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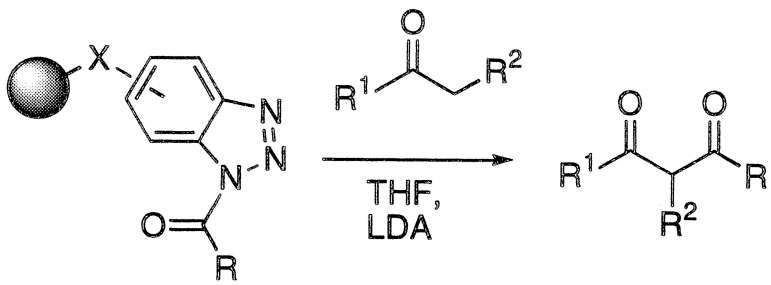

X = O, C-C bond, amide

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Polymer-Supported Triazole and Benzotriazole Leaving Groups. Three New Examples and a Comparison of Their Efficiency

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Three polymer-supported heterocyclic (triazole **4** and benzotriazoles **2**, **8**) leaving groups are described. The loading of **8** was clearly superior to those of **2** and **4**. The efficiency of **8** was higher than those of previously reported benzotriazole resins **9a**,**b** in the C-acylation of ketones.

Introduction

The search for synthetic efficiency ranging from the "atom economy" concept[1] to the very different techniques of polymer-supported chemistry[2] has dominated the recent evolution of synthetic methods. This is exemplified by its influence on the development of polymer linkers. Recently, the perception of a polymer linker as a rather elaborate protecting group[3] has been extended by the advent of specially designed leaving group linkers.[4a−c] Such linkers increase the synthetic efficiency of the entire synthesis by allowing a wider variety of bond formations at the linkage site.

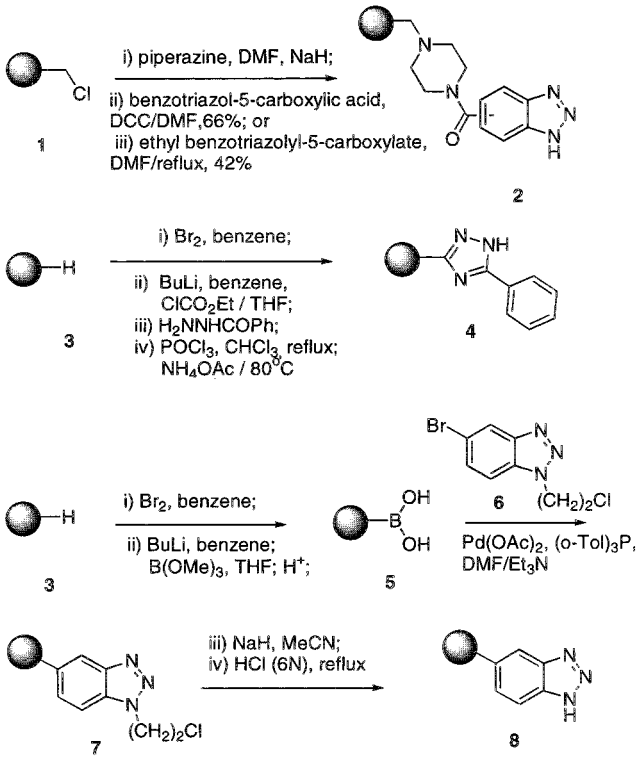
Previously, bifunctional sulfones[4a] and phosphonium salts[4b] have served as such linkers. Our interest was to develop new types of immobilized leaving groups. Heterocycles can be tolerant to a wide range of reaction conditions, behave as efficient leaving groups,[5a−f] and be easily introduced into a molecule. Thus, heterocycles could be promising candidates for polymer-attached leaving groups.

An efficient application of this concept was illustrated by the preparation of libraries of amines[6a−c] and sulfonamides[6a] based on the benzotriazole preloaded resins. Extensive solution-phase studies of heterocycle-mediated syntheses[5e,7] indicate the potential of such polymer-supported reagents for diverse nucleophilic substitutions. We have now investigated three novel examples (**2**, **4**, **8**, Scheme 1) of immobilized heterocyclic linkers designed for the preparation of polymer-supported azolides and to serve as a leaving group; of these we propose resins **8** to be suitable for further use.

