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One-pot approach for the regioselective synthesis of β-keto sulfones based on acid-catalyzed reaction of sulfonyl chlorides with arylacetylenes and water

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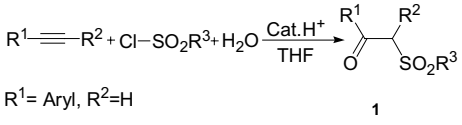
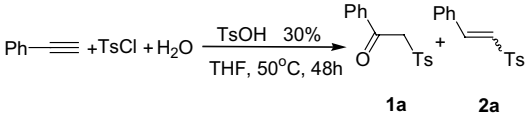
Abstract—Reaction of sulfonyl chlorides with arylacetylenes and water in the presence of a catalytic amount of sulfonic acid in THF provided β-keto sulfones in good yields with excellent regioselectivity.

Sulfone compounds have drawn increasing attention in organic synthesis. Among their derivatives, β-keto sulfones display a broad range of synthetic versatilities[1,2] and some exhibit fungicidal activity.[3] Considering the importance of β-keto sulfones, the development of synthetic methodology for β-keto sulfones is of great interest. The existing approach includes: (i) acylation of α-sulfonyl carbanions;[4] (ii) alkylation of metallic arene sulfinates;[5] (iii) oxidation of β-keto sulfides, β-keto sulfoxides or β-hydroxy sulfones;[6] (iv) reaction of sulfonyl chlorides with silyl enol ethers catalyzed by a ruthenium(II) complex;[7] (v) reaction of diazo sulfones with aldehydes catalyzed by $SnCl_2$;[8] (vi) free-radical rearrangement of enol sulfonates.[9] However these methods are deficient in some aspects such as the use of strong base, strict reaction conditions, complicated procedures or unavailable starting materials. The most attractive one seems to be the direct hydroxyl sulfonylation of alkynes, in which C–S and C–O bond also formed in a one-pot procedure. To the best of our knowledge, reaction of sulfonyl chlorides with alkynes resulting in β-keto sulfones has not been reported so far. Herein we would like to report a one-pot procedure for the synthesis of β-keto sulfones via the reaction of sulfonyl chlorides with arylacetylenes and water in the presence of a catalytic amount of sulfonic acid (Scheme 1).



Scheme 1.

Encouraged by our previous study of preparation of β-hydroxyl sulfones based on the acid-promoted reaction,[10] we investigated the reaction of phenylacetylene with *p*-toluenesulfonyl chloride (TsCl) and water in the presence of a catalytic amount of *p*-toluenesulfonyl acid (TsOH) in THF at 50 °C. Interestingly, 1-phenyl-2-(*p*-toluenesulfonyl) ethanone **1a** was formed in good isolated yield with excellent regioselectivity (Scheme 2).[11] Besides the desired compound **1a**, styryl-*p*-tolyl-sulfone **2a** was also obtained in 10% isolated yield. These two products **1a** and **2a** could be easily separated by using column chromatography. It is noted that the result is dependent on which solvent was used. Using $CHCl_3$ or DMSO solvent instead of THF, no product **1a** was obtained. In addition, using alcohols such as MeOH, BuOH or $PhCH_2OH$ instead of water, the same product was also obtained.



Scheme 2.

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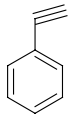
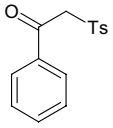
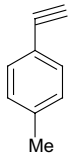
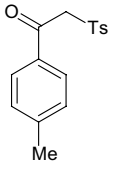
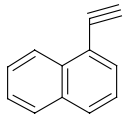
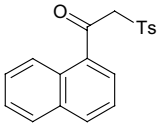
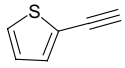
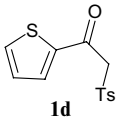
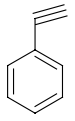
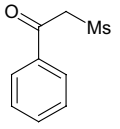
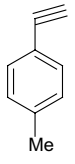
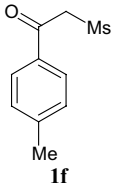
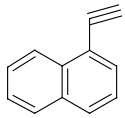
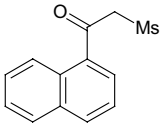
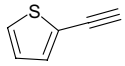
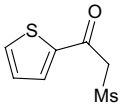
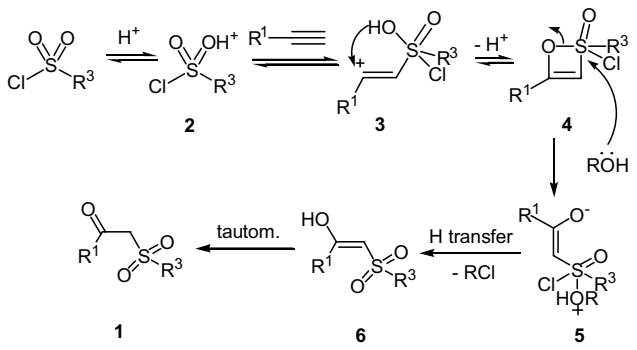
To investigate the reaction further, we mixed TsCl, phenylacetylene and water together in the absence of H^+ in THF for 48 h at 50 °C, however no desired product **1a** was obtained. This indicated that sulfonic acid was necessary to initiate the reaction. Moreover, to confirm the desired product did not derive from direct reaction of TsOH with alkynes, we mixed TsOH, phenylacetylene and water in THF at 50 °C for 48 h. No product **1a** was formed. This result indicated that the role of sulfonic acid was a catalyst and unlikely to be a reactant.

