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Bicyclo[1.1.1]pentyl Sulfoximines: Synthesis and Functionalizations

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Abstract: Herein we present the first synthesis of bicyclo[1.1.1]pentyl (BCP) sulfoximines from the corresponding sulfides. Both BCPs and sulfoximines are bioisosteres used in medicinal chemistry and therefore desirable motifs. The access to BCP sulfides was enabled by the thiol addition to [1.1.1]propellane as published before. A broad scope with specific limitations was discovered for the sulfoximination. To diversify the sulfoximines, *N*-acylations and *N*-arylations were performed. As the *N*-arylation was low yielding we optimized the copper(I) catalyzed reaction. A wide range of aryl iodides could be deployed and competitive reactions showed that aryl bromides react equally fast. In a scale-up we prepared a suitable precursor for a BCP drug analogue.
In this work several molecular structures could be determined by single-crystal X-ray diffraction.

Keywords: bicyclo[1.1.1]pentane; bioisostere; sulfoximine; copper; arylation

Introduction

Medicinal chemistry constantly demands novel building blocks and further exploration of chemical space. The recent focus on saturated hydrocarbons as structural motifs ('escape from flatland')[1] has drawn the attention of many groups towards bicyclo[1.1.1]pentanes (BCPs).[2] Derived from [1.1.1]propellane (**4**), there have been numerous contributions to the synthesis of BCPs with C–C,[3] C–N[4] and C–S[5] bond formations. The modification of these products is an emerging field[6] and besides oxidation[5a,7] BCP sulfides **5** have not been addressed so far.

Sulfoximines have been described as 'neglected opportunity in medicinal chemistry'.[8] With increasing interest in these bioactive compounds in the last decade several examples for drug candidates with this polar sulfur(VI) group have been published (Figure 1).

The development of Roniciclib (**1**), a promising pan-CDK inhibitor by Bayer, was unfortunately stopped in phase II due to a safety signal.[9] In a diabetes-related SAR study by Amgen compound **2** showed improved *in vivo* pharmacokinetic properties and is currently under further investigation.[10] Compound **3** has been disclosed as inhibitor of neutrophil elastase activity by Boehringer Ingelheim.[11]

Overall, the replacement of other sulfur-based functional groups by sulfoximines can have positive effects on physicochemical properties and metabolic stability.[12] Recently, polycyclic sulfoximines gained interest for their 3D scaffold and easy diversification.[13]

After early syntheses of sulfoximines from sulfoxides with hydrazoic acid,[14] the available methods underwent significant improvements.[15]

Unprotected sulfoximines can be synthesized from sulfoxides involving a transition-metal catalyst[16] or metal-free using ammonium carbamate.[17] The direct synthesis of sulfoximines from sulfides using the same ammonium source with diacetoxyiodobenzene as

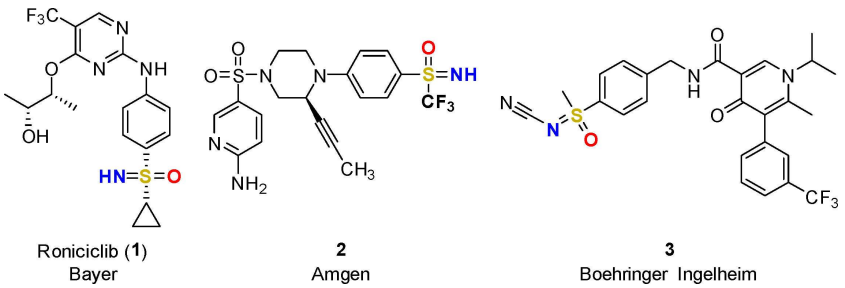


Figure 1. Sulfoximine-containing drug candidates by Bayer (**1**), Amgen (**2**) and Boehringer Ingelheim (**3**).

