

One-pot Microwave-assisted Tandem Deprotection of Arylmethanesulfonates / S_NAr Reaction for K_2CO_3 -mediated C(Aryl)–O Bond Formation

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One-pot microwave-assisted tandem deprotection of arylmethanesulfonates / nucleophilic aromatic substitution reaction (S_NAr) with activated aryl halides to synthesize asymmetrical diaryl ethers is described.

Key words: Tandem Reaction, Arylmethanesulfonates, S_NAr , Aryl Halides, Cross-coupling

Introduction

As biaryl ethers are very important intermediates in natural products chemistry as well as in numerous biologically active compounds such as vancomycin and riccardin, carbon(aryl)-oxygen bond formation is a powerful and important tool of modern organic synthesis [1]. The classical Ullmann-type ether synthesis often requires high temperature (200–300 °C), long reaction times (24 h), and strongly polar and toxic solvents [2]. Recently, considerable efforts have been made to develop valuable methodologies for the formation of diaryl ethers [3–5]. The methanesulfonyl group is a useful and potent protecting group for a phenol, and therefore it is interesting that the methanesulfonyl protecting group for a phenol is unmasked under the conditions of the S_NAr reaction with an aryl halide, producing diaryl ether directly [6]. Although Dinsmore reported the synthesis of diaryl ethers from arylmethanesulfonates and 2-fluoronitrobenzene, this method required the use of expensive Cs_2CO_3 in excess and very long reaction times (6–48 h) and had a narrow application scope of substrates [6]. Microwave irradiation as an alternative energy source leading to a

remarkable decrease in reaction times, increased yields, and easier workup, consistent with green chemistry protocols, has become a very popular and useful technology in synthetic organic chemistry [7–8].

As part of the development of environmentally benign new methodologies [9–10], herein we wish to report our studies on the microwave-assisted S_NAr -type direct C–O bond formation from activated aryl halides and various aryl methanesulfonates in the presence of K_2CO_3 at an irradiation power of 230 W (Fig. 1).

Results and Discussion

Initially we investigated the microwave-assisted coupling of 4-fluoronitrobenzene (1.0 mmol) with 4-chlorophenyl methanesulfonate in DMSO (10 mL) at an irradiation power of 230 W for optimization of the reaction conditions, and the results are summarized in Table 1. The best yield was obtained when K_2CO_3 was used as the base at a reaction time of 10 min and applying 2.5 equiv. of 4-chlorophenyl methanesulfonate.

Based on the above finding, we further studied the coupling reaction of different aryl methanesulfonates with activated aryl halides in the presence of K_2CO_3

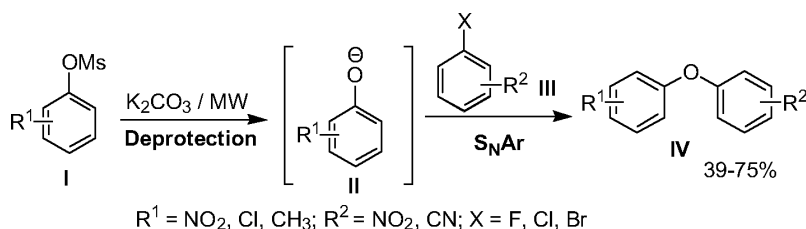
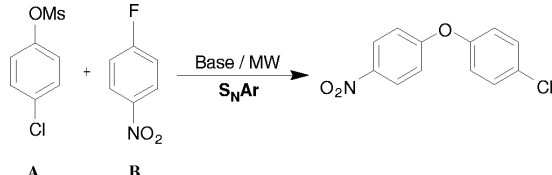


Fig. 1. Microwave-assisted tandem deprotection of arylmethanesulfonates / S_NAr reaction to synthesize unsymmetrical diaryl ethers.

Table 1. Optimization of microwave-assisted synthesis of 4-(4'-chlorophenoxy)nitrobenzene.



