Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2024, **34**, 709–710
Mendeleev Communications

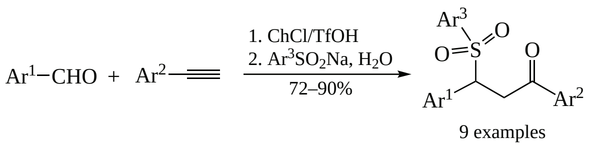
One-pot two-step synthesis of γ-keto sulfones in deep eutectic solvent

Lisha Ye,[a] Zhida Zhao,[b] En-xue Lei[c] and Liang Wang*[c]

[a] *Ningbo University of Finance and Economics, 315175 Zhejiang, P. R. China*
[b] *Ningbo University of Technology, 315211 Zhejiang, P. R. China*
[c] *School of Chemical and Pharmaceutical Engineering, Changzhou Vocational Institute of Engineering, 213164 Changzhou, P. R. China. Fax: +86 5198 633 2059; e-mail: lwcczu@126.com*

DOI: 10.1016/j.mencom.2024.09.027

Acidic deep eutectic solvent was prepared from choline chloride and trifluoromethanesulfonic acid at room temperature. Reaction between aromatic aldehydes and arylacetylenes in this solvent gave chalcones whose *in situ* reaction with sodium arenesulfinates in water successfully provided γ-keto sulfones in good yields. This deep eutectic solvent could be easily recovered and reused for several runs.



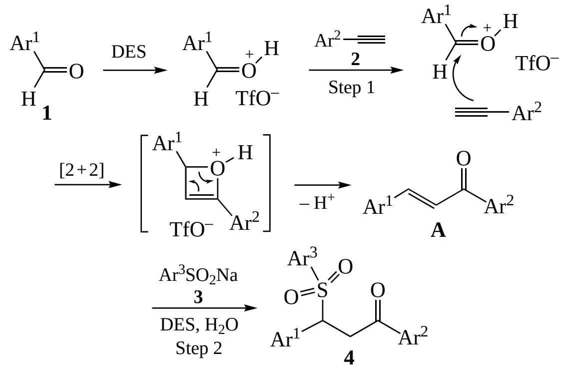
Keywords: γ-keto sulfones, deep eutectic solvent, aromatic aldehydes, arylacetylenes, sodium arenesulfinates, one-pot synthesis.

γ-Keto sulfones are very important and useful organic compounds, which have a wide range of applications in the field of pharmaceuticals and functional materials.[1–3] The most convenient way to access γ-keto sulfones is the sulfa-Michael reaction. Diverse sulfonyl sources including sulfinic acids,[4] sulfinates,[5,6] sulfonyl imines,[7] sulfonyl hydrazine[8] and *N*-tosylhydrazones[9] successfully reacted with chalcones to deliver the target γ-keto sulfones. However, most of the reported methods suffered from the drawbacks such as unsatisfactory yields, harsh reaction conditions and the use of toxic organic solvents or excessive amount of corrosive acids.

In past decades, the application of deep eutectic solvents (DESs) in organic synthesis has received extensive attention.[10] Those DESs were mainly composed of quaternary ammonium salts with hydrogen bond donors. Easy preparation, cheap starting materials, good biodegradability, low flammability and low toxicity make them popular in synthetic chemistry.[11] In recent years, our group has also made some attempts in this field.[12–14] Just recently, our group realized the sulfa-Michael reaction in choline chloride/*p*-toluenesulfonic acid (ChCl/TsOH) deep eutectic solvent.[15] This kind of DES not only showed good catalytic activity but also could be recovered and reused for several runs.

With our interests in organic transformations in DESs, and in order to broaden the substrates for sulfa-Michael reaction, we herein reported a one-pot, two-step synthesis of γ-keto sulfones. As shown in Scheme 1, we assumed that aldehydes **1** and alkynes **2** could generate chalcone derivatives of type **A** *via* the [2 + 2] cycloaddition reaction in a strongly acidic DES at room temperature (generally, chalocones are prepared from aldehydes and ketones in the presence of a strong base under heating). Without isolation, the chalcones were supposed to be treated with aqueous sodium arenesulfinates **3**, and upon the nucleophilic addition with the assistance of acidic DES the desired γ-keto sulfones **4** might be formed.

