ORGANIC
LETTERS

2000
Vol. 2, No. 20
3111−3113

Polymer Support Assisted Selective Functionalization of Azoles Using a Palladium-Catalyzed Coupling Reaction

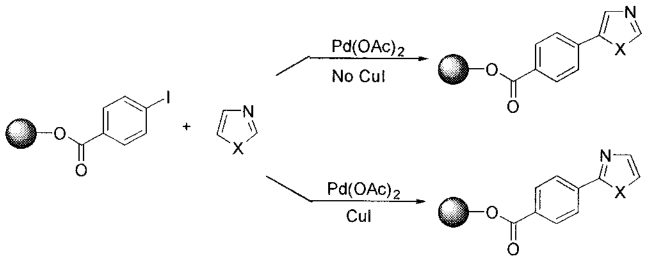
Yoshinori Kondo,* Takashi Komine, and Takao Sakamoto

*Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Aoba-ku,
Sendai 980-8578, Japan*

ykondo@mail.pharm.tohoku.ac.jp.

Received July 11, 2000

ABSTRACT



Regioselective palladium-catalyzed monoarylation of azoles was achieved using iodobenzoate immobilized on an insoluble polymer support. The positional selectivity for the coupling reaction was dramatically influenced by the presence of CuI. No diarylation was observed in either case. Unsymmetrical diarylation was also obtained with the polymer support using sequential coupling reactions.

Recently, solid-phase organic chemistry has been regarded as one of the important new fields in synthetic organic chemistry.[1] Solid-phase organic synthesis has drawn the attention of many chemists, as it is a powerful method for accelerating the process of drug discovery, owing to a faster and increased production of compounds than allowed by conventional solution-phase synthesis. The products of solid-phase synthesis can be easily purified with a simple wash of the insoluble resin, making this method interesting in both technical and practical terms.[2] In 1970, H. Rapoport introduced the concept of high dilution effect in solid-supported chemistry.[3] There are also a number of reports on this effect in the literature.[4] However, more examples should be

---

(1) (a) *Combinatorial Chemistry*; Jung, G., Ed.; Wiley-VCH: Weinheim, 1999. (b) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Pergamon: Oxford, 1998. (c) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: Oxford, 1998. (d) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, 1998. (e) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M., Kerwin, J. F., Jr., Eds.; Wiley-Liss: New York, 1998. (f) *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997. (g) *Annual Reports in Combinatorial Chemistry and Molecular Diversity*; Moos, W. H., Pavia, M. R., Ellington, A. D., Kay, B. K., Eds.; ESCOM: Leiden, 1997; Vol. 1. (h) *Combinatorial Chemistry*; Wilson, S. R., Czarnik, A. W., Eds.; John Wiley & Sons: New York, 1997. (i) *Combinatorial libraries, Synthesis, Screening, and Application Potential*; Cortese, R., Ed.; Walter de Gruyter; Berlin, 1996. (j) *Molecular Diversity and Combinatorial Chemistry*; Chaiken, I. M., Janda, K. D., Eds.; American Chemical Society: Washington, DC, 1996. (k) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251, 1385−1401. (l) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135−8173. (m) Lowe, G. *Chem. Soc. Rev.* **1995**, 309−317. (n) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (o) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. (p) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (q) DeWitt, S. H.; Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 114−122. (r) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (s) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132−143. (t) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144−154. (u) Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155−163. (v) Hsieh-Wilson, L. C.; Xiang, X.-D.; Schultz, P. G. *Acc. Chem. Res.* **1996**, *29*, 164−170. (w) Floyd, C. D.; Lewis, C. N.; Whittaker, M. *Chem. Br.* **1996**, 31−35. (x) Czarnik, A. W.; DeWitt, S. H. *Chem. Br.* **1996**, 43−45. (y) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527−4554. Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643−5678.

(2) *Solid-Phase Synthesis*; Blossey, E. C.; Neckers, D. C., Eds.; Dowden, Hutchinson & Ross, Inc.: Stroudsburg, 1975.

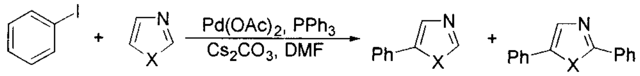
(3) Crowly, J. I.; Rapoport, H. *Acc. Chem. Res.* **1976**, *9*, 135−145.