Entry	Base	Amount of			Time (min)	Yield (%)
		base (mmol)	A (mmol)	B (mmol)		
1	K ₂ CO ₃	2	1.5	1.0	8	45
2	NaHCO ₃	2	1.5	1.0	8	4
3	CaO	2	1.5	1.0	8	10
4	CaCl ₂	2	1.5	1.0	8	5
5	NaOH	2	1.5	1.0	8	30
6	K ₂ CO ₃	2	1.5	1.0	10	65
7	K ₂ CO ₃	2	1.5	1.0	11	65
8	K ₂ CO ₃	2	1.5	1.0	12	51
9	K ₂ CO ₃	2	2.0	1.0	10	69
10	K ₂ CO ₃	2	2.5	1.0	10	75
11	K ₂ CO ₃	2	3.0	1.0	10	79
12	K ₂ CO ₃	1.5	2.5	1.0	10	64
13	K ₂ CO ₃	2.5	2.5	1.0	10	73

under microwave irradiation. From the results shown in Table 2 it can be seen that a range of aryl methanesulfonates, including those with electron-deficient and electron-rich substituents, were effective for this C–O cross-coupling S_NAr reaction even with electron-deficient aryl halides (X = F, Cl, Br) such as 2-fluoronitrobenzene, 4-fluoronitrobenzene, 2-fluorobenzonitrile, 2-chloronitrobenzene and 4-bromonitrobenzene in the presence of 2 equivalents of K₂CO₃ as the base under microwave irradiation in DMSO medium (Table 2, entries 2–9). Moderate to good yields (39–75 %) were obtained in 10–12 min without any catalyst.

It should be recalled at this point that aryl methanesulfonates with electron-deficient substituents behave poorly or are completely inert toward diaryl ether formation. According to entry 6, even the reaction with the extremely electron-poor 4-nitrophenyl methanesulfonate afforded 2-(4'-nitrophenoxy)-nitrobenzene in 39 % yield.

Conclusion

In conclusion, we have introduced an efficient one-pot tandem-type reaction to synthesize unsymmetrical diaryl ethers *via* consecutive deprotection of aryl methanesulfonates (including those with electron-deficient substituents) and C–O bond cross-coupling in the presence of K₂CO₃ under microwave irradiation. The

reaction times are very short (10–12 min) and moderate to good yields (39–75 %) were achieved without any catalyst for a wide substrate range including aryls with electron-deficient substituents. Moreover, K₂CO₃ is a cheaper base as compared to the previously used Cs₂CO₃ [6].

Experimental Section

The materials were used as purchased, and DMSO was used directly without any additional purification. Melting points are uncorrected. ¹H NMR spectra were recorded on a Bruker Avance DMX 400 instrument using TMS as internal standard and CDCl₃ as solvent. HR and EI mass spectra were obtained with APEX II Bruker 4.7T AS and Thermo DSQ GC/MS instruments, respectively. Microwave irradiation was performed in a Haier microwave oven, MO-2270M1.

General procedure

To a mixture of an activated aryl halide (X = F, Cl, Br, 1 mmol), an aryl methanesulfonate (2.5 mmol) and K₂CO₃ (2 mmol) was added DMSO (10–25 mL). The reaction was found not to be sensitive to air and moisture, hence DMSO was used directly without any additional purification, and there was no need for inert-atmosphere techniques. The mixture was placed in a microwave oven and irradiated at a power of 230 W for 10–12 min. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to r.t., poured into ice water (40 mL) and stirred for 5 min. Then 60 mL of EtOAc was added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with brine (40 mL) and dried over anhydrous MgSO₄. After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (PTLC) to give the pure diaryl ether.

2-(3'-Methylphenoxy)nitrobenzene (1)

Pale yellow liquid. – ¹H NMR (400 MHz, CDCl₃): δ = 2.34 (3H, s), 6.83 (2H, m), 6.99 (2H, m), 7.15 (1H, t, *J* = 7.6 Hz), 7.23 (1H, t, *J* = 8.0 Hz), 7.46 (1H, dt, *J* = 8.0 Hz, *J* = 1.6 Hz), 7.93 (1H, dd, *J* = 7.6 Hz, *J* = 1.6 Hz). – HRMS-FAB: *m/z* = 247.1080 (calcd. 247.1077 for C₁₃H₁₁NO₃, [M+NH₄]⁺).

2-(4'-Chlorophenoxy)nitrobenzene (2)

Pale yellow liquid. – ¹H NMR (400 MHz, CDCl₃): δ = 6.96 (3H, m), 7.21 (1H, t, *J* = 8.0 Hz), 7.31 (2H, m), 7.51 (1H, dt, *J* = 8.4 Hz, *J* = 1.6 Hz), 7.95 (1H, dd, *J* = 8.4 Hz,

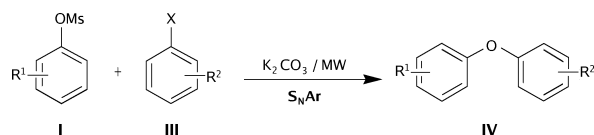


Table 2. Microwave-assisted synthesis of unsymmetrical diaryl ethers.

