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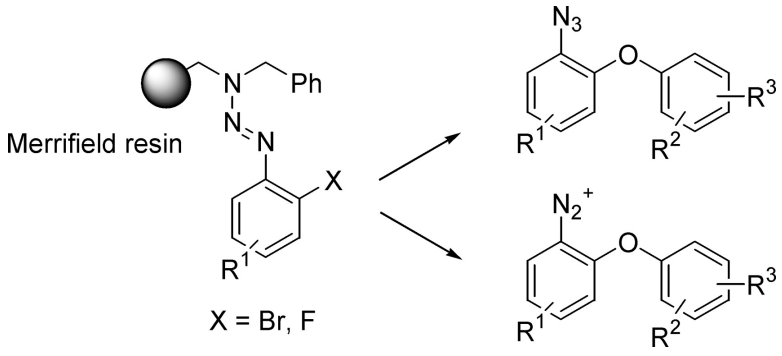

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Efficient Synthesis of Highly Substituted Diaryl Ethers on Solid Supports Using the Ullmann Reaction

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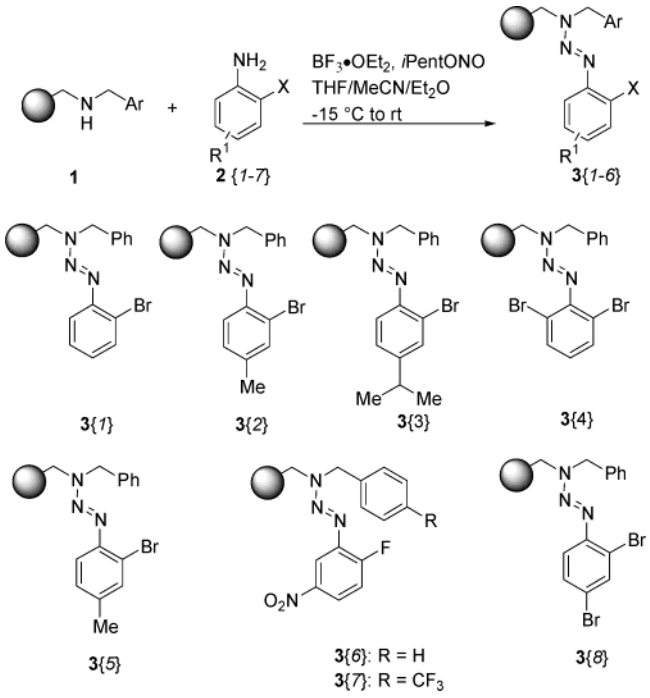
Diaryl ethers are important structures found in both nature and biologically active compounds. Some diaryl ethers exert considerable pharmacological activity, such as perrottetines, riccardin B, and marchantin quinone, all of which influence blood coagulation;[1] the antiviral cyclic peptide K-13;[2] and the glycopeptide antibiotics Vancomycin, Teicoplanin, and Complestatin.[2−5] Until recently, the synthesis of diaryl ethers having sensitive groups remained a challenge.[6−8] Therefore, diaryl ethers are a promising class of potentially useful pharmacologically active compounds, and their synthesis in liquid phase, particularly by nucleophilic aromatic substitution and Ullmann-type reactions, has found widespread application in organic chemistry.[9] The solid-phase synthesis of diaryl ethers mainly focuses on nucleophilic displacement of fluoronitroarenes in an intermolecular or intramolecular sense, furnishing 7-,[10] 13-,[11] 14-,[11−13] 15-, 16-,[11,12,14] and 17-membered rings,[11] as demonstrated in the total synthesis of OF 4949.[14] Analogously, cyclic alkylaryl ethers[15] and thioethers[16] were synthesized using this strategy.

