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Palladium-Catalyzed Regioselective Arylation of Imidazo[1,2-*a*]pyrimidine

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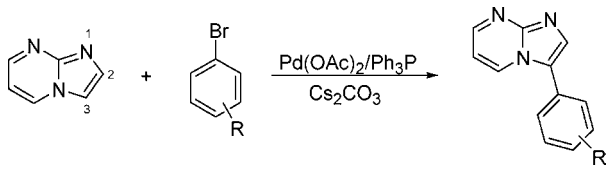
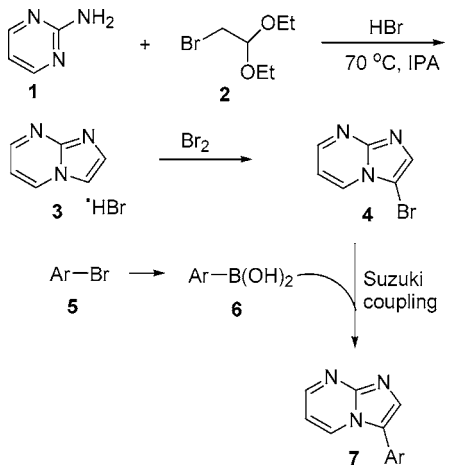
ABSTRACT



Imidazo[1,2-*a*]pyrimidine can be arylated at the 3-position with aryl bromides in the presence of base and a catalytic amount of palladium. This provides an efficient one-step synthesis of 3-arylimidazo[1,2-*a*]pyrimidines from the unsubstituted heterocycle.

Many biologically active compounds contain bicyclic heterocycles with a bridgehead nitrogen atom. Significant efforts have been devoted to new synthetic methods and chemical reactivities regarding these ring systems.[1] We are interested in preparing 3-arylimidazo[1,2-*a*]pyrimidines as intermediates for synthesizing pharmaceutically active compounds. Our initial approach involved a bromination at the 3-position of imidazo[1,2-*a*]pyrimidine (**3**),[2] which was prepared using modified literature procedures,[3] followed by Suzuki coupling with arylboronic acids (**6**) to give the desired products (**7**) (Scheme 1).[4] Although this sequence was successful, a shorter and more efficient route was desired. It has been reported that various electron-rich (π-excessive) aromatic heterocycles such as furans,[5] thiophenes,[5a,d,6] imidazoles,[5b,7,8] oxazoles,[5b] and thiazoles[5b,8] react with aryl halides in the presence of catalytic palladium to give the biaryl products. In many cases, these reactions show strong evidence of

Scheme 1



electrophilic character, with arylation occurring at the site most susceptible to electrophilic attack.[5c,d,7] In the bicyclic system of imidazo[1,2-*a*]pyrimidines, the A ring is π-deficient and usually subjected to nucleophilic attack, whereas electrophilic addition/substitution typically occurs on the π-excessive B ring (Figure 1).[9] Therefore, similar electrophilic arylation reactions would likely occur selectively on the B ring of an imidazo[1,2-*a*]pyrimidine. The fact that the

(1) (a) Katritzky, A. R.; Rees, C. W. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, part 4A. (b) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry II*; Jones, G., Ed.; Pergamon: Oxford, 1996; Vol. 8.

(2) Paudler, W. W.; Kuder, J. E. *J. Org. Chem.* **1966**, *31*, 809−813.

(3) Khazanchi, R.; Yu, P.-L.; Johnson, F. *J. Org. Chem.* **1993**, *58*, 2552−2556.

(4) For reviews of Suzuki reaction, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. For a close example, see: Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. *J. Org. Chem.* **2000**, *65*, 6572−6575.

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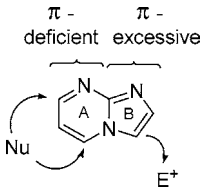
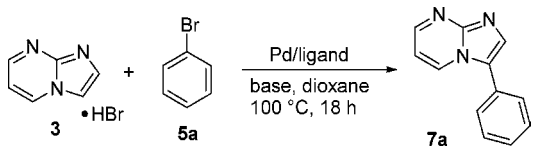


Figure 1.

bromination occurred exclusively at the 3-position (Scheme 1) also suggested the potential high regioselectivity for the arylation. Therefore, we set out to investigate the direct arylation of imidazo[1,2-*a*]pyrimidine with aryl halides.

The arylation reaction was examined using unsubstituted imidazo[1,2-*a*]pyrimidine hydrobromide and bromobenzene. In the presence of $Pd(OAc)_2$ (2 mol %), Ph_3P (4 mol %), and Cs_2CO_3 (2 equiv), the reaction proceeded smoothly in 1,4-dioxane at 100 °C to give 3-phenylimidazo[1,2-*a*]-pyrimidine (**7a**) as the only product (Scheme 2). The choice

Scheme 2

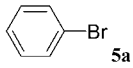
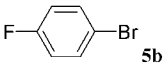
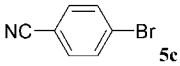
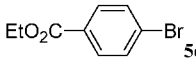
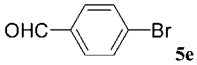
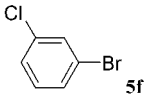
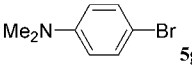
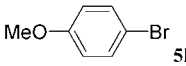
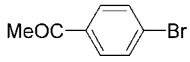
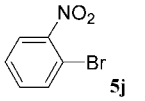
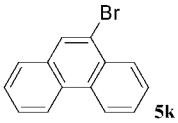
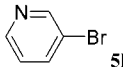


of base was very important for this reaction, as cesium carbonate and potassium carbonate gave excellent yields, while sodium carbonate and potassium phosphate failed to give reasonable conversion, probably due to their low solubility in the reaction media. Several amine bases (including Hünig's base and dicyclohexylmethylamine) were also tested and found to be completely ineffective. $Pd(OAc)_2$ was a better catalyst than $Pd(dba)_2$, and Ph_3P was the best ligand for this reaction. Similar yields were observed in DMF and dioxane under the best conditions ($Pd(OAc)_2/Ph_3P$, K_2CO_3, 100 °C). However, the reaction was very sluggish in nonpolar solvents such as toluene (<10% conversion after overnight at 100 °C).

