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An Improved Method for the Palladium Cross-Coupling Reaction of Oxazol-2-ylzinc Derivatives with Aryl Bromides

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Abstract:

An improved and scalable procedure to couple ozaxole and thiazole to aryl halides has been demonstrated. The required organozinc reagents were prepared from the aryllithium and solid $ZnCl_2$. These reagents have been successfully coupled to a variety of aryl bromides and aryl iodides in good to excellent yields.

Introduction

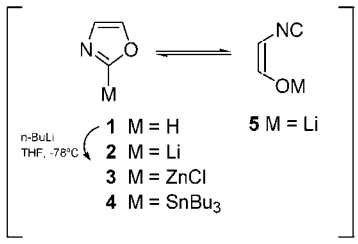
Organometallic cross-coupling reactions continue to play a vital role in organic synthesis. Although there are many examples of these types of couplings reported in the literature, we had the need to carry out a cross-coupling reaction between an aryl bromide and oxazole itself, for which there are few literature examples.[1] Given the lack of literature precedent and the biological importance of oxazole-containing molecules, we sought to develop a method for this novel cross-coupling. This report summarizes our results.

Results and Discussion

Although oxazole can be readily metalated by alkyllithiums giving oxazol-2-yllithium **2**, this species is in equilibrium with its isonitrile tautomer **5** (Scheme 1).[1,2] An exception to this tautomerization is the known 2-stannyloxazole **4**;[3] however, due to the high toxicity of organostannes, this option was not considered for scale-up.

Relevant to our interest was work published by Anderson and Harn who reported that this equilibrium (**2** to **5**) could be made to favor the ring-closed product by the addition of excess zinc chloride.[1] The authors suggested that the addition of the zinc chloride favors **3** due to the strong covalent carbon−zinc bond along with zinc's low oxophilicity. Anderson and Harn reported modest to good yields (52−83%) for the palladium cross-coupling of **3** with various aryl iodides and aryl triflates. However, they reported that the coupling of **3** with 1-bromonaphthlene only gave a 38% yield of the oxazole-coupled product (Table 1, entry 1). While we were encouraged that we could readily prepare **3**, the relatively modest yields for this coupling, particularly with an aryl bromide, was a cause for concern. Also, because

Scheme 1



commercially available $ZnCl_2$ is sold as a dilute solution in THF or Et_2O, the large volume of solvent for this reaction upon scale-up was unattractive.[4] The preparation or purchase of the corresponding aryl iodide or triflate was not practical for our needs; thus, we sought to develop an efficient cross-coupling reaction of **3** with an aryl bromide. Herein, we report that we have modified Anderson and Harn's protocol to provide a simple, efficient, and scalable methodology for the palladium cross-coupling reaction of **3** with both aryl bromides and iodides (Scheme 2, X = Br or I).

We feel that the use of solid $ZnCl_2$ in these coupling reactions was key to our success. Unlike Anderson and Harn who reported using 1 M $ZnCl_2$ in Et_2O, we found significant improvement in yields and decreased reaction times when solid $ZnCl_2$ was employed in these coupling reactions. In the cases tested, good to excellent yields for the oxazole-coupled product were obtained. Using our procedure, significantly higher yields were obtained for the oxazole-coupled product when compared to the yields reported by Anderson and Harn (Table 1, entries 1, 6, 7). We found that no additional purification of the zinc was required. No differences in yield or reaction rate were observed for couplings using anhydrous zinc chloride or "wet" zinc chloride that had to be ground (under nitrogen) with a mortar and pestle because of clumps. Addition of large quanitities of $ZnCl_2$ ($\leq$3 kg) to reactions run in 22-L glassware was easily and safely accomplished by using a funnel to add the solid portion-wise to the flask. To test whether the yields reported by Anderson and Harn were a result of dilution in the cases when $ZnCl_2$ was used in solution, control experiments were done at the appropriate concentration. Solid $ZnCl_2$ was then added, affording good to excellent yields for the coupled product, suggesting that the reaction is sensitive to the physical nature of the zinc. For the substrates tested at higher dilution using solid $ZnCl_2$, the reactions required slightly longer to go to completion. Metalation of oxazole with *n*-BuLi required temperatures below −50 °C.[5]

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(1) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583 and references therein.

(2) (a) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber./Recl.* **1997**, *130*(9), 1213. (b) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192. (c) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449.

(3) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Perdini, P. *Synthesis* **1987**, 693.

(4) $ZnCl_2$ was purchased from Sigma-Aldrich as a 0.5 M solution in THF or as a 1.0 M solution in Et_2O.

