Efficient Synthesis of 2-Substituted Imidazoles by Palladium-Catalyzed Cross-Coupling with Benzylzinc Reagents

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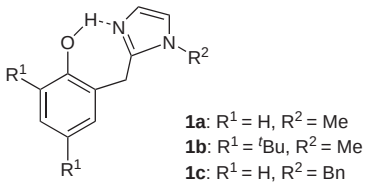
Abstract: Substituted benzylzinc reagents have been used in novel cross-coupling reactions with 2-iodo imidazoles to form compounds containing both a phenol and an imidazole moiety. The intramolecular hydrogen-bonding properties of these compounds were subsequently studied.

Key words: cross-coupling, palladium, zinc, benzylation, heterocycles

Hydrogen bonding has recently been recognized to modify the redox properties and electron transfer rates of the amino acid tyrosine in certain enzymes.[1] This is of great importance in Photosystem II (PSII) in the photosynthesis, where a tyrosine residue (Tyr_Z) acts as an electron transfer mediator between the water-oxidizing manganese complex and the special pair of chlorophyll molecules called P680.[2] A histidine residue (His190) is also involved in this process, but the exact actions around the site remain unclear.[3]

As a model system for the interactions between Tyr_Z and His190 in PSII, we are currently investigating phenols where imidazole can act as a hydrogen bond acceptor and thus lower the phenol oxidation potential. According to preliminary density functional calculations,[4] a strong intramolecular hydrogen bond could be expected in 7-membered rings such as compounds **1** (Figure 1). We thus designed structures **1a**–**c**, having various degrees of sterical hindrance, as target molecules for this study, and herein describe the synthesis and preliminary hydrogen bond measurements of these interesting compounds.



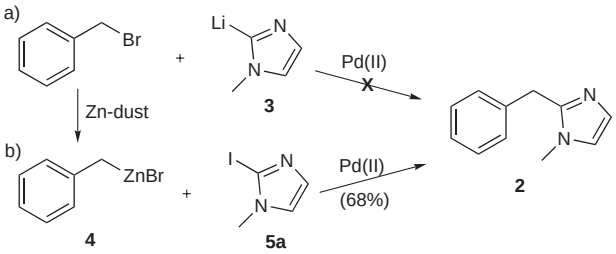
1a: R^1 = H, R^2 = Me
1b: R^1 = ^{t}Bu, R^2 = Me
1c: R^1 = H, R^2 = Bn

Figure 1 General structure of target compounds **1**

As structures **1** contain a methylene bridge between the two aromatic rings, their synthesis is not trivial. Previous routes to similar compounds are sensitive to steric hindrance[5] or involve several steps with limited possibilities to vary the substituents.[6]

Three different coupling strategies were thus investigated with test substrates to yield 2-benzyl-1-methylimidazole (**2**,[6] Scheme 1). Our first attempt involved the coupling of benzaldehyde with lithiated imidazole **3**,[7,8] but this strategy was hampered by problems in the subsequent reduction of the formed alcohol. Next, benzyl bromide was reacted with lithiated imidazole **3**, which resulted in a complicated mixture of products both in the presence[9] and absence[8] of $PdCl_2(PPh_3)_3$ (Scheme 1, a).

To avoid the use of a basic lithium compound, which could deprotonate the relatively acidic benzyl halide,[8] we looked into the possibility of employing a zinc reagent as transmetallating agent in a Negishi coupling.[10] Benzylzinc reagents can be prepared by treating the corresponding benzyl halide with activated Zn dust,[11] and have successfully been employed in couplings with various halogenated heterocycles.[12]



Scheme 1 Strategies investigated towards imidazole **2**

Benzyl bromide was thus converted to benzylzinc bromide (**4**[13]) and reacted with 2-iodo-imidazole **5a**[14] in the presence of $PdCl_2(PPh_3)_2$ (Scheme 1, b). Gratefully, the coupling could be smoothly accomplished at room temperature. An excess of zinc reagent **4** was used to assure full conversion, and compound **2** could be obtained in 68% yield.

Having found suitable coupling conditions, the benzylzinc reagents needed to form target compounds **1** were synthesized (Scheme 2). Starting from commercially available alcohol **6a**, the unsubstituted phenol derivative **7a**[15] could be obtained in two steps, and *tert*-butyl derivative **7b** was formed from aldehyde **8** in a similar manner. The zinc reagents could conveniently be stored in the fridge until use.

