Solid-Phase Synthesis of Alkyl Aryl Ethers via the Ullmann Condensation

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Alkyl aryl ether formation is a frequently employed reaction in organic synthesis. Ullmann condensation is an alternative method to the widely used Mitsunobu reaction and is very useful in situations where application of the Mitsunobu reaction is limited. By application of this reaction to solid-phase synthesis of a series of alkyl aryl ethers, reaction conditions (catalyst, solvent, temperature, time, etc.) for a sterically hindered class of alcohols were investigated and optimized. A range of aryl halides was used to explore the scope of the reaction in solid phase.

Alkyl aryl ether formation is an important reaction in organic synthesis and has generated significant interest in the past decade. Methods to effect this transformation include the classic Williamson procedure,[1] the Mitsunobu reaction,[2] and the Ullmann condensation.[3−6] Both the Williamson reaction, which involves alkylation of phenoxide anions with alkylating reagents such as alkyl halides and sulfonates, and the Mitsunobu reaction, in which free phenols are alkylated with alkyl alcohols, have been applied to solid-phase synthesis of aryl alkyl ethers.[7,8] Although application of these two reactions in solid phase approaches has been successful in syntheses of a variety of alkyl aryl ethers, there are cases where none of these reactions can afford satisfactory results. One such example is ether formation using alkyl alcohols that are sterically hindered and/or prone to rearrangement.[9,10] This problem is amplified when the alcohols are immobilized on solid supports and their respective activated species become the limiting reagent.

The Ullmann condensation culminates in aryl ether formation as a result of the reaction of aryl oxides or alkoxides and aryl halides. Unlike the Mitsunobu reaction, which requires a C−O bond breakage, the Ullmann condensation involves reaction on the oxygen rather than the carbon.[3−6] The result of this difference is reduced steric hindrance at the reaction site as well as avoidance of the C−O bond rearrangement inherent in the Mitsunobu approach. Hence, it is proposed that application of the Ullmann condensation approach in aryl ether formation from hindered and/or rearrangement-prone alcohols, where conventional Mitsunobu conditions do not perform satisfactorily, would afford a significant advantage. In our continuing efforts to develop efficient combinatorial library syntheses on solid supports, we encountered such an example where formation of alkyl aryl ethers from a resin-bound secondary alcohol bearing an α-amino group (Scheme 1) was required. A thorough investigation of a variety of Mitsunobu conditions[11−13] yielded unsatisfactory results, possibly due to both steric hindrance of the resin-bound secondary alcohol and potential rearrangements caused by participation of the neighboring amino group.[9,10] We therefore turned our attention to application of the Ullmann condensation in the solid-phase synthesis of alkyl aryl ethers and report our results here.

Results and Discussions

The typical solution-phase Ullmann condensation involves heating an alkoxide and an aryl halide with a Cu(I) halide in a suitable solvent between 100 and 200 °C. A wide variety of variations, including temperature, solvent, catalyst, and order of reagent addition, have been reported for the Ullmann condensation in solution-phase syntheses.[3−6] It was obvious that to effectively apply the Ullmann reaction to our α-amino alcohols attached to divinylbenzene crossed-linked polystyrene resin via a *p*-alkoxybenzyl linkage, we would need to investigate and optimize (1) reaction temperature, (2) reaction time, (3) solvent, (4) order of reagent addition, and (5) scope of applicable aryl halides. A literature research suggested that a set of conditions for Ullmann condensations reported by Whitesides et al.[6] would be a promising starting point for our solid-phase investigations.

