A truce on the Smiles rearrangement: revisiting an old reaction—the Truce–Smiles rearrangement

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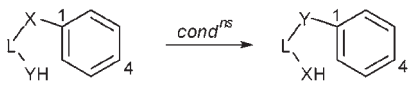
The Smiles rearrangement is the intramolecular nucleophilic aromatic substitution reaction incorporating a heteroatom as the nucleophilic component and an activated electrophilic arene. One particular variation—the Truce–Smiles rearrangement—utilises a carbon-based nucleophile and an electrophilic arene which does not require additional activation. Such a variation generates a new carbon–carbon bond and the synthetic utility of this relatively under-utilised rearrangement is discussed in this *tutorial review*.

Introduction

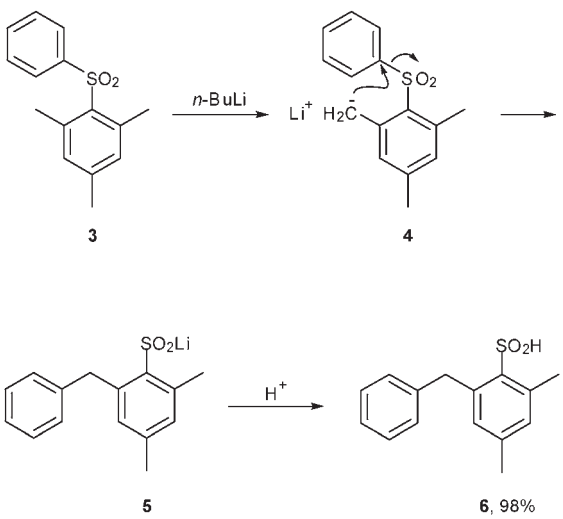
Rearrangement reactions are an extremely useful tool in synthesis since they provide access to structures of a complex nature, often from precursors which are more simply synthesised. In other words, rearrangements can convert an "easy-to-prepare" precursor into a desired "difficult-to-make" product and this has proven to be a very powerful tool indeed.[1] Examples of common rearrangements are the Beckmann rearrangement;[2] the Claisen rearrangement;[3] the Favorskii rearrangement;[4] the Nazarov rearrangement;[5] the semi-pinacol rearrangement;[6] the Smiles rearrangement;[7] and the Wittig rearrangement,[8] to name a few. In particular, the Smiles rearrangement is a reaction which has seen widespread use in organic chemistry,[9] however, a simple variant of this reaction—the Truce–Smiles rearrangement—has been little used in recent times, despite it arguably being more synthetically useful due to the selective formation of carbon–carbon (C–C) bonds, Scheme 1.[10–16]



1 **2**

Scheme 1 The Smiles (Y = O, S, NR) and the Truce–Smiles (Y = RC^-) rearrangements; X is usually S, SO, SO_2, O or COO; L = linking unit.

Traditionally, the definition of this particular variant follows two important differences to the more common Smiles rearrangement, these are: (1) a carbanion is the nucleophile rather than a heteroatom and (2) whereas the Smiles rearrangement requires an activating substituent in the migrating aryl unit (*e.g. ortho* or *para*-nitro groups), such activation is not needed, and perhaps would not be tolerated, in the Truce–Smiles rearrangement.[17] However, more recently, reference to the Truce–Smiles rearrangement has been extended to mean variations of the rearrangement which utilise carbanions in general.[18]



Scheme 2

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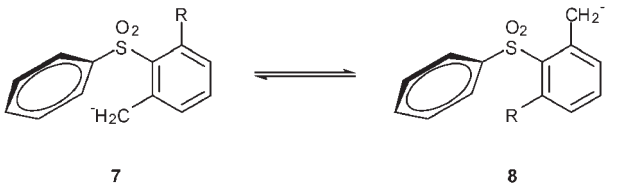


7 8

Scheme 3

Rearrangements of diaryl sulfones

W. E. Truce developed this variant in the late fifties,[10] and went on to show that it was a reliable method for the synthesis of a variety of substituted aromatic sulfinic acids, Scheme 2.

