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Palladium catalyzed synthesis of 4-substituted-2-phenylimidazoles from *N*-propargyl-benzamidine

Giorgio Abbiati,[a,*] Antonio Arcadi,[b] Valentina Canevari[a] and Elisabetta Rossi[a]

[a]*Istituto di Chimica Organica 'Alessandro Marchesini', Facoltà di Farmacia, Università degli Studi di Milano, Via G. Venezian 21, 20133 Milano, Italy*
[b]*Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università degli Studi dell'Aquila, Via Vetoio, 67010 Coppito (AQ), Italy*

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Abstract—Preliminary results of an original approach to 4-substituted-2-phenylimidazoles starting from readily available *N*-propargyl-benzamidine and aryl halides are reported. Best yields were obtained using aryl halides bearing an electron-withdrawing group. Plausible mechanisms are also discussed.

The interest for imidazoles is connected with the presence of their structure in a great number of molecules characterized by a variety of biological and pharmacological activities.[1] For instance, the imidazole nucleus is the skeleton of a wide range of historical antimycotic and antiprotozoic agents.[2] Moreover, cimetidine, the prototypical histamine H_2-receptor antagonist, contains an imidazole moiety. More recently, some new 4-aminomethyl-2-phenylimidazoles showed a strong affinity for dopaminergic D_4-receptors becoming potential candidates for the treatment of schizophrenia.[3]

Due to their importance, many methodologies have been developed for assembling the imidazole ring. Conventional methods usually consist of cyclocondensation reactions. Representative strategies are the reaction of α-diketones and α-haloketones (or their derivatives) with formamide, usually known as Bredereck synthesis and the base-promoted cyclization between *p*-tosylmethylisocyanide and aldimines (or imidoyl chlorides) known as van Lausen's Tos-MIC chemistry.[4] Some other original approaches have also been reported recently.[5] On the other hand, starting from the preformed imidazole nucleus, the functionalization on C2 has been obtained by metalation followed by reaction with a proper electrophile (such as an aldehyde or an isocyanate)[6] or, more recently, by the reaction of an azolium ylide with a reactive carbonyl.[7]

Surprisingly, only few catalytic reactions which produce imidazoles have been reported.[8] For instance, Abell and co-workers developed a new synthetic method for trisubstituted imidazoles based on the palladium catalyzed intramolecular amino-Heck reaction of *N*-allyl-*N*-benzyl-*N*′-perfluorobenzoyloxyamidines.[9] Siamaki and Arndtsen recently reported a direct synthesis of tetrasubstituted imidazoles by a palladium catalyzed multicomponent coupling reaction starting from two imines and acid chlorides under CO atmosphere.[10] On the basis of a classical preparative method an improved multicomponent approach has been developed by Sharma and co-workers starting from aldehydes, benzil and ammonium acetate in the presence of a catalytic amount of $ZrCl_4$.[11] The synthesis of imidazole nucleus by means of homodimerization of isocyanates catalyzed by silver[12] or copper[13] has also been reported. Finally, Frantz et al. developed the one-pot strategy that involves the synthesis of α-ketoamides via the thiazolium catalyzed addition of aldehydes to acylimines and subsequent treatment with amines.[14]

In connection with our ongoing interest in the study of cyclization reaction involving alkynes and heteronucleophiles,[15] we herein report the preliminary results of a

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* Corresponding author. Tel.: +39 02 50314474; fax: +39 02 50314476; e-mail: giorgio.abbiati@unimi.it

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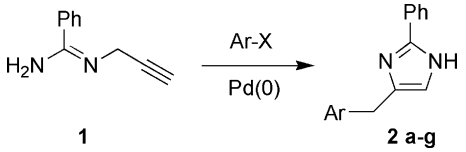


Scheme 1.

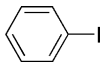
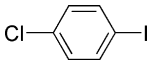
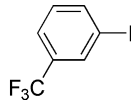
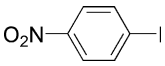
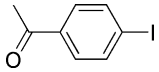
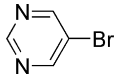
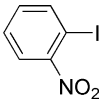
new tandem palladium catalyzed synthesis of 4-substituted-2-phenyl imidazoles **2a**–**g** starting from readily available *N*-propargyl-benzamidine **1** and aryl halides (Scheme 1).