Table 1. Screening Reaction Conditions

solvent	catalyst/ligand	base	yield
dioxane	$Pd(OAc)_2/Ph_3P$	Cs_2CO_3	97%
dioxane	$Pd(OAc)_2/Ph_3P$	K_2CO_3	96%
dioxane	$Pd(OAc)_2/Ph_3P$	Na_2CO_3	0%
dioxane	$Pd(OAc)_2/Ph_3P$	K_3PO_4	8%
DMF	$Pd(OAc)_2/Ph_3P$	K_2CO_3	97%
dioxane	$Pd(OAc)_2$/(*o*-Tol)$_3$P	K_2CO_3	43%
dioxane	$Pd(OAc)_2$/(2-Fur)$_3$P	K_2CO_3	92%
dioxane	$Pd(dba)_2/Ph_3P$	K_2CO_3	50%
dioxane	$Pd(dba)_2$/dppf	K_2CO_3	21%
dioxane	$Pd(dba)_2$/(2-Fur)$_3$P	K_2CO_3	19%

Table 2. Arylation of Imidazo[1,2-*a*]pyrimidine

entry	aryl bromide	product (yield)
1	 **5a**	**7a** (96%)
2	 **5b**	**7b** (85%)
3	 **5c**	**7c** (78%)
4	 **5d**	**7d** (84%)
5	 **5e**	**7e** (80%)
6	 **5f**	**7f** (94%)
7	 **5g**	**7g** (39%)
8	 **5h**	**7h** (50%)
9	 **5i**	**7i** (73%)
10	 **5j**	**7j** (61%)
11	 **5k**	**7k** (96%)
12	 **5l**	**7l** (55%)

The scope of the reaction was explored by applying the optimized reaction conditions to imidazo[1,2-*a*]pyrimidine hydrobromide (**3**) and various aryl bromides. The results (Table 2) indicate that **3** can be effectively arylated with various aryl bromides, although the yield is dependent on

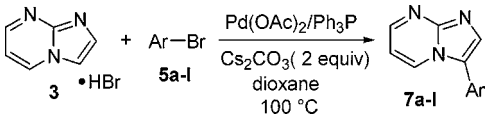
(5) (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951−1958. (b) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257−272. (c) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677−1680. (d) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301−304.

(6) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286−5287.

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

(8) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111−3113.

Scheme 3



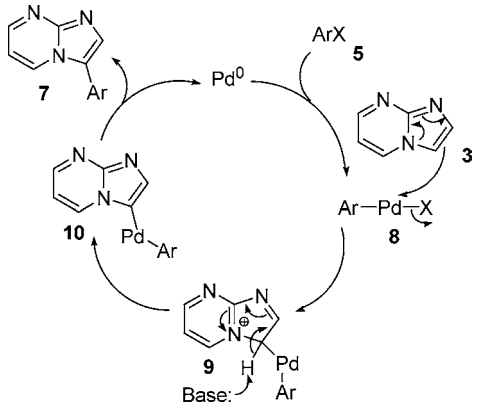


Figure 2.

the nature of the aryl bromide. Aryl bromides with electron-donating groups gave lower yields (entries 7 and 8). This is consistent with previously published results for arylation of furan.[5a,d] In every case, the arylation occurs exclusively at the 3-position of the heterocycle (Scheme 3).

The mechanism of this arylation is believed to be analogous to that proposed by Miura in the arylation of azole compounds.[7] It involves an electrophilic attack by the aryl-palladium halide species **8** to the 3-position of the imidazopyrimidine to form **9**, followed by deprotonation to give the aryl(imidazopyrimidyl)palladium(II) intermediate **10**. Subsequent reductive elimination gives product **7** and regenerates the palladium(0) catalyst (Figure 2). The 3-position is arylated predominantly over the 2-position because attacking at the 3-position gives rise to a more stable arenium ion. One form of this arenium ion can be drawn as **9**, in which ring A has a complete sextet. On the other hand, attacking at the 2- position would fail to give such a stable arenium ion (Figure 3).[10]

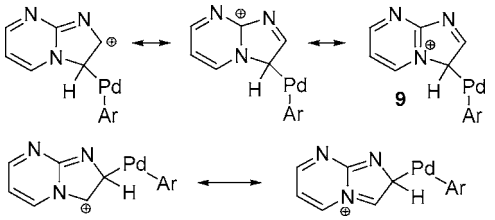


Figure 3.

In conclusion, we have developed a palladium-catalyzed highly regioselective arylation of imidazo[1,2-*a*]pyrimidine, which can be used to prepare numerous 3-arylimidazo[1,2-*a*]pyrimidines in one step.

Acknowledgment. We thank Prof. Nicos Petasis for helpful suggestions and discussions.

Supporting Information Available: Experimental procedures and characterizations for compounds **7a**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Gueiffier, A.; Viols, H.; Blache, Y.; Chavignon, O.; Teulade, J. C.; Aumelas, A.; Chapat, J.-P. *Heterocycles* **1994**, *38*, 551−558. (b) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40* (5), 1170−1176.

(10) For a review of direct arylation reaction and its mechanism, see: Miura, M.; Nomura, M. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 2002; Vol. 219.