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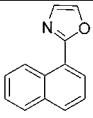
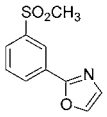
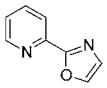
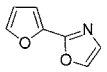
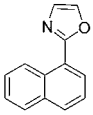
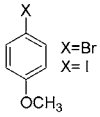
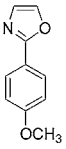
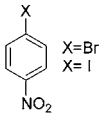
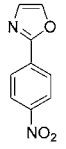
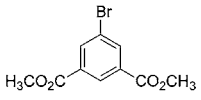
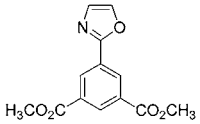
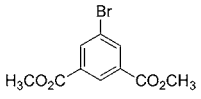
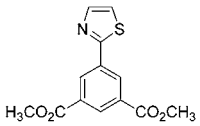
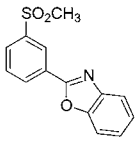
Table 1. **Oxazole Coupling of Various Aryl Halides**

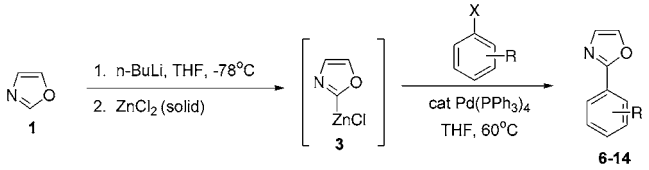
Entry	Bromide	Product	Time (h)	Yield[a] (%)
1		 **6**	24	73 (38)[b]
2		 **7**	0.5	90
3		 **8**	24	19
4		 **9**	24	>80[c]
5		 **6**	24	---
6		 **10**	Br= 24 I= 0.5	Br= 82[b] I= 98 (64)[b]
7		 **11**	Br= 24 I= 1	Br=60[d] I= 77 (56)[b]
8		 **12**	1	>90%[d,e]
9		 **13**	1	>90%[d,e]
10		 **14**	1	67%

[a] Isolated yield after chromatography. [b] Literature yield. [c] Estimated yield based on HPLC. [d] Yield determined by quantative HPLC. [e] Required a modified workup due to the poor solubility of the product, see experimental details for more information.

At temperatures above −40 °C, a dark, black solution resulted (indicative of decomposition), and no coupling was observed. Consistent with Anderson and Harn, our procedure required that the contents be heated above 50 °C to drive the coupling reaction to completion. At temperatures below

(5) The *n*-BuLi should be added at such a rate to maintain an internal temperature below −55 °C.

Scheme 2



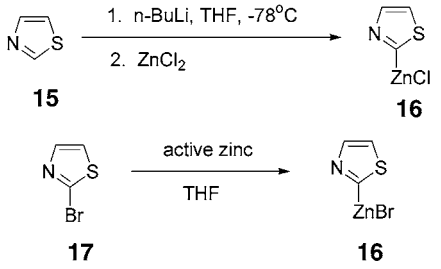
1 **3** **6-14**

45 °C, the reactions were significantly slower and often did not go to completion. Similar to Anderson and Harn's work, we too found that a 3-fold excess of $ZnCl_2$ proved optimal to obtain good yields of the final product. Using less than 3 equiv of $ZnCl_2$ decreased our yields by as much as 20%. The large excess of $ZnCl_2$ required to promote high yields in these cross-coupling reactions is not easily rationalized. The only observable difference between our procedure and the one reported by Anderson and Harn was that, unlike couplings that employed 1 M $ZnCl_2$ that become a homogeneous solution upon warming to room temperature in the conversion of **2** to **3**, reactions in which solid $ZnCl_2$ was added to a homogeneous solution of **2** remained a slurry even upon warming to room temperature to give **3**. Efforts to better understand how the stoichiometry of the $ZnCl_2$ influences this cross-coupling reaction are being tested. Due to a large in-house inventory of $Pd(PPh_3)_4$, we have not yet explored other palladium catalysts at this time. Much of our development work was done using 5 mol % $Pd(PPh_3)_4$; however, we did find that our coupling reaction works equally as well using 1 mol % $Pd(PPh_3)_4$. The recommended solvent for these coupling reactions is THF which does not have to be distilled or degassed.[6] Attempting this cross-coupling reaction in MTBE resulted in a thick and difficult-to-stir slurry after addition of the $ZnCl_2$, and no coupled product was obtained. A workup procedure involving quenching with 1 N HCl and extraction of the product into an organic solvent was found to be problematic. A significant amount of zinc salts was carried through with the product which required a difficult and tedious purification using silica gel chromatography. An improved workup method was developed in that, upon completion of the reaction, the solvent was removed under vacuum, affording solids which were then partitioned between saturated NH_4Cl and EtOAc. Subsequent extraction with EtOAc and washing the combined organic layers with saturated NH_4Cl afforded the crude product that could often be used without further purification and contained low levels of zinc salts.[7] We did observe that if saturated NH_4Cl was added to the reaction mixture without first removing the THF, a significant amount of solids resulted that made workup cumbersome.[8]