Similar synthetic approaches using acetylenes containing proximate nitrogen nucleophiles have been reported for the synthesis of indoles,[16] pyrroles,[17] pyrrolo[2,3-*b*]quinoxalines,[18] alkyliden-oxazolidinones,[19] alkyliden-pyrrolidines[20] and alkyliden-piperidines.[21] Nevertheless, two key features characterize our domino synthesis: (1) the unprecedented use of an ammidine substrate and (2) the involvement of a nitrogen nucleophile lacking acidic hydrogens.[22]

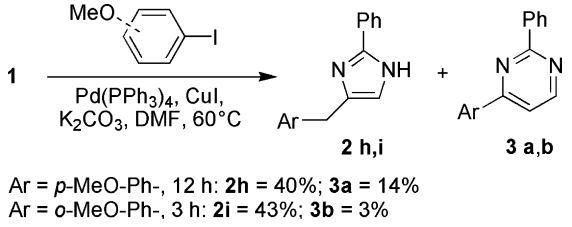
An example of the potential of *N*-propargyl-benzamidine in heterocyclic synthesis has been reported by Tice and Bryman.[23] In the course of a more extensive investigation on the regioselective preparation of 4-pyrimidones, the authors found that unpurified *N*-propargyl-benzamidine in acetonitrile spontaneously cyclize over the course of several days at rt to afford the corresponding 4-methyl-2-phenylimidazole. The process is accelerated by heat and by acidic conditions but the yields are always moderate (56%). We were able to prepare and purify the *N*-propargyl-benzamidine **1** in 76% yield,[24] thus we found that such cyclization is efficiently promoted by catalytic amounts of Lewis acids such as $TiCl_4$[25] and $NaAuCl_4$[26] yielding the 4-methyl-2-phenylimidazole in almost quantitative yields. After that, we decided to extend the approach to internal alkynes. Thus, we planned to functionalize the triple bond of *N*-propargyl-benzamidine by means of a typical Sonogashira coupling. Thus **1** was reacted with aryl halides in DMF at 60 °C in the presence of a catalytic system constituted by $Pd(PPh_3)_4$, CuI and K_2CO_3. Nevertheless, under these reaction conditions a serendipitous direct formation of the coupling/5-*exo*-dig cycloisomerization products has been observed (Scheme 1, Table 1).[27]

The reaction worked well with aryl halides bearing an electron-withdrawing group on the ring (entries 2–5) and with activated heteroaryl halides as pyrimidine (entry 6), whereas unactivated aryl halides gave poorer yield and required longer reaction time (entry 1). Also sterically hindered 1-iodo-2-nitrobenzene quickly reacted with **1** although the yields were moderate (entry 7). Interestingly, the reaction of aryl halides bearing electron-donating groups, even if sterically demanding, gave lower yields of the imidazole derivatives, beside small amounts of the corresponding pyrimidines rising from a formal coupling/cyclization/oxidation reaction (Scheme 2).

Table 1. Reactions of benzamidine **1** with aryl halides **2**[a]

Entry	Ar-X	*t* (h)	Yields[b] (%)
1		24	**2a** 42
2		1	**2b** 65
3		2	**2c** 83
4		1	**2d** 86
5		1	**2e** 77
6		2	**2f** 86
7		2	**2g** 40

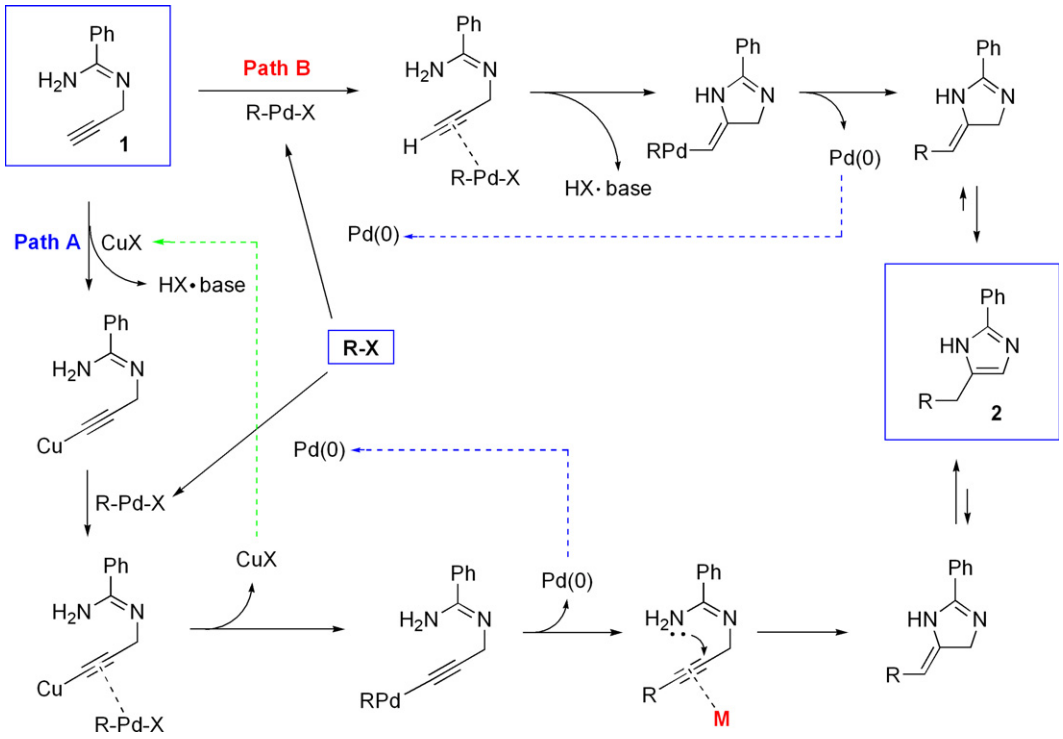
[a] Reaction conditions: ratio **1**:**2**:K_2CO_3:$Pd(PPh_3)_4$:CuI = 1:1.05:5:0.02:0.04 in anhydrous DMF ([**1**] = 0.3 M) at 60 °C under a N_2.
[b] Yields refer to single runs and are given for isolated products.