Reaction Time and Temperature. Resin-bound amino alcohol **1**[14] (mixture of two diastereomers, Scheme 2) was

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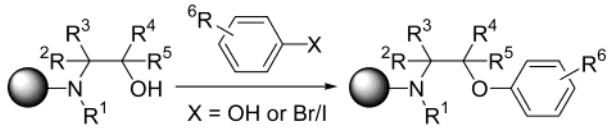
Scheme 1



treated with excess CH_3Li (20 equiv) in anhydrous DME at room temperature for 30 min followed by addition of excess CuCl (30 equiv). The reaction was agitated at room temperature for 60 min to form the copper alkoxide[6] on the resin. The solution was removed using a syringe, and excess iodobenzene (20 equiv) in anhydrous pyridine was added. The reaction mixture was heated at several temperatures for various lengths of time to investigate the efficiency of formation of the resin-bound amino aryl ether **2**. Cleavage using α-chloromethyl chloroformate yielded amino aryl ethers **3** as a 1:1 mixture of two diastereomers (Scheme 2).

As summarized in Table 1, it is clear that the reaction can be best performed at 115 °C for 24 h to afford the desired product in 62% overall yield and at >80% purity as estimated by ^{1}H NMR analysis (entry 1, Table 1). Extended reaction time increases the yield slightly but at the expense of compound purity (entry 2, Table 1). Alternatively, the reaction does proceed quite well at temperatures as low as 80 °C but necessitates prolonged reaction time (entry 3, Table 1) and again affords unsatisfactory product purities. Finally, it is evident that temperatures below 80 °C are not desirable for this transformation (entries 4 and 5, Table 1).

Effect of Solvents and Order of Addition. The above reaction procedures required removal of excess copper reagents prior to addition of aryl halides. This step proved to be quite cumbersome and could potentially lead to significant experimental variability. Therefore, feasibility of using a single solvent, effect of solvents other than pyridine, and use of halide-free CH_3Cu were investigated in the generation of resin-bound copper alkoxides.[6] Results of these experimental variations are summarized in Table 2.

Reactions under the original procedures, employing DME with pyridine as a cosolvent (method A), leave 15−30% unreacted starting material (entry 1, Table 2). Using pyridine as the sole reaction solvent does not improve the overall conversion (entry 2, Table 2). Likewise, using HMPA as a cosolvent with DME as opposed to pyridine produces similarly disappointing results (entry 4, Table 2). Generation of the resin-bound copper alkoxide using halide-free CH_3Cu, employed in method C, does not measurably improve the reaction (entry 3, Table 2). However, optimum results are obtained when the order of addition of CH_3Li and CuCl is reversed. Therefore, excess CH_3Li (20 equiv) was added to a suspension of excess CuCl (30 equiv) and the resin-bound alcohol in anhydrous DME at room temperature. The resulting suspension was then stirred at room temperature for 2 h followed by addition of an aryl halide (20 equiv) in anhydrous pyridine. The reaction mixture was heated to 115 °C without agitation for 24 h to form the alkyl aryl ether on resin. Under these conditions, the starting alcohol was completely consumed and the desired product was typically isolated in 60−85% yield and 80−90% purity as estimated by ^{1}H NMR analysis (entry 5, Table 2). It is not clear at the present time why the reversed addition improves the reactions.

Scope of Aryl Halides. With optimized reaction conditions, the scope of aryl halides for the Ullmann ether formation on solid supports was investigated. A variety of alkylating reagents ranging from electron-deficient to electron-rich aryl halides and triflates were examined in this reaction. Results (Table 3) indicate that electron-neutral, *moderately* electron-rich, and *moderately* electron-deficient aryl iodides are well-behaved counterparts in this reaction (entries 1−5). However, strongly electron-deficient aryl halides are not suitable (entry 6, Table 3). Likewise, aryl triflates and heterocyclic halide derivatives do not afford the desired products (entries 5, 7, and 8, Table 3). These results are in agreement with reported observations for solution-phase Ullmann condensations.[4,15]

Conclusion

It is clear from our studies that with resin-bound alcohols that are sterically hindered and prone to rearrangements, aryl ethers can be efficiently synthesized by the well-known Ullmann condensation. With the modified procedures described herein, these reactions have been optimized to provide high yields and purity of the desired products. We have discovered that addition of *moderately* electron-rich, electron-neutral, or *moderately* electron-deficient aryl iodides to a resin-bound copper alkoxide in DME/pyridine (1:1, v/v) at 115 °C for 24 h provided the best results in terms of product yields and purities. Further study of the scope of applicable alcohols, as well as application of the described solid-phase Ullmann condensation methodology in compound library synthesis, is currently in progress.

