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Synthesis of Sulfoximines and Sulfilimines with Aryl and Pyrazolylmethyl Substituents

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Abstract: Sulfoximines bearing pyrazolylmethyl and aryl substituents, which are relevant to the crop protection industry, and their corresponding sulfilimine intermediates, have been prepared from sulfide precursors by either iron-catalyzed nitrogen transfer reactions or metal-free imination procedures. Whereas the former approach leads to *N*-nosyl-substituted products, the latter affords *N*-cyano derivatives.

Keywords: heterocycles; imination; iron catalysis; metal-free conditions; sulfoximines

Sulfoximines have been widely used as building blocks for the synthesis of chiral ligands[1] and pseudopeptides,[2] and they are of increasing interest due to their potential as bioactive molecules.[3,4] Although a number of synthetic approaches for the preparation of sulfoximines have been described,[5] the synthesis of derivatives with heteroaryl and, in particular, arylmethyl substituents remains highly challenging. Sulfoximines containing pyrazolylmethyl groups, and *N*-cyano substituents (such as **A** and **B**, respectively, Figure 1) are of particular interest to the crop protection industry.[3]

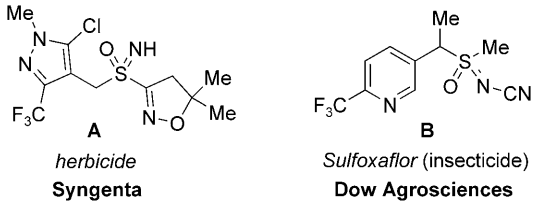
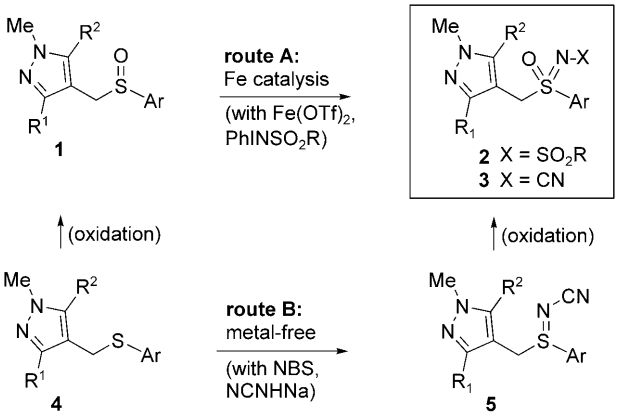


Figure 1. Examples of sulfoximines in crop protection.

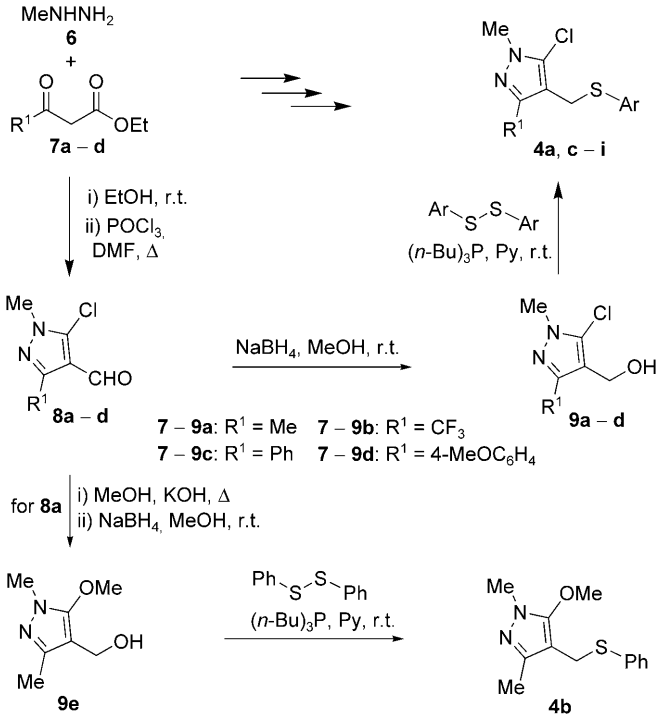
Herein, we report the development of two synthetic approaches towards sulfoximines with such substitution patterns.