Results and Discussion

Preparation of Resins. We have prepared the three novel triazole preloaded resins **2**, **4**, and **8** (Scheme 1). Benzotriazole resin **2** was prepared from 1,2,3-benzotriazole-5-carboxylic acid by a two-step reaction sequence starting from Merrifield resin **1** with loading 0.97 mmol/g. Functionalization of **1** with piperazine proceeded in a good yield (as judged by CHN analysis), and the resulting resin was treated with either (i) benzotriazole-5-carboxylic acid in the presence of DCC or (ii) ethyl benzotriazolyl-5-carboxylate to yield the desired resin **2** with loadings (as indicated by CHN and cleavage results) of 0.66 and 0.42 mmol/g and substitution 68% and 43%, respectively. According to elemental analysis, no chloromethyl groups remained.

Scheme 1



1,2,4-Triazole resin **4** was designed with a phenyl substituent blocking the position 5 to minimize the possibility of undesired side reactions. 1,2,4-Triazole possesses a reactivity similar to that of benzotriazole;[8,9] we recently reported a 1,2,4-triazole-functionalized solid support with a Wang linker.[10] Our present route provides for direct attachment of the heterocyclic moiety with a carbon−carbon bond. Resin **3** was brominated by a standard procedure[11] and then sequentially lithiated, treated with ethyl chloroformate, and heated with benzhydrazide in DMF at 120 °C for 36 h. Final refluxing in chloroform and $POCl_3$, followed by heating with NH_4OAc at 80 °C, yielded the desired polymer **4.** The loading according to CHN analysis was only 0.3 mmol/g,

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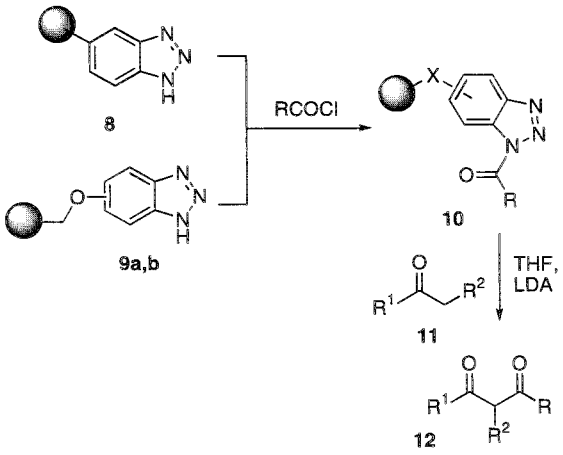
Scheme 2



probably due to the high temperature needed for this transformation. Indeed, the swelling properties of the resin were greatly diminished, which likely indicates significant cross-linking as a consequence of the prolonged heating of the resin.

To attach the benzotriazole moiety directly to a polymer support via a carbon−carbon bond, we employed the Suzuki coupling reaction. Upon treatment of benzotriazole with bromochloroethane in the presence of NaH followed by direct bromination, the desired 5-bromo compound **6** was isolated together with traces of the 7-bromo isomer in 58% yield. Compound **6** was heated with polymer-bound boronic acid, prepared according to the published procedure[11] in the presence of a palladium catalyst at 90 °C for 24 h. Subsequent deprotection afforded **8**, and the loading was determined by CHN analysis as 1.3 mmol/g. Thus **8** has clear advantages regarding loading over **2** and **4**; hence **8** was chosen for further testing.

Enolate Acylation by Solid-Phase Acylating Agent. We tested the heterocyclic leaving group approach in enolate C-acylation sequences (Scheme 2). Acylation of enolates in solution is often accompanied by O-acylation;[12] the utility of *N*-acyl azoles ("azolides") is recognized as advantageous from the point of regioselectivity.[7,13] Two benzotriazole preloaded resins with an ether linker **9a**,**b** were prepared according to the protocol elaborated earlier in our group.[6a] The application of different Merrifield resins with various loading afforded two resins **9a**,**b** with corresponding loadings 0.68 and 0.49 mmol/g and different swelling abilities.

Polymer supports **8** and **9a**,**b** were further transformed into the corresponding polymer azolides **10** which were subsequently reacted with ketone **11** lithio enolates to yield 1,3-diketones **12** (Scheme 2, Table 1). Their ^{1}H NMR spectra indicated that such acylation is regiospecific and yielded only products of C-acylation which is consistent with solution-phase preparations.[13] The derivatives of resins **9a**,**b** afforded compounds **12** in 18−41% yields while polymer azolides based on resin **8** gave 47−77% of corresponding diketones. Such differences are not connected with the low swelling abilities of the starting benzotriazole resins which were observed for all three substrates and have been reported earlier.[13,14] We believe that the resin **8**, which bears a benzotriazole moiety attached to the polymer support with a C−C bond, is less prone to side reactions as compared to the ether-linked resins **9a**,**b**. Such side processes could involve abstraction of linker benzylic proton in strong basic media (LDA) and further reaction of the resulting polymer benzylic anion with ketone **11** similarly to that shown in reference 14. This changes the stoichiometry of the reaction and decreases the yields of diketones **12**.

