Vietnam Journal of Catalysis and Adsorption
Tạp chí xúc tác và hấp phụ Việt Nam

https://chemeng.hust.edu.vn/jca/

Copper ferrite catalyst for direct arylation of acidic C-H bonds in azoles with aryl aldehydes

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ARTICLE INFO

Received: 02/7/2021
Accepted: 17/8/2021
Published: 20/8/2021

Keywords:

copper ferrite, arylation, heterogeneous

ABSTRACT

Coupling reagents toward direct arylation of C2-H bonds in aryl azoles are often limited to aryl halides. Herein we report a functionalization of the acidic sp^2 C-H bonds in benzothiazoles with benzaldehyde derivatives. Reactions proceeded in the presence of commercially ready $CuFe_2O_4$ catalyst. Scope of functional groups included chloro, nitro, cyano, and ester groups.

Introduction

2-Aryl-substituted benzothiazoles find ubiquitous uses in commercial drugs and functional materials [1-3]. The targeted compounds could be obtained via a direct arylation of C2−H bonds in azoles with aryl halides and isosteres. Most of the available methods often require the use of scarce transition metals, strong bases, and harsh conditions [4-7]. Examples of mild C−H arylation in the presence of cheap, abundant first-row metals are rare. Li and Deng reported a method for aerobic arylation of benzoazoles with aryl aldehydes in the presence of $FeSO_4$ catalyst [8]. Our group recently presented a nearly identical transformation, yet using metal-organic framework $Fe_3O(BDC)_3$ (H_2BDC = terephthalic acid) as a heterogeneous catalyst [9]. Notably, both mentioned reports suffered from the use of non-recyclable catalyst or non-commercial material.

The commercially available copper ferrite nanoparticles have been utilized for direct functionalization of C−H bonds [10]. As the material is easily recovered, by applying external magnet, and reusable, many methods have been attempted to extend its catalytic uses. One of the earliest examples focusing on the direct arylation of sp^2 C−H bonds assisted by copper-based magnetite catalyst was reported by Glorius and co-workers [11]. The heterogeneous coupling of heteroarenes and diaryliodonium salts presumably proceeded via a mechanism of electrophilic substitution. Meta arylation of C−H bonds in anilides was feasible in the presence of CuO/Fe_3O_4 catalyst [12]. Herein we report our attempt to functionalize the acidic C2−H bonds in benzothiazoles with aryl aldehydes in the presence of commercial $CuFe_2O_4$ nanoparticles. The material was easily removable and reusable without a significant loss of catalytic activity.

Experimental

Copper ferrite nanoparticles were commercially obtained from Sigma Aldrich. Other organic compounds were purchased from Acros, Macklin, Energy Chemicals, and directly used without further purification. Unless other notice, a typical experiment should be as follows: to a 5 mL vial equipped with a magnetic stir bar was charged with benzothiazole (0.3 mmol, 40.6 mg), an aryl aldehyde (0.2 mmol), $CuFe_2O_4$

https://doi.org/10.51316/jca.2021.070

(0.04 mmol, 9.6 mg), and ethanol (0.4 mL). The vial was purged with oxygen then placed into a preheated bath at 100 °C for 20 h. Upon completion, the mixture was diluted with brine (5 mL) and ethyl acetate (EtOAc, 5 mL). The aqueous phase was further extracted with EtOAc (2 x 5 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated. For determination of gas chromatographic (GC) yields, the crude mixture was added diphenyl ether internal standard (0.2 mmol, 34.2 mg) and diluted with EtOAc (5 mL). GC Analyses were performed using a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 µm). For isolated yields, the crude mixture was purified using hexanes/EtOAc eluent. The NMR spectra were recorded on Bruker AV 400 and 500 spectrometers using residual solvent peaks as the reference.

Results and discussion

Our study firstly paid attention to the arylation of benzothiazole **1a** with benzaldehyde **2a** as the model reaction. The 2-phenyl benzothiazole product **3aa** was obtained in the presence of 20 mol% $CuFe_2O_4$ catalyst and ethanol solvent (Figure 1). Chemical structure of **3aa** was confirmed by NMR characterization. The result as follows: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 8.18 – 8.14 (m, 1H), 8.13 – 8.05 (m, 3H), 7.62 – 7.53 (m, 4H), 7.48 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6, ppm) δ 167.2, 153.5, 134.4, 132.8, 131.3, 129.3, 127.1, 126.6, 125.5, 122.8, 122.3.