Initially, two routes were envisaged for the preparation of aryl pyrazolylmethyl sulfoximines **2** and **3** (Scheme 1): firstly, a straightforward iron-catalyzed imination of sulfoxides **1** which was recently developed within our laboratories [route A, to give **2** (X = SO_2R)][6–8] and, secondly, a metal-free approach employing an NBS-mediated sulfur imination of sulfides **4** with cyanogen amine followed by oxidation of the resulting aryl pyrazolylmethyl sulfilimines **5** [route B, to give **3** (X = CN)].[9,10]

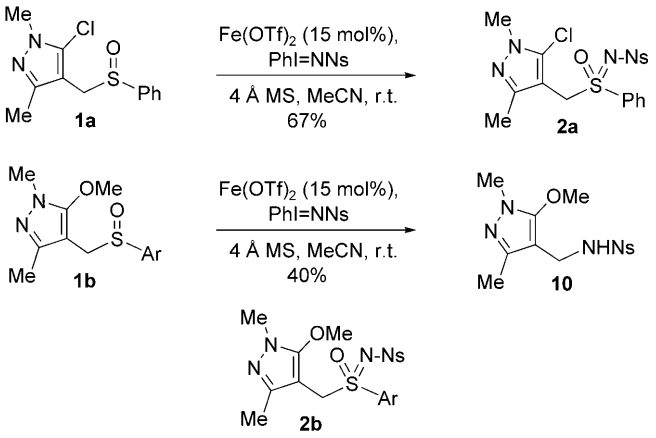
For both approaches sulfides **4** were the key intermediates. Their synthesis began with condensation of methylhydrazine (**6**) with a range of β-keto esters **7a**–



Scheme 1. Approaches towards aryl pyrazolylmethyl sulfoximines **2** and **3**.



Scheme 2. Synthesis of aryl pyrazolylmethyl sulfides **4**.



Scheme 3. Imination of aryl pyrazolylmethyl sulfoxides **1a** and **1b** under catalysis with $Fe(OTf)_2$.

d (Scheme 2). Subsequent Vilsmeier–Haack chloroformylation led to aldehydes **8a–d**. Reduction led to the corresponding hydroxymethylpyrazoles **9a–d**. Alternatively, treatment of aldehyde **8a** with a solution of KOH in methanol at elevated temperature gave the 5-methoxy derivative **9e** following reduction.[11] Sulfides **4** were finally obtained by treatment of **9a–e** with various aromatic and heteroaromatic disulfides in the presence of an excess of $(n\text{-Bu})_3P$ in pyridine at ambient temperature (in yields ranging from 57 to 92%).

Previous studies within our laboratories identified $Fe(OTf)_2$ as a highly efficient catalyst, when used in conjunction with PhI=NNs, for sulfur imination reactions.[6c] Application of this methodology to the direct synthesis of the aryl pyrazolylmethyl sulfoximines **2** from sulfoxides **1** (prepared by oxidation of sulfides **4** with *m*-CPBA) was initially investigated (route A, Scheme 1). Indeed, when the established imination conditions [15 mol% $Fe(OTf)_2$, 0.5 h] were applied to compound **1a**, the imination proceeded well, affording exclusively the corresponding sulfoximine **2a** in 67% yield. However, in the case of sulfoxide **1b**, the desired product **2b** was not formed, instead sulfonamide **10**, resulting from substitution at the activated methylene, was obtained in 40% yield (Scheme 3). We suspected that the electron-donating methoxy substituent at the 5 position of pyrazole **1b** was responsible for this undesired reaction path.

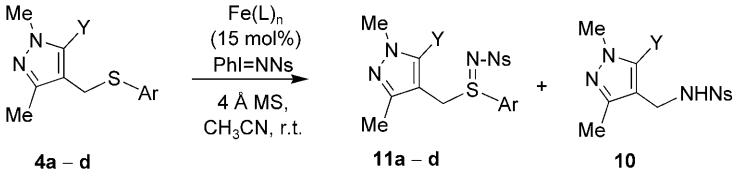
Since our previous studies revealed that sulfides were more reactive than sulfoxides with respect to iron-catalyzed sulfur iminations, a reaction sequence starting with imination of sulfides **4** was considered. Subsequent oxidation of the resulting sulfilimines **11** would then provide sulfoximines **2**.

