

The Ligand-Free N-Arylation of 1,2,4-triazoles at Room Temperature

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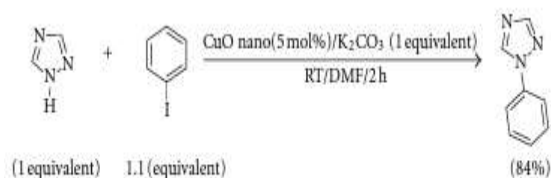
Abstract:

By using prominent (111) facet Cuco nanoparticles as a catalyst in a ligand-free state, a straightforward and effective technique for N-arylation of 1,2,4-triazole at room temperature was developed. In addition to the catalyst's reusability, a wide range of substrates provides a high yield of N-arylation product in a relatively rapid reaction time. Since this catalyst is so versatile, we looked at transformations involving less reactive nitrogen nucleophiles such as imidazole and pyrazoles. We were pleasantly surprised to discover that several different azole derivatives may be coupled efficiently with aryl iodide to produce the required N-arylated product.

Introduction

Due to their versatility in biology and increasing interest as hole-transport molecules for organic light-emitting diodes (LEDs), N-aryl derivatives of azoles have emerged as a key class of organic chemicals for organic synthesis. Metal-mediated processes such as the Ullmann coupling [1, 2], aromatic nucleophilic substitution [3, 5], and Pd or Cu catalysed arylation [6] were used to N-arylate azole. However, their usefulness was limited, particularly for industrial-scale production, due to the need of using a chelating ligand, a stoichiometric quantity of Cr (CO), and severe reaction conditions. The N-arylation of azoles with aryl halides catalysed by transition metals is one of the most potent and effective ways for the production of N-aryl derivatives [7, 8]. However, there may be limits to present approaches due to the high cost of the transition-metal catalysts required for these conversions. These catalysts include palladium [9], rhodium [10], nickel [11], and cobalt [12] complexes. For this reason, it is currently difficult to filter out metal catalysts for the N-arylation of azoles that are both cheap and safe for the environment [13]. Copper catalysts functionalized with a wide variety of ligands proved to be a cheap and effective tool for the N-arylation of nitrogen-containing heterocycles with aryl halides. The Cu-catalysed reactions used a wide variety of ligands, such as beta-diketones [14], 1,2-diamines [15], phenanthrolines [16], bipyridines [17], -amino acids [18], phosphines [19], and others [20]. An essential function of chelating ligands is to regulate the concentration of active catalytic species, although these ligands might potentially introduce

unwanted impurities into the final products [21]. To save time and effort, catalysts that don't need ligands could be a viable option. Chui [22] and Cu₂O [23] have been used as catalysts for this cross-coupling reaction in the absence of organic ligands with great success in recent years. However, these catalytic systems often need either an abundance of substrates or a substantial loading of catalysts [24]. This kind of coupling reaction was found to be catalysed by simple inorganic copper (II) salts without the need for any additional ligands [25]. For the first time, Route Tal has reported using Cuco nanoparticles in a cross-coupling process. [26]. Efficacious catalysts for organic synthesis have been investigated, and they are found to be Cuco nanoparticles with a high surface area and reactive morphologies [27, 28]. Cuco nanoparticles were of great interest because of their potential applications in catalysis, metallurgy, and high-temperature superconductors [29, 30]. It was discovered that these nanoparticles are efficient catalysts for the oxidation of CO and NO.















SCHEME 1: N-arylation of 1,2,4-triazole.

other than methanol and oxidation of other volatile organic chemicals [31, 32]. Nanocrystalline Cuco has been used in new asymmetric processes reported by Kanam et al. [33, 34]. These reactions include the hydrolysis of prochiral ketones, the direct aldol reaction, and the N-arylation of heterocycles. The catalytic operations were carried out by the Cuco nanoparticles' (111) plane, which has a larger number and higher density of active sites

than bulk Cuco. Previously [35], we showed the powerful catalytic activity of nanoparticles with a mainly (111) facet in the N-arylation of indoles. Here, we extend that study to the N-arylation of azoles and report on our success under ideal conditions. N-arylation of 1,2,4-triazole was accomplished at room temperature with decreased reaction time and high yield because to the extraordinary catalytic activity of these mainly (111) facet Cuco nanoparticles. Our initial aim was to develop a simple method for N-arylation of azoles using a highly active predominance (111) faceted Cu NanoparticlesalsahatergenemuscatelStainland-free setting. In light of this, we report our results and talk about Temuco nanoparticles with a pronounced (111) plane were created in our lab using a thermally-assisted green process at reflux temperature, as reported in [35]. In Section 2.1, we investigate the aryl iodide reactions of 1,2,4-triazole. Unlike the previously published approach [36], which is limited by a longer reaction time and problematic in separation of ligand, our method allows the Cuconano catalyst to be easily separated and recycled for at least five times without much loss in yield of the product. It was using aryl iodides that the N-arylation of 1,2,4-triazole was first investigated (Scheme 1). By reacting iodobenzamide with 1,2,4-triazole at room temperature, a high yield of 1-phenyl-1H-1,2,4-triazole was achieved (84%), while a higher yield of 91% was obtained by using 4-nitro-1-iodobenzene, which is more reactive than iodobenzamide towards 1,2,4-triazole. Under the identical experimental circumstances, 4-iodoanisole and 2-iodotoluene, which are both rich in electrons, are more reactive than they are to 1,2,4-triazole, which has fewer (Table 1, Entry 5 and 6). We tested a range of reaction temperatures to see whether temperature had an effect on product yield, but found no discernible correlation between temperature and yield.