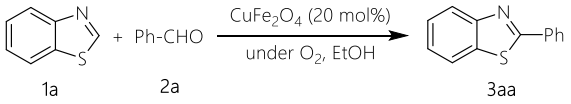


Figure 1: Arylation of C2–H bond in benzothiazole with benzaldehyde catalyzed by $CuFe_2O_4$ nanoparticles

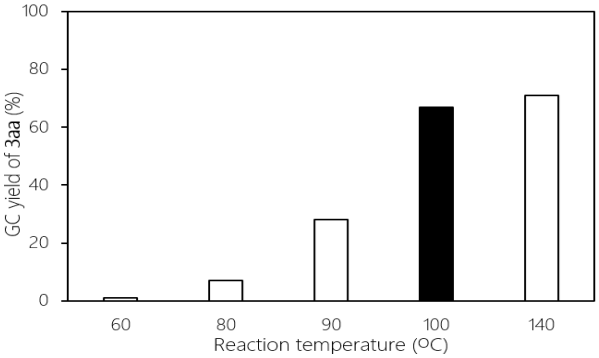


Figure 2: Effect of reaction temperature on the yield of the desired product. Yields are GC yields using diphenyl ether as internal standard

The reaction was optimized with respect to reaction temperature. The results are shown in Figure 2. Low yields (i.e., lower than 10% yield) of **3aa** were obtained when the reactions were carried out at the temperature at 80 °C or lower. The arylation afforded 28% yield of the arylation product at 90 °C. Running the reaction at 100 °C or above dramatically improved the yield. The temperature of choice was 100 °C, as 67% yield of **3aa** was obtained.

Effect of solvent was next studied. The results are presented in Figure 3. Generally, the $CuFe_2O_4$-catalyzed arylation of benzothiazole C–H bond was feasible in alcohol solvents. Among those tested, ethanol gave the best yield of the arylation product **3aa**. Running the coupling in iso-propanol (*i*PrOH) afforded 47% yield of **3aa**. A 25% yield of 2-phenyl benzothiazole was obtained if glycerol solvent was used. The copper ferrite catalyzed arylation was not tolerant of neither polar, aprotic solvents such as NMP and DMF nor non-polar solvents including toluene and chlorobenzene.

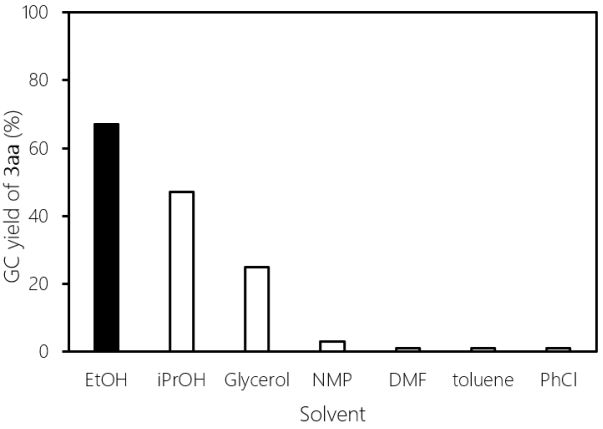


Figure 3: Effect of solvents on the yield of the desired product. Yields are GC yields using diphenyl ether as internal standard

The concentration of $CuFe_2O_4$ nanoparticles was optimized toward the arylation of benzothiazole **1a**. The results are shown in Figure 4. Omitting $CuFe_2O_4$ gave no arylation product, somewhat confirming the crucial role of the nanoparticles. If 5 mol% copper ferrite was employed, 11% yield of **3aa** was obtained. Increasing the catalyst concentration to 10 mol% gave a better yield of the arylation product. Notably, nearly identical yields of **3aa** were obtained when the arylation was run with more than 20 mol% $CuFe_2O_4$.

Our next concern was whether the copper ferrite was truly heterogeneous or not, as it would result in the recoverability and reusability. Herein heterogeneity test was perfomed on the catalyst with the leaching study.

https://doi.org/10.51316/jca.2021.070

The arylation of benzothiazole **1a** with benzaldehyde **2a** was run in the presence of 20 mol% $CuFe_2O_4$. After 2 h, the reaction was stopped and rapidly cooled down to room temperature.

