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Micellar Reactions

Aerobic Oxidation in Nanomicelles of Aryl Alkynes, in Water at Room Temperature**

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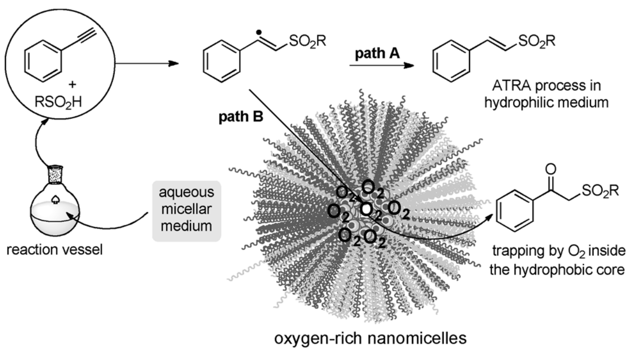
Abstract: *On the basis of the far higher solubility[7] of oxygen gas inside the hydrocarbon core of nanomicelles, metal and peroxide free aerobic oxidation of aryl alkynes to β-ketosulfones has been achieved in water at room temperature. Many examples are offered that illustrate broad functional group tolerance. The overall process is environmentally friendly, documented by the associated low E Factors.*

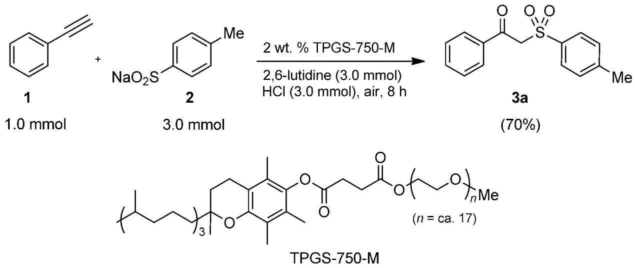
Reactions in alternative media represent one approach to decreasing the huge amounts of organic waste generated by use of organic solvents in organic chemistry.[1] While such options as ionic liquids, supercritical CO_2, and fluorinated media, among others, have made important inroads in this regard, the most likely and perhaps logical choice is water.[2] Although we have investigated many processes enabled by designer surfactants where water serves as the gross reaction medium,[3] synthetic advantage has yet to be taken of the well established far greater solubility of gases in organic media than in water.[4] Since our reported cross-couplings and related reactions take place within the lipophilic cores of tailor-made micellar arrays, gases, as well as reactants and catalysts, should likewise co-exist in high concentrations and be available to participate in a given transformation. Surprisingly, there appears to be limited methodology[5] of synthetic utility focused on the use of gases in micellar catalysis. Here we describe one such process involving dissolved oxygen serving as the stoichiometric oxidant, along with readily available aryl alkynes and sulfinic acids that leads to valuable β-ketosulfones under very mild, metal-free, and green conditions.

β-Ketosulfones can be derived from a radical reaction between an arylacetylene and a stoichiometric amount of a sulfinic acid. However, the short lifetime of the vinyl radical so generated[6] (Scheme 1) makes trapping with oxygen difficult and prevents the desired reaction from having any generality in a purely aqueous or wet organic solvent. On the other hand, by virtue of the hydrophobic effect[7] operating within the water-free lipophilic inner core of a nanomicelle, H-atom abstraction by a reactive vinyl radical by atom transfer radical addition (ATRA) from water or another molecule of alkyne should be minimized (path A). Rather, trapping of the vinyl radical by molecular oxygen is highly favored and ultimately leads to β-ketosulfone formation (path B). By contrast, related literature reports on this topic are far less environmentally friendly, as they take place in dry organic solvents at elevated temperatures with the use of metals and/or peroxide initiators,[8] and offer no opportunities to recycle the reaction mixture. β-Ketosulfones are highly desirable materials, known to have fungicidal,[9] antibacterial,[10] as well as other biological properties.[11] Moreover, numerous derivatives, such as olefins, disubstituted alkynes,[12] allenes,[13] and chiral vinyl sulfones[14] and ketones[13,14] have been prepared from such intermediates.



Scheme 1. Aerobic oxosulfonylation of arylacetylenes within nanomicelles in water.

