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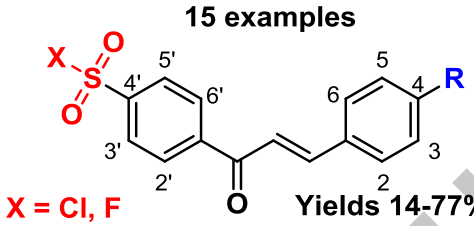

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Efficient synthesis of chalcone-4'-sulfonyl chlorides and fluorides

Dmitrii Semenok[a,b], Alexey Kletskov[c], Evgenij Dikusar[c], Vladimir Potkin[c], and Oleg Lukin[a,*]

[a] *Skolkovo Institute of Science and Technology, 143026 Moscow, 3 Nobel St., Russia*
[b] *Moscow Institute of Physics and Technology, 141700 Dolgoprudny, Moscow Region, Russia*
[c] *Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, 13 Surganov St., 220072 Minsk, Belarus*

**Corresponding author. Tel./fax: +7 495 270 41481; e-mail: o.lukin@skoltech.ru, oleg.lukin@gmail.com*

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ABSTRACT

A library of 4'-chloro- and 4'-fluorosulfonyl-substituted chalcones was prepared *via* the aldol-type condensation reactions of 4-acetylbenzene-1-sulfonyl halides with various aromatic aldehydes, either in absolute ethanol or glacial acetic acid, in the presence of dry HCl. This represents the first examples of chalcone sulfonyl halides in which the phenone ring bears one of these functional groups. The reactivity of the chalcone sulfonyl halides were strongly dependent on the styrene ring substituents; sulfonyl chlorides reacted with most nucleophiles (e.g. amines, alcohols), while sulfonyl fluorides reacted only with charged nucleophiles (e.g. phenolates).

1. Introduction

Compounds bearing a carbonyl group conjugated with a carbon-carbon double bond are important subunits of biologically active species[1] and monomers for functional polymers.[2,3] Recent interest in these compounds is associated with the design of covalent inhibitors,[4] which represent promising drugs for the treatment of thrombosis and various cancers. In this context, benzylidene acetophenones (chalcones) are attractive building blocks for introducing the conjugated motif into potential drugs or monomers. Notably, the substituted chalcone structural unit (Fig. 1) is found in many marketed and investigational drugs as well as other biologically active compounds.[5]

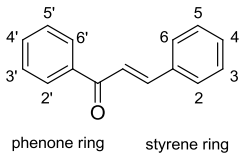
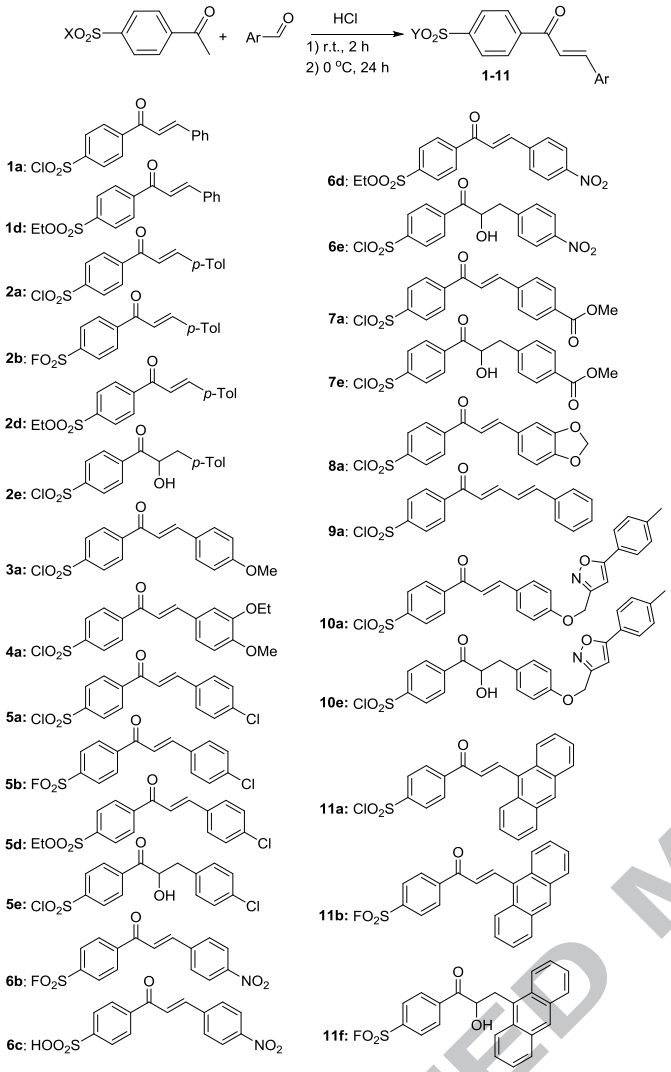


Figure 1. Structure and aromatic carbon atom numbering scheme of the parent chalcone.