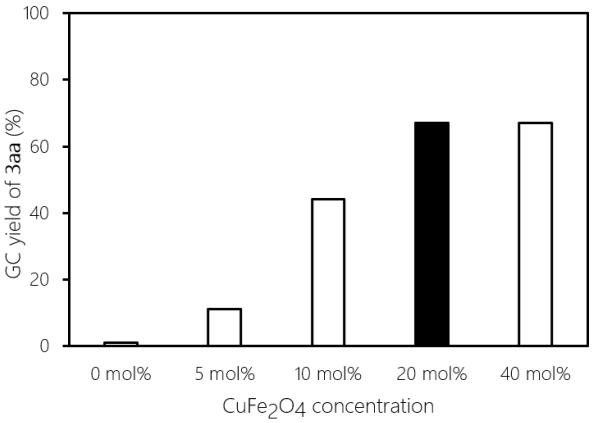


Figure 4: Effect of $CuFe_2O_4$ concentration on the yield of the desired product. Yields are GC yields using diphenyl ether as internal standard

The external magnet was applied to remove the copper ferrite. The mother liquor was then stirred at 100 °C for an additional 16 h. The results are shown in Figure 5. There was a minor difference with respect to yields of **3aa** after removal of $CuFe_2O_4$. This somewhat confirmed that $CuFe_2O_4$ was truly heterogeneous under the standard condition. Additionally, the copper ferrite obtained after the completion of the arylation was characterized. The TEM micrograph of the used $CuFe_2O_4$ was obtained using a JEOL JEM-1400 transmission electron microscope at 70 kV. The result is shown in Figure 6. It could be observed that the structure of $CuFe_2O_4$ nanoparticles was remained after the arylation.

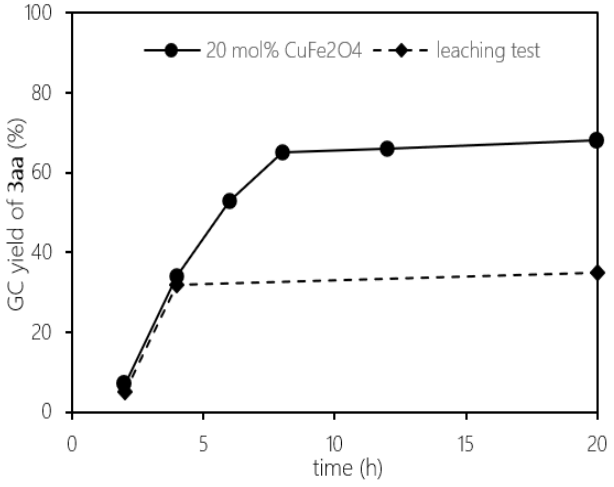


Figure 5: Leaching test. Yields are GC yields using diphenyl ether as internal standard

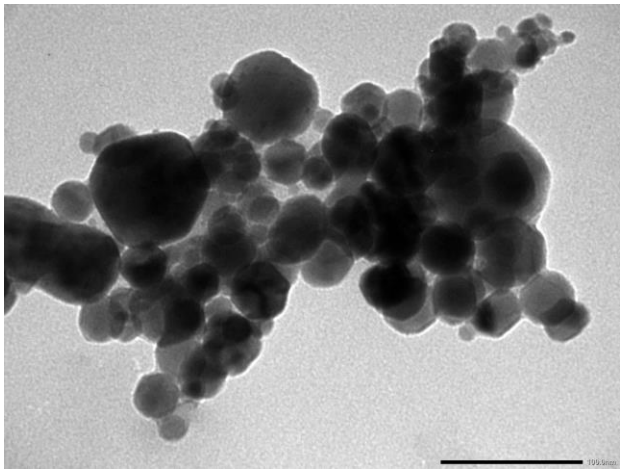
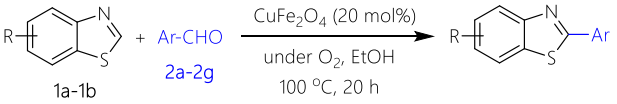
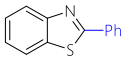
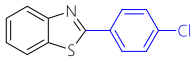
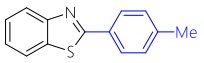
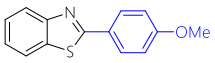
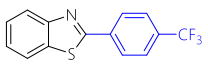
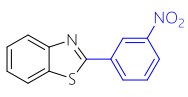
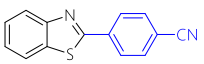


Figure 6: TEM micrograph of the used $CuFe_2O_4$

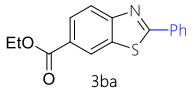
Scope of the reaction with respect to aryl aldehydes and benzothiazole derivatives was next studied. The results are shown in Table 1. Generally, electron-rich benzaldehydes (**3ac**, **3ad**) were more reactive than electron-poor compounds (**3ae**, **3af**, **3ag**) toward the arylation. Functionalities such as chloro (**3ab**), nitro (**3af**), cyano (**3ag**), and ester (**3ba**) groups were compatible with reaction conditions. It should be noted that unreacting aryl aldehydes were oxidized to afford derivatives of benzoic acid, rather than furnishing the Ullmann-typed biaryl products.