A model reaction between phenylacetylene **1** with *p*-toluenesulfinic acid sodium salt **2** was run at ambient temperature in an aqueous medium containing 2 wt.% TPGS-750-M (Scheme 2).[15] The acid was generated in situ by the reaction of inexpensive **2** and HCl. Only traces of the desired product, however, were observed after 24 h. A large amount of unreacted phenylacetylene was recovered, along with byproducts, most likely due to rapid autoxidation of *p*-tolylsulfinic to the sulfonic acid and quenching of the vinyl radical by



Scheme 2. Aerobic difunctionalization of an arylacetylene.

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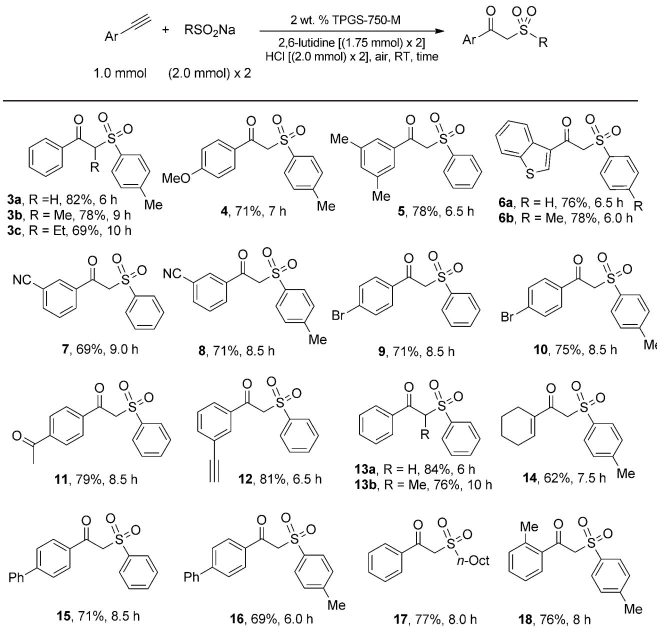
ATRA.[6b,16] Preventing autoxidation of a sulfinic acid to a sulfonic acid by introducing 2,6-lutidine into the reaction medium greatly improved formation of the desired product.[17] After stirring at room temperature for 8 h, β-ketosulfone **3a** was isolated in 70% yield, to the complete exclusion of the corresponding vinylsulfone.

Optimization of this conversion documented its dependence on several reaction variables, including 1) the choice of surfactant; 2) source of oxygen; 3) temperature; 4) base; 5) conditions for neutralization of the sodium arylsulfinate with HCl; 6) ratio of arylsulfinic acid to base; 7) equivalents of sulfinic acid needed to drive the reaction to completion; 8) surfactant concentration in water; 9) arylacetylene concentration in the surfactant; and 10) portion-wise addition of reagents. After extensive screening (see Supporting Information), the optimum conditions were determined to be: TPGS-750-M (2% weight percent) as surfactant in water, 2,6-lutidine as base, 4.0 equivalents of arylsulfinic acid, 0.3 M arylacetylene in the aqueous medium, along with ambient temperature and light.

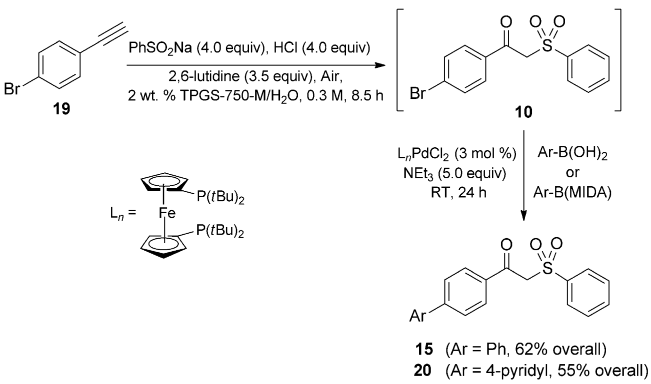
Substrate scope was next explored (Table 1). Good-to-excellent yields were obtained with electron-donating substituents on the aryl ring of the alkynes, leading to products **4**, **5** and **18**. Heteroaromatic and sensitive nitrile functional groups were all well tolerated, and 69–78% yields were obtained for aducts **6–8**. Challenging electron-withdrawing groups in the educts, nonetheless, afforded products bearing bromo (**9** and **10**), acetyl (**11**), ethynyl (**12**), cyano (**7** and **8**), and amide (**25** and **26**; Scheme 4) residues, Similarly, a representative *alkyl*sulfinic acid also led to the desired sulfone **17**. Electronic rather than steric effects were found to be of greater consequence, as no reaction was observed with a substrate containing CF_3 groups in the 3- and 5-positions of the aromatic ring of an arylacetylene. It is noteworthy that only one ethynyl group showed reactivity in 3-ethynyl phenylacetylene to afford product **12**. A cycloalkenyl group was also well tolerated (**14**).[18]