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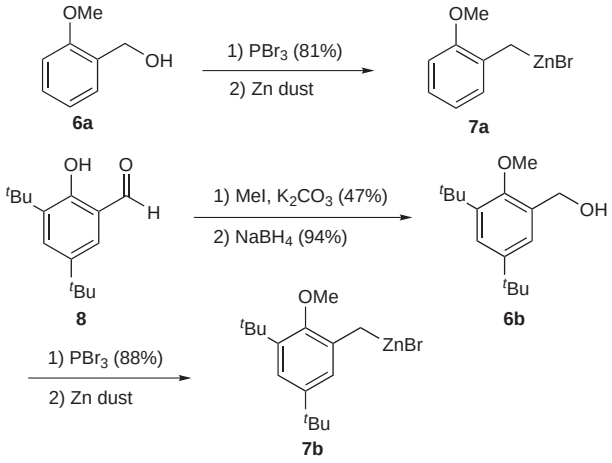
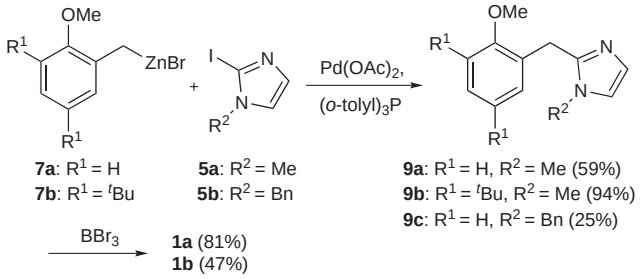


Scheme 2 Synthesis of zinc reagents **7**

Fortunately, the coupling of zinc reagent **7a** with 2-iodoimidazole **5a** in the presence of $PdCl_2(PPh_3)_3$ was successful, yielding compound **9a** in 62% (Scheme 3). In an attempt to improve the yield, two other metal catalysts were employed in the coupling.[10] $Pd(OAc)_2$ together with tri(*o*-tolyl)phosphine resulted in 59% yield of **9a** whereas $NiCl_2(dppp)_2$ only gave traces of the desired product. As the two Pd catalysts gave similar results, $Pd(OAc)_2$ was chosen for further reactions due to easier purification.



Scheme 3 Synthesis of target molecules **1**

To our delight, the $Pd(OAc)_2$-catalyzed coupling of *tert*-butyl-substituted zinc reagent **7b** with imidazole **5a** resulted in compound **9b** in excellent yield. Unfortunately, the coupling of **7a** with 1-benzyl-substituted imidazole **5b**[8] was sluggish, and product **9c** could only be isolated in 25% yield together with recovered starting material.

Demethylation of the coupling products **9a**,**b** was accomplished with BBr_3 to yield the desired target molecules **1a** and **1b**.[16]

Finally, NMR studies were performed to elucidate whether hydrogen bonds were present in compounds **1a**,**b**. In $CHCl_3$, the phenolic proton of 2,4-di(*tert*-butyl)phenol has a chemical shift of 4.62 ppm. Upon addition of 1-methylimidazole (1:1), intermolecular hydrogen bonds form to some extent, resulting in a downfield shift of the phenolic proton to 5.84 ppm. In an unpolar solvent, such as benzene-d_6, the hydrogen bonding becomes more pronounced, shifting the phenolic proton down to 11 ppm.

In $CHCl_3$, the target phenols **1a**,**b** showed broad, downfield peaks for the phenolic protons at 10 ppm for **1a** and at 10.7 ppm for **1b**. This strongly indicates a high degree of intramolecular hydrogen bonding, as suggested by our calculations. Further studies of the properties of these interesting compounds are underway and will be reported separately.

To summarize, novel 2-substituted imidazoles could be synthesized by a palladium-catalyzed cross-coupling between benzylzinc reagents and 2-iodoimidazoles. The coupling is a promising alternative to existing routes towards these heterocycles, and is insensitive to steric hindrance in the benzylic moiety whereas the substituent in the 1-position of the imidazole seems important.