Conclusion

Novel approaches to the polymer-supported heterocyclic leaving groups are proposed. The C−C bond-linked benzotriazole resin **8** showed clear advantages in loadings and efficiency in the C-acylation of ketones compared to that of previously reported ether-linked benzotriazole resins.

Experimental Section

General Procedure for the Preparation of Benzotriazole Resin (2). Attachment of the Piperazine Spacer. A total of 5 g of the Merrifield resin (0.97 mmol/g) swollen in anhydrous DMF (100 mL), piperazine (0.86 g, 0.01 mol), and sodium hydride (0.24 g, 0.01 mol) were shaken at room temperature for 24 h. The resulting resin was filtered off and washed successively with DMF (50 mL), THF (50 mL), THF−H_2O 50% (100 mL), H_2O (100 mL), THF−H_2O 50% (100 mL), MeOH (100 mL), and ethyl ether (100 mL). Loading: 0.96 mmol/g by nitrogen content (%N = 2.68).

Preparation of the Resin 2 (Method A). Piperazine preloaded resin (2 g, 1.92 mmol) swollen in anhydrous DMF (100 mL), DCC (0.62 g, 3.0 mmol), and benzotriazole-5-carboxylic acid (0.49 g, 3.0 mmol) were shaken at 40 °C for 24 h. The resulting resin was filtered off and washed successively with DMF (50 mL), THF (50 mL), THF−H_2O 50% (100 mL), H_2O (100 mL), THF−H_2O 50% (100 mL), MeOH (100 mL), and ethyl ether (100 mL). Loading: 0.66 mmol/g by cleavage with TFA/CH_2Cl_2 (1:1).

Preparation of the Resin 2 (Method B). Piperazine preloaded resin (2 g, 1.92 mmol), swollen in anhydrous DMF (100 mL), and ethyl 1,2,3-benzotriazole-5-carboxylate (0.58 g, 3.0 mmol) were refluxed for 24 h. The resulting resin was filtered off and washed successively with DMF (50 mL), THF (50 mL), THF−H_2O 50% (100 mL), H_2O (100 mL), THF−H_2O 50% (100 mL), MeOH (100 mL), and ethyl ether (100 mL). Loading: 0.42 mmol/g by cleavage with TFA/CH_2Cl_2 (1:1).

General Procedure for the Preparation of Triazole Resin (4). Preparation of the 4-(Ethoxycarbonyl)phenyl Resin. To 5 g of the 4-bromophenyl resin[11] (5 mmol/g) swollen in anhydrous benzene (80 mL) was added 40 mL of BuLi (1.5 M) via syringe dropwise under argon. The resulting mixture was stirred and heated at 80 °C for 4 h, and then the solvent was removed under argon and the resin was washed with anhydrous benzene (3 × 50 mL). The resulting resin was swollen in anhydrous THF (70 mL) under argon, and ethyl chloroformate (28 mL, 0.30 mol) was added in one pot at room temperature. After being stirred overnight at room temperature, the resin was filtered off and washed successively with THF (50 mL), THF−H_2O 50% (100 mL), H_2O (100 mL), THF−H_2O 50% (100 mL), MeOH (100 mL), and ethyl ether (100 mL). Loading: 5.5 mmol/g by weight.

Table 1. Synthesis of 1,3-Diketones via Polymer-Supported Azolides **8** and **9a**,**b**

				isolated yield by acylation with resin, %		
diketone	R^1	R^2	R	**8**	**9a**	**9b**
12a	1-indanone		Ph	74	35	29
12b	Ph	H	Ph	77	41	28
12c	*i*-Pr	Et	Ph	61	32	18
12d	Et	Me	Ph	63	33	21
12e	4-*tert*-butyl-cyclohexanone		$CH_2C(CH_3)_3$	55	36	21
12f	4-*tert*-butyl-cyclohexanone		CH_3	59	34	22
12g	4-*tert*-butyl-cyclohexanone		Ph	52	27	25
12h	3,5-dimethyl-2-cyclohexene-1-one		Ph	47	28	28

Preparation of the Di(benzoylhydrazine) Resin. To 2 g of the 4-(ethoxycarbonyl)phenyl resin (5.5 mmol/g) swollen in anhydrous DMF (40 mL) was added benzoylhydrazine (8.17 g, 60 mmol) under nitrogen, and the mixture was stirred and heated at 120 °C for 48 h. After cooling to room temperature, the resulting resin was filtered off and washed successively with DMF (50 mL), DMF−H_2O 50% (100 mL), H_2O (100 mL), MeOH−H_2O 50% (100 mL), MeOH (100 mL), acetone (100 mL), CH_2Cl_2 (100 mL), and ethyl ether (100 mL). Loading: 0.43 mmol/g (%N, 1.21).

