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A Convenient Method for the Preparation of Aryl Cyclopropyl Ethers from Phenols

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Abstract: A general method for the synthesis of cyclopropyl ethers from phenols is described. Alkylation of a phenol using 1-iodo-1-(phenylthio)cyclopropane followed by removal of the phenylthio group furnishes the cyclopropyl ethers in modest to excellent yields. The procedure tolerates a wide range of functional groups.

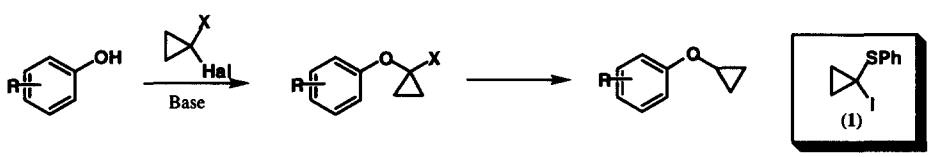
Keywords: Cyclopropanes; Phenols; Alkylation; Ethers

During recent work in our laboratories we became interested in synthetic routes to aryl cyclopropyl ethers. Aryl and alkyl cyclopropyl ethers have been reported in the literature although relatively scarcely. Known syntheses fall into four categories: i) alkylation of an alkoxide or phenoxide anion using cyclopropyl bromide;[1] ii) methylenation of a vinyl ether under Simmons-Smith conditions;[2] iii) dihalomethylation of a vinyl ether with a dihalocarbene followed by reductive dehalogenation;[3] iv) reaction of a vinyl ether with a sulfonium ylid.[4]

None of these methods is ideal. All suffer from either poor yields, strong substrate dependency or are incompatible with anything but the simplest of molecules. A need exists for a general, experimentally simple method for the introduction of this functional group.

We thought the most efficient strategy would be to incorporate all three carbon atoms of the cyclopropyl unit directly using a suitably functionalised cyclopropane-containing reagent, an approach which differs from most other routes to this functional group. However, alkylation of a phenoxide anion with cyclopropyl bromide is not a satisfactory reaction because cyclopropyl bromide is a poor alkylating agent under both S_N1 and S_N2 conditions. When reaction does occur (*e.g.* in solvolysis reactions), the major pathway is often loss of bromide with concerted ring opening to give the allylic cation which leads to allylated products.[5]

We reasoned that alkylation using a halocyclopropane would be aided by an α-substituent (X) capable of stabilising an adjacent positive charge. Subsequent removal of this group would lead overall to O-cyclopropylation (Scheme 1).[6]



Scheme 1

Sulfur atoms can stabilise positive charge at neighbouring carbon atoms and we therefore chose as our electrophile 1-iodo-1-(phenylthio)cyclopropane (**1**).[7] Our choice of electrophile was influenced by the

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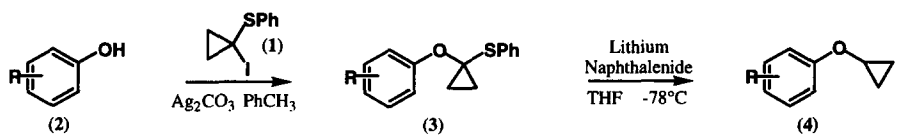
observation that this reagent readily undergoes methanolysis in the presence of base and, moreover, that the phenylthio function could, in theory, be removed reductively.[7]

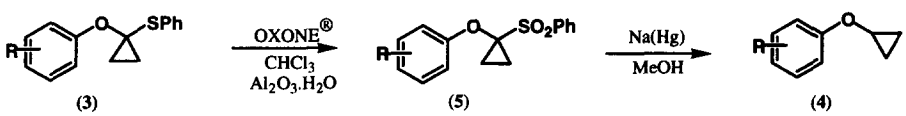
We were delighted to observe that alkylation of phenols (**2**)[8] with (**1**) proceeded smoothly using silver carbonate as base and toluene[9] as solvent to give the desired aryl 1'-(phenylthio)cyclopropyl ethers (**3**) in moderate to good yield (Table 1). The reaction proceeded efficiently at room temperature with two equivalents of both electrophile and base, although the conversion was generally slow taking several days in some cases. Warming to 50 °C or 75 °C shortened reaction times to a few hours although at these temperatures some decomposition of the electrophile was observed and larger excesses of iodide and base were required. Various aromatic substituents are tolerated in this reaction, both electron-donating and electron-withdrawing (Table 1, entries a-e) and substituents in the 2-, 3-, and 4- positions are all tolerated (entries e-g). The moderate yields achieved for entries b and d are at least partly due to the difficulty in separation of the desired products from the co-eluting byproducts derived from the excess electrophile.

