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Iron complex-catalyzed N-arylation of pyrazoles under aqueous medium

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ABSTRACT

Commercially available $FeCl_3{\cdot}6H_2O$ with conformationally rigid diamine ligand is a highly effective catalyst for N-arylation of pyrazoles using aryl and heteroaryl iodides. It is notable to show that this complex is tolerable under aqueous medium and particularly the whole reaction utilizes water as the sole solvent without any additional organic co-solvents and surfactants. Attempted study using other nitrogen nucleophiles is described. This newly developed system provides an alternative protocol to Cu- and Pd-catalyzed N-arylation reactions.

1. Introduction

Transition metal-catalyzed cross-coupling methodologies are important in the application of structurally diversified small molecule synthesis.[1] These catalytic protocols can be utilized practically in preparing pharmaceutically useful intermediate.[2] In general, palladium complexes[3] have been found superior in these processes and copper complexes[4] also exhibit high efficiency in related protocols. Recently, Bolm[5] and others[6] reported that Fe complexes were capable in catalyzing carbon–carbon and carbon-heteroatom bond forming reactions.[7] These notable advancements have been identified as a new area of cross-coupling technology[8] carried out under relatively mild reaction conditions.

There has been considerable interest in recent years in the study of solvent-free reactions. The catalytic organic transformation using solventless medium is particularly desirable because of the environmental concerns.[9] Solvent-free reactions sometimes additionally offer higher reaction rate presumably due to more concentrated reaction medium.[10] Inspired by this advantage and our continuous interests in cross-coupling reactions,[11] we applied solventless conditions for Fe-catalyzed cross-coupling reactions. However, our initial study showed that there was exceeding difficulty for agitation in the absence of solvent. This problem may arise due to the excess of solid base. To overcome this problematic issue, we turned our prototypical study using water to dissolve the inorganic base and thus focused on the feasibility of Fe-catalyzed cross-coupling under aqueous conditions.[12,13] Under this attempted investigation, we expect that the organic reagent droplets are suspended and surrounded by the aqueous alkaline medium, thus efficiently providing additional surface area of contact for reagents. In fact, this is a preferable reaction medium than just in solid inorganic base/liquid organic reagents contact under solventless conditions. Herein, we disclose our results in Fe-catalyzed N-arylation of pyrazoles using water as the reaction medium.[14] This catalytic system is highly attractive which comprises economical $FeCl_3{\cdot}6H_2O$ with commercially available diamine ligand.

In our initial study, we found that the solventless conditions obviously suffering from difficult agitation gave only 22% yield of the desired product (Table 1, entry 1). Gratifyingly, by employing water to dissolve the inorganic base, a much higher product yield was obtained (entry 2). These results provided important ground work for our further investigations. A survey of commercially available diamine ligands showed that **L1** is the most suitable ligand while **L2** and **L4** provided slightly lower yields (entries 2, 3, and 5). TMEDA and 1,10-phenathroline were found to be inferior (entries 4 and 6). Picolinic acid, which we demonstrated as highly active at room temperature in Cu-catalyzed C–C bond coupling reaction,[15] gave only a trace amount of the desired product in the Fe-catalyzed N-arylation of pyrazole (entry 7). Control experiment showed that no N-arylated pyrazole was afforded in the absence of ligand as judged by GC–MS analysis (entry 8). Commonly used bases, such as K_3PO_4 and K_2CO_3 gave good yields of product while NaO*t*-Bu provided poor conversion (entries 9–11). Increasing the amount of either $FeCl_3{\cdot}6H_2O$ or **L1** showed slight improvements on the product yield (entries 12 and 13). Interestingly, we found the concentration of base in the reaction medium also affecting the aryl iodide conversion. Concentration of base from 2 M to 4 M was the best range for this reaction (entries 14–16).

