PAPER

Check for updates

Three-component synthesis of β-sulfonyl enamines and dienamines enabled by silver(I) acetate†

Jakub Koudelka and Tomáš Tobrman [ID] *

We have developed a novel three-component synthesis of sulfonyl enamines by reacting secondary and tertiary amines with sodium sulfinic acid salt, a reaction that is mediated by silver acetate. The choice of solvent determines whether sulfonyl enamines or dienamines are obtained. The overall atom economy of this multicomponent reaction was further improved by isolating the resulting elemental silver and reconverting it into silver acetate.

Introduction

Organic synthesis has undergone rapid development over the last few decades, leading to the creation of new procedures for the preparation of amines,[1] ethers,[2] heterocyclic compounds,[3] and both tetrasubstituted[4] and trisubstituted[5] alkenes. In addition to the above-mentioned substances, vinyl sulfones represent an important class of compounds that are the subject of intense study in terms of their synthesis and application. For example, rigosertib[6] and other vinyl sulfones exhibit significant antitumor activity,[7] neuroprotective effects against Parkinson's disease,[8] cysteine protease inhibition,[9] and antiparasitic activity.[10] Moreover, significant attention has been paid to sulfonyl enamines due to their medicinal applications. In this regard, cyclic sulfonyl enamines form the key structural motif of Xestoadociaminals A and B, compounds that have been isolated from the Indonesian marine sponge *Xestospongia* sp. (Fig. 1).[11] Some cyclic sulfonyl enamines are formed during the microsomal metabolism of artemisone.[12] Furthermore, the artificially synthesized sulfonyl enamines **A** and **B** have been characterized based on their antimicrobial activity[13] and their role as activators of nuclear factor erythroid 2-related factor 2 (Nrf2).[14]

The practical significance of both vinyl sulfones and sulfonyl enamines is closely tied to the development of efficient methods for their preparation. Traditional methods for the preparation of sulfonyl enamines include the conjugate addition of amines to sulfonylacetylenes[15] and the C–H sulfonylation of enamides.[16] However, a distinct approach to the formation of sulfonyl enamines involves the oxidative sulfonylation of cyclic amines,[17] formal C–H activation with the insertion of sulfur

Department of Organic Chemistry, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic. E-mail: tomas.tobrman@vscht.cz

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ra08480b

dioxide,[18] and the direct reaction of tertial amines with sulfonyl chlorides[19] or sulfonyl hydrazides.[20]

