Preprint Title	Facile access to 3-sulfonyl quinolines *via* Knoevenagel condensation/aza-Wittig reaction cascade involving *ortho*-azidobenzaldehydes and β-keto sulfonamides and sulfones
Authors	Ksenia Malkova, Andrey Bubyrev, Stanislav Kalinin and Dmitry Dar'in
Publication Date	04 Apr. 2023
Article Type	Full Research Paper
Supporting Information File 1	Malkova ESI.pdf; 3.2 MB
ORCID® iDs	Ksenia Malkova - https://orcid.org/0000-0003-4443-0427; Dmitry Dar'in - https://orcid.org/0000-0002-0413-7413

Facile access to 3-sulfonyl quinolines *via* Knoevenagel condensation/aza-Wittig reaction cascade involving *ortho*-azidobenzaldehydes and β-keto sulfonamides and sulfones

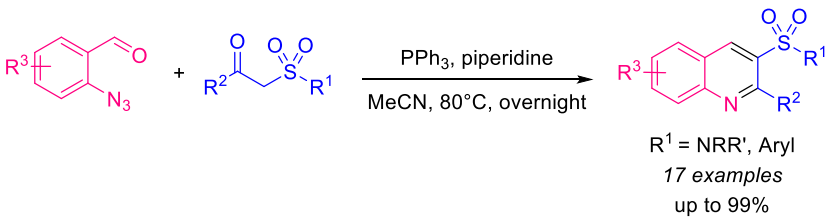
Ksenia Malkova, Andrey Bubyrev, Stanislav Kalinin, Dmitry Dar'in*

Saint Petersburg State University, Saint Petersburg 199034, Russian Federation

In commemoration of the 300th anniversary of St Petersburg State University's founding

Email: Dmitry Dar'in* - d.dariin@spbu.ru

* Corresponding author



Keywords: quinolines, sulfonamides, cyclocondensation, aza-Wittig reaction, azides

Abstract

Quinoline based sulfonyl derivatives, and especially sulfonamides, are relevant and promising structures for drug design. We have developed a new convenient protocol for the synthesis of 3-sulfonyl substituted quinolines (sulfonamides and sulfones). The approach is based on Knoevenagel condensation/aza-Wittig reaction cascade involving *o*-azidobenzaldehydes and ketosulfonamides or ketosulfones as key building blocks. The protocol is appropriate both for ketosulfonyl reagents and α-sulfonyl alkyl acetates providing the target quinoline derivatives in good to excellent yields.

Introduction

The quinoline scaffold has wide occurrence among natural products [1] and is a key structural component of several pharmaceuticals, agrochemicals, dyestuffs, and materials. Particularly, the well-known antimalarial alkaloid quinine isolated from *Cinchona* bark comprises quinoline core (Figure 1a) [2]. Moreover, numerous quinoline derivatives have been recently reported to possess intriguing pharmacological activities [3] including antiprotozoal [4-7], antitubercular [8,9], anti-cancer [10,11], anti-inflammatory [12], antioxidant [13], anti-HIV [14], antifungal [15], and an antineurodegenerative effect [16]. Hence, designing novel quinoline construction and functionalization techniques resulting in its new or rare derivatives is an important mission in the field of drug discovery and medicinal chemistry.

A sulfonamide group is a known privileged motif in drug design often serving as a linker or pharmacophore group. In fact, more than one hundred FDA-approved drugs are sulfonamide-bearing small molecules. Screening libraries of aromatic and heteroaromatic sulfonamides gave rise to the discovery of multiple physiologically active compounds [17-20] including important pharmaceuticals, such as sulfamethoxazole and sulfasalazine (Figure 1a). In this context, combining sulfonamide and quinoline fragments promises to be a fruitful strategy to identify diverse types of therapeutically relevant compounds. The effectiveness of this approach is demonstrated by a series of recently developed bioactive structures, and, significantly, quinoline-3-sulfonamides are frequently encountered among such pharmacologically active hybrids (Figure 1b) [21-24].

