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Sulfoxide-Mediated α-Arylation of Carbonyl Compounds

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Supporting Information

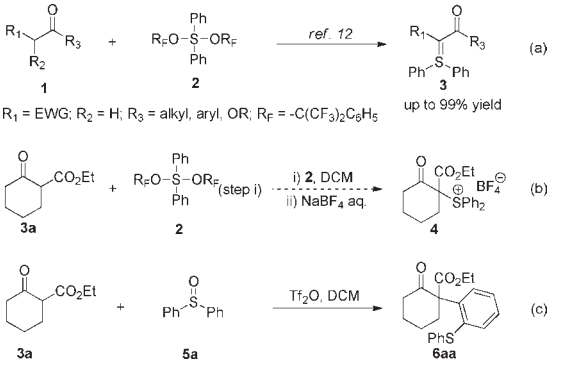
ABSTRACT: A novel sulfoxide-mediated α-arylation of carbonyl compounds is reported. This reaction proceeds under very mild conditions at room temperature and does not require any transition-metal promoter or catalyst.

The selective introduction of an aryl substituent at the position α to a carbonyl group is a transformation of central importance in organic chemistry. In contrast to the broad variety of long-known α-alkylation methods for carbonyl derivatives,[1] significant progress in α-arylation technology has flourished mostly in the past two decades and relies heavily on the advent of powerful transition-metal catalysts.[2] Useful transition-metal-free α-arylation processes[3] typically involve stoichiometric reactions of enolate anions (or equivalents thereof) with electrophilic aromatic derivatives of Bi(V),[4] Pb(IV),[5] I(III),[6] or benzyne.[7] Recently, elegant organocatalytic approaches for enantioselective α-arylation of carbonyl compounds have also been developed.[8−11] In spite of these remarkable advances, the challenge of developing metal-free direct arylations of carbonyl compounds remains alive within the synthetic community.[3]

We recently reported an efficient ylide transfer reaction between Martin's sulfurane **2** and activated carbonyl derivatives **1** (Scheme 1a).[12,13] As part of our mechanistic studies of this reaction, we investigated the reactivity of **2** toward more substituted homologues of **1** ($R_2 \neq H$), for which ylide formation should not be possible. Disappointingly, when ketoester **3a** was employed in this process (Scheme 1b), swift decomposition of **2** took place, and none of the anticipated sulfonium salt **4** could be detected in the reaction mixture by NMR or ESI-MS analysis (Scheme 1b). In search of a surrogate for **2** that might be more effective, we turned our attention to the known combination of diphenyl sulfoxide (**5a**) and a suitable activating agent.[14] To our surprise, when triflic anhydride (Tf_2O) was employed as the electrophilic activator, arylated ketoester **6aa**[15] was obtained as the main reaction product without any discernible formation of a sulfonium salt (Scheme 1c). This intriguing result suggested that fundamentally different reaction modes might be operative in these transformations. We report herein our preliminary results on the transition-metal-free arylation of carbonyl compounds using in situ-activated sulfoxides as aryl donor reagents.[16]

Encouraged by this initial outcome, we then sought to compare different anhydrides as activating reagents. As shown in Table 1, acetic anhydride was ineffective (Table 1, entries 1 and 2), leading to only traces of the desired product **6aa**. In contrast, employing a stronger activating reagent such as Tf_2O proved beneficial (entry 3), and increasing the amount of sulfoxide **5a** to 1.2 equiv also enhanced the reaction rate (entry 4), although further increases in the amount of reagents did not have a marked impact (entry 5). Solvent screening revealed dichloromethane to be the most suitable medium for this reaction (entries 6−9), and in this solvent, the amount of Tf_2O could be further reduced to 1.5 or 1.2 equiv while retaining high yields of product **6aa**. It is interesting to note that trifluoroacetic anhydride (TFAA) also provided very good results (entry 10), particularly in acetonitrile as the solvent (entry 11).

Scheme 1. Previous Work and an Unexpected Observation



Having uncovered two sets of optimal conditions for this direct arylation, we next investigated the substrate scope further. As matters transpired, Tf_2O was not always the best activating agent (method A), and eventually TFAA (method B) was found to be more general in the majority of cases (Scheme 2).

