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A homologous enolate Truce–Smiles rearrangement

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Abstract—During preparation of a series of diphenyl ethers it was observed that displacement of an activated aryl fluoride with *ortho*-hydroxyacetophenone afforded a product that was *C*-arylated adjacent to the ketone. Evidence suggested this product was formed by Smiles rearrangement of an *O*-arylated intermediate.

While preparing a series of diphenyl ethers[1] by S_NAr of activated arylfluorides with phenols an anomaly was noted with *ortho*-hydroxyacetophenone. When the three isomers of hydroxyacetophenone were treated separately with *para*-fluoronitrobenzene (K_2CO_3, DMF, 120 °C) the sole products obtained from the *para*- and *meta*-isomers were consistent with the desired diphenyl ethers (**1** and **2**) (Table 1, entries 1 and 2), whereas the major product obtained from reaction with *ortho*-hydroxyacetophenone was not. It contained a phenolic peak in the ^1H NMR spectrum and lacked the resonance for the methyl of the acetophenone; microanalysis and the mass spectrum indicated a formula identical to the desired compound, while a two proton singlet at 4.64 ppm in the ^1H NMR indicated that it was isomeric by virtue of being *C*-arylated (**3**) rather than *O*-arylated (Scheme 1).[2]

The *C*-arylated product **3** could have formed directly, but this seemed unlikely since no *C*-arylated product was detected in the case of the isomeric acetophenones and, furthermore, a reaction with 2-methoxyacetophenone gave only unchanged starting materials. We suspected that it was instead the result of a stabilized Truce–Smiles rearrangement.

The Smiles rearrangement[3] is the intramolecular nucleophilic aromatic substitution reaction represented in Scheme 2. Linker L is typically two atoms and less commonly one or three atoms. The nucleophile Y is most often the conjugate base of SH, SO_2NHR, SO_2NH_2, NH_2, NHR, OH, OR. Examples where Y is a carbanion are less common but do exist; for example the Truce–Smiles rearrangement is the case where L–YH is an *o*-tolyl group. The prototypical Truce–Smiles rearrangement requires use of a strong base to form the benzylic carbanion that undergoes the rearrangement.[4]

More recently Truce–Smiles rearrangements with stabilized benzylic carbanions have been reported[5] and the term has been extended to rearrangements of carbanions in general,[6] although even including these, comparatively few examples have been reported.[7–9] Truce–Smiles rearrangements of sulfones that proceed through a six-membered transition state (linker L is three atoms) have been reported.[10]

If the present example were taking place through a Truce–Smiles rearrangement the *O*-arylated product should be an intermediate. Indeed, we were able to isolate some of the *O*-arylated material **4** (21%) when the reaction was run at lower temperature (60 °C) and to partial conversion.[11] When this diphenyl ether (**4**) was submitted to the previously used reaction conditions (K_2CO_3, DMF, 120 °C) quantitative conversion to *C*-arylated product **3** was observed thus providing support for a rearrangement mechanism (Scheme 3).

Although no attempt was made to determine the exact temperature that rearrangement took place the presence of rearranged material at 60 °C indicated that rearrangement was occurring at least slowly at this temperature. Additionally, the presence of varying amounts

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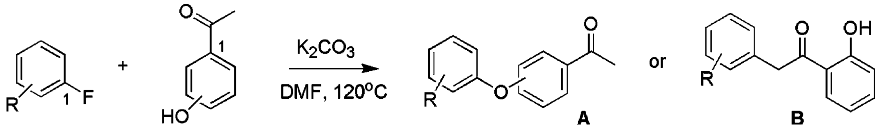
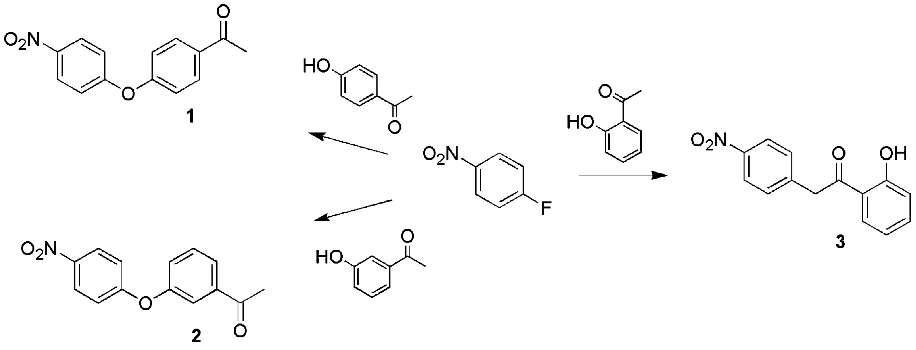
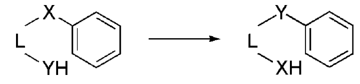
Table 1. Summary of reactions[12]



Entry	R	Position of –OH	Isolated % yield **A**	Isolated % yield **B**
1	4-NO_2	4	99	—
2	4-NO_2	3	95	—
3	4-NO_2	2	—	73
4	2-NO_2	4	96	—
5	2-NO_2	3	88	—
6	2-NO_2	2	—	33