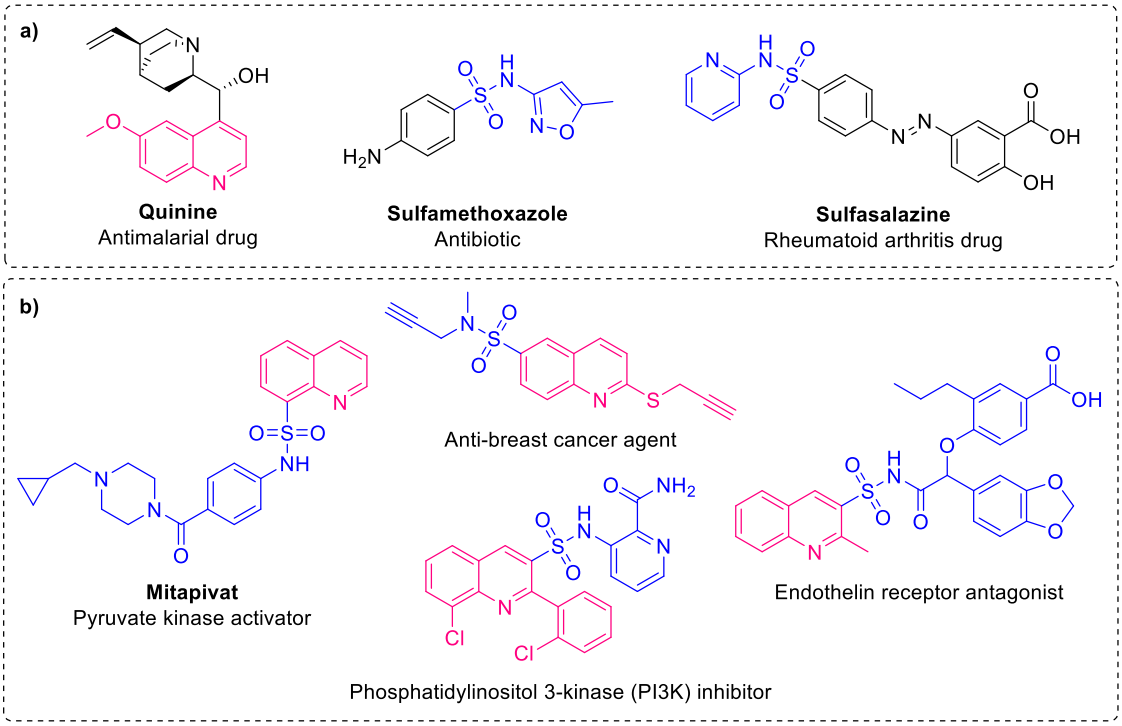


Figure 1: a) Conventional drugs containing either a sulfonamide fragment or a quinoline core; b) biologically active quinoline sulfonamides

Despite these facts, the diversity of quinoline-3-sulfonamides reported in the literature is limited due to obstacles in the synthesis of quinoline-3-sulfonyl chlorides which are the most common reagents for their preparation. As a possible solution, the approach to heterocyclic core construction from sulfonamide containing building block may be considered. In turn, diversely substituted quinoline-3-sulfones are available through a range of recently suggested synthetic methodologies. Cyclization strategies [25-34] as well as cycloaddition/cyclocondensation [35-40] techniques represent those with hetero-ring construction. Alternative approaches rely on a peripheral modification of various substrates, such as 3-bromoquinolines [41-44], quinoline-3-boronic acids [45], and diazonium salts [46].

When considering general methods for the quinoline core formation, aromatic *ortho*-substituted carbonyl compounds attract attention as decent and easily available reagents. While the *ortho*-amino carbonyl reagents are not always easily accessible and sometimes unstable (e.g.

aminoaldehydes), both *o*-azidoaldehydes [47-54] and *o*-azidoketones [55-58] have been proved to be appropriate substrates for quinoline derivatives synthesis. Recently, the method for the synthesis of 3-acyl-substituted quinolines from *o*-azidobenzaldehydes and 1,3-dicarbonyl compounds was reported [59] (Figure 2a). A combination of Knoevenagel condensation and aza-Wittig reaction allowed to build up target products in high yields. The procedure was predominantly applied for the preparation of corresponding esters.

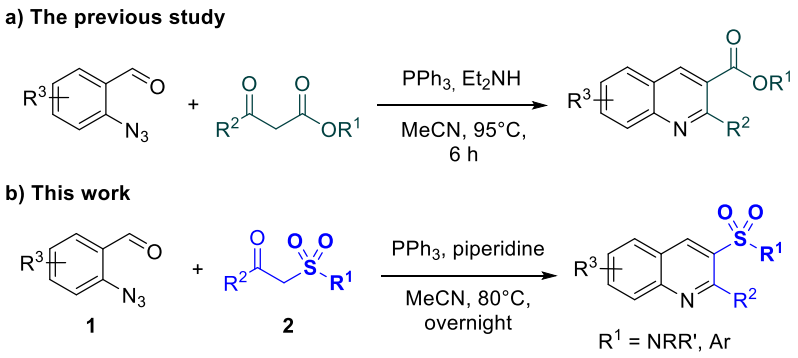
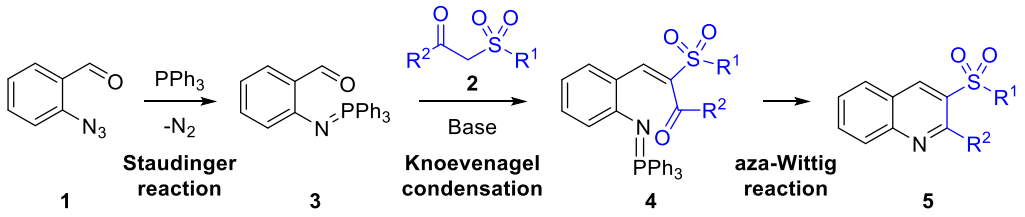


