Synthesis of 1*H*-Benzotriazoles via Reductive Amination on Solid Supports

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Abstract: An efficient synthesis of *N*-benzyl-1*H*-benzotriazoles utilizing a two-step reductive amination reaction on solid supports has been achieved. The method is suitable for combinatorial synthesis.

Key words: solid-phase synthesis, nitrogen heterocycles, imines, benzotriazoles, reductive amination reaction

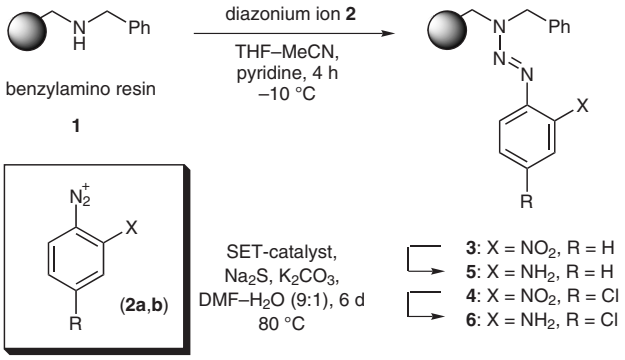
The benzotriazolyl moiety has shown to be an important, but still underdeveloped, pharmacophore.[1] Recently, we disclosed a straightforward solid-phase synthesis of 1-alkyl-1*H*-benzotriazoles via nucleophilic displacement,[2] and of 1-alkyl- and 1-aryl-1*H*-benzotriazoles via Hartwig–Buchwald amination.[3] The latter reaction allows a wide range of substituents in 1-position, except for the 1-benzyl substituent, since no reaction could be achieved between benzylic amines and haloarenes on solid supports. Thus an alternative entry to 1-alkyl- and 1-benzyl-1*H*-benzotriazoles was investigated.

Previously, we reported that stabile imines can be formed on solid supports with immobilized *para*-aminobenzenes,[4] however the formation of *ortho*-iminobenzenes on triazene linker and their further modifications with organometallic reagents have not yet been explored.

In this communication, we disclose the reductive amination of triazene-bound anilines to give benzotriazoles after cleavage.

The required *ortho*-nitroarene triazene resins **3** and **4** were synthesized via optimized procedures from the corresponding anilines and benzylaminomethyl polystyrene (**1**), which is available from chloromethylated polystyrene (1–2% cross-linked).[5,6] The anilines were immobilized on Merrifield resin under standard conditions via their diazonium salts **2a**,**b** (Scheme 1). The loadings were determined by elemental analysis. The amino resins **5** and **6** were synthesized by reduction of the nitro resins **3** and **4** by sodium sulfide in the presence of SET- and the phase-transfer catalyst viologen.[7]

The reductive amination of various carbonyl compounds **7** with triazene-linked 2-aminobenzenes **5** and **6** was performed via a two-step reaction (Scheme 2). At first, the corresponding immobilized imines **8** were formed by heating the reaction mixture at 80 °C in toluene in the presence of a drying agent. In the second step, the imines



Scheme 1 Attachment of diazonium ions to solid supports

8 were treated with 5–13 equivalents of $NaBH_3CN$, resulting in a clean conversion to immobilized secondary amines **9**.

In general, benzaldehydes **7c–l** were found to be very good substrates for the reductive amination reaction. While cyclohexanone (**7a**) provided good results, 4-methoxyacetophenone (**7b**) gave only poor ones. Fluorine, chlorine and bromine atoms were tolerated, along with nitro, dimethylamino, aceto and etheral oxygen groups. Electron-withdrawing groups (as in benzaldehydes **7d**,**j**) as well as electron-donating groups (as in benzaldehyde **7i**) were well suitable.

Mild acidic cleavage (5 mol% TFA in CH_2Cl_2, r.t., 5 min) of the triazene linker provided *ortho*-amino-substituted arene diazonium ions **11**, which immediately cyclized to give the corresponding 1*H*-benzotriazoles **12** in good to excellent purities. The results are summarized in Table 1.

Primary and secondary *ortho*-amino (nucleophilic) substituents result in quantitative formation of benzotriazoles **12** due to the quick cyclization reaction. The theoretically possible hydrolysis of 1-substituted benzotriazoles during the workup was not observed. Thus, this cleavage protocol is suitable for analytical purposes, for example for rapid gas chromatographic analysis. The resulting purities of the desired benzotriazoles actually reflect the overall turnover of the two-step reaction on the solid support.