Reaction of 1-methoxy-1-(phenylthio)cyclopropane with lithium naphthalenide is known to produce 1-lithio-1-methoxycyclopropane.[7] It was gratifying to find that an analogous reaction of aryl 1'-(phenylthio)cyclopropyl ethers (**3**) with two equivalents of lithium naphthalenide[10] (Method A) produced, after quenching with water, the desired cyclopropyl ethers (**4**) *via* the corresponding α-lithio ethers in good to excellent yield (Table 1, entries a,b,d). Thus, a simple two-step procedure for the preparation of aryl cyclopropyl ethers from phenols has been established (Scheme 2).



Scheme 2

We were aware, however, that for general usage the requirement for lithium naphthalenide as reductant precluded the use of certain reducible functional groups in the starting phenols. We therefore sought a milder set of conditions for removal of the phenylthio activating group; this was achieved using a two-step oxidation-cleavage protocol (Scheme 3).



Scheme 3

Thus oxidation of aryl 1'-(phenylthio)cyclopropyl ethers (**3**) using OXONE® as oxidant according to the method of Greenhalgh[11] gave the corresponding sulfones (**5**) in good yield. The sulfone groups were then removed under mild conditions with sodium amalgam in methanol.[12] Using this procedure (Method B), smooth

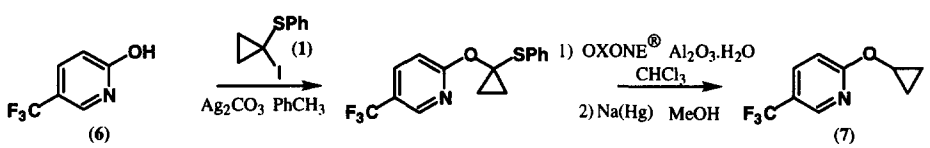
conversion of phenols containing a wide range of functional groups (*e.g.* cyano group, methyl ester) to their corresponding cyclopropyl ethers (**4**) was achieved (Table 1, entries b-g).

Table 1

Entry	Phenol (**2**) R=	Alkylation Time and Temperature	Alkylation Yield of (**3**) (%)†	Method A Yield of (**4**) (%)†	Method B Yield of (**5**) (%)†	Method B Yield of (**4**) (%)†
a	4-OCF_3	RT, 60h	93	60	-	-
b	4-Cl	RT, 48h then 50°C, 2h§	58	83	90	88
c	4-CO_2Me	RT, 48h	63	-	100	94*
d	4-OSi^iPr_3	RT, 60h then 75°C, 2h§	35	98	83	79
e	2-CN	RT, 60h	92	-	89	90*
f	3-CN	RT, 60h	90	-	66	45
g	4-CN	RT, 48h	75	0	88	63

All compounds showed satisfactory spectral data. † Quoted yields are of isolated material after chromatography where required. § A further one equivalent each of (**1**) and Ag_2CO_3 added prior to heating. * THF co-solvent was used.

To illustrate that this chemistry may also be applied to heterocyclic systems, an example of a cyclopropyl pyridyl ether (**7**) was prepared from the corresponding hydroxypyridine (**6**) (Scheme 4). Alkylation of (**6**) proceeded in 41% yield and the oxidation – reduction steps for removal of the phenylthio function (Method B) proceeded in 96% and 86% yields respectively.



