Preparation of 1,2-bis(pyrazol-1-yl)benzene: "Modern" Cross-Coupling *vs.* the "Classic" Nucleophilic Substitution Approach

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Abstract: Several potential methods for the preparation of 1,2-bis(pyrazol-1-yl)benzene, a prospective ligand for transitional metals, starting from 1,2-dihalobenzenes and pyrazole have been studied. Cross-couplings of 1,2-dichloro-, -dibromo- and -diiodobenzenes with pyrazole using palladium and copper catalysts were unsatisfactory because of dehalogenation side reactions or a lack of reactivity. On the other hand, nucleophilic aromatic substitution of fluorine in 1,2-difluorobenzene under the action of sodium pyrazolide gave a good yield of the desired product.

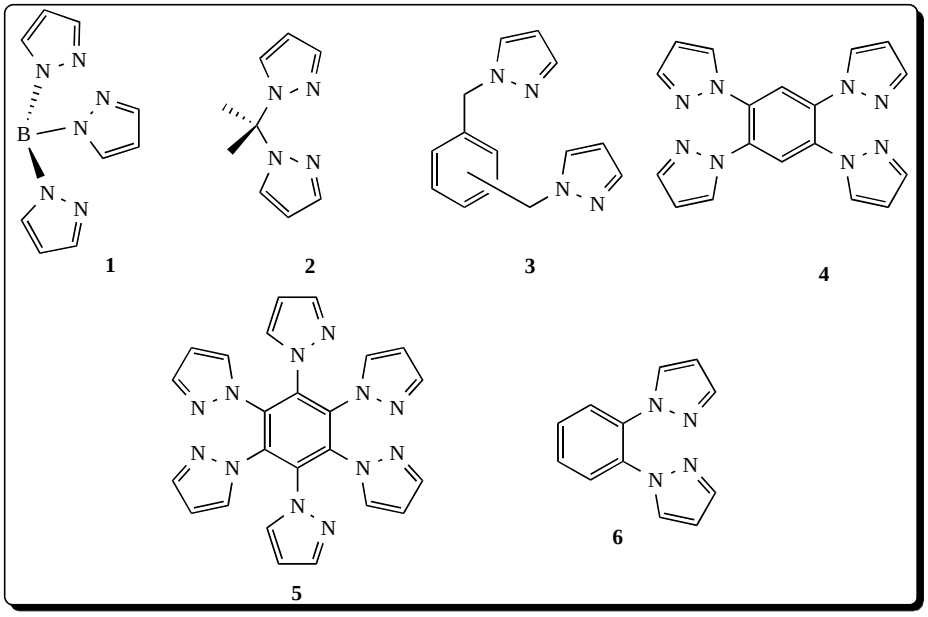
Keywords: 1,2-bis(pyrazol-1-yl)benzene, pyrazole, 1,2-dihalobenzenes, C-N cross-coupling, fluorine nucleophilic substitution.

1. INTRODUCTION

Chelating polykis(pyrazole-1-yl)benzenes are an almost unexplored type of ligand for transition metals, in contrast to the well studied polykis(pyrazol-1-yl)borates (**1**) [1], -methanes (**2**) [2] and polykis(pyrazol-1-ylmethyl)benzenes (**3**) [3].

At present, only one report on the preparation of 1,2,4,5-tetrakis(pyrazol-1-yl)benzene (**4**) and its unusual metallacyclophane complex with copper (II) [4] has been published, although several papers from the Elguero group, who have intensively studied hexakis(pyrazol-1-yl)benzene (**5**) [5] are available. However, the elementary member of this class, 1,2-bis(pyrazol-1-yl)benzene (**6**), is still unknown, despite the fact that this compound could demonstrate unusual behavior when complexed with transition metals. Additionally, these complexes will be interesting starting points for subsequent investigations into their catalytic activity.

Although pyrazole-containing derivatives can be prepared by the cyclization of hydrazines with difunctional compounds [6], the preparations of **1**-**5** almost exclusively use substitution methods, whereby a halogen or other functional group in the starting material is displaced under the action of pyrazoles. While compounds **1**-**3** are prepared by the action of a pyrazole-based nucleophile on the relatively reactive aliphatic halogen atom, the same transformation to make compounds **4**-**5** requires the substitution of much less reactive aromatic halides, which require harsh reaction conditions and give lower yields. Lately, transition metal-



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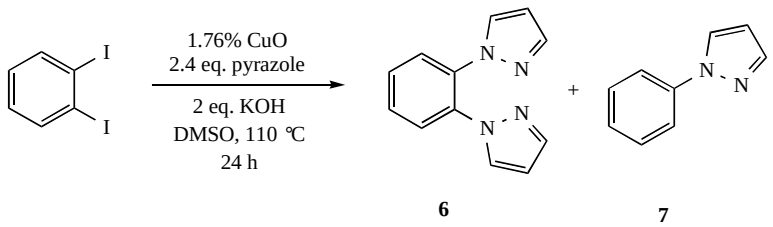


Scheme 1.

catalyzed cross-coupling reactions have been suggested as effective methods for C-N bond formation with activated-, non- or even deactivated haloarenes [7]. With this perspective in mind, it is interesting to compare the classic S_NAr substitution and modern cross-coupling approaches toward the preparation of 1,2-bis(pyrazol-1-yl)benzene (**6**).

