Hypervalent iodine in synthesis 57 : an efficient method for the synthesis of N-arylimidazoles by the cobalt-catalysed coupling of diaryliodonium salts with imidazoles[†] Li Wang and Zhen-Chu Chen^{*}

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Cobalt-catalysed N-arylation of imidazole with diaryliodonium salt can be accomplished using $Co(OAC)_2$ as a catalyst and K_2CO_3 as a base in DMF at 80 °C in high yields.

N-Arylazoles are significant compounds because of their biological activity. For example, some N-arylimidazoles are useful as phosphodiesterase III inhibitors,¹ thromboxane synthase inhibitors,^{2a-2c} AMPA receptor antagonists,^{2f} and antiglaucoma agents.^{2g} Furthermore, N-arylation has been used for the protection of the imidazole ring of histidine.³ As such, there is a continued need to develop efficient methods for their preparation.

The most straight forward route to N-arylimidazoles involves the direct formation of the aryl-nitrogen bond. The current methods for constructing the C-N bond are essentially based upon the nucleophilic aromatic substitution, 2a,d,e,f or Ullmann-type coupling of imidazoles with aryl halides.^{2b,c,e,g} The former method is suitable for the aryl halides that possess strongly electron-withdrawing substituents. The reaction is performed in a polar solvent such as DMF or DMSO usually at high temperatures (>150 °C). The Ullmann type of coupling has a broader substrate scope with respect to the aryl halides. However, this reaction also requires the use of high temperatures and very often it gives low yields. Although several other arylating reagents have occasionally been reported to react with some imidazoles, including aryne,⁴ p-tolyllead triacetate,⁵ and triphenylbismuth diacetate,⁶ only one example has been reported for these reactions. Recently, Lam et al., reported the arylation of imidazole using arylboronic acid / cupric acetate to afford a new method for the formation of C-N bond.⁷ However, this reaction requires long times (2 days) and stoichiometric amounts of cupric acetate. On the other hand, Kiyomori and co-worker improved the Ullmann N-arylimidazole synthesis using (CuOTf)₂ •benzene as a copper source and CS_2CO_3 as a base in xylene at relatively low temperatures (100-125 °C).8 This reaction gave N-arylimidazoles in high yields. However, it also required long reaction times (1–2 days) and the addition of 1,10-phenanthroline and trans, trans-dibenzylideneacetone proved crucial to the success of the process.

In the course of our studies on the transition metal catalyzed cross-coupling reaction of diaryliodonium salt, as an aryl carbocation synthetic equivalent, with a nucleophile,⁹ we have discovered that the Cobalt-catalysed N-arylation of imidazoles with diaryliodonium salts can be accomplished using $Co(OAc)_2$ as a catalyst and K_2CO_3 as a base in DMF at relatively low temperatures (80 °C).

Simply stirring the diaryliodonium salts (1) with the imidazoles (2) and potassium carbonate in DMF in the presence of $Bu_4N^+\Gamma$ and a catalytic amount of Co(OAc)₂ at 80 °C gave, after work up and isolation, the desired products, N-arylimidazoles (3), in good yields as given in Table 1.

The product were characterized by their m.p. spectral data and by comparison of experimental values with literature values.



The reaction was found to be general. Several diaryliodonium salts containing various substituents, such as methoxy, methyl, bromo, chloro and nitro groups were successfully reacted. Substituted imidazole, *e.g.*. 2-methyl-5-nitroimidazole, also underwent N-arylation with the diaryliodonium salt (entry 10). The reaction could be extended to pyrazoles under the same conditions (entries 8, 9). It is interesting that this reaction is promoted by adding a phase transfer catalyst (*n*-Bu₄N⁺\Gamma). For example, the reaction of the iodonium salt [(*p*-CH₃C₆H₄)₂I⁺BF₄⁻] with imidazole in the presence of *n*-Bu₄N⁺\Gamma at 80 °C provided the desired product in 86% yield after 5 h (Table 1, entry 2). It took 9 hours for 82% 1-(4'methylphenyl)imidazole to be formed in the absence of *n*-Bu₄N⁺\Gamma under similar conditions (entry 3).

In conclusion, in the presence of phase transfer catalyst $Bu_4N^+I^-$ using K_2CO_3 as a base, the cobalt-catalysed N-arylation of imidazole with diaryliodonium salts has been demonstrated to be an efficient process. The products, N-arylimidazoles, were isolated in high yields. It has some advantages over the existing ones such as accessible starting materials, mild conditions, simplicity of the procedure and high yields. Further investigations of the N-arylation of other N–H containing heteroarenes with diaryliodonium salts will be reported in due course.

Experimental

¹H-NMR spectra were recorded on a PMX-60 spectrometer, using CDCl₃ as the solvent with TMS as an internal standard. IR spectra were determined on a PE-683 Spectrophotometer. Melting points are uncorrected.

