

CsF-Al₂O₃ mediated rapid condensation of phenols with aryl halides: comparative study of conventional heating vs. microwave irradiation†

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Received (in Montpellier, France) 28th February 2000, Accepted 14th April 2000
Published on the Web 14th June 2000

Biaryl ethers and thio ethers are formed in high yields by the condensation of phenols and thiophenols with electron-deficient aryl halides using CsF supported on Al₂O₃ under microwave irradiation in solvent-free conditions.

Biaryl ethers are synthetically challenging compounds used in the field of drugs and agrochemicals.¹ The important Ullmann's protocol for the synthesis of biaryl ethers involves the reaction of an aryl halide with an alkali metal aryl oxide in the presence of copper salts.² Other methods for their synthesis include Pummerer-type rearrangements,³ inter- and intramolecular S_NAr reactions,⁴ arene metal complexes,⁵ thallium-promoted oxidative couplings,⁶ phenolic addition to cyclohexene oxides,⁷ and Diels–Alder cyclisation.⁸ The S_NAr strategy is employed for the formation of simple biaryl ethers through the condensation of phenols with electron-deficient aromatic halides in the presence of base. Several bases like Li₂CO₃, K₂CO₃, Cs₂CO₃, NaHCO₃, P₄Bu^t, NaH–pyridine, etc.,⁹ have been used for biaryl ether formation through macrocyclisation during the synthesis of many important natural products. Although KF–Al₂O₃¹⁰ has been used for the synthesis of biaryl ethers, the method involves long reaction times ranging between many hours to several days and often uses large quantities of solvents like DMSO or acetonitrile, which require tedious aqueous work-up. Ullmann's procedure for the synthesis of biaryl ethers suffers from the competitive reduction of the aryl halide to the dehalogenated arene, drastic reaction conditions, long reaction times at elevated temperatures and often the use of toxic solvents. Recently, an improved protocol for the formation of biaryl ethers through Ullmann's procedure has been reported.¹¹ Furthermore, several non-Ullmann methods developed for this purpose involve expensive and/or hazardous reagents, unsatisfactory yields and cumbersome experimental and/or work-up procedures. Organic reactions on solid supported reagents coupled with microwaves¹² are currently of increasing interest due to their greater selectivity, enhanced reaction rates, cleaner reaction products and operational simplicity. In continuation of our work on solid supported reagents¹³ coupled with microwaves, herein we report a novel, efficient and high yielding protocol for the synthesis of biaryl ethers using CsF–Al₂O₃ as catalyst.

Several substituted phenols were reacted with electron-deficient aryl halides under microwave irradiation in the presence of 37% CsF on Al₂O₃ (Scheme 1) to afford high yields of biaryl ethers in solvent-free conditions. Similarly, biaryl thio ethers are formed in high yields by the reaction of thiophenols with activated aryl halides. The results summarised in Table 1 clearly show the scope of the method with respect to various substituted phenols and also aryl chlorides, bromides and

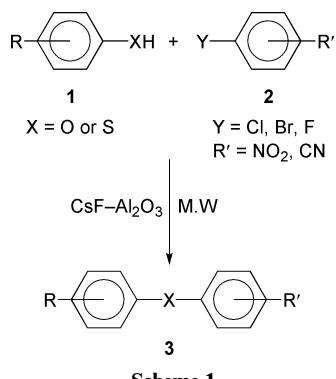
fluorides bearing nitro or cyano groups. The extent of electron deficiency and the nature of the substituent on the aryl halide moiety show some effect on this conversion. The cyano-substituted aryl halides require comparatively longer irradiation times (5–6 min) to attain yields (75–90%) comparable with those of their nitro-substituted counterparts (80–90%). Different inorganic fluorides like LiF, NaF, KF and CsF doped on an Al₂O₃ matrix were studied for their effect. CsF–Al₂O₃ is found to be more efficient in terms of conversion and reaction times than KF.