Preparation of the Triazole-Resin 4. Di(benzoylhydrazine) resin (2 g, 0.43 mmol/g) swollen in phosphorus oxychloride (25 mL) and chloroform (25 mL) was refluxed for 24 h. After cooling to room temperature, ammonium acetate (6.93 g, 90 mmol) was added, and the mixture was refluxed again for another 24 h. The mixture was allowed to cool to room temperature, and the resulting resin was filtered off and washed successively with chloroform (100 mL), DMF (50 mL), DMF−H_2O 50% (100 mL), H_2O (100 mL), MeOH−H_2O 50% (100 mL), MeOH (100 mL), acetone (100 mL), CH_2Cl_2 (100 mL), and ethyl ether (100 mL). Loading: 0.30 mmol/g (calculated from nitrogen content 1.30%).

General Procedure for the Preparation of Benzotriazole Resin 8. 1-(2-Chloroethyl)-1*H*-1,2,3-benzotriazole and Its 2-Isomer. To a suspension of NaH (500 mg, 20 mmol) in anhydrous DMF (20 mL) at 0 °C under nitrogen was added a solution of benzotriazole (2.38 g, 20 mmol) in DMF (10 mL) via syringe dropwise. The resulting mixture was stirred at room temperature for 30 min, then 1-chloro-2-bromoethane (20 mmol) was added in one portion, and the mixture was stirred at room temperature for 24 h. The reaction was quenched at this temperature with water (30 mL), extracted with diethyl ether (2 × 100 mL), and the organic fractions were washed with saturated sodium bicarbonate solution (2 × 50 mL) and water successively. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness to give an oil mixture of Bt-1 and Bt-2 derivatives which were separated by column chromatography on silica gel (hexanes/EtOAc 3:1).

1-(2-Chloroethyl)-1*H*-1,2,3-benzotriazole: white needles (33%), mp 110−111 °C; ^{1}H NMR δ 8.08 (d, 1H, J = 8.5 Hz), 7.60 (d, 1H, J = 8.2 Hz), 7.52 (t, 1H, J = 8.0 Hz), 7.39 (t, 1H, J = 7.7 Hz), 4.96 (t, 2H, J = 6.0 Hz), 4.06 (t, 2H, J = 6.0 Hz); ^{13}C NMR δ 145.8, 133.4, 127.7, 124.1, 120.1, 109.3, 49.4, 42.2. Anal. Calcd for $C_8H_8ClN_3$: C, 52.90; H, 4.45; N, 23.14. Found: C, 52.88; H, 4.22; N, 23.00.

2-(2-Chloroethyl)-2*H*-1,2,3-benzotriazole: white needles (44%), mp 39−40 °C; ^{1}H NMR δ 7.87 (dd, 2H, J = 6.5 Hz), 7.40 (dd, 2H, J = 6.5 Hz), 5.04 (t, 2H, J = 6.3 Hz), 4.16 (t, 2H, J = 6.3 Hz); ^{13}C NMR δ 144.5, 126.7, 118.1, 57.4, 41.5. Anal. Calcd for $C_8H_8ClN_3$: C, 52.90; H, 4.45; N, 23.14. Found: C, 53.06; H, 4.28; N, 23.22.

Preparation of 5-Bromo-1-(2-chloroethyl)-1*H*-1,2,3-benzotriazole (6). A mixture of 1-(2-chloroethyl)benzotriazole (5 mmol), *N*-bromosuccinimide (7.5 mmol), and concentrated sulfuric acid (1.25 mmol) was refluxed at 70 °C in trifluoroacetic acid (3 mL) for 20 h. The mixture was then allowed to cool to room temperature, diluted with dichloromethane (50 mL), and washed with water (3 × 30 mL). The organic extracts were dried over magnesium sulfate, filtered, and evaporated to dryness to give an oil which was purified by column chromatography on silica gel (hexanes/EtOAc 3:1): white needles (58%), mp 54−55 °C; ^{1}H NMR δ 8.21 (s, 1H), 7.59 (d, 1H, J = 8.7 Hz), 7.50 (d, 1H, J = 8.5 Hz), 4.95 (t, 2H, J = 5.8 Hz), 4.05 (t, 2H, J = 5.8 Hz); ^{13}C NMR δ 146.8, 132.5, 131.0, 122.5, 117.2, 110.7, 49.6, 42.3. Anal. Calcd for $C_8H_7BrClN_3$: C, 36.88; H, 2.71; N, 16.13. Found: C, 36.39; H, 2.54; N, 15.75.

