



EXPLORING THE STRECKER REACTION FOR SYNTHESIZING SULFOXIMINE BUILDING BLOCKS IN MEDICINAL CHEMISTRY.

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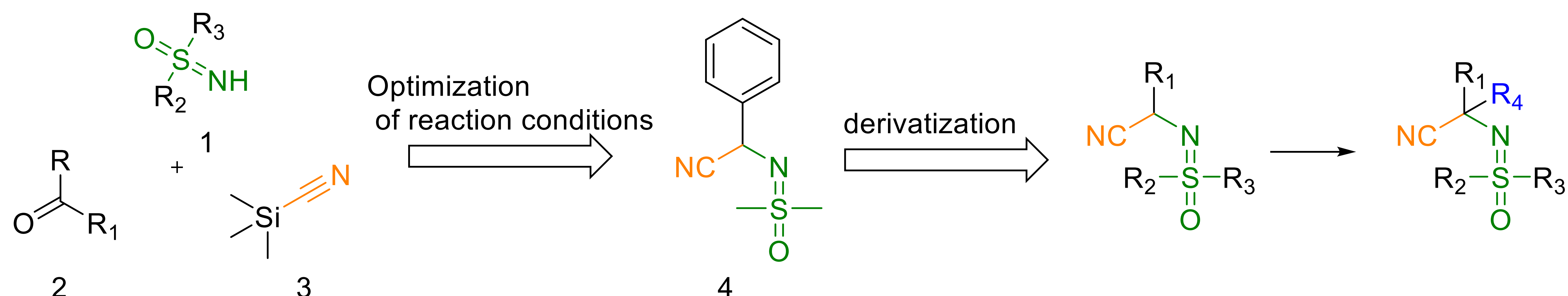
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BACKGROUND. The sulfoximine group has a great potential as a substituent in drug discovery and can be viewed as an isosteric alternative to sulfone [1]. One of the disadvantages of the sulfone group is that it introduces poor solubility due to intermolecular interactions in the solid state. Hence, introduction of the bioisosteric sulfoximine can improve this characteristics. Moreover, it offers unique H-bond donor/acceptor capabilities and has been shown to mimic the transition substrate-enzyme transition states, thus allowing for the design of potent enzyme inhibitors.

Multicomponent reactions (MCRs), such as Strecker condensations constitute a powerful tool to create molecular diversity of drug-like compounds. Therefore, we decided to examine the use of the Strecker reaction as a synthetic path to obtain designed sulfoximine derivatives[2]. The first goal was to find optimal conditions for the Strecker reaction. Next, we synthesized a diverse range of novel sulfoximine building blocks, using different sulfoximine or aldehydes and ketones as a versatile starting material. That leads us to the library of new sulfoximino-nitrile analogues that we hope will further enhance the usage of the sulfoximine group by medicinal chemists in drug discovery.



OPTIMIZATION OF REACTION CONDITION. This step aimed to determine the Strecker reaction conditions under which products are obtained with the highest possible yield. The reaction chosen for assessing the conditions was the synthesis of 2-((dimethyl(oxo)-λ⁶-sulfanylidene)amino)-2-phenylacetonitrile (4). The optimal reaction conditions were selected through optimization: the type of solvent used; the temperature at which the reaction was conducted the duration of the reactions, the stoichiometry of the reagents (1), (2) and (3), and finally the type of catalyst employed. The results have been compiled in Tables 1 and 2.

Table 2. Optimization of reaction conditions.