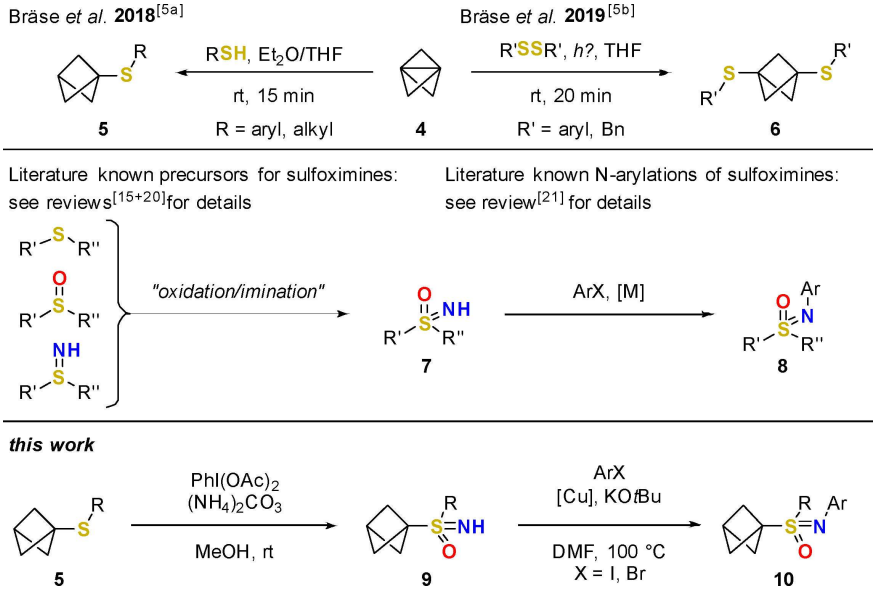
oxidant was simultaneously investigated by Bull and Luisi[18] and Reboul.[19] Sulfoximine syntheses from sulfilimines and different *N*-substituted sulfoximines are summarized in a recent review[20] (Scheme 1). The modification of sulfoximines **7** at the nitrogen, e. g. arylations to **8**, has also been heavily investigated.[21]

In this work we converted BCP sulfides **5**[5a] to sulfoximines **9**. In a scale-up reaction we prepared a precursor **11 f** for a BCP-Roniciclib analogue **13**. Further, we investigated the *N*-arylation of **9** *via* copper(I)-catalysis to **10**.

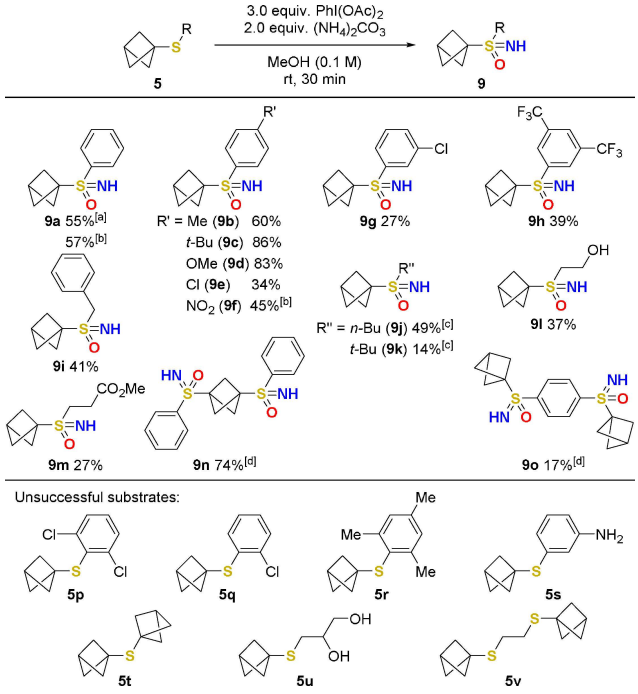
Results and Discussion

We started our investigations with literature conditions for the sulfoximine synthesis by Li *et al.* (Scheme 2).[22] With model substrate **5 a** we obtained a moderate yield of 55%. In a scale-up (6.81 mmol) with slightly increased equivalents of oxidant ($PhI(OAc)_2$) and ammonium source ($(NH_4)_2CO_3$) the product **5 a** could be isolated in 57% yield. With the two-step route through the sulfoxide (see SI) a similar yield of 62% (over two steps) was obtained. However, the two-step route required two purifications by column chromatography. Therefore, the reaction from the sulfides **5** seemed advantageous. For the scope we decided to keep the larger excess of oxidant and ammonium source of 3.0 and 2.0 equiv., respectively.