2. RESULTS AND DISCUSSION

2.1. Cross-Coupling

It is clear from the recent literature that transition metal catalyzed C-N bond forming reactions provide unprecedented versatility, universality and effectiveness. Among these methods palladium and copper systems are the most promising [7].

Systems composed of 1,2-dichloro-, -dibromobenzenes and a palladium catalyst, as well as 1,2-diiodobenzene and a copper catalyst, were selected for a coupling study with pyrazole for the preparation of **6**.

While we did not find any examples in the literature of azole arylation under Pd(0) catalysis, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, namely XPhos, which is considered one of the best ligands for Pd(0) catalyzed C-N bond forming reactions [8], and $Pd(OAc)_2$/ Pd_2dba_3 as Pd(0) precursors were chosen for study.

Surprisingly, in all the conditions we tried only the starting dihaloarenes were detected by GC/MS in the reaction mixture. We varied numerous parameters including: the solvent (toluene, dioxane, THF), the reaction temperature (60, 100, 110 °C), the precatalyst and ligand loading, the nature of base (Cs_2CO_3, NaO*t*Bu, NaO*t*Am) and the equivalents of pyrazole used (1 or 2). This problem has also recently arisen in Buchwald's work; he connected these problems with high basicity of pyrazole, which leads to slow reductive elimination of the Pd aryl/amido intermediate. They overcame it by using the more bulky 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*tert*-Butyl XPhos) as the ligand [9]. However, reproduction of these Buchwald conditions again gave us only a starting compound, as determined by GC/MS. We think that the main explanation for these failures are the great steric difficulties involved with the formation of a Pd aryl/amido intermediate in the presence of a large halogen atom in the *ortho*-position to the reaction center and the bulky ligand used. In the case of 1,2-dichlorobenzene an additional factor effecting the reaction could be the low reactivity of the C-Cl bond, since Buchwald's work only demonstrates the use of activated chloroarenes.

Alternatively, Cu-based catalyst systems looked more promising, since many examples of coupling iodoarenes with pyrazoles exist [10]. Despite this precedent, no data on the reaction of azoles with 1,2-diiodobenzene is known. From the large assortment of available catalytic systems we have selected the three most universal and effective.

The CuI/benzotriazole system, although not previously used for pyrazole arylation, has demonstrated very good results for imidazole coupling [11]. However, even after prolonged heating the starting compound did not undergo any change, as indicated by GC/MS, and was recovered at the end of the reaction. Similar results were obtained with the CuI/L-proline system, which had been used in several studies investigating the coupling of pyrazole with several iodo- and even bromoarenes [12]. The sole system, with which we finally succeeded in obtaining the coupled product, employed CuO (nanoparticle) as the catalyst [13]. But even in this case after 24 h the reaction mixture still contained 57% of the starting compound, and only 32% of desired compound **6** along with 11% of 1-phenylpyrazole (**7**) detected in the reaction mixture by GC/MS (Scheme **1**).

Compound **7** may have arisen from the protodehalogenation of 1-(2-iodophenyl)pyrazole, the product of mono cross-coupling, and indicates the strong steric interactions during the reaction that we believe are responsible for the problems in preparing **6** by cross-coupling approaches.

2.2. Nucleophilic S_NAr Substitution

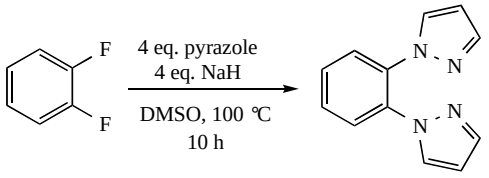
Since cross-coupling approaches gave disappointing results, we pursued a traditional S_NAr substitution approach, although it is not always so effective.

Taking into account the low reactivity of neutral pyrazole in previous investigations, it was logical to investigate nucleophilic substitution with the more reactive sodium pyrazolide, generated in the reaction mixture from NaH and pyrazole. As we expected, neither 1,2-dichloro- nor 1,2-dibromobenzene reacted with sodium pyrazolide despite conducting the reaction in dipolar aprotic solvents (DMF and DMSO) for up to 7 days in a sealed tube at 110 °C.

On the other hand, we recently demonstrated the great potential of fluorine electrophiles in nucleophilic substitution for the preparation of a large number of varied polykis(dialkylamino)substituted benzenes and naphthalenes [14]. From this point of view, the use of 1,2-difluorobenzene in the reaction with sodium pyrazolide was reasonable.