Results and Discussion

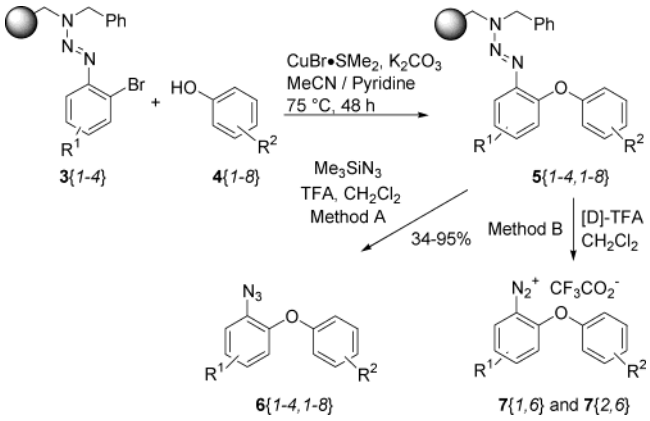
We were intrigued by the possibility of generating diaryl ethers on solid supports using the Ullmann reaction variant reported by Nicolaou et al.,[5] since this reaction is particularly suitable for the synthesis of triazenyl-substituted diaryl ether and has been used in the total synthesis of the glycopeptide antibiotic Vancomycin.[5,17] The reaction temperature required is in contrast to classical Ullmann conditions compatible with solid-phase chemistry. Triazenes are masked diazonium ions and are convertible to a broad range of heterocycles.[18] In this manuscript, we disclose the first solid-phase Ullmann−Nicolaou reaction.

The required *ortho*-halo triazene resins **1**{*1*−*6*} were synthesized via optimized procedures from anilines and arylmethylaminomethyl polystyrenes, which are available from chloromethylated polystyrene (1−2% cross-linked) in one synthetic step in large quantities (Scheme 1).[19,20] Five different anilines[21] were immobilized on benzylamine-substituted Merrifield resin under standard conditions using this route.[22] The loadings were determined by elemental analysis.

Scheme 1. Synthesis of *ortho*-Haloaryltriazenyl Resins **3**{*1*−*8*}



Scheme 2. Ullmann-Type Reactions on a Solid Support



The Nicolaou variant of the Ullmann reaction was performed on the resins **3**{*1*−*4*} (500-mg scale) at 75−85 °C in acetonitrile/pyridine or dimethylformamide/pyridine for 36−48 h with 1.1−5.0 equiv of eight different phenols **4**{*1*−*8*}[21] in the presence of the soluble copper complex CuBr·SMe_2 (1 equiv) (Scheme 2). During the reaction, a color change of the resin from a slightly reddish color into a deep red color was observed. Heteroatoms such as nitrogen or oxygen atoms and simple functional groups (double bonds, amides, amines) at the phenolic moiety were tolerated; however, it was puzzling to note that extension to mono and

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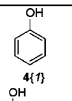
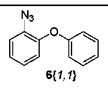
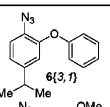
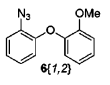
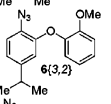
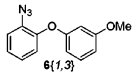
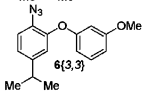
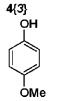
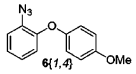
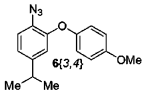
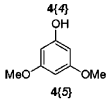
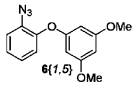
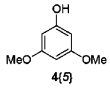
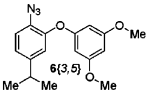
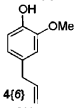
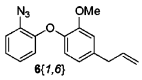
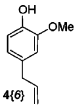
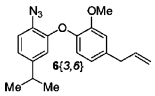
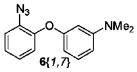
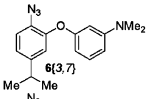
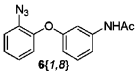
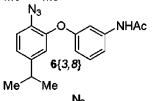
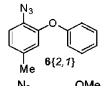
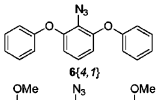
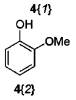
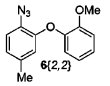
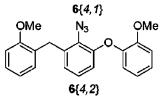
Table 1. Functionalized Azido Diaryl Ether Prepared