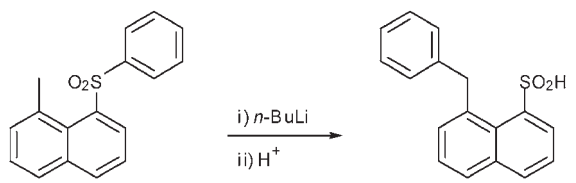
In this example the base (typically *n*-BuLi) deprotonates a methyl group resulting in the formation of anion **4**. This reactive nucleophile subsequently attacks the electron deficient *ipso*-carbon atom (that bearing the sulfur atom), following which, elimination of the sulfur species (RSO_2^-) results in the rearranged product **6**, after protonation.[10]

The factors affecting orientation and reactivity in the Truce–Smiles rearrangement have been studied. The rate of the rearrangement has been measured for a variety of metalated sulfones and it was found to be first order with respect to the metalated sulfone when the rate of initial metalation was very high.[19] Sulfones with a methyl group at the 6-position of the ring containing the lithiated alkyl group were found to react approximately one order of magnitude more rapidly than those with an unsubstituted 6-position. This effect can be interpreted by assuming that the metalated sulfone **4** exists in a conformational equilibrium (see Scheme 3) whereby the analogous conformer, **7**, reacts to give the Truce–Smiles product. Therefore, factors which effect the equilibrium so as to favour this conformer should accelerate the rearrangement. Accordingly, when R = H, conformer **8** becomes favoured for steric reasons and the reaction occurs more slowly.[20–22]

Over the course of the next 25 years or so, Truce went on to report the rearrangement of various *o*-methyl-diaryl sulfones into arylsulfinic acids in high yield.[10–14] It was found that only compounds with *o*-methyl groups underwent the rearrangement, however it has also been demonstrated that potassium *tert*-butoxide in DMSO is capable of effecting the rearrangement.[13]

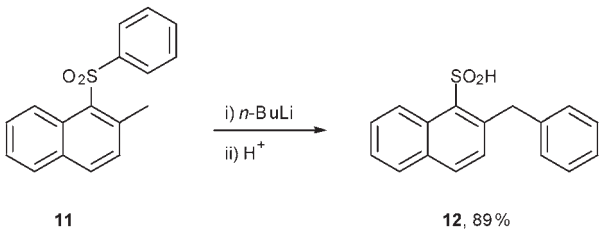
Rearrangement of methylnaphthyl phenyl sulfones

The rearrangement has been demonstrated on the naphthalene nucleus as well, Scheme 4, whereby compound **9** is deprotonated resulting in phenyl migration from sulfur to carbon to give benzyl naphthalenesulfinic acid **10** in 24% yield.[12] A



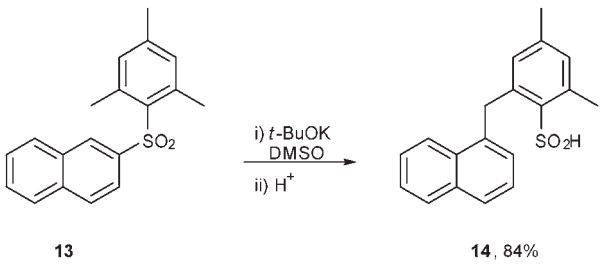
9 **10**, 24%

Scheme 4



11 **12**, 89%

Scheme 5



13 **14**, 84%

Scheme 6

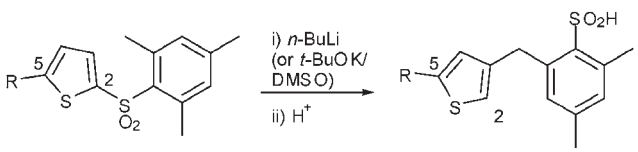
similar rearrangement has also been demonstrated on the isomeric compound **11** in 89% yield, Scheme 5.[12]

However, in the naphthalene case, an alternative reaction takes place with potassium *tert*-butoxide in DMSO when the migrating group itself is naphthalene. In this instance, nucleophilic addition across the 1,2-bond of naphthalene is followed by β-elimination to generate **14**, Scheme 6.[13]

