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

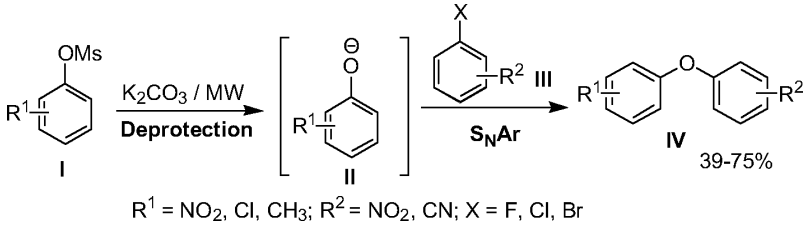

Fig. 1. Microwave-assisted tandem deprotection of arylmethanesulfonates / S_NAr reaction to synthesize unsymmetrical diaryl ethers.

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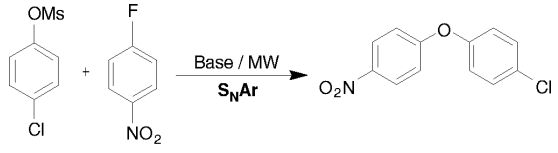
Table 1. Optimization of microwave-assisted synthesis of 4-(4′-chlorophenoxy)nitrobenzene.



A **B**

Entry	Base	Amount of base (mmol)	**A** (mmol)	**B** (mmol)	Time (min)	Yield (%)
1	K_2CO_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_2CO_3	2	1.5	1.0	10	65
7	K_2CO_3	2	1.5	1.0	11	65
8	K_2CO_3	2	1.5	1.0	12	51
9	K_2CO_3	2	2.0	1.0	10	69
10	K_2CO_3	2	2.5	1.0	10	75
11	K_2CO_3	2	3.0	1.0	10	79
12	K_2CO_3	1.5	2.5	1.0	10	64
13	K_2CO_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 substitutents, 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 K_2CO_3 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 K_2CO_3 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, K_2CO_3 is a cheaper base as compared to the previously used Cs_2CO_3 [6].

Experimental Section

The materials were used as purchased, and DMSO was used directly without any additional purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DMX 400 instrument using TMS as internal standard and $CDCl_3$ 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 K_2CO_3 (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 $MgSO_4$. 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. – ^{1}H NMR (400 MHz, $CDCl_3$): 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 $C_{13}H_{11}NO_3$, $[M+NH_4]^+$).

*2-(4′-Chlorophenoxy)nitrobenzene (**2**)*

Pale yellow liquid. – ^{1}H NMR (400 MHz, $CDCl_3$): 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,

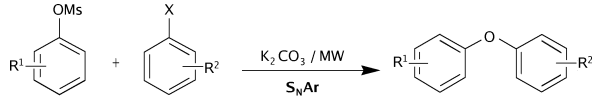
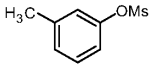
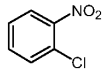
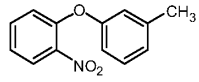
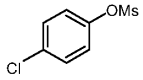
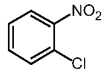
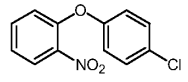
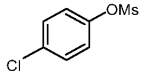
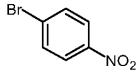
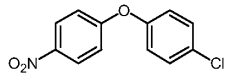
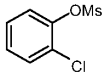
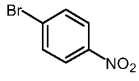
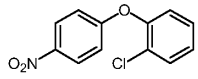
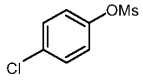
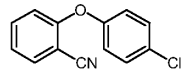
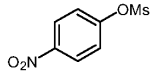
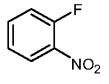
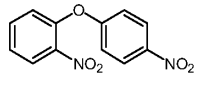
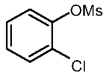
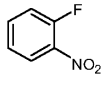
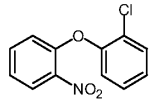
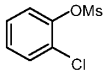
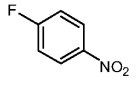
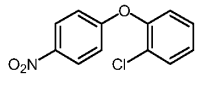
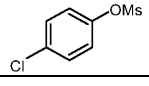
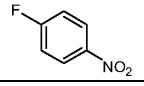
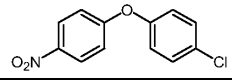


Table 2. Microwave-assisted synthesis of unsymmetrical diaryl ethers.

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. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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 $C_{12}H_8NO_3Cl$, $[M+NH_4]^+$).

*4-(2′-Chlorophenoxy)nitrobenzene (**4**) and (**8**)*

White solid, m. p. 76.8 – 77.0 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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 $C_{12}H_8NO_3Cl$, $[M+NH_4]^+$).

*2-(4-Chlorophenoxy)benzonitrile (**5**)*

White solid, m. p. 85.0 – 85.7 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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 $C_{13}H_8NOCl$, $[M+NH_4]^+$).

*2-(4′-Nitrophenoxy)nitrobenzene (**6**)*

Yellow solid, m. p. 101.1 – 101.9 °C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (2H, m), 7.23 (1H, dd, J = 8.4 Hz, J = 1.2 Hz), 7.41 (1 H, dt, J = 8.0 Hz, J = 1.6 Hz), 7.67 (1 H, 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, $CDCl_3$): 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 $C_{12}H_8NO_3Cl$, $[M+NH_4]^+$).

Acknowledgements

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