To verify the above hypothesis, initially, some acidic DESs were prepared and evaluated for the synthesis of simplest chalcone ($Ar^1 = Ar^2 = Ph$, see Scheme 1, step 1). It is worth noting that the acid should have a significant effect on both two steps of the reaction, thus the selection of a suitable acidic DES is the key factor. Unfortunately, some common acidic DESs reported in the literature did not show any catalytic activity in this reaction even if the reaction was prolonged (Table 1, entries 1–4). Pleasingly, switching the DES to ChCl/TfOH (1 : 1) provided the desired chalcone in 65% yield after 3 h (entry 5). Further survey suggested that ChCl/TfOH (1 : 1.5) was the optimal (entry 6) and gave chalcone in 89% yield. It should be



Scheme 1

Table 1 Optimization of the reaction conditions for step 1.[a]

Entry	DES (molar ratio)	*T*/°C	*t*/h	Yield of chalcone[b] (%)
1	ChCl/TsOH (1 : 1)	25	12	0
2	ChCl/$HO_2C(CH_2)_nCO_2H$[c] (1 : 1)	25	12	0
3	ChCl/citric acid (1 : 1)	50	12	0
4	ChCl/$FeCl_3$ (1 : 1)	25	12	0
5	ChCl/TfOH (1 : 1)	50	3	65
6	ChCl/TfOH (1 : 1.5)	25	3	92
7	ChCl/TfOH (1 : 2)	25	3	84
8	TfOH[d]	25	3	61

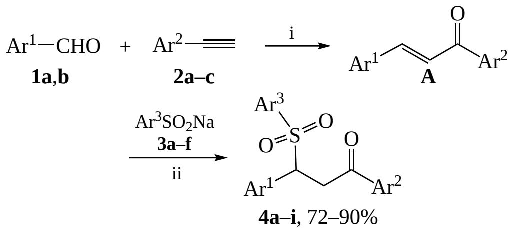
[a] Reaction conditions: PhCHO **1a** (0.2 mmol), PhC≡CH **2a** (0.3 mmol), DES (1 ml). [b] Isolated yield of chalcone. [c] n = 0, 1 and 2. [d] TfOH (1 equiv.).

pointed out that the viscosity of ChCl/TfOH would decrease with increasing molar ratio of TfOH to ChCl and the high viscosity of ChCl/TfOH would decrease its catalytic activity. Also, the acidity of ChCl/TfOH (1 : 2) is too strong, and some by-products were observed during the reaction (entries 5–7). It is worth noting that when 1 equiv. of TfOH was added, the reaction was very violent (entry 8), and byproduct such as styryl triflate was detected. This result indicates that in the DES medium, the reaction between TfOH and phenylacetylene is slowed down. Thus, ChCl/TfOH (1 : 1.5) mixture was of choice.

Next, we tried the one-pot synthesis of γ-keto sulfone **4a** (Scheme 2). After the step 1 was complete, aqueous sodium *p*-toluenesulfinate **3a** was directly added to the mixture without isolation of chalcone. The reaction proceeded very rapidly (within 20 min), and a large number of white solids were precipitated. The filtered substance was pure enough and needed no further purification. The DES is dissolved in water, and it can be recovered by rotary evaporation to remove the water (see Online Supplementary Materials). This simple protocol afforded the γ-keto sulfone **4a** in 90% yield (overall yield from two steps).

The substrate scope was then explored (see Scheme 2).[†] All the reactions proceeded well to give the desired γ-keto sulfones in good yields. Picolinaldehyde **2b** also showed good reactivity to deliver the corresponding product **4b**, albeit in a moderate yield. Likewise, other arylacetylenes **2b**,**c** reacted well to afford products **4c** and **4d**. A range of sodium arenesulfinates **3a–f** were then evaluated, and all of them gave the corresponding products in good yields (**4e–i**, 78–88%). Sodium alkanesulfinates such as sodium methanesulfinate and sodium trifluomethanesulfonate were not compatible and no reaction was observed.

The gram-scale (5 mmol) synthesis of **4a** was also performed and it was obtained in 80% yield. Also, using this model reaction as example, we checked the reusability of DES ChCl/TfOH. Once the reaction was finished, water was added and the product was filtered off. Ethyl acetate was then added to extract the residual organic components. After removing the water by rotary evaporation, the DES was thus recovered. Recycle studies showed that the DES could be reused in up to five consecutive runs with slight loss of the yields (90, 86, 82, 80 and 74%, respectively). Since TfOH was not only a catalyst, but also a stoichiometric reagent, its efficiency gradually decayed after several cycles. Also, the presence of large amounts of residual inorganic salts might influence the intrinsic structure of DES.



