An Economical Noncatalytic Approach to the Synthesis of Congested Diaryl Ethers and Aryl Benzyl Thioethers through C–C Insertion

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Abstract: An efficient one-pot synthesis of diaryl ethers and aryl benzyl thioethers has been delineated through base-induced ring transformation of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles, methyl 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carboxylates and 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles by either 1-phenoxypropan-2-one, 1,3-diphenoxypropan-2-one or 4-arylthiobutan-2-one, under very mild reaction conditions, in excellent yield.

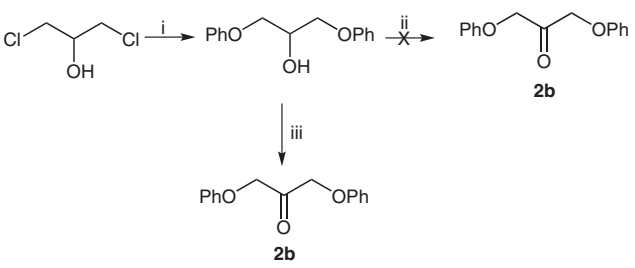
Key words: 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles, ring transformation, diaryl ethers, 1,3-diphenoxypropan-2-one

Diaryl ethers and diaryl thioethers are important structural motifs that are present as sub-structures in a wide variety of natural products, and are employed as 'building blocks' in organic synthesis, material science, pharmaceuticals and agrochemicals. These compounds have been isolated as breakdown products, depsidones[1] from lichens, bastadines[2] from sponges, combretastatines[3] from plants, riccardin B[4] from mosses and piperazinomycin[5] from different microorganisms. In various natural products, the diaryl ether basic structure is present as mono-, di- and repeated units within macrocyclic frame-works,[6,7] and is responsible for a diverse range of pharmacological activities[8] such as anticancer, anti-inflammatory, analgesic, antiviral, antibacterial and antipyretic actions.[9] The multifarious pharmacological activities and lack of noncatalytic synthetic approaches led us to develop an efficient and economical route to the construction of highly congested aryl ethers with mono- and di-ether linkages.

The synthesis of diaryl ethers commonly begins with classical Ullman ether synthesis[10] from Cu(I)-mediated coupling reaction of phenols with aryl halides. However, the harsh reaction conditions are often incompatible with many functional groups at higher temperature, thus severely limiting its application in organic synthesis. Thereafter, many alternative synthetic strategies have been developed in order to improve the yields of diaryl ethers by using either ionic liquid[11] or catalysts such as copper-phenanthroline complexes,[12] 1,3-diketone,[13] amino acids,[14] or glyoxalhydrazone.[15] The palladium-catalyzed coupling, using electron-rich phosphine ligands[16] and S_N Ar-based reactions of aryl fluorides[17] or metal arene complexes, have also been used for the synthesis of aryl ethers. Nucleophilic aromatic substitution under metal-free coupling conditions can also be an important alternative.[18] Recently, diaryl ethers have also been synthesized under very mild reaction conditions through oxidative arylation of phenols with *N*,*N*-dialkyl-4-phenylthioanilines in the presence of 1,8-bis(diphenylmethylium)naphthalenediyl[19] in moderate yield.

Despite the development of numerous protocols for the construction of diaryl ethers, mild reaction procedures are still in high demand. Herein, we report an economical and efficient synthesis of congested diaryl ethers through base-induced ring transformation of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles (**1a**, **1b**, **1d** and **1e**), methyl 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carboxylates (**1c**, **1f** and **1g**) and 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles (**1h**) by either 1-phenoxypropan-2-one (**2a**) or 1,3-diphenoxypropan-2-one (**2b**), using anhydrous potassium carbonate and powdered potassium hydroxide as a base in *N*,*N*-dimethylformamide under stirring at room temperature for 2–3 hours. Under analogous conditions, aryl benzyl thioethers have also been prepared by the ring transformation of **1a** by 4-arylthiobutan-2-one.

The precursors, 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles/carboxylates **1** were prepared[20] by the reaction of aryl methyl ketone with either methyl 2-cyano-3,3-dimethylthioacrylate or methyl 2-carbomethoxy-3,3-dimethylthioacrylate. Amination[21] of **1b** with piperidine in boiling ethanol afforded **1h** in good yield. 1,3-Diphenoxypropan-2-one (**2b**), which was used to generate the carbon nucleophile, was synthesized through a sequence of reactions from glycerol as depicted in Scheme 1. Selective halogenation of glycerol followed by coupling with phenol, afforded 1,3-diphenoxypropan-2-ol.[22] Oxidation of the latter to the corresponding ketone **2b** by a range of oxidizing agents failed; however, ultimately, use of Jones



Scheme 1 *Reagents and conditions*: (i) phenol, K_2CO_3, DMF, 135 °C, 8 h, 52%; (ii) (a) Dess–Martin periodinane; (b) Swern oxidation; (c) PCC; (iii) CrO_3, H_2SO_4, 6 h, quantitative.