Table 1 showed several representative examples of sulfonic acid catalyzed reactions of sulfonyl chlorides with various arylacetylenes and water affording β-keto sulfones under mild condition. Using methanesulfonyl chloride (MsCl) or TsCl and terminal alkynes, the regioselectivity of product was always favouring introduction of sulfone group to the terminal carbon of alkynes and the oxo group to the benzylic position. Besides the desired product of β-keto sulfones, corresponding vinyl sulfones have been detected as side products in 10% to 20% isolated yields (entries 1, 2, 4, 5 and 6)

Table 1. Reaction of sulfonyl chlorides with arylacetylenes and water

Entry	Arylacetylenes	Sulfonyl chloride	Reaction time (h)	Product	Yield (%)[a]
1		TsCl	48	 **1a**	49
2		TsCl	48	 **1b**	48
3		TsCl	72	 **1c**	55
4		TsCl	72	 **1d**	54
5		MsCl	48	 **1e**	53
6		MsCl	48	 **1f**	45
7		MsCl	72	 **1g**	51
8		MsCl	72	 **1h**	49

[a] Yield of isolated pure products after column chromatography on silica gel.



Scheme 3.

and a trace amount of **2h** was detected by GC–MS (entry 8). For the reaction of sulfonyl chlorides with 1-ethynyl-naphthalene, compound **1c** or **1g** was obtained as the sole product (entry 3 and 7). However, when terminal aliphatic alkynes such as 1-hexyne and internal alkynes such as 1-phenyl propyne were used, only trace desired products were detected by GC–MS even with the increased reaction temperature and prolonged reaction time. The possible reason is that aliphatic alkyne is not so active as arylacetylene and in the case of internal alkyne, the hindrance of substituted group could also retard the reaction.

Based on the above results, a stepwise mechanism for the formation of β-keto sulfones is proposed in Scheme 3. In the presence of protic acid, electrophile **2**, that is more reactive is formed. It's attacked by arylacetylenes to produce carbocation **3**, which subsequently undergoes deprotonation to form four-membered oxathietene **4**. Then the cleavage of the O–S bond by a protic compound such as water or alcohol, results in intermediate **5**, which undergoes H-transfer and elimination of HCl or RCl in sequence to give enol **6**. It produces β-keto sulfones **1** instantly via tautomerism into a much stable keto form.

In conclusion, we have developed a new method for the synthesis of β-keto sulfones. The advantages of this method over previous ones include simple procedure, mild condition and readily available starting materials.

The investigations into the mechanism of the formation of side products and expansion of the reaction scope are now being undertaken in this laboratory.

Acknowledgements

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10. Xi, C.; Lai, C.; Chen, C.; Wang, R. *Synlett* **2004**, 1595–1597.
11. *Representative procedure for sulfonic acid catalyzed reaction of sulfonyl chloride with alkyne and water*: *Preparation of 1-phenyl-2-(p-toluenesulfonyl) ethanone* (**1a**): *p*-Toluenesulfonyl chloride (228 mg, 1.2 mmol) and *p*-toluenesulfonic acid (52 mg, 0.30 mmol) were dissolved in 5 mL THF. To the solution was added phenylacetylene (116 mL, 1.0 mmol) and H_2O (22 mL, 1.2 mmol) at ambient temperature. The mixture was warmed up to 50 °C and stirred for 48 h. Then it was quenched with H_2O and the aqueous layers were extracted with ethyl acetate (20 mL) for 3 times and the combined organic layers were dried over Na_2SO_4. The extract was evaporated and the crude product was purified by column chromatography on silica gel (EtOAc/petroleum ether = 1:4) to afford compound **1a** (134 mg) as white solid in 49% isolated yield. ^1H NMR ($CDCl_3$, $SiMe_4$): δ 2.36 (s, 3 H), 4.65 (s, 2H), 7.22–7.43 (m, 5H), 7.69 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ 21.7, 63.6, 128.6 (2C), 128.8 (2C), 129.3 (2C), 129.8 (2C), 134.3, 135.8 (2C), 145.4, 188.2; ESI-MS: 281($M+Li^+$).