1H, J=8.3), 8.90 (d, 2H, J=4.9). ^{13}C Nmr ($CDCl_3$): δ 114.6, 119.4, 119.8, 125.0, 129.1, 131.4, 146.5, 156.0, 158.8. Anal. Calcd for $C_{10}H_7N_5$: C, 60.89; H, 3.58; N, 35.53. Found: C, 60.76; H, 3.53; N, 35.96.

1-Trifluoromethanesulfonylbenzotriazole (11): Trifluoromethanesulfonic anhydride (16.8 ml, 0.1 mol) was added dropwise to a stirred solution of benzotriazole (11.91 g, 0.1 mol) and dry pyridine (8.9 ml, 0.11 mol) in dry methylene chloride (200 ml) at -78 °C. The mixture was stirred at this temperature for 1 h and at room temperature for 12 h. Water (80 ml) was added, and the aqueous layer extracted with methylene chloride (3 × 50 ml). The combined organic phase was dried ($MgSO_4$), filtered through celite, and concentrated in vacuo to give 22.5 g of crude product. Purification by column chromatography afforded 21.86 g (87%) of pure product, mp 37 °C. ^{1}H Nmr ($CDCl_3$): δ 7.65 (symm m, 1H), 7.81 (symm m, 1H), 7.96 (d, 1H, J=8.4), 8.24 (d, 1H, J=8.3). ^{13}C Nmr ($CDCl_3$): δ 111.7, 119.2, 121.5, 127.2, 131.9, 131.9, 145.4. Anal. Calcd for $C_7H_4N_3O_2F_3S$: C, 33.47; H, 1.61; N, 16.73. Found: C, 33.46; H, 1.59; N, 16.65.

1,1-Bis(benzotriazol-1-yl)-2-chloro-2-methylpropane (12): A saturated solution of 1-chlorobenzotriazole (6.14 g, 40 mmol) in methylene chloride was added dropwise to a stirred solution of 1-(benzotriazol-1-yl)-2-methylpropene (**10**) (6.92 g, 40 mmol) and benzoyl peroxide (0.1 g) in methylene chloride (200 ml) at room temperature. The reaction mixture was stirred for 5 days. During that period benzoyl peroxide was added three times in small portions (0.1 g). Water (200 ml) was then added, and the solution extracted with methylene chloride (3 × 100 ml). The combined extracts were washed with water (100 ml), dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed with hexane and ethyl acetate (20:1) as the eluent to give 2.59 g (31%) of product, mp 203-204 °C (decomp.). ^{1}H Nmr ($CDCl_3$): δ 2.07 (s, 6H), 7.37 (t, 2H, J=8.0), 7.50 (t, 2H, J=8.0), 7.81 (s, 1H), 7.82 (d, 2H, J=8.0), 8.06 (d, 2H, J=8.0). ^{13}C Nmr ($CDCl_3$): δ 30.5, 69.6, 78.3, 110.6, 120.3, 124.8, 128.8, 132.7, 145.7. Anal. Calcd for $C_{16}H_{15}N_6Cl$: C, 58.88; H, 4.64; N, 25.76. Found: C, 59.08; H, 4.62; N, 25.85.

1,1-Di(benzotriazol-1-yl)-2-methylpropene (13): Sodium hydride (0.08 g, 3.3 mmol) was added to a stirred solution of **11** (0.98 g, 3.0 mmol) in THF (10 ml) at room temperature. The reaction mixture was refluxed at 90 °C for 4 h, and poured into water (100 ml). The resulting mixture was extracted with ether (3 × 50 ml). The

organic layers were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was crystallized on standing to yield 2.8 g (86%) of product, mp 101-102 °C. ^{1}H Nmr ($CDCl_3$): δ 1.97 (s, 6H), 7.35 (dt, 2H, J=8.3, 1.0), 7.45 (dt, 2H, J=8.3, 1.0), 7.57 (dd, 2H J=8.3, 0.7), 8.05 (dd, 2H, J=8.3, 0.9). ^{13}C Nmr ($CDCl_3$): δ 20.0, 110.0, 120.0, 121.2, 124.6, 128.7, 132.8, 142.5, 145.3. Anal. Calcd for $C_{16}H_{14}N_6$: C, 66.18; H, 4.86; N, 28.96. Found: C, 66.13; H, 4.89; N, 29.33.

