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Preparation of Polymer-Bound 1*H*-Benzotriazole, a New Potential Scaffold for the Compilation of Organic Molecule Libraries

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An efficient method for the preparation of polymer-bound 1*H*-benzotriazole has been devised. The reaction of Merrifield resin with sodium 3-nitro-4-aminophenolate and the subsequent reduction and reaction with isoamyl nitrite afforded benzotriazole preloaded resin. A series of tertiary amines and a tosylamide were prepared using solid-phase benzotriazole-mediated transformations.

Introduction

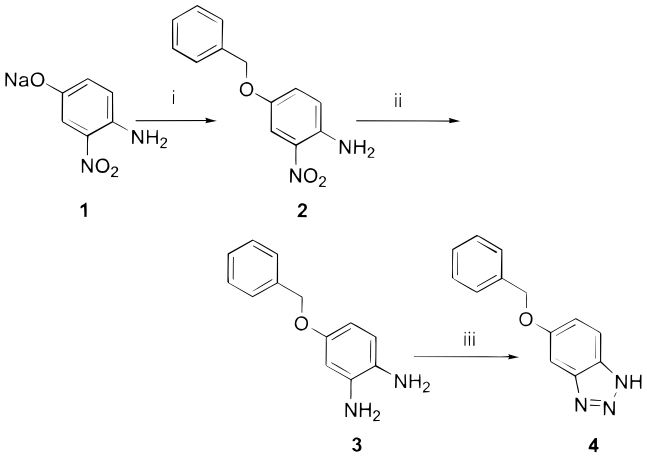
Synthetic applications of solid-phase organic chemistry have, in recent years, received an enormous boost from the expeditious development of the combinatorial approach. The use of solid-phase-bound reagents and catalysts allows much simplier workup procedures and, in many cases, eliminates the need for strict control of reagent ratios. Over two decades resin-bound 1-hydroxybenzotriazole has been known to be an efficient reagent for the formation of peptide bonds.[1] Recently, several publications have described the preparation and utilization of various versions of this reagent.[2a−c] The utility of 1*H*-benzotriazole in a variety of organic transformations is well documented (for recent reviews, see ref 3a,b). We now report the first preparation of solid-phase attached 1*H*-benzotriazole and some of its reactions.

Results and Discussion

For the reactions on the solid support we envisaged the use of an ether linker, which was expected to be inert toward many potential applications (Mannich reactions, displacement reactions involving organometallic reagents and other nucleophiles, etc.). Thus, we investigated in solution a model sequence involving 4-benzyloxy-2-nitroaniline, 4-benzyloxy-1,2-phenylenediamine, and 4-benzyloxy-1*H*-benzotriazole (Scheme 1).

The sodium salt of 4-amino-3-nitrophenol (**1)** was reacted with benzyl chloride in *N*,*N*-dimethylacetamide (DMA) to give 4-(benzyloxy)-2-nitroaniline (**2**). Compound **2** was subsequently reduced to 4-(benzyloxy)-1,2-phenylenediamine (**3**) either by using (i) stannous chloride in DMA or (ii) hydrazine and Raney Ni in ethanol. The NMR spectra of both products were identical, but it was difficult to remove the DMA completely using the first method. Products **3** were both used without purification for subsequent reactions. The 5-(benzyloxy)-1*H*-benzotriazole (**4**) hetero ring was successfully formed using isoamyl nitrite in dioxane (instead of water or mixed aqueous solutions); thus, we employed this modification in the preparations of a resin-bound benzotriazole nucleus. Compounds **2** and **4** were characterized by ^{1}H and ^{13}C NMR spectroscopy and CHN analysis.

Scheme 1[a]



[a] Reagents and conditions: (i) $PhCH_2Cl$, DMA; (ii) $SnCl_2 \cdot 2H_2O$, DMA; or N_2H_4, Ni Raney, ethanol; (iii) *i*-$AmNO_2$, dioxane, H^+.