A variety of functional groups was tolerated in the reaction. Alkyl- (**9 b**, **c**), chloro- (**9 e**, **g**), trifluoromethyl- (**9 h**) and methoxy-benzenes (**9 d**) worked reasonably well as long as they were substituted in *meta*- or *para*-position. We found that all *ortho*-substituted substrates did not convert to the desired products. The reason for this might be steric hindrance as the BCP is already a sterically demanding group. To back-up this assumption bis-BCP sulfide **5 t** was also subjected to the reaction. No corresponding sulfoximine could be detected.



Scheme 1. Preliminary work by our group in the synthesis of BCP-sulfides **5** and **6**, summary of sulfoximine precursors, *N*-arylations of sulfoximines and content of this work.



Scheme 2. Scope of the sulfoximine synthesis from the BCP-sulfides **5**. Reaction scale: **5**, 0.16–0.60 mmol. [a] Reaction conditions: 2.3 equiv. $PhI(OAc)_2$, 1.5 equiv. $(NH_4)_2CO_3$. [b] Reaction scale: **5a**, 6.81 mmol; **5f**, 4.52 mmol. [c] Yield after two steps from **4**. [d] Reaction conditions: 6.0 equiv. $PhI(OAc)_2$, 4.0 equiv. $(NH_4)_2CO_3$, MeOH (0.05 M).

The following trend could be observed for the aryl substituted sulfides. Electron-withdrawing groups like in **9e**, **9g** or **9h** led to decreased yields, whereas electron-donating groups like in **9b** and **9c** increased the yield compared to **9a**. For the methoxy substituted compound **9d** the +M effect outweighs the −I effect. The sulfur is being oxidized during the reaction which is favored by a higher electron density.

Purely alkyl substituted sulfides provided the desired products in generally lower yields. Both BCP-butyl sulfides (**5j**, **5k**) are volatile. Therefore, the substrates were not purified completely after the thiol addition to **4**, but rather used with residual solvent. With **9l** and **9m** the tolerance of alcohols and esters could also be confirmed.

A double sulfoximination could be performed in a good yield of 74% to obtain **9n**. The sulfide **5o** only led to a low yield of 17%. Presumably, after oxidation/imination of the first sulfide the electron density in the benzene ring is lowered which leads to a reduced reactivity in this reaction (see above). For both products **9n** and **9o** we were not able to distinguish or separate the diastereomers by HPLC. For **9n** the *meso* diastereomer (*R**,*S**) could be confirmed by single crystal X-Ray diffraction (SI).

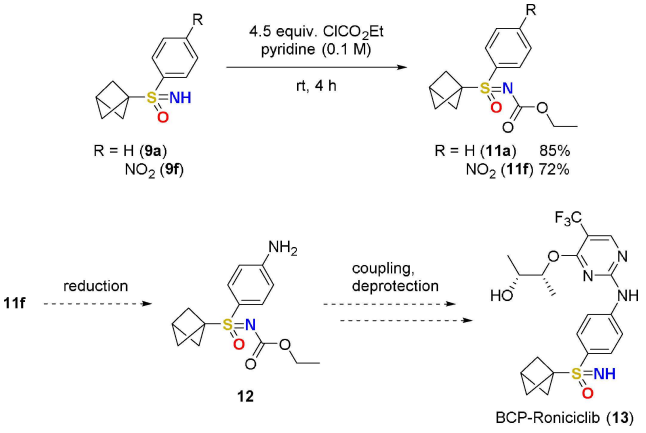
For the enantioselective synthesis of sulfoximines we considered a route through enantioselective oxidation to the sulfoxide (**S4**).[23] However, in all our attempts with chiral titanium complexes we obtained a racemic mixture of **S4**.