With the key reaction variables optimized, we focused our attention on examining the scope of this coupling reaction. A variety of aryl bromides, iodides, and chlorides were subjected to our standard coupling conditions (Table 1). We were delighted to find that good to excellent yields of the desired oxazole-coupled products were obtained for

(6) Both small- and large-scale experiments have been carried out using THF (E&M brand) directly from the bottle.
(7) Residual inorganic content was determined by ROI and TGA analysis.
(8) Filtration of these salts was found to be difficult for large-scale (>100 g) coupling.

Scheme 3



various aryl bromides and iodides. We have observed that both electron-poor (entries 2, 7−10) and electron-rich (entries 4, 6) aryl halides undergo this cross-coupling reaction. Even an unactivated aryl bromide such as 1-bromo-naphthalene (entry 1) gave a good yield of the coupled product **6** after 24 h. Aryl iodides afforded excellent yields and had short reaction times (entries 6, 7), whereas, 1-chloronaphthlene (entry 5) was unreactive under our reaction conditions. Benzoxazole (entry 10) (via benzoxazol-2-ylzinc chloride) was also found to undergo cross-coupling to afford **14** in good yield. Although not examined as extensively, thiazole **15** (via thiazol-2-ylzinc chloride (**16**)) undergoes cross-coupling with an aryl bromide (entry 9) to afford a high yield of the cross-coupled product **13**. To the best of our knowledge, this is the first reported example of performing a thiazole cross-coupling reaction in which the organozinc chloride reagent **16** has been prepared by treatment with *n*-BuLi and solid $ZnCl_2$ (Scheme 3). A previous preparation of 2-thiazolezinc bromide **16** describes treating 2-bromothiazole **10** with activated zinc in THF.[9] The scope of these thiazole cross-coupling reactions will be reported in due course.

Summary

Herein, we have described an improved method to couple oxazol-2-ylzinc and thiazol-2-ylzinc derivatives with aryl bromides and aryl iodides, affording the coupled products in excellent yields. The key to the success of this coupling was shown to be the use of solid $ZnCl_2$. These coupling conditions have proven quite general, tolerating an array of functional groups on the aryl ring. This coupling has been successfully scaled to prepare over 1 kg of cross-coupled product, thus making bulk quantities of the oxazole-coupled products readily available.

Experimental Data

General Information. ^1H and ^{13}C spectral were obtained using a Bruker 400 MHz spectrometer in dilute d_6-DMSO or $CDCl_3$ solution. Chemical shifts are reported as δ (ppm) values from Me_4Si. High-resolution mass spectral data was obtained using a Q-Tof Ultima API instrument. Melting points were obtained using a Mettler Toledo FP62 melting point apparatus and are uncorrected.

General Cross-Coupling Procedure for Oxazol-2-ylzinc (3) and Aryl Halides. Oxazole (1.4 equiv) dissolved in THF (1 mol oxazole/L) under nitrogen at −78 °C is treated with *n*-BuLi (1.2 equiv based on oxazole) maintaining an internal temperature below −60 °C. After stirring for 10 min, solid $ZnCl_2$ (3 equiv) is added portion-wise to avoid clumping, the cooling bath is removed, and the contents are warmed to room temperature.[10] Once at room temperature, the catalyst (5 mol %) and aryl halide (1 equiv) are added, and the contents are heated to 60 °C and stirred until the reaction is complete. The solvent is then removed in vacuo, and the contents are partitioned between saturated NH_4Cl and EtOAc.[11] Subsequent extractions with EtOAc and washing the combined organic layers with saturated NH_4Cl followed by concentration in vacuo affords the crude coupled product. Analytically pure products were obtained by purification of the crude reaction mixture using silica gel chromatography.

2-(1-Naphthyl)-1,3-oxazole (6). Following the general procedure, purification of the product on silica gel chromatography afforded the desired product (73%) as a light yellow oil. Spectral data were consistent with literature values.[1]

2-[3-(Methylsulfonyl)phenyl]-1,3-oxazole (7). Following the general procedure, purification of the product on silica gel chromatography afforded the desired product (90%) as a solid. ^1H NMR (DMSO-d_6) δ 8.63 (s, 1 H), 8.36 (d, J = 7.88 Hz, 1 H), 8.04 (d, J = 7.84 Hz, 1 H), 7.79 (s, 1 H), 7.70 (t, J = 7.8 Hz, 1 H), 7.31 (s, 1 H), 3.12 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 141.58, 139.48, 131.14, 129.99, 128.82, 128.68, 125.22, 44.36; HRMS: ($C_{10}H_9NO_3S$) calculated 223.0303, found: 224.0376 (M + H), mp 112 °C.