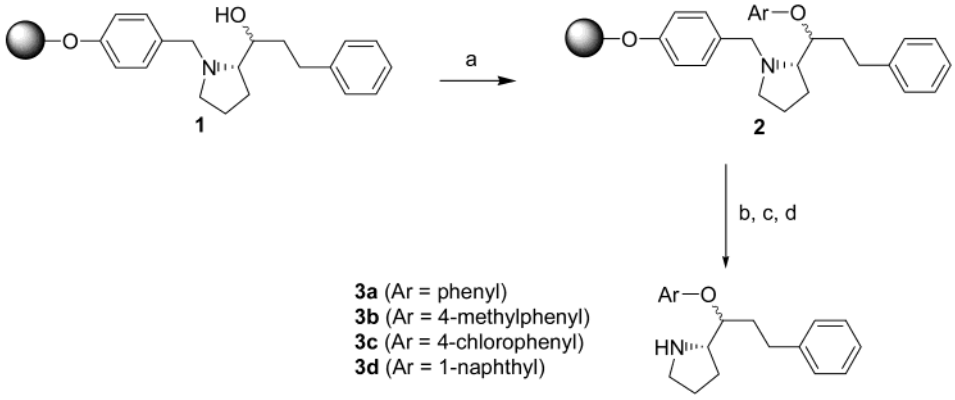
Experimental Section

General Procedures. All moisture-sensitive reactions were performed in sealed glass vessels under inert atmosphere. Reagents and solvents were purchased from Aldrich. Br−Wang polystyrene resin (100−200 mesh, 1.0 mmol/g) was purchased from Nova Biochem. Hygroscopic solvents were dried according to standard laboratory procedures prior to use. All reagents and nonhygroscopic solvents were used as received without further treatment.

Abbreviations. DME, 1,2-dimethoxyethane; HMPA, hexamethylphosphoramide; Et_2O, diethyl ether; THF, tetrahydrofuran; DIEA, diisopropylethylamine; TMS, tetramethylsilane; IBX, *o*-iodoxybenzoic acid; LRMS, low-resolution mass spectrometry.

Ullmann Condensation: Method A. Amino alcohol resin **1**[14] (25 mg, 25 μmol, 1 equiv) was suspended in anhydrous DME (2 mL). CH_3Li (0.36 mL, 1.4 M/Et_2O, 0.50 mmol, 20 equiv) was added dropwise at room temperature with gentle agitation under argon. After the mixture was stirred at room temperature for 30 min, CuCl (75 mg, 0.75 mmol, 30 equiv) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction solution was carefully removed with a syringe under argon. An aryl halide (0.50 mmol, 20 equiv) in anhydrous pyridine (2 mL) was added, and the reaction mixture was heated at 115 °C without

Scheme 2[a]



[a] Reagents and conditions: (a) 1) CH_3Li, CuI, DME; (2) pyridine, Ar−X, various temperatures and times; (b) α-chloromethyl chloroformate, DIEA, CH_2Cl_2, room temp, 24 h; (c) MeOH, 65 °C; (d) Amberlyst-26, CH_2Cl_2, room temp, 24 h.

Table 1. Solid-Phase Ullmann Condensations at Various Reaction Times and Temperatures[a]

entry	Ar−X	reaction temp (°C)	reaction time (h)	product yield,[b] %	product purity,[b] %
1	Ph−I	115	24	62	>80
2	Ph−I	115	100	74	∼50
3	Ph−I	80	100	72	∼50
4	Ph−I	50	100	18	*c*
5	Ph−I	25	100	0	*c*

[a] Method A in the Experimental Section was used. [b] Yield and purity of product (**3a**) were estimated by ^{1}H NMR analysis with an internal standard (TMS). [c] Not applicable.