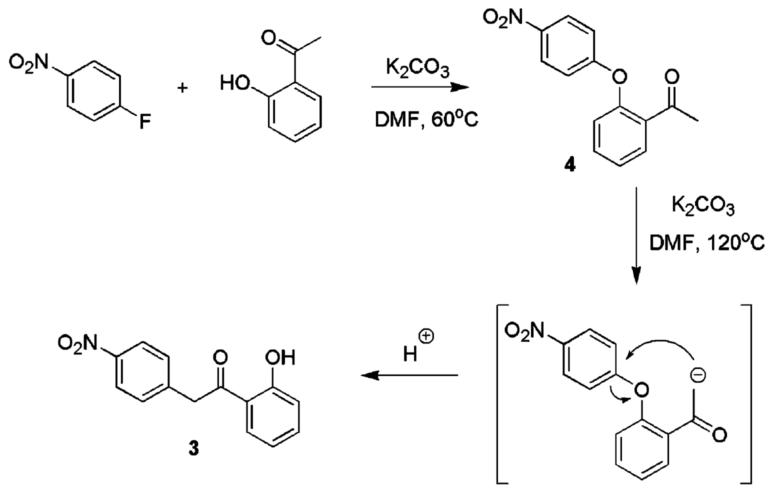
Scheme 1.



Scheme 2.

of rearranged product from different substrates under similar conditions suggests the rate of rearrangement is substrate dependent.

The *C*-arylated compound was also the major product in the reaction of 2′-hydroxyacetophenone with *ortho*-fluoronitrobenzene (Table 1, entry 6). In cases where the *C*-arylated product was formed a small amount of the intermediate *O*-arylated material was seen in the ^{1}H NMR spectra of the crude reaction mixtures; this was removed by a single trituration from ether/hexane to give pure *C*-arylated material. The lower yield noted for entry 6 was due to decomposition occurring before complete conversion of the *O*-arylated intermediate into the *C*-arylated product.



Scheme 3.

This reaction has some notable features: it is the first example of a homologous enolate Truce–Smiles rearrangement, that is, it involves a six-membered transition state rather than a five-membered transition state (the linker, L, in Scheme 2 is three atoms long); additionally, the intermediate that undergoes the rearrangement (*O*-arylated compound **4**) is formed under the same conditions in which it rearranges (to *C*-arylated compound **3**) and this type of one-pot two-step reaction appears unprecedented.

This rearrangement provides a method for carbon–carbon bond formation under mild conditions. It could also prove useful if the acetyl, or maybe a substituted acetyl, was coupled after diphenyl ether formation, or if alternate diaryl ether formations were used, for example, reversing the sense of the coupling such that an *ortho*-fluoroacetophenone was the electrophilic partner. Additionally, it is interesting to contemplate whether this reaction could be used successfully for ring expansion or contraction in cases where the two aryl rings were linked.

Acknowledgements

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References and notes

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2. The ^{1}H NMR spectrum in $CDCl_3$ for **3** is consistent with that previously reported by Kaneeda, M.; Sugawara, Y.; Kawai, H.; Okano, K.; Adachi, Y. PCT Int. Appl. WO 2001035955, 2001. Other data for **3**: δ_H (400 MHz, DMSO-d_6) 11.55 (s, 1H), 8.18 (AA′ of AA′XX′, 2H), 7.97 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.54 (XX′ of AA′XX′, 2H), 7.50–7.53 (m, 1H), 6.99–6.95 (m, 2H), 4.64 (s, 2H); MS (APCI) m/z 256 (M−1). Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%. Found: C, 65.14; H, 4.07; N, 5.34%.
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11. Data for **4**: δ_H (400 MHz, DMSO-d_6) 8.24 (AA′ of AA′XX′, 2H), 7.86 (dd, $J = 8.3$, 2.2 Hz, 1H), 7.66 (ddd, $J = 8.3$, 7.3, 2.2 Hz, 1H), 7.41 (ddd, $J = 8.3$, 7.3, 1.0 Hz, 1H), 7.22 (dd, $J = 8.3$, 1.0 Hz, 1H), 7.12 (XX′ of AA′XX′, 2H), 2.47 (s, 3H); MS (APCI) m/z 256 (M−1). Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%. Found: C, 65.11; H, 4.09; N, 5.39%.
12. All products analyzed correctly by microanalysis. *Representative procedure:* A mixture of 4-fluoronitrobenzene (0.5 mL, 4.7 mmol), 2′-hydroxyacetophenone (0.96 g, 7.1 mmol), and potassium carbonate (2.0 g, 14.0 mmol) in DMF (20 mL) was heated with stirring at 120 °C for 2 h. The reaction mixture was poured into an ice water mixture and the resulting tan solid was collected by filtration and dried. The solid was triturated with ether/hexane to cleanly give **3** as a cream colored solid, 0.89 g (73%).