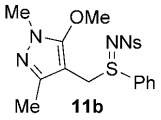
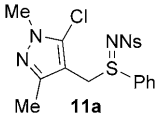
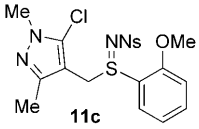
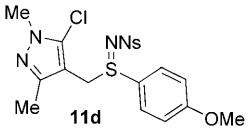
Taking into account the previous observations, the imination of methoxy-substituted sulfide **4b** was expected to be most challenging and thus, this substrate was chosen for a brief catalyst optimization study (Table 1, entries 1–3). Pleasingly, imination with either $Fe(NTf_2)_2$[12] or $Fe(OTf)_2$[6c] gave the desired sulfilimine **11b**, in moderate yield after only 0.5 h (51 and 71% yields, respectively) albeit with small amounts of by-product **10**. Use of less active catalysts such as $Fe(acac)_3$[6a] led to longer reactions times (16 h), resulting in poorer yields and greater quantities of **10**.

As in the sulfoxide imination, changing the 5-methoxy substituent of the pyrazole to a chloro group led to a more efficient transformation, and sulfilimine **11a** was obtained from sulfide **4a** in 92% yield (Scheme 4, Table 1, entry 4). Formation of the corresponding sulfonamide was not observed. A methoxy substituent in the *ortho* position of the aryl group inhibited the iron-catalyzed imination as revealed by the attempted conversion of sulfide **4c**, which led only to the decomposition of starting material (Table 1, entry 5). In contrast, when the methoxy group was located in the *para* position of the phenyl ring, as in sulfide **4d**, the corresponding sulfilimine **11d** was obtained in 54% yield (Table 1, entry 6).

Unfortunately, a brief investigation into the oxidation of sulfilimines **11** with peracids did not yield the desired sulfoximines. Thus, subsequent efforts were focused on route B (Scheme 1) taking into account that heterocyclic sulfoximines bearing a cyano group at the sulfoximine nitrogen are of particular biological relevance to the crop protection industry. As a method for the synthesis of *N*-cyano sulfilimines **5**, the recently introduced metal-free sulfide imination

Table 1. Iron-catalyzed iminations of sulfides **4a–d** to give the corresponding sulfilimines **11a–d**.[a]

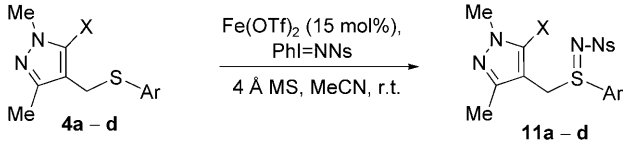


Entry	4	$Fe(L)_n$	T [h]	Expected Product	Yield of **11** [%][b]	Yield of **10** [%][b]
1	**4b**	$Fe(OTf)_2$	0.5	 **11b**	71	8
2		$Fe(NTf_2)_2$	0.5		51	17
3		$Fe(acac)_3$	16		7	59
4	**4a**	$Fe(OTf)_2$	0.5	 **11a**	92	
5	**4c**	$Fe(OTf)_2$	0.5	 **11c**	–[c]	
6	**4d**	$Fe(OTf)_2$	0.5	 **11d**	54	

[a] *Reaction conditions:* Sulfide **4** (1 equiv.), iron salt (15 mol%), PhI=NNs (1.3 equiv.) and 4 Å MS in MeCN (0.1 M) at room temperature.
[b] After column chromatography.
[c] Decomposition of the starting material and formation of a complex reaction mixture.

with cyanogen amine mediated by NBS was considered.[9a] A slight variation of this protocol, employing preformed NCNHNa in methanol at room temperature, was successful and various sulfilimines with *N*-cyano substituents were prepared accordingly. Although this protocol failed to give the desired product with 5-methoxypyrazolyl derivative **4b** (Table 2, entry 2), it worked well with substrates bearing a chloro group at that position (entries 1, 3–7).

Using the NBS/NCNHNa method 5-chloropyrazolyl derivatives **4a**, **c–g** with a variety of substituents at the 3-position of the pyrazole ring and/or various aryl groups at the sulfur could efficiently be iminated under metal-free conditions. Generally, the yields of the resulting *N*-cyano sulfilimines **5** were high (82–93%). In the cases of **4h** and **4i** no reaction was observed, presumably due to the reduced nucleophilicity of sulfur in these sulfides (Table 2, entries 8 and 9). The metal-free imination with $PhI(OAc)_2$ and $NCNH_2$ was also evaluated, but did not represent a valuable alternative, with product yields generally being lower (58–76%; Table 2, entries 1, 3, and 4, results given in parentheses) compared to those obtained using the standard NBS/NCNHNa protocol.



