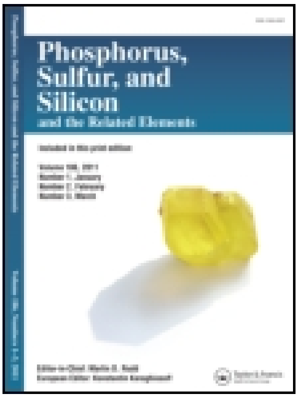

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THREE-COMPONENT REACTION OF β-KETOSULFONE, FORMALDEHYDE, AND THIOL OR THIOPHENOL IN WATER

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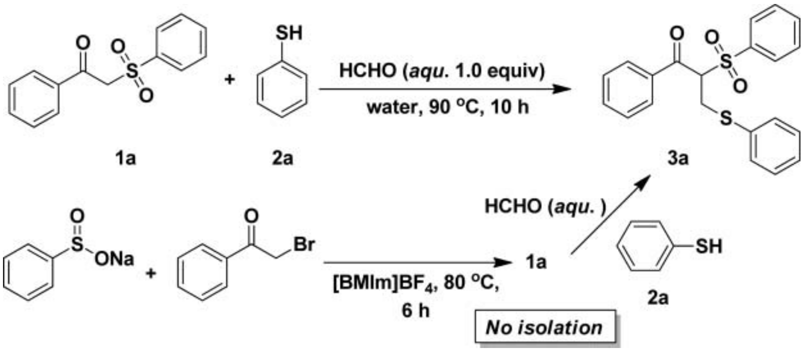
GRAPHICAL ABSTRACT



Abstract *A three-component reaction of β-ketosulfone, formaldehyde, and thiol or thiophenol was developed. The reaction was performed in pure water under a catalyst-free condition, and the corresponding Mannich-type thioethers were obtained in good to excellent yields. Finally, a one-pot stepwise four-component reaction of sodium benzenesulfinate, α-bromoketone, β-ketosulfone, and thiophenol was also developed.*

Keywords β-Ketosulfone; mannich reaction; organic reaction in water; three-component reaction

INTRODUCTION

In 1980, Breslow discovered that the Diels–Alder reaction performed in water can be subject to huge rate accelerations.[1] Since then, organic reactions in water have attracted

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considerable interest in recent times because of their environmental acceptability and unique reactivity that cannot be attained in conventional organic solvents.[2] On the other hand, the ever increasing demand for novel medicinally active compounds and the laborious process of lead discovery and optimization have resulted in the continuous search for simple and efficient methods for generation of libraries for biological screening. In this context, multicomponent reactions are a promising tool for synthetic chemists, since they allow complicated molecules to be created using one reaction in a fast, efficient, and timesaving manner.[3] Particularly, multicomponent reactions in water have gained much attention because of their green characteristics in meeting the sustainability requirements of current organic synthesis.[4] Although some promising results were obtained in this field, in order to further improve the synthetic efficiency and extend the applicability of water solvent, new examples of water-mediated multicomponent reactions that enable selective formation of complex molecules from simple substrates are still appealingly needed.

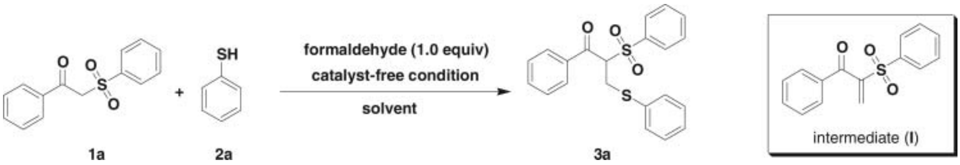
β-Ketosulfones are active C—H acids, and have been widely used in many organic transformations.[5] However, multicomponent reactions by using a β-ketosulfone as a nucleophile have been rarely investigated.[6] Because C—H acids are generally very active in the electrophilic alkylation of an aldehyde, it is conceivable that a β-ketosulfone should also be a viable nucleophile in this type of reaction. Recently, electrophilic reactions of an aldehyde with two kinds of nucleophiles have frequently been considered as an effective method for developing three-component reactions.[7] In view of the high reactivity of β-ketosulfones, we envisaged that, under suitable conditions, β-ketosulfones might be good nucleophiles to react with aldehyde and another nucleophile, accomplishing a new three-component reaction. Herein, we wish to report our preliminary results on this topic. A three-component reaction of formaldehyde, β-ketosulfone, and thiol or thiophenol will be presented in this communication, which provides a specific class of thioethers in good to excellent yields. Particularly, the reaction was performed in pure water without the use of any catalyst.