In conclusion, the solid-phase synthesis of diverse N-substituted benzotriazoles using the two-step reductive amination[9] reaction starting from readily available compounds is shown. The products were obtained in high purities. The presented work substantially extends the chemical transformations to be carried out on solid supports to give the desired benzotriazoles. This route to the

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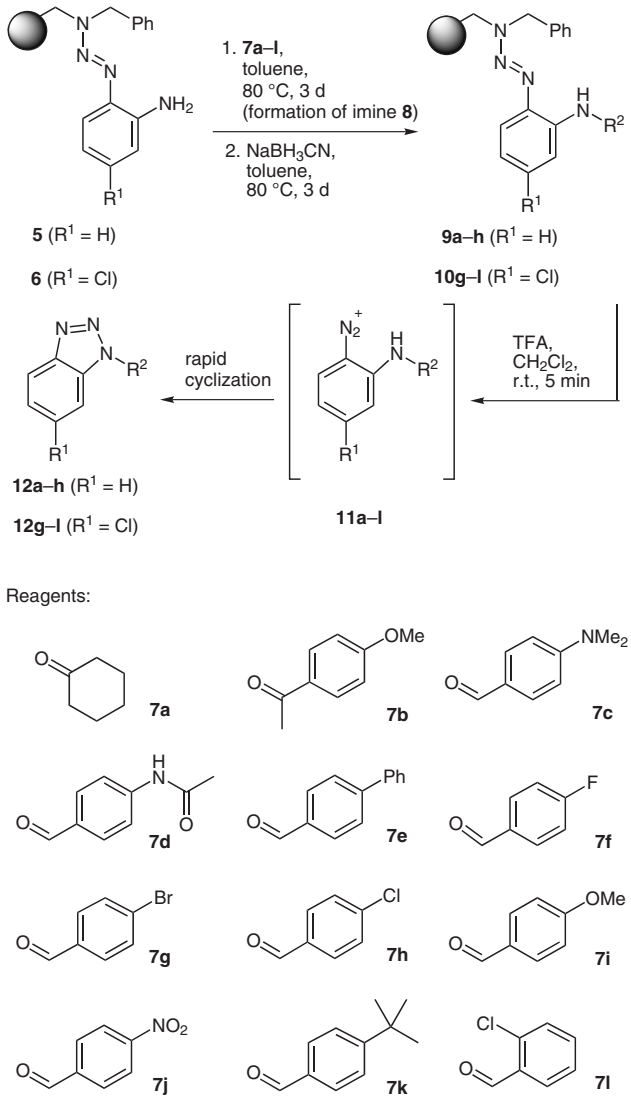


Scheme 2 Reductive amination with immobilized amines

immobilized N-substituted 2-anilines allows a larger set of substitution pattern of the N-substituents and gives a prospect on a straightforward synthesis of novel 1*H*-benzotriazoles. In comparison to the straightforward alkylation of benzotriazoles in solution, the presented method offers the significant advantage of being applicable as a useful step in a multistep combinatorial synthesis strategy on solid support, giving access to diverse compound libraries.

Table 1 Results of the Two-Step Reductive Amination Reaction[8]

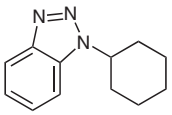
Resin	Reactant	Benzotriazole	Purity[a]
5	**7a**	 **12a**	93%

Table 1 Results of the Two-Step Reductive Amination Reaction[8] (continued)

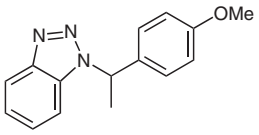
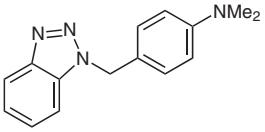
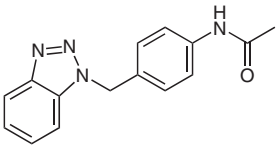
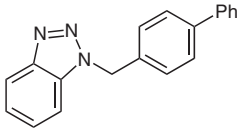
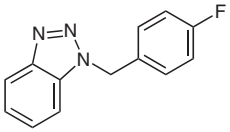
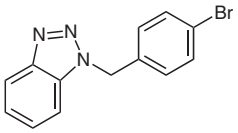
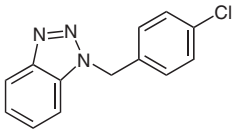
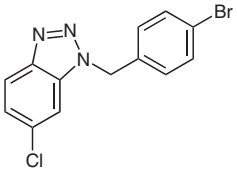
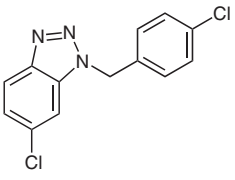
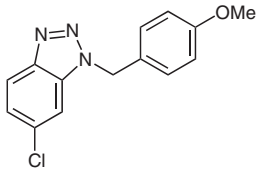
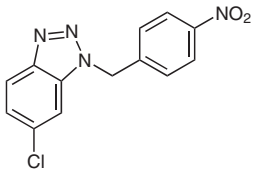
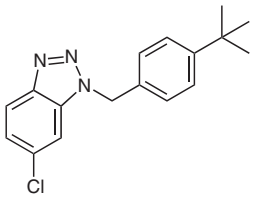
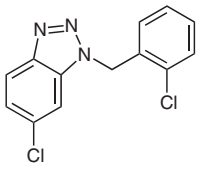
Resin	Reactant	Benzotriazole	Purity[a]
5	**7b**	 **12b**	12%
5	**7c**	 **12c**	99%
5	**7d**	 **12d**	95%
5	**7e**	 **12e**	95%
5	**7f**	 **12f**	95%
5	**7g**	 **12g**	71%
5	**7h**	 **12h**	95%
6	**7g**	 **12i**	95%
6	**7h**	 **12j**	95%

Table 1 Results of the Two-Step Reductive Amination Reaction[8] (continued)

Resin	Reactant	Benzotriazole	Purity[a]
6	**7i**	 **12k**	95%
6	**7j**	 **12l**	95%
6	**7k**	 **12m**	95%
6	**7l**	 **12n**	95%

[a] Purity of the water-washed product.

