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[e010]

Microwave Assistance in the Copper-Catalyzed Reactions of Aliphatic Alcohols with Aryl Iodides

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Abstract: We report the cross-coupling of n-hexanol and aryl iodides using Cu(I) catalysis under microwave reaction conditions. The aryl ethers were obtained in good yield. The use of 1,10-phenanthroline as the ligand was found effective in these reactions.

Keywords: Cu-catalyzed cross-coupling, microwave-assisted reaction, arylether

Introduction

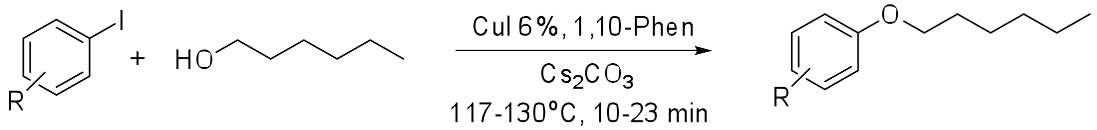
Aryl ethers are important starting materials for the preparation of pharmaceuticals, cosmetics, polymers and fragrances [1-5]. Various strategies to improve the copper-catalyzed Ullmann aryl ether synthesis have been explored [2, 6-9] to find more efficient and higher yielding reactions. In a recent report, Buchwald[10] investigated ligand-assisted copper catalysis, and suggested that the more electron rich tetramethylphenanthroline was superior to the less expensive 1,10-phenanthroline in promoting the coupling.

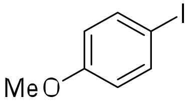
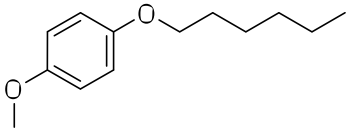
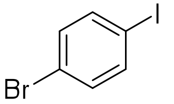
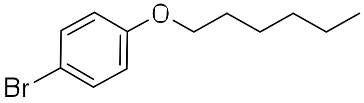
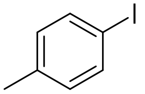
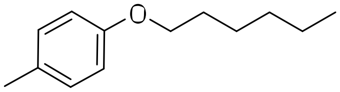
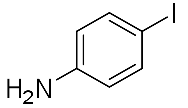
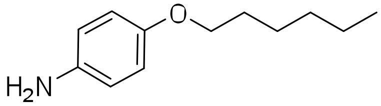
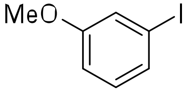
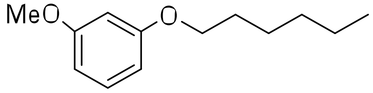
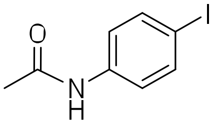
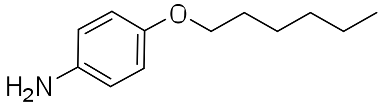
Thasana[11] utilized microwave-assisted organic reactions (MAOR) for the intramolecular coupling of aryl halides and carboxylates at 200°C. Lipshutz[12] incorporated a microwave-assisted reaction in order to prepare diaryl ethers from aryl bromides and phenolic alcohols using copper on carbon as the catalyst and 1,10-phenanthroline as the ligand. The reaction time varied from 25 to 180 minutes, with temperatures of 180 to 220°C.

Given this background, we undertook to enhance the synthesis of aryl ethers from an aliphatic alcohol (n-hexanol) and aryl iodides using Cu(I) catalysis and 1,10-phenanthroline under microwave reaction conditions. In addition to a shortened reaction time, the ability to use 1,10-phenanthroline as the ligand would lower the cost. These results demonstrate that microwave irradiation gives a faster reaction, a better yield and a cleaner reaction.

Results and Discussion

Using the standard experimental procedure detailed below, the results of the coupling reactions of n-hexanol with a variety of aryl iodides are reported below. Each reaction was optimized for both yield and time. It is useful to contrast the microwave results with those previously reported using standard heating.



Entry	Starting Material	Product	temperature (°C)	time (min)	yield (%)[a]
1			120	18	89[b]
2			120	10	80[c]
3			117	23	86
4			120	20	66
5			130	18	86[d]
6			120	20	45[e]

[a] *The yields were determined by GC, though clean products are obtained after flash chromatography.*

[b] *The reported result*[10] *was 87% yield with 5% CuI, 80°C, 20 h reaction in toluene.*

[c] *Two other minor products were resulted, one of them can be characterized by HNMR ((1,4-bis(hexyloxy)benzene)*

[d] *The reported result* [10] *was 77% yield with 5% CuI, 130°C, 24 h reaction in 0.50 mL n-hexanol.*

[e] *The starting material was 4-iodoacetanilide. The products were 4-(hexyloxy)aniline and hexyl acetate*

Iodoanisole (Entry 1) was converted to the ether in 89% yield, comparable to that reported [10] previously (87%). However, the previous conversion resulted from 20 hours reaction time in toluene as solvent, using 5% catalyst and 10 percent of Me_4Phen at a temperature of 80°C. The microwave reaction can be carried out with 6% CuI and 1,10-Phen under microwave irradiation using solventless conditions for 18 minutes [10]. Similar results and comparisons can be made for entries 3 and 5. For example, we started with 3-iodoanisole and 2 mol equivalent of alcohol for entry 5. In 18 minutes reaction time, the the aryl ether was prepared in 86% yield. Buchwald[10] reported using 3-bromoanisole and a yield of 77% at 130°C and 24 hours using 4 equivalents of alcohol, 5% catalyst and 10 percent of Me_4Phen [10].

Entries 2, 4 and 6 used four equivalents of alcohol. The results of entry 2 establish the selectivity for substitution for iodide over bromide, as was expected. Reaction entries 4 and 6 were used to examine whether a protection step was needed for the substitution reactions on anilines. While the reactions were successful, the yields were hampered by some decomposition. The only product isolated from the acetanilide, entry 6, was that from substitution accompanied by deprotection to the aniline.

Conclusion

A microwave method for the copper catalyzed cross-coupling reactions of aryl iodides with n-hexanol has been demonstrated. Using 1,10-phenanthroline as a ligand was effective in optimized microwave-assisted reactions. These reactions provide efficient routes toward arylether synthesis, particularly between aryliodides and alcohols. Further research using other alcohols is ongoing.

Experimental

Microwave reactions were carried out on a CEM Discover microwave synthesizer. GC/MS data was collected on a Varian-2000 instrument. All of the starting materials were available commercially, except 4-iodoacetanilide which was synthesized based on the known method.

General procedure for the Cu(I)-catalyzed cross-coupling of n-hexanol with aryl iodides

CuI (0.011 g, 0.060 mmol), 1,10-phenanthroline (0.018 g, 0.100 mmol), aryl iodide (1.000 mmol), Cs_2CO_3 (0.490 g, 1.500 mmol), and n-hexanol (0.250 to 0.500 mL, 2.000 to 4.000 mmol) were mixed in a microwave tube with a magnetic stir bar. The reaction tube was then fitted with its screw cap, and stirred at room temperature for 30 minutes under nitrogen gas. The reaction was carried out under microwave irradiation at 120 to 130°C for 10 to 23 minutes. After cooling to room temperature, the crude reaction mixture was diluted with ethyl acetate (10 mL) and filtered through silica gel, then washed with additional ethyl acetate (15 mL). The filtrate was analyzed by GC/MS. The filtrate was concentrated and the residue was purified by preparative TLC (ethyl acetate/n-hexane 0/100 to 25/75 percent) and identified by standard spectral methods.

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