Sequential reactions involving initial β-ketosulfone formation are also possible. For example, after an initial reaction giving β-ketosulfone **10**, Suzuki–Miyaura couplings with either an arylboronic acid or MIDA boronate[19] within the same pot led to final products **15** and **20** in 62% and 55% overall yields, respectively (Scheme 3).

Table 1: Substrate scope of micellar aerobic difunctionalization of aryl acetylenes.

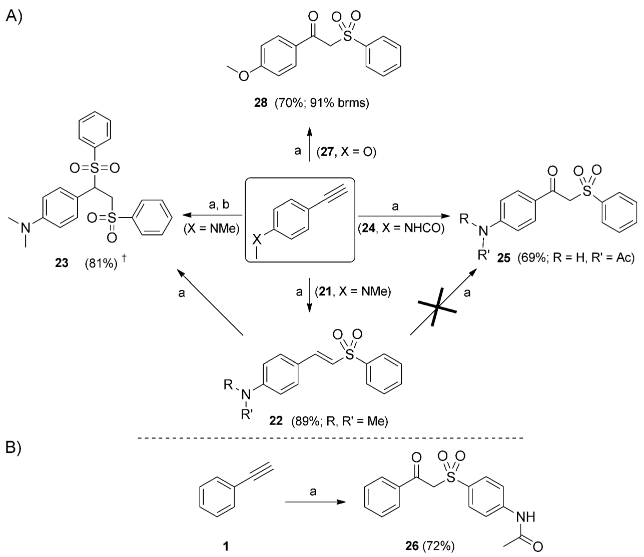


Conditions: 1 mmol, 0.3 M phenylacetylene in 2 wt.% TPGS-750-M in water, 4.0 mmol sodium *p*-toluenesulfinate, 4.0 mmol aq. HCl*, 3.5 mmol 2,6-lutidine (all these reagents were added in two portions in 80 min intervals), RT, air balloon. *After HCl addition to the solution of sodium *p*-toluenesulfinate in TPGS-750-M, the mixture was stirred for 2–3 min before addition of 2,6-lutidine (for details, see the Supporting Information).



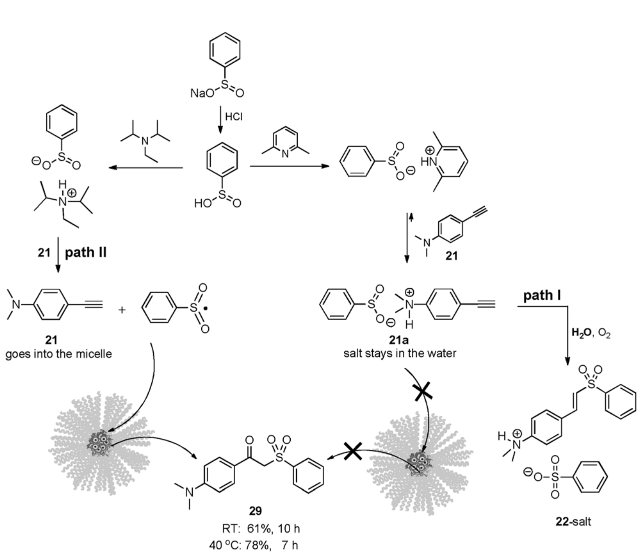
Scheme 3. Sequential 1-pot aerobic oxidation/Suzuki–Miyaura coupling.

