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Four-Component Reaction Leading to Highly Functionalized Sulfoalkoxy Carbonyl Compounds

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A facile regio- and diastereoselective four-component protocol has been developed involving an α,β -unsaturated carbonyl compound, a cyclic ether, a sulfonic acid and a 10 halogen reagent to access highly *anti*- α -bromo- β -sulfoalkoxy carbonyl derivatives. Some of these products have high toxicity against human chronic myeloid leukemia cells.

One of the major driving forces in organic chemistry is to expand our capacity to access new chemical structures. Methods 15 for diversity-oriented synthesis continue to be developed in order to deliver more compounds for drug discovery and related areas.^[1] Among those synthetic methods, multicomponent reactions (MCR) are fundamental masterpieces of synthetic efficiency and routinely offered new opportunities for building 20 complex molecules in more convergent and atom economic manner.^[2, 3] Though success is accounted on MCR, it remains challenging to devise new reaction sequences in this area.^[4] It is well known that nucleophilic ring opening of highly energetic aziridines, epoxides and activated cyclopropanes can generate 25 active intermediates. These intermediates are labile to initiate subsequent reactions leading to the formation of products from multicomponents.^[5] However, it is less documented that other relatively stable cyclic ethers such as oxetane, tetrahydrofuran (THF) and tetrahydropyran were involved in ring opening -linked ³⁰ cascade reactions.^[6] The versatility of α , β -unsaturated carbonyl compounds for conjugate addition is well-recognized,^[7] particularly in MCR and cascade reactions.^[8] To merge nucleophilic ring opening activity of cyclic ethers^[9] and the reactivity of α , β -unsaturated carbonyl compounds, we envisioned

³⁵ a reaction sequence shown in Scheme 1.



Scheme 1. NBS mediated new paradigm of four component reaction

As the other two components, the acid BA^[10] and an enol capturer E,^[11] are involved, it assumes a four-component reaction leading ⁴⁰ to α -substituted- β -alkoxy carbonyl derivatives. These compounds can be valuable as synthesis in synthetic organic chemistry^[12] or as candidates in the discovery of anticancer agents.^[13] It should also be noted that conjugate addition of *O*-nucleophiles to α , β -

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unsaturated carbonyl compounds is less common and successful 45 examples were achieved by using *N*-heterocyclic carbenes or strong basic species as catalysts.^[14] Therefore, it remains intriguing to find suitable acid and electrophile to realize the proposed transformation.

To realize the proposed reaction sequence, we used chalone **1a** as ⁵⁰ the carbonyl component, THF as the cyclic ether and N-

bromosuccinimide (NBS) as the enol capturer (Table 1). Fortunately, the addition of *para*-toluenesulfonic acid **2a** (PTSA) led to the formation of the sulfoalkoxy product **3a** in 20% yield (Table 1, entry 1). When solid acid Nefion NR 50 or Amberlyst-

⁵⁵ 15 was applied, yields were slightly improved (Table 1, entries 2, 3) along with the formation of 2,3-dibromo-1,3-diphenylpropan-1-one.^[15]

Table 1. Acid catalyzed nucleophilic conjugate addition of THF to $chalcone^{[a]}$

Ph	0 + Ph	D₃H <u>NXS, THF</u> Catalyst		¥000
₆₀ 1a	2a		3a X = B	r X
Entry	Catalyst	NXS	Temp. (°C)	Yield (%) ^[b]
1		NBS	25	20
2 ^[c]	Nefion (NR 50)	NBS	25	36
3	Amberlyst-15(H)	NBS	25	29
4	AlCl ₃	NBS	25	52
5	ZnCl ₂	NBS	25	58
6	ZnCl ₂	NBS	-78	5
7	ZnCl ₂	NBS	0	38
8	ZnCl ₂	NBS	65	24
9 ^[d]	ZnCl ₂	NBS	25	83
10	ZnCl ₂	NCS	25	41
11	ZnCl ₂	NIS	25	Trace

[a] Chalcone 1a (0.10 mmol), acid 2a (0.15 mmol), catalyst (10 mol%), and NXS (0.15 mmol, 1.5 Equiv.) were stirred for 24 h under argon. [b] Isolate yield. [c] 20 mol% of solid acid was used. [d] NBS (0.15 mmol, 1.5 Equiv.) was added slowly (0.05 mmol, 0.5 Equiv) as a solution in ⁶⁵ THF (0.2 mL).