Entry	I	III	IV	Time (min)	Yield (%)
1				12	50
2				12	50
3				10	63
4				10	53
5				10	50
6				12	39
7				12	61
8				12	51
9				10	75

$J = 1.6$ Hz). – GC/MS (EI, 70 eV): m/z (%) = 251 (10.8), 249 (32.5) $[M]^+$, 122 (100).

4-(4'-Chlorophenoxy)nitrobenzene (3) and (9)

White solid, m. p. 75.8–76.1 °C. – ^1H NMR (400 MHz, CDCl_3): $\delta = 7.00$ (4H, m), 7.38 (2H, dd, $J = 6.8$ Hz, $J = 2.4$ Hz), 8.20 (2H, d, $J = 7.2$ Hz, $J = 2.4$ Hz). – HRMS-FAB: $m/z = 267.0532$ (calcd. 267.0531 for $\text{C}_{12}\text{H}_8\text{NO}_3\text{Cl}$, $[M+\text{NH}_4]^+$).

4-(2'-Chlorophenoxy)nitrobenzene (4) and (8)

White solid, m. p. 76.8–77.0 °C. – ^1H NMR (400 MHz, CDCl_3): $\delta = 6.93$ (2H, m), 7.16 (1H, dd, $J = 8.0$ Hz, $J = 1.6$ Hz), 7.23 (1H, dt, $J = 8.0$ Hz, $J = 1.6$ Hz), 7.33 (1H, dt, $J = 8.0$ Hz, $J = 1.6$ Hz), 7.51 (1H, dd, $J = 8.0$ Hz, $J =$

1.6 Hz), 8.19 (2H, m). – HRMS-FAB: $m/z = 267.0529$ (calcd. 267.0531 for $\text{C}_{12}\text{H}_8\text{NO}_3\text{Cl}$, $[M+\text{NH}_4]^+$).

2-(4-Chlorophenoxy)benzonitrile (5)

White solid, m. p. 85.0–85.7 °C. – ^1H NMR (400 MHz, CDCl_3): $\delta = 6.85$ (1H, d, $J = 8.8$ Hz), 7.01 (2H, m), 7.14 (1H, t, $J = 7.2$ Hz), 7.35 (2H, m), 7.47 (1H, m), 7.66 (1H, dd, $J = 8.0$ Hz, $J = 2.0$ Hz). – HRMS-FAB: $m/z = 247.0633$ (calcd. 247.0627 for $\text{C}_{13}\text{H}_8\text{NOCl}$, $[M+\text{NH}_4]^+$).

2-(4'-Nitrophenoxy)nitrobenzene (6)

Yellow solid, m. p. 101.1–101.9 °C. – ^1H NMR (400 MHz, CDCl_3): $\delta = 7.03$ (2H, m), 7.23 (1H, dd, $J = 8.4$ Hz, $J = 1.2$ Hz), 7.41 (1H, dt, $J = 8.0$ Hz, $J = 1.6$ Hz), 7.67 (1H, dt, $J = 8.0$ Hz, $J = 1.2$ Hz), 8.06 (1H, dd, $J =$

8.0 Hz, *J* = 1.6 Hz), 8.22 (2H, m). – GC/MS (EI, 70 eV): *m/z* (%) = 260 (9.9) [M]⁺, 139 (53.8), 122 (100).

2-(2'-Chlorophenoxy)nitrobenzene (7)

Pale yellow liquid. – ¹H NMR (400 MHz, CDCl₃): δ = 6.83 (1H, dd, *J* = 8.4 Hz, *J* = 1.2 Hz), 7.07 (1H, dd, *J* = 8.0 Hz, *J* = 1.6 Hz), 7.16 (3 H, m), 7.47 (2H, m), 7.97 (1H, dd, *J* = 8.0 Hz, *J* = 1.6 Hz). – HRMS-FAB: *m/z* = 267.0535 (calcd. 267.0531 for C₁₂H₈NO₃Cl, [M+NH₄]⁺).

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