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Effect of microwave heating on Ullmann-type heterocycle-aryl ether synthesis using chloro-heterocycles

Noel D. D'Angelo,[a] Joseph J. Peterson,[b] Shon K. Booker,[a] Ingrid Fellows,[c] Celia Dominguez,[a] Randall Hungate,[a] Paul J. Reider[a] and Tae-Seong Kim[a,*]

[a]*Department of Chemistry Research and Development, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, United States*
[b]*Department of Chemistry, Rochester Institute of Technology, 85 Lomb Memorial Drive, Rochester, NY 14623-5603, United States*
[c]*Chemistry Department, California State University Fresno, 2555 E. San Ramon Ave, Fresno, CA 93740, United States*

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Abstract—Ullmann ether synthesis was conducted on a variety of chloro-heterocycles with different phenols using optimized conditions involving copper powder and cesium carbonate. On many substrates, microwave heating afforded higher yields in significantly shorter reaction times compared to conventional heating conditions. These findings provide a facile method for aryl ether synthesis from chloropyridines, chloroquinolines, and chlorobenzothiazoles.

The Ullmann ether synthesis has been widely employed in organic chemistry since its discovery in the early 20th century.[1] In particular, the copper-mediated coupling of aryl halides and phenols has proven to be one of the primary methods for aryl ether synthesis.[2] Initially, this reaction required high temperatures (>200 °C) and toxic solvents and often afforded low yields. Consequently, its scope was rather limited.[3–6] However, recent modifications have allowed for this reaction to be run under milder conditions (90–110 °C) on chemically diverse substrates, often furnishing products in high yields.[7] These improvements have been achieved mainly by the introduction of palladium[8] and copper catalysis.[9] With these improvements, the scope of the Ullmann ether synthesis has been extended to heterocycle-alkyl ether synthesis.[10] To our knowledge, however, there has been no report on its application to heterocycle-aryl ether synthesis to date.

The advent of microwave technology has provided another means of improving the efficiency of many organic reactions.[11] This technology has also been explored for the Ullmann ether synthesis by Wu and later by Wang for synthesis of aryl ethers and *N*-aryl heterocycles.[12] Cherng reported microwave-assisted nucleophilic substitution of halo-heterocycles with sodium phenoxide on pyridine, quinoline, isoquinoline, pyrazine, and pyrimidine systems.[13] However, with inactivated heterocycles such as halopyridines, the coupling reaction is still difficult and requires a large excess of the phenoxide and toxic solvents such as HMPA for best yields even for iodopyridines.[13c]

Here we report a facile method with microwave irradiation for Ullmann ether synthesis between electronically diverse phenols and nitrogen containing chloro-heterocycles such as chloropyridines, chloroquinolines, and chlorobenzothiazoles. Chloro-heterocycles are stable and easy to make relative to bromo- and iodo-heterocycles, but, as a consequence, they are also less reactive. Thus, the primary objective was to determine how effective microwave heating would be in improving the yields of Ullmann ether synthesis between different phenols and chloro-heterocycles.

Our first approach was to identify the optimized reaction conditions using 4-chloropyridinium hydrochloride (**1**) and phenol (**2**, R = H). This was performed by systematically varying the solvent, copper source, and base under

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* Corresponding author. Tel.: +1 805 447 8895; fax: +1 805 480 3016; e-mail: tkim@amgen.com

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microwave (CEM, Discover®) conditions of 100 °C and 60 W for 10 min. The first conditions examined used copper powder, DMF, and potassium hydroxide and afforded 4-phenoxypyridine (**3**) in 20% yield. Changing the copper source to copper(I) salts such as CuI and CuCl resulted in yields ranging from 8% to 11%. Likewise, with other solvents such as NMP, toluene, and a 1:1 DMF/pyridine mixture, the yields were still below 10%. The base had the greatest influence on the reaction, and while K_3PO_4, K_2CO_3, and KOH also afforded yields under 10%, the use of Cs_2CO_3 in the presence of copper powder in DMF afforded **3** in 69% isolated yield.[14] Once these optimized conditions had been identified, they were used in all subsequent conventional heating and microwave reactions.[15]

Using these conditions, the Ullmann ether synthesis of **1** with different phenols was conducted in order to investigate the sensitivity of this reaction to electronics. For this series, the phenol was varied from electron donating to electron withdrawing, and the Ullmann ether synthesis was then conducted on the bench top and in the microwave using the optimized conditions. The isolated yields were then compared and are summarized below in Table 1.

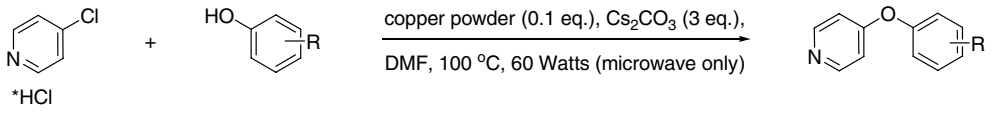
Two noteworthy trends are apparent. First, the yields in most cases were higher in the microwave than on the bench top, demonstrating the advantage of using the microwave for these substrates. This is important from a practical point of view, as the reactions under conventional heating were run under nitrogen for 18 h in a 100 °C oil bath, while the microwave reactions took 10 min. Second, under microwave conditions, the yields observed increased with more electron deficient phenols. No such trend was observed on the reactions under conventional heating, suggesting that microwave heating is especially beneficial for electron-deficient phenols.