Table 2. Modification of Reaction Conditions for Solid-Phase Ullmann Condensations

entry	method[a]	number of runs	remaining starting material,[b] %	product yield,[b] %	product purity,[b] %
1	A	6	5−30	50−70	40−90
2	B	1	60	35	*c*
3	C	1	15	50	*c*
4	D	1	30	55	*c*
5	E	5	0	60−85	80−90

[a] Detailed reaction procedures are described in the Experimental Section. [b] Yield and purity of products were estimated by ^{1}H NMR analysis with an internal standard (TMS). [c] Not applicable.

agitation for 24 h. After cooling to room temperature, the resin was filtered and washed with 1% (HCl−THF)/H_2O (1:1, v/v) and THF alternately (1 mL × 10) and with 5% DIEA−CH_2Cl_2 (1 mL × 5). The resin was dried under vacuum for 24 h, affording resin **2**.

Ullmann Condensation: Method B. Amino alcohol resin **1** (25 mg, 25 μmol, 1 equiv) and CuCl (75 mg, 0.75 mmol, 30 equiv) were suspended in anhydrous pyridine (2 mL). CH_3Li (0.36 mL, 1.4 M/Et_2O, 0.50 mmol, 20 equiv) was added dropwise under argon with gentle agitation at room temperature. After the mixture was stirred for 1 h, an aryl halide (1.0 mmol, 40 equiv) in anhydrous pyridine (2 mL) was added and the reaction mixture was heated at 115 °C without agitation for 24 h. The reaction was worked up using the same procedures as in method A to yield resin **2**.

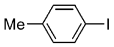
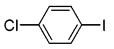
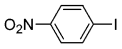
Ullmann Condensation: Method C. Freshly prepared CH_3Cu (2.0 mL, 0.25 M/pyridine, 0.50 mmol, 20 equiv)[6] was added to amino alcohol resin **1** (25 mg, 25 μmol, 1 equiv) at room temperature. The reaction mixture was stirred gently at room temperature for 2 h. An aryl halide (1.0 mmol, 40 equiv) was added, and the reaction mixture was heated at 115 °C without agitation for 24 h. The reaction was worked up using the same procedures as in method A to afford resin **2**.

Ullmann Condensation: Method D. Amino alcohol resin **1** (25 mg, 25 μmol, 1 equiv) was suspended in anhydrous DME (2 mL). CH_3Li (0.36 mL, 1.4 M/Et_2O, 0.50 mmol, 20 equiv) was added dropwise with gentle agitation at room temperature. After the mixture was stirred for 30 min, CuCl (75 mg, 0.75 mmol, 30 equiv) and dry HMPA (0.35 mL, 2.0 mmol, 80 equiv) were added and the reaction mixture was gently stirred at room temperature for 1 h. An aryl halide (1.0 mmol, 40 equiv) was added, and the reaction mixture was heated at 115 °C without agitation for 24 h. The reaction was worked up using the same procedures as in method A to yield resin **2**.

Ullmann Condensation: Method E. Amino alcohol resin **1** (25 mg, 25 μmol, 1 equiv) and CuCl (75 mg, 0.75 mmol, 30 equiv) were suspended in anhydrous DME (2 mL). CH_3Li (0.36 mL, 1.4 M/Et_2O, 0.50 mmol, 20 equiv) was added dropwise with gentle agitation at room temperature. The reaction mixture was gently stirred at room temperature for 2 h. An aryl halide (1.0 mmol, 40 equiv) in anhydrous pyridine (2 mL) was added, and the reaction mixture was heated at 115 °C without agitation for 24 h. The reaction was worked up using the same procedures as in method A to afford resin **2**.