As we were interested in building blocks for medicinal chemistry, we chose to prepare a BCP-Roniciclib precursor. Therefore, we subjected the 4-nitrobenzene substituted BCP sulfide **5f** to the reaction in a larger scale (4.52 mmol). The product **9f** was obtained in 45% yield.

The free NH of the sulfoximine group can be problematic in some reactions. To overcome this issue, we used a standard *N*-acylation protocol to protect the nitrogen (Scheme 3). For the model substrate **9a** a very good yield of 85% was obtained. The BCP-Roniciclib precursor **11f** was obtained in a good yield (72%) as well. The following steps to **13** were not included in this study, but should be possible analogous to known Roniciclib syntheses.[24]

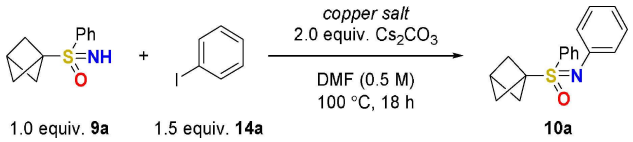
For the *N*-arylation we started our optimization with model compound **9a** and conditions by Bolm *et al.* (Table 1).[25] The initial yield was encouraging with 37% (Entry 1). The variation of the copper(I) source to different halide salts and more soluble complexes did not improve the yield of the reaction (Entries 2–9). Only copper(I) acetate led to an increase of 2%. The lower cost of copper(I) oxide and the minor difference in yield made us stick to the latter. A test reaction with copper(II) was performed and confirmed that the catalytically active species is copper (I) (Entry 10). Increasing the catalyst loading from 10 to 20 mol% led to a slightly improved yield of 42% (Entry 11).

With the designated catalyst, we changed the base to K_2CO_3 (Table 2, Entry 1) but obtained a significantly lower yield. KO*t*Bu finally increased the yield



Scheme 3. *N*-acylation of BCP-sulfoximines **9** with ethyl chloroformate. **11f** is a suitable precursor for a BCP-Roniciclib analogue **13**.

Table 1. Screening of different copper catalysts for the *N*-arylation of sulfoximine **9a**.[a]

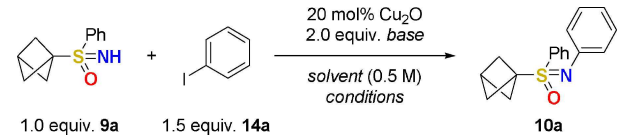


1.0 equiv. **9a** 1.5 equiv. **14a** **10a**

Entry	Copper salt	Yield [%][b]
1	10 mol% Cu_2O	37
2	10 mol% CuI	3
3	10 mol% CuBr	15
4	10 mol% CuCl	7
5	10 mol% CuCN	15
6	10 mol% CuOAc	39
7	10 mol% CuTC	1
8	10 mol% CuOTf-toluene	15
9	10 mol% $Cu(CH_3CN)_4PF_6$	31
10	10 mol% CuO	–
11	20 mol% Cu_2O	42

[a] Reaction scale: **9a**, 0.24 mmol.
[b] Isolated yield.

Table 2. Screening of different bases, solvents and conditions for the *N*-arylation of sulfoximine **9a**.[a]



1.0 equiv. **9a** 1.5 equiv. **14a** **10a**

Entry	Base	Solvent	Conditions (temperature, time)	Yield [%][b]
1	K_2CO_3	DMF	100 °C, 18 h	5
2	KO*t*Bu	DMF	100 °C, 18 h	63
3	KO*t*Bu	ACN	100 °C, 18 h	31
4	KO*t*Bu	DMSO	100 °C, 18 h	48
5	KO*t*Bu	toluene	100 °C, 18 h	38
6	KO*t*Bu	DMF	120 °C, 18 h	57
7	KO*t*Bu	DMF	140 °C, 18 h	54
8	KO*t*Bu	DMF	100 °C, 24 h	57
9	KO*t*Bu	DMF	100 °C, 48 h	56
10	KO*t*Bu	DMF	100 °C, 18 h	70[c]