To probe the efficiency of this aqueous catalytic system, a range of aryl iodides were examined (Table 2). Substituted group with different electronic properties on the electrophile gave good to excellent yield of the corresponding products (entries 1–6). Particularly noteworthy was that free $-NH_2$ group was tolerable under these reaction conditions (entry 7). 3-Iodobenzyl alcohol was a

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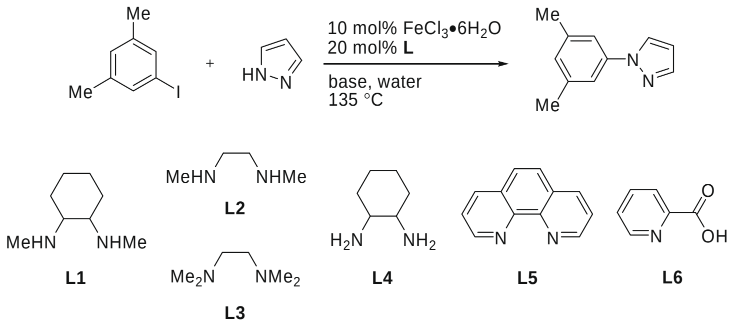
Table 1

Initial screenings on the feasibility of aqueous Fe-catalyzed N-arylation of pyrazole[a]



Entry	Base	Ligand **L**	Solvent	%Yield[b]
1	$K_3PO_4·H_2O$	**L1**	No solvent	22
2	$K_3PO_4·H_2O$	**L1**	Water	74
3	$K_3PO_4·H_2O$	**L2**	Water	70
4	$K_3PO_4·H_2O$	**L3**	Water	<1
5	$K_3PO_4·H_2O$	**L4**	Water	69
6	$K_3PO_4·H_2O$	**L5**	Water	<1
7	$K_3PO_4·H_2O$	**L6**	Water	<1
8	$K_3PO_4·H_2O$	No ligand	Water	0
9	K_3PO_4	**L1**	Water	74
10	K_2CO_3	**L1**	Water	72
11	NaO*t*-Bu	**L1**	Water	23
12[c]	$K_3PO_4·H_2O$	**L1**	Water	80
13[d]	$K_3PO_4·H_2O$	**L1**	Water	77
14	$K_3PO_4·H_2O$	**L1**	Water (4 M)[e]	75
15	$K_3PO_4·H_2O$	**L1**	Water (2 M)[e]	70
16	$K_3PO_4·H_2O$	**L1**	Water (1 M)[e]	27

[a] Reaction conditions: aryl iodide (1.5 mmol), pyrazole (1.0 mmol), $FeCl_3·6H_2O$ (0.1 mmol), ligand **L** (0.2 mmol), solvent (0.5 mL), and base (2.0 mmol) under N_2 for 24 h.

[b] Isolated yields.

[c] 20 mol % $FeCl_3·6H_2O$ and 40 mol % **L1** were used.

[d] 40 mol % **L1** was used.

[e] Molarity of base (4 M = 0.5 mL water; 2 M = 1.0 mL water; 1 M = 2.0 mL water).

feasible coupling partner in this catalysis (entry 10). Sterically hindered 2-iodotoluene provided good yield of the desired product (entry 11).

It is of high challenge to use heteroaryl substrate in the cross-coupling reaction as the heteroatom usually renders the transition metal complex coordinatively saturated, and thus retarded the rate of reaction. Upon applying the $FeCl_3·6H_2O$/**L1** catalyst system, the heteroaryl substrates were efficiently transformed to the corresponding product in good yields (Table 3). Nitrogen-containing heterocycles provided slightly better yield than sulfur-containing heterocycles (Table 3, entries 1–4). These results represent the first examples of heteroarylation in Fe-catalyzed pyrazole arylation.