These results indicated the acid strength of the reaction system played a key role. Further, we tested some Lewis acid catalysts to explore additional reaction activation pathway.^[16] The yield increased to 52% and 58%, respectively, in the presence of AlCl₃ 70 and ZnCl₂ at 10 mol% catalyst loading (Table 1, entries 4, 5). We



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then used $ZnCl_2$ as the catalyst and optimized the reaction conditions.^[17,18] It was observed that reactions at lower or higher temperatures resulted in reduced yields (Table 1, entries 6-8). Significantly, the addition sequence of the reaction components

- ⁵ had major affects on reaction yields.^[15] Accordingly, modifying the manoeuvre by slow addition of NBS as a solution in THF led to a high yield of 83% (Table 1, entry 9). Comparatively, low yield was obtained in case of NCS and almost no desired product was found in case of NIS (Table, entries 10, 11). The analytical
- ¹⁰ data of **3a** by ¹H NMR, ¹³C NMR, HSQC and HRMS confirmed the formation of single diastereomer. Profoundly, in ¹H NMR, coupling constant of J=9.2 Hz between the protons at C-1 and C-2 position at 4.85 ppm and 5.08 ppm, respectively, revealed a *trans* configuration. This assured high *anti*-diastereoselectivity
- ¹⁵ around the double bond due to enol capturing at the opposite face of an oxonium cation.^[19] The formation of 1,4-addition product disfavored the possibility of bromonium cation in this transformation.
- Although sulfonic acids have been used as catalysts for ring-²⁰ opening polymerization of lactones and cyclic carbonates, ^[20] however, to the best of our knowledge, this is the first example in which sulfonic acid was involved for the ring opening of a cyclic ether. More significantly, it led to an apparent conjugate addition of oxygen-centred nucleophilic specie to α , β -unsaturated ²⁵ carbonyl compounds.^[21]

Having identified $ZnCl_2$ as appropriate Lewis acid and NBS as the enol capturer, we tested other sulfonic acids in combination with ketone **1a** (Table 2).

Table 2. Sulfoalkoxylation of chalcone using various sulfonic acid^[a]

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[a] Chalcone **1a** (0.1 mmol), acid (0.15 mmol, 1.5 Equiv.) and $ZnCl_2$ (10 mol%) were stirred in THF (1 mL) for 5 min. NBS (0.15 mmol, 1.5 Equiv.) was added slowly (0.05 mmol, 0.5 Equiv) as a solution in THF (0.2 mL) and stirred for 24 h. [b] Isolate yield.

³⁵ Although CF₃SO₃H did not participate in this transformation,^[22] excellent yield was achieved in the presence of CH₃SO₃H (Table 2, entry 1). Benzenesulfonic acid and sterically demanding sulfonic acids were readily accommodated with good yields (Table 2, entries 2-4). It was observed that 2,4-40 dinitrobenzenesulfonic acid and 4-nitrobenzenesulfonic acid produced higher yields as compared to 4-chlorobenzenesulfonic acid (Table 2, entries 5-7). Less acidic partner, 4-hydroxybenzenesulfonic acid and 4-aminosulfonic acid produced lower yields (Table 2, entries 8, 9). Under the same conditions,

45 naphthionic acid did not give appreciable amount of product probably due to its poor solubility in the reaction solvent (Table View Article Online DOI: 10.1039/C4CC10403J

Having successfully demonstrated the possibility of sulfoalkoxylation with different sulfonic acids, we next explored ⁵⁰ other α , β -unsaturated compounds as reaction substrates, and achieved moderate to excellent yields in many cases (Table 3).

Table 3. Sulfoalkoxylation of carbonyl compounds^[a]



_		_	_	
Entry	Product	R_1	R_2	Yield
				(%) ^[b]
1	4b	$CH(CH_3)_2$	CH ₃	35
2	4c	C_6H_5	CH ₃	45
3	4d	$4-ClC_6H_4$	C_6H_5	79
4	4e	4-BrC ₆ H ₄	C_6H_5	72
5	4 f	$4-FC_6H_4$	C_6H_5	69
6	4g	$4-NO_2C_6H_4$	C_6H_5	42
7	4h	$4-NH_2C_6H_4$	C_6H_5	NR
8	4i	C_6H_5	4 ⁻ -ClC ₆ H ₄	56
9	4j	C_6H_5	4 $ CH_3C_6H_4$	91
10	4 k	C_6H_5	4 - CF ₃ C ₆ H ₄	92
11	41	C_6H_5	4 ⁻ OMeC ₆ H ₄	88
12 ^[c]	4 m	C_6H_5	OCH ₂ CH ₃	92
13 ^[c]	4n	$4-BrC_6H_4$	OCH ₂ CH ₃	83
14 ^[c]	40	C_6H_5	OCH ₂ C ₆ H ₅	81
15 ^[c]	4p	C_6H_5	$OC(CH_3)_3$	75
16 ^[c]	4q	C_6H_5	Н	Trace

[a] α , β -Unsaturated carbonyl compound (0.10 mmol), **2a** (0.15 mmol, 1.5 Equiv.) and ZnCl₂ (10 mol%) were stirred in THF (1 mL) for 5 min. NBS (0.15 mmol, 1.5 Equiv.) was added slowly (0.05 mmol, 0.5 Equiv) as a solution in THF (0.2 mL) and stirred for 24 h. [b] Isolate yield. [c] Reaction mixtures were stirred for 36 h.