Figure 2: Knoevenagel condensation/aza-Wittig reaction cascade for the quinoline core formation

Inspired by this study, we became interested to utilize *o*-azidobenzaldehydes **1** in combination with ketosulfonamides/ketosulfones **2** as precursors in a new convenient synthetic procedure leading towards 3-sulfonyl substituted quinolines (sulfonamides and sulfones) (Figure 2b). Herein, we report the successful implementation of such approach.

Results and discussion

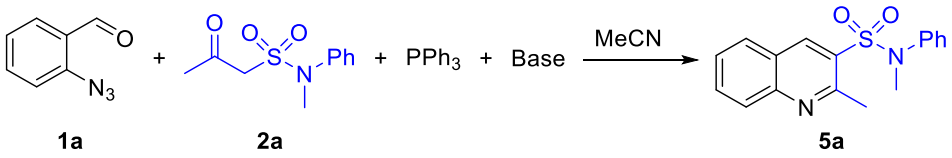
The Knoevenagel condensation/aza-Wittig reaction cascade was implemented for the preparation of 3-sulfonyl substituted quinolines. The process proceeds in a domino fashion including the following steps: the formation of iminophosphorane **3** from *o*-azidoaldehyde **1** and PPh_3 followed by the base-mediated Knoevenagel condensation results in the compound **4**; the subsequent intramolecular aza-Witting reaction leads to the desired product **5** (Scheme 1).



Scheme 1: Key reaction steps during the 3-sulfonyl substituted quinolines synthesis

Starting from the reaction conditions reported previously, we began our investigation using *o*-azidobenzaldehyde **1a**, 2-oxopropanesulfonamide **2a**, triphenylphosphine, and diethylamine as reagents for the quinoline-3-sulfonamide assembly (Table 1). The reaction mixture was stirred in MeCN at 95 °C for 6 h which led to mediocre yield of the target compound **5a** estimated by NMR (Table 1, entry 1). Different organic bases were tested among which piperidine performed most efficiently (Table 1, entry 4). Next it was found that using *o*-azidobenzaldehyde **1a**, PPh_3, and piperidine excesses in relation to ketosulfonamide **2a** resulted in higher yields of quinoline **5a**. The optimal solvent volume was chosen considering both reaction yields and practical reasons. Subsequent tuning of temperature and reaction time ensured quantitative NMR yield in the model reaction (Table 1, entry 15).

Table 1: Optimization of reaction conditions[a]