In addition to six-membered cyclic β-ketoesters, five-membered substrates bearing different ester groups afforded the corresponding arylated products in very good yields under similar conditions (Scheme 2, **6aa**−**da** and **6ka**). When ketoester **3e** derived from α-tetralone was employed, a lower conversion was observed, and 34% of the starting material was recovered (**6ea**). Conversely, derivatives of 1-indanone proved to be better candidates for this reaction (**6fa**−**ja**). The presence of electron-withdrawing substituents on the aromatic ring (**3g** and **3h**) had a positive effect on this process, and the corresponding products **6ga** and **6ha** were obtained in high yields. In the case of acyclic β-ketoester **3l**, a slower reaction was observed, and **6la** was obtained in an acceptable yield after stirring at room temperature for 2 days. This process also displayed high levels of diastereoselectivity: arylated product **6ma** with a *tert*-butyl group at position 4 of the six-membered ring was formed in 75% yield with a 9:1 diastereomeric ratio (dr).[17]

Other diaryl sulfoxides were also examined as arylating agents. As shown in Scheme 3, the corresponding products **6ab** and **6ac** were obtained in moderate yields.

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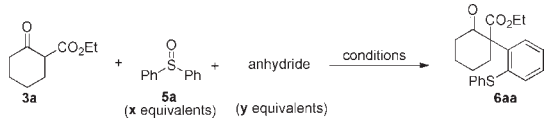
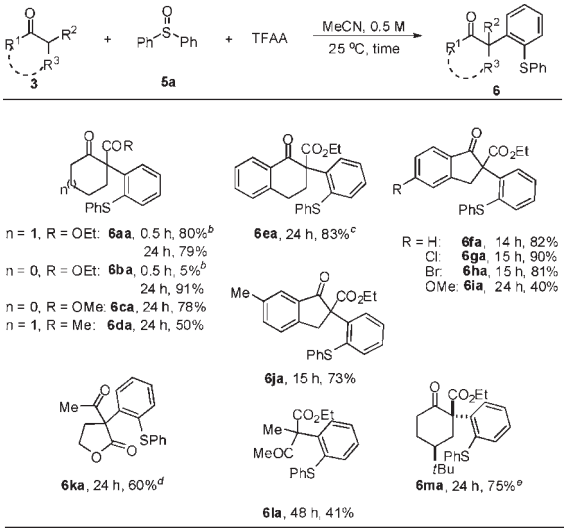
Table 1. Optimization of the Direct Arylation of β-Ketoester 6a with Sulfoxide 5a[a]



Entry	x	y	Anhydride	Reaction time (h)	Solvent	Conc. (M)	Yield[b] (%)
1	1	2	Ac_2O	24	CH_2Cl_2	0.25	-[c]
2	1.2	2		48			-[c]
3	1	2	Tf_2O	0.5			66
4	1.2	2					79
5	2	2					53
6	1.2	2			$EtNO_2$		60
7	1.2	2			Et_2O		-[c]
8	1.2	2			PhMe		35
9	**1.2**	**1.5**			CH_2Cl_2	**0.5**	**80**
10	1.2	2	TFAA	36	CH_2Cl_2	0.25	64
11	**1.2**	**1.5**		**24**	**MeCN**	**0.5**	**79**

[a] Performed at 25 °C, unless mentioned otherwise. [b] Yields of pure, isolated material after column chromatography. [c] Not determined.

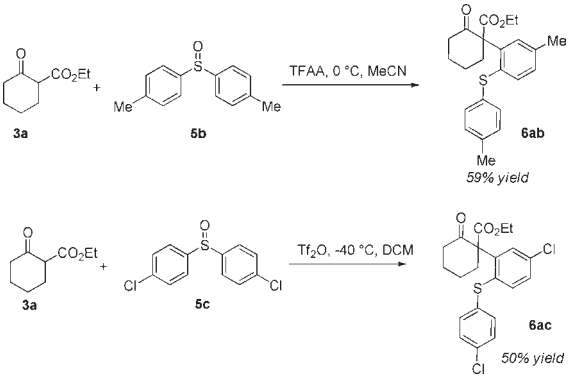
Scheme 2. Direct Arylation of Carbonyl Compounds with Sulfoxide 5a[a]



[a] Method A: 1.5 equiv of Tf_2O, 1.2 equiv of sulfoxide **5a**, CH_2Cl_2, 0.5 M, 25 °C. Method B: 1.5 equiv of TFAA, 1.2 equiv of sulfoxide **5a**, MeCN, 0.5 M, 25 °C. Method B was applied, unless mentioned otherwise. [b] Method A was employed. [c] Based on recovered starting material (34% of **3e** was recovered). [d] The reaction was run at 0 °C. [e] Combined yield with a dr of 9:1 (as determined by GC).