General procedure for synthesis of N-arylimidazoles: The imidazole (1 mmol) was added to a stirred solution of diaryliodonium tetrafluoroborate (1 mmol), Bu_4N^+I (370 mmg, 1 mmol) cobalt(II) acetate (9 mg, 5 mol%) and K_2CO_3 (345 mg, 2.5 mmol), anhydrous DMF (6 ml) under a nitrogen atmosphere. The mixture was heated at 80 °C and for the times indicated in Table 1. After completion of the reaction, the mixture was diluted with CHCl₃ (20 ml), and the solution was poured into 30 ml saturated aqueous H_2S . The biphasic system was vigorously stirred at room temperature for an hour and filtered to remove the insoluble inorganic species. The organic layer was washed twice with water (20 ml); dried over anhydrous Na₂SO₄ and evaporated *in vacuo*. The crude product was separated by preparative thin layer chromatography on silica gel with 3:10 ethyl acetate-hexane as eluent to afford the desired N-arylimidazole product.

1-Phenylimidazole oil (entry 1):oil: (Lit¹⁰ Bp, 118 °C) ¹H-NMR 7.45–6.90 (m, 8H) I.R. (oil film) 1610, 1515, 1485, 1440, 1380, 1310, 1250, 1115, 1055, 960, 900, 865, 780, 690, 655 cm⁻¹.

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[†] This is a Short Paper, there is therefore no corresponding material in J Chem. Research (M).

Table 1 N-arylation of imidazoles^a



^aReagent and conditions: 1 mmol iodonium salt, 2.5 mmol K_2CO_3 , 1 mmol n-Bu₄N⁺I⁻, 5 mol % Co(OAc)₂ and 1 mmol imidazoles, in 5 ml DMF at 80 °C under a nitrogen atmosphere. ^bIsolated yields. ^cAbsence of phase transfer catalyst *n*-Bu₄N⁺I⁻.

1-(4'-methylphenyl)imidazole (entry 2,3): oil (Lit⁵) H-NMR 2.40 (s, 3H), 7.45–6.75 (m, 7H), IR (oil film) 3100, 2930, 1610, 1523, 1490, 1460, 1380, 1300, 1260, 1245, 1110, 1055, 965, 900, 815, 735, 655 cm⁻¹.

1-(4'-methoxyphenyl)imidazole (entry 4): m.p. 61–63 °C (Lit¹¹ 63–64.5 °C) H¹-NMR 3.80 (s, 3H), 6.80–7.60 (m, 7H), I.R. 3050, 1605, 1585, 1520, 1500, 1485, 1450, 1385, 1250, 1105, 1050, 820, 800, 780, 690, 650 cm⁻¹.

 $l\$ -(4'-chlorophenyl)imidazole (entry 5): m.p. 83–86 °C (Lit¹² 85–87 °C) H¹-NMR 7.10–7.80 (m 7H), I.R. (KBr) 3045, 1585, 1523, 1500, 1460, 1385, 1350, 1300, 1260, 1245, 1115, 1075, 1045, 965, 900, 800, 750, 655 cm⁻¹.

1-(3'-nitrophenyl)imidazole (entry 6): m.p. 109–110 °C (Lit^{13} 112–112.5 °C) ¹H-NMR 7.85–7.40 (m, 6H), 8.20 (s, 1H), I.R. (KBr) 3040, 1585, 1560, 1525, 1500, 1376, 1324, 1300, 816, 734, 700, 660 cm⁻¹.

 $I\text{-}(4'\text{-}bromophenyl)imidazole (entry 7): m.p. 119–120 °C (Lit^{11} 118–120.5 °C) ^1H-NMR 7.20–7.95 (m, 7H), I.R. (KBr) 1605, 590, 1520, 1465, 1380, 1345, 1250, 1110, 1050, 960, 895, 865, 780, 665 cm^{-1}.$

1-phenyl-3-methyl-pyrazole (entry 8): oil (Lit¹⁴ Bp_{0,25} 76–78 °C) ¹H-NMR 2.35 (s, 3H), 6.00 (s, 1H), 7.70–6.90 (m, 6H), I.R. 1540, 1520, 1450, 1390, 1240, 1200, 1120, 1015, 920, 660 cm⁻¹.

l-(4'-methylphenyl)-3-methyl-pyrazole (entry 9): oil (Lit¹⁵ B.p. 272 °C) ¹H-NMR 2.00 (s, 3H), 2.33 (s, 3H), 5.95 (s, 1H), 7.60–6.75 (m, 5H), I.R. 2900, 1740, 1540, 1520, 1450, 1390, 1240, 1200, 1120, 1015, 920, 650 cm⁻¹.

1-(4'-methylphenyl)-2-methyl-5-nitroimidazole (entry 10): m.p. 130.5 C ¹H-NMR 2.40 (s, 3H), 2.50 (s, 3H), 7.20–7.45 (m, 4H), 8.00 (s, 1H), I.R. (KBr) 3030, 2900, 1540, 1500, 1450, 1415, 1380, 1300,

1275, 1210, 1140, 1040, 1015, 990, 830, 800, 750, 720, 670 cm⁻¹. Mass spectrum, *m/e* 217 (9.67), 145 (34.87), 118 (13.37), 91 (36.13), 65 (24.02), 43 (100.00) Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.83; H, 5.07; N, 19.36. Found: C, 59.90; H, 5.35.

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