Treatment of Merrifield resin with sodium salt **1** (Scheme 2) afforded the corresponding resin-bound nitroaniline **6** whose gel-phase (GP) ^{13}C NMR spectrum contained signals similar to those of the model analogue **3** (e.g., the signal of benzylic carbon appeared in both cases at ca. 70 ppm). We reduced resin **6** with stannous chloride in DMA in order to prepare resin **8**. The GP ^{13}C NMR spectrum of **8** in $CDCl_3$ gave poor resolution. At the same time a mixed deuterated solvent ($CDCl_3$:DMSO-d_6, 1:1 v/v) simultaneously broadened and weakened all the peaks.

In a separate experiment, the 3-nitro-4-aminophenol was reduced by hydrazine on Raney Ni in ethanol to give 4-hydroxy-1,2-phenylenediamine, which was reacted as its Na salt **7** in DMA solution with Merrifield resin to give resin **8** with a GP ^{13}C NMR spectrum *identical* to that of the resin **8** obtained from **6** via reduction of the nitro group on solid support.

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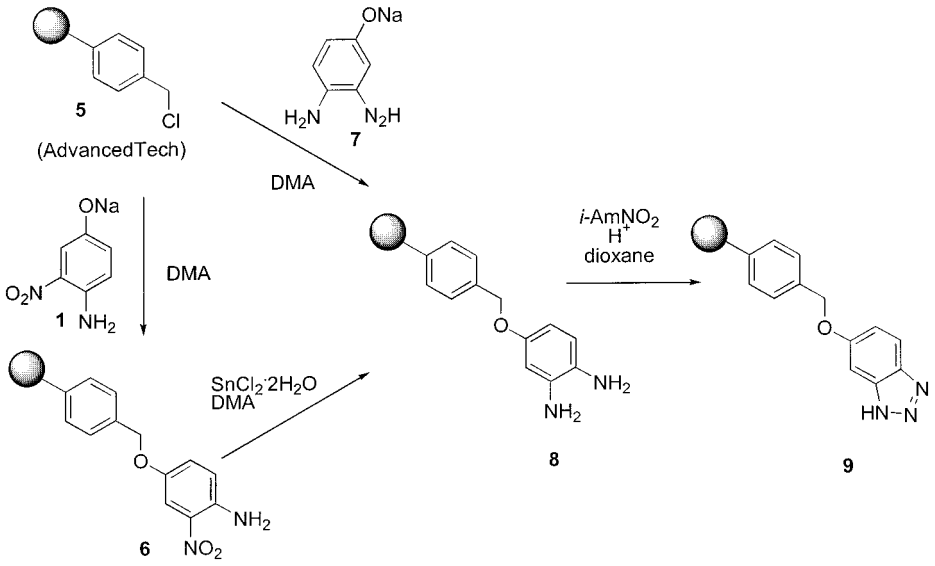
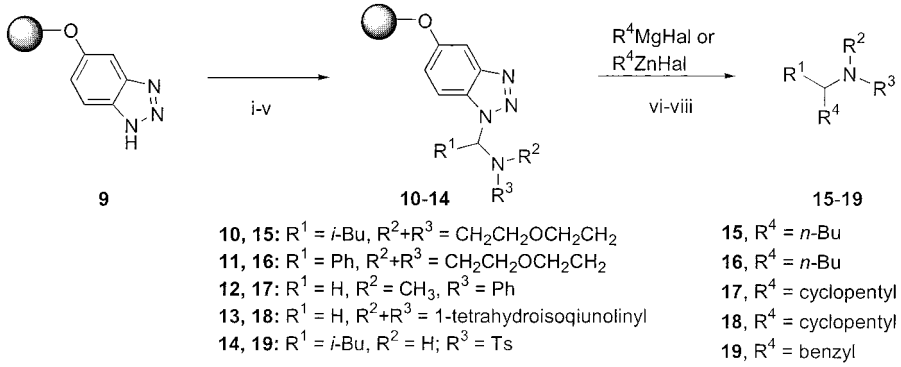
Scheme 2



Scheme 3[a]