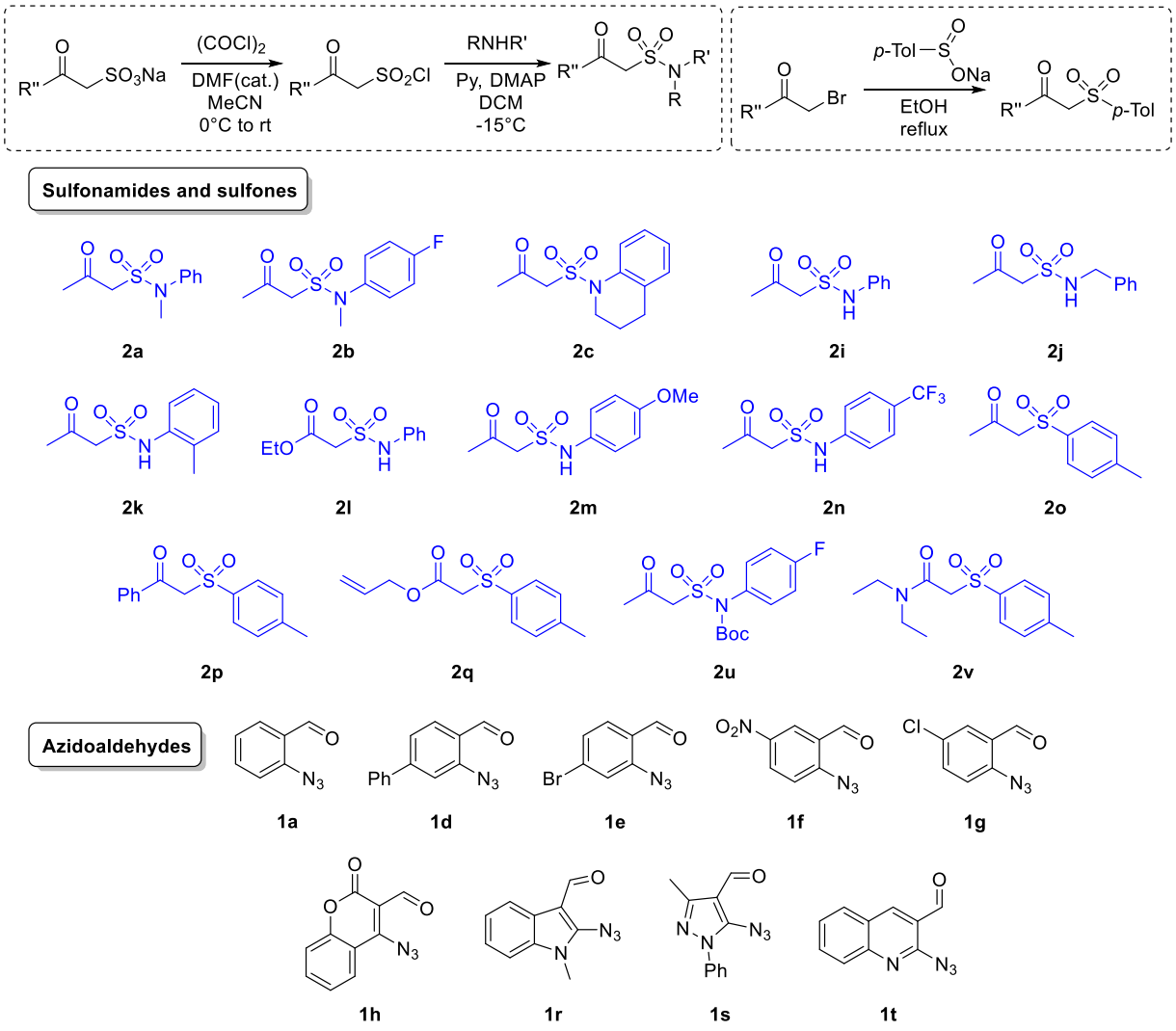


№	Base (eq)	1a, eq	2a, eq	PPh_3, eq	V_{solv}, ml	Δ, °C	NMR yield, %
1	Et_2NH (1.0)	1.0	1.2	1.2	0.68	95	31
2	Et_3N (1.0)	1.0	1.2	1.2	0.68	95	43
3	Pyrrolidine (1.0)	1.0	1.2	1.2	0.68	95	45
4	Piperidine (1.0)	1.0	1.2	1.2	0.68	95	63
5	Piperidine (1.0)	1.0	1.1	1.2	0.68	95	62
6	Piperidine (1.0)	1.0	1.0	1.2	0.68	95	63
7	Piperidine (1.1)	1.1	1.0	1.3	0.68	95	69
8	Piperidine (1.25)	1.25	1.0	1.5	0.68	95	82

9	Piperidine (0.5)	1.25	1.0	1.5	0.68	95	73
10	Piperidine (1.0)	1.25	1.0	1.5	0.68	95	81
11	Piperidine (1.5)	1.25	1.0	1.5	0.68	95	75
12	Piperidine (1.25)	1.25	1.0	1.5	0.34	95	58
13	Piperidine (1.25)	1.25	1.0	1.5	1.36	95	91
14	Piperidine (1.25)	1.25	1.0	1.5	2.68	95	95
15	Piperidine (1.25)	1.25	1.0	1.5	1.36	80	99[b]
16	Piperidine (1.25)	1.25	1.0	1.5	1.36	65	91

[a] Reaction scale – 0.1 mmol, reaction time – 6 h; [b] Reaction was run overnight (16 h).