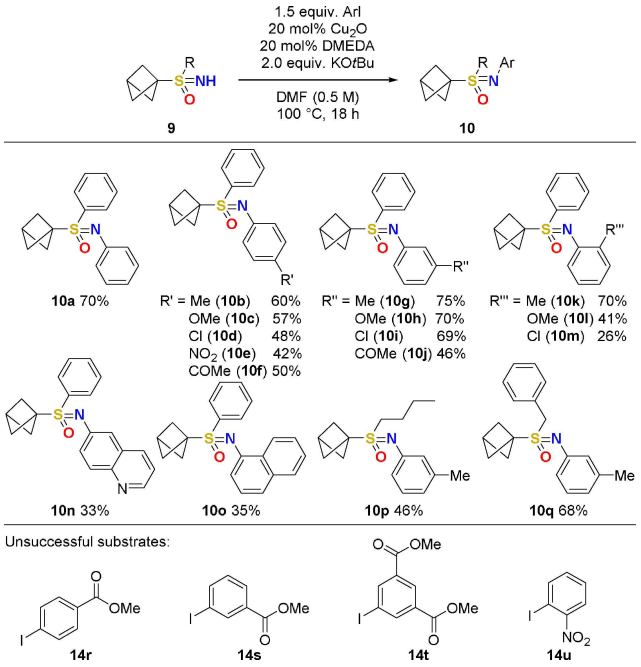
[a] Reaction scale: **9a**, 0.24 mmol.
[b] Isolated yield.
[c] 20 mol% 1,2-dimethylethylenediamine (DEMDA) as additive.

to 63% (Entry 2). After different variations in solvents, temperature and time with no improvement in yield (Entries 3–9), we stick with the initial conditions with DMF at 100 °C for 18 h. The addition of 1,2-dimethylethylenediamine (DMEDA) as a ligand gave a final boost to an acceptable yield of 70% (Entry 10).

With the optimized conditions for the *N*-arylation of BCP sulfoximines **9** we examined the aryl iodide scope with model compound **9a** (Scheme 4). Substitution in *meta*-, *ortho*- and *para*-position did not disturb the reaction. The functional group tolerance was very good, as alkyl- (**10b**, **g**, **k**), methoxy- (**10c**, **h**, **l**), chloro- (**10d**, **I**, **m**), nitro- (**10e**) and acyl-groups (**10f**, **j**) could successfully be retained in this reaction. Carboxylic esters were not tolerated. *Meta*-substitutions generally led to the highest yields, close to the model compound. 3-Iodotoluene even exceeded the model compound with 75% yield for **10g**. Therefore, this iodide was chosen to react with purely alkyl substituted BCP sulfoximines to **10p** and **10q**. With larger aromatic systems the desired products were obtained in lower yields (**10n**, **o**).

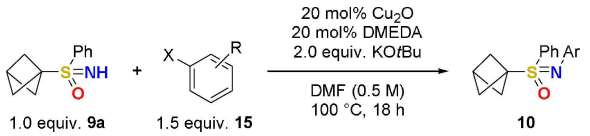
During the scope investigation two different bromoiodobenzenes **15a**, **b** were used and in both cases mixtures of products were obtained (Table 3, Entries 1–2). The yield was determined by NMR and revealed a 1:1.2 and 1:1 ratio of the products, respectively. This result was supported by mass spectrometry and the products were confirmed by HRMS. As the two halides seemed to react equally fast, 3-bromo-5-chloroiodobenzene (**15c**) was also subjected to the reaction. Again, both bromide and iodide reacted but no product from a reaction of the chloride could be observed (Entry 3).