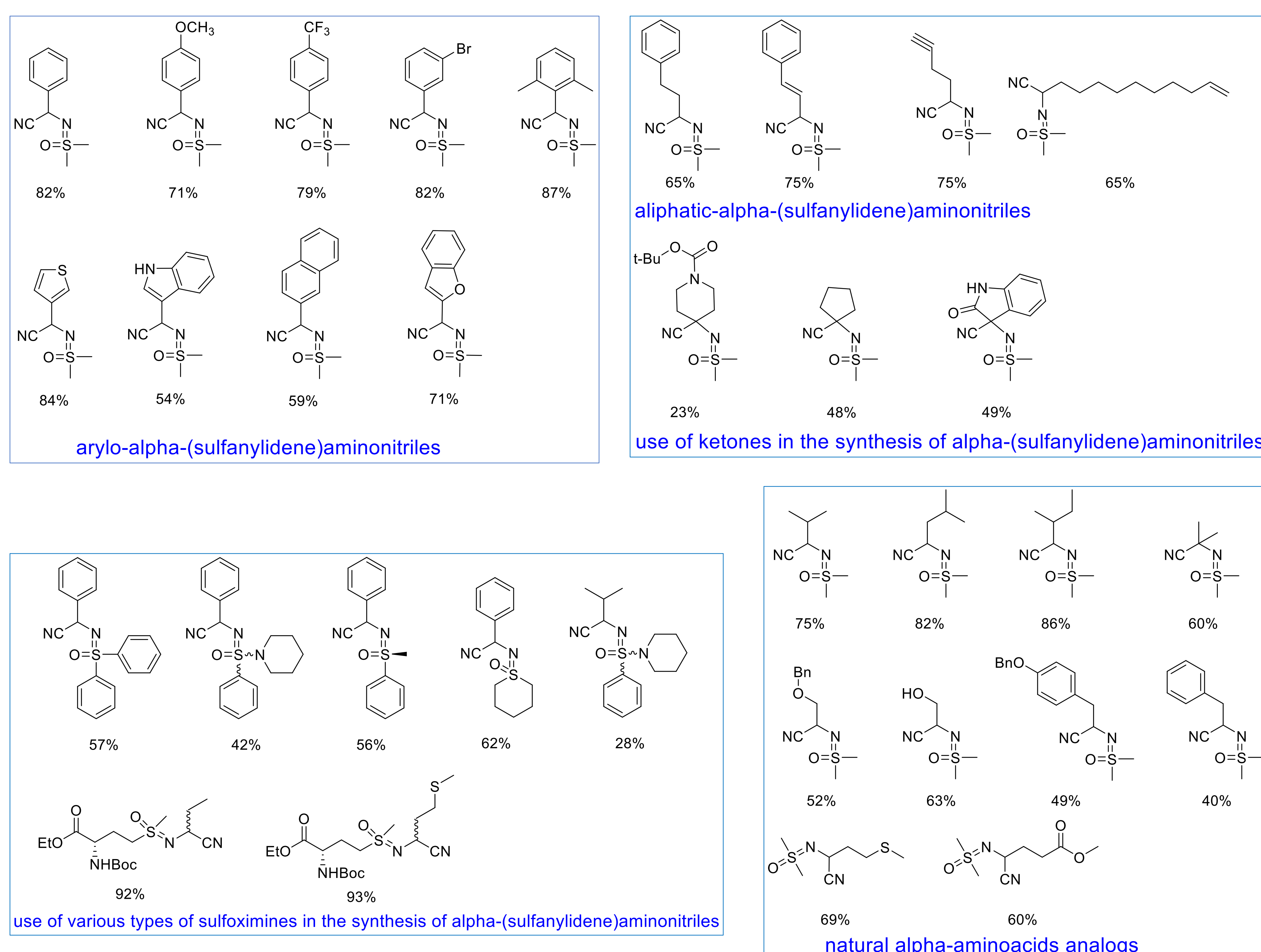
solvent	temp.	time	eq 1/2/3	yield
DCE	60°C	48h	1/1/1	75%
DCE	rt	72h	1/1/1	67%
DCE	60 °C	24h	1/1/1	72%
DCE	rt	24h	1/1/1	67%
THF	rt	24h	1/1/1	49%
ACN	rt	24h	1/1/1	26%
MeOH	rt	24h	1/1/1	68%
HFIP	rt	24h	1/1/1	60%
MeOH	rt	24h	1/1/1.2	72%
MeOH	rt	24h	1/1/1.5	62%
H ₂ O	rt	24h	1/1/1.2	45%
neat	rt	24h	1/1/1.2	34%

Table 2. Optimization of reaction conditions.

catalyst	yield	catalyst	yield
TEA	37%	ZnCl ₂	75%
PhP(O)(OH)	82%	<i>p</i> -TsOH	76%
Sc(OTf) ₂	64%	fromic acid	74%

Condition: eq 1/2/3(TMSCN); temp; time; solvent: 1/1/1.2; rt; 24h; MeOH (1mL)

DERIVATIZATION RESULTS. The obtained results confirm the validity of choosing the Strecker reaction as a synthesis method for the studied group of compounds, derivatives of α-(sulfoximino)aminonitriles. In the Strecker reaction, along with TMSCN and various types of sulfoximines, aromatic and aliphatic aldehydes were successfully utilized, resulting in respective sulfoximinonitriles. Noteworthy, aliphatic ketones and isatin were also reactive. In components having higher degrees of steric hindrance, such as ketones and sulfoximines other than dimethylsulfoximine, elevated temperature conditions (55°C) resulted in a significant increase in yields.



CONCLUSIONS. Optimization of the reaction conditions leading to sulfoximine derivatives via multicomponent Strecker reaction was accomplished, along with the synthesis of a small library of α-sulfoximinonitriles. These compounds may be regarded useful building blocks for synthesis of biologically useful compounds.

REFERENCES

- [1] Y. Han et al., "Application of sulfoximines in medicinal chemistry from 2013 to 2020," *Eur. J. Med. Chem.*, vol. 209, p. 112885, 2021.
- [2] Á. Cores, J. Clerigué, E. Orocio-Rodríguez, and J. C. Menéndez, "Multicomponent Reactions for the Synthesis of Active Pharmaceutical Ingredients," *Pharmaceuticals*, vol. 15, no. 8, 2022.

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