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Functionalized azobenzenes through cross-coupling with organotrifluoroborates

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Abstract—The development of an azobenzene building block for Suzuki couplings and its application in the synthesis of photochromic agonists and antagonists is reported.

Azobenzene photoswitches are valuable tools to influence protein activity.[1–4] Generally, the strategies employed to this end have involved (a) covalent attachment of an azobenzene derivative to the protein[5] or (b) use of an azobenzene derivative as a noncovalently bound photochromic ligand, where one isomer has a greater affinity for the protein than the other.[6–8]

Classical methods for the synthesis of azobenzenes include electrophilic aromatic substitution involving aryl diazonium salts, condensation of nitrosobenzenes with anilines, and oxidative coupling of two anilines.[9–12] More recently, Buchwald-type couplings of aryl hydrazines with aryl iodides, followed by oxidation, have been employed (Fig. 1).[13]

Further functionalization of azobenzenes typically involves amide, carbamate, ester, or ether linkages. Thus, functionalization possibilities have mostly been limited to elaborations that do not involve the formation of carbon–carbon bonds. In the context of developing photochromic ligands, we became interested in cross-coupling azobenzenes with heterocyclic building blocks functionalized as iodides. Although cross-couplings have been reported for azo bond formation,[10] they have rarely been used to append azobenzenes to a ligand scaffold.[14–16] We now wish to report a general method for attaching the azobenzene moiety onto aryl and vinyl

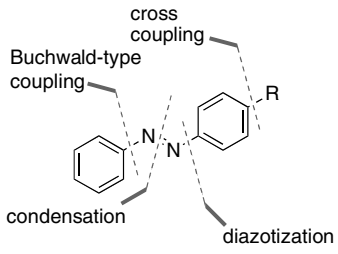

Figure 1. Azobenzene synthesis.

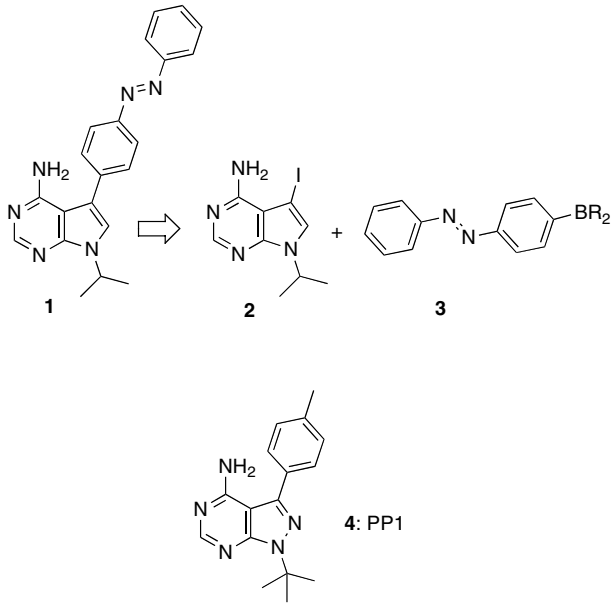

Figure 2. Retrosynthetic analysis of azobenzene **1**.

Keywords: Azobenzene; Cross-coupling; Trifluoroborate.
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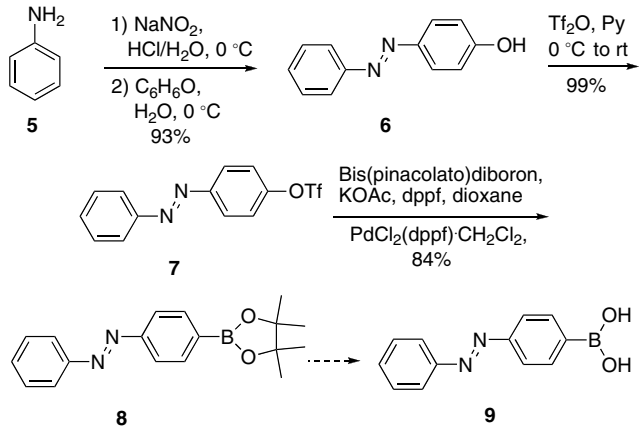
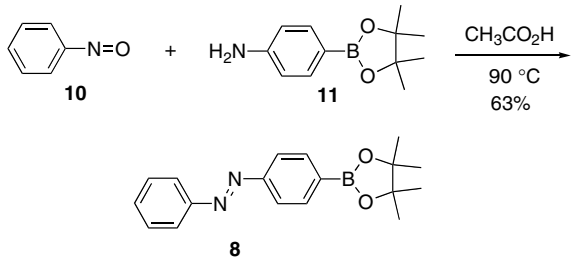