[a] Reagents and conditions: (i) *i*-BuCHO, morpholine, THF/methoxyethanol, 60 °C, 12 h; (ii) PhCHO, morpholine, TsOH (cat.), toluene, reflux, Dean–Stark trap, 12 h; (iii) CH_2O (aq), *N*-methylaniline, THF/methoxyethanol, 60 °C, 8 h; (iv) CH_2O (aq), tetrahydroisoquinoline, THF/methoxyethanol, 60 °C, 8 h; (v) *i*-BuCHO, $TsNH_2$, TsOH (cat.), THF/methoxyethanol, 60 °C, 24 h; (vi) BuMgBr, THF, reflux, 4 h; (vii) C_5H_9MgCl, THF, reflux, 4 h; (viii) $PhCH_2Br$, Zn, THF, 60 °C, 12 h.

The successful formation of the 1,2-phenylenediamine moiety in **8** was supported by the comparative FTIR study of nitro-containing resin **6** and sample of resin **8** (KBr pellets). In the spectrum of resin **6**, several characteristic signals are present, which confirmed attachment of the phenolic moiety to the resin. There are two strong bands at 3500 and 3381 cm^{-1}, typical for an amino group, and also a strong band at 1517 cm^{-1} and two medium bands at 1331 and 1248 cm^{-1}, all typical for the absorption of the nitro group. Reduction of the nitro group in **6** resulted in the appearance in **8** of broadened bands at 3420 and 1172 cm^{-1} (medium) and the disappearance of signals at 1517, 1331, and 1248 cm^{-1}, which indicates the conversion of the nitro group into the amino group.

Subsequent treatment of **8** with isoamyl nitrite and the formation of the benzotriazole hetero ring on the solid support afforded resin **9**. The GP ^{13}C NMR spectrum of **9** was unresolved, even after a lengthy (NT = 50 000) acquisition. However, the FTIR spectrum of **9** shows a very broad band (2700–3400 cm^{-1}), which was attributed to the NH group of the hetero ring (its broadening is explained by the quick transition of the 1*H*-, 2*H*-, and 3*H*-isomers in the benzotriazole backbone). Additionally, **9** showed a new strong band at 1240 cm^{-1} which resulted from the ring-stretching vibrations of the benzotriazole hetero ring. No peaks at 1517 cm^{-1} (nitro group stretching) or at 1172 cm^{-1} (amino group stretching) appeared in the spectrum of **9**.

We next prepared resin-bound Mannich bases **10**–**13** from benzotriazole-containing resin **9** (Scheme 3). Reaction of **9** with isobutyraldehyde/morpholine, benzaldehyde/morpholine, formaldehyde/*N*-methylaniline, and formaldehyde/tetrahydroisoquinoline (entries i–iv) gave the corresponding resins **10**–**13**, respectively. In the preparations of resins **10**, **12**, and **13** we used the mixed solvent system (tetrahydrofuran (THF)/methoxyethanol, 1:1 v/v) which led to better swelling of the polymer. The use of the less reactive benzaldehyde to give **11** demanded harsher conditions (entry ii).

In the GP ^{13}C NMR spectra of **10**, signals at 48.6 and 67.0 ppm correspond to the carbons of the morpholine ring of the prepared model 1-(2-methyl-1-morpholinopropyl)-2*H*-1,2,3-benzotriazole (**20b**, Figure 1). The spectrum of the model compound demonstrates two aminal carbon signals at 85.7 ppm (1-benzotriazolyl, structure **20a**) and 92.5 ppm (2-benzotriazolyl, structure **20b**); however, only a single signal at 92.3 ppm was observed in the GP spectrum of **10**.

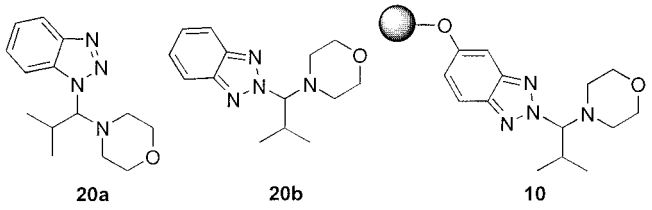


Figure 1.

