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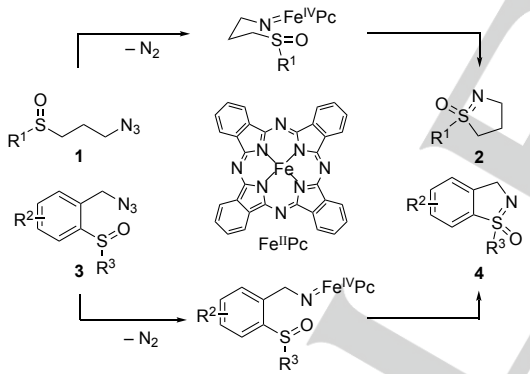
Three-Dimensional Heterocycles by Iron-Catalyzed Ring-Closing Sulfoxide Imidation

Hao Yu, Zhen Li, and Carsten Bolm*

Abstract: A general and atom-economical method for the synthesis of cyclic sulfoximines by intramolecular imidations of azido-containing sulfoxides using a commercially available Fe^{II} phthalocyanine ($Fe^{II}Pc$) as catalyst has been developed. The method conveys a broad functional group tolerance and the resulting three-dimensional heterocycles can be modified by cross-coupling reactions.

Three-dimensional heterocycles are important molecular scaffolds in medicinal and crop protection chemistry.[1] A high degree of saturation and the presence of stereogenic centers are also relevant factors for successful transitions of newly identified hits through clinical trials to drugs.[2,3] Aiming at expanding the rather limited chemical space of heterocyles,[4] we began studying synthetic opportunities leading to rather under-represented sulfur-based three-dimensional ring systems such as benzothiazines,[5] benzo[*c*]isothiazole 2-oxides[6] and related structures.[7] In most protocols preformed sulfoximines were used as starting materials. Here, we introduce an alternative strategy. It starts from azido-substituted sulfoxides (**1** and **3**) and applies readily available Fe^{II} phthalocyanine ($Fe^{II}Pc$) as catalyst for ring-closing sulfur imidations providing products **2** and **4**, respectively (Scheme 1).



Scheme 1. Iron-catalyzed intramolecular imidation of sulfoxides.

[*] H. Yu, Dr. Z. Li, Prof. Dr. C. Bolm
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: carsten.bolm@oc.rwth-aachen.de
Homepage: http://bolm.oc.rwth-aachen.de/

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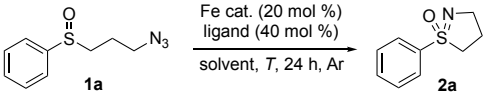
In recent years, iron has been recognized as important metal for homogeneous catalysis.[8] Its use in catalyzed nitrene transfer reactions has led to convenient methods for C–H bond aminations.[9] In many cases, organoazides have been applied as nitrene precursors, which is attractive because molecular nitrogen is the only byproduct being released during substrate activation.[10-13] We[14] and others[12b,15] used combinations of iron catalysis and organoazides in sulfur imidations.[16] As a result, sulfilimines and sulfoximines were obtained, which proved interesting for asymmetric synthesis[17] and applications in crop protection and medicinal chemistry.[18] We now wondered if such approach could also be utilized in the synthesis of sulfur-based three-dimensional heterocycles. The results of a proof-of-concept study are summarized here.

In our previous work on *inter*molecular imidations of sulfoxides with hydroxylamine triflic acid salts, an $FeSO_4$/phenanthroline combination or $Fe^{II}Pc$ was used as catalyst.[14g] Those systems were applied here, attempting to cyclize [(3-azidopropyl)sulfinyl]benzene (**1a**) to 4,5-dihydro-3*H*-isothiazole 1-oxide **2a** by intramolecular imidation. The first one, however, did not give any of the desired product (in benzene at 60 °C or 100 °C for 24 h; Table 1, entries 1 and 2). With $Fe^{II}Pc$ as catalyst, only traces of **2a** were observed when the reaction was performed at 60 °C (Table 1, entry 3). To our delight, the yield of **2a** increased to 80% at 100 °C (Table 1, entry 4).