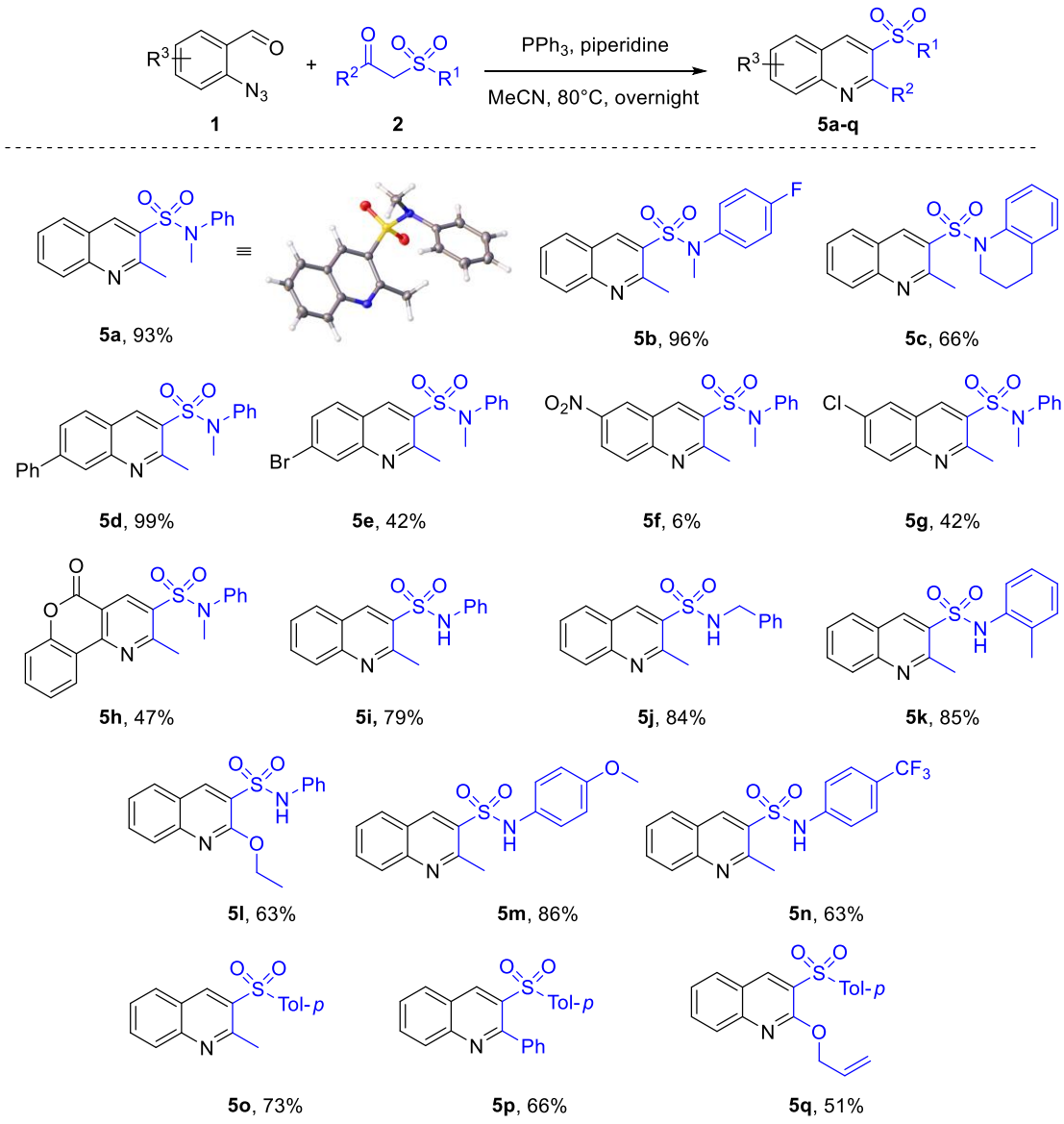
A remarkable advantage of the approach devised is that all starting materials including sulfonyl compounds are easily accessible. Furthermore, the preparation techniques are flexible concerning the substituents variations, which is of high importance for the potential medicinal chemistry applications. Scheme 2 illustrates unobstructed synthetic routes [60-62] to sulfonamides and sulfones **2**, and the diversity of reagents used to prepare the target products **5**.



Scheme 2: Synthetic routes to sulfonamides and sulfones **2** and the set of reagents for the preparation of compounds **5**

With the reaction conditions optimized, a series of novel tertiary quinoline-3-sulfonamides and quinoline-3-sulfones was successfully generated. In case of secondary quinoline-3-sulfonamide synthesis, the increase of reagents excesses in relation to ketosulfonamide resulted in the conversion and yield rise as observed by TLC (see **GP2** in Experimental section).

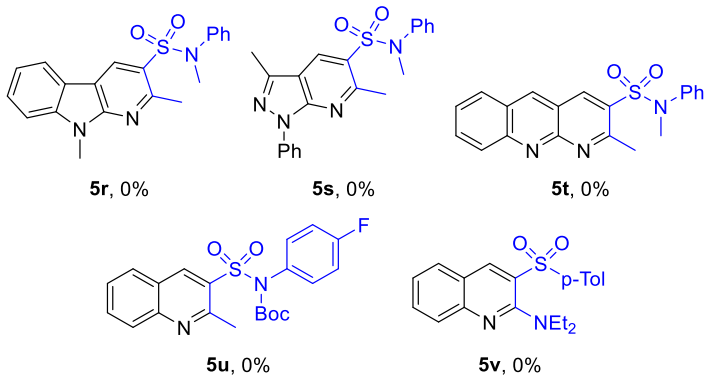
Chromatographic purification afforded compounds **5a-q** mostly in good to excellent yields (Scheme 3). The product structures were confirmed by the standard set of characterization data as well as the single-crystal X-ray structure of the representative compound (**5a**).