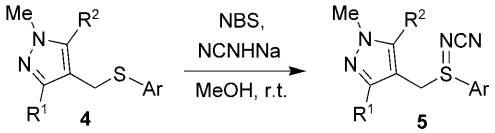
a: X = Cl, Ar = Ph **b**: X = OMe, Ar = Ph
c: X = Cl, Ar = 2-$MeOC_6H_4$ **d**: X = Cl, Ar = 4-$MeOC_6H_4$

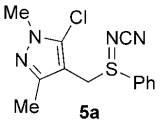
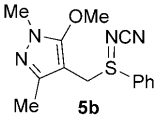
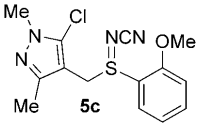
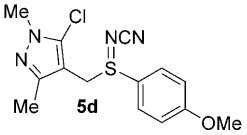
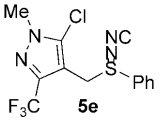
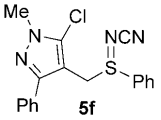
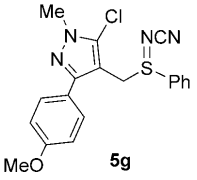
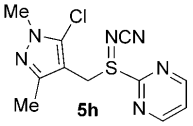
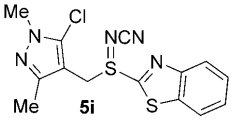
Scheme 4. Iron-catalyzed iminations of sulfides **4**.

Next, the oxidation of the *N*-cyano sulfilimines **5** to the corresponding sulfoximines **3** was studied. Sulfilimine **5a** was chosen as a model substrate and various oxidation systems were assessed. Notably, H_2O_2/AcOH (at 0 °C) and Oxone®/wet-Al_2O_3/CH_2Cl_2 (at 60 °C) led to decomposition of the sulfilimine. Encouragingly, use of *m*-CPBA/$NaHCO_3$ in EtOH at room temperature provided the desired sulfoximine, albeit in 40% yield due to partial conversion of the starting material. Furthermore, when the oxidation was performed with $KMnO_4$ in wet acetone,[13] a clean reaction occurred that afforded sulfoximine **3a** in good yield (Table 3, entries 1 and 2). Similarly, sulfilimines **5c–g** gave the corresponding *N*-cyano sulfoximines **3c–g** (at 50 °C) in moderate to very good yields (58–98%, entries 3–7) under the same conditions.

Although with the preparation of sulfoximines **3** the inital goal of the study was reached, attempts to

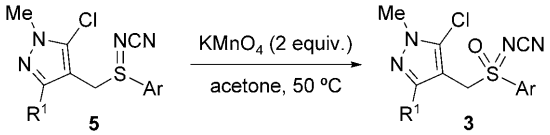
Table 2. NBS-mediated iminations of sulfides **4** to give *N*-cyano sulfilimines **5**.[a]



Entry	R^1	R^2	Ar	**5**	Yield [%][b]
1	Me	Cl	Ph	 **5a**	83 (58)[c]
2	Me	MeO	Ph	 **5b**	–[d]
3	Me	Cl	2-$MeOC_6H_4$	 **5c**	93 (76)[c]
4	Me	Cl	4-$MeOC_6H_4$	 **5d**	86 (68)[c]
5	CF_3	Cl	Ph	 **5e**	85[e]
6	Ph	Cl	Ph	 **5f**	83[e]
7	4-$MeOC_6H_4$	Cl	Ph	 **5g**	82[e]
8	Me	Cl	2-Pyr[g]	 **5h**	–[f]
9	Me	Cl	2-Bzth[g]	 **5i**	–[f]

[a] *Reaction conditions:* Sulfide **4** (1 equiv.), NBS (1.5 equiv.) and NCNHNa (1.4 equiv.) in methanol (0.1 M) at room temperature.
[b] After column chromatography.
[c] Yields obtained upon imination with $PhI(OAc)_2$ (1.2 equiv.) and $NCNH_2$ (2.0 equiv.) in acetonitrile at room temperature.
[d] Decomposition occurred.
[e] Purification after 5 min reaction time. With prolonged reaction times partial or total decomposition of the product was observed.
[f] No reaction was observed and the corresponding sulfides could be recovered in 80–90% yield.
[g] Pyr = pyrimidine, Bzth = benzothiazole.