***cis*-2-(Benzotriazol-1-yl)-3-chlorotetrahydrofuran (14):** 4,5-Dihydrofuran (3.85 g, 55 mmol) was added dropwise with stirring to a cooled (-40 °C) solution of 1-chlorobenzotriazole (7.67 g, 50 mmol) in CH_2Cl_2 (100 ml). Stirring was continued for 2 h at -40 °C and then at ambient temperature for 16 h. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel using hexane and ethyl acetate (20:1) as the eluent to give 1.8 g (16%) of oil as the third fraction. ^{1}H Nmr ($CDCl_3$): δ 2.65-2.85 (m, 2H), 4.24 (dd, 1H, J=15.5, 7.4), 4.65 (dt, 1H, J=8.3, 5.2), 4.78 (dt, 1H, J=8.0, 5.3), 6.63 (d, 1H, J= 5.3), 7.37 (ddd, 1H, J=8.0, 7.0, 1.0), 7.49 (ddd, 1H, J=8.0, 7.0, 1.0), 7.64 (dd, 1H, J=8.4, 0.8), 8.08 (dd, 1H, J=8.3, 0.9). ^{13}C Nmr ($CDCl_3$): δ 33.3, 57.8, 68.3, 88.8, 110.3, 119.8, 123.9, 127.6, 133.3, 145.4. Anal. Calcd for $C_{10}H_{10}N_3OCl$: C, 53.80; H, 4.52; N, 18.83. Found: C, 53.93; H, 4.62; N, 18.80.

2-(Benzotriazol-1-yl)-4,5-dihydrofuran (15): A solution of potassium *tert*-butoxide (1.34 g, 12 mmol) in THF (20 ml) was added dropwise to a solution of *cis*-2-(benzotriazol-1-yl)-3-chloro-tetrahydrofuran (**13**) (1.97 g, 8.8 mmol). The mixture was refluxed for 48 h, then poured into cold water (100 ml), and extracted with ether (3 × 50 ml). The combined organic layers were washed with water (3 × 60 ml), dried with $MgSO_4$ and concentrated in vacuo. The residue was separated by column chromatography using hexane and ethyl acetate (20:1) to yield 1.22 g (74%) of solid product, mp 70-71 °C. ^{1}H Nmr ($CDCl_3$): δ 2.96 (td, 2H, J=9.0, 2.7), 4.70 (t, 2H, J=9.0), 5.39 (t, 1H, J=2.7), 7.37 (td, 1H, J=8.0, 1.0), 7.49 (td, 1H, J=8.0, 1.0), 7.81 (dd, 1H, J=8.0, 1.0), 8.05 (dd, 1H, J=8.0, 1.0). ^{13}C Nmr ($CDCl_3$): δ 28.7, 70.2, 85.2, 111.6, 119.3, 124.0, 127.9, 130.8, 145.0, 147.1. Anal. Calcd for $C_{10}H_9N_3O$: C, 64.15; H, 4.85; N, 22.46. Found: C, 64.02; H, 4.83; N, 22.37.

1-(Benzotriazol-1-yl)-1-morpholino-2-methylpropene (18): A benzotriazole chloride (3.07 g, 20 mmol) solution in ether (100 ml) was added dropwise to a stirred solution of 1-morpholino-2-methyl-1-propene (2.82 g, 20 mmol) in ether (100 ml) at -30 °C. The reaction mixture was stirred for 2 h at -30 °C and a solution of potassium *tert*-butoxide (2.46 g, 22 mmol) in THF (25 ml) was added dropwise. The stirring was continued for 5 h at 35 °C. After that period the reaction mixture was cooled to room temperature and poured into water (500 ml). The aqueous layer was extracted with ether (3 × 50 ml), washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was separated by column chromatography (silica gel,

hexane/ethyl acetate = 20:1) to yield 2.11 g (37%) of oil. ^{1}H Nmr ($CDCl_3$): δ 1.36 (s, 3H), 2.11 (s, 3H), 2.68 (t, 4H, J=5.0), 3.71 (t, 4H, J=5.0), 7.39 (t, 1H, J=8.0), 7.40 (d, 1H, J=8.0), 7.50 (t, 1H, J=8.0), 8.10 (d, 1H, J=8.0). ^{13}C Nmr ($CDCl_3$): δ 18.4, 18.7, 49.6, 66.5, 109.6, 119.6, 123.4, 127.4, 127.8, 133.7, 133.9, 144.3. Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.08; H, 7.03; N, 21.70. Found: C, 65.45; H, 7.15; N, 21.60.