The formation of only the 2-benzotriazolyl isomer in the resin **10** is explained by steric effects in the globular structure of cross-linked (1% divinylbenzene) polystyrene resin.

The GP ^{13}C NMR spectra in $CDCl_3$ and $CDCl_3$/DMSO mixed solvent for derivatives **11**−**13** gave poor resolution, so their structures were studied by a FTIR analysis. The vibrational peak found at 1420 cm^{-1} in **9** had disappeared in the cases of **11**−**13**. New peaks were observed for **13** at 1148, 962, and 936 cm^{-1} (C−N stretching). The FTIR spectra of **11** and **12** were not as well resolved because of overlapping between product peaks and the peaks of the polymer support.

Subsequent treatment of **10**−**13** with Grignard reagents in dry THF followed by a standard workup procedure and flash chromatography afforded the substituted tertiary amines **15**−**18** in good yields. Compounds **15**−**18** were characterized by ^1H and ^{13}C NMR spectroscopy and CHN analysis.

These successful results prompted us to synthesize another polymer-bound adduct **14**. In the FTIR spectrum of **14,** new peaks at 3121 cm^{-1} (N−H stretching) and at 1375 and 1141 cm^{-1} (S−O stretching) were observed while the vibrational peak of the benzotriazole ring at 1420 cm^{-1} fully disappeared. The reaction of **14** with a Reformatsky reagent afforded tosylamine **19** in 58% yield, and the product was characterized by ^1H and ^{13}C NMR spectroscopy and CHN analysis.

Conclusions

The method for the preparation of polymer-bound 1*H*-benzotriazole was developed. A series of new tertiary amines and a tosylamide were synthesized by the cleavage of polymer-supported benzotriazole Mannich adducts in reactions with Grignard and organozinc reagents. This preloaded resin can be considered to be an appropriate scaffold for solid-phase benzotriazole-mediated synthesis.[4]

Experimental Section

Melting points were determined on a hot stage apparatus without correction. NMR spectra were obtained using a Varian Gemini-300 spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C in chloroform-*d* and DMSO-d_6. Chemical shift values are reported as δ downfield from tetramethylsilane as an internal standard for ^1H and solvent as the internal standard for ^{13}C. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer.

THF was distilled from benzophenone/sodium metal under nitrogen immediately prior to use. Column chromatography was performed using MCB silica gel (230−400 mesh). Other chemicals were obtained from commercial sources and used without further purification.

The loading of resins **6**, **8**, and **9** was determined by the reversed titration with perchloric acid in a water−dioxane mixture (1:1). Yields of compounds **15**−**19** are reported relative to the loading of the resin **9**.

Preparation of 4-(Benzyloxy)-2-nitroaniline (2). Benzyl chloride (0.7 mL, 6.1 mmol) was added to a solution of sodium 3-nitro-4-aminophenolate (0.933 g, 6.1 mol) in DMA (25 mL) and stirred at 80 °C for 6 h. After cooling, water (100 mL) was added, and the formed precipitate was filtered and recrystallized from ethanol: yield 56%; mp = 112 °C; ^1H NMR δ 5.00 (s, 2H), 6.43 (s, 2H), 6.86 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 7.35−7.41 (m, 5H), 7.59 (s, 1H); ^{13}C NMR δ 70.3, 107.1, 120.0, 126.9, 127.3, 127.7, 128.2, 130.3, 136.0, 140.7, 148.9. Anal. Calcd for $C_{13}H_{12}N_2O_3$: N, 11.47. Found: N, 11.47.