RESULTS AND DISCUSSION

Initially, a three-component reaction of β-ketosulfone **1a**, formaldehyde, and thiophenol **2a** was investigated. As shown in Table 1, when formalin was used as source of formaldehyde, the reaction proceeded very well in water, and a thioether **3a** was obtained in 90% of yield after 10 h of reaction at 90 °C (entry 1). Paraformaldehyde that is a solid at room temperature can also be used in this system, but the yield is inferior as compared with formalin (entry 2). Another form of formaldehyde, 1,3,5-trioxane, was also examined, however, only a trace amount of **3a** was obtained (entry 3). Further investigation revealed that the reaction was also affected by reaction time and temperature, and the optimal condition was found to be 10 h and 90 °C (entries 4 and 5). The solvent also played an important role in this reaction. Addition of some extra amount of water into the system was proved to be helpful for improving the reaction yield (entry 6). Replacement of water with ethanol, acetonitrile, and 1,4-dioxane results in an appreciable decrease of the reaction yield (entries 7 to 9). In order to check the applicability of our reaction in practical synthesis, the reaction was then performed in a large scale, i.e., 10 mmol. As we expected, the yield of **3a** remains unchanged (entry 10), and therefore, the presented reaction herein is, indeed, valuable for organic synthesis.

The substrate scope with respect to both thiophenol and β-ketosulfone was then examined. As shown in Table 2, when **1a** was used as substrate, various thiophenols and thiols

Table 1 Three-component reaction of **1a** with **2a** and formaldehyde in different solvents[a]



Entry	Formaldehyde form	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	HCHO *aqu.* (37%)	water	10	90	90
2	$(HCHO)_n$	water	10	90	78
3	$(HCHO)_3$	water	10	90	trace
4	HCHO *aqu.* (37%)	water	6	90	70
5	HCHO *aqu.* (37%)	water	10	70	61
6[b]	HCHO *aqu.* (37%)	water	10	90	77
7	HCHO *aqu.* (37%)	ethanol	10	90	82
8	HCHO *aqu.* (37%)	CH_3CN	10	90	68
9	HCHO *aqu.* (37%)	1,4-dioxane	10	90	59
10[c]	HCHO *aqu.* (37%)	water	10	90	90

[a] Solvent: 1.0 mL, **1a**: 1.0 mmol, **2a**: 1.0 mmol, formaldehyde: 1.0 mmol; [b] No extra water solvent was added; [c] The reaction scale: 10 mmol.

could be used in the three-component reaction, and the corresponding thioethers were obtained in generally high yields. The scope of the reaction with respect to β-ketosulfone was next investigated and also found to be excellent. As Table 3 illustrates, many β-ketosulfones could be employed without significantly affecting the yield of the three-component reaction with **2a** and formalin. Particularly, β-ketosulfones containing sulfur- or oxygen-heterocycle functionalities were also applied in the reaction uneventfully (entries 7 and 8). It should be noted that synthesis of **3a**-type thioethers has been rarely investigated before. The only available method was reported by Yamauchi,[8] who utilized *N*-(methylthiomethyl) piperidine-HCl salt as a methylthiomethylation reagent of β-ketosulfone. Obviously, our method showed a clear advantage in terms of using cheap and easily available material as substrate and avoiding the generation of waste.

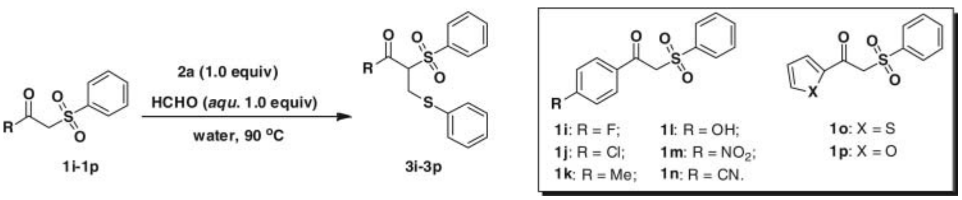
The model three-component reactions might proceed through a cascade reaction pathway involving (i) a Knovenagel reaction between **1a** and formaldehyde that was known to be preferably performed in water,[9] which provides an α-methylene-β-ketosulfone (**I**, see

Table 2 Three-component reactions of **1a** with formalin and thiophenol or thiol in water[a]

Entry	Thiophenol or thiol		Product	Time (h)	Yield (%)
1	4-methoxythiophenol	**2b**	**3b**	10	91
2	4-chlorothiophenol	**2c**	**3c**	10	86
3	2-methylthiophenol	**2d**	**3d**	10	92
4	2-methoxythiophenol	**2e**	**3e**	10	91
5	3,5-dimethylthiophenol	**2f**	**3f**	10	93
6	benzylthiol	**2g**	**3g**	12	95
7	cyclohexylthiol	**2h**	**3h**	18	87

[a] Water: 1.0 mL, **2a**: 1.0 mmol, HCHO: 1.0 mmol, thiol or thiophenol: 1.0 mmol.