Therefore, the development of reliable methods for the preparation of building blocks containing the chalcone scaffold is of significance in drug discovery and materials chemistry. Previously reported methods for incorporation of the chalcone subunit include the use of chalcone acyl-[3] or sulfonyl-[6-8] chlorides. The latter are especially useful synthetic building blocks since the biologically relevant sulfo-group is introduced along with the valuable chalcone fragment. The preparation and use of diverse chalcone-2-,[8] 3-,[6,7] and 4-sulfonyl chlorides[6,7] *via* direct sulfochlorination of the corresponding chalcones with chlorosulfonic acid has been reported. However, there is only one report describing the preparation of a chalcone-4'-sulfonyl fluoride *via* the condensation reaction of benzaldehyde with SO_2F-substituted acetophenone.[9] To the best of our knowledge, there are no reports describing chalcone-4'-sulfonyl chlorides in which the chlorosulfo-group is attached to the phenone ring (Fig. 1). Given the potential of chalcone sulfonyl chlorides in drug discovery and materials chemistry, it seems important to have access to all isomeric forms. Herein, we describe the synthesis of diverse chalcone-4'-sulfonyl chlorides and fluorides.

2. Results and Discussion

The synthetic route towards chalcone-4'-sulfonyl halides is outlined in Scheme 1. Commercially available 4-acetylbenzenesulfonyl chloride or 4-acetylbenzenesulfonyl fluoride (prepared from the chloride *via* a Finkelstein-type reaction with sodium fluoride) were reacted at room temperature with various aldehydes in ethanol or glacial acetic acid in the presence of dry HCl.



Scheme 1. Chalcone-4'-sulfonyl halides and their derivatives obtained as by-products.

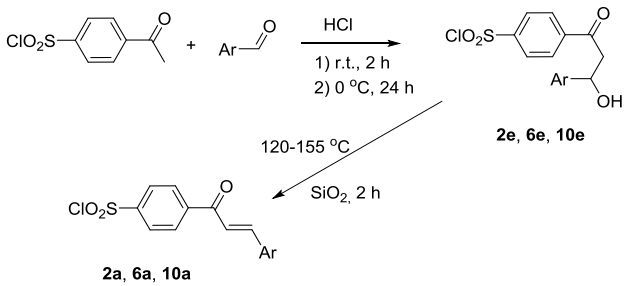
The products typically crystallized from the reaction mixture upon standing for 24 hours at 5 °C. A number of reaction conditions were investigated; all details are given in the ESI (Table S1), while the most important results are presented in Table 1. The reaction outcomes and yields were substantially dependent on the aldehyde structure. Thus, the presence of electron donating groups (**2**-**4**, **8**), electron withdrawing groups (**5**-**7**), bulky substituents (**11**), and branched elements (**8**, **10**) on the aldehyde component required individual adjustments to the reaction conditions. In the case of electron donating substituents (Table 1, entries 5, 9, and 18), chalcone-4'-sulfonyl chlorides were obtained in 30-46% yield. In some cases (*e.g.* entry 10) the aldol product **2e** was the major component of the reaction; this could be easily dehydrated by heating in the solid phase to give chalcone **2a**. The limitations of the reaction include the unsuccessful use of 2-furancarbaldehyde, which polymerized under the acidic conditions, and the attempted synthesis of (*E*)-4-(3-(phenanthren-9-yl)acryloyl)benzene-1-sulfonyl chloride, which rapidly hydrolyzed to the corresponding sulfonic acid. The reactions of 4-acetylbenzenesulfonyl chloride with aldehydes bearing electron withdrawing groups in ethanol gave the corresponding ethyl sulfonates as the sole products (Entries 3-4). In comparison, the use of glacial acetic acid as the solvent led to chalcone-4'-sulfonyl chlorides as the major products (Entries 10-18). However, aldol adducts **5e**-**7e** were formed in considerable quantities along with the corresponding chalcones (Entries 13-15). In the case of *p*-nitrobenzaldehyde, aldol product **6e** (Entry 14) was the major component of the condensation reaction. This compound was transformed into chalcone **6a** by heating at 155 °C in the presence of SiO_2 to facilitate dehydration (Scheme 2).