From a practical perspective, it is advantageous to perform the synthesis of sulfonyl enamines using the method described by Gui *et al.*, who developed the tetrabutylammonium iodide-catalyzed synthesis of sulfonyl enamines in the presence of stoichiometric amounts of *tert*-butyl hydroperoxide (TBHP) (Scheme 1a).[21] By contrast, Yuan observed the significant effect of solvents on the course of the reaction between sodium sulfinates and tertiary amines. In this respect, water favored the formation of sulfonamides, while dimethyl sulfoxide (DMSO) favored the formation of sulfonyl enamines (Scheme 1b).[22] In both cases, the iminium salt **Im1** and enamine **Im2** were proposed as intermediates during the preparation of sulfonyl enamines.[21,22] Our research interest in the synthesis of alkenes,[23] along with the predicted formation of the iminium salt **Im1** and the significant effect of *N*-substitution on the stability of iminium salts,[24] led us to propose a new multicomponent synthesis procedure of β-sulfonyl enamines
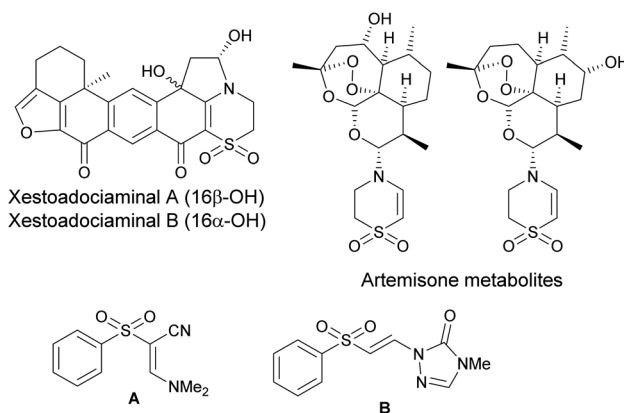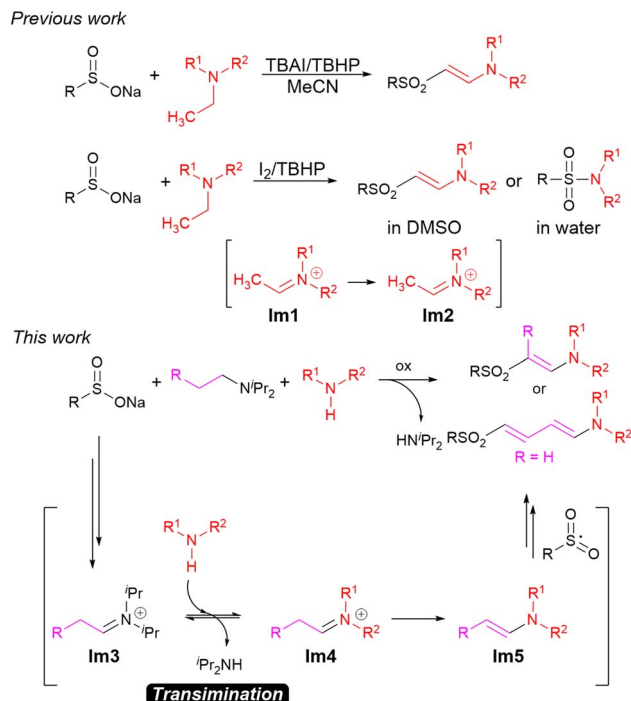

Fig. 1 Structures of some biologically relevant sulfonyl enamines.

Previous work

This work

Scheme 1 Concept of our work.

(Scheme 1, this work). In this new multicomponent reaction, we expected the formation of the more stable iminium salt **Im4** by means of transimination from iminium salt **Im3**.

Result and discussion

In terms of the proposed multicomponent reaction, we aimed to optimize the reaction conditions. We quickly discovered that most oxidants, including CuI, I_2/TBHP, I_2, $FeCl_3$, and MnO_2, when used in either stoichiometric or catalytic amounts, were ineffective, meaning that the desired product **4aaa** was not formed (see the ESI† for further details). However, using three equivalents of silver acetate in dimethylformamide (DMF) or dimethylsulfoxide (DMSO) yielded the enamine **4aaa**, albeit in a low yield (Table 1, entries 1 and 2). Through solvent variation, we found that the most effective transformation occurred in tetrahydrofuran (THF) with six equivalents of silver acetate (Table 1, entries 3–6). It is important to note that lithium benzenesulfinate (**1a$^{\text{Li}}$**) and potassium benzenesulfinate (**1a$^{\text{K}}$**) yielded the enamine **4aaa** in a lower yield (Table 1, entries 7 and 8). Further solvent variation revealed that significant amounts of diene **5aaa** were formed in acetonitrile and ethanol, respectively (Table 1, entries 9–11). Ultimately, a mixture of ethanol and acetonitrile produced only diene **5aaa**, although in a moderate isolated yield (Table 1, entry 12). The effect of the solvent on the formation of enamine **4aaa** and dienamine **5aaa** remains unclear and will be explored in future studies.

After identifying the optimal reaction conditions, we evaluated their scope (Scheme 2). Both the cyclic and acyclic aliphatic secondary amines reacted as expected, forming enamines **4aaa**–**4aae**. Similar reactivity was observed with *N*-methylallylamine (**2f**) and *N*-methyl(benzyl)amine (**2g**). Additionally, the secondary amines with bulky cyclohexyl and isopropyl