Scheme 2.

All compounds were identified on the basis of analytical and spectral data (IR, ^1H NMR, ^{13}C NMR, MS). The well known tautomeric equilibrium of imidazole nucleus made, in some cases, the NMR identification of the C2, C4 and C5-H of the heterocyclic ring difficult. The C5-H carbon has been unequivocally identified through a C–H HETCOR experiment for compound **2c**.

From a mechanistic point of view, two different mechanisms can justify in the formation of the imidazole ring (Scheme 3). The first (Path A) implies the functionalization of triple bond by a Sonogashira coupling[28] followed by an intramolecular nucleophilic attack of nitrogen on the triple bond activated by one of the metal species present in the reaction environment (palladium or copper).[29] Afterwards, the resulting alkyliden-dihydroimidazole spontaneously rearranges in the more stable imidazole isomer **2**. The second (Path B) involves the coordination of the organopalladium compound to triple bond followed by the intramolecular nucleophilic attack of nitrogen to give the aminopalladation adduct.[30] Finally, the reductive elimination of Pd(0)



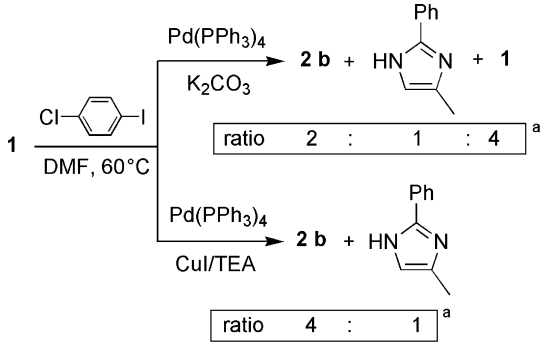
Scheme 3.

affords the alkyliden-dihydroimidazole which rearranges in the more stable aromatic isomer **2**. Moreover, the formation of the pyrimidines **3a**–**b** arising from a 6-*endo*-dig type cyclization can be ascribed to a different polarization of triple bond induced by the presence of the electron-donating substituent on the phenyl ring.

With the aim to deduce some additional information on the mechanism, we did some additional experiments reacting **1** and *p*-chloroiodobenzene under different catalytic conditions.

Under standard conditions but in the absence of palladium, no reaction products were observed and **1** was recovered in quantitative yield after 24 h, that means copper alone is unable to catalyze the coupling nor the cyclization of propargyl-benzamidine **1**. On the other hand, the reaction took place very slowly also in the absence of copper salt. After 24 h at 60 °C, the formation of imidazole **2b** was observed in a mixture with 4-methyl-2-phenylimidazole and the unreacted reagent **1** in a ratio 2:1:4 (Scheme 4). Moreover, the reaction performed in the presence of triethylamine (that is known to play a key role promoting the formation of Sonogashira coupling product versus the heteropalladation adduct)[31] resulted in the formation of a mixture of **2b** and 4-methyl-2-phenylimidazole in a ratio 4:1 (Scheme 4). Finally, the reaction performed under standard Sonogashira conditions but without aryl halides failed giving rise to a complex mixture of by-products in which only traces of 4-methyl-2-phenylimidazole were detectable by ^{1}H NMR.

On the basis of these results and the literature data it is our opinion that the mechanism involving the



[a] Ratio determined by the analysis of ^{1}H NMR spectrum of the crude.

Scheme 4.

aminopalladation/reductive elimination (Path B) is the most probable one. Nevertheless, the Sonogashira coupling/cyclization mechanism (Path A) as competitive pathway cannot be definitively ruled out, although we have never been able to isolate the internal alkyne or identify it by analyzing the NMR of the crude reaction mixtures.