Alkyl Aryl Ether 3. Resin-bound aryl ether **2** (25 mg) was gently stirred in 1 M α-chloromethyl chloroformate in CH_2Cl_2 (1 mL, containing 0.1 M DIEA) at room temperature for 24 h. The resin was filtered and washed with MeOH (0.5 mL × 3). The solutions were combined and concentrated. The residue was dissolved in MeOH (1 mL) and heated at 65 °C for 3 h. The solution was concentrated, and the residue was dissolved in CH_2CH_2 (1 mL) and treated with Amberlyst-26 (100 mg, basic) at room temperature for 24 h. Filtration and concentration yielded alkyl aryl ether **3** as the free amine (1:1 mixture of two diastereomers). The

Table 3. Scope of Solid-Phase Ullmann Condensations

entry	Ar-X	method[a]	remaining starting material[b]	product yield[b]
1		E	0	60%
2		E	0	58%
3		E	0	83%
4		E	0	82%
5		E	44%	38%
6		A	21%	28%
7		A	74%	0
8		A	N.A.[c]	N.A.[c]

[a] Detailed reaction procedures are described in the Experimental Section. [b] Yield and purity of products were estimated by ^{1}H NMR analysis with an internal standard (TMS). [c] Decomposition occurred. No starting material or desired product was identifiable.

cleaved product was directly used in ^{1}H NMR analysis with an internal standard (TMS) for quantification.

3a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.15 (m, 8 H), 6.96−6.89 (m, 2 H), 4.35−4.20 (m, 1 H), 3.36−3.28 (m, 1 H), 3.05−2.95 (m, 1 H), 2.88−2.80 (m, 1 H), 2.80−2.72 (m, 1 H), 2.72−2.64 (m, 1 H), 2.30−1.90 (m, 2 H), 1.88−1.82 (m, 1 H), 1.75−1.60 (m, 3 H) ppm; LRMS (electrospray) *m*/*z* [M + H] 282, calcd for $C_{19}H_{24}NO$ 282.

3b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.20 (m, 2 H), 7.19−7.10 (m, 3 H), 7.08−7.00 (m, 2 H), 6.82−6.76 (m, 2 H), 4.25−4.15 (m, 1 H), 3.10−2.95 (m, 1 H), 2.90−2.60 (m, 4 H), 2.28, 2.27 (two singlets, 3 H), 2.30−2.00 (m, 3 H), 2.00−1.60 (m, 3 H) ppm; LRMS (electrospray) *m*/*z* [M + H] 296, calcd for $C_{20}H_{26}NO$ 296.

3c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.20 (m, 2 H), 7.20−7.12 (m, 3 H), 7.11−7.05 (m, 2 H), 6.86−6.78 (m, 2 H), 4.31−4.25 (m, 1 H), 4.18−4.08 (m, 1 H), 3.34−3.28 (m, 1 H), 3.05−2.94 (m, 1 H), 2.90−2.60 (m, 3 H), 2.12−2.1.90 (m, 3 H), 1.88−1.60 (m, 3H) ppm; LRMS (electrospray) *m*/*z* [M + H] 316, calcd for $C_{19}H_{23}ClNO$ 316.

3d: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32−8.25 (m, 1 H), 7.78−7.75 (m, 1 H), 7.48−7.40 (m, 2 H), 7.41 (d, J = 8.2 Hz, 1 H), 7.32 (t, J = 8.2 Hz, 1 H), 7.25−7.20 (m, 1 H), 7.18−7.05 (m, 4 H), 6.85, 6.82 (two doublets, J_1 = 7.5 Hz, J_2 = 7.8 Hz, 1 H), 4.68−4.62 (m, 1 H), 4.53−4.48 (m, 1 H), 3.52−3.42 (m, 1 H), 3.08−2.37 (m, 1 H), 2.90−2.70 (m, 3 H), 2.25−2.05 (m, 2 H), 2.00−1.70 (m, 4 H) ppm; LRMS (electrospray) *m*/*z* [M + H] 332, calcd for $C_{23}H_{26}NO$ 332.

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