Table 1. Evaluation of reaction conditions.[a]



Entry	Fe cat.	Ligand[b]	Solvent	*T* [°C]	Yield [%][c]
1	$FeSO_4$	1,10-phen	benzene	60	n.r.
2	$FeSO_4$	1,10-phen	benzene	100	n.r.
3	$Fe^{II}Pc$	-	benzene	60	trace
4	$Fe^{II}Pc$	-	benzene	100	80
5	$Fe^{II}Pc$	-	toluene	100	95
6	$Fe^{II}Pc$	-	toluene	80	58
7	$Fe^{II}Pc$	-	PhCl	100	92
8	$Fe^{II}Pc$	-	CH_3CN	100	42
9	$Fe^{II}Pc$	-	DCE	100	66
10	$Fe^{II}Pc$	-	dioxane	100	90
11[d]	$Fe^{II}Pc$	-	toluene	100	95
12[e]	$Fe^{II}Pc$	-	toluene	100	93
13	-	-	toluene	100	n.r.

[a] Reaction conditions: **1a** (0.20 mmol), Fe catalyst (0.04 mmol, 20 mol %), ligand (0.08 mmol, 40 mol %), solvent (0.2 M), under argon, 24 h. [b] 1,10-phen = 1,10-phenanthroline. [c] n.r. = no reaction. [d] Fe catalyst (0.02 mmol, 10 mol %). [e] Fe catalyst (0.01 mmol, 5 mol %).

To further optimize the reaction conditions, various solvents were screened (Table 1, entries 5-10). Toluene was identified as

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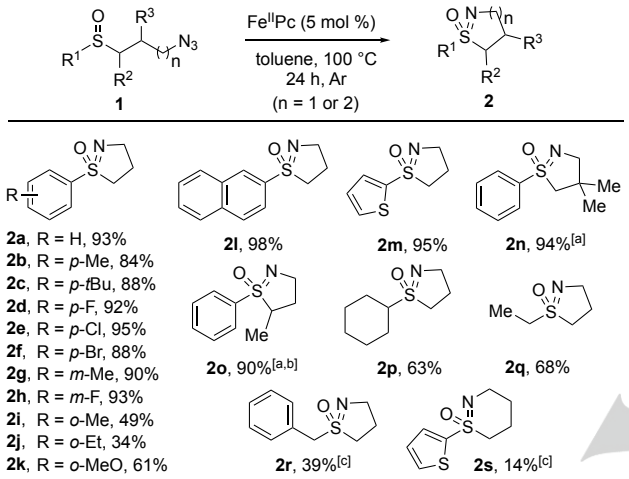
optimal medium leading to **2a** in 95% yield (Table 1, entry 5). Decreasing the reaction temperature from 100 °C to 80 °C lowered the yield of **2a** (Table 1, entry 5 versus entry 6). Noteworthy, the catalyst loading could be reduced from 20 mol % to 5 mol % without significantly affecting the product yield (Table 1, entry 5 versus entries 11 and 12). In the absence of the iron catalyst, no cyclization occurred (Table 1, entry 13).

