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NOTE

An Effective N-Ligand for Copper-Catalyzed N-Arylation of Triazole

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An effective N-ligand for copper-catalyzed N-arylation of 1*H*-1,2,4-triazole has been developed. In the presence of Cu_2O, Cs_2CO_3, N-ligand-B, 1*H*-1,2,4-triazole were coupled with toluene to afford the corresponding products in moderate condition and with excellent yields.

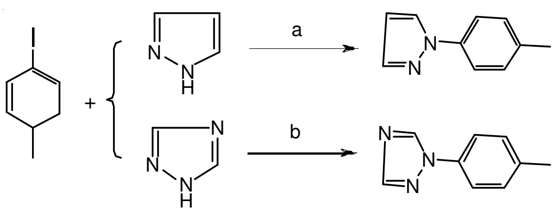
Key Words: N-Ligand, C-N Bond cross-coupling, Copper-catalyzed, 1*H*-1,2,4-Triazole.

The transition metal-catalyzed N-arylation of nitrogen-containing heterocycles (*e.g.*, pyrazoles and triazoles) reactions has received considerable attention in recent years due to their successful uses in the preparation of N-aryl compounds in pharmaceuticals, crop-protection chemicals and material sciences[1,2]. Traditional procedures, such as the Ullmann reaction[3], usually require very high temperatures and give variable yields. On the other hand, arylation of amines and anilines using aryl halides/palladium or nickel catalyst has been well documended[4] by Hartwig and Buchwald. But attempts to extend the palladium-catalyzed cross-coupling methodology to 1*H*-1,2,4-triazole was failed[5].

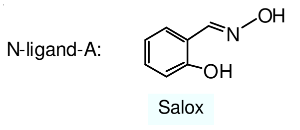
Recently, N-arylation of pyrazoles with aryl-bromides or iodides in the presence of copper catalysts and N-ligands has been investigated[6-8], we attempt to extend the method for N-arylation of 1*H*-1,2,4-triazole and find in the presence of Cu_2O, Cs_2CO_3, N-ligand-B, 1*H*-1,2,4-triazole were coupled with 4-iodo toluene to afford the corresponding products in moderate condition and with excellent yields. This search for new suitable ligands for 1*H*-1,2,4-triazole N-arylation was first undertaken for the parallel reaction between pyrazole and 1*H*-1,2,4-triazole. Each ligands was examined (Table-1) in the presence of alternative aprotic solvents (CH_3CN, DMF). DMF was the better solvent for 1*H*-1,2,4-triazole owing to its poor solubility of cesium salt of 1,2,4-triazole (pKHA = 14.75 in DMSO) in acetonitrile, which led to incomplete conversion of 4-iodo toluene even after prolonged heating. N-Ligand-B was found more suitable than N-ligand-A due to the weaker nucleophilicity of 1,2,4-triazole compared to pyrazole. N-Ligand-B was also synthesized in our laboratory. All reaction conditions were shown in (**Scheme-I** and **II**).

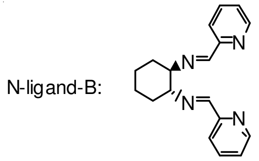
TABLE-1
SCREENING THE OPTIMUM CONDITION

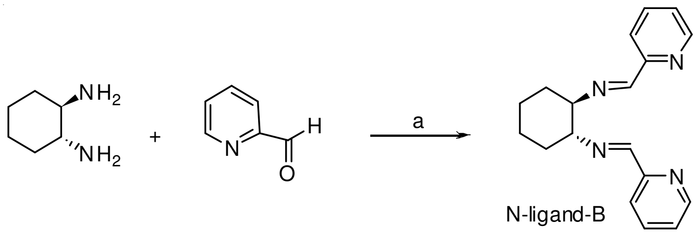
Entry	SM	L	Solvent	Yield (%)
1	Pyrazole	N-Ligand-A	CH_3CN	80
2	[1,2,4]-Triazole	N-Ligand-A	CH_3CN	10
3	[1,2,4]-Triazole	N-Ligand-A	DMF	40
4	[1,2,4]-Triazole	N-Ligand-B	CH_3CN	30
5	[1,2,4]-Triazole	N-Ligand-B	DMF	80