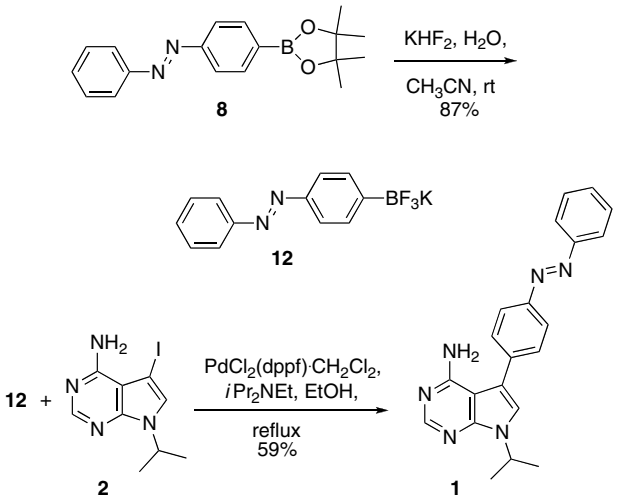
Scheme 1. Ester synthesis via diazotization.



Scheme 2. Ester synthesis via condensation.

iodides. This method proceeds via a Suzuki cross-coupling reaction employing an azobenzene trifluoroborate.[17]

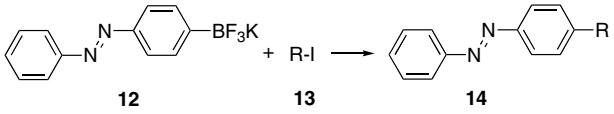
Our interest in azobenzene derivatization was established during the synthesis of compound **1**, which was developed as a photoswitchable kinase inhibitor. The pyrrolopyrimidine part of this molecule is derived from the known Src kinase inhibitor PP1 (**4**).[18] We planned to form the central bond of **1** through cross-coupling of the known iodo pyrrolopyrimidine **2**[19] with an appropriate azobenzene partner **3** (Fig. 2).



Scheme 3. Suzuki coupling of the trifluoroborate azobenzene.

Our first target was therefore an azobenzene boronic acid **9**, which we hoped would undergo a cross-coupling reaction with **2** (Scheme 1).[20] Synthesis of the target azobenzene proceeded via two different possible routes. The first route began with diazonium coupling of aniline with phenol, followed by triflation to yield triflate **7**. Palladium-catalyzed cross-coupling of **7** with bis(pinacolato)diboron gave boronic ester **8** (Scheme 1). The second route gave boronic ester **8** in one step via the condensation of commercially available aniline boronic ester **11** with nitrosobenzene **10** (Scheme 2).

Table 1. Suzuki coupling reactions



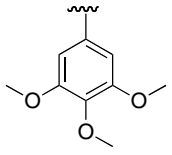
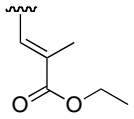
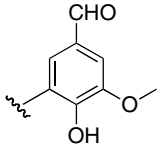
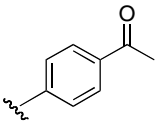
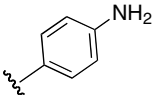
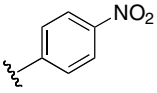
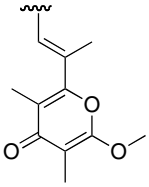
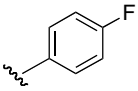
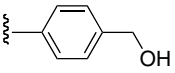
Product	R	Conditions	Yield (%)
14a		$PdCl_2(dppf)$, Cs_2CO_3, MeOH, 65 °C, 3.5 h	72
14b[a]		$PdCl_2(dppf)$, Cs_2CO_3, MeOH, 65 °C, 18 h	41
14c		$PdCl_2(dppf)$, Cs_2CO_3, MeOH, 65 °C, 4.7 h	49