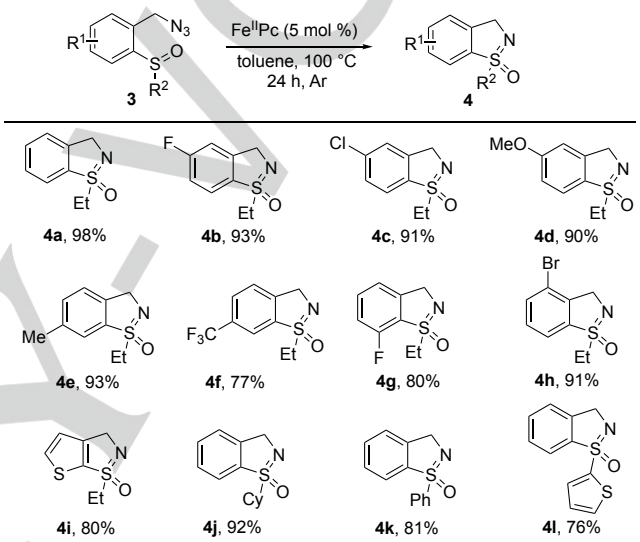
Under the optimized conditions using 5 mol % of $Fe^{II}Pc$ as catalyst, various 3-azidoalkyl sulfoxides (**1a**-**r**) were subjected to the intramolecular imidation conditions next. As a result, the corresponding cyclized products **2** were obtained in yields up to 98% (Scheme 2).



Scheme 2. Iron-catalyzed intramolecular imidations of 3-azidosulfoxides **2** (0.2 mmol scale). [a] Use of 20 mol % of $Fe^{II}Pc$ at 140 °C. [b] d.r. = 1 : 1. [c] Use of 20 mol % of $Fe^{II}Pc$.

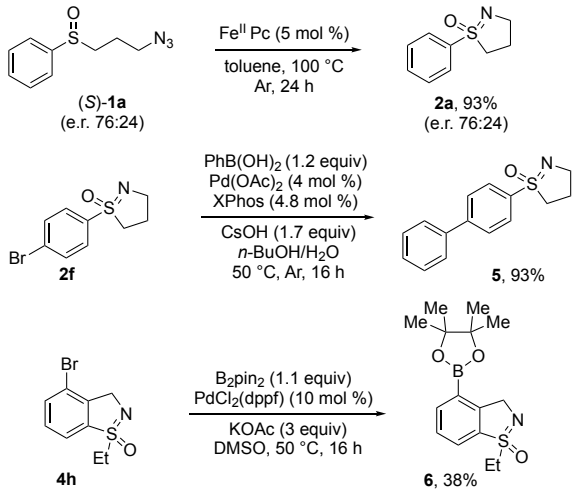
In the series of 1-phenyl 4,5-dihydro-3*H*-isothiazole 1-oxides **2a**-**k** a wide range of substituents (including various alkyl and halo groups) were tolerated, and generally, high yields were achieved for products having *para*- and *meta*-substituted arenes (**2a**-**h**). *Ortho*-substituents on arenes appeared to hamper the cyclization leading to products **2i**-**k** in only moderate yields (34-61%). 2-Naphthyl and 2-thiophenyl 3-azidopropyl sulfoxides (**1l** and **1m**) were very viable substrates providing the corresponding 4,5-dihydro-3*H*-isothiazole 1-oxides **2l** and **2m** in 98% and 95% yield, respectively. To our surprise, cyclizations of sulfoxides with methyl-substituted azidoalkyl chains (**1n** and **1o**) proved difficult and starting materials remained. However, raising the temperature from the common 100 °C to 140 °C and applying 20 mol % of the catalyst (instead of the normally used 5 mol %) allowed to isolate products **2n** and **2o** (with a d.r. of 1:1) in 94% and 90% yield, respectively.[19] Non-aromatic products **2p** and **2q** were obtained in yields of 63% and 68%. Even with a catalyst loading 20 mol %, the yields of products **2r** and **2s** remained moderate. Presumaby due to subsequent reactions at the rather sensitive benzylic position, product **2r** was isolated in 39% yield. Although 3,4,5,6-tetrahydro-1,2-thiazine 1-oxide **2s** was formed in only 14% yield, the reaction was relevant as it indicated that also 4-azidobutyl sulfoxides could be applied as substrates.[20]