It was found that difluorobenzene did not react with the nucleophile at room temperature even after prolonged stirring. Stepwise increases in the temperature increased the conversion of the starting compound to product **6**, which became 100% at 100 °C (Scheme **2**). Subsequent increases in

temperature did not have any effect. The optimal reaction time was found to be 10 h, and DMSO was preferred as the solvent over DMF, as the use of DMF resulted in a product that was contaminated with unidentified impurities, possibly due to solvent decomposition.



6 (71%)

Scheme 2.

Interestingly, attempts to prepare 1-(2-fluorophenyl) pyrazole, which would be of interest because substitution of the remaining fluorine by other functional groups would allow for the preparation of "mixed" ligands, failed. Even in presence of one equivalent of sodium pyrazolide, only **6** was formed. Lowering the reaction temperature and time also had no effect, and only lowered the yields of **6**, until no reaction between difluorobenzene and the nucleophile was observed. Simple semi-empirical calculations using the PM3 method [15] allow us to understand this phenomenon. The calculated charge on carbons connected to fluorine in 1,2-difluorobenzene is +0.041, whereas the charge on the equivalent carbon atom in 1-(2-fluorophenyl)pyrazole is +0.073, so the introduction of the pyrazole ring activates the remaining fluorine atom for subsequent substitution to the extent that it is more reactive than the starting compound.

In conclusion, despite the popularity of cross-coupling methods, some time is still needed to solve all the problems involved in their application; on the other hand, "the best wine comes out of an old vessel," and S_NAr substitution reactions still have great potential in synthesis.

EXPERIMENTAL

General

1,2-dichloro-, -dibromo-, -difluorobenzenes, $Pd(OAc)_2$ and Pd_2dba_3 were purchased from Alfa Aesar. A 60% suspension of NaH in mineral oil and 1,2-diiodobenzene were purchased from Acros. XPhos, *tert*-Butyl XPhos and CuO (nanoparticle) were purchased from Sigma-Aldrich. Solvents were purified and dried according to the literature [16]. NMR spectra were recorded on a Bruker DPX-250. ^{1}H NMR, and ^{13}C NMR spectra were recorded at 250 MHz and 63 MHz, respectively, both using Me_4Si as an internal standard. GC/MS traces were recorded on an Agilent 6890 equipped with an Agilent 5973N mass selective detector, a quartz capillary column HP-5MS (30 m length, internal diameter 0.32 mm), and helium was used as a carrier gas at a flow rate of 1 mL/min. Melting points were determined in capillary on a PTP apparatus and are not corrected.

Cross-coupling experiments were conducted according to [8] and [9] if palladium was used as a catalyst, and according to [11-13] for copper-catalyzed transformations. After the appropriate time, the composition of the reaction mixture was analyzed by GC/MS.

1,2-Bis(pyrazol-1-yl)benzene

Twenty-five milliliters of anhydrous DMSO was added to 0.16 g of NaH as a 60% suspension in mineral oil (4 mmol). 0.27 g of pyrazole (4 mmol) was carefully added to the resulting mixture under vigorous stirring (**CAUTION! Rapid hydrogen evolution**), and the reaction mixture was stirred for an additional 30 min at r.t. After the reaction mixture had become a clear solution, 0.097 mL (1 mmol) of 1,2-difluorobenzene was added, and stirring was continued for 10 h at 100°C. The mixture was cooled to r.t. and poured into 100 mL of water. The products were extracted with toluene; the organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. 0.15 g of 1,2-bis(pyrazol-1-yl)benzene was isolated with a 71% yield. The product was crystallized from a pentane-methanol mixture to obtain the pure product as white crystals. M.p. 67-68 °C. ^{1}H NMR ($CDCl_3$): 6.28 (dd, $J_{3',4'}$=1.9, $J_{4',5'}$=2.4 Hz, 2H, pyrazole H-4′); 6.99 (d, 2H, pyrazole H-5′); 7.50 (m, 2H, $J_{4,5}$=0.1, $J_{3,4}$=7.7, $J_{3,5}$= $J_{4,6}$=1.2, $J_{5,6}$=8.4 Hz, H-4,5); 7.68 (m, 2H, H-3,6); 7.69 (d, 2H, pyrazole H-3′). ^{13}C NMR ($CDCl_3$): 107.9 (2 pyrazole C-4'); 127.3 (2 arom. C-3,6); 129.2 (2 arom. C-4,5); 130.8 (2 pyrazole C-5'); 135.0 (2 arom. C-1,2); 141.6 (2 pyrazole C-3'). EI-MS (70 eV): 210 (100, M^+), 209 (100), 182 (42), 170 (14), 155 (19), 129 (16), 102 (18), 77 (19), 52 (24), 39 (26). Anal. Calc'd. for $C_{12}H_{10}N_4$ (210.23): C, 68.56; H, 4.79; N, 26.65. Found: C, 68.55; H, 4.80; N, 26.67.

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