To gain insight regarding the location of the reaction under micellar conditions, an arylalkyne **21** bearing a *p*-dimethylamino group on the aryl ring of the alkyne was subjected to protonation (aq. HCl) under aerobic oxidation conditions (Scheme 4A). Rather than the expected β-ketosulfone, only arylvinylsulfone **22** was obtained (89%). The water-soluble ammonium salt is unlikely to enter the oxygen-rich nonpolar lipophilic core of the micelle and hence, dioxygen trapping is precluded. Instead, the vinyl radical is converted to the corresponding olefin **22** by an ATRA process. In the presence of twice the typical amount of sulfinic acid, a second addition of arylsulfonyl to **22** ensues forming **23** in 81% yield. Similar results were obtained when **22** was isolated and re-subjected to the optimized reaction conditions, leading to **23** in 84% isolated yield. Protection of the amine functionality in **21** (X = NH) as the derived acetamide **24** (X = NHCO) negated salt formation and led, exclusively, to β-ketosulfone **25** in 69% yield. Inverting the location of the acetamide group from arylacetylene **24** to the arylsulfinic acid coupling partner gave similar results (Scheme 4B): β-ketosulfone product **26** was isolated in 72% yield. Replacing nitrogen in the arylalkyne with oxygen (i.e., **27**, X = O) afforded results similar to those from **24**, again suggesting that the reaction is taking place within the micellar core. In this case, β-ketosulfone **28** was obtained in 70% isolated yield (91% yield based on recovered starting material).



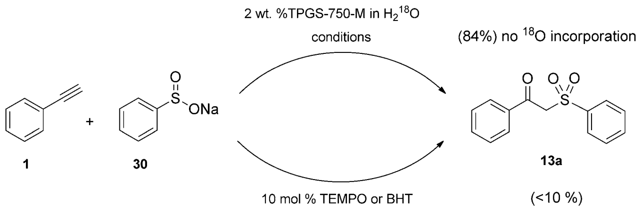
Scheme 4. Sequence of events within micelles leading to products. Conditions: a) 1 mmol, 0.3 M arylacetylene in 2 wt.% TPGS-750-M, 4.0 mmol sodium *p*-toluenesulfinate in (A); sodium 4-(*N*-acetylamino)-benzenesulfinate in (B), 4.0 mmol aq. HCl, 3.5 mmol 2,6-lutidine (all reagents were added in two portions in 80 min intervals), RT, air balloon, up to 24 h. After HCl addition to the solution of sodium *p*-toluenesulfinate in TPGS-750-M, the mixture was stirred for 2–3 min. before addition of 2,6-lutidine (see Supporting Information). b) Addition of extra 4.0 (1×4) equivalents of arylsulfinic acid at 1.5 h intervals. † Yield 84% when reaction run with **22** as starting material.

Additional evidence regarding the likely location of these reactions could be obtained by altering the reaction medium such that the conversion of *p*-dimethylaminophenylacetylene **21** to the corresponding β-ketosulfone occurred (Scheme 5). To achieve salt-free conditions, the stronger base *N*,*N*-diisopropylethylamine (DIPEA) was used in place of 2,6-lutidine. As postulated, DIPEA inhibited formation of salt **21a** thereby allowing uncharged **21** to gain entry to the micellar core facilitating generation of the desired product **29** (path II). Variable yields were obtained depending upon the reaction temperature (e.g., 61% at room temperature, 78% at 40°C). Comparatively weaker bases such as pyridine, 2,4,6-collidine, and 4-picoline gave the same undesirable results seen with 2,6-lutidine, where protonation took place leading to a polar intermediate that remains in the poorly oxygenated water and produces an olefinic product (path I).



Scheme 5. Use of base strength to determine reaction pathway.