For the next series, different chloro-heterocycles and halopyridines were explored using phenol (**2**) as the nucleophile. For this series, the reactions were run under the same conditions as before, and again the yields in the microwave and on the bench top were obtained and are summarized in Table 2. For the first three aryl chlorides, the yields on the bench top and in the microwave were similar, with the microwave yields being about 10% higher. The similar yields could be the result of these chloro-heterocycles being more reactive than 4-chloropyridine.

Different halopyridines were also explored, where the halide substituent and its position were varied. For these experiments, 2-chloropyridine, 2-bromopyridine, and 2-iodopyridine were studied, as well as their 4-halopyridine counterparts. The chloropyridine substrates showed low reactivity under conventional heating conditions, regardless of 2-, 3-, or 4-positioning. The yields under conventional heating clearly improved when bromine and iodine were used. The microwave conditions afforded moderate to good yields for all three halogenated substrates, however the improvement in yield relative to the conventional heating conditions was most dramatic for the chloropyridine species. Finally, under microwave conditions, 2-chloropyridine and 4-chloropyridine afforded the desired product in moderate to good yield, while 3-chloropyridine hardly gave any product. From these results, one can conclude that microwave heating is most advantageous for chloro-heterocycle substrates, in terms of shortening reaction times and, most significantly, improving reaction yields.

In summary, microwave heating can be quite effective in improving the yields and decreasing the reaction times of Ullmann ether synthesis, especially for couplings that are otherwise sluggish and low yielding. Primarily, microwave heating enables the use of less reactive chloro-heterocycles for these couplings, thereby expanding their synthetic utility. Even for reactive substrates such as iodopyridines, microwave heating affords the advantage of dramatically decreased reaction times (10 min vs 18 h) with similar, if not better, yields. These conditions should facilitate the synthesis of aryl ethers and thereby aid in the discovery of new drug candidates. Further efforts toward this end will be reported in due course.

Table 1. Effect of microwave on Ullmann ether synthesis yields with different phenols

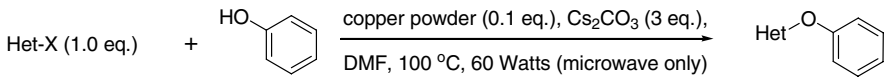


1 (1 eq.) **2** (1.5 eq.) **3-8**

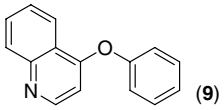
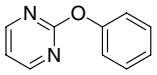
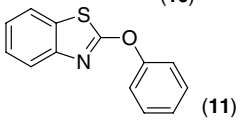
Entry	R	Product	Conventional heating yield[a] (%)	Microwave heating yield[a] (%)
1	H	(**3**)	17	69
2	4-Methoxy	(**4**)	36	34
3	4-Methyl	(**5**)	31	38
4	4-Fluoro	(**6**)	26	76
5	3-Fluoro	(**7**)	29	72
6	2-Fluoro	(**8**)	23	79

[a] Isolated yield.

Table 2. Effect of microwave on Ullmann ether synthesis yields with different heterocycles



2 (R=H) **9-13**

Entry	Het–X	Product	Conventional heating yield[a] (%)	Microwave heating yield[a] (%)
1	4-Chloroquinoline	 (**9**)	72	80
2	2-Chloropyrimidine	 (**10**)	85	97
3	2-Chlorobenzothiazole	 (**11**)	76	87
4	4-Bromopyridine	4-Phenoxypyridine (**3**)	32	83
5	4-Iodopyridine	4-Phenoxypyridine (**3**)	82	75
6	3-Chloropyridine	3-Phenoxypyridine (**12**)	Trace	4
7	2-Chloropyridine	2-Phenoxypyridine (**13**)	11	49
8	2-Bromopyridine	2-Phenoxypyridine (**13**)	64	83
9	2-Iodopyridine	2-Phenoxypyridine (**13**)	91	86

[a] Isolated yield.

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14. Microwave irradiation of just the copper powder in DMF, followed by coupling using conventional heating at 100 °C for 18 h afforded only a modest increase in the yield of **3**, from 17% to 25%.
15. *General microwave reaction procedure*: 4-chloropyridine hydrochloride (224 mg, 1.5 mmol) and phenol (221 mg, 2.24 mmol) were suspended in DMF (3.3 ml) in a microwave vial and copper powder (9.5 mg, 0.15 mmol, Aldrich 99%, 1–5 μm), and cesium carbonate (1.45 g, 4.45 mmol)

were added. The vial was sealed, shaken for 10 s, and then placed in the microwave (CEM, Discover®). The reaction was run by ramping the temperature setting to 100 °C over 5 min and then maintaining this temperature setting for 10 min. For the entire experiment, the power setting was held at 60 W. The reaction was then cooled to room temperature and diluted with CH_2Cl_2 (25 ml). The organic phase was washed with 1 N NaOH (60 ml) and water, dried over sodium sulfate, filtered, and concentrated. The crude material was purified via flash chromatography (50:1 CH_2Cl_2/MeOH) to afford 4-phenoxypyridine (**3**, 175 mg, 69%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, $J = 4.0$ Hz, 2H), 7.44 (t, $J = 8.0$ Hz, 2H), 7.29–7.25 (m, 1H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.85 (d, $J = 8.0$ Hz, 2H); MS (API-ES) calcd for $C_{11}H_{10}NO$ $(MH)^+$: 172.1, found 172.0 m/z; Elemental analysis calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.02; H, 5.25; N, 8.06.