Graphical Abstract

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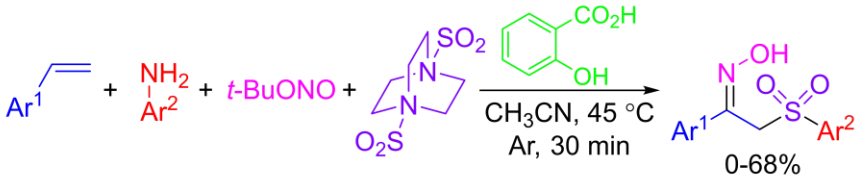

0-68%

Ar^1 = Ph, substituted phenyl, 2-Nap

Ar^2 = Ph, substituted phenyl

▪ **Organocatalyzed** ▪ **Four-component reaction** ▪ **Easy handling**

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Synthesis of α-sulfonyl ketoximes through a salicylic acid-catalyzed four-component reaction involving radical sulfonylation followed by arylsulfonylation and oximation

Satish Jakkampudi, Nagaraju Sakkani, John C.-G. Zhao*
Department of Chemistry, University of Texas at San Antonio, One UTSA Circle, San Antonio, Texas 78249-069, USA

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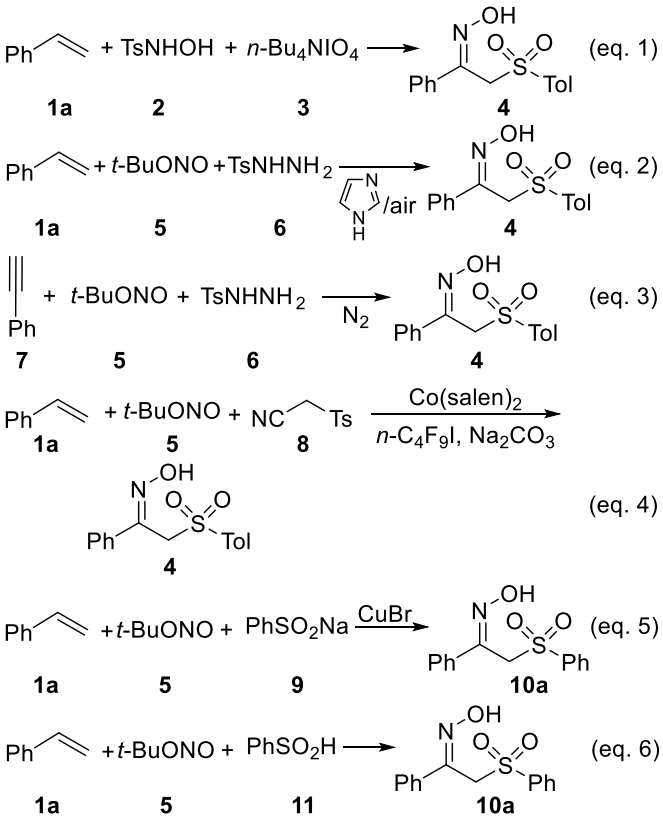
ABSTRACT

A four-component reaction of styrene derivatives, anilines, *t*-butyl nitrite, and DABSO was used to prepare α-sulfonyl ketoximes. The reaction was realized through a salicylic acid-catalyzed aryl radial formation and ensuing sulfonylation by DABSO, followed by arylsulfonylation and oximation of styrenes. Under the optimized conditions, the title compounds were obtained in good yields within 30 min.

α-Sulfonyl ketoximes, which contain multiple functional groups, are biologically active compounds and versatile synthetic building blocks in organic synthesis. [1,2] We recently became interested in using α-sulfonyl ketoximes as substrates in organocatalytic reactions, for which we needed a synthesis of these molecules. A survey of the literature revealed that several synthetic methods have been reported for the synthesis of α-sulfonyl ketoximes, as summarized in Scheme 1. In 2012, He and co-workers reported the first synthesis of α-sulfonyl ketoximes by reacting an alkene, such as styrene (**1a**), with *N*-tosylhydroxylamine (**2**) under the oxidation of *n*-Bu_4NIO_4 (**3**) (Eq. 1). [3] Wang and co-workers later reported the synthesis of **4** through the reaction of styrene (**1a**), *t*-butyl nitrite (**5**), and *N*-tosylhydrazine (**6**) under the oxidation of air in the presence of imidazole (Eq. 2). [4] Most recently, the same group also realized a synthesis of α-sulfonyl ketoxime **4** from phenylacetylene (**7**), *t*-butyl nitrite (**5**), and *N*-tosylhydrazine (**6**) (Eq. 3). [5] The synthesis of **4** was also achieved recently by Loh, Sheng, and co-workers *via* a $Co(salen)_2$-catalyzed reaction of styrene (**1a**), *t*-butyl nitrite (**5**), and 2-tosylacetonitrile (**8**) (Eq. 4). [6] In 2016, a CuBr-catalyzed reaction between styrene (**1a**), *t*-butyl nitrite (**5**), and sodium phenylsulfinate (**9**) was utilized by Peng, Li, and co-workers to access α-sulfonyl ketoxime **10a** (Eq. 5). [7] The synthesis of **10a** was also realized by Han, Yu, and co-workers through the reaction of styrene (**1a**), *t*-butyl nitrite (**5**), and phenylsulfinic acid (**11**) (Eq. 6). [2] While all of these methods involve radical-mediated arylsulfonylation and oximation, only two of them are catalytic methods mediated by metals. [6,7] To the best of our knowledge, there is no organocatalytic method for the synthesis of these interesting compounds. Moreover, in all these reported methods, the arylsulfonyl groups were introduced to the final products from an existing arylsulfonyl group in the substrates