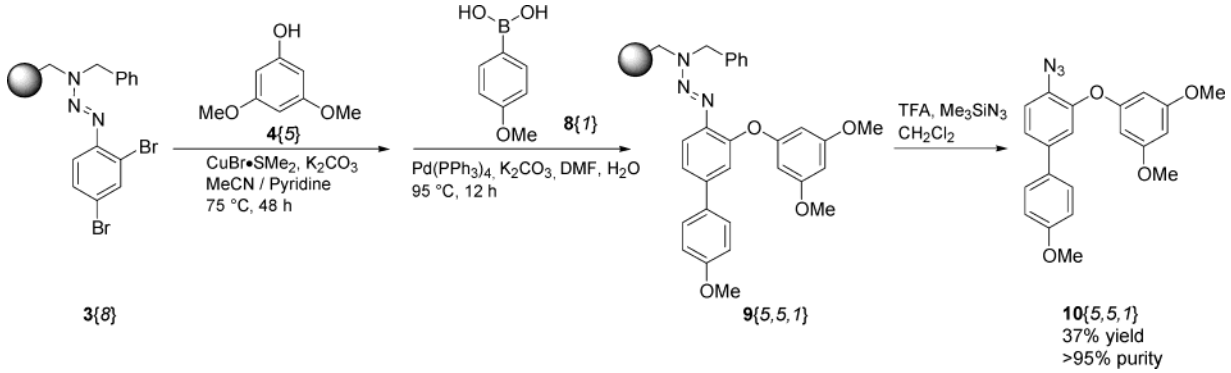
	Resin	Phenol	Products obtained	Yield (%)[a]		Resin	Phenol	Products obtained	Yield (%)[a]
1	**3**{*1*}	 4{*1*}	 6{*1,1*}	70	17	**3**{*3*}	 4{*1*}	 6{*3,1*}	56
2	**3**{*1*}	 4{*2*}	 6{*1,2*}	77	18	**3**{*3*}	 4{*2*}	 6{*3,2*}	61
3	**3**{*1*}	 4{*3*}	 6{*1,3*}	51	19	**3**{*3*}	 4{*3*}	 6{*3,3*}	47
4	**3**{*1*}	 4{*4*}	 6{*1,4*}	44	20	**3**{*3*}	 4{*4*}	 6{*3,4*}	47
5	**3**{*1*}	 4{*5*}	 6{*1,5*}	34	21	**3**{*3*}	 4{*5*}	 6{*3,5*}	48
6	**3**{*1*}	 4{*6*}	 6{*1,6*}	45	22	**3**{*3*}	 4{*6*}	 6{*3,6*}	57
7	**3**{*1*}	 4{*7*}	 6{*1,7*}	52	23	**3**{*3*}	 4{*7*}	 6{*3,7*}	52
8	**3**{*1*}	 4{*8*}	 6{*1,8*}	45	24	**3**{*3*}	 4{*8*}	 6{*3,8*}	50
9	**3**{*2*}	 4{*1*}	 6{*2,1*}	47	25	**3**{*4*}	 4{*1*}	 6{*4,1*}	51
10	**3**{*2*}	 4{*2*}	 6{*2,2*}	51	26	**3**{*4*}	 4{*2*}	 6{*4,2*}	63
11	**3**{*2*}	4{*3*}	6{*2,3*}	51	27	**3**{*4*}	4{*3*}	6{*4,3*}	83
12	**3**{*2*}	4{*4*}	6{*2,4*}	53	28	**3**{*4*}	4{*4*}	6{*4,4*}	71
13	**3**{*2*}	4{*5*}	6{*2,5*}	44	29	**3**{*4*}	4{*5*}	See [23]	
14	**3**{*2*}	4{*6*}	6{*2,6*}	50	30	**3**{*4*}	4{*6*}	6{*4,6*}	95
15	**3**{*2*}	4{*7*}	6{*2,7*}	54	31	**3**{*4*}	4{*7*}	6{*4,7*}	45
16	**3**{*2*}	4{*8*}	6{*2,8*}	45	32	**3**{*4*}	4{*8*}	6{*4,8*}	39

[a] Isolated yield of purified material over three steps based on the loading of the Merrifield resin used (see Supporting Information). 5% TFA, 5% Me_3SiN_3, CH_2Cl_2, 5 min.

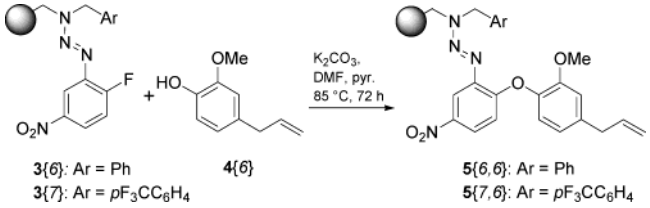
dichlorphenols, *m*-nitrophenol, and substituted salicylaldehydes failed at this point with all resins and under various reaction temperatures (60−100 °C) and times (12−96 h). Only the unreacted bromo derivatives were isolated after the cleavage (vide infra). This is in sharp contrast to the reaction reported with bromoaryltriazenes in liquid phase.[5] It is possible that this is due to the higher acidity and, hence, lower nucleophilicity of the electron-poor phenols.