The reaction with the aliphatic ketone produced 4b in low yield 60 (Table 3, entry 1) and slightly higher yield was obtained for aryl substituted unsaturated compound (Table 3, entry 2). The reaction was tolerant for a variety of functional groups and yields were significantly affected by the electronic nature of the constituents on the benzene ring. In general, chalcones with a halogen atom 65 on either benzene ring afforded the desired products, however, the yields decreased when more electronegative halogen atom was present at C-4 position (Table 3, entries 3-5), and chlorine atom at the C-4' position led to lower yield of 56% (Table 3, entry 3 vs entry 8). Other substrate with electron withdrawing 70 group, 4-NO₂ chalcone produced desired product in lower yield (Table 3, entry 6), indicating that decreasing electron density of the C=C bond was detrimental. A substrate bearing 4-NH₂ did not participate in the reaction for unknown reasons (Table 3, entry 7). High yield was obtained with 4'-Me chalcone (Table 3, entry 9). 75 The substrate containing 4'-CF₃ constituent was also able to achieve a highest yield of 92% (Table 3, entry 10). Substrate having electron donating group, 4'-OMe chalcone returned excellent yield (Table 3, entry 11). It was observed that esters are also amenable to this protocol and products were isolated in 80 excellent yields after longer reaction time (Table 3, entries 12-15). Good yields were recorded for ethyl cinnamate and, substrate having electron withdrawing group, 4-Br ethylcinnamate (Table

^{2 |} Journal Name, [year], [vol], 00-00

3, entries 12, 13). Besides, ester moiety was altered and the increased size of the ester moiety led to lower yield (Table 4, entries 14-15). Attempts to use α,β -unsaturated aromatic aldehyde have been unsuccessful, thus, only a trace amount of the ⁵ desired product was detected (Table 3, entry 16).

- The scope of sulfoalkoxylation appeared to be quite broad and other cyclic ethers were also found competent nucleophile in lieu of THF under optimized conditions using **1a**, **2a** and NBS as the reaction partners (Table 4). High yield was obtained in case of
- ¹⁰ oxetane (Table 4, entry 1) and mixture of diastereomers was isolated in case of substituted THF (Table 4, entry 2). Moreover, the reaction with tetrahydropyran also afforded the expected product in 53% yield (Table 4, entry 3).

Table 4. Sulfoalkoxylation of chalcone 1a and sulfonic acid 2a in the 15 presence of different cyclic ethers^[a]



[a] Chalcone **1a** (0.10 mmol), **2a** (0.15 mmol, 1.5 Equiv.) and $ZnCl_2$ (20 mol%) were stirred in the corresponding cyclic ether (2 mL) for 5 min. NBS (0.2 mmol, 2 Equiv.) was added slowly (0.05 mmol, 0.5 Equiv) and stirred for 36 h. [b] Isolate yield.

- ²⁰ Further, based on the results of a number of probe experiments,¹⁵ we favour a mechanism shown in Scheme 2. The reaction may involve the activation of the carbonyl functionality, followed by a reversible nucleophilic conjugate addition of THF leading to the enolate intermediate **A**. Subsequently, the electrophilic
- ²⁵ brominating source RSO₃Br, produced by the reaction of a sulfonic acid and NBS, adds bromine to the double bond of the enol at the face opposite to the oxonium cation. Finally, an intermolecular attack of the sulphate anion to the oxonium cation results in the ring opening of THF and the formation of ³⁰ sulfoalkoxy products.
- It was noticed to us that these sulfoalkoxylated compounds were reminiscent of busulfan (butane-1,4-diyl dimethyl disulfate), a clinical useful drug for the treatment of myeloproliferative disorder such as chronic myeloid leukemia (CML) since 1950.^[23]
- ³⁵ A number of busulfan analogs have been prepared and diverse biological activities have been demonstrated.^[13, 24] Because these compounds act as alkylating agents,^[25] it remains challenging to find new structures to reduce side effects and long-term damages associated with the problem of their low specificity.^[26, 27] We
- ⁴⁰ tested the anticancer activity of compound **3a** and **3b** against human CML cell line K562 cells (Fig. **1**). It was found that these two compounds had substantially higher (> 6-fold) activity than busulfan. However, it remains unclear to what extent the presence of the bromine atom contributed to the cell-killing activity.

⁴⁵ Noting that about 30 sulfoalkoxylated compounds with a broad structural diversity are readily available now according to the new protocol described herein, it is appealing to <u>User Analysical Contine</u> the structures and to explore their activities against CML cells as well as other tumour cells.



Scheme 2. Plausible reaction mechanism of sulfoalkoxylation



Figure 1. Cellular toxicity assay results. Human chronic myeloid leukemia 55 K562 cells were incubated at 37 °C for 48 h in present of 130 μM busulfan, 3a or 3b. Assays were done by using the CCK-8 kit (Dojindo Laboratories, Kumamoto, Japan) according to the manufacturer's protocol. Experiments were done in triplicate and error bars indicated s.d.

- In summary, diverse *anti*- α -bromo- β -sulfoalkoxy carbonyl ⁶⁰ compounds were formed under mild conditions in moderate to excellent yields *via* highly regio- and diastereoselective fourcomponent reaction involving a halogenating agent, a cyclic ether, a sulfonic acid and an α , β -unsaturated carbonyl compound. This protocol holds great promise for the design of similar MCR
- 65 that will ultimately tame the even more useful and highly functionalized compounds. Moreover, preliminary results indicated that these sulfoalkoxy compounds may be explored as potential anticancer agents.

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