10.1021/ol000183u CCC: $19.00

provided to further support the advantages of the particular environment in polymer matrix-based reactions. In connection with our recent studies on polymer-supported organometallic chemistry,[5] we initiated the investigation on the regioselective arylation of azoles catalyzed by palladium, in a media for polymer matrix-assisted reaction. Many biologically active compounds contain azole moieties, and some examples of solid-phase azole synthesis have been reported.[6] Still, the selective functionalization of azoles at the desired position is one of the many important subjects in azole chemistry.

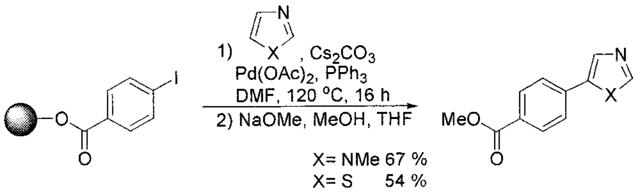
Direct arylation of azoles employing palladium-catalyzed solution-phase chemistry has been reported by Miura et al.[7] However, the selectivity for monoarylation is not satisfactory, leading to the formation of 2,5-diarylated products as well (Scheme 1). In this study, we focused our interest in applying solid-phase chemistry to the arylation of azoles, expecting that the pseudodilution effect provided by the polymer matrix would improve the selectivity of monoarylation.

Scheme 1



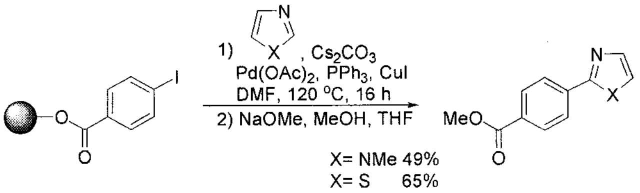
We first examined the palladium-catalyzed coupling reaction of immobilized iodobenzoate with *N*-methylimidazole and thiazole. The immobilized iodobenzoate was prepared using conventional methods, i.e., by the reaction in DMF of chloromethylated polystyrene with iodobenzoic acid, Cs_2CO_3, and KI. The loading was estimated from the yield of methyl iodobenzoate after cleavage of the resin with NaOMe in THF−MeOH.[5a] The cross coupling reaction of *N*-methylimidazole with the immobilized iodobenzoate was carried out in the presence of $Pd(OAc)_2$, PPh_3, and Cs_2CO_3 in DMF at 120 °C for 16 h. After cleavage with NaOMe in THF−MeOH, the 5-arylated *N*-methylimidazole was obtained with a yield of 67%. The suitable amount of $Pd(OAc)_2$ was found to be 10 mmol %. The coupling reaction of thiazole with the immobilized iodobenzoate under the same reaction conditions also produced the 5-arylated thiazole, with a yield of 54% after cleavage (Scheme 2).[8]

Scheme 2



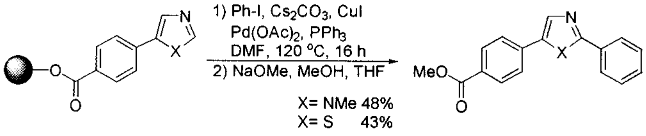
On the other hand, in the presence of CuI as an additive, the cross coupling reaction was found to proceed exclusively at position 2, as it is the case for the reaction in solution-phase chemistry. The 2-arylated *N*-methylimidazole and the 2-arylated thiazole were obtained with respective yields of 49% and 65% after cleavage (Scheme 3).[9]

Scheme 3



Synthesis of the unsymmetrical 2,5-diarylated azoles was also investigated using sequential palladium-catalyzed coupling reactions. The immobilized 5-arylated azoles described in Scheme 2 were reacted with iodobenzene in the presence of $Pd(OAc)_2$, PPh_3, Cs_2CO_3, and CuI as an additive, in DMF at 120 °C for 16 h. After cleavage of the azoles from the polymer support, the desired unsymmetrical 2,5-diarylated azoles were obtained (Scheme 4).

Scheme 4



The present study indicates that the palladium-catalyzed coupling reaction of azoles proceeds more selectively when employed in solid-phase synthesis than in solution-phase synthesis. The pseudodilution effect of the polymer matrix

---

(4) (a) Leznoff, C. C. *Chem. Soc. Rev.* **1974**, *3*, 65−85. (b) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327−333. (c) Akelah, A. *Synthesis* **1981**, 413−438. (d) Frechet, J. M. J. *Tetrahedron* **1981**, *37*, 663−683. (e) Frechet, J. M. J. *Pure Appl. Chem.* **1988**, *60*, 353−364. (f) Hodge, P. *Chem. Soc. Rev.* **1997**, *26*, 417−424.