Rearrangement of heteroaromatic and alkyl aryl sulfones

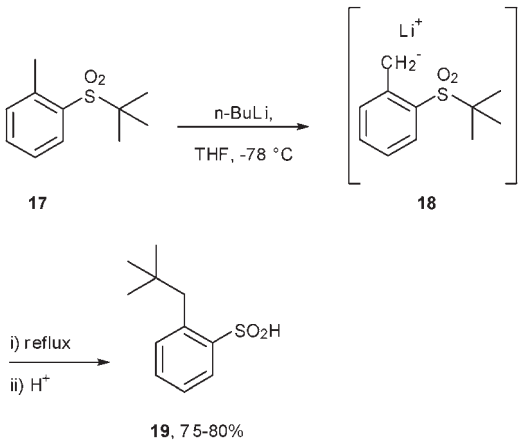
Truce and co-workers have also shown that other aromatic functional groups can participate in the rearrangement. For example, it has been shown that substituted thienyl sulfones **15** (R = Me) undergo the Truce–Smiles rearrangement *via* an addition–elimination sequence to generate sulfinic acids **16**, Scheme 7.[14] Here, the reaction proceeds *via* addition of the anion to the thiophene ring at position C-3, and not *via* a spiro-cyclic intermediate as usual.

However, the thienyl unit (in contrast to the previously mentioned naphthyl and substituted phenyl groups) migrates with a change in orientation regardless of the base/solvent system used. It was found that two equivalents of base are needed when the thiophene ring is unsubstituted at the 5-position (R = H) since in this case, with 1 eq. of base, the ring is deprotonated at C-5 and the resulting monometalated product decomposes. Such a rearrangement (with R = Me) was, at the time, the first example of the rearrangement proceeding with a change in aryl orientation in aprotic media.[14]

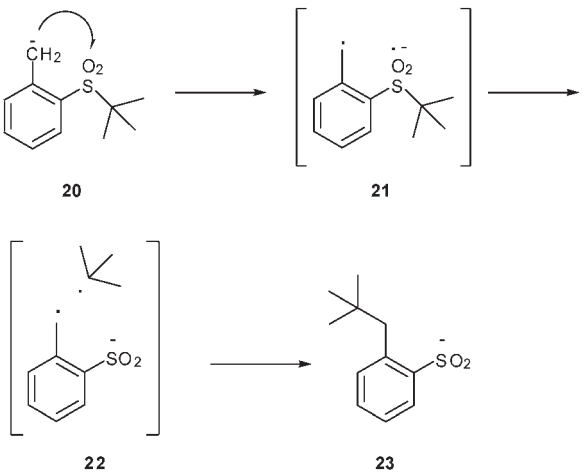


15 16

Scheme 7



Scheme 8

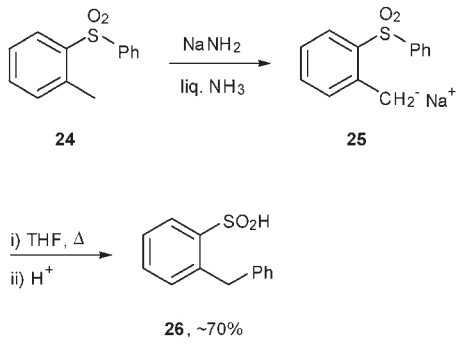


Scheme 9

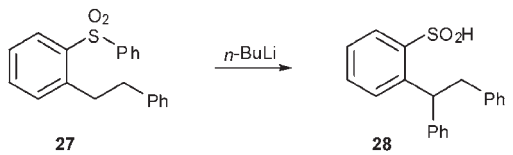
To this point the Truce–Smiles rearrangement has only involved diaryl sulfones. However, in 1979 Truce again demonstrated the first example of the rearrangement in which the migrating group is alkyl rather than aryl, Scheme 8.[15] In the course of investigating several reactions of metalated *o*-tolyl *tert*-butyl sulfone, it was found that refluxing the lithiated species **18** in THF for several hours led to the formation of *o*-neopentylbenzenesulfinic acid **19** in 75–80% yield.[15]