We were pleased, however, to find that even the dibrominated resin **3**{*4*} underwent coupling with different phenols to give bisaryloxy resins in moderate to excellent yields. In addition, we examined the influence of the triazene moiety on the regioselectivity of the Ullmann−Nicolaou variant (Scheme 3). Thus, resin **3**{*8*} with two bromo residues was subjected to the diaryl ether-forming reaction. Subsequently, a Suzuki cross-coupling was performed under

Scheme 3. Regioselective Ullmann Reaction and Subsequent Suzuki Reaction on a Solid Support Using Dibromo Resin **3**{*8*}



Scheme 4. Nucleophilic Displacement on a Solid Support Using Fluoronitro Resins **3**{*6*}, **3**{*7*}



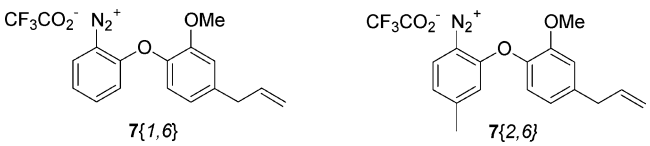
standard conditions. After cleavage (see below), the desired diaryl ether was isolated in excellent purity, showing that this Ullmann variant works only on *ortho*-triazenylaryl-halides.

After the copper-mediated reactions, copper salts were efficiently removed using extensive washing with a solution of sodium diethylaminodithiocarbamate (Cupral) in DMF (5%).[24] Subsequently, the resins were washed with different polar and nonpolar solvents (see Supporting Information).

To compare this method of diaryl ether formation with other strategies, diaryl ethers were also prepared via nucleophilic substitution on the Sanger-type nitrofluoroaryl resins **3**{*6*} and **3**{*7*}.[25] Starting from resin **3**{*6*} or **3**{*7*}, reaction of the model phenol **4**{6} yielded the diaryl ether resins **5**{*6,6*} and **5**{*7,6*}, respectively. The use of potassium carbonate proved to be most efficient for complete conversion (Scheme 4).

The cleavage of resins **5** (300−500 mg) yielding the azides **6** was carried out with trifluoroacetic acid (5%) in the presence of trimethyl silyl azide (1−5%) (Scheme 2, cleavage method A).[25] The novel azides **6** (∼17 to 80 mg) were obtained in purities >90% and yields between 34 and 95% without further purification, as judged by integration of the GC or ^{1}H NMR signals.

Alternatively, cleavage of the resins **5** was performed with 5% trifluoroacetic acid in dichloromethane to yield stable diazonium salts **7** (Scheme 2, cleavage method B), which could be investigated spectroscopically (see Supporting Information).



Due to the numerous possibilities achievable with both azides[26] and diazonium salts in liquid phase, these methods will give access to highly functionalized small molecule libraries.

The first solid-phase synthesis of diaryl ethers using the Ullmann−Nicolaou reaction starting from bromoaryl triazenes is presented. Highly substituted diaryl ethers were obtained in high purities and moderate to excellent overall yields after cleavage from the resin. A simple workup procedure to remove the contamination by copper salt, simple and readily accessible building blocks (2-bromoanilines, phenols), mild reaction conditions, and avoidance of carcinogenic triazenes in liquid phase are key features of this process. The presented work substantially extends the chemical transformations to be carried out on solid supports to give diaryl ethers in which two building blocks and the cleavage method can be varied.

Acknowledgment. Our work was supported by the Deutsche Forschungsgemeinschaft (BR1750-2, Graduiertenkolleg 804) and Fonds der Chemischen Industrie. We also thank the BASF AG, Bayer AG, and Calbiochem-Novabiochem AG for the donation of chemicals.

Supporting Information Available. Experimental details and results and compound data are available as supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Eicher, T.; Fey, S.; Puhl, W.; Büchel, E.; Speicher, A. *Eur. J. Org. Chem.* **1998**, 877−888.
(2) (a) Zhu, J. P. *Synlett* **1997**, 133−144. (b) Bigot, A.; Bois-Choussy, M.; Zhu, J. P. *Tetrahedron Lett.* **2000**, *41*, 4573−4577.
(3) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem.* **1998**, *110*, 2868−2872; *Angew. Chem., Int. Ed.* **1998**, *37*, 2704−2708.
(4) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem.* **1998**, *110*, 2864−2868; *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704.
(5) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T.-Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421−3422.
(6) Rama Rao, A. V.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135−2167.
(7) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem.* **1999**, *111*, 2230−2287; *Angew. Chem., Int. Ed.* **1999**, *38*, 2096−2152.
(8) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045−5065.