Suzuki-Coupling of 6 with the Acid Phenylboronic Resin 5. A mixture of resin **5**[11] (3 g, 4 mmol/g), 5-bromo-1-(2-chloroethyl)-1*H*-1,2,3-benzotriazole (**6**) (3.38 g, 13.2 mmol), palladium acetate (135 mg, 0.6 mmol), tris-*o*-tolylphosphine (365 mg, 1.2 mmol), and triethylamine (8.3 mL, 60 mmol) was heated in anhydrous DMF at 100 °C for 24 h. The mixture was allowed to cool to room temperature, and the resulting resin was filtered off and washed successively with DMF (50 mL), DMF−H_2O 50% (100 mL), H_2O (100 mL), 1 N HCl (100 mL), H_2O−MeOH 50% (100 mL), MeOH (100 mL), MeOH−CH_2Cl_2 50% (100 mL), CH_2Cl_2 (100 mL), and ethyl ether (100 mL). Loading: 1.6 mmol/g (%N, 6.66).

Preparation of the Benzotriazole Resin (8). The 1-(2-chloroethyl)-1*H*-1,2,3-benzotriazole-protected resin **7** (3.6g, 1.6 mmol/g) was swollen in anhydrous acetonitrile (100 mL) under nitrogen, then sodium hydride (546 mg, 21.6 mmol) was added, and the mixture was heated under reflux for 10 h. After cooling to room temperature, 6 N hydrochloric acid (36 mL) was added dropwise, and the mixture was heated again at 80 °C overnight. The resulting mixture was cooled again to room temperature followed by the addition of a solution of sodium acetate (19.4 g, 0.24 mol) in water (33 mL). The mixture was stirred at room temperature for 2 h, and the resulting resin was then filtered off and washed

successively with H_2O (200 mL), H_2O−MeOH 50% (100 mL), MeOH (100 mL), MeOH−CH_2Cl_2 (100 mL), CH_2Cl_2 (100 mL), and ethyl ether (100 mL). Loading: 1.3 mmol/g (%N, 5.49).

General Procedure for the Preparation of Polymer-Supported Azolides 10. Lithium bis(trimethylsilyl)amide (3 mL, 3 mmol, 1 N solution in hexanes) and benzotriazole resin **8**, **9a**, or **9b** respectively (2 mmol) preswelled in 1-methyl-2-pyrrolidinone (50 mL) were stirred for 1 h at room temperature, and the solution of the corresponding acyl chloride (3 mmol) in dry THF (10 mL) was added dropwise. The slurry was stirred at room temperature for 6 h and then at 60 °C for 2 h, cooled, and washed successively with DMF (50 mL), DMF−MeOH 50% (100 mL), MeOH (100 mL), H_2O−MeOH 50% (100 mL), MeOH (100 mL), and ethyl ether (100 mL).

General Procedure for the C-Acylation of Ketones with Polymer-Supported Azolides 10. A 50 mL round-bottom flask with septum inlet was charged with a solution of LDA (1 mL, 0.15 M solution in hexanes) in dry THF (10 mL) under nitrogen and cooled to −78 °C, and a solution of the corresponding ketone **11** (1.5 mmol) in dry THF (15 mL) was added dropwise. After stirring for 1 h at this temperature, the resulting mixture was added dropwise to the slurry of a resin **8**, **9a**, or **9b** (0.5 mmol) in dry THF (50 mL) by cannula, and the mixture was stirred for another 12 h while the temperature was allowed to rise to 20 °C. The resin was separated and washed with THF (20 mL), and the organic layer was washed with 10% NH_4Cl (2 × 50 mL) and water (50 mL) and then dried (Mg_2SO_4 anhydrous). Chromatography on silica gel with hexanes/ethyl acetate (4:1) as an eluent gave diketones **12**, which were analyzed by LCMS.

Supporting Information Available. LCMS traces for diketones **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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