It was believed that this novel rearrangement can be rationalised in terms of an electron-transfer radical-anion pathway, Scheme 9, in contrast to the mechanism described in Scheme 2. For the interested reader, the full details of this alternative mechanism can be found in the original paper and references therein.[15]

Following on from this work Truce and co-workers went on to show that lithiation of appropriate methylaryl alkyl sulfones is followed by migration of the alkyl group from sulfur to the benzylic carbon.[16] Product studies, relative reactivities and cross-over experiments are consistent with a radical–radical anion chain process for this rearrangement, similar to that shown in Scheme 9, the details of which are outside the scope of this review. Further details can be found



Scheme 10



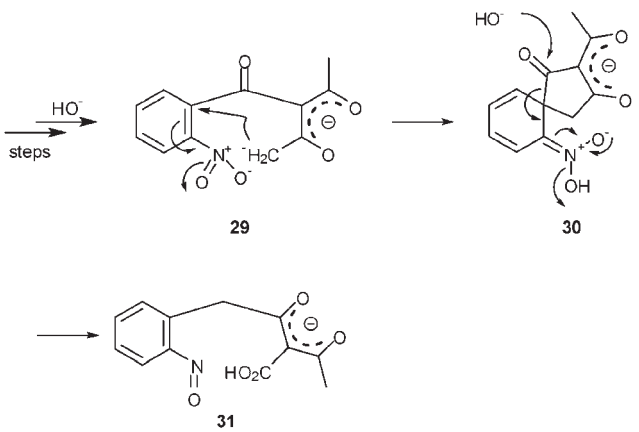
Scheme 11

in the references.[16] It has also been found that, under the influence of amide bases, *p*-methyl groups can undergo metalation and rearrangement in an analogous manner to **20**.[16]

Alternative reaction conditions

In 1968, Crowther and Hauser demonstrated that the deprotonation products of phenyl *o*-tolyl sulfones, using sodium amide, underwent the Truce–Smiles rearrangement when the solvent was changed from ammonia to tetrahydrofuran and the resulting mixture was heated at reflux. In doing so, the resulting benzylbenzenesulfinic acid **26** was obtained in good yield, Scheme 10.[23]

They also found that the sodium salt **25** could be trapped by various intermolecular electrophiles in better yields than those obtained using the *n*-BuLi conditions developed by Truce.[23] Moreover, these condensation products (*e.g.* **27**) were also found to undergo the Truce–Smiles rearrangement, Scheme 11.



Scheme 12

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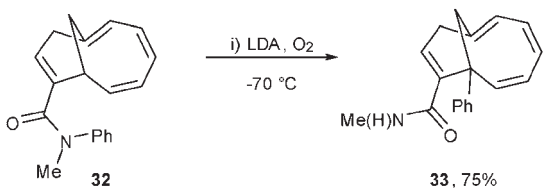
1,3-Diketones as nucleophiles

In 1975, Tennant and co-workers demonstrated the ability for 2-(2′-nitrobenzoyl) derivatives of certain 1,3-diketones to undergo base-catalysed cyclisation to hitherto inaccessible 2-acyl-3-hydroxyquinolines by a process which they believed to be a variant of the Smiles rearrangement, and which in essence is a fragmented Truce–Smiles rearrangement, Scheme 12.[24] The reaction (**29** to **31**) is readily explained in terms of a mechanism which involves the intramolecular nucleophilic attack of the enolate at C-1′ generating spirocyclic intermediate **30**. Unlike the corresponding species in the Truce–Smiles rearrangement (see **29**, SO_2 replaces CO) **30** cannot achieve stabilisation by ejection of the C-1′ sulfonyl leaving group. Consequently, in this alternative pathway, shown in Scheme 12 (*i.e.* **29** to **30** to **31**), nucleophilic attack by hydroxide at the carbonyl group leads to ring scission and concomitant reduction of the nitro group to nitroso.[24]