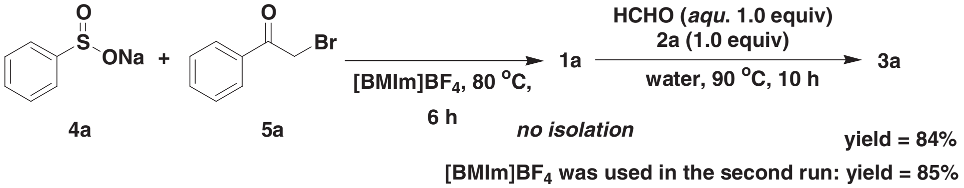
Table 3 Substrate scope for β-ketosulfones[a]



Entry	β-ketosulfone	Product	Time (h)	Yield (%)
1	**1i**	**3i**	10	93
2	**1j**	**3j**	12	95
3	**1k**	**3k**	10	92
4	**1l**	**3l**	18	90
5	**1m**	**3m**	10	86
6	**1n**	**3n**	10	91
7	**1o**	**3o**	24	88
8	**1p**	**3p**	24	94

[a] Acetonitrile: 1.0 mL, indole: 1.0 mmol, α,β-unsaturated compound: 1.0 mmol.

Table 1); and (ii) Michael addition of thiophenol to the intermediate (**I**) to form **3a**. It is well known that β-ketosulfone could be obtained by a reaction of sodium benzenesulfinate and α-bromoketone.[10] In view of the fact that this is a typical S_N2-type reaction, we envisaged that the condition of the synthesis of β-ketosulfones might be compatible with the present three-component reaction. We, thus, investigated the feasibility of preparing **3a** from sodium benzenesulfinate and α-bromoketone. As shown in Scheme 1, **1a** was initially prepared in an ionic liquid, [BMIm]BF_4, from **4a** and **5a**. By monitoring the reaction with TLC, we are able to know the end of the first reaction. When the other materials including formalin, **2a** and water were added into the reaction system, after 10 hours of reaction at 90 °C, **3a** was obtained in 84% of yield. After removal of all the organic components by extraction with ethyl acetate, the recovered aqueous solution was then subjected to a vacuum condition (10 mmHg). After 30 min of treatment at 80 °C, [BMIm]BF_4 could be recovered quantitatively. In a reaction with the recovered ionic liquid, 85% of yield was obtained, indicating the good performance of [BMIm]BF_4.



Scheme 1 One-pot stepwise synthesis of **3a** from **4a** and **5a**.

In conclusion, a three-component reaction of β-ketosulfone, formaldehyde, and thiophenol or thiol in water was developed. Many substrates could be used in these reactions, and the corresponding products were obtained in good to excellent yields. This reaction was found to be compatible with the synthesis of β-ketosulfones from sodium benzenesulfinate and α-bromoketones. Thus, a one-pot stepwise reaction of **4a**, **5a**, formaldehyde, and **2a** was then developed successfully.

EXPERIMENTAL

All reagents were obtained from commercial suppliers and used without further purification. All melting points were determined uncorrected. NMR spectra were measured using a Bruker AV400 Avance spectrometer at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C), respectively. Chemical shifts were reported in ppm relative to TMS in $CDCl_3$. IR spectra were recorded on a Nicolet6700 FT spectrometer in KBr with absorptions in cm^{-1}.

General Procedure

All reactions were conducted in a 10 mL U-type tube equipped with magnetic stirring. In a typical reaction, **1a** (260.0 mg, 1.0 mmol) and **2a** (110.0 mg, 1.0 mmol) were mixed with formalin (37 wt%, 81.0 mg, 1.0 mmol) and water (1.0 mL) under air. The mixture was then heated at 90 °C for 10 h. After the reaction, the mixture was cooled to room temperature, and then extracted with ethyl acetate (4.0 mL × 3). The obtained organic phase was then combined and dried with anhydrous Na_2SO_4. After concentration, the solution was subjected to isolation with preparative TLC. The desired product **3a** was obtained in 90% of yield (344.0 mg).