Lithiation of *N*-Substituted Benzotriazoles (2), (6), (8), (13), (15), (18), (21a), (26), (28). General Procedure: Butyllithium (2.5 M in hexane, 1.3 ml, 3.3 mmol) was added with stirring at -78 °C to a solution of *N*-substituted benzotriazole (3 mmol) in THF (50 ml). The resultant colored solution was stirred at this temperature for 2 h. The electrophile (3.3 mmol, in 1 ml THF) was added, and the reaction mixture stirred for an additional 4 h at this temperature, then overnight at ambient temperature. The reaction mixture was poured into saturated NH_4Cl solution (50 ml), and the aqueous layer extracted with ether (3 × 30 ml). The combined organic layers were washed with water, dried with $MgSO_4$ and concentrated in vacuo. The products were isolated by column chromatography with hexane and ethyl acetate (20:1) as the eluent.

2-(Benzotriazol-1-yl)-3-methylpyridine (21a): Obtained as colorless crystals (37%), mp 72-73 °C. ^{1}H Nmr ($CDCl_3$): δ 2.52 (s, 3H), 7.36 (dd, 1H, J=7.7, 4.7), 7.44 (ddd, 1H, J=8.1, 7.0, 1.0), 7.55 (ddd, 1H, J=8.1, 7.0, 1.0), 7.82 (dt, 1H, J=7.7, 1.0), 7.92 (dd, 1H, J=8.3, 0.9), 8.14 (dd, 1H, J=8.3, 1.0), 8.50 (dd, 1H, J=4.7, 1.2). ^{13}C Nmr ($CDCl_3$): δ 18.8, 112.3, 119.6, 123.6, 124.4, 128.2, 128.6, 132.8, 141.4, 145.5, 146.3, 148.7. Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.54; H, 4.80; N, 26.66. Found: C, 68.46; H, 4.90; N, 26.24.

2-(Benzotriazol-1-yl)-3-[(2-methoxyphenyl)hydroxymethyl]pyridine (21b): Obtained as colorless crystals (55%), mp 148-149 °C. ^{1}H Nmr ($CDCl_3$): δ 3.33 (s, 3H), 4.39 (d, 1H, J=4.6), 6.29 (d, 1H, J=4.6), 6.65 (d, 1H, J=8.1), 6.93 (t, 1H, J=7.4), 7.15 (t, 1H, J=6.3), 7.35 (dd, 1H, J=7.4, 5.0), 7.45 (t, 1H, J=8.3), 7.50-7.60 (m, 2H), 7.87 (dd, 1H, J=7.4, 1.5), 7.93 (d, 1H, J=8.3), 8.12 (d, 1H, J=8.3), 8.53 (symm m, 1H). ^{13}C Nmr ($CDCl_3$): δ 54.9, 65.9, 110.1, 112.4, 119.6, 120.4, 124.0, 124.7, 126.7, 128.5, 128.6, 129.4, 132.8, 134.6, 138.9, 145.6, 147.5, 147.7, 155.5. Anal. Calcd for $C_{19}H_{16}N_4O_2$: C, 68.65; H, 4.86; N, 16.86. Found: C, 68.48; H, 4.81; N, 16.77.

2-(Benzotriazol-1-yl)-3-[(1-hydroxycyclohexyl)methyl]pyridine (22): Obtained as a colorless solid (43%), mp 132-133 °C. ^{1}H Nmr ($CDCl_3$): δ 1.10-1.60 (m, 10H), 2.99 (s, 2H), 3.38 (s, 1H), 7.36-7.46 (m, 2H), 7.55 (t, 1H, J=7.6), 7.85 (d, 1H, J=8.3), 7.94 (dd, 1H, J=7.6, 1.7), 8.11 (d, 1H, J=8.3), 8.53 (dd, 1H, J=4.6, 1.7). ^{13}C Nmr ($CDCl_3$): δ 21.8, 25.5, 37.9, 42.6, 71.0, 112.4, 119.7, 123.5, 124.7, 128.6, 128.9, 133.1, 142.8, 145.5, 146.9, 149.1. Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.09; H, 6.54; N, 18.18. Found: C, 70.23; H, 6.58; N, 18.25.