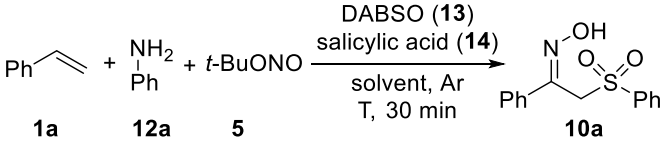
Scheme 1. Reported methods for the synthesis of α-sulfonyl ketoximes.

* Corresponding author.
Email address: cong.zhao@utsa.edu

(e.g., tosyl, arylsulfinic acid, or arylsulfinate group). Apparently, developing a novel organocatalytic method for the synthesis of these interesting compounds from readily available starting materials is still warranted.

Most recently, Gonzalez-Gomez and co-workers reported that salicylic acid (**14**) is a good organocatalyst for generating aryl radicals from the diazonium salt formed *in situ* from arylamines and *t*-butyl nitrite (**5**). [8,9] They have demonstrated the aryl radical produced could be utilized for some very useful synthetic transformations. [8] On the other hand, through the initial work of Willis, Wu, and others, [10] 1,4-diazabicyclo[2.2.2]octane-sulfur dioxide (DABSO, **13**) [11] has been demonstrated as a convenient and safe surrogate for sulfur dioxide in radical-mediated arylsulfonylation reactions. [10,12] These reports inspired us to investigate the possible synthesis of α-sulfonyl ketoximes using DABSO as the sulfonylation reagent and salicylic acid as the organocatalyst. Herein, we wish to report the first organocatalytic synthesis of α-sulfonyl ketoximes through the four-component reaction of styrene derivatives, anilines, *t*-butyl nitrite, [13] and DABSO using salicylic acid as the catalyst, in which the arylsulfonyl group was introduced through the direct radical sulfonylation with DABSO.

Table 1
Optimization of the reaction conditions for the salicylic acid-catalyzed four-component reaction [a]



1a **12a** **5** **10a**

Entry	T (°C)	**5** (equiv.)	**13** (equiv.)	Solvent	Yield **10a** (%)[b]
1	rt	3.0	1.5	CH_3CN	51
2[c]	rt	3.0	1.5	CH_3CN	NR[d]
3	45	3.0	1.5	CH_3CN	67
4	65	3.0	1.5	CH_3CN	55
5	45	3.0	1.0	CH_3CN	47
6	45	3.0	2.0	CH_3CN	68
7	45	2.0	1.5	CH_3CN	48
8	45	4.0	1.5	CH_3CN	67
9	45	3.0	1.5	CH_2Cl_2	55
10	45	3.0	1.5	$CHCl_3$	52
11	45	3.0	1.5	$(CH_2Cl)_2$	58
12	45	3.0	1.5	THF	45
13	45	3.0	1.5	Dioxane	34
14	45	3.0	1.5	EtOAc	45
15	45	3.0	1.5	DMF	30
16	45	3.0	1.5	Toluene	32

[a]Unless otherwise indicated, all reactions were carried out using styrene (**1a**, 1.0 mmol), aniline (**12a**, 1.5 mmol), *t*-butyl nitrite (**5**, 3.0 mmol), DABSO (**13**, 1.5 mmol), and salicylic acid (**14**, 0.10 mmol, 10 mol%) in the specified solvent (5.0 mL) under argon at the specified temperature for 30 min.