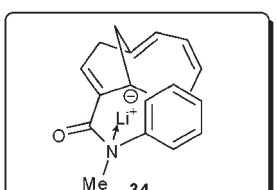
Rearrangement of a substituted anilide

During the course of an attempted synthesis of 1,5-methano[10]-annulene for crystallographic analysis, Itô *et al.* discovered a unique Truce–Smiles rearrangement of substituted anilide intermediate **32** upon exposure to LDA, Scheme 13.[25] When *N*-methylanilide **32** was subjected to an oxidative process (LDA, THF, O_2, −70 °C) the rearranged product **33** was obtained in 75% yield instead of the desired oxidation product; structural confirmation was determined by NMR and X-ray crystallographic analysis; the proposed geometry of the transition state is depicted in Scheme 13.

It was suggested that this rearrangement was the result of a Truce–Smiles rearrangement which occurs *via* the intramolecular nucleophilic attack of a bulky carbanion on the *ipso* position of the anilide **34**, followed by expulsion of the amide nitrogen to give the product in good yield.[25]



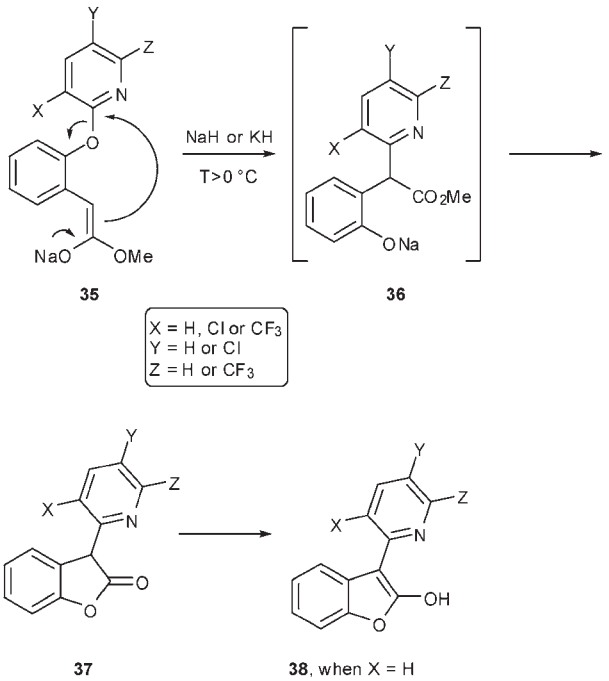
32 **33**, 75%



34

Proposed geometry of the transition-state

Scheme 13

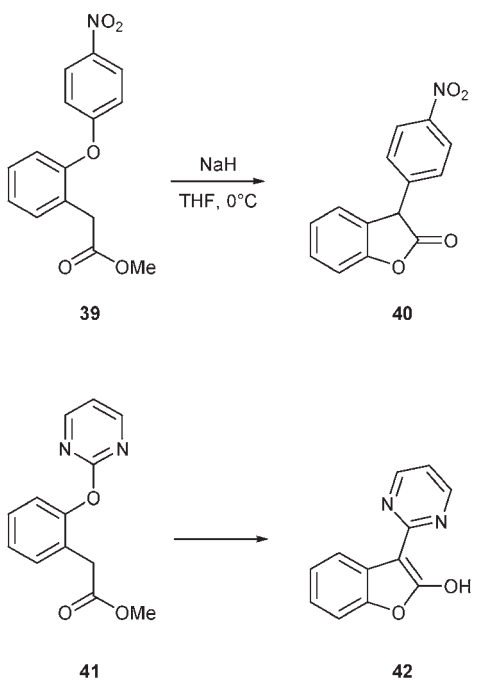


35 **36** **37** **38**, when X = H

Scheme 14

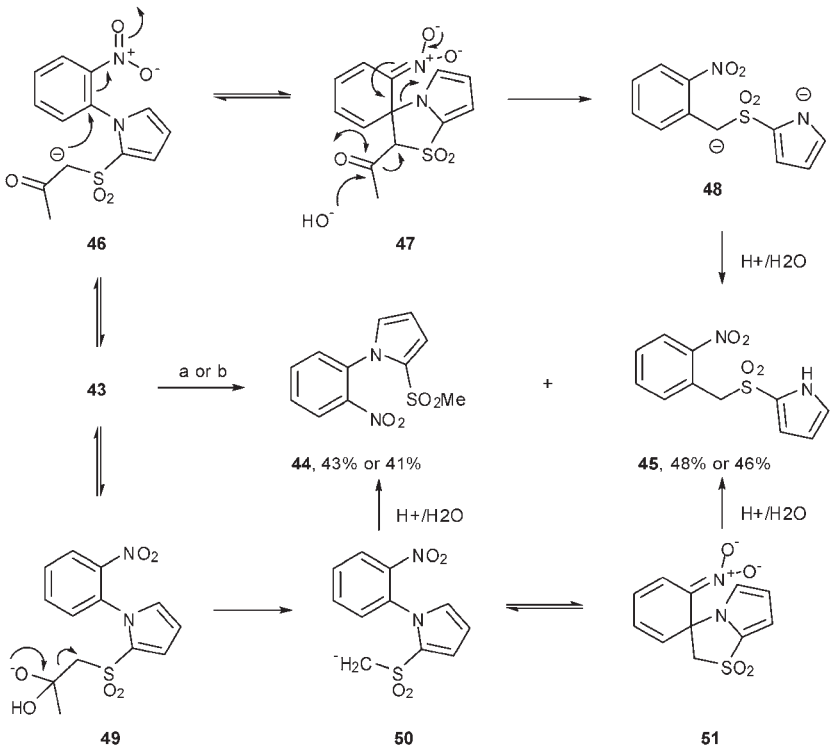
More recent studies

Since the work by Itô *et al.* in 1982 there were no further examples of the Truce–Smiles rearrangement until 2000. In view of its synthetic utility it is surprising that such little work has been carried out on this rearrangement and it was not until 2000 that Erickson and McKennon unexpectedly observed the Truce–Smiles rearrangement as part of a study into the synthesis of anti-fungal compounds.