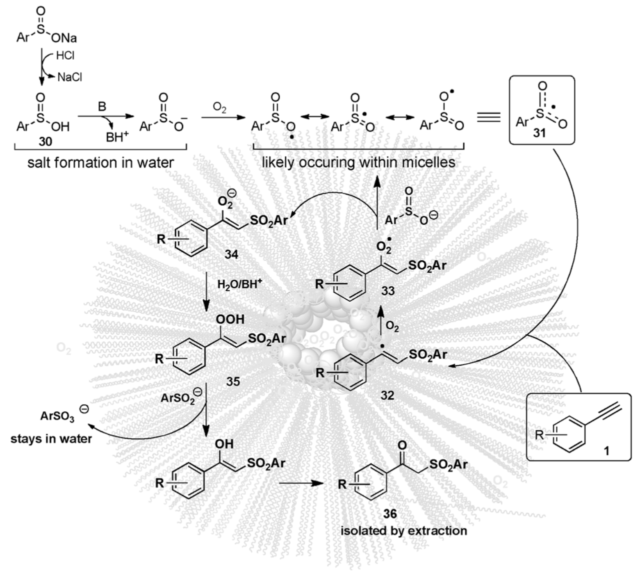
To confirm that air, rather than water, was the source of oxygen in the products, a reaction in 2% TPGS-750-M in ^{18}O-labelled water was conducted. As expected, no incorporation of ^{18}O was observed in the product (Scheme 6, top). The



Scheme 6. Isotopic labeling and radical quenching experiments.

radical nature of these reactions was further confirmed by inclusion of catalytic amounts of inhibitors BHT or TEMPO; product **13a** was formed only to the extent of 7 and 9%, respectively (Scheme 6, bottom).

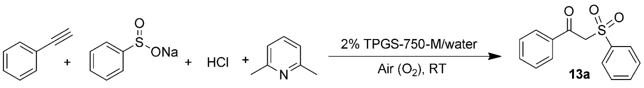
A plausible mechanism for the overall sequence starts from in situ generation of free arylsulfinic acid **30** from its sodium salt and HCl (Scheme 7). No aerobic oxidation reaction occurs without this initial neutralization, followed by exposure to 2,6-lutidine as base. Thus, generation of sulfonyl radical **31** requires a lutidinium salt under ambient light, rather than the corresponding sodium salt. An aryl sulfonyl radical is then generated after single electron transfer (SET) to oxygen that is highly localized within the micelle. Radical **31** then adds to arylacetylene **1** to give vinyl radical **32**



Scheme 7. Mechanistic rationale for the conversion of **1** to β-ketosulfone **37**.

which is then trapped by oxygen to generate intermediate **33**. SET from another molecule of arylsufinate to **33** generates arylperoxide anion **34**. The newly generated arylsulfonyl radical enters the next cycle, while **34** undergoes protonation either by water or a pyridinium cation to form arylhydroperoxide species **35**. Oxidation of arylsulfinate to arylsulfonate by **35** generates an enol that tautomerizes to final product **36**. The arylsulfonic acid generated as a byproduct remains in the aqueous phase, while the organic product can be isolated by extraction.

An E Factor[20] of 5.3 was determined on the basis of organic solvent utilized for the model system (Scheme 8).[21]



$$\text{E Factor} = \frac{\text{organic waste (kg)}}{\text{product (kg)}} = 5.3$$

Recycling of the reaction medium

Run	% Yield **13a**
1st	78
2nd	70
3rd	53

Scheme 8. E Factor and recycling studies.

This value compares quite favorably with those typical of the pharma and fine chemicals industries,[22] as well as related literature.[8,23] Moreover, recycling of the aqueous mixture led to good-to-excellent yields being obtained over three reaction cycles. The yield for the third cycle was noticeably lower, but this was due to practical considerations, as buildup of the sulfonic acid salt caused thickening and, therefore, problems with stirring on the scale at which the reaction was run.

In summary, an environmentally friendly aerobic oxidation has been developed for converting arylalkynes and arylsulfinate salts to β-ketosulfones. This process relies on the far greater solubility of oxygen in hydrocarbon media as found within micellar arrays than in the surrounding water. The process, enabled by a commercially available designer surfactant, is metal-free, takes place in water at room temperature using air as the stoichiometric oxidant, and is amenable to recycling of the aqueous reaction medium in which the amphiphile remains. Minimal amounts of organic solvent can be used to recover the desired product, which leads to a low E Factor. Experiments supporting a radical-based process are provided, along with data suggesting that the oxidation is taking place within the lipophilic core of the nanomicelles present in aqueous solution.

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