Table 1: Scope of the reaction



Entry	R	Ar	products	yield (%)
1	H	Ph	 **3aa**	64
2	H	4-ClC_6H_4	 **3ab**	62
3	H	4-MeC_6H_4	 **3ac**	66
4	H	4-$MeOC_6H_4$	 **3ad**	72
5	H	4-$CF_3C_6H_4$	 **3ae**	52
6	H	3-$NO_2C_6H_4$	 **3af**	37
7	H	4-CNC_6H_4	 **3ag**	41

https://doi.org/10.51316/jca.2021.070

8	6-CO_2Et	Ph	 3ba	70

Reaction conditions: benzothiazoles **1a/1b** (0.3 mmol), aryl aldehydes **2a-2g** (0.2 mmol), $CuFe_2O_4$ nanoparticles (0.04 mmol), EtOH (0.4 mL), under O_2, at 100 °C for 20 h. Yields are isolated yields.

Structural identification of the 2-aryl benzothiazoles was confirmed by NMR spectra. The results are as follows:

- Compound **3ab**, entry 2, Table 1: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 8.17 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.14 – 8.10 (m, 2H), 8.08 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.57 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.49 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6, ppm) δ 165.9, 153.4, 136.0, 134.5, 131.6, 129.4, 128.8, 126.7, 125.7, 122.9, 122.4.

- Compound **3ac**, entry 3, Table 1: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 8.16 – 8.10 (m, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.54 (td, *J* = 7.7, 1.2 Hz, 1H), 7.45 (td, *J* = 7.7, 1.2 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, ppm) δ 167.3, 153.5, 141.4, 134.3, 130.2, 129.9, 127.1, 126.5, 125.3, 122.7, 122.2, 21.0.

- Compound **3ad**, entry 4, Table 1: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 8.11 (d, *J* = 7.9 Hz, 1H), 8.03 (m, 3H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, ppm) δ 167.0, 161.8, 153.6, 134.2, 128.8, 126.5, 125.5, 125.0, 122.4, 122.1, 114.7, 55.5.

- Compound **3ae**, entry 5, Table 1: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.19 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 166.1, 154.0, 136.8, 135.1, 132.6 (q, *J* = 32.7 Hz), 127.7, 126.7, 126.1 (q, *J* = 3.8 Hz), 125.7, 123.8 (q, *J* = 272.0 Hz), 123.4, 121.7.

- Compound **3af**, entry 6, Table 1: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 8.82 (t, *J* = 1.9 Hz, 1H), 8.50 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H), 8.41 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H), 8.24 – 8.19 (m, 1H), 8.18 – 8.12 (m, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.61 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 7.53 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6, ppm) δ 164.8, 153.2, 148.4, 134.7, 134.1, 133.4, 131.2, 127.0, 126.1, 125.5, 123.3, 122.6, 121.1.

- Compound **3ag**, entry 7, Table 1: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16 (d, *J* = 8.3 Hz, 2H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 165.2, 154.0, 137.5, 135.2, 132.7, 127.7, 126.8, 126.1, 123.8, 121.7, 118.3, 114.0.

- Compound **3ah**, entry 8, Table 1: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.28 – 8.25 (m, 3H), 8.15 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.55 (m, 3H), 4.46 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 166.2, 165.7, 150.8, 146.1, 132.4, 129.3, 128.1, 127.9, 126.9, 126.5, 119.7, 112.5, 61.3, 14.5.

Conclusion

In conclusion, we have developed a method for heterogeneously $CuFe_2O_4$ nanoparticle catalyzed arylation of C2–H bonds in benzothiazoles with aryl aldehydes. The reactions proceeded in ethanol solvent and O_2 atmosphere without any other external oxidants. Reaction conditions were tolerant of many useful functionalities. The structure of used $CuFe_2O_4$ nanoparticles were remained as proven by the TEM result.

Acknowledgments

This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.01-2019.44.

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