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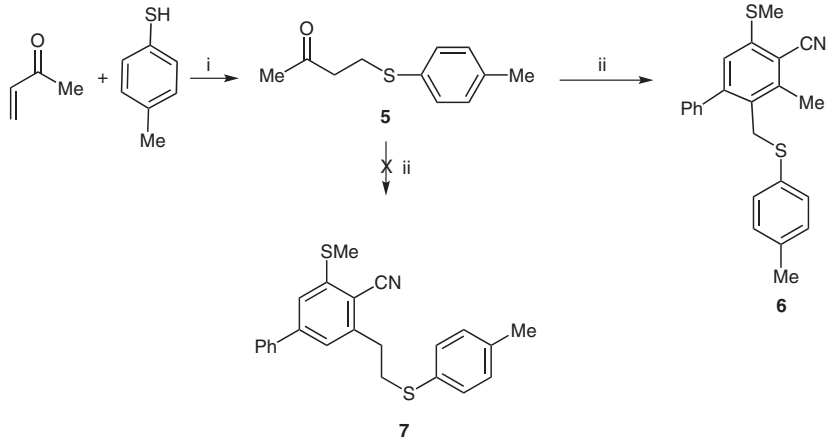

Scheme 2 *Reagents and conditions*: (i) $Bi(NO_3)_3$, CH_2Cl_2, 25 °C, 3 h, 50%; (ii) **1a**, KOH, DMF, r.t., 5 h, 52%.

reagent[23] gave desired product in quantitative yield. The 4-phenylthiobutan-2-one (**5**), used as a carbanion source for the ring transformation, was prepared by Bismuth nitrate catalyzed Michael addition of thiophenols on methyl vinyl ketone (Scheme 2).[24]

Analysis of the molecular makeup of 6-aryl-4-methylthio-2*H*-pyran-2-one-3-carbonitriles/carboxylates **1** revealed the presence of three electrophilic sites at C-2, C-4, and C-6, in which the latter was the most electron-deficient due to both extensive conjugation and to the presence of an electron-withdrawing CN or CO_2Me substituent at the 3-position of the pyran ring. The C-6 position of the pyran ring, being a harder electrophilic centre compared to C-2 and C-4, is preferentially attacked by hard carbanion nucleophiles, generated in situ either from 1-phenoxypropan-2-one (**2a**) or 1,3-diphenoxypropan-2-one (**2b**) in the presence of powdered K_2CO_3/KOH. However, while attack at the C-4 center by a carbanion in the initial step will lead to the formation of an intermediate substitution product which may cyclize to a bicyclic product, in case of C-2 attack there is a possibility for the formation of either a ring-opened or a cyclized product, depending upon the nature of nucleophile used. In practice, we neither isolated nor characterized such respective products (IR, Mass and NMR spectroscopy).

The progress of the reaction was clearly observed from evolution of carbon dioxide bubbles. Thus, a mixture of **1a** and ketone **2a** was stirred with anhydrous potassium carbonate in *N*,*N*-dimethylformamide at room temperature for 2–3 hours then poured onto crushed ice with vigorous stirring followed by neutralization with 10% aqueous HCl. The resulting precipitate was filtered, washed with water, dried and purified by silica gel column chromatography. The isolated compound was identified as 3-methyl-5-methylthio-2-phenoxybiphenyl-4-carbonitrile (**3a**; Table 1).

The initial step in this reaction is possibly the formation of a Michael adduct by attack of a carbanion generated in situ from ketone **2** at C-6, with subsequent ring-opening and recyclization involving the carbonyl function and C-3 of the pyran ring together with elimination of carbon dioxide and water as depicted in Scheme 3, path **A**. The possibility for the formation of 3-methylthio-5-(phenoxymethyl)biphenyl-4-carbonitrile **4** was also envisaged from the reaction of **1a** with **2a** through Path **B**, however, in practice, only **3a** was isolated (Scheme 3). The reason for the exclusive formation of **3a** rather than **4a** is possibly due to the combined negative inductive effects of both the phenoxy and carbonyl groups in the former, which leads to facile generation of a carbanion at the methylene carbon compared to methyl group.

Under analogous conditions, reaction of **1** with 1,3-diphenoxypropan-2-one (**2b**) in the presence of potassium carbonate did not take place but went smoothly when powdered potassium hydroxide was used as a base to give 5-methylthio-2-phenoxy-3-(phenoxymethyl)biphenyl-4-carbonitrile/carboxymethyl compounds **3d**–**g** and **3h** in very good yields (Table 1).