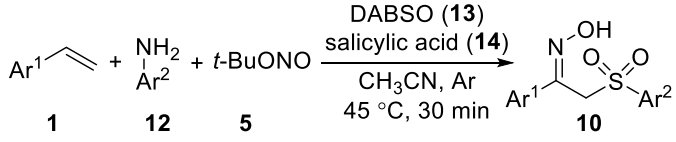
[b]Yield of the isolated product after column chromatography.

[c]Reaction was performed without salicylic acid.

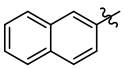
[d]No reaction.

Using styrene (**1a**), aniline (**12a**), *t*-butyl nitrite (**5**), and DABSO (**13**) as the model substrates, we first attempted the reaction in acetonitrile under argon with salicylic acid (**14**, 10 mol%) as the catalyst at room temperature. Gratifyingly, the desired product **10a** was obtained in 51% yield after just 30 min reaction time (Table 1, entry 1). No reaction was observed in a control reaction conducted without adding **14** as the catalyst (Entry 2). These results clearly show the observed formation of **10a** is indeed the result of the catalysis of **14**. Next the reaction conditions were further optimized, as summarized in Table 1. It was found the yield of **10a** could be improved to 67% by adjusting the reaction temperature to 45 °C (Entry 3). Nonetheless, further increasing the reaction temperature led to a lower yield (Entry 4). Decreasing the DABSO loading to 1.0 equiv. also led to a lower yield (Entry 5), while increasing its loading to 2.0 equiv. showed no improvement in the yield of **10a** (Entry 6). Similarly, a poorer yield of **10a** was observed when the loading of *t*-butyl nitrite (**5**) was decreased from 3.0 equiv. to 2.0 equiv. (Entry 7), while increasing its loading to 4.0 equiv. led to no improvement in the yield (Entry 8). Different organic solvents were then evaluated with the best loadings, and it was found that all the other solvents we screened were inferior to acetonitrile (Entries 9-16). Thus, the reaction conditions listed in entry 3 were identified as the best conditions for this reaction.

Table 2
Synthesis of α-sulfonyl ketoximes (**10**)[a]



1 **12** **5** **10**

Entry	Ar^1	Ar^2	**10**/Yield (%)[b]
1	C_6H_5	C_6H_5	**10a**/67
2	C_6H_5	4-FC_6H_4	**10b**/62
3	C_6H_5	4-ClC_6H_4	**10c**/62
4	C_6H_5	4-BrC_6H_4	**10d**/60
5	C_6H_5	4-CNC_6H_4	**10e**/62
6	C_6H_5	4-$NO_2C_6H_4$	**10f**/68
7	C_6H_5	4-$MeOC_6H_4$	**10g**/65
8	C_6H_5	4-$AcNHC_6H_4$	trace
9	C_6H_5	2-ClC_6H_4	**10h**/61
10	C_6H_5	3-ClC_6H_4	**10i**/63
11	C_6H_5		complex mixture
12	4-$MeOC_6H_4$	C_6H_5	**10j**/51
13	3-$MeOC_6H_4$	C_6H_5	**10k**/55
14[c]	2-$MeOC_6H_4$	C_6H_5	**10l**/26
15	4-FC_6H_4	C_6H_5	**10m**/64
16	4-ClC_6H_4	C_6H_5	**10n**/63
17[c]	4-CNC_6H_4	C_6H_5	**10o**/51
18		C_6H_5	**10p**/67

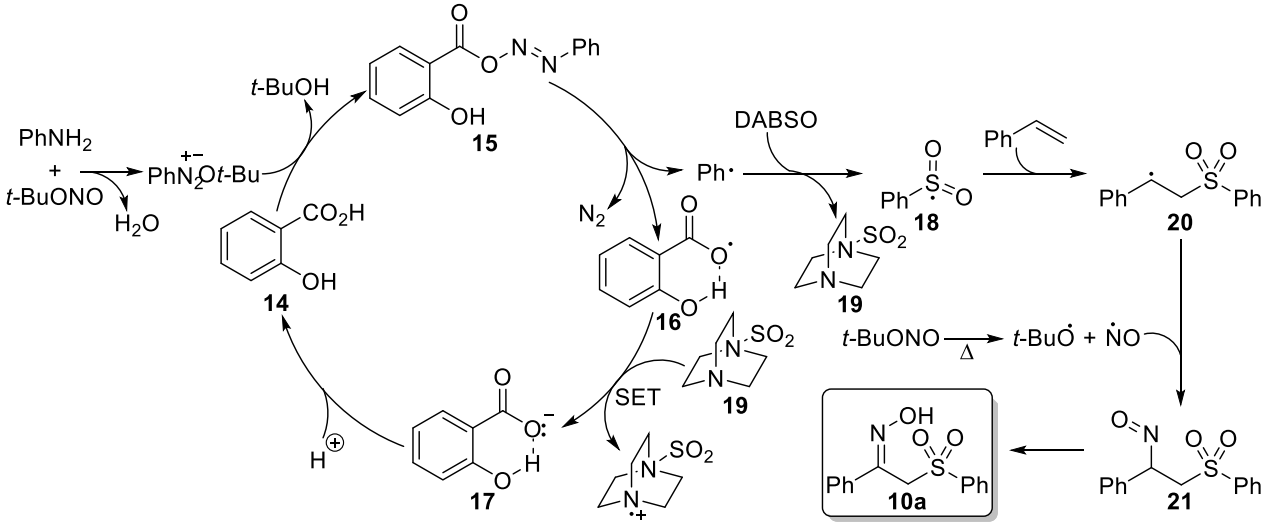
[a]Unless otherwise indicated, all reactions were carried out using **1** (1.0 mmol), **12** (1.5 mmol), **5** (3.0 mmol), **13** (1.5 mmol), and salicylic acid (**14**, 0.10 mmol, 10 mol%) in CH_3CN (5.0 mL) under argon at 45 °C for 30 min.