(5) (a) Kondo, Y.; Komine, T.; Sakamoto, T. *J. Comb. Chem.* **1999**, *1*, 123−126. (b) Kondo, Y.; Inamoto, K.; Sakamoto, T. *J. Comb. Chem.* **2000**, *2*, 232−233.

(6) (a) Tortolani, D. R.; Biller, S. A. *Tetrahedron Lett.* **1996**, *37*, 5687−5690. (b) Zhang, C.; Moran, E. J.; Woiwode, T. F.; Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 751−754. (c) Sarshar, S.; Siev. D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835−838. (d) Stadlwieser, J.; Ellmerer-Muller, E. P.; Tako, A.; Maslouh, N.; Bannwarth, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1402−1404. (e) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196−200. (f) Goff, D.; Fernandez, J. *Tetrahedron Lett.* **1999**, *40*, 423−426. (g) Pons, J.-F.; Mishir, Q.; Nouvet, A.; Brookfield, F. *Tetrahedron Lett.* **2000**, *41*, 4965−4968.

(7) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467−473.

(8) **Typical procedure for Scheme 2:** Immobilized iodobenzoate (1.0 g, 0.33 mmol), $Pd(OAc)_2$ (7.41 mg, 0.033 mmol), PPh_3 (17.2 mg, 0.066 mmol), and Cs_2CO_3 (107.1 mg, 0.33 mmol) were placed in a 50 mL round-bottom flask and then dried in vacuo for 1 h. *N*-Methylimidazole (0.13 mL, 1.63 mmol) and DMF (4 mL) were then added, and the resulting mixture was stirred under argon at 120 °C for 16 h. After cooling, the mixture was filtered and washed with THF and MeOH for several cycles. The resin was treated with NaOMe in MeOH (0.4 mL, 2.0 mmol) and THF−MeOH (2:1, 12 mL), and the mixture was stirred at room temperature for 6 h. Methyl 4-(1-methyl-1*H*-imidazol-5−yl)benzoate (47.9 mg, 67%) was then obtained.

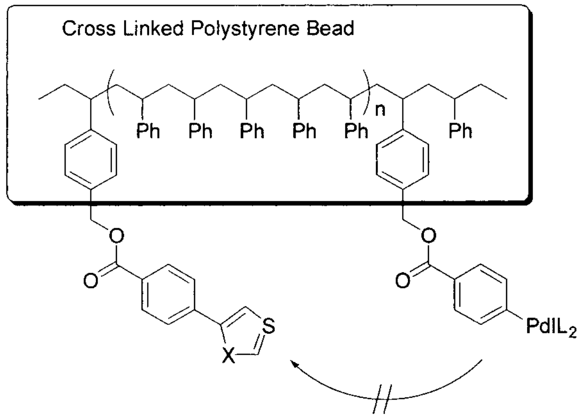


Figure 1. Dilution Effect for Selective Monoarylation.

is considered to work advantageously to selectively monofunctionalize the substrate, providing an ideal reaction environment to minimize undesired diarylation (Figure 1).

In summary, positionally selective palladium-catalyzed monoarylation of azoles was achieved using iodobenzoate immobilized on an insoluble polymer support. The positional selectivity for the coupling reaction was dramatically influenced by the presence of CuI, and no diarylation was observed in both cases. Further application of the selective coupling reaction in solid-phase synthesis is underway.

Acknowledgment. This work was partly supported by the Grant-in-Aid for Scientific Research (No. 12557198) from the Ministry of Education, Science, Sports and Culture of Japan and by Tokuyama Science Foundation.

OL000183U

---

(9) **Typical procedure for Scheme 3:** Immobilized iodobenzoate (1.0 g, 0.53 mmol), Pd(OAc)$_2$ (11.6 mg, 0.053 mmol), PPh$_3$ (27.7 mg, 0.106 mmol), Cs$_2$CO$_3$ (172.8 mg, 0.53 mmol), and CuI (609.7 mg, 3.2 mmol) were placed in a 50 mL round-bottom flask and then dried in vacuo for 1 h. *N*-Methylimidazole (0.13 mL, 1.63 mmol) and DMF (6 mL) were then added, and the resulting mixture was stirred under argon at 120 °C for 16 h. After cooling, the mixture was filtered and washed with THF and MeOH for several cycles. The resin was treated with NaOMe in MeOH (0.4 mL, 2.0 mmol) and THF−MeOH (2:1, 12 mL), and the mixture was stirred at room temperature for 6 h. Methyl 4-(1-methyl-1*H*-imidazol-2−yl)benzoate (56.3 mg, 49%) was then obtained.