Scheme 3: Preparation of 3-sulfonyl substituted quinolines **5a-q**

The presence of an electron withdrawing group in *o*-azidobenzaldehyde leads to decreased yields of target products (Scheme 3, **5e** and **5g**). The drop was especially dramatic for the nitro group containing reagent **1f**. To our delight, the protocol turned out to be suitable for α-sulfonyl substituted alkyl acetates leading to 2-alkoxyquinolines. The compounds **5l** an **5q** were obtained in 63 and 51% yields respectively (Scheme 3). It is worth noticing that chromenopyridine-3-sulfonamide **5h** derived from heterocyclic azidoaldehyde **1h** was also successfully synthesized following the methodology designed.

Some limitations on the substrate scope for the proposed protocol were found out during the course of the study. Indole and pyrazole based azidoaldehydes **1r** and **1s** failed to provide desired compounds **5r** and **5s** (Scheme 4). The reaction stopped on the iminophosphorane formation and did not progress further likely due to carbonyl group deactivation. Furthermore, while implementing the protocol for 2-azidoquinoline-3-carbaldehyde (**1t**), the low conversion of this reagent was detected, which can be explained by the fact that **1t** tends to exist in the inactive tetrazole form. In addition, our attempt to involve Boc-protected ketosulfonamide **2u** in the transformation resulted in the *N*-deprotected product. Finally, *N*,*N*-diethyl-2-tosylacetamide **2v** appeared to be incapable of entering the Knoevenagel condensation in the suggested conditions.



5r, 0% **5s**, 0% **5t**, 0%

5u, 0% **5v**, 0%

Scheme 4: 3-Sulfonyl substituted quinolines **5r-v** that failed to be synthesized

Conclusions

In summary, we have successfully developed a new straightforward protocol for the synthesis of 3-sulfonyl substituted quinolines (sulfonamides and sulfones). The approach is based on Knoevenagel condensation/aza-Wittig reaction cascade for the quinoline core assembly. Hence, *o*-azidobenzaldehyde, ketosulfonamide or ketosulfone were utilized as key building blocks. The proposed method proved to be a convenient approach to the preparation of 3-sulfonyl substituted quinolines. The desired compounds were obtained in good to excellent yields. Importantly, the protocol was found suitable not only for ketosulfonyl reagents but also for α-sulfonyl substituted alkyl acetates providing a pathway to 2-alkoxyquinolines.

Deposition number 2242072 (for **5a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Supporting Information

Supporting Information File 1

General experimental information, X-ray crystallographic data, synthetic procedures, analytical data and NMR spectra for the reported compounds.

Acknowledgements

We thank the Research Center for Magnetic Resonance, the Center for Chemical Analysis and Materials Research, and the Center for X-ray Diffraction Methods of Saint Petersburg State University Research Park for obtaining the analytical data.

Funding

This research was supported by the Russian Science Foundation (project grant 21-73-00220).

ORCID® iDs

Dmitry Dar'in - https://orcid.org/0000-0002-0413-7413

References

1. Michael, J. P. *Nat. Prod. Rep.* **2008,** *25* (1), 166-187.
2. Achan, J.; Talisuna, A. O.; Erhart, A.; Yeka, A.; Tibenderana, J. K.; Baliraine, F. N.; Rosenthal, P. J.; D'Alessandro, U. *Malar. J.* **2011,** *10* (1), 144.
3. Ajani, O. O.; Iyaye, K. T.; Ademosun, O. T. *RSC Adv.* **2022,** *12* (29), 18594-18614.

4. Dorababu, A. *ChemistrySelect* **2021,** *6* (9), 2164-2177.

5. Gryzło, B.; Kulig, K. *Mini-Rev. Med. Chem.* **2014,** *14* (4), 332-344.

6. Gorka, A. P.; de Dios, A.; Roepe, P. D. *J. Med. Chem.* **2013,** *56* (13), 5231-5246.

7. Reynolds, K. A.; Loughlin, W. A.; Young, D. J. *Mini-Rev. Med. Chem.* **2013,** *13* (5), 730-743.

8. Vaitilingam, B.; Nayyar, A.; Palde, P. B.; Monga, V.; Jain, R.; Kaur, S.; Singh, P. P. *Bioorg. Med. Chem.* **2004,** *12* (15), 4179-4188.