Selected Spectroscopic Data of New Compounds

1-Phenyl-2-(phenylsulfonyl)-3-(phenylthio)propan-1-one (3a): Yellow solid, mp: 80–81 °C; ^{1}H NMR: 3.47 (dd, $J_a = 11.2$ Hz, $J_b = 13.6$ Hz, 1H), 3.69 (dd, $J_a = 2.8$ Hz, $J_b = 13.2$ Hz, 1H), 5.22 (dd, $J_a = 2.8$ Hz, $J_b = 11.2$ Hz, 1H), 7.18–7.29 (m, 5H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.50 (t, $J = 8.0$ Hz, 2H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.70–7.79 (m, 4H); ^{13}C NMR: 31.4, 68.5, 127.7, 128.7, 129.1, 129.3, 129.4, 129.7, 130.9, 133.4, 134.3, 134.7, 136.3, 137.2, 191.4; IR: 3077, 2928, 1686, 1584, 1482, 1442, 1413, 1331, 1308, 1211, 1132, 1054, 1020, 998, 915, 834, 764, 734; HRMS *m/z* (ESI) calcd. for $C_{21}H_{18}NaO_3S_2$ $[M + Na]^+$ 405. 0595 found 405.0588.

2-(Phenylsulfonyl)-3-(phenylthio)-1-(thiophen-2-yl)propan-1-one (3o): Yellow liquid; ^{1}H NMR: 3.41 (dd, $J_a = 11.6$ Hz, $J_b = 13.6$ Hz, 1H), 3.66 (dd, $J_a = 2.8$ Hz, $J_b = 13.2$ Hz, 1H), 4.92 (dd, $J_a = 2.8$ Hz, $J_b = 11.6$ Hz, 1H), 7.04 (dd, $J_a = 3.2$ Hz, $J_b = 4.8$ Hz, 1H), 7.20–7.28 (m, 5H), 7.44–7.54 (m, 3H), 7.64 (tt, $J_a = 1.2$ Hz, $J_b = 7.6$ Hz, 1H), 7.71 (dd, $J_a = 1.2$ Hz, $J_b = 4.8$ Hz, 1H), 7.76 (dd, $J_a = 1.2$ Hz, $J_b = 8.0$ Hz, 2H); ^{13}C NMR: 31.1, 70.9, 127.4, 128.7, 129.2, 129.4, 129.8, 130.8, 133.1, 134.5, 134.6, 136.2, 136.3, 144.5, 182.8; IR: 3099, 2930, 1721, 1657, 1581, 1514, 1474, 1448, 1412, 1353, 1271, 1244, 1155, 1087, 846, 821, 738; HRMS *m/z* (ESI) calcd. for $C_{19}H_{16}NaO_3S_3$ $[M + Na]^+$ 411.0159 found 411.0150.

Supplementary Data

Selected data for products **3b–3p** are available. Supplementary data associated with this article can be found in the online version.

REFERENCES

1. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980,** 102, 7816-7817.
2. Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009,** 109, 725-748.
3. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: New York, **2005**; pp. 944-945.
4. Gu, Y.; De Sousa, R.; Frapper, G.; Bachmann, C.; Barrault, J.; Jérôme, F. *Green Chem.* **2009,** 11, 1968-1972.
5. Pulkkinen, J.; Aburel, P. S.; Halland, N.; Jorgensen, K. A. *Adv. Synth. Catal.* **2004,** 346, 1077-1080.
6. Kuninobu, Y.; Matsuzaki, H.; Nishi, M.; Takai, K. *Org. Lett.* **2011,** 13, 2959-2961; (b) Huang, X.; Xue, J. *J. Org. Chem.* **2007,** 72, 3965-3968; (c) Marco, J. L. *J. Org. Chem.* **1997,** 62, 6575-6581; (d) Kumar, D.; Sundaree, M. S.; Patel, G.; Rao, V. S.; Varma, R. S. *Tetrahedron Lett.* **2006,** 47, 8239-8241.
7. Qu, Y.; Ke, F.; Zhou, L.; Li, Z.; Xiang, H.; Wu, D.; Zhou, X. *Chem. Commun.* **2011,** 47, 3912-3914.
8. Yamauchi, M.; Katayama, S.; Watanabe, T. *Synthesis* **1982,** 14, 935-936.
9. Frapper, G.; Bachmann, C.; Gu, Y.; De Sousa, R. C.; Jérôme, F. *Phys. Chem. Chem. Phys.* **2011,** 13, 628-636.
10. Kumar, D.; Sundaree, S.; Rao, V. S.; Varma, R. S. *Tetrahedron Lett.* **2006,** 47, 4197-4199.