While N-arylation of 1,2,4-triazole proceeded smoothly in air, iodobenzamide proved more reactive than bromobenzene. Under these conditions, chlorobenzene is less reactive than bromobenzene and iodobenzamide. According to their relative reactivity, iodobenzamide, bromobenzene, and chlorobenzene behaved as follows: (Table 1, entries 2, 3, and 4). The reaction could not have happened if Cuco nanoparticles weren't there. N-Arylation of 1,2,4-triazole at room temperature is reported for the first time. There were no unwanted C-arylation or beryl-related by-products, and everything went according to plan. A variety of bases were tried to examine how they influenced the iodobenzamide-triazole reaction. The yield was increased when N-arylation was utilised to increase basicity prior to the addition of carbonates. Despite the usage of Cs₂CO₃ and t-Buna, only trace amounts of the product were generated. The catalytic agents K₂CO₃ and Rb₂CO₃ worked effectively in our setup. The use of the stronger bases may make the Cuconano catalyst useless. One equivalent of the base significantly speed up the reaction, although a reasonable yield could be reached with half an equivalent of the base. Imidazole and pyrazole underwent identical N-arylation. Excellent activity in this reaction was observed to be promoted by both K₂CO₃ and Rb₂CO₃, however it was discovered that K₂CO₃ was more practically favoured (Table2, entry 5 and 10). Triazole-iodobenzamide reactions conducted in toluene at ambient temperature for 12 hours resulted in a 65% yield, but the conversion was lower when using acetonitrile, methanol, and chloroform (Table 2). Thus, we investigated the effects of synthesising N-aryl triazole in dimethylformamide using 5mol% Cuco as a nano catalyst and 1 equivalent of potassium carbonate. Imidazole and Pyrazole N-Arylation 2.2. Imidazole and pyrazole are examples of the azoles that we expanded our research to cover (Table 3). First attempts at the reaction at room temperature resulted in a limited yield of product. The N-arylated product yield increases substantially with increasing temperature, reaching a high of 97% after just 3 hours of reflux (Scheme 2). Since imidazole and pyrazole are less reactive, hydrogen abstraction from the nucleophile is difficult at room temperature, suggesting that the N-arylation process occurred at refluxed temperatures. The rate of each reaction was measured using Co-TLC, and the products were characterised and the catalytic efficiency of each tested catalyst was evaluated using LCMS, ¹HNMR, and ¹³C NMR. We compared the catalytic performance of this mostly (111) faceted Cuco

Entry	Azole	Aryl iodide	Reaction temperature (°C)	Yield (%)
(1)			RT (25)	84%
(2)			RT (25)	91%
(3)			RT (25)	72%
(4)			RT (25)	60%
(5)			RT (25)	78%
(6)			RT (25)	60%

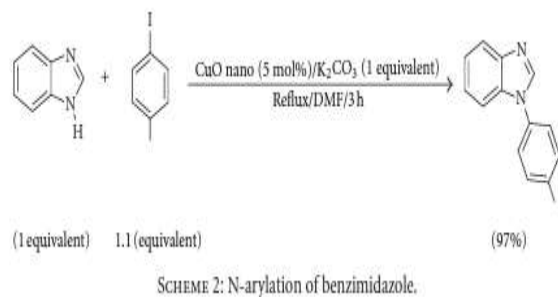


Table2: Optimization of reaction condition for the N-arylation of 1,2,4-triazole with iodobenzene.

Entry	Solvent	Base	Reaction time (h)	(Isolated yield) ^a
1	Toluene	K ₂ CO ₃	12	65%
2	CH ₃ CN	K ₂ CO ₃	12	40%
3	CH ₃ OH	K ₂ CO ₃	12	25%
4	CHCl ₃	K ₂ CO ₃	12	15%
5	DMF	K ₂ CO ₃	2	84%
6	DMF	K ₂ CO ₃	8	84%
7	DMF	CS ₂ CO ₃	5	45%
8	DMF	t-BuONa	5	55%
9	DMF	NaOH	5	35%
10	DMF	Rb ₂ CO ₃	4	75%