The aryl thioketone **5**, used for the ring transformation of **1** was prepared through Michael addition of 4-methylthiophenol on methyl vinyl ketone. Thus, stirring an equimolar mixture of 4-(4-methylphenyl)thiobutan-2-one (**5**) and 2-pyranone **1a** in the presence of powdered potas-

Table 1 Formation of Congested Diaryl Ethers and Aryl Benzyl Thioethers **3a**–**h**

1,3	Ar	X	Y	R	Base	Yield (%)
a	Ph	SMe	CN	H	K_2CO_3	72
b	4-BrC_6H_4	SMe	CN	H	K_2CO_3	74
c	4-BrC_6H_4	SMe	CO_2Me	H	K_2CO_3	68
d	Ph	SMe	CN	OPh	KOH	82
e	4-BrC_6H_4	SMe	CN	OPh	KOH	86
f	Ph	SMe	CO_2Me	OPh	KOH	85
g	4-BrC_6H_4	SMe	CO_2Me	OPh	KOH	84
h	4-BrC_6H_4	piperidin-1-yl	CN	OPh	KOH	82

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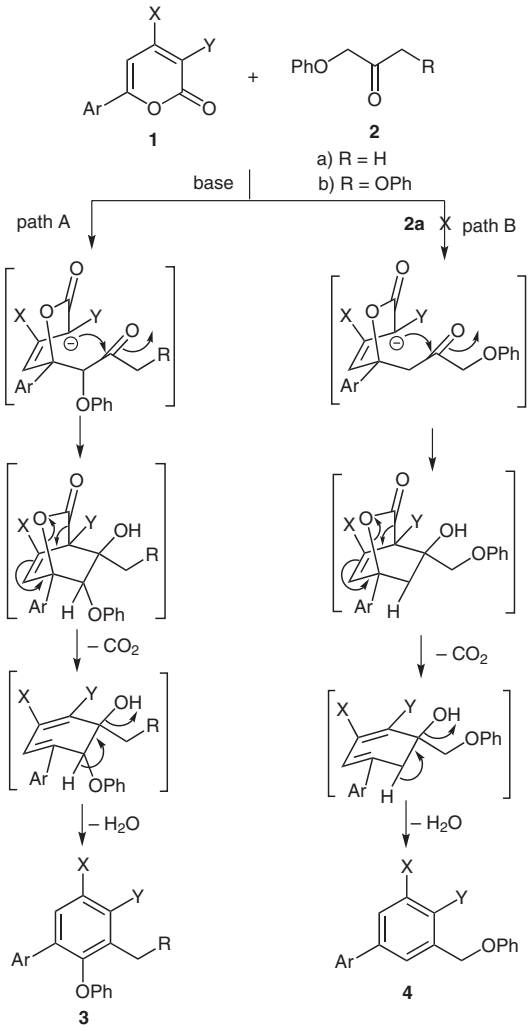

Scheme 3 *Reagents and conditions*: K_2CO_3, KOH, DMF, r.t., 2–3 h, 68–82%.

sium hydroxide in *N*,*N*-dimethylformamide for five hours provided 3-methylthio-5-methyl-6-(4-methylphenylthiomethyl)biphenyl-4-carbonitrile (**6**) after usual workup and purification by silica gel column chromatography (Scheme 2). Theoretically, there was also a possibility for the formation of 3-methylthio-5-[2-(4-methylphenylthio)ethyl]biphenyl-4-carbonitrile (**7**) but, in practice, only **6** was isolated.

The obvious reason for the formation of **6** was due to the generation of the carbanion at C-3 rather than at C-1 in **5** because of the combined negative inductive effect of both the arylthio and acetyl groups.

All the synthesized compounds were characterized by spectroscopic techniques and data of representative compounds are presented in the reference section.[25]

In summary, the synthesis of aryl ethers and aryl benzyl thioether (**3** and **6**) is reported for the first time. The method uses base-catalyzed ring transformation of suitably functionalized 2-pyranones with 1-phenoxy-2-propanone, 1,3-diphenoxy-2-propanone, and 4-arylthiobutan-2-one, through C–C insertion, and gives excellent yields. The protocol provides an economical, noncatalytic approach to the synthesis of congested unsymmetrical diaryl ethers and aryl benzyl thioethers under very mild reaction conditions.