Table 3. Oxidation of *N*-cyano sulfilimines **5** to give sulfoximines **3**.[a]

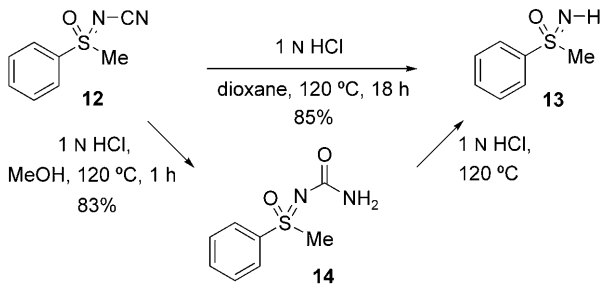


Entry	5	R^1	Ar	3	Yield [%][b]
1	**5a**	Me	Ph	**3a**	77
2[c]	**5a**	Me	Ph	**3a**	64
3	**5c**	Me	2-$MeOC_6H_4$	**3c**	65
4	**5d**	Me	4-$MeOC_6H_4$	**3d**	98
5	**5e**	CF_3	Ph	**3e**	71
6	**5f**	Ph	Ph	**3f**	84
7	**5g**	4-$MeOC_6H_4$	Ph	**3g**	58

[a] *Reaction conditions:* Sulfilimine **5**, $KMnO_4$ (2 equiv.) in acetone (0.1 M) at 50 °C in a sealed tube.
[b] After column chromatography.
[c] Reaction at 60 °C.

cleave the *N*-cyano group were initiated in order to expand the product scope further. Treatment of sulfoximine **3a** with TFAA followed by methanolysis (K_2CO_3/MeOH)[9a] was unsuccessful, leading to rapid decomposition of the starting material. The direct hydrolysis of the cyano group under aqueous acidic conditions[14] was first explored using *N*-cyanomethyl phenyl sulfoximine **12** as a model substrate (Scheme 5). Upon treatment of **12** with 1 N aqueous HCl in dioxane at 120 °C in a sealed tube, the NH-sulfoximine **13** was obtained in 85% yield. When the reaction was carried out in MeOH, the corresponding urea-type product **14** was isolated as the major product (83%). Both longer reaction times in MeOH and post-treatment of **14** (16–18 h) with 1 N aqueous HCl in dioxane led to the NH-sulfoximine **13**.

On the basis of these results, the hydrolysis of the *N*-cyano group of aryl pyrazolylmethyl sulfoximines **3** at 100 °C in a 1:1 mixture of 1 N aqueous HCl and dioxane was attempted. However, instead of the expected N–C-bond cleavage, two alternate reaction pathways were observed. Thus, 3-methyl pyrazolylmethyl sulfoximines **3a**, **c**, **d** led to the corresponding sulfones **15a**, **c**, **d** in 68–79% yields,[15] and alcohols **9b–d** were obtained as the major products from 3-substituted derivatives **3e–g** (Figure 2).



Scheme 5. Cleavage of the *N*-cyano group under aqueous acidic conditions.

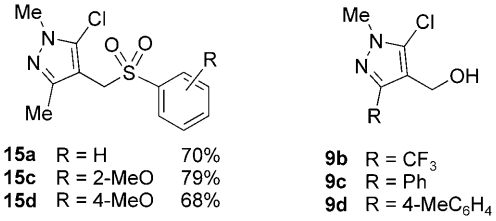


Figure 2. Products obtained in attempted hydrolyses of sulfoximines **3**.