References and Notes

(1) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

(2) (a) Lormann, M. E. P.; Walker, C. H.; Es-Sayed, M.; Bräse, S. *Chem. Commun.* **2002**, 1296. (b) Bräse, S. *Acc. Chem. Res.* **2004**, *37*, 805.

(3) Zimmermann, V.; Bräse, S. *J. Comb. Chem.* **2007**, *9*, 1114.

(4) Avemaria, F.; Zimmermann, V.; Bräse, S. *Synlett* **2004**, 1163.

(5) Merrifield resin (0.93 mmol/g) was obtained from Polymer Laboratories.

(6) Dahmen, S.; Bräse, S. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C.; Hanko, R.; Hartwig, W., Eds.; Wiley-VCH: Weinheim, **2002**, Chap. 4.

(7) Zimmermann, V.; Avemaria, F.; Bräse, S. *J. Comb. Chem.* **2007**, *9*, 200.

(8) **Representative Experimental Procedure**:[10]
Resin: Resin **6** (0.600 g, 0.384 mmol, 1.0 equiv), 4-methoxybenzaldehyde (**7i**; 0.523 g, 3.84 mmol, 10 equiv) and molecular sieve (2 g) were suspended in anhyd toluene (15 mL) in a 20-mL glass vial and the vessel was sealed with a PTFE-coated cap. The mixture was heated at 80 °C for 3 d and occasionally shaken through. After cooling, the resin was separated from the molecular sieve, filtered on a polypropylene plastic frit, subsequently roughly washed with anhyd acetone, CH_2Cl_2 and pentane and dried in air stream for 5 min. The molecular sieve was disposed and the glass vial was briefly rinsed with anhyd toluene. The resin was then immediately placed back into the glass vial, $NaBH_3CN$ (0.145 g, 3.84 mmol, 10 equiv) and anhyd toluene (15 mL) were added and the vessel was sealed. The mixture was heated at 80 °C for another 3 d and occasionally shaken through. After cooling, the resin was filtered on a polypropylene plastic frit, subsequently washed with MeOH, 2 × [THF, pentane (2 ×)], 3 × [CH_2Cl_2, pentane (2 ×)], and dried in vacuo for 12 h, to give the resin **10i**.
Cleavage: The resin **10i** (0.400 g) was placed into a glass vial and a solution of trifluoroacetic acid (0.100 mL) in CH_2Cl_2 (10 mL) was added. After 5 min, the mixture was filtered on a glass frit (polypropylene plastic frits are not suitable) and washed with CH_2Cl_2 (8 mL). The combined filtrates were washed with H_2O (2 × 10 mL), the solvent was removed by distillation, and the product was dried in vacuo to yield the benzotriazole **12k** with 95% purity (^{1}H NMR).

(9) For leading references, see: (a) Review: Baxter, E. W.; Reitz, A. B. *Org. React. (N. Y.)* **2002**, *59*, 1. For recent examples, see: (b) Rodriguez Loaiza, P.; Löber, S.; Hübner, H.; Gmeiner, P. *J. Comb. Chem.* **2006**, *8*, 252.
(c) DiCesare, J. C.; White, C. E.; Rasmussen, W. E.; White, B. M.; McComas, C. B.; Craft, L. E. *Synth. Commun.* **2005**, *35*, 663. (d) Groth, T.; Grötli, M.; Lubell, W. D.; Miranda, L. P.; Meldal, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4258.

(10) Spectroscopic data for **12c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.02 (s, 6 H, NMe_2), 5.79 (s, 2 H, CH_2), 7.12 (br d, ^3J = 8.67 Hz, 2 H, 3′-H, 5′-H), 7.30 (br d, ^3J = 8.67 Hz, 2 H, 2′-H, 6′-H), 7.32–7.45 (m, 3 H, 5-H, 6-H, 7-H), 8.05 (ddd, ^3J = 8.10 Hz, ^4J = 1.13 Hz, ^5J = 0.94 Hz, 1 H, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.5 (+, NMe), 51.7 (−, CH_2), 109.6 (+, CAr), 117.3 (+, 2 × C, CAr′), 119.9 (+, CAr), 124.3 (+, CAr), 127.7 (+, CAr), 129.3 (+, 2 × C, CAr′), 129.9 (quart, C-7a), 132.7 (quart, C-1′), 145.9 (quart, C-4′), 146.8 (quart, C-3a).