Preparation of 5-(Benzyloxy)-1*H*-benzotriazole (4). A Raney nickel slurry in water (3 g) was added to a solution of 4-(benzyloxy)-2-nitroaniline (**2**) (0.4 g, 1.6 mmol) in ethanol (50 mL), and then hydrazine hydrate (3 mL, 85% solution in water) was added dropwise at 60 °C while stirring. The reaction mixture was refluxed for 1 h and filtered, and the solvent was evaporated. The obtained oil was dissolved in a mixture of dioxane (20 mL), acetic acid (7 mL), and concentrated hydrochloric acid (5 mL). To this solution, isoamyl nitrite (2 mL, 0.015 mol) in dioxane (10 mL) was added. The reaction mixture was stirred at room temperature for 6 h and then diluted with water. The precipitate was filtered and recrystallized from ethanol−water (1:1): yield 64%; mp = 98 °C; ^1H NMR δ 5.06 (s, 2H), 7.02 (d, J = 9.2 Hz, 1H), 7.22−7.49 (m, 8H); ^{13}C NMR δ 69.8, 106.5, 120.7, 127.6, 127.7, 127.8, 128.4, 129.0, 136.8, 142.0, 148.1. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 69.31; H, 4.93. Found: C, 69.36; H, 5.10.

Preparation of Polymer-Bound 2-Nitroaniline (6). To a suspension of Merrifield resin (1.58 g, Novabiochem, product no. 01-64-0007, 200-400 mesh, loading 1 mmol/g) in DMA (30 mL) was added sodium 3-nitro-4-aminophenolate (0.7 g, 3.9 mmol), and the mixture was stirred at 80 °C for 6 h. After cooling, the resin was filtered, washed sequentially with DMA, DMA/water (1:1), THF/water (1:1), THF, and CH_2Cl_2, and then dried: yield 1.75 g; loading 0.94 mmol/g.

Preparation of Polymer-Bound 1,2-Phenylenediamine (8). The suspension of the resin **6** (0.4 g, loading 0.94 mmol/g) and $SnCl_2 \cdot 2H_2O$ (1 g, 4.4 mmol) in DMA (20 mL) was stirred at 60 °C for 5 h and then at room temperature overnight. After diluting the mixture with water (5 mL), the resin was filtered, washed sequentially with DMA, DMA/water (1:1), THF/water (1/1), THF, and CH_2Cl_2, and dried: yield of the resin **8** 0.38 g; loading 0.91 mmol/g.

As the alternative to a suspension of Merrifield resin (0.56 g, Novabiochem, product no. 01-64-0007, 200-400 mesh, loading 1 mmol/g) in DMA (20 mL), sodium 3,4-diaminophenolate **7** (0.5 g, 3.4 mmol) was added and stirred at 80 °C for 6 h. After cooling, the resin was filtered, washed sequentially with DMA, DMA/water (1:1), THF/water (1:1), THF, and CH_2Cl_2, and then dried: yield of the resin **8** 0.60 g; loading 0.89 mmol/g.

Preparation of Polymer-Bound 1*H*-Benzotriazole (9).

To the suspension of the resin **8** (0.2 g, loading 0.91 mmol/g) in the mixture of dioxane (20 mL), acetic acid (5 mL), and concentrated hydrochloric acid (3.5 mL) was added a solution of isoamyl nitrite (2 mL, 15 mmol) in dioxane (10 mL). The reaction mixture was stirred at room temperature for 24 h and then heated to 50−60 °C for 0.5 h. The resin was filtered, washed sequentially with dioxane, THF, and CH_2Cl_2, and then dried: yield of the resin **9** 0.19 g; loading 0.7 mmol/g.

General Procedure for the Preparation of Compounds 15−19. Polymer-bound benzotriazole derivatives **10−14** were obtained starting from 0.2 g of the resin **9** (loading 0.7 mmol/g) and using the 10-fold excesses of the corresponding amine (tosylamide for compound **14**) and aldehyde under the reaction conditions listed in Scheme 3. The standard workup procedure involved filtration, washing with THF (5 × 10 mL) and ether (1 × 15 mL), then drying. Further reaction with a 4-fold excess of the corresponding Grignard reagent (for **15−18**) or organozinc reagent (for **19**) was performed according to the reaction conditions listed in Scheme 3. After standard workup (ice-cold water and saturated ammonium chloride or hydrochloric acid for **19**), the resin was filtered and washed with THF. The combined filtrates were extracted with ether (30 mL), and the organic layer was separated, washed with water, and dried with anhydrous Na_2SO_4. Solvent was removed in vacuo to afford the corresponding amines **15−18** or sulfonamide **19**.