Table 1 Optimization of reaction conditions

| Entry	**1a** (equiv.)	**2a** (equiv.)	AgOAc (equiv.)	Solvent	**4aaa/5aaa**^{a} (%)
1	1.2	1.2	3	DMF	14/—
2	1.2	1.2	3	DMSO	14/3
3	1.2	1.2	3	Toluene	22/4
4	1.2	1.2	3	CpOMe	11/—
5	1.2	1.2	3	THF	63/—
6	2.4	2.4	6	THF	90 (67^b)/—
7	2.4^c	2.4	6	THF	—(46^b)/—
8	2.4^d	2.4	6	THF	—(55^b)/—
9	1.2	2.2	3	MeCN	15/25
10	1.2	2.2	3	EtOH	0/30
11	1.2	4.2	3	MeCN/EtOH^e	0/53 (22^b)
12	2.4	4.2	6	MeCN/EtOH^e	0/— (35^b)

^{a} ^{1}H NMR yields. ^{b} Isolated yield. ^{c} PhSO$_2$Li (**1a$^{\text{Li}}$**) was used instead of **1a**. ^{d} PhSO$_2$K (**1a$^{\text{K}}$**) was used instead of **1a**. ^{e} A mixture of MeCN and EtOH in 1 : 3 v/v was used.

Scheme 2 Scope of the developed conditions for enamine and dienamine synthesis.

substituents yielded the corresponding enamines **4aah**, **4aai** and **4aaj** in satisfactory yields. For selected secondary amines, we also obtained dienamines **5aaa**, **5aac**, **5aaf**, **5aag**, and **5aaj**, albeit in lower isolated yields, which is consistent with the

Scheme 3 Reaction of benzenesulfinic acid sodium salt with *tert*-amines.

optimization experiments. The primary amines and certain secondary amines did not yield the expected products. Moreover, no reactivity was observed for *N*-ethylaniline and indole.

The optimized reaction conditions are not limited to the preparation of disubstituted alkenes. Notably, in the case of more complex tertiary amines, we successfully prepared trisubstituted alkenes (Scheme 3). Excellent reactivity was observed for amines with aliphatic substituents, yielding enamines **4aba**, **4aca** and **4ada**. In contrast, a tertiary amine containing the homobenzyl group **2f** yielded a mixture of the diisopropylamine **4afj** and the morpholine derivative **4afa**. Substituting morpholine (**3a**) with diisopropylamine (**3j**) resulted in the exclusive formation of amine **4afj** in a 27% isolated yield, while the tertial amine **2e** containing a three-carbon spacer resulted in the clean formation of transimination product **4aea**. These results suggest that the exchange of the N^iPr_2 for the morpholine moiety occurs significantly slower than in other cases. In addition, the tertial amine **2g** bearing a 2-thienyl group did not react at all.

The structure of the sulfinic acid sodium salt also plays a significant role in the course of the multicomponent reaction (Scheme 4). Sodium salts derived from substituted benzenesulfinic acids reacted satisfactorily, yielding alkenes **4baa**, **4caa**, and **4daa**. Similar isolated yields of the enamines **4eaa** and **4faa** were obtained for even 1-naphthyl- and 1-pyrenylsulfinic acid sodium salts. However, *n*-butylsulfinic acid sodium salt produced the enamine **4gaa** in only a 9% yield. The reactivity of the styrenyl and heterocyclic sulfinic acid sodium salts differed markedly. Here, 3-pyridylsulfinic acid sodium salt did not react

© 2025 The Author(s). Published by the Royal Society of Chemistry
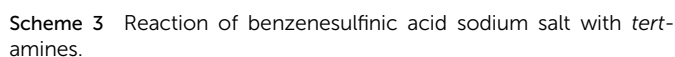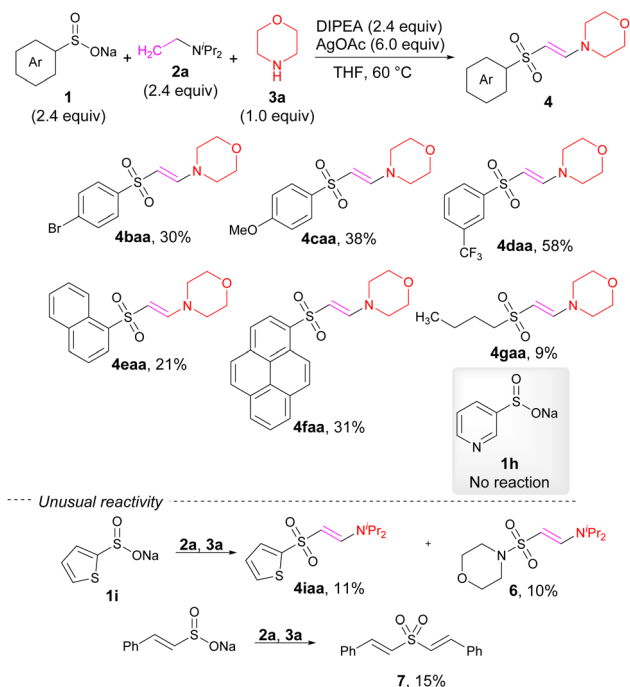
Scheme 4 Scope of the sulfinic acid sodium salts in the developed enamine synthesis.