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(25) General procedure for the synthesis of 5-methylthio-2-phenoxy-3-(phenoxymethyl)biphenyl-4-carbonitriles/carboxylates (**3d**–**h**): An equimolar mixture of **1** and **2b** and powdered KOH in DMF was stirred for 2–3 h. During this period, evolution of carbon dioxide bubbles ceased and starting materials were consumed completely (reaction monitored by TLC). The reaction mixture was poured into ice-cold H_2O with vigorous stirring. The precipitate thus obtained was filtered and purified by silica gel column chromatography to give the product in 68–86% yield. Compound **3d**: mp 133–135 °C. IR (KBr): 2212 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 5.13 (s, 2 H), 6.59 (d, *J* = 8.70 Hz, 2 H), 6.83–6.93 (m, 4 H), 7.03–7.08 (m, 2 H), 7.19–7.28 (m, 5 H), 7.36–7.41 (m, 3 H); MS (FAB): *m*/*z* = 424 [M^+ + 1]; Anal. Calcd for $C_{27}H_{21}NO_2S$: C, 76.57; H, 5.00; N, 3.31. Found: C, 76.66; H, 5.18; N, 3.42. Compound **3e**: mp 152–154 °C. IR (KBr): 2210 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.61 (s, 3 H), 5.11 (s, 2 H), 6.56 (d, *J* = 8.70 Hz, 2 H), 6.82–6.96 (m, 3 H), 7.06–7.09 (m, 2 H), 7.19–7.28 (m, 4 H), 7.36 (d, *J* = 8.70 Hz, 2 H), 7.65 (d, *J* = 8.70 Hz, 2 H); MS (FAB): *m*/*z* = 503 [M^+ + 1]; Anal. Calcd for $C_{27}H_{20}BrNO_2S$: C, 64.55; H, 4.01; N, 2.79. Found: C, 64.65; H, 4.16; N, 2.90. Compound **3f**: mp 154–156 °C. IR (KBr): 1768 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H), 3.83 (s, 3 H), 5.07 (s, 2 H), 6.62 (d, *J* = 8.80 Hz, 2 H), 6.82–6.96 (m, 4 H), 7.06–7.09 (m, 2 H), 7.19–7.28 (m, 6 H), 7.36–7.39 (m, 2 H); MS (FAB): *m*/*z* = 457 [M^+ + 1]; Anal. Calcd for $C_{28}H_{24}O_4S$: C, 73.66; H, 5.30; Found: C, 73.77; H, 5.22. Compound **3g**: mp 144–146 °C. IR (KBr): 1764 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H), 3.80 (s, 3 H), 5.13 (s, 2 H), 6.76 (d, *J* = 7.60 Hz, 2 H), 6.89–6.99 (m, 3 H), 7.02–7.05 (m, 1 H), 7.11–7.16 (m, 2 H), 7.21–7.31 (m, 5 H), 7.47 (d, *J* = 7.60 Hz, 2 H); MS (FAB): *m*/*z* = 536 [M^+ + 1]; Anal. Calcd for $C_{28}H_{23}BrO_4S$: C, 62.81; H, 4.33. Found: C, 62.77; H, 4.44. Compound **3h**: mp 138–140 °C. IR (KBr): 2210 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.62–1.64 (m, 2 H), 1.81–1.82 (m, 4 H), 3.20 (t, *J* = 4.8 Hz, 4 H), 5.09 (s, 2 H), 6.56 (d, *J* = 9.0 Hz, 2 H), 6.83–6.95 (m, 4 H), 7.01–7.19 (m, 3 H), 7.21–7.30 (m, 4 H), 7.38–7.41 (m, 2 H); MS (FAB): *m*/*z* = 540 [M^+ + 1]; Anal. Calcd for $C_{31}H_{27}BrN_2O_2$: C, 69.02; H, 5.04; N, 5.19. Found: C, 69.18; H, 5.26; N, 5.29. Synthesis of 3-methylthio-5-methyl-6-(4-methylphenylthio-ethyl)biphenyl-4-carbonitrile (**6**): A mixture of 2-pyranone **1** (1 mmol), 4-arylthiobutan-2-one **5** (1.2 mmol) and powdered KOH (1.5 mmol) in anhydrous DMF (8 mL) was stirred at r.t. for 5 h. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl. The precipitate obtained was filtered, washed with H_2O and finally purified by silica gel column chromatography to afford **6** in moderate yield (52%). Mp 90–92 °C. IR (KBr): 2214 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.51 (s, 3 H), 2.70 (s, 3 H), 3.94 (s, 2 H), 6.97 (s, 1 H), 7.01–7.11 (m, 4 H), 7.37–7.39 (m, 5 H); MS (FAB): *m*/*z* = 376 [M^+ + 1]; Anal. Calcd for $C_{23}H_{21}NS_2$: C, 73.56; H, 5.64; N, 3.73. Found: C, 73.18; H, 5.52; N, 4.06.

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