Compare commercially available Cuco nanoparticles and bulk Cuco powder (bought from Merck) to those made from scratch. High catalytic activity of prominent (111) facet Cuco nanoparticles in N-arylation of azoles is shown by these data. 2.4. Effect of Catalyst Concentration. The effect of catalyst concentration on the yield of product has been investigated. Table 5 displays the outcomes of this process with varying concentrations of Cuco catalyst. From a 6% yield at a catalyst concentration of 2.5 mol% to a 97% yield at a concentration of 5 mol%, additional increases in catalyst concentration had no effect on the total yield of the product. 2.5. Mechanism. The increased catalytic activity of Cuco nanoparticles over bulk Cuco powder suggested that the reactions took place on the nano catalyst's predominant (111) face rather than throughout the material. Accordingly, the Cuco nanoparticles may undergo a reaction with an aryl halide to produce intermediate X, where the surplus positive charge acquired over time may be distributed among the Cu On nanoparticles.

Entry	Azole	Aryl iodide	Reaction temperature/h	Yield ^a
(1)			Reflux/3h	97%
(2)			Reflux/3h	98%
(3)			Reflux/3h	84%
(4)			Reflux/3h	87%

Azole (3 mmol), iodobenzamide (3.3 mmol), Cuco nanoparticles (0.15 mmol), potassium carbonate (3 mmol), and N, N-dimethylformamide (10 mL) at reflux for 3 hours; isolated yield.

Table4: Comparison of catalytic activity of (111) facet Cu On nanoparticle.







Entry	Product	Structure	Yield (%)	Reaction time (h)	Yield (%)
1			60%	3	60%
2			97%	3	97%
3			97%	3	97%
4			96%	3	96%

Table5: Effect of catalyst concentration on the N-arylation of benzimidazole.

Entry	Catalyst conc. (mol%)	Reaction time (h)	Yield (%) ^a
1	2.5	3	60
2	5	3	97
3	10	3	97
4	15	3	96

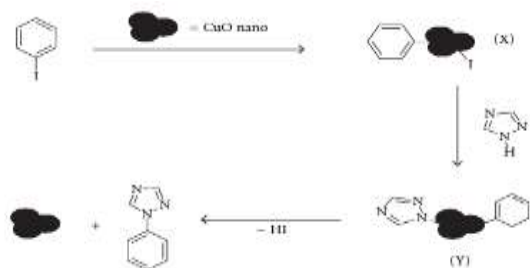
Table6: Recyclability of Cuconan particle cocatalyst.

Entry	Cycle	(Yield %) ^a
1	1st	97
2	2nd	93
3	3rd	90
4	4th	80
5	5th	78

Isolated yield, reaction conditions: 3 mmol of azole, 3.3 mmol of iodobenzamide, 0.15 mmol of Cuconan particles, 3 mmol of K₂CO₃, and 10 mL of N-N dimethylformamide at reflux for 3 hours (Scheme3). X may then react with triazole to produce intermediate Y, which may complete the catalytic cycle by forming the N-arylated product. Upon completion of the reaction, the Cuconan nanoparticles are released. 2.6. Recyclability of Catalyst. Finally, the catalyst's activity and stability were examined by cycle-use tests. Catalytic activity of Cuconan nanoparticles was maintained over five cycles of recycling (Table6). Before being reused in the next reaction, the spent catalyst was centrifuged to remove it from the reaction mixture and washed two or three times in hot water. Recyclability and reusability of catalyst without considerable loss of its catalytic activity were shown by the fact that product yield was not significantly reduced during recycling trials.

Experimental Section

General Procedure for the N-Arylation of 1,2,4-Triazole. An amount of 1,2,4-triazole (3 mmol), iodobenzamide (3.3 mmol), Cuconan nanoparticles (0.15 mmol), potassium carbonate (3 mmol), n-n dimethylformamide (10 mL), and water (10 mL) were added to a glass reactor. The reaction mixture was stirred at room temperature and the progress of the reaction was tracked by Co-TLC. Following the reaction's conclusion, dilute the resulting reaction mixture with 20 mL of water. Ethyl acetate (2 x 10 millilitres) was used to wash the entire reaction mixture. We separated the Cuconan catalyst from the aqueous layer using centrifugation. In order to remove moisture from the combined organic extracts, we used a brine solution and sodium sulphate. Reduced-pressure solvent evaporation was followed by flash column chromatography on silica gel using ethyl acetate: petroleum ether (1:9) as the eluent to produce an analytically pure product.



Scheme 3: Proposed mechanism for N-arylation of triazole catalysed by Cuco.

Conclusion:

N-arylation of 1,2,4-triazoles at room temperature with aryl iodides under ligand-free condition has been disclosed; the reaction is catalysed by Cuco nanoparticles with a prominent (111) facet. In addition to being recyclable, the catalyst also promoted high-yield reactions over a wide range of substrates. We looked at transformations involving less-reactive azoles like imidazole and pyrazole due to the catalyst's broad reach. We were ecstatic to discover that several different azole derivatives interacted with aryl iodide to produce high quantities of the required N-arylated compounds. You may get other information at doi:10.1155/2012/515092.

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