Starting from aryl sulfoxides with benzylic azido groups **3**, 3*H*-1λ^4-arylo[*d*]isothiazole 1-oxides **4** could be prepared (Scheme 3).[21] In the series of products with an 1-ethyl substituent and a benzo[*d*]isothiazole core (**4a**-**h**), the unsubstituted aryl derivative **4a** gave the highest yield (98%). Otherwise, neither electronic nor steric effects induced by substituents appeared to play a major role leading to yields ranging for 77% (**4f**) to 93% (**4b** and **4e**) for such compounds. 1-Ethyl-3*H*-1λ^4-thieno[*d*]isothiazole 1-oxides **4i** was obtained in 80% yield. Also starting from aryl sulfoxides with cyclohexyl, phenyl and 2-thienyl groups was possible, and the corresponding products (**4j**: 92%, **4k**: 81%, and **4l**: 76%) were formed in good to high yields.



Scheme 3. Iron-catalyzed intramolecular imidations providing 3*H*-1λ^4-arylo[*d*]isothiazole 1-oxides **4** (0.2 mmol scale).

As demonstrated for the cyclization of (*S*)-**1a**, the intramolecular sulfur imidation is stereospecific (Scheme 4, top).[22]



Scheme 4. Stereospecific imidation (top) and cross couplings with **2f** and **4h** (middle and bottom).

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With the goal to demonstrate the synthetic applicability of the products, 4,5-dihydro-3*H*-isothiazole 1-oxide **2f** and 3*H*-1λ^4-arylo[*d*]isothiazole 1-oxide **4h** were subjected to metal-catalyzed cross coupling conditions. Using **2f** in a Suzuki-type arylation reaction with phenylboronic acid in the presence of cesium hydroxide under catalysis with palladium/XPhos afforded cross coupling product **5** in 93% yield (Scheme 4, middle). Next, treating **4h** with bis(pinacolato)diboron (B_2Pin_2), $PdCl_2$(dppf) and potassium acetate in DMSO at 50 °C led to pinacol boronic acid ester **6** in 38% yield (Scheme 4, bottom). We consider product **6** as useful building block for further functionalizations as recently demonstrated for related sulfoximine derivatives.[6b,23]

In summary, we developed an intramolecular imidation of sulfoxides using alkyl azides as nitrene precursors.[24] Employing commercially available Fe^{II}phthalocyanine ($Fe^{II}Pc$) as catalyst, various cyclic sulfoximine derivatives can be accessed in up to 98% yield. The substrate scope is broad, leading to products, which can further be derivatized by metal-catalyzed cross-couplings.

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Keywords: azide • cyclic sulfoximine • intramolecular imidation • iron • nitrene transfer

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[22] Both (*S*)-**1a** and **2a** had an e.r. of 76:24. Based on previous work (refs. 12b, 14a, and 14c) we assume that the imidation occurred with retention of configuration at sulfur.

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[24] To the best of our knowledge, this is the first use of alkyl azides in such iron-catalyzed sulfoxide imidations. The previous conversions (ref. 14 and 15) involved azides with acyl, tosyl, or related electron-withdrawing substitutents.

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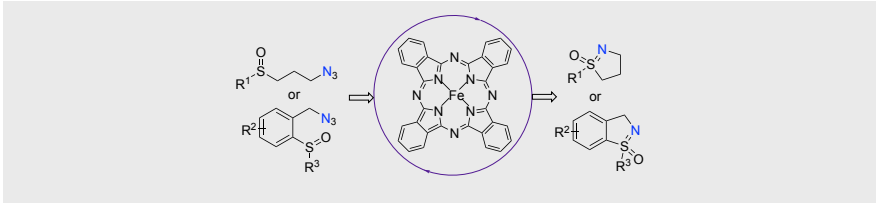

An iron-catalyzed intramolecular imidation of azido-substituted sulfoxides was developed. The reactions furnish cyclic sulfoximines in high yields and exhibit a broad substrate scope. The products can further be functionalized

*Hao Yu, Zhen Li, and Carsten Bolm**

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