at all, whereas 2-thienylsulfinic acid sodium salt yielded a mixture of sulfonamide **6** and enamine **4iaa**, with no observed transimination. Styrenylsulfinic acid sodium salt only produced sulfone **7** in a low isolated yield.

To further expand the portfolio of trisubstituted alkenes, we performed the gram-scale synthesis of alkene **4aaa**, achieving a 70% isolated yield (Scheme 5). In addition to the target alkene **4aaa**, elemental silver was recovered and converted back into silver acetate using nitric acid and sodium acetate. The recycled

Scheme 5 (a) Gram-scale synthesis of alkene **4aaa**, (b) late-stage modification of enamine **4aaa** and (c) attempted conversion of **4aaj** to **4aaa**.

silver acetate provided the alkene **4aaa** with a 57% yield on a 0.5 mmol scale, thereby improving the overall atom economy of the developed multicomponent reaction. In addition, the prepared alkene **4aaa** was lithiated to the alkene **4aaaLi** using *n*-butyllithium, and the subsequent reactions with organohalides produced the trisubstituted enamines **4aha**, **4aea**, and **4aia** in high yields. This approach successfully expanded the scope of the trisubstituted enamines available *via* novel three-component synthesis, starting from the readily available disubstituted enamine **4aaa**. The mechanism of this novel multicomponent reaction will be further explored; however, we hypothesize that the key step involves the transimination of the iminium salt from **Im3** to **Im4** (Scheme 1, this work). Experimental evidence suggests that enamines **4** are not generated through nucleophilic substitution of the N^{i}Pr$_2$ group by a secondary amine, as demonstrated by the reaction of the enamine **4aaj** with morpholine under typical reaction conditions, which did not yield the anticipated product **4aaa** (Scheme 5c).

Conclusions

In conclusion, we developed a new multicomponent reaction for the preparation of di- and trisubstituted sulfonyl enamines. The optimized reaction conditions involve reacting tertiary and secondary amines with the sodium salt of arylsulfinic acid in the presence of silver acetate in THF at 60 °C. Substituting THF with an ethanol–acetonitrile mixture can yield the corresponding dienamines. These optimized conditions allow for the gram-scale synthesis of enamines. The overall atom economy of the multicomponent reaction is improved by isolating the silver by-product and reconverting it into silver acetate. Late-stage modification of disubstituted enamines further expands the portfolio of prepared trisubstituted enamines.

Data availability

The data supporting this article (additional optimization experiments, experimental procedures, analytical data of synthesized compounds, copies of ^{1}H and ^{13}C NMR spectra) have been included as part of the ESI.†
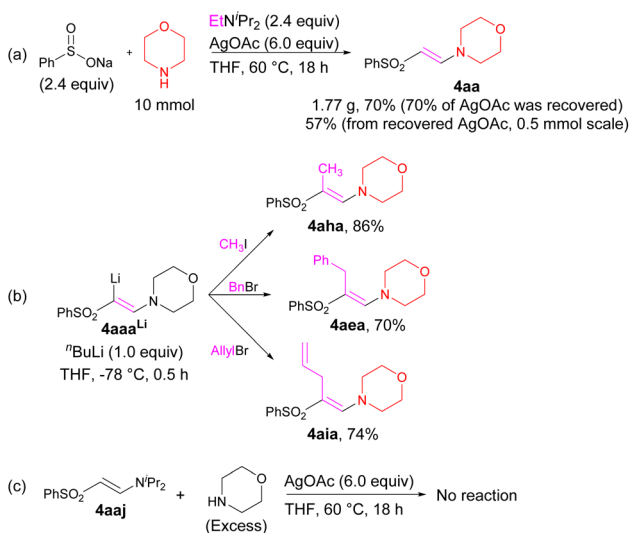
Author contributions