2-(Benzotriazol-1-yl)-4-butylpyrimidine (23): Obtained as a solid (25%), mp 61-62 °C. ^{1}H Nmr ($CDCl_3$): δ

0.98 (t, 3H, J=7.3), 1.45 (m, 2H), 1.84 (symm m, 2H), 2.93 (t, 2H, J=7.8), 7.20 (d, 1H, J=5.1), 7.46 (td, 1H, J=7.1, 1.0), 7.62 (td, 1H, J=7.2, 1.0), 8.15 (dd, 1H, J=8.3, 0.8), 8.58 (dd, 1H, J=8.4, 0.8), 8.76 (d, 1H, J=5.1). ^{13}C Nmr ($CDCl_3$): δ 13.8, 22.3, 30.6, 37.5, 114.8, 118.4, 120.0, 125.0, 129.0, 131.7, 146.7, 156.1, 158.4, 173.8. Anal. Calcd for $C_{14}H_{15}N_5$: C, 66.37; H, 5.97; N, 27.66. Found: C, 66.55; H, 6.02; N, 27.90.

1,1-Bis(benzotriazol-1-yl)-3-(1-hydroxycyclohexyl)-2-methylpropene (24): Obtained as a viscous oil (64%). ^{1}H Nmr ($CDCl_3$): δ 1.10-1.90 (m, 10H), 2.05 (s, 3H), 2.47 (s, 2H), 2.75 (s, 1H), 7.35 (t, 2H, J=8.1), 7.45 (t, 2H, J=8.1), 7.53 (d, 1H, J=8.3), 7.60 (d, 1H, J=8.3), 8.03 (d, 2H, J=8.3). ^{13}C Nmr ($CDCl_3$): δ 20.4, 22.0, 25.3, 38.9, 45.8, 71.3, 110.0, 110.5, 120.0, 120.1, 123.0, 124.7, 124.8, 128.9, 129.0, 132.8, 132.9, 144.1, 145.3, 145.4. Anal. Calcd for $C_{22}H_{24}N_6O$: M^+=388.2090. Hrms found: M^++1=389.2082.

2-[7-(1-Hydroxycyclohexyl)benzotriazol-1-yl]-2-(benzotriazol-1-yl)propane (25): Obtained as a viscous oil (18%). ^{1}H Nmr ($CDCl_3$): δ 1.6-2.2 (m, 10H), 2.73 (s, 6H), 3.91 (s, 1H), 6.57 (d, 1H, J=8.3), 6.74 (dd, 1H, J=8.3, 1.0), 7.11 (symm m, 1H), 7.16-7.30 (m, 3H), 8.05 (dd, 1H, J=8.2, 0.9). ^{13}C Nmr ($CDCl_3$): δ 21.4, 25.1, 27.1, 29.2, 37.4, 73.3, 78.5, 108.3, 109.8, 119.1, 119.9, 124.1, 127.8, 130.8, 131.4, 141.9, 144.3, 146.6. Anal. Calcd for $C_{21}H_{24}N_6O$: M^+=376.2090. Hrms found: M^++1=377.2080.

2-(Benzotriazol-1-yl)-3-methyl-4,5-dihydrofuran (26): This compound was prepared as a colorless solid according to the general procedure for lithiation of *N*-substituted benzotriazoles (61%), mp 75-76 °C. ^{1}H Nmr ($CDCl_3$): δ 1.87 (t, 3H, J=1.3), 2.93 (td, 2H, J=9.3, 1.3), 4.59 (t, 2H, J=9.3), 7.38 (ddd, 1H, J=8.0, 7.0, 1.0), 7.51 (ddd, 1H, J=8.0, 7.0, 1.0), 7.69 (dd, 1H, J=8.3, 1.0), 8.07 (dd, 1H, J=8.3, 1.0). ^{13}C Nmr ($CDCl_3$): δ 11.5, 35.5, 68.8, 101.4, 111.8, 120.1, 124.7, 128.5, 132.8, 140.7, 145.4. Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.64; H, 5.51; N, 20.89. Found: C, 65.79; H, 5.56; N, 20.98.