[26] When they attempted to implement a simple procedure to formylate an ester enolate followed by



39 **40** **41** **42**

Scheme 15



Scheme 16 *Reagents and conditions*: (a) Zn, NaOH, H_2O, EtOH, reflux; (b) NaOH, H_2O, EtOH, reflux.

O-methylation, Scheme 14, no formylation products were produced when compounds such as **35** were submitted to the literature conditions. Instead, enolate attack onto the pyridine ring was observed. The authors rationalised the results as the product of a Truce–Smiles rearrangement and went on to reveal this, initially undesired transformation, as a new method for the preparation of 3-pyridyl-2-benzofuranones.[26]

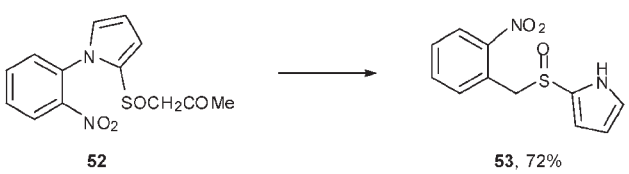
The synthesis of a number of esters, such as **35**, was performed and upon exposure of them to either NaH or KH at temperatures above 0 °C induced the rearrangement, producing an intermediate phenoxide (ArO^-M^+) which spontaneously lactonised to the benzofuranone **37**. In certain cases, when X = H, the benzofuranone tautomerised resulting in the isomeric products **38**, Scheme 14.

The generality of the rearrangement, was briefly examined with other activated aromatic systems, such that the treatment of **39** with NaH in THF at 0 °C gave the lactone **40**, Scheme 15. Similarly, the rearrangement of **41** was facile giving hydroxybenzofuran **42**.[26]