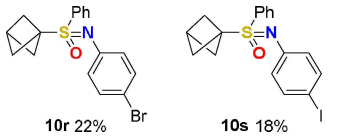
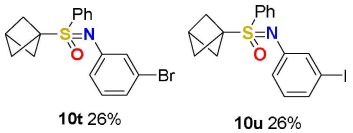
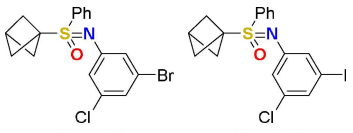
In the course of this study we could obtain several single crystals and determine the structure by X-Ray diffraction (SI).



Scheme 4. Scope of the *N*-arylation of sulfoximines **9**. Reaction scale: **9**, 0.23–0.27 mmol.

Table 3. *N*-arylation of 9a with different aryl halides 15.[a] The products could not be separated, the yield was determined by NMR.



Entry	15	Products
1	1-I, 4-Br (**15a**)	 **10r** 22% **10s** 18%
2	1-I, 3-Br (**15b**)	 **10t** 26% **10u** 26%
3	1-I, 3-Br, 5-Cl (**15c**)	 **10v** 17% **10w** 17%

[a] Reaction scale: **9a**, 0.24 mmol.

Conclusion

The synthesis of BCP sulfoximines from sulfides shows great functional group tolerance and can be used to prepare variable building blocks. The conditions are simple and the reaction can be scaled-up easily. A limitation can occur with a second sterically demanding substituent at the sulfide. To diversify the products *N*-acylations can be performed as well as copper(I)-catalyzed *N*-arylations with aryl halides. The conditions for the *N*-arylation were optimized in this work and a good scope could be shown. For future applications C2-substituted BCPs would be highly desirable.[26] The combination with sulfoximines leads to a great extension of the accessible chemical space.

Experimental Section

Standard Procedure for BCP Sulfoximine Synthesis:

To a stirred solution of sulfide **5a** (150 mg, 0.85 mmol) in MeOH (8.5 mL) were added $(NH_4)_2CO_3$ (163 mg, 1.70 mmol) and $PhI(OAc)_2$ (740 mg, 2.55 mmol) at rt. The reaction mixture was stirred for 30 min (open flask). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (*c*Hex/EtOAc 1:1) to give 100 mg (0.48 mmol, 57% yield) of the desired product **9a** as a white solid.

Standard Procedure for *N*-arylation of BCP-sulfoximines:

An oven-dried vial was charged with a magnetic stir bar, the sulfoximine **9a** (50 mg, 0.24 mmol), Cu_2O (6.9 mg, 0.05 mmol) and KO*t*Bu (54 mg, 0.48 mmol). The vial was evacuated and backfilled with argon for three times. Then, dry DMF (0.5 mL), DMEDA (5 µL, 0.05 mmol) and iodobenzene (**14a**, 40 µL, 74 mg, 0.36 mmol) were added *via* syringe and the reaction mixture was stirred at 100 °C for 18 h. After cooling to rt, the mixture was diluted with CH_2Cl_2 (5 mL), filtered through a short silica pad and concentrated under reduced pressure. The crude product was purified by column chromatography (*c*Hex/EtOAc 10:1) to give 48 mg (0.17 mmol, 71% yield) of the desired product **10a** as a white solid.

Full experimental details and analytical data (^{1}H NMR, ^{13}C NMR, X-ray analysis) are provided in the Supporting Information (SI).

CCDC 1951387 (**9a**), 1951388 (**9c**), 1951389 (**9f**), 1951390 (**9i**), 1951391 (**9n**), 1951392 (**10a**), 1951393 (**11a**), and 1951394 (**11f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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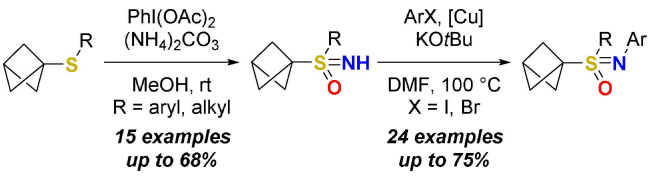

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