9. Keri, R. S.; Patil, S. A. *Biomed. Pharmacother.* **2014,** *68* (8), 1161-1175.

10. Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011,** *18* (10), 1488-1508.

11. Afzal, O.; Kumar, S.; Haider, M. R.; Ali, M. R.; Kumar, R.; Jaggi, M.; Bawa, S. *Eur. J. Med. Chem.* **2015,** *97*, 871-910.

12. Mukherjee, S.; Pal, M. *Drug Discov. Today* **2013,** *18* (7), 389-398.

13. Orhan Puskullu, M.; Tekiner, B.; Suzen, S. *Mini-Rev. Med. Chem.* **2013,** *13* (3), 365-372.

14. Musiol, R. *Curr. Pharm. Des.* **2013,** *19* (10), 1835-1849.

15. Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Polanski, J. *Curr. Med. Chem.* **2010,** *17* (18), 1960-1973.

16. Bongarzone, S.; Bolognesi, M. L. *Expert Opin. Drug Discov.* **2011,** *6* (3), 251-268.

17. Moskalik, M. Y. *Molecules* **2023,** *28* (1).

18. Azevedo-Barbosa, H.; Dias, F. D.; Franco, L. L.; Hawkes, A. J.; Carvalho, T. D. *Mini-Rev. Med. Chem.* **2020,** *20* (19), 2052-2066.

19. Ajeet, A.; Mishra, A. K.; Kumar, A. *Am. J. Pharmacol. Sci.* **2015,** *3* (1), 18-24.

20. Ovung, A.; Bhattacharyya, J. *Biophys. Rev.* **2021,** *13* (2), 259-272.

21. Marciniec, K.; Pawełczak, B.; Latocha, M.; Skrzypek, L.; Maciążek-Jurczyk, M.; Boryczka, S. *Molecules* **2017,** *22* (2), 300.

22. Harvey, C. M.; Sargent, C.; Siegl, P. K. S. Endothelin receptor antagonists for the treatment of emesis. WO1996009818, April 4, 1996.

23. Chen, Y.; Cushing, T. D.; Hao, X.; He, X.; Reuchelt, A.; Rzasa, R. M.; Seganish, J.; Shon, Y.; Zhang, D. δ3-Substituted quinoline or quinoxaline derivatives and their use as phosphatidylinositol 3-kinase (PI3K) inhibitors. WO2008118455, October 2, 2008.

24. Marciniec, K.; Rzepka, Z.; Chrobak, E.; Boryczka, S.; Latocha, M.; Wrześniok, D.; Beberok, A. *Molecules* **2023,** *28* (6).

25. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003,** *59* (3), 385-390.

26. Zhang, L.; Chen, S.; Gao, Y.; Zhang, P.; Wu, Y.; Tang, G.; Zhao, Y. *Org. Lett.* **2016,** *18* (6), 1286-1289.

27. Sun, D.; Yin, K.; Zhang, R. *Chem. Commun.* **2018,** *54* (11), 1335-1338.

28. Wang, B.; Jin, S.; Sun, S.; Cheng, J. *Orga. Chem. Front.* **2018,** *5* (6), 958-961.

29. Li, L.; Zhang, X.-G.; Hu, B.-L.; Zhang, X.-H. *Chem. Asian J.* **2019,** *14* (23), 4358-4364.

30. Zhang, Y.; Chen, W.; Jia, X.; Wang, L.; Li, P. *Chem. Commun.* **2019,** *55* (19), 2785-2788.

31. Yuan, J.-M.; Li, J.; Zhou, H.; Xu, J.; Zhu, F.; Liang, Q.; Liu, Z.; Huang, G.; Huang, J. *New J. Chem.* **2020,** *44* (8), 3189-3193.

32. Liu, J.; Wang, M.; Li, L.; Wang, L. *Green Chem.* **2021,** *23* (13), 4733-4740.

33. Zhou, N.; Xia, Z.; Wu, S.; Kuang, K.; Xu, Q.; Zhang, M. *J. Org. Chem.* **2021,** *86* (21), 15253-15262.

34. Ma, Q.; Li, M.; Chen, Z.; Ni, S.-F.; Wright, J. S.; Wen, L.-R.; Zhang, L.-B. *Green Chem.* **2022,** *24* (11), 4425-4431.

35. Kang, S.; Yoon, H.; Lee, Y. *Chem. Lett.* **2016,** *45* (12), 1356-1358.

36. Wang, F.; Xu, P.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2018,** *20* (8), 2204-2207.

37. Chan, C.-K.; Lai, C.-Y.; Lo, W.-C.; Cheng, Y.-T.; Chang, M.-Y.; Wang, C.-C. *Org. Biomol. Chem.* **2020,** *18* (2), 305-315.

