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A concise approach to the preparation of 2-hydroxydiarylketones by an intramolecular acyl radical *ipso* substitution†

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Abstract

Substituted 2-hydroxydiarylketones have been simply prepared using an intramolecular acyl radical [1,6] *ipso* substitution reaction.

The 2-hydroxydiarylketone unit occurs in many target molecules of importance for organic synthesis, encompassing both natural products such as cotoin, balanol and daunomycinone as well as purely synthetic biologically active drugs.[1] It also functions as an ultraviolet screen in products such as dioxybenzone, mexenone and oxybenzone and has also found use in this context within the paints and plastics industry (e.g. benzophenone-6, benzoresorcinol).[1] Although a variety of methods for the construction of this moiety have been developed as a direct consequence of these varied properties, the most often used strategies are firmly rooted in the ionic tradition with reactions such as Friedel–Crafts acylation[2] or the Fries rearrangement.[3]

Within the last few years, we have developed a novel approach for the synthesis of biaryls by using an intramolecular free radical *ipso* substitution reaction of a suitably constituted sulphonyl substituted aromatic derivative by a second *ortho* substituted σ aryl radical.[4] This concept of intramolecular free radical arylation for biaryl construction has been skilfully extended by several groups in recent times.[5–9] To date however, our work has always centred around the initial generation of an aryl radical as the trigger for carbon–carbon bond formation to the second sulphonyl substituted aromatic acceptor. In the present communication, we wish to describe a new synthesis of 2-hydroxydiarylketones using a similar strategy but involving the substitution of those sulphonyl derivatives by an aromatic acyl radical as the key step (Scheme 1).

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† Dedicated with respect and admiration to Professor Harry Wasserman, an exemplary scholar, gentleman and enthusiast for organic chemistry on the occasion of his 80th birthday.

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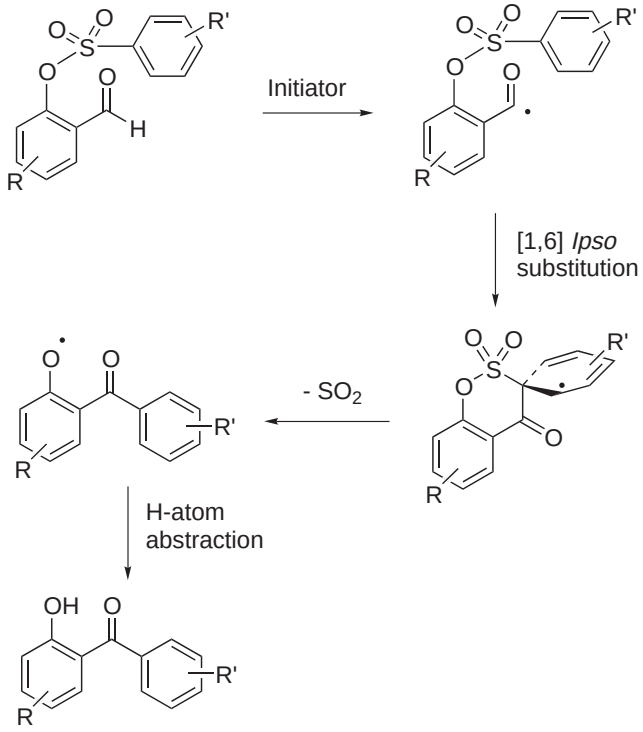
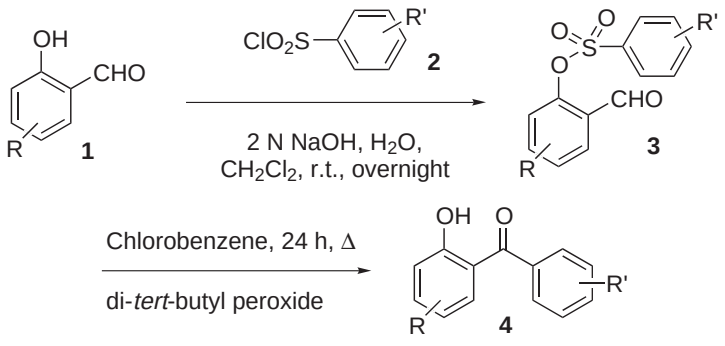


Scheme 1.