In conclusion, we have found a new versatile domino palladium catalyzed approach to 4-substituted-2-phenyl imidazoles starting from readily available *N*-propargyl-benzamidine. Current efforts are now directed to fully explore the scope and limitation of this approach, for instance, optimizing the reaction conditions, testing the reactivity of other aryl and vinyl halides or triflates, and performing the reaction in the presence of carbon monoxide to obtain 4-acyl-2-phenyl imidazoles.

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24. *Preparation of N-propargyl-benzamidine* **1**: A suspension of ethyl benzimidate hydrochloride (6.00 g, 32.4 mmol) and sodium bicarbonate (3.26 g, 33.9 mmol) in anhydrous dichloromethane (18 mL) was stirred vigorously at rt for 40 min. After that, propargylamine (1.87 g, 33.9 mmol) was added and the mixture was stirred for further 2 h. The mixture was quickly filtered in vacuum over a celite pad, and the pad washed with anhydrous dichloromethane (10 mL). The solvent was evaporated at low temperature (25 °C) under reduced pressure, and the crude was purified by flash chromatography on a silica gel column (eluent: hexane/ethyl acetate/triethylamine = 8:2:3) yielding 3.90 g (76%) of *N*-propargyl-benzamidine as waxy light yellow solid. The pure product is stable at −24 °C for several weeks. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.28$ (t, 1H, Csp-H, $J = 2.6$ Hz), 4.15 (d, 2H, CH_2, $J = 2.6$ Hz), 4.70 (bs, 2H, NH_2), 7.36–7.43 (m, 3H, C–H arom.), 7.44–7.58 (m, 2H, C–H arom.) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 33.9$ (CH_2), 71.6 (Csp-H), 81.1 (Csp), 99.0 (C10-H), 102.9 (C4-H), 109.2 (C6-H), 121.0 (C8-H), 121.8 126.4, 128.8, 130.4 (CH arom.), 137.1 (C arom.), 162.2 (C=N) ppm. IR (NaCl) $\nu = 3292$, 3202, 2115, 1643, 1610, 1573, 1378, 701 cm^{-1}. ESI-MS *m*/*z* (%): 159 [M$^+$+1] (100). ESI-MS/MS *m*/*z* (%) (parent ion: 159): 142 (100), 133 (25), 104 (38), 56 (21). Anal. calcd for $C_{10}H_{10}N_2$ (158.20): C, 75.92; H, 6.37; N, 17.71. Found: C, 75.70; H, 6.31; N, 17.78.
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27. *General method for the reaction of* **1** *with aryl halides*: The appropriate aryl halide (0.66 mmol) is added to a stirred suspension of *N*-propargyl-benzamidine **1** (100 mg, 0.63 mmol) and K_2CO_3 (437 mg, 3.16 mmol) in anhydrous DMF (2 mL) under a nitrogen atmosphere. Then, $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) and CuI (5 mg, 0.025 mmol) were added. The reaction mixture was stirred at 60 °C until no more starting product was detectable by TLC, poured in to a saturated solution on NaCl (100 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The crude was purified by flash chromatography over a silica gel column. Compound **2b**: Eluent for chromatography: hexane/ethyl acetate (7:3). Yellow ochre solid. Yield 110 mg (65%). Mp: 166–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.94$ (s, 2H, CH_2), 4.20 (bs, 1H, NH), 6.74 (s, 1H, C5-H), 7.16 (d, 2H, C–H arom., $J = 8.4$ Hz), 7.24 (d, 2H, C–H arom., $J = 8.4$ Hz), 7.35–7.37 (m, 3H, C–H arom.), 7.79 (dd, 2 H, C–H arom., $J = 7.8$ and 1.5 Hz) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 33.2$ (CH_2), 119.2 (C5-H), 96.0 (C1-H), 125.4, 128.8, 128.9, 129.1, 130.3 (C–H arom), 130.2, 132.4, 138.0 (C arom., one signal obscured), 146.8 (N=C—N) ppm. IR (KBr) $\nu = 3436$, 1571, 1490, 1463, 1438, 1407, 1139, 1095, 780, 707, 688 cm^{-1}. ESI-MS *m*/*z* (%): 269 [M$^+$+1] (100). ESI-MS/MS *m*/*z* (%) (parent ion: 269): 157 (100), 125 (13). Anal. calcd for $C_{16}H_{15}ClN_2$ (270.76): C, 70.98; H, 5.58; N, 10.35. Found: C, 71.11; H, 5.55; N, 10.36.
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