Bulky aldehydes (*e.g.* **11**) did not affect the reaction and the corresponding chalcone was isolated in 30% yield (Entry 18). Similarly, sulfonyl chloride **10a** bearing a branched isoxazole derivative was obtained in 45% yield. The reaction by-product aldol **10e** which was isolated in 27% yield, was transformed into **10a** using solid phase thermolysis (Scheme 2).

Table 1. Isolated yields of sulfonyl halides and side-products as shown in Scheme 1.

Entry	X	Ar	Solvent	**Products** (Yield) Y = Cl (**a**), F (**b**), OH (**c**), OEt (**d**); aldol (Y = Cl (**e**), F (**f**))
1	Cl	1	EtOH	**1a** (39%), **1d** (11%)
2	Cl	2	EtOH	**2a** (45%), **2d** (20%)
3	Cl	5	EtOH	**5d** (34%)
4	Cl	6	EtOH	**6d** (15%)
5	Cl	10	EtOH	**10a** (45%), **10e** (27%)
6	F	2	EtOH	**2b** (77%)
7	F	5	EtOH	**5b** (58%)
8	F	6	EtOH	**6b** (14%)
9	F	11	EtOH	**11b** (46%), **11f** (14%)
10	Cl	2	AcOH	**2a** (16%), **2e** (32%)
11	Cl	3	AcOH	**3a** (30%)
12	Cl	4	AcOH	**4a** (46%)
13	Cl	5	AcOH	**5a** (33%), **5e** (11%)
14	Cl	6	AcOH	**6c** (7%), **6e** (43%)
15	Cl	7	AcOH	**7a** (34%), **7e** (10%)
16	Cl	8	AcOH	**8a** (50%)
17	Cl	9	AcOH	**9a** (21%)
18	Cl	11	AcOH	**11a** (30%)

The synthesis of chalcone-4'-sulfonyl fluorides (Entries 6-9) proceeded with better yields (up to 77%) compared the corresponding sulfonyl chlorides. However, as in the case of sulfonyl chlorides, aldehydes bearing electron withdrawing groups and bulky groups gave low yields (e.g. 14% for **6b**) and aldol products (**11f**). Unlike the preparation of chalcone-4'-sulfonyl chlorides, the synthesis of the corresponding sulfonyl fluorides is much less sensitive to the reaction media on account of their moderate reactivity. For example, ethanol was the most suitable solvent for the synthesis of chalcone-4'-sulfonyl fluorides and alcoholysis, as observed with sulfonyl chlorides, was not detected.



Compound	Conditions (T, °C / time)	Yield (%)
2a:	120 / 2 h	75
6a:	155 / 4 h	35
10a:	130 / 2 h	45

Scheme 2. Formation of aldol products and their solid-state dehydration.

The use of other solvents for the synthesis of sulfonyl fluorides, such as methanol and glacial acetic acid, resulted in incomplete conversion and by-product formation (see Table 1, Scheme 2, and ESI).

In order to investigate the reactivity of the obtained chalcone-4'-sulfonyl halides, the reactions of selected sulfonyl halides were carried out with 4-aminophenol, 6-aminohexan-1-ol, and 3-methoxypropylamine. Thus, the reaction of sulfonyl fluoride **5b** with 4-aminophenol in the presence of triethylamine gave sulfonate **5B** in 58% yield; the amino-group remained unaffected. However, **5b** did not react with 6-aminohexan-1-ol or 3-methoxypropylamine under these conditions. At the same time, sulfonyl fluoride **2b** showed moderate reactivity in the reaction with 3-methoxypropylamine yielding sulfonamide **2B** (40% conversion after 72 h, yield 81%). Compared with **2b,** sulfonyl chloride **8a** exhibited greater reactivity in the reaction with 3-methoxypropylamine, giving sulfonamide **8A** in 94% yield. Unlike compound **5b**, different chalcone sulfonyl chlorides reacted unselectively with 4-aminophenol, leading to mixtures of *O*- and *N*-sulfonylated products. Reactions of chalcone-4'-sulfonyl chlorides with aliphatic aminoalcohols proceed selectively to give the corresponding sulfonamides. For example, the reaction of sulfonyl chloride **7a** with 6-aminohexan-1-ol gave sulfonamide **7A** in 84% yield.