[b]Yield of the isolated product after column chromatography.

[c]The reaction was performed at room temperature.

Once the reaction conditions were optimized, we then studied the scope of this four-component reaction, as summarized in Table 2. Besides aniline (Entry 1), *para*-substituted anilines also work well for this reaction. Similar yields were obtained for anilines

with an electron-withdrawing or an electron-donating group in the *para*-position (Entries 2-7), which indicates that the electronic effects of the substituent have almost no influence on this reaction. Nonetheless, 4-acetylamino-substituted aniline failed to yield the desired product (Entry 8), which may be due to the high reactivity of the substrate or the substituent. When the same substituent is placed in the *meta*- or *ortho*-positions, there is no difference in the yield (Entries 9 and 10 vs. Entry 3), either. Nonetheless, the use of pyridin-2-amine as the substrate led to the formation of a complex reaction mixture (Entry 11). On the other hand, as expected, substituted styrenes are good substrates for this reaction and the electronic nature of the substituents on the phenyl ring has only a minimal influence on the yield (Entries 12-13, 15-17): The yields are either comparable to (Entries 16-17) or only slightly lower than that of styrene (Entries 12-13, 15). Nevertheless, *ortho*-methoxy-substituted styrene gave a much lower yield (Entry 14), which may be due to steric effects. In addition, 2-vinylnaphthalene is also a very good substrate for this reaction, and 67% yield of the desired product was obtained, which is comparable to that of styrene (Entry 18). However, our attempt to use an alkyl-substituted alkene, such as, cyclohexene, in this reaction failed to yield the desired product. Instead, a complex reaction mixture was obtained (data not shown).



Scheme 2. Proposed mechanism for the salicylic acid-catalyzed four-component reaction.

Based on the previous studies, [2,8,10,12] a plausible reaction mechanism for this four-component reaction is proposed (Scheme 2). As shown in Scheme 2, aniline (**12a**) and *t*-butyl nitrite (**5**) first react with each other to from a diazonium salt. The latter reacts with salicylic acid (**14**) to give diazo intermediate **15**, which produces the desired phenyl radical and the hydrogen-bond stabilized salicyloyl radical (**16**) *via* a homolytic cleavage that is facilitated by the formation of N_2. [8] Radical **16** is reduced to the salicylate anion (**17**) by **19** (or DABCO), formed from DABSO after the sulfur dioxide transfer, *via* a SET mechanism. The catalytic cycle closes when **17** abstracts a proton from the reaction mixture. Meanwhile, the phenyl radical produced in the homolysis of **15** reacts with DABSO (**13**) to produce the phenylsulfonyl radical (**18**) and **19**. The addition of radical **18** to styrene (**1a**) yields the alkyl radical **20**. On the other hand, the homolysis of *t*-butyl nitrite (**5**) yields the nitrosyl radical. The reaction of **20** and nitrosyl radical give nitroso compound **21**, which tautomerizes to yield the more stable oxime **10a**. To support this proposed radical mechanism, we conducted the optimized reaction (Table 2, entry 1) in the presence of TEMPO (2.0 equiv.), and no desired product was obtained.

In summary, we have developed an organocatalytic method for the synthesis of α-sulfonyl ketoximes, in which the four-component reaction of styrene derivatives, aniline derivatives, *t*-butyl nitrite, and 1,4-diazabicyclo[2.2.2]octane-sulfur dioxide (DABSO) was used to access the desired products directly. The reaction is believed to proceed through a salicylic acid-catalyzed aryl radial formation and their ensuing sulfonylation by DABSO, followed by arylsulfonylation and oximation of styrenes. Under the optimized conditions, the desired α-sulfonyl ketoximes were obtained in good yields within a short reaction time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at

References

[1] V. Padmavathi, B. C. O. Reddy, P. Thriveni, A. V. Nagendra Mohan, Synth. Commun. 37 (2007) 3127-3142.