Preparation of Zinc Reagents – Synthesis of 2-Methoxybenzylzinc Bromide (7a)

Zn dust (1.48 g, 22.7 mmol) was suspended in anhyd THF (5 mL) in a dried three-neck flask and heated to 60 °C under inert atmosphere. 1,2-Dibromoethane (0.08 mL, 0.93 mmol) was added and the mixture was stirred for 15 min at 60 °C. The flask was cooled to r.t. and TMSCl (0.1 mL, 0.78 mmol) was added. The mixture was stirred for 30 min at r.t., then a solution of 2-methoxybenzyl bromide (3.8 g, 18.9 mmol) in THF (20 mL) was added over 2 h and the flask was sealed and stored in the fridge over night to let the Zn-dust settle. The concentration of the Zn reagent was not determined; 100% conversion was assumed. The solution could be stored in the fridge and the supernatant liquid was subsequently used in the Pd-coupling.

General Pd-Coupling Procedure – Synthesis of 2-(2-Methoxybenzyl)-1-methylimidazole (9a)

$Pd(OAc)_2$ (15 mg, 0.068 mmol) and tri(*o*-tolyl)phosphine (41 mg, 0.13 mmol) were dissolved in anhyd THF (1 mL) under inert atmosphere. The mixture was stirred for 5 min before addition of imidazole **5a**[14] (0.28 g, 1.35 mmol). The reaction mixture was cooled to 0 °C and the solution of **7a** (9 mL, 5 equiv) was added over 5 min, and then the reaction was stirred at r.t. over night. Then, H_2O and $CHCl_3$ were added and the pH of the aqueous layer was adjusted to ca. 14 with NaOH (aq). The aqueous layer was extracted 3 times with $CHCl_3$, the combined organic layers were washed with 1 M NaOH, dried with $MgSO_4$, and the solvent was evaporated. Column chromatography of the residue with EtOAc–MeOH = 14:1 afforded **9a** as a pale yellow oil (0.16 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (dt, 1 H, *J* = 7.7, 1.6 Hz), 6.98–6.96 (m, 2 H), 6.89–6.85 (m, 2 H), 6.80 (s, 1 H), 4.07 (s, 2 H), 3.85 (s, 3 H), 3.48 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 146.6, 129.9, 127.7, 127.2, 125.7, 120.6, 120.6, 110.2, 55.3, 32.6, 26.7. IR (CH_2Cl_2): 3054, 2987, 1494, 1421 cm^{-1}.

2-(1-Methyl-imidazol-2-ylmethyl)phenol (1a)

Mp 171.5–172.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.00–9.00 (br s, 1 H), 7.15 (t, 1 H, *J* = 7.8 Hz), 7.07 (d, 1 H, *J* = 7.2 Hz), 6.97 (d, 1 H, *J* = 7.8 Hz), 6.90 (s, 1 H), 6.80 (t, 1 H, *J* = 7.2 Hz), 6.73 (s, 1 H), 4.00 (s, 2 H), 3.67 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 147.8, 129.9, 129.1, 126.3, 124.0, 120.7, 120.1, 119.4, 33.2, 30.2. IR (KBr tablet): 2940, 1594, 1501, 1455 cm^{-1}.

2,4-Di-*tert*-butyl-6-(1-methylimidazol-2-ylmethyl)phenol (1b)

Mp 158–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.7 (br s, 1 H), 7.24 (d, 1 H, *J* = 2.4 Hz), 6.97 (d, 1 H, *J* = 2.4 Hz), 6.88 (d, 1 H, *J* = 1.4 Hz), 6.71 (d, 1 H, *J* = 1.4 Hz), 3.98 (s, 2 H), 3.70 (s, 3 H), 1.43 (s, 9 H), 1.29 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7,

148.2, 141.6, 138.8, 126.2, 124.5, 124.1, 123.5, 120.6, 35.4, 34.4, 33.2, 31.9, 30.8, 30.0. IR (KBr tablet): 3118, 1677, 1584, 1526 cm^{-1}.

2-(3,5-Di-*tert*-butyl-2-methoxybenzyl)-1-methylimidazole (9b)
Mp 99–100 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, 1 H, *J* = 2.7 Hz), 6.96 (d, 1 H, *J* = 1.5 Hz), 6.78 (m, 2 H), 4.15 (s, 2 H), 3.79 (s, 3 H), 3.28 (s, 3 H), 1.40 (s, 9 H), 1.19 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 147.5, 146.1, 141.7, 130.2, 127.4, 125,2, 122.7, 121.0, 61.9, 35.5, 34.6, 32.8, 31.6, 31.3, 28.4. IR (KBr tablet): 3102, 2961, 1500, 1477 cm^{-1}.

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