Later in 2004, Varvounis and co-workers discovered an unusual Truce–Smiles type rearrangement when attempting a synthesis of the pyrrolo[1,2-*a*][3.1.6]benzothiadiazocine ring system, Scheme 16.[27] For example, treatment of compound **43** with hot aqueous ethanolic sodium hydroxide yielded a mixture of two new compounds **44** and **45** in 43 and 48% yield, respectively. A speculative mechanism is proposed for the synthesis of **45** where the hydroxide anion can act as both a base and nucleophile, Scheme 16; intramolecular attack on the benzene ring by carbanion **46** would give the Meisenheimer-type intermediate **47** that could ring-open prior to or after addition of hydroxide anion to the acetyl group to give, after loss of acetate anion, pyrrolyl dianion **48**. On the other hand, addition of hydroxide ion to the acetyl group of **43** would give intermediate **49** from which loss of acetate anion would lead to products **50** and **51**. The formation of **45** is considered to be an unusual case of a Truce–Smiles rearrangement.[27] In general, it is believed that in the cases where an electron deficient arene takes part in the rearrangement the reaction proceeds *via* an intermediate anionic spiro adduct analogous to that depicted by **47**.

The analogous sulfoxide **52** was prepared and it was also shown to react under similar conditions (NaOH, H_2O, EtOH, reflux) to give the product **53**, presumably as a result of the Truce–Smiles type rearrangement, in 72% yield. The explanation for the lack of formation of the sulfoxide analogue of carbanion **50** is due to the sulfoxide analogue being less stabilised than **50** itself and is therefore not formed, Scheme 17.

Finally, in 2004 Mitchell and Barvian showed that a Truce–Smiles rearrangement was in operation when they analysed the unexpected products obtained from the reaction of 2′-hydroxyacetophenone and both 2- and 4-fluoronitrobenzene.[18] While preparing a series of diphenyl ethers by the S_NAr reaction of activated aryl fluorides with phenols an anomaly was noted with 2′-hydroxyacetophenone. For



Scheme 17 *Reagents and conditions*: Zn, NaOH, H_2O, EtOH, reflux; or NaOH, H_2O, EtOH, reflux.

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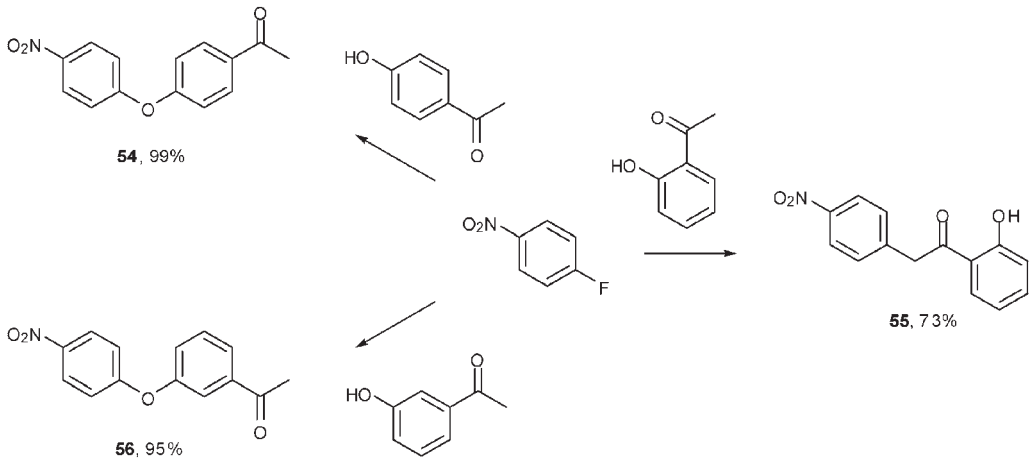
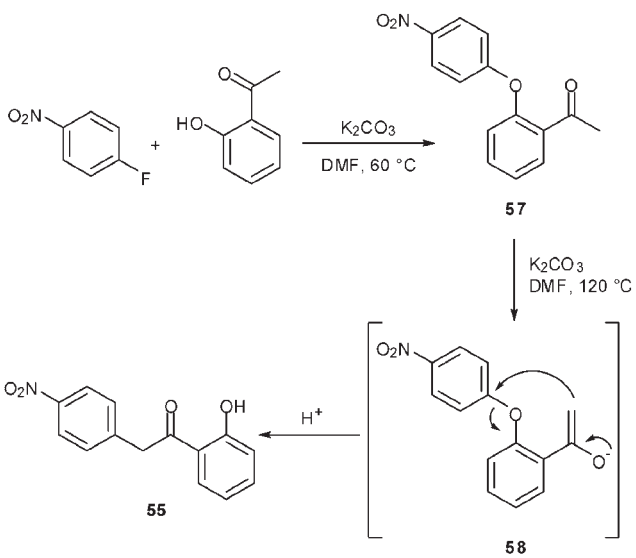