Scheme-I: (a) Cu_2O, N-ligand-A, Cs_2CO_3, CH_3CN, 100 °C, 22 h, 80 %, (b) Cu_2O, N-ligand-B, Cs_2CO_3, DMF, 100 °C, 22 h, 80 %







Scheme-II: (a) EtOH, room temperature, 20h, then refluxed 2.5 h

The ^1H NMR spectrum were obtained on a Varian INOVA-400 instrument (400 MHz working frequency for H). The HPLC-MS were recorded on Agilent 1100 Series LC/MSD 2.1.

Preparation of 1-*p*-tolyl-1*H*-pyrazole (1): The reaction mixture of 4-iodo toluene (1 g, 4.59 mmol), pyrazole (0.47 g, 6.88 mmol), cesium carbonate (3.74 g, 11.47 mmol), copper(I) oxide (33 mg, 0.23 mmol) and N-ligand-A Salox (126 mg, 5 % mmol) in dry acetonitrile (15 mL) was stirred at 100 °C under nitrogen for 22 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane and filtered. The filtrate was concentrated in vacuum to yield a residue that was dissolved in dichloromethane. The residue was purified by silica gel (mobile phase: PE/EA = 10/1) to give pure compound 1-*p*-tolyl-1*H*-pyrazole. Yield (%): 610 mg (80). LC-MS: 15$(M + H)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.93-7.92 (dd, 1H), 7.74 (dd, 1H), 7.66-7.63 (d, 2H), 7.49-7.46 (d, 2H), 6.48 (m, 1H), 2.42 (s, 3H) ppm.

Preparation of 1-*p*-tolyl-1*H*-1,2,4-triazole: The reaction mixture of 4-iodo toluene (5 g, 23.0 mmol), 1*H*-1,2,4-triazole (1 g, 15.3 mmol), cesium carbonate (10 g, 30.6 mmol), copper(I) oxide (220 mg, 0.76 mmol) and N-ligand-B (900 mg, 3.1 mmol) in dry DMF was stirred at 100 °C under nitrogen for 24 h. The reaction mixture was cooled to room temperature. The residue was purified by silica gel (mobile phase: PE/EA = 10/1) to give pure compound 1-*p*-tolyl-1*H*-1,2,4-triazole after removing solvent. Yield (%): 1.91 g (55.5). LC-MS: 159.1 $(M + H)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.43 (s, 1H), 8.15 (s, 1H), 8.10-7.98 (m, 4H), 2.42 (s, 3H) ppm.

Preparation of N-ligand-B: Anhydrous magnesium sulphate (4.15 g, 35.0 mmol) and rac-*trans*-1,2-diaminocyclohexane (1.4 mL, 11.67 mmol) successively added to a solution of 2-pyridylaldehyde (2.22 mL, 23.3 mmol) in absolute EtOH (20 mL). The mixture was stirred for 20 h at room temperature, heated at reflux for 2.5 h and filtered. The solid was discarded and the filtrate was concentrated in vacuum. The residue was recrystallized in EtOH to give desired compound ligand-B. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.3 (dd, 2H), 7.87 (m, 2H), 7.63 (m, 2H), 7.22 (t, 2H), 3.50 (m, 2H), 1.83 (m, 6H), 1.4 (m, 2H).

In conclusion, an efficient synthetic method of 1*H*-1,2,4-triazole has been developed. An effective N-ligand for copper-catalyzed N-arylation of 1*H*-1,2,4-triazole has been developed. The advantages of this approach are high yield and easy expriments. Further application of this method for substituted 1*H*-1,2,4-triazole with halogenated aryl or heteroaryl is underway in our laboratory.

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