In conclusion, starting from the corresponding sulfoxides and sulfides, aryl pyrazolylmethyl-substituted sulfoximines and sulfilimines have been prepared. Either iron-catalyzed or NBS-mediated nitrogen transfer reactions were applied to achieve the required sulfur iminations. Smooth oxidation of the readily synthesized *N*-cyano sulfilimines with $KMnO_4$ in acetone provided the corresponding sulfoximines in good yields. An exceptionally high dependence of the reactivity and stability of the aryl pyrazolylmethyl derivatives on the substitution pattern at the pyrazole ring and the aryl group at sulfur was observed. Thus, some standard reactions within sulfoximine chemistry, such as the transformation of the *N*-cyano sulfoximines into their corresponding NH-derivatives under acidic hydrolysis conditions provided unexpected products.[16]

Experimental Section

General Procedure for the $Fe(OTf)_2$-Catalyzed Sulfur Imination Reaction[6a–c]

A mixture of **1** or **4** (0.20 mmol), $Fe(OTf)_2$ (11 mg, 0.03 mmol), 4 Å MS (0.4 g $mmol^{-1}$), and PhI=NNs (105 mg, 0.26 mmol) in CH_3CN (2 mL) was stirred at room tempera-

ture for 10–60 min. Once the starting material was consumed (monitored by TLC), the reaction mixture was concentrated to half its volume under reduced pressure. The residue was purified by flash column chromatography.

***N*-(4-Nitrobenzenesulfonyl) (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl phenyl sulfoximine (2a):** Following the general method, the imination reaction of sulfoxide **1a** (54 mg, 0.20 mmol) with PhI=NNs in the presence of $Fe(OTf)_2$ gave **2a** as a white solid; yield: 63 mg (67%). Chromatography: gradient of ethyl acetate/pentane 1:2 to 1:1; mp 120–121 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$ (d, $J = 8.9$ Hz, 2H), 8.10 (d, $J = 8.9$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.65 (t, $J = 8.0$ Hz, 1H), 7.48 (t, $J = 8.0$ Hz, 2H), 4.82 and 4.36 (AB system, $J = 14.8$ Hz, 2H), 3.61 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.7$ (C), 149.3 (C), 149.2 (2C), 135.0 (CH), 134.8 (C), 129.6 (CH), 128.9 (CH), 128.1 (CH), 124.0 (CH), 101.9 (C), 55.3 (CH_2), 36.4 (CH_3), 12.2 (CH_3); MS (EI): *m/z* (relative intensity) = 343 [$(M-Ph-SO)^+$, 3], 282 [$(M-Ns)^+$, 1], 186 [3], 143 [100]; HR-MS (ESI^+): *m/z* = 491.0202, calcd. for $C_{18}H_{17}ClN_4O_5S_2{\cdot}Na$: 491.0221.

General Procedure for the Imination of Sulfides with NBS/NCNHNa[9a]

To a solution of sulfide **4** (1.0 mmol) and NCNHNa (105 mg, *ca.* 85%, 1.4 mmol) in MeOH (8 mL) at room temperature, was added NBS (267 mg, 1.5 mmol). Once the starting material was consumed (monitored by TLC), the reaction mixture was concentrated under reduced pressure, saturated aqueous $Na_2S_2O_3$ was added and the mixture extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography.

***N*-Cyano (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl phenyl sulfilimine (5a):** Following the imination method, the reaction of sulfide **4a** (253 mg, 1.0 mmol) with NCNHNa and NBS gave **5a** as a white solid; yield: 244 mg (83%). Chromatography: gradient of ethyl acetate/pentane 1:1 to ethyl acetate; mp 116–117 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.61$–7.54 (m, 3H), 7.51–7.45 (m, 2H), 4.24 and 4.07 (AB system, $J = 13.5$ Hz, 2H), 3.68 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.7$ (C), 133.8 (C), 133.3 (CH), 130.0 (CH), 129.0 (C), 126.6 (CH), 120.9 (C), 102.9 (C), 49.4 (CH_2), 36.5 (CH_3), 12.3 (CH_3); MS (EI): *m/z* (relative intensity) = 294 [M^+ (^{37}Cl), 0.2], 292 [M^+ (^{35}Cl), 0.5], 145 [34], 143 [100], 109 [12]; HR-MS (ESI^+): *m/z* = 315.0429, calcd. for $C_{13}H_{13}ClN_4S{\cdot}Na$: 315.0442; anal. calcd. for $C_{13}H_{13}ClN_4S{\cdot}1/3H_2O$: C 52.26, H 4.61, N 18.75; found: C 52.02, H 4.55, N 18.60.