Scheme 4

Typical experimental procedures are detailed below:

Alkylation of phenols (**2**): Phenol (**2**) (2.0 mmol) was dissolved in toluene (10 ml) and silver carbonate (1.10 g, 4.0 mmol) and 1-iodo-1-(phenylthio)cyclopropane (1.10 g, 4.0 mmol) were added. The mixture was stirred at room temperature until all starting material was consumed, then filtered through a fibreglass filter, washing the solids thoroughly with ethyl acetate. Evaporation under reduced pressure and purification of the residue by flash column chromatography gave the corresponding aryl 1'-(phenylthio)cyclopropyl ether (**3**).

Lithium Naphthalenide Reductions (Method A): Aryl 1'-(phenylthio)cyclopropyl ether (**3**) (1.0 mmol) was dissolved in THF (5 ml) and the solution was cooled to –78 °C under an argon atmosphere. Lithium naphthalenide (ca. 0.6 M in THF)[10] was then added dropwise until the intense green coloration persisted. Water (10 ml) and saturated aqueous ammonium chloride (5 ml) were added and the mixture was extracted with ethyl acetate (2 x10 ml). The combined organic phases were dried (Na_2SO_4), evaporated and purified by flash column chromatography to give the corresponding aryl cyclopropyl ether (**4**).

Sulfide Oxidations (Method B): Aryl 1'-(phenylthio)cyclopropyl ether (**3**) (0.78 mmol) was dissolved in chloroform (10 ml) and 'wet alumina' (780 mg) [a mixture of Brockman grade 1 alumina-water (5 g:1 ml)] and OXONE® (960 mg, 1.57 mmol) were added. The reaction mixture was heated under reflux until reaction was complete. The mixture was filtered, the solids were thoroughly washed with chloroform and the filtrate was evaporated to give (after chromatography where necessary) the corresponding sulfone (**5**).

Sulfone Reductions (Method B): Sulfone (**5**) (1.13 mmol) was dissolved in methanol (5 ml) (with tetrahydrofuran co-solvent (5 ml, if required) at room temperature and sodium hydrogen phosphate (633 mg, 4.46 mmol) was added. Sodium mercury amalgam (10% Na, 1.05 g, 4.56 mmol) was then added in one portion and the reaction monitored by tlc. On completion, water (5 ml) and saturated aqueous sodium bicarbonate (5 ml) were added and the mixture extracted with ethyl acetate (2 x 10 ml). The combined organic phases were dried (Na_2SO_4), evaporated and purified by flash column chromatography (where necessary) to give the corresponding aryl cyclopropyl ether (**4**).

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2) Shostakovskii, S.M., L'vov, A.I., Kimel'fel'd, Ya. M., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1966, 1754. (CA 66:37558); Retinskii, A.A., Shostakovskii, S.M., Kositsyna, E.I., *Izv. Akad. Nauk SSSR, Ser. Khim.* 1972, 1778 (CA 77:151590); Furukawa, J., Kawabata, N. and Nishimura, A., *Tetrahedron*, 1968, **24**, 53.

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4) Cimetiere, B. and Julia, M., *Synlett*, 1991, 271.

5) See Freidrich, E.C. in 'The Chemistry of the Cyclopropyl Group, Part 1' Wiley, Ed. Z. Rappoport 1987, 633.

6) A related strategy utilising an alkoxy stabilising substituent has been reported for the N-cyclopropylation of anilines, see: Kang, J., and Kim, K.S., *J. Chem. Soc., Chem. Commun.*, 1987, 897.

7) Cohen, T. and Matz, J.R., *J. Am. Chem. Soc.*, 1980, **102**, 6900.

8) Starting phenols were commercially available except for 4-(triisopropylsilyloxy)phenol which was synthesised by silylation of 4-(benzyloxy)phenol followed by palladium catalysed hydrogenolysis of the benzyl group.

9) Dichloromethane was also found to be a suitable solvent.

10) Prepared according to the procedure of Azuma et al: Azuma,T., Yanagida, S., Sakurai, S., Sasa, S. and Yoshino, K., *Synth. Commun.*, 1982, 137.

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