In order to further explore the substrate scope, we attempted to investigate other nitrogen nucleophiles (Table 4). Intriguingly, similar structures of indole and azaindole showed significantly different reactivity in the arylation reaction, and the azaindole furnished the desired product in 87% yield. Sterically congested carbazole afforded the product in low yield. Substituted pyrazole derivatives, indazole and 3,5-dimethylpyrazole gave moderate yield of the corresponding products.

In addition to the heterocycles that have one or two nitrogen atoms, we also tried the cross-coupling of triazoles. Moderate yield was obtained when 1,2,4-triazole was coupled with 2-iodopiperizine (Scheme 1).

In conclusion, we have established an effective and economical catalyst system, $FeCl_3·6H_2O$/**L1**, for N-arylation of pyrazoles and their derivatives. This catalytic system has beneficial feature of using aqueous base as the reaction medium. Aromatic amino group and benzyl alcohol moiety on electrophilic partners are compatible under these reaction conditions. Notably, we have successfully showed the first examples of heteroaromatics in this type of Fe-catalyzed pyrazole arylation. This new system is believed to have potential of being an alternative protocol for accessing a variety of N-arylated pyrazoles and their derivatives.

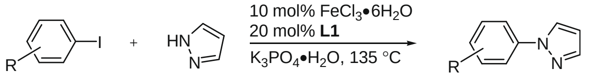
2. Experimental section

2.1. General considerations

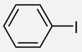
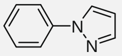
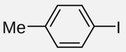
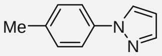
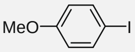
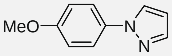
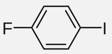
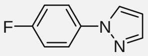
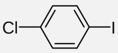
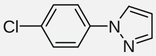
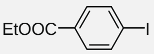
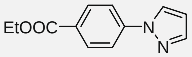
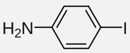
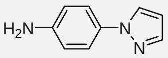
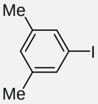
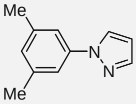
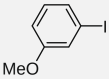
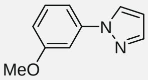
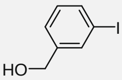
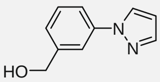
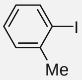
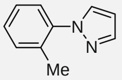
Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. DMF was pre-dried by calcium hydride and distillated under reduced pressure. Toluene was distilled from sodium benzophenone ketyl under nitrogen. Commercially available aryl iodides (liquid form only) were purified by passing through a short plug (0.5 cm wide × 4 cm height) of neutral alumina or distillation under reduced pressure. GC analysis was conducted on a HP G1800C GCD system using a HP5MS column (30 m × 0.25 mm). Known products were characterized by NMR and mass spectroscopy and compared to the literature data or to those of authentic sample analysis.

General procedures. $FeCl_3·6H_2O$ (0.1 mmol), **L1** (0.2 mmol), ArI (1.5 mmol, if solid), pyrazole (1.0 mmol), and $K_3PO_4·H_2O$ (2.0 mmol) were charged to a Teflon screw-capped Schlenk tube (approx. 10 mL size). The tube was evacuated and backfilled with nitrogen (3 cycles). Water (0.5 mL, previously bubbled with N_2 gas for 10 min) and ArI (1.5 mmol, if liquid) were added to the reaction mixture. The tube was sealed and magnetically stirred in a pre-heated oil bath for 24 h (*note*: reaction time for each sub-

Table 2
Fe-catalyzed N-arylation of pyrazole under aqueous medium[a]



1a-1k **2a** **3**

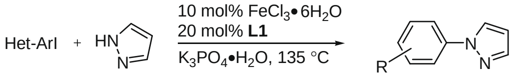
Entry	Aryl		Product		%Yield[b]
1		**1a**		**3aa**	90
2		**1b**		**3ba**	89
3		**1c**		**3ca**	90
4		**1d**		**3da**	82
5		**1e**		**3ea**	87
6		**1f**		**3fa**	Trace[c]
7		**1g**		**3ga**	53
8		**1h**		**3ha**	75
9		**1i**		**3ia**	92
10		**1j**		**3ja**	85
11		**1k**		**3ka**	76

[a] Reaction conditions: aryl iodide (1.5 mmol), pyrazole (1.0 mmol), $FeCl_3{\cdot}6H_2O$ (0.1 mmol), ligand **L1** (0.2 mmol), water (0.5 mL), and $K_3PO_4{\cdot}H_2O$ (2.0 mmol) under N_2 for 24 h (reaction times are not optimized for each substrate).