4-(1-Isopropylpentyl)morpholine (15): oil, yield 0.023 g, 82%; ^{1}H NMR δ 0.87−0.93 (m, 9H), 1.28−1.31 (m, 4H), 1.37−1.47 (m, 2H), 1.74−1.80 (m, 1H), 1.97−2.00 (m, 1H), 2.50−2.61 (m, 4H), 3.63−3.66 (m, 4H); ^{13}C NMR δ 14.1, 19.8, 20.9, 23.1, 26.9, 29.7, 31.3, 49.9, 67.7, 70.3. Anal. Calcd for $C_{12}H_{25}NO$: N, 7.03. Found: N, 7.20.

4-(1-Phenylpentyl)morpholine (16): oil, yield 0.029 g, 89%; ^{1}H NMR δ 0.79−0.84 (m, 3H), 0.97−1.19 (m, 2H), 1.21−1.32 (m, 2H), 1.64−1.75 (m, 1H), 1.83−1.94 (m, 1H), 2.32−2.39 (m, 2H), 2.41−2.46 (m, 2H), 3.16−3.19 (m, 1H), 3.65−3.68 (m, 4H), 7.21−7.33 (m, 5H); ^{13}C NMR δ 13.9, 22.8, 28.3, 32.2, 51.1, 67.2, 70.6, 126.9, 128.0, 128.6, 140.7. Anal. Calcd for $C_{15}H_{23}NO$: N, 6.00. Found: N, 6.06.

***N*-(Cyclopentylmethyl)-*N*-methylaniline (17)**: oil, yield 0.022 g, 84%; ^{1}H NMR δ 1.15−1.27 (m, 2H), 1.43−1.78 (m, 6H), 2.22−2.29 (m, 1H), 2.94 (s, 3H), 3.23 (d, J = 7.2 Hz, 2H), 6.63−6.70 (m, 3H), 7.18−7.24 (m, 2H); ^{13}C NMR δ 24.9, 30.8, 38.8, 38.9, 57.7, 111.9, 115.6, 129.0, 144.9. Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.14; N, 7.40. Found: C, 82.30; H, 10.32; N, 11.54.

2-(Cyclopentylmethyl)-1,2,3,4-tetrahydroisoquinoline (18): oil, yield 0.023 g, 76%; ^{1}H NMR δ 1.19−1.28 (m, 2H), 1.49−1.64 (m, 4H), 1.74−1.84 (m, 2H), 2.13−2.22 (m, 1H), 2.42 (d, J = 7.5 Hz, 2H), 2.72 (t, J = 6.0 Hz, 2H), 2.88 (t, J = 6.0 Hz, 2H), 3.62 (s, 2H), 6.99−7.11 (m, 4H); ^{13}C NMR δ 25.2, 29.0, 31.4, 37.4, 51.1, 56.5, 64.3, 125.4, 125.9, 126.5, 128.6, 134.5, 135.13. Anal. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.85; N, 6.51. Found: C, 83.58; H, 10.11; N, 6.60.

***N*-(1-Benzyl-2-methylpropyl)-4-methylbenzenesulfonamide (19)**: mp 112 °C; yield 0.028 g, 63%; ^{1}H NMR δ 0.85 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H), 1.75−1.84 (m, 1H), 2.39 (s, 3H), 2.54 (dd, J = 7.2 Hz, J = 13.8 Hz, 1H), 2.65 (dd, J = 7.2 Hz, J = 13.8 Hz, 1H), 3.27−3.34 (m, 1H), 4.73 (d, J = 8.4 Hz, 1H), 6.96−6.97 (m, 2H), 7.15−7.19 (m, 5H), 7.61 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 16.9, 18.7, 21.5, 29.9, 37.8, 60.5, 126.3, 126.9, 128.4, 129.1, 129.5, 137.8, 142.9. Anal. Calcd for $C_{18}H_{23}NO_2S$: C, 68.10; H, 7.32; N, 4.41. Found: C, 68.19; H, 7.72; N, 4.40.

References and Notes

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(4) The benzotriazole resin described in this article will be available from Novabiochem from the middle of 1999.

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