While acyl radicals have been known for nearly a century, they have only recently emerged as an important tool for organic synthesis.[10] However, their reactions with aromatic[11] and heteroaromatic[12] compounds have been little studied.

Although acyl radicals can be generated from many precursors, most notably by the reductive stannane protocol from acyl selenides,[10a] we elected to generate our required intermediate by simple hydrogen atom abstraction from an aldehyde since the starting materials, **3a**–**o**, were all readily prepared in a single step from inexpensive and commercially available *o*-hydroxybenzaldehydes (Scheme 2).



Scheme 2.

Thus, the reaction of **1a**–**o** with the appropriate arylsulphonyl chloride in a two-phase system of aqueous sodium hydroxide and dichloromethane at room temperature furnished the desired sulphonates **3a**–**o** in high yields.[13,14]

In an initial experiment, we studied the reaction of a solution of **3a** in chlorobenzene at reflux for 24 h in the presence of one equivalent of di-*tert*-butyl peroxide as initiator. Examination of the reaction mixture at this time revealed a 4:1 ratio of **3a**:**4a** in favour of the starting material although the desired ketone was isolated, after column chromatography in 15% yield. Neither the conversion nor the yield in this experiment could be improved by using longer reaction times.

This result indicated to us that any putative chain propagation step involving abstraction of the aldehydic hydrogen atom by the aryloxy radical formed on loss of sulphur dioxide was clearly inefficient although each of the steps is formally favoured in terms of polar effects. In the event, the most practical and expedient solution proved to be the addition of ten equivalents of initiator whereupon **4a** was isolated in 80% yield.[15] A non chain radical reaction is certainly involved. It was of further interest to note that products arising from decarbonylation or [1,7] addition to the sulphonyl substituted acceptor ring were not detected.

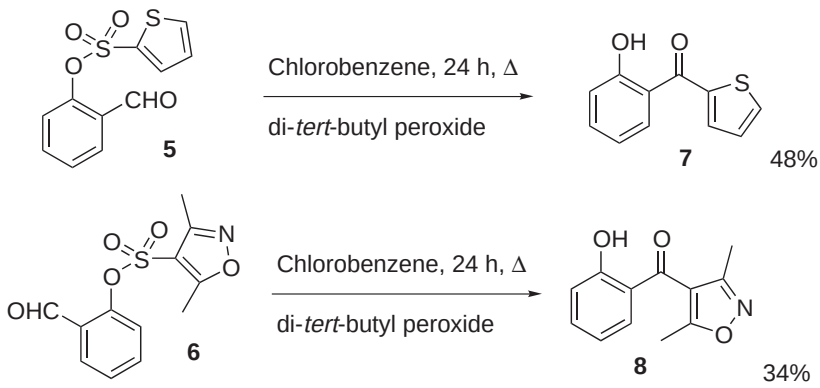
Our attention was then directed towards a study of the series of substituted derivatives shown in Table 1. Examination of the results reveals that both electron donating and electron withdrawing groups are generally well tolerated in the aromatic sulphonyl acceptor ring (Entries a–i), although, as expected, incorporation of the radicophilic cyano group (Entry k) led to a much lower yield. In stark contrast to our studies in the biaryl series, where increasing steric hindrance actually favours the reaction by virtue of an orthogonal approach,[4d] the conformational constraints imposed by such substituents are clearly unfavourable in the present [1,6] *ipso* substitution process, as witnessed by the case of the mesityl derivative (Entry j).