The present study has unequivocally confirmed that conventional heating at 110 °C and longer reaction times are required for the condensation of phenols with activated aryl halides. These conditions are improved using microwave irradiation, which is becoming an alternate heating source. When 1 equiv. of phenol, 1 equiv. of activated aryl halide and CsF–Al₂O₃ (3 wt. equiv.) were admixed thoroughly in a Pyrex test tube and exposed to microwave irradiation at 450 W for 3–6 min., high yields (82–94%) of biaryl ethers were obtained after filtration through a small silica gel column. These reactions, however, require approximately 6–24 h of heating at 110 °C (highest temperature observed during microwave irradiation) to achieve yields comparable with those obtained by microwave irradiation. Invariably the products obtained by microwave irradiation were purified with more ease.

In conclusion, this letter describes a rapid and efficient procedure for the condensation of phenols with aryl halides mediated by CsF–Al₂O₃, either in solution or in solvent-free conditions, for the first time. The method offers several advantages like inexpensive catalyst, very short reaction times, cleaner reactions and high yields of products, which makes our method a useful addition to the existing methods.

Experimental

Melting points were recorded on a Buchi-535 apparatus. ¹H NMR spectra were recorded on Varian Gemini 200 spectrometers. The spectra were recorded in CDCl₃ using tetramethylsilane as the internal standard. Mass measurements



Scheme 1

† IICT communication No. 4393.

Table 1 CsF-Al₂O₃ mediated condensation of phenols with activated aryl halides

Entry	Phenol	Halide	Reaction time (yield/%)	
			Microwave irradiation ^a	Conventional heating ^b
a			5 min (88)	15 h (75)
b			4 min (94)	16 h (80)
c			6 min (87)	20 h (70)
d			4 min (92)	12 h (75)
e			5 min (88)	18 h (68)
f			5 min (90)	12 h (75)
g			3 min (90)	10 h (75)
h			4 min (88)	16 h (70)
i			5 min (86)	8 h (80)
j			6 min (82)	15 h (62)
k			5 min (87)	10 h (77)
l			5 min (90)	8 h (75)
m			4 min (92)	6 h (78)
n			6 min (75)	24 h (70)
o			4 min (88)	15 h (73)
p			4 min (90)	12 h (70)
q			6 min (84)	20 h (62)

^a Microwave was carried out at 450 W using BPL, BMO, 700 T microwave oven by pulsed irradiation technique (1 min with 20 s interval).^b Conventional heating at 110 °C.

were carried out on a CEC-21-110B double focussing mass spectrometer operating at 70 eV.

Typical procedures

Method A (microwave irradiation). Sesamol (1.38 g, 10 mmol) and 1-bromo-4-nitrobenzene (2 g, 10 mmol) were admixed in a Pyrex test tube with 37% CsF on Al_2O_3 (3 wt. equiv. of phenol) and subjected to microwave irradiation at 450 W using BPL, BMO, 700 T focused microwave oven for 5 min. Then the reaction mass was cooled to room temperature and charged directly onto a small silica gel column (Aldrich, 100–200 mesh) and eluted with a gradient mixture of ethyl acetate–hexane (1 : 9) to afford pure product **3a** (2.28 g, 88% yield) as a brown colourless solid. Mp 81–82 °C. ^1H NMR (CDCl_3): δ 6.0 (s, 2H), 6.5–6.8 (m, 3H), 7.05 (d, 2H, J = 8.8 Hz), 8.2 (d, 2H, J = 8.8 Hz). EI-MS: m/z 259 (M^+), 213, 137, 122, 91, 57, 40.

Method B (conventional heating). A mixture of sesamol (1.38 g, 10 mmol), 1-bromo-4-nitrobenzene (2 g, 10 mmol) and CsF– Al_2O_3 was heated at 110 °C for the specified time as required to complete the reaction. On completion the reaction mass was charged directly onto a small silica gel column and eluted with a gradient mixture of ethyl acetate–hexane (1 : 9) to afford pure product **3a** (1.94 g, 75% yield).

Acknowledgement

BVSR thanks CSIR, New Delhi for the award of a fellowship.

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