2-[7-(1-Hydroxycyclohexyl)benzotriazol-1-yl]-3-methyl-4,5-dihydrofuran (27): Obtained as an oil (18%). ^{1}H Nmr ($CDCl_3$): δ 1.2-2.2 (m, 13H), 2.95 (dt, 2H, J=9.5, 1.3), 3.85 (br s, 1H), 4.60 (t, 2H, J=9.5), 7.39 (dd, 1H, J=7.2, 1.1), 7.46 (td, 1H, J=8.2, 0.9), 7.57 (dd, 1H, J=8.1, 1.1). ^{13}C Nmr ($CDCl_3$): δ 11.5, 22.2, 25.9, 35.6, 38.2, 68.9, 74.1, 101.8, 110.4, 119.7, 128.6, 133.5, 140.7, 142.3, 143.2. Anal. Calcd for $C_{17}H_{21}N_3O_2$: M^+=299.1712. Hrms found: M^++1=300.1703.

cis-**1-[7-(1-Hydroxycyclohexyl)benzotriazol-1-yl]-1-ethoxypropene (29a):** Obtained as an oil (12.5%). ^{1}H Nmr ($CDCl_3$): δ 1.39 (t, 3H, J=7.0), 1.53 (d, 3H, J=7.0), 1.60-2.20 (m, 10H), 3.93 (q, 2H, J=7.0), 3.96 (s, 1H), 5.14 (q, 1H, J=7.0), 7.30-7.50 (m, 3H). ^{13}C Nmr ($CDCl_3$): δ 11.2, 14.3, 21.8, 25.6, 37.9, 64.9, 73.7, 97.0, 109.1, 119.1, 128.1, 133.3, 142.0, 142.8, 144.4. Anal. Calcd for $C_{17}H_{23}N_3O_2$: M^+=301.1790. Hrms found: M^+=301.1810.

cis-**1-{7-[(3-Methylphenyl)hydroxymethyl]benzotriazol-1-yl}ethoxypropene (29b):** Obtained as an oil (15%). ^{1}H Nmr ($CDCl_3$): δ 1.34 (t, 3H, J=7.0), 1.53 (d, 3H, J=7.0), 2.33 (s, 3H), 3.92 (q, 2H, J=7.0), 5.12 (q, 1H, J=7.0), 6.53 (br s, 1H), 7.09 (d, 1H, J=7.5), 7.20-7.50 (m, 7H). ^{13}C Nmr ($CDCl_3$): δ 11.2, 14.3, 21.5, 65.0, 73.6, 97.0, 109.7, 121.3, 123.8, 127.3, 128.3, 128.4, 133.1, 136.2, 138.1, 142.6, 143.0, 144.4. Anal. Calcd for $C_{17}H_{23}N_3O_2$: M^+=323.1634. Hrms found: M^+=323.1587.

1-(1-Morpholinoisobutenyl)-7-[(3-methylphenyl)hydroxymethyl]benzotriazole (30a): Obtained as a viscous oil (11%). ^{1}H Nmr ($CDCl_3$): δ 1.35 (s, 3H), 2.09 (s, 3H), 2.35 (s, 3H), 2.66 (t, 4H, J=4.6), 3.69 (t, 4H, J=4.6), 4.10 (br s, 1H), 6.55 (br s, 1H), 7.09 (d, 1H, J=7.5), 7.20-7.30 (m, 3H), 7.35-7.45 (m, 3H). ^{13}C Nmr ($CDCl_3$): δ 18.9, 19.2, 21.5, 50.1, 66.9, 73.7, 109.1, 121.0, 123.8, 127.3, 128.0, 128.1, 128.3, 128.4, 134.3, 134.5, 136.3, 138.1, 142.6, 142.7. Anal. Calcd for $C_{22}H_{26}N_4O_2$: M^++1=379.2134. Hrms found: M^++1=379.2202.

1-(1-Morpholinoisobutenyl)-7-(2-hydroxyisopropyl)benzotriazole (30b): Obtained as an oil (16%). ^{1}H Nmr δ ($CDCl_3$): δ 1.37 (s, 3H), 1.85 (s, 6H), 2.11 (s, 3H), 2.68 (t, 4H, J=4.6), 3.71 (t, 4H, J=4.6), 4.50 (br s, 1H), 7.29 (symm m, 2H), 7.45 (dd, 1H, J=8.1, 1.0). ^{13}C Nmr ($CDCl_3$): δ 18.9, 19.2, 30.8, 50.1, 66.9, 73.1, 108.8, 118.8, 127.9, 128.6, 134.3, 134.7, 141.4, 142.4. Anal. Calcd for $C_{17}H_{24}N_4O_2$: C, 64.52; H, 7.65; N, 17.71. Found: C, 64.63; H, 7.76; N, 17.69.

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