[2] a) F. Chen, N.-N. Zhou, J.-L. Zhan, B. Han, W. Yu, Org. Chem. Front. 4 (2017) 135-139; b) J. Xiang, M. Ipek, V. Suri, M. Tam, Y. Xing, N. Huang, Y. Zhang, J. Tobin, T. S. Mansour, J. McKew, Bioorg. Med. Chem. 15 (2007) 4396-4405.

[3] N. Liu, P. Yin, Y. Chen, Y. Deng, L. He, Eur. J. Org. Chem. (2012) 2711-2714.

[4] B. Wang, L. Tang, L. Liu, Y. Li, Y. Yang, Z. Wang, Green Chem. 19 (2017) 5794-5799.

[5] B. Wang, Z. Yan, L. Liu, J. Wang, Z. Zha, Z. Wang, Green Chem. 21 (2019) 205-212.

[6] X.-Q. Chu, D. Ge, T.-P. Loh, Z.-L. Shen, Org. Chem. Front. 6 (2019) 835-840.

[7] J. Yang, Y.-Y. Liu, R.-J. Song, Z.-H. Peng, J.-H. Li, Adv. Synth. Catal. 358 (2016) 2286-2292.

[8] a) M. Estruch-Blasco, D. Felipe-Blanco, I. Bosque, J. C. Gonzalez-Gomez, J. Org. Chem. 85 (2020) 14473-14485; b) D. Felipe-Blanco, F. Alonso, J. C. Gonzalez-Gomez, Adv. Synth. Catal. 359 (2017) 2857-2863; c) D. Felipe-Blanco, J. C. Gonzalez-Gomez, Adv. Synth. Catal. 360 (2018) 2773-2778; d) D. Felipe-Blanco, J. C. Gonzalez-Gomez, Eur. J. Org. Chem. 2019 (2019) 7735-7744.

[9] For other reported organocatalysts for this reaction, see: a) F. P. Crisóstomo, T. Martín, R. Carrillo, Angew. Chem. Int. Ed. 53 (2014) 2181-2185; b) M. D. Perretti, D. M. Monzón, F. P. Crisóstomo, V. S. Martín, R. Carrillo, Chem. Commun. 52 (2016) 9036-9039.

[10] For some leading examples, see: a) B. Nguyen, E. J. Emmett, M. C. Willis, J. Am. Chem. Soc. 132 (2010) 16372-16373; b) Y. An, D. Zheng, J. Wu, Chem. Commun. 50 (2014) 11746-11748; c) D. Zheng, Y. An, Z. Li, J. Wu, Angew. Chem. Int. Ed. 53 (2014) 2451-2454. For reviews, see: d) K. Suta, M. Turks, Chem. Heterocycl. Compd. 54 (2018) 584-586; e) E. J. Emmett, M. C. Willis, Asian J. Org. Chem. 4 (2015) 602-611; f) M. C. Willis, Phosphorus Sulfur Silicon Relat. Elem. 194 (2019) 654-657.

[11] P. S. Santos, M. T. S. Mello, J. Mol. Struct. 178 (1988) 121-133.

[12] For some select recent examples, see: a) T. Zhu, J. Wu, Org. Lett. 22 (2020) 7094-7097; b) F. Herrera, A. Luna, P. Almendros, Org. Lett. 22 (2020) 9490-9494; c) E. J. Emmett, B. R. Hayter, M. C. Willis, Angew. Chem. Int. Ed. 52 (2013) 12679-12683; d) T.-H. Zhu, X.-C. Zhang, X.-L. Cui, Z.-Y. Zhang, H. Jiang, S.-S. Sun, L.-L. Zhao, K. Zhao, T.-P. Loh, Adv. Synth. Catal. 361 (2019) 3593-3598; e) T. Zhu, P. Rojsitthisak, J. Wu, Org. Chem. Front. 7 (2020) 4050-4056; f) P. K. T. Lo, G. A. Oliver, M. C. Willis, J. Org. Chem. 85 (2020) 5753-5760.

[13] For reviews, see: a) A. Dahiya, A. K. Sahoo, T. Alam, B. K. Patel, Chem. Asian J. 14 (2019) 4454-4492; b) K. Nader Ghaffari, Mini-Rev. Org. Chem. 17 (2020) 3-25.