Table 1
Synthesis of 2-hydroxydiarylketones **4a**–**o**

Entry	Substrate **3** (yield %)	Product **4** (yield %)
a	R = H, R′ = 4-CH_3 (71%)	80%
b	R = H, R′ = 4-F (70%)	53%
c	R = H, R′ = 2-F (63%)	57%
d	R = H, R′ = 2,4-diF (61%)	68%
e	R = H, R′ = 4-OCH_3 (64%)	56%
f	R = H, R′ = 3,4-diOCH_3 (78%)	49%
g	R = H, R′ = 2-NO_2 (76%)	40%
h	R = H, R′ = 4-NO_2 (73%)	52%
i	R = H, R′ = 3-CH_3 (70%)	76%
j	R = H, R′ = 2,4,6-triCH_3 (56%)	38%
k	R = H, R′ = 2-CN (80%)	30%
l	R = 3-OCH_3, R′ = 4-CH_3 (46%)	Traces
m	R = 6-OCH_3, R′ = 4-CH_3 (78%)	37%
n	R = 5-OCH_3, R′ = 4-CH_3 (71%)	28%
o	R = 4-OCH_3, R′ = 4-CH_3 (84%)	33%

It was also of mechanistic interest to note that the incorporation of even a single methoxy group in the donor ring (Entries l–o), led to a significant decrease in the yield, irrespective of its position, and indeed, in the case of the 3-methoxy derivative (Entry l) to complete destruction of the starting material. It has not escaped our attention that the production of a phenolic free radical inhibitor as the product of a radical reaction is somewhat unusual and the above observation is in accord with the trend that the more electron rich phenols are highly efficient antioxidants. Competitive hydrogen atom abstraction from the methoxy groups may also, of course be problematic.

Finally, as shown in Scheme 3, we have also extended this approach to the synthesis of heterocyclic systems, with the preparation of the sulphonates **5** and **6** in 73 and 76% yield, respectively, from their corresponding sulphonyl chlorides. The reactions of **5** and **6** under the conditions stated above afforded the unsymmetrical heterodiarylketones **7** and **8** in 48 and 34% yield, respectively, thus confirming once again the sensitivity of the reaction to steric hindrance.



Scheme 3.

In summary, the foregoing results provide a simple, inexpensive and experimentally convenient two step method for the construction of the 2-hydroxydiaryl ketone unit which bypasses the more commonly employed Lewis acidic conditions used for carbon–carbon bond formation.

Acknowledgements

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14. Satisfactory analytical (combustion and/or high-resolution mass) and spectral (IR, NMR and MS) data were obtained for all new compounds. Yields refer to purification by crystallisation or flash chromatography on silica gel.
15. Typical procedure for the synthesis of 2-hydroxydiarylketones: To a refluxing solution of **6** (2.81 g, 10 mmol), in chlorobenzene (50 ml) was added di-*tert*-butylperoxide (19 ml, 100 mmol). The solution was refluxed for 24 h under nitrogen. The solvent was evaporated giving a dark oil that was purified by column chromatography on silica gel eluted with petrol and dichloromethane furnishing (2-hydroxyphenyl)-(3,5-dimethylisoxazol-4-yl)-methanone, **8**, as a yellow solid (742 mg, 34%), mp 106–108°C (diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 6.90 (ddd, 1 H, $J=8.0$, $J'=7.2$ and $J''=0.7$ Hz, 5′-H), 7.04 (dd, 1 H, $J=8.6$ and $J'=0.7$ Hz, 3′-H), 7.41 (dd, 1 H, $J=8.0$ and $J'=1.7$ Hz, 6′-H), 7.52 (ddd, 1 H, $J=8.6$, $J'=7.0$ and $J''=1.7$ Hz, 4′-H), 11.7 (s, 1 H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.9 (CH_3), 13.0 (CH_3), 115.8 (C), 118.6 (CH), 119.1 (CH), 119.8 (C), 132.2 (CH), 137.1 (CH), 158.9 (C), 162.7 (C), 170.6 (C), 194.3 (C); IR (KBr): 2930, 1612, 1592, 1482, 1425, 1247, 1150, 1110, 918, 767 cm^{-1}; MS (FAB): 218 (M^{+1}, 100), 217 (M^+, 23), 200 (8), 177 (8), 161 (4). HRMS $C_{12}H_{12}NO_3$ requires: 218.0817; found: 218.0822. $C_{12}H_{12}NO_3$ (217.22) calcd: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.09; H, 5.21; N, 6.18.