Table 1 (*continued*)

Product	R	Conditions	Yield (%)
14d		$PdCl_2(dppf)$, K_2CO_3, MeOH, 65 °C, 2 h	65
14e		$PdCl_2(dppf)$, K_2CO_3, MeOH, 65 °C, 2 h	61
14f		$Pd(OAc)_2$, PPh_3, K_2CO_3, MeOH, 65 °C, 14 h	61
14g		$PdCl_2(dppf)$, Cs_2CO_3, MeOH, 65 °C, 3.5 h	66
14h		$PdCl_2(dppf)$, K_2CO_3, MeOH, 65 °C, 17 h	60
14i		$PdCl_2(dppf)$, Cs_2CO_3, MeOH, 65 °C, 2 h	47
14j		$PdCl_2(dppf)$, $i Pr_2NEt$, MeOH, 65 °C, 2 h	61

[a] The product was the methyl ester. When ethanol was used as the solvent, ethyl ester was produced in a 14% yield.

Unfortunately, attempted hydrolysis of **8** resulted in the recovery of starting material, inseparable mixtures, or decomposition.[21–23] In one case, in which $NaIO_4$ was employed, the boronic ester was successfully hydrolyzed, but oxidation of the azo bond also occurred. We therefore attempted the Suzuki coupling with the parent boronic ester **8**. However, these conditions resulted in consistently low yields (<20%).

We then decided to convert the boronic ester into the corresponding trifluoroborate salt, using the conditions developed by Molander.[17] Hydrolysis of the ester using KHF_2 gave the azobenzene trifluoroborate salt **12**, which was again subjected to cross-coupling conditions to afford the desired compound **1** in a 59% yield (Scheme 3).

To map the functional group compatibility of this reaction, we have employed the azobenzene trifluoroborate **12** in Suzuki reactions with a variety of vinylic and aromatic iodides (Table 1). The reaction was found to proceed well with both electron-donating and withdrawing vinylic and aromatic iodides.[24] A wide range of functional groups was compatible with the reaction, including aldehydes, alcohols, ketones, anilines, phenols, esters, aryl fluorides, and various heterocycles.

All of the starting iodides were commercially available except **13b** and **13i**, which have been previously described.[25,26] The reaction was usually carried out with $PdCl_2(dppf)$ in refluxing methanol. When triphenyl phosphine was used as a ligand or under microwave conditions, yields typically decreased.

In summary, we have described the application of a recently developed variant of the Suzuki reaction for azobenzene functionalization via carbon–carbon bond formation. The biological evaluation of compound **1** is under investigation, and the results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.043.