1a Ar^1 = Ph
1b Ar^1 = 2-pyridyl

2a Ar^2 = Ph
2b Ar^2 = 4-$MeOC_6H_4$
2c Ar^2 = 4-ClC_6H_4

3a Ar^3 = 4-MeC_6H_4
3b Ar^3 = 4-$MeOC_6H_4$
3c Ar^3 = 4-ClC_6H_4
3d Ar^3 = 4-BrC_6H_4
3e Ar^3 = 2-MeC_6H_4
3f Ar^3 = Ph

4a $Ar^1 = Ar^2$ = Ph, Ar^3 = 4-MeC_6H_4
4b Ar^1 = 2-pyridyl, Ar^2 = Ph, Ar^3 = 4-MeC_6H_4
4c Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, Ar^3 = 4-MeC_6H_4
4d Ar^1 = Ph, Ar^2 = 4-ClC_6H_4, Ar^3 = 4-MeC_6H_4
4e $Ar^1 = Ar^2$ = Ph, Ar^3 = 4-$MeOC_6H_4$
4f $Ar^1 = Ar^2$ = Ph, Ar^3 = 4-ClC_6H_4
4g $Ar^1 = Ar^2$ = Ph, Ar^3 = 4-BrC_6H_4
4h $Ar^1 = Ar^2$ = Ph, Ar^3 = 2-MeC_6H_4
4i $Ar^1 = Ar^2 = Ar^3$ = Ph

Scheme 2 *Reagents and optimized conditions*: i, aldehyde **1** (0.2 mmol), alkyne **2** (0.3 mmol), ChCl/TfOH (1 : 1.5, 1 ml), room temperature, 3 h; ii, arenesulfinate **3** (0.2 mmol), H_2O (1 ml), room temperature, 20 min.

In summary, a one-pot two-step synthesis of γ-keto sulfones in DES (ChCl/TfOH) has been developed. This DES can not only efficiently promote the [2 + 2] cycloaddition reaction between aldehydes and alkynes, but also greatly promote the following nucleophilic addition of sodium arenesulfinate to the *in situ* formed chalcones. The addition of water can efficiently enhance the solubility of the substrates and DES, thereby promoting the reaction process *via* acceletaring the proton transfer.[5] The products obtained do not require further purification. Moreover, the DES can be readily recovered and reused.

This project was supported by the Joint Innovation and Entrepreneurship Cooperation Project for College Students and the ‘333’ High-level Talent Project of Jiangsu Province.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.027.

References

1 A. Guerrini, A. Tesei, C. Ferroni, G. Paganelli, A. Zamagni, S. Carloni, M. D. Donato, G. Castoria, C. Leonetti, M. Porru, M. De Cesare, N. Zaffaroni, G. L. Beretta, A. Rio and G. Varchi, *J. Med. Chem.*, 2014, **57**, 7263.
2 M. Feng, B. Tang, S. H. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200.
3 F. Cheng, H. Wang, W. He, B. Sun, J. Zhao, J. Qu and Q. Wang, *ACS Sustainable Chem. Eng.*, 2019, **7**, 9112.
4 R. T. Eyck and I. Danishefsky, *J. Org. Chem.*, 1951, **16**, 1683.
5 G. Lu, C. Cai, F. Chen, R. Ye and B. Zhou, *ACS Sustainable Chem. Eng.*, 2016, **4**, 1804.
6 X. Cheng, S. Wang, Y. Wei, H. Wang and Y. Lin, *RSC Adv.*, 2022, **12**, 35649.
7 Z. Jin, J. Xu, S. Yang, B.-A. Song and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2013, **52**, 12354.
8 B. Aegurla and R. K. Peddinti, *Asian J. Org. Chem.*, 2018, **7**, 946.
9 M. Fernandez, U. Uria, L. Orbe, J. L. Vicario, E. Reyes and L. Carrillo, *J. Org. Chem.*, 2014, **79**, 441.
10 E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, 2014, **114**, 11060.
11 F. Del Monte, D. Carriazo, M. C. Serrano, M. C. Gutierrez and M. L. Ferrer, *ChemSusChem*, 2014, **7**, 999.
12 L. Wang, D. Dai, Q. Chen and M. He, *J. Fluorine Chem.*, 2014, **158**, 44.
13 L. Wang, D. Dai, Q. Chen and M. He, *Asian J. Org. Chem.*, 2013, **2**, 1040.
14 L. Wang, L. Zhang and L. Gong, *Mendeleev Commun.*, 2023, **33**, 243.
15 Y. Fan, D. Wang and L. Wang, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2023, **198**, 981.

Received: 15th April 2024; Com. 24/7467

[†] *General procedure for the synthesis of compounds* **4**. A 10 ml round-bottomed flask equipped with a stirring bar was charged with aldehyde **1** (0.2 mmol), alkyne **2** (0.3 mmol) and DES ChCl/TfOH (1 : 1.5, 1.0 ml). The mixture was stirred at room temperature for 3 h (TLC monitoring). After the completion of the reaction, sodium arenesulfinate **3** (0.2 mmol) and H_2O (1 ml) were added, and the mixture was further stirred for 20 min. Then water was added, which caused precipitation of product **4**. After isolation of the product **4**, the reaction mixture was extracted with EtOAc (3 × 7105 ml) to remove the residual organic starting materials. After removing water by rotary evaporation, the DES was recovered and reused for the next run.