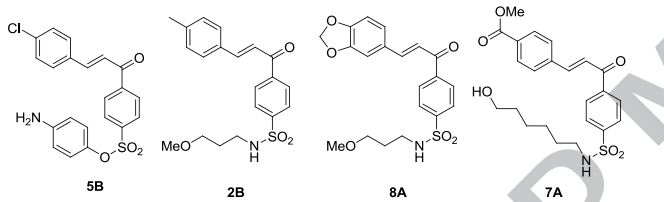


Figure 2. Products of selected reactions of chalcone-4'-sulfonyl halides with different nucleophiles

3. Conclusion

The described approach allows the preparation of hitherto unavailable chalcone-4'-sulfonyl halides bearing different substituents on the styrene ring. Despite the apparent ease of the aldol reaction, the condensation is highly sensitive to the aldehyde nature, solvent, temperature, and reaction time. The reactivity of the sulfonyl halides was dependent on the styrene ring substituent and the halide, resulting in highly variable yields (14-77%). The prepared sulfonyl halides are promising building blocks for medicinal and materials chemistry.

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References and Notes

1. Serafimova, I. M.; Pufall, M. A.; Krishnan, S.; Duda, K.; Cohen, M. S.; Maglathlin, R. L.; McFarland, J. M.; Miller, R. M.; Frödin, M.; Taunton, J. *Nature Chem. Biol*. **2012**, *8*, 471.
2. Schmidt G. M. J. *Pure Appl. Chem*. **1971**, *27*, 647.
3. van Heijst, J.; Corda, M.; Lukin, O. *Polymer* **2015,** *70*, 1.
4. (a) Ostrem, J. M.; Peters, U.; Sos, M. L.; Wells, J. A.; Shokat, K. M. *Nature* **2013**, *503*, 548. (b) Lewis, H. D.; Liddle, J.; Coote, J. E.; Atkinson, S. J.; Barker, M. D.; Bax, B. D.; Bicker, K. L.; Bingham, R. P.; Campbell, M.; Chen, Y. H.; Chung, C.; Craggs, P. D.; Davis, R. P.; Eberhard, D.; Joberty, G.; Lind, K. E.; Locke, K.; Maller, C.; Martinod, K.; Patten, C.; Polyakova, O.; Rise, C. E.; Rüdiger, M.; Sheppard, R. J.; Slade, D. J.; Thomas, P.; Thorpe, J.; Yao, G.; Drewes, G.; Wagner, D. D.; Thompson, P. R.; Prinjha, R. K.; Wilson D. M. *Nature Chem. Biol*. **2015**, *11*, 189.
5. According to www.drugbank.ca (accessed in September 2017) there are 13 marketed and over 20 investigational drugs bearing the chalcone substructure.
6. Cremlyn, R. J.; Swinbourne, F. J.; Shode, O. O. *J. Chin. Chem. Soc*. **1984**, *31*, 383.
7. Cremlyn, R. J.; Swinbourne, F. J.; Bassin, P.; Dane, D.; Higgins, K.; Mitchell, P. *Phosphorus, Sulfur, and Silicon* **1991**, *63*, 385.
8. Patel, C.; Bassin, J. P.; Scott, M.; Flye, J.; Hunter, A. P.; Martin, L.; Goyal, M. *Molecules* **2016**, *21*, 861.
9. Orlov, V. D.; Vorob'eva, N. P.; Tishchenko, A. A.; Pikalev, O. M.; Popov, V. I.; Yagupol'skii, L. M. *Chem. Heterocycl. Comp*. **1991**, *27*, 942.

Supplementary Material

Supplementary material (experimental procedures and spectral data) associated with this article can be found, in the online version, at

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- Synthesis of hitherto unavailable chalcone sulfonyl halides was achieved
- For every condensation case the optimal reaction conditions were developed
- The halogen type and substituents impact the reactivity of the sulfonyl halides

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