When phenyl methyl sulfoxide **5d** (1.2 equiv) was employed as an aryl donor to ketoester **3a**, a rapid reaction ensued that was complete within 2 h (Scheme 4). Surprisingly, arylated **6ad** was still obtained as the major product of the reaction, and only traces of the "normal" Pummerer product **7ad** could be detected in the reaction mixture (Scheme 4a).[18,19] This result was all the more noteworthy in view of the fact that exposure of **5d** to the action of TFAA almost instantaneously generated trifluoroacetate **8** in very high yield (Scheme 4b). The fact that **6ad** was obtained preferentially over its isomer **7ad** despite the rapid conversion of the latter into **8** by a "background" process strongly suggests that the mechanism of these arylations is fundamentally different from the classical Pummerer reaction.

Scheme 3. Reaction of 3a with Sulfoxides 5b and 5c



Enticed by this result, we probed other aryl alkyl sulfoxides (Scheme 5). On one hand, changing the nature of the alkyl residue (R^2) did not change the efficiency of the process, and the corresponding arylated product **6ae** was still obtained in moderate yield. The aryl moiety could also be modified (**6ag**−**ai**). It is remarkable that such arylated products were obtained by employing a sulfoxide from which a classical Pummerer reaction would have been anticipated.[20]

From a mechanistic point of view, two distinct reaction pathways can be envisaged for this novel transformation (Scheme 6). It is well-established that the treatment of sulfoxide **5** with TFAA should lead to the formation of activated intermediate **10**. After enolization of the β-ketoester nucleophile **1**, nucleophilic attack at the aromatic position ortho to the cationic sulfur would lead to the dearomatized intermediate **12** (pathway A), with concomitant expulsion of trifluoroacetate.[21,22] Rearomatization by proton loss would account for the formation of product **6**. More interestingly, if the nucleophilic attack takes place at sulfur, the intermediate **11** would be formed instead (pathway B). A charge-accelerated [3,3] sigmatropic rearrangement should then convert **11** to the same dearomatized intermediate **12** as described previously.[23−26]

Pathway A (Scheme 6) would be akin to an extended Pummerer reaction of an aromatic ring.[21] The extended Pummerer chemistry of heteroarenes has been reported by both Kita and Feldman,[22] but to the best of our knowledge, all of these processes require strongly electron-rich aromatic systems (e.g., furan, thiophene, or indole). In particular, Kita reported[22d] the arylation of 2,4-pentanedione (**13a**) with heteroaromatic furan- and thiophene-derived sulfoxides **14** (Scheme 7a). It is interesting to note that when the analogous 1,3-dicarbonyls **13a** and **13b** were employed in our system, no arylated products **16** (or their enol tautomers) were detected (Scheme 7b). Strikingly, use of the stronger activator Tf_2O gave sulfonium ylides **17a** and **17b** as the only detected products (Scheme 7c).[12]

All of experimental evidence thus far points toward pathway B (Scheme 6) being operative. Indeed, the reaction is exquisitely

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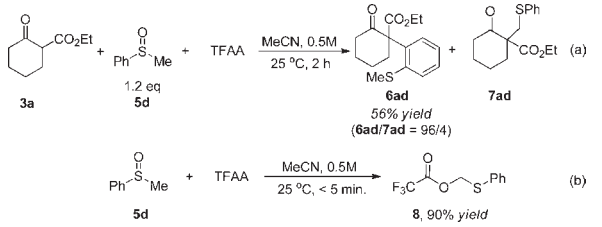
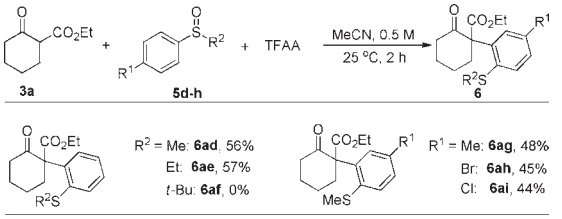
Scheme 4. Reaction of 3a with Sulfoxide 5d

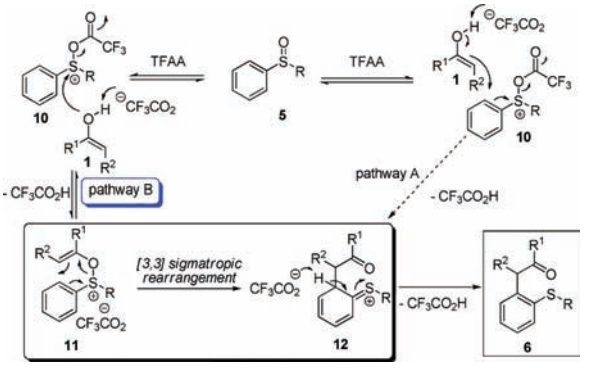


Scheme 5. Reaction of 3a with Sulfoxides 5d–h[a,b]



[a] Conditions: 1.5 equiv of TFAA, 1.2 equiv of sulfoxide **5**, MeCN, 0.5 M, 25 °C. [b] Ratios of **6** to **7** as determined by GC: **6ad**/**7ad** = 96/4; **6ae**/**7ae** = 99/1; **6ag**/**7ag** = 99/1; **6ah**/**7ah** = 93/7; **6ai**/**7ai** = 96/4.