Scheme 18



Scheme 19

example, when the three isomers of hydroxyacetophenone were treated separately with 4-fluoronitrobenzene (K_2CO_3, DMF, 120 °C) the sole products of the reactions with 3′- and 4′-hydroxyacetophenone were consistent with the desired diphenyl ethers **54** and **56** (Scheme 18), whereas the major product obtained from reaction with 2′-hydroxyacetophenone was not. The products from the unexpected reactions contained a phenolic signal in the ^{1}H NMR and lacked the signal corresponding to the methyl group of the methyl ketone; instead, a two proton singlet at 4.64 ppm was seen, which indicated that the product was in fact isomeric compound **55**, which was *C*-arylated rather than *O*-arylated, Schemes 18 and 19.

It was thought that the *C*-arylated product **55**, could not have been formed directly since no *C*-arylated product was detected in the case of the isomeric acetophenones. Furthermore, an analogous reaction with 2′-methoxyacetophenone gave only unreacted starting materials. As a consequence, it was suspected that the result was due to a Truce–Smiles rearrangement. This rearrangement thus provided a method for carbon–carbon bond formation under mild conditions.

Indeed Mitchell and Barvian went on to demonstrate that the intermediate in the Truce–Smiles rearrangement—the diaryl ether **57**—could be isolated (in 21% yield) when the reaction was run at lower temperature (60 °C) and to partial conversion.[18] Further evidence for the rearrangement came when diaryl ether **57** was subjected to the previously used reaction conditions (K_2CO_3, DMF, 120 °C) and quantitative conversion to the *C*-arylated product **55** was observed. Additional results suggested that the exact conditions necessary for the rearrangement to take place are substrate dependent. The authors went on to discuss some notable features of the reaction: (1) this variant of the rearrangement is the first example of a homologous enolate Truce–Smiles rearrangement, that is, it involves a six-membered transition state and (2) the intermediate that undergoes the rearrangement (diaryl ether **57**) is formed under the same conditions in which it rearranges to the *C*-arylated product **55** and this type of one-pot two-step reaction appears unprecedented.

The synthetic utility of the Truce–Smiles rearrangement was recognised by Mitchell and Barvian in their summary where they projected that the rearrangement provides a method for carbon–carbon bond formation under mild conditions, and may also prove useful if the acetyl, or a substituted acetyl was coupled after diphenyl ether formation, or if alternative diaryl ether formations were used. For example, they suggested reversing the sense of the coupling such that an *ortho*-fluoroacetophenone was the electrophilic partner. Additionally, they considered that it would be interesting to contemplate whether this reaction could be used successfully for ring-expansion or contraction in cases where the two aryl rings were linked.[18]

However, despite such a promising projection there have been no examples, to our knowledge, of the Truce–Smiles rearrangement since 2004, and with it constituting such a mild procedure for carbon–carbon bond formation this seems surprising. Time will tell if such a potentially useful reaction will see success in the field of total synthesis.[28]

Conclusions

The Truce–Smiles rearrangement is well established as part of the synthetic chemists toolbox for the synthesis of substituted

arylsulfinic acids. However, despite a few sporadic examples of other systems the reaction has rarely appeared in complex organic syntheses. With the importance that is imparted to carbon–carbon bond forming reactions, it is unusual that such a reaction has seen such little use, and when the fact that most of the more recent examples shown here involve a serendipitous discovery, this number is smaller still. The Truce–Smiles variant of the reaction therefore offers unique opportunities to prepare synthetically useful reaction products which are not easily accessible by other synthetic methods. With this in mind, the Truce–Smiles rearrangement could feature more heavily in synthesis in the future.

Acknowledgements

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