(9) Ley, S. V.; Thomas, A. W. *Angew. Chem.* **2003**, *115*, 5558−5607; *Angew. Chem., Int. Ed. Engl*. **2003**, *42*, 5400−5449.
(10) (a) Ouyang, X.; Kiselyov, A. *Tetrahedron Lett*. **1999**, *40*, 5827−5830. (b) Ouyang, X.; Chen, Z.; Liu, L.; Dominguez, C.; Kiselyov, A. *Tetrahedron* **2000**, *56*, 2369−2377.
(11) (a) Feng, Y.; Wang, Z.; Jin, S.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 10768−10769. (b) Feng, Y.; Burgess, K. *Chem.Eur. J.* **1999**, *5*, 3261−3272. (c) Feng, Y.; Burgess, K. *Chem. Eur.—J.* **1999**, *5*, 3273−3278. (d) Feng, Y.; Pattarawarapan, M.; Wang, Z.; Burgess, K. *Org. Lett.* **1999**, *1*, 121−124. (e) Feng, Y.; Burgess, K. *Biotechnol. Bioeng.* **2000**, *71*, 3−8.
(12) Kiselyov, A. S.; Smith, L.; Tempest, P. *Tetrahedron* **1999**, *55*, 14813−14822.
(13) Goldberg, M.; Smith, L.; Tamayo, N.; Kiselyov, A. *Tetrahedron* **1999**, *55*, 13887−13898.
(14) Burgess, K.; Lim, D.; Bois-Choussy, M.; Zhu, J. P. *Tetrahedron Lett*. **1997**, *38*, 3345−3348.
(15) Jefferson, A.; Swayze, E. E. *Tetrahedron Lett.* **1999**, *40*, 7757−7760.
(16) Fotsch, C.; Kumaravel, G.; Sharma, S.; Wu, A.; Gounarides, J.; Nirmala, N.; Petter, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2125−2130.
(17) Nicolaou, K. C.; Koumbis, A. E.; Takayanagi, M.; Natarajan, S.; Jain, N. F.; Bando, T.; Li, H.; Hughes, R. *Chem.—Eur. J.* **1999**, *5*, 2622−2647.
(18) Bräse, S.; Dahmen, S.; Lormann, M. E. P. *Methods Enzymol.* **2003**, *369*, 127−150.
(19) Merrifield resin (1.06 mmol/g) was obtained from Polymer Laboratories.
(20) (a) Dahmen, S.; Bräse, S. In *Handbook of Combinatorial Chemistry;* Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; VCH: Weinheim 2002, Chapter 4. (b) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem.* **1998**, *110*, 3614−3616; *Angew. Chem. Int. Ed.* **1998**, *37*, 3413−3415.
(21) The phenols and 2-bromoanilines are commercially available from Aldrich and Acros.
(22) All new nonpolymeric compounds were characterized by NMR, IR, MS, and HRMS. The purity was determined using NMR techniques. Polymeric compounds were characterized using IR and elemental analysis (CHN) (see Supporting Information).
(23) If the cleavage was conducted on electron-rich resins, such as **5**{*4*,*5*} with trifluoroacetic acid (Scheme 2; Table 1, entry 29), oxadiazadibenzo[*a*,*d*]cycloheptenes were obtained in good yields by intramolecular azo coupling. The minimal requirement for the intramolecular azo coupling under acidic conditions is the presence of two alkoxy substituents or one dialkylamino substituent. The azo coupling is suppressed in the presence of the azide ion (e.g., see Table 1, entry 31). Intramolecular azo coupling reactions have been reported for only a few examples in the literature.
(24) Stary, J. *Solvent Extraction of Metal Chelates*; Pergamon: Oxford, 1964.
(25) Lormann, M. E. P.; Walker, C. H.; Es-Sayed, M.; Bräse, S. *Chem. Commun*. **2002**, 1296−1297.
(26) (a) Demko, Z. P.; Sharpless, K. B. *Angew. Chem*. **2002**, *114*, 2214−2217; *Angew. Chem. Int Ed*. **2002**, *41*, 2113−2116. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem*., accepted.

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