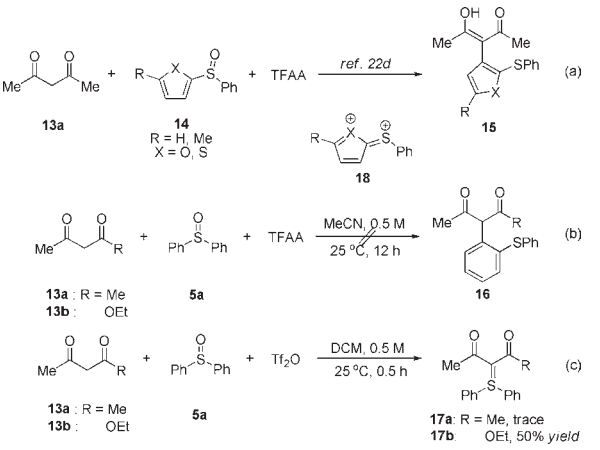
Scheme 6. Mechanistic Proposal for Sulfoxide-Mediated α-Arylation of Carbonyl Compounds



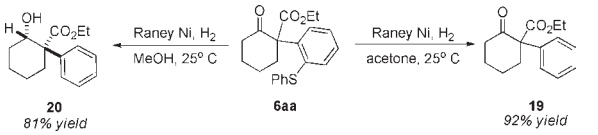
ortho-selective, and we did not detect any traces of isomers resulting from nucleophilic attack at the para position of the aromatic ring. Such para-substituted products would be strongly anticipated and should have been observed if pathway A were dominant, particularly on steric grounds. Additionally, the success observed with electron-neutral and even slightly electron-poor diaryl sulfoxides (such as **5c**) is difficult to reconcile with the prior stringent requirement for activated, electron-rich aryl substituents in the extended Pummerer work of Kita.[22] Without doubt, the intermediacy of an extended dearomatized species such as **18** appears to be crucial in Kita's work (Scheme 7a).

The most compelling piece of evidence comes from consideration of aryl alkyl sulfoxides **5d**–**h** (Scheme 5). It is remarkable that arylated products could still be obtained in reasonable yields in spite of the fast "background" Pummerer transformation that sulfoxides **5d**–**h** undergo in the absence of a nucleophile (Scheme 5). These unambiguous results suggest that the process described herein not only is fundamentally different

Scheme 7. Reaction of Acyclic Dicarbonyl Compounds 13 with Various Sulfoxides [Equation (a) Depicts Prior Work by Kita[22d]]



Scheme 8. Functionalization of α-Arylated Product 6aa



from the conventional Pummerer reaction but can also disrupt it significantly.

Finally, preliminary manipulation of the adducts **6** was sought (Scheme 8).[27] The arylsulfur appendage could be easily excised by hydrogenation with Raney Ni in acetone, leading quantitatively to desulfurized product **19**, which is formally the product of phenylation. When the reaction was conducted in methanol instead of acetone, further diastereoselective reduction of the ketone carbonyl took place, affording cyclohexanol **20** as a single stereoisomer in high yield.

In summary, we have developed a mild, metal-free stereoselective arylation of carbonyl compounds using aryl sulfoxides as arylating reagents. The ability to use simple and easily available reagents in a room-temperature transformation is a distinctive feature of this process, for which an intriguing sigmatropic rearrangement mechanism has been proposed. This approach also provides an entry into densely functionalized, aryl-substituted, all-carbon quaternary stereocenters.[28] Further studies directed toward broadening the scope and elucidating the mechanism of this novel transformation are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The configuration of the major isomer was determined by nuclear Overhauser effect (NOE) experiments. See the SI for details.

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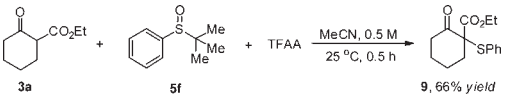
(19) The ratio of **6ad** to **7ad** was 96/4, as measured by GC. For details of the preparation of an authentic sample of **7ad**, see the SI.

(20) The use of sulfoxide **5f** bearing a *tert*-butyl group led to α-(phenylsulfanyl) ketoester **9** in good yield:



3a **5f** **9**, 66% *yield*

See: Redon, M.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1997**, *53*, 15717 and references therein.

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