2-(1,3-Oxazol-2-yl)pyridine (8). Following the general procedure, purification of the product on silica gel chromatography afforded the desired product (19%) as a light yellow oil. ^1H NMR (DMSO-d_6) δ 8.74 (d, J = 4.64 Hz, 1 H), 8.15 (d, J = 7.96 Hz, 1 H), 7.84−7.28 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 149.93, 139.77, 131.98, 131.90, 129.06, 128.73, 124.67, 121.99; HRMS: ($C_8H_6N_2O$) calculated 146.0480, found: 147.0554 (M + H).

2-(2-Furyl)-1,3-oxazole (9). Following the general procedure, purification of the product on silica gel chromatography afforded the desired volatile product (>80%) as a light yellow oil. ^1H NMR (DMSO-d_6) δ 8.05 (s, 1 H), 7.64 (s, 1 H), 7.50 (s, 1 H), 7.019 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 143.89, 142.49, 137.78, 127.77, 108.49; HRMS: ($C_7H_5NO_2$) calculated 135.0320, found: 136.0403 (M + H).

2-(4-Methoxyphenyl)-1,3-oxazole (10). Following the general procedure, purification of the product on silica gel chromatography afforded the desired product (82%, X = Br) and (98%, X = I) as a light yellow oil. Spectral data were consistent with literature values.[1]

2-(4-Nitrophenyl)-1,3-oxazole (11). Following the general procedure, purification of the product on silica gel chromatography afforded the desired product (60%, X = Br) and (77%, X = I) as a light yellow oil. Spectral data were consistent with literature values.[1]

(9) Fantucci, M.; Santangelo, F. WO9831687, 1997.

(10) **Caution**: Upon warming to room temperature, butane is rapidly evolved, and care should be taken not to warm the contents too quickly. Because butane is flammable, all necessary safety precautions should be observed.

(11) Residual solids can easily be filtered at this point to provide homogeneous layers.

Dimethyl 5-(1,3-oxazol-2-yl)isophthalate (12). Following the general procedure, once the reaction was judged complete, the contents were cooled to room temperature and poured into saturated NH_4Cl. The product was extracted into CH_2Cl_2, and the combined organic extracts were washed with saturated NH_4Cl and then concentrated in vacuo to afford the desired product (90%) which could be used without purification. ^{1}H NMR (DMSO-d_6) δ 8.67 (s, 2 H), 8.51 (s, 1 H), 8.32 (s, 1 H), 7.47 (s, 1 H), 3.92 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 164.74, 141.21, 131.37, 130.75, 130.10, 129.02, 128.12, 52.84; HRMS ($C_{13}H_{11}NO_3$) calculated: 161.0715, found: 262.0724 (M + H), mp 212 °C.

Dimethyl 5-(1,3-thiazol-2-yl)isophthalate (13). Following the general procedure, once the reaction was judged complete, the contents were cooled to room temperature and poured into saturated NH_4Cl. The product was extracted into CH_2Cl_2, and the combined organic extracts were washed with saturated NH_4Cl and then concentrated in vacuo to afford the desired product (90%) which could be used without purification. ^{1}H NMR (DMSO-d_6) δ 8.63 (s, 2 H), 8.47 (s, 1 H), 8.00 (s, 1 H), 7.92 (s, 1 H), 3.93 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 164.83, 144.35, 134.15, 131.56, 130.39, 128.83, 122.00, 52.79; HRMS: ($C_{13}H_{11}NO_4S$) calculated 277.0487, found: 278.0493 (M + H), mp decomosition above 200 °C.

2-[3-(Methylsulfonyl)phenyl]-1,3-benzoxazole (14). Following the general procedure, the desired product was isolated as a solid (67%) and could be used without purification. ^{1}H NMR (DMSO-d_6) δ 8.66 (s, 1 H), 8.53 (d, J = 7.88 Hz, 1 H), 8.18 (d, J = 7.88 Hz, 1 H), 7.91 (m, 3 H), 7.47 (m, 2 H), 3.43 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 160.80, 150.39, 142.04, 141.30, 131.94, 130.86, 130.15, 127.52, 126.21, 125.60, 125.27, 120.21, 111.25, 43.40; HRMS: ($C_{14}H_{12}NO_3S$) calculated 273.0538, found: 274.0547 (M + H), mp 198 °C

Acknowledgment

We thank Diane Strother for providing analytical HPLC−MS data for our examples. We also thank Dave Houser for providing sourcing of bulk oxazole and thiazole.

Supporting Information Available

Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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