Investigation, methodology, visualization, writing – original draft, writing – review & editing (JK); funding, conceptualization, writing – original draft, writing – review & editing (TT).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

References

1 (a) P. A. Forero-Cortés and A. M. Haydl, *Org. Process Res. Dev.*, 2019, **23**, 1478; (b) M. M. Heravi, Z. Kheilkordi, V. Zadsirjan, M. Heydari and M. Malmir, *J. Organomet. Chem.*, 2018, **861**, 17.

2 (a) S. Mandal, S. Mandal, S. K. Ghosh, P. Sar, A. Ghosh, R. Saha and B. Saha, *RSC Adv.*, 2016, **6**, 69605; (b) E. N. Pitsinos, V. P. Vidali and E. A. Couladouros, *Eur. J. Org Chem.*, 2011, 1207; (c) D. J. Winternheimer, R. E. Shade and C. A. Merlic, *Synthesis*, 2010, 2497.

3 (a) W. R. Bowman, M. O. Cloonan and S. L. Krintel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2885; (b) J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Acc. Chem. Res.*, 2016, **49**, 1911; (c) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395.

4 (a) T. Edlová, M. Čubiňák and T. Tobrman, *Synthesis*, 2021, **53**, 255; (b) P. Polák, H. Váňová, D. Dvořák and T. Tobrman, *Tetrahedron Lett.*, 2016, **57**, 3684; (c) T. Tobrman and S. Mrkobrada, *Organics*, 2022, **3**, 210; (d) F. Buttard, J. Sharma and P. A. Champagne, *Chem. Commun.*, 2021, **57**, 4071; (e) A. B. Flynn and W. W. Ogilvie, *Chem. Rev.*, 2007, **107**, 4698; (f) N. Mukherjee, S. Planer and K. Grela, *Org. Chem. Front.*, 2018, **5**, 494.

5 (a) A. H. Hoveyda, C. Qin, X. Z. Sui, Q. Liu, X. Li and A. Nikbakht, *Acc. Chem. Res.*, 2023, **56**, 2426; (b) R. Manikandan and M. Jeganmohan, *Org. Biomol. Chem.*, 2015, **13**, 10420; (c) E.-i. Negishi, G. Wang, H. Rao and Z. Xu, *J. Org. Chem.*, 2010, **75**, 3151; (d) K. A. Ouzounthanasis, S. R. Rizos and A. E. Koumbis, *Eur. J. Org Chem.*, 2023, **26**, e202300626.

6 K. Gumireddy, M. V. R. Reddy, S. C. Cosenza, R. B. Nathan, S. J. Baker, N. Papathi, J. Jiang, J. Holland and E. P. Reddy, *Cancer Cell*, 2005, **7**, 275.

7 (a) T. Lu, C. A. Laughton, S. Wang and T. D. Bradshaw, *Mol. Pharmacol.*, 2015, **87**, 18; (b) L. Tang, T. Chen, H. Yang, X. Wen, Y. Sun, S. Liu, T. Peng, S. Zhang and L. Wang, *RSC Adv.*, 2021, **11**, 37462.

8 S. Y. Woo, J. H. Kim, M. K. Moon, S.-H. Han, S. K. Yeon, J. W. Choi, B. K. Jang, H. J. Song, Y. G. Kang, J. W. Kim, J. Lee, D. J. Kim, O. Hwang and K. D. Park, *J. Med. Chem.*, 2014, **57**, 1473.

9 B. D. Fennell, J. M. Warren, K. K. Chung, H. L. Main, A. B. Arend, A. Tochowicz and M. G. Götz, *J. Enzyme Inhib. Med. Chem.*, 2013, **28**, 468.