References and notes

1. Banghart, M. R.; Borges, K.; Isacoff, E. Y.; Trauner, D.; Kramer, R. H. *Nat. Neurosci.* **2004**, *7*, 1381.
2. Volgraf, M.; Gorostiza, P.; Numano, R.; Kramer, R. H.; Isacoff, E. Y.; Trauner, D. *Nat. Chem. Bio.* **2006**, *2*, 47.
3. Flint, D. G.; Kumita, J. R.; Smart, O. S.; Woolley, G. A. *Chem. Biol.* **2002**, *9*, 391.
4. Lester, H. A.; Krouse, M. E.; Nass, M. M.; Wasserman, N. H.; Erlanger, B. F. *J. Gen. Physiol.* **1980**, *75*, 207.
5. Inada, T.; Terabayashi, T.; Yamaguchi, Y.; Kato, K.; Kikuchi, K. *J. Photochem. Photobiol.* **2005**, *175*, 100.
6. Kaufman, H.; Vratsanos, S. M.; Erlanger, B. F. *Science* **1968**, *162*, 1487.
7. Pearson, D.; Abell, A. D. *Org. Biomol. Chem.* **2006**, *4*, 3618.
8. Fujita, D.; Murai, M.; Nishioka, T.; Miyoshi, H. *Biochemistry* **2006**, *45*, 6581.
9. Priewisch, B.; Ruck-Braun, K. *J. Org. Chem.* **2005**, *70*, 2350.
10. Pozhidaeva, N.; Cormier, M.-E.; Chaudhari, A.; Woolley, G. A. *Bioconj. Chem.* **2004**, *15*, 1297.
11. Behrendt, R.; Schenk, M.; Musiol, H.-J.; Moroder, L. *J. Peptide Sci.* **1999**, *5*, 519.
12. Haghbeen, K.; Tan, E. W. *J. Org. Chem.* **1998**, *63*, 4503.
13. Kim, K.-Y.; Shin, J.-T.; Lee, K.-S.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 117.
14. Izumi, A.; Teraguchi, M.; Nomura, R.; Masuda, T. *Macromolecules* **2000**, *33*, 5347.
15. Ando, H.; Takahashi, T.; Nakano, H.; Shirota, Y. *Chem. Lett.* **2003**, *32*, 710.
16. Han, M. R.; Hashizume, D.; Hara, M. *Acta Crystallogr., Sect. E* **2006**, *62*, o3001.
17. Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
18. Arnold, L. D.; Calderwood, D. J.; Dixon, R. W.; Johnston, D. N.; Kamens, J. S.; Munschauer, R.; Rafferty, P.; Ratnofsky, S. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2167.
19. Tanaka, M.; Bateman, R.; Rauh, D.; Vaisberg, E.; Ramachandani, S.; Zhang, C.; Hansen, K. C.; Burlingame, A. L.; Trauman, J. K.; Shokat, K. M.; Adams, C. L. *PloS Biol.* **2005**, *3*, e128.
20. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
21. DiCesare, N.; Lakowicz, J. R. *Org. Lett.* **2001**, *3*, 3891.
22. Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029.
23. Falck, J. R.; Bondlela, M.; Venkataraman, S. K.; Srinivas, D. *J. Org. Chem.* **2001**, *66*, 7148.
24. *Representative procedure*: To a solution of **12** (25 mg, 0.0868 mmol) in MeOH (1 mL) was added 2-iodo-thiophene (18.3 mg, 0.0868 mmol), anhydrous potassium carbonate (36.0 mg, 0.2604 mmol, 3 equiv), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.708 mg, 0.000868 mmol). The reaction mixture was stirred at 70 °C for 2 h. After cooling, it was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were washed once with water, dried over $MgSO_4$, and evaporated in vacuo. Chromatography (1% MeOH/CH_2Cl_2) afforded 1-phenyl-2-(4-(thiophen-2-yl)phenyl)diazene, **14e**, (14.0 mg, 61%) as an orange crystalline solid. R_f 0.91 (9% MeOH/CH_2Cl_2). UV λ_{max} (100% DMSO): 374 nm; ^{1}H NMR (400 MHz): δ 7.95 (m, 4H), 7.76 (m, 2H), 7.52 (m, 3H), 7.41 (m, 1H), 7.34 (m, 1H), 7.12 (m, 1H). ^{13}C NMR (500 MHz): 152.7, 151.6, 143.4, 136.9, 131.0, 129.1, 128.3, 126.3, 125.9, 124.1, 123.6, 122.9. IR: 3437, 1644, 1440 cm^{-1}. HRMS (EI+) calcd for $C_{16}H_{13}N_2S$ 265.0794, found 265.0758. See also Supplementary data.
25. Liang, G.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 819.
26. Miller, A. K.; Byun, D. H.; Beaudry, C. M.; Trauner, D. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12019.