General Procedure for the Oxidation with $KMnO_4$[13]

To a mixture of sulfilimine **5** (0.5 mmol) and $KMnO_4$ (158 mg, 1.0 mmol) in acetone (5 mL) was heated at 50 °C in a sealed tube. Once the starting material was consumed (monitored by TLC), the solvent was removed under reduced pressure and the resulting residue purified by flash column chromatography.

***N*-Cyano (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl phenyl sulfoximine (3a):** Following the general procedure, the reaction of sulfilimine **5a** (147 mg, 0.5 mmol) with $KMnO_4$ gave **3a** as a white solid; yield: 119 mg (77%). Chromatography: gradient of ethyl acetate/pentane 1:1 to ethyl acetate; mp 128–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$–7.67 (m, 3H), 7.58–7.50 (m, 2H), 4.44 and 4.33 (AB system, $J = 14.8$ Hz, 2H), 3.64 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.2$ (C), 135.6 (CH), 133.5 (C), 130.0 (CH), 129.6 (C), 129.3 (CH), 111.9 (CN), 101.3 (C), 53.6 (CH_2), 36.4 (CH_3), 12.2 (CH_3); MS (EI): *m/z* (relative intensity) = 310 [M^+ (^{37}Cl), 0.3], 308 [M^+ (^{35}Cl), 1], 145 [33], 143 [100], 125 [8]; anal. calcd. for $C_{13}H_{13}ClN_4OS$: C 50.57, H 4.24, N 18.14; found: C 50.56, H 4.21, N 18.24.

General Procedure for the Hydrolysis with HCl[14]

To a stirred solution of sulfoximine **3** or **12** (0.3 mmol) in 1,4-dioxane or MeOH (1.5 mL) at room temperature, was added 1 N HCl (1.5 mL). The mixture was heated to 100 °C or 120 °C in a sealed tube and allowed to react until the starting material was consumed (monitored by TLC). The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography.

***N*-Aminoformyl methyl phenyl sulfoximine (14):** Following the general procedure, the reaction of sulfoximine **12** (180 mg, 1.0 mmol) with 1 N aqueous HCl in MeOH at 120 °C gave **14** as a white solid; yield: 164 mg (83%). Chromatography: ethyl acetate; mp 194–195 °C; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.97$ (br d, $J = 7.5$ Hz, 2H), 7.69 (tt, $J = 7.5$, 1.4 Hz, 1H), 7.62 (br t, $J = 7.5$ Hz, 2H), 4.83 (s, 3H), 3.30 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 163.4$ (C=O), 139.5 (C), 133.2 (CH), 129.1 (CH), 127.1 (CH), 43.4 (CH_3); MS (EI): *m/z* (relative intensity) = 199 [$(M+H)^+$, 6], 183 [100], 182 [27], 77 [24]; HR-MS (EI): *m/z* = 183.0232, calcd. for $C_8H_{10}N_2O_2S$-CH_3 ($C_7H_7N_2O_2S$): 183.0228.

(5-Chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl phenyl sulfone (15a): Following the general procedure, the reaction of sulfoximine **3a** (100 mg, 0.32 mmol) with 1 N aqueous HCl in 1,4-dioxane at 100 °C in a sealed tube gave **15a** as a white solid; yield: 64 mg (70%). Chromatography: ethyl acetate/pentane 1:1; mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (br d, $J = 7.5$ Hz, 2H), 7.58 (br t, $J = 7.5$ Hz, 1H), 7.44 (br t, $J = 7.5$ Hz, 2H), 4.06 (s, 2H), 3.65 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.6$ (C), 137.9 (C), 133.9 (CH + C), 129.1 (CH), 128.7 (CH), 103.8 (C), 52.3 (CH_2), 36.3 (CH_3), 12.3 (CH_3); MS (EI): *m/z* (relative intensity) = 286 [M^+ (^{37}Cl), 0.3], 284 [M^+ (^{35}Cl), 1], 145 [33], 143 [100]; HR-MS (ESI^+): *m/z* = 285.0464, calcd. for $C_{12}H_{13}ClN_2O_2S{\cdot}H$ ($C_{12}H_{14}ClN_2O_2S$): 285.0459; anal. calcd. for $C_{12}H_{13}ClN_2O_2S$: C 50.61, H 4.60, N 9.84; found: C 50.84, H 4.64, N 9.66.

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