10 I. D. Kerr, J. H. Lee, C. J. Farady, R. Marion, M. Rickert, M. Sajid, K. C. Pandey, C. R. Caffrey, J. Legac, E. Hansell, J. H. McKerrow, C. S. Craik, P. J. Rosenthal and L. S. Brinen, *J. Biol. Chem.*, 2009, **284**, 25697.

11 F. He, L. H. Mai, A. Longeon, B. R. Copp, N. Loaëc, A. Bescond, L. Meijer and M.-L. Bourguet-Kondracki, *Mar. Drugs*, 2015, **13**, 2617.

12 L. Grobler, A. Grobler, R. Haynes, C. Masimirembwa, R. Thelingwani, P. Steenkamp and H. S. Steyn, *Expert Opin. Drug Metab. Toxicol.*, 2014, **10**, 313.

13 M. R. Shaaban, *Heterocycles*, 2008, **75**, 3005–3014.

14 V. Markovtsov, M. A. J. Duncton, A. Bagos, S. Yi, S. Braselmann, S. Bhamidipati, I. S. Darwish, J. Yu, A. M. Owyang, B. Fernandez, B. Samant, G. Park, E. S. Masuda and S. J. Shaw, *ACS Med. Chem. Lett.*, 2023, **14**, 1700.

15 (a) S. Cossu, O. De Lucchi and R. Durr, *Synth. Commun.*, 1996, **26**, 4597; (b) E. Petit, L. Bosch, J. Font, L. Mola, A. M. Costa and J. Vilarrasa, *J. Org. Chem.*, 2014, **79**, 8826.

16 H. Jiang, X. Chen, Y. Zhang and S. Yu, *Adv. Synth. Catal.*, 2013, **355**, 809.

17 (a) R. J. Griffiths, W. C. Kong, S. A. Richards, G. A. Burley, M. C. Willis and E. P. A. Talbot, *Chem. Sci.*, 2018, **9**, 2295; (b) K. Muralirajan, R. Kancherla and M. Rueping, *Angew. Chem., Int. Ed.*, 2018, **57**, 14787; (c) X. Rong, J. Guo, Z. Hu, L. Huang, Y. Gu, Y. Cai, G. Liang and Q. Xia, *Eur. J. Org Chem.*, 2020, 701; (d) J. Tong, H. Li, Y. Zhu, P. Liu and P. Sun, *Green Chem.*, 2022, **24**, 1995.

18 Y. He, J. Yang, Q. Liu, X. Zhang and X. Fan, *J. Org. Chem.*, 2020, **85**, 15600.

19 (a) M. Chen, Z. T. Huang and Q. Y. Zheng, *Org. Biomol. Chem.*, 2014, **12**, 9337; (b) H. Wei, G. Wang, B. Li, J. Huang, H. Li, O. P. Pereshivko and V. A. Peshkov, *Heterocycl. Commun.*, 2016, **22**, 333; (c) R. Zhang, Y. Cai, D. Sun, S. Xu and Q. Zhou, *Synlett*, 2017, **28**, 1630; (d) S. Firoozi and M. Hosseini-Sarvari, *J. Org. Chem.*, 2021, **86**, 2117.

20 H. S. Kim and S. Lee, *Eur. J. Org Chem.*, 2019, 6951.

21 H. Jiang, X. Tang, Z. Xu, H. Wang, K. Han, X. Yang, Y. Zhou, Y.-L. Feng, X.-Y. Yu and Q. Gui, *Org. Biomol. Chem.*, 2019, **17**, 2715.

22 J. Lai, L. Chang and G. Yuan, *Org. Lett.*, 2016, **18**, 3194.

23 (a) J. Koudelka and T. Tobrman, *Eur. J. Org Chem.*, 2021, 3260; (b) T. Edlová, H. Dvořáková, V. Eigner and T. Tobrman, *J. Org. Chem.*, 2021, **86**, 5820.

24 A. M. Costa, A. Castro-Alvarez, D. Fillot and J. Vilarrasa, *Eur. J. Org Chem.*, 2022, e202200627.