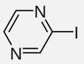
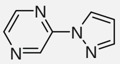
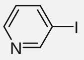
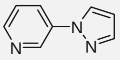
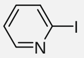
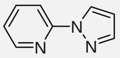
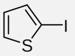
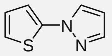
[b] Isolated yields.

[c] Starting material decomposed during the course of the reaction.

Table 3
Fe-catalyzed N-heteroarylation of pyrazole[a]



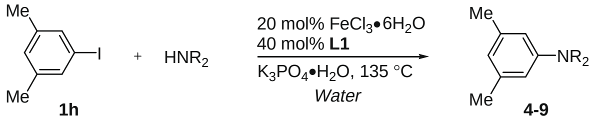
1l-1o **2a** **3**

Entry	Aryl		Product		%Yield[b]
1		**1l**		**3la**	84
2		**1m**		**3ma**	92
3		**1n**		**3na**	87
4		**1o**		**3oa**	70

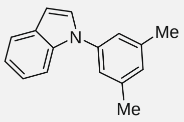
[a] Reaction conditions: heteroaryl iodide (1.5 mmol), pyrazole (1.0 mmol), $FeCl_3{\cdot}6H_2O$ (0.1 mmol), ligand **L1** (0.2 mmol), water (0.5 mL), and $K_3PO_4{\cdot}H_2O$ (2.0 mmol) under N_2 for 24 h.

[b] Isolated yields.

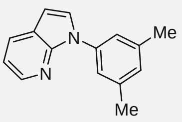
Table 4
Fe-catalyzed N-arylation of nitrogen-containing nucleophiles[a]



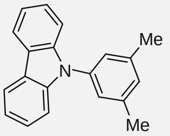
1h **4-9**



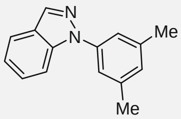
4: 38% yield[b]



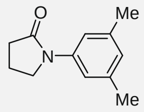
5: 87% yield[c]



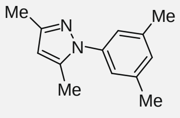
6: 17% yield[b]



7: 50% yield[c,d]



8: 18% yield[c]



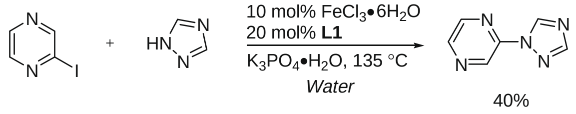
9: 37% yield[c]

[a] Reaction conditions: aryl iodide (1.5 mmol), nitrogen heterocycle (1.0 mmol), $FeCl_3{\cdot}6H_2O$ (0.2 mmol), ligand **L1** (0.4 mmol), water (0.5 mL), and $K_3PO_4{\cdot}H_2O$ (2.0 mmol) under N_2 for 24 h.

[b] GC yields.

[c] Isolated yields.

[d] A mixture of N-substituted regioisomers.



Scheme 1.

strate was not optimized). The tube was allowed to reach room temperature and the reaction mixtures were extracted with ethyl acetate (3 × 10 mL). (Tiny amount of the aliquot was taken out for GC-FID and GC–MS analyses). The combined organic phases were concentrated and the crude mixtures were purified by column chromatography on silica gel using hexane/ethyl acetate solvent mixtures as the eluent. See Supplementary data for detailed procedures and characterization data.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.018.

References and notes

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