38. Kim, A. R.; Lim, H. N. *RSC Adv.* **2020,** *10* (13), 7855-7866.

39. Baek, J.; Si, T.; Kim, H. Y.; Oh, K. *Org. Lett.* **2022,** *24* (27), 4982-4986.

40. Fobi, K.; Bunce, R. A. *Molecules* **2022,** *27* (13).

41. Liu, N.-W.; Liang, S.; Margraf, N.; Shaaban, S.; Luciano, V.; Drost, M.; Manolikakes, G. *Eur. J. Org. Chem.* **2018,** *2018* (10), 1208-1210.

42. Chen, L.; Liang, J.; Chen, Z.-y.; Chen, J.; Yan, M.; Zhang, X.-j. *Adv. Synth. Catal.* **2019,** *361* (5), 956-960.

43. Phanindrudu, M.; Jaya, P.; Likhar, P. R.; Tiwari, D. K. *Tetrahedron* **2020,** *76* (25), 131263.

44. Jiang, S.; Zhang, Z.-T.; Young, D. J.; Chai, L.-L.; Wu, Q.; Li, H.-X. *Org. Chem. Front.* **2022,** *9* (5), 1437-1444.

45. Luo, Y.; Ding, H.; Zhen, J.-S.; Du, X.; Xu, X.-H.; Yuan, H.; Li, Y.-H.; Qi, W.-Y.; Liu, B.-Z.; Lu, S.-M.; Xue, C.; Ding, Q. *Chem. Sci.* **2021,** *12* (27), 9556-9560.

46. Wang, L.; Zhang, L.-f. *Synlett* **2022,** *33* (19), 1929-1932.

47. Vidyacharan, S.; Sagar, A.; Sharada, D. S. *Org. Biomol. Chem.* **2015,** *13* (28), 7614-7618.

48. Gharpure, S. J.; Nanda, S. K.; Adate, P. A.; Shelke, Y. G. *J. Org. Chem.* **2017,** *82* (4), 2067-2080.

49. Mao, X.-F.; Zhu, X.-P.; Li, D.-Y.; Liu, P.-N. *J. Org. Chem.* **2017,** *82* (13), 7032-7039.

50. Zhang, X.; Dhawan, G.; Muthengi, A.; Liu, S.; Wang, W.; Legris, M.; Zhang, W. *Green Chem.* **2017,** *19* (16), 3851-3855.

51. Yi, R.; Li, X.; Wan, B. *Org. Chem. Front.* **2018,** *5* (23), 3488-3493.

52. Zheng, L.; Zeng, Z.; Yan, Q.; Jia, F.; Jia, L.; Chen, Y. *Adv. Synth. Catal.* **2018,** *360* (21), 4037-4042.

53. Gharpure, S. J.; Nanda, S. K.; Fartade, D. J. *Adv. Synth. Catal.* **2021,** *363* (10), 2562-2567.

54. Sun, M.; Yu, Y.-L.; Zhao, L.; Ding, M.-W. *Tetrahedron* **2021,** *80*, 131868.

55. Amaresh, R. R.; Perumal, P. T. *Tetrahedron* **1998,** *54* (47), 14327-14340.

56. Kamal, A.; Reddy, S. K.; Khan, A. M. N.; Shetty, V. C. R. N. C. R.; Ahmed, K. S.; Kumar, P. K.; Murty, S. N. U. *Lett. Drug Des. Discov.* **2007,** *4* (8), 580-586.

57. Yang, W.; Xu, L.; Chen, Z.; Zhang, L.; Miao, M.; Ren, H. *Org. Lett.* **2013,** *15* (6), 1282-1285.

58. Su, H.; Bao, M.; Huang, J.; Qiu, L.; Xu, X. *Adv. Synth. Catal.* **2019,** *361* (4), 826-831.

59. Zhang, X.; Ma, X.; Qiu, W.; Evans, J.; Zhang, W. *Green Chem.* **2019,** *21* (2), 349-354.

60. Klochkova, A.; Bubyrev, A.; Dar'in, D.; Bakulina, O.; Krasavin, M.; Sokolov, V. *Synthesis* **2021,** *53* (10), 1795-1804.

61. Swenson, R. E.; Sowin, T. J.; Zhang, H. Q. *J. Org. Chem.* **2002,** *67* (26), 9182-9185.

62. Bubyrev, A.; Dar'in, D.; Kantin, G.; Krasavin, M. *Eur. J. Org. Chem.* **2020,** *2020* (27), 4112-4115.