Sulfoximine- and Sulfilimine-Based DAPSON Analogues; Syntheses and Bioactivities

Xiao Yun Chen,[a] Helmut Buschmann,[b] Carsten Bolm*[a]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax +49(241)8092391; E-mail: carsten.bolm@oc.rwth-aachen.de

[b] Sperberweg 15, 52076 Aachen, Germany

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Abstract: Sulfoximine- and sulfilimine-based diamino-diphenyl sulfone (DAPSON) analogues have been prepared and their COX-1 and COX-2 inhibition potencies as well as LTB_4 and TNF binding properties were studied. Furthermore, their antiproliferative activities on cancer cell growth were investigated. Neither compounds showed significant bioactivities.

Key words: drug discovery, cancer, oxidation, sulfoximine, sulfilimine

Diamino-diphenyl sulfone (DAPSON; **1**) was first synthesized in 1908 by Fromm and Wittmann, who were interested in the dying properties of this rather simple diaryl sulfone.[1] In 1937, when medicinal chemists entered the field, two groups concurrently reported on the anti-inflammatory potencies of DAPSON in induced infections in mice.[2] Today, it is in clinical use for the treatment of various infections and chronic inflammatory diseases,[3] and, in particular, in dermatology, DAPSON is often regarded as the drug of choice.[4] For example, in combination with other antibiotic agents it has proved useful for treating mutibacillary and paucibacillary leprosy[5] as well as a variety of neutrophilic, eosinophilic, and autoimmune dermatoses. Despite many investigations, the precise mode of action of DAPSON is still unknown. Furthermore, it often shows adverse events including hematologic, nervous system, and gastrointestinal/hepatic effects.[4] Consequently, the development of DAPSON variants that exhibit the positive therapeutic properties of the original drug but lack unwanted side effects is clearly desirable. In the light of our recent findings on COX-blocking properties of sulfoximines,[6] we wanted to investigate the biological impact of formal oxygen-to-nitrogen exchanges at the central sulfonyl core of DAPSON.[7] Here, we report on the syntheses and biological properties, with respect to inflammatory events, of sulfoximine **2**, being the mono-aza analogue of diaryl sulfone DAPSON (**1**), and *N*-cyano sulfilimine **3**, which represents a new related structural variant (Figure 1).

The syntheses of sulfoximine **2** and sulfilimine **3** proceeded via bis(4-nitrophenyl)sulfane (**5**), which was available from 4-nitrobromobenzene (**4**) by nucleophilic substitution with sodium sulfide (Scheme 1). Unfortunately, the

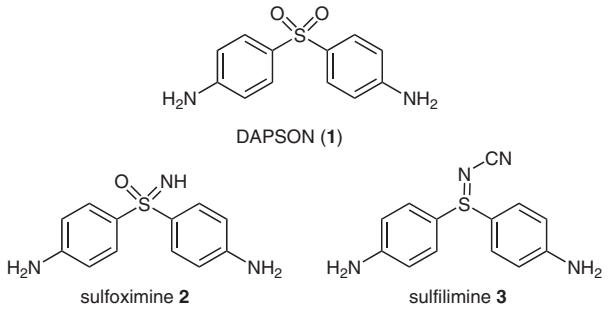

Figure 1 DAPSON and structural analogues prepared here

direct imination of **5** with $PhI(AcO)_2$ and NH_2CN to form the corresponding sulfilimine (not shown) was unsuccessful, presumably due to the presence of the strong electron-withdrawing nitro groups on the two arenes. Consequently, bis-aniline **6** became a preferred target. Its synthesis proceeded well (83% yield) by treatment of **5** with iron powder and concentrated HCl in ethanol–water (4:1).[8] However, both **6** and *N*,*N*′-di(Boc)-protected **7** proved to be unstable under the reaction conditions of the imination, thus, an alternative protected derivative had to be found. To our delight, easily accessible *N*,*N*′-[4,4′-thiobis(4,1-phenylene)]diacetamide (**8**) proved suitable. It was prepared by double acetylation of **6** and allowed sulfur imination using the metal-free method with cyanamide as nitrogen source under conditions reported by us earlier.[9] In this manner, *N*-cyano sulfilimine **9** was obtained in 47% yield.[10]

To obtain *N*-cyano sulfoximine **10**, sulfilimine **9** was oxidized with a combination of MCPBA and K_2CO_3 in methanol (78% yield). Finally, both the cyano and the acetyl group were cleaved upon treatment with concentrated HCl in methanol to give NH-sulfoximine **2** in 85% yield.

Initially, we expected to prepare *N*-cyano sulfilimine **3** in a similar manner to that of **2**. However, the use of diacetyl-protected **8** was excluded because the anilide bonds could not be cleaved without affecting the *N*-cyano moiety at the sulfilimine core. Finally, **6** was treated with phthalic anhydride to give diprotected intermediate **11** in 79% yield (Scheme 2). Its imination under standard conditions[10] gave *N*-cyano sulfilimine **12**, which could be converted into the desired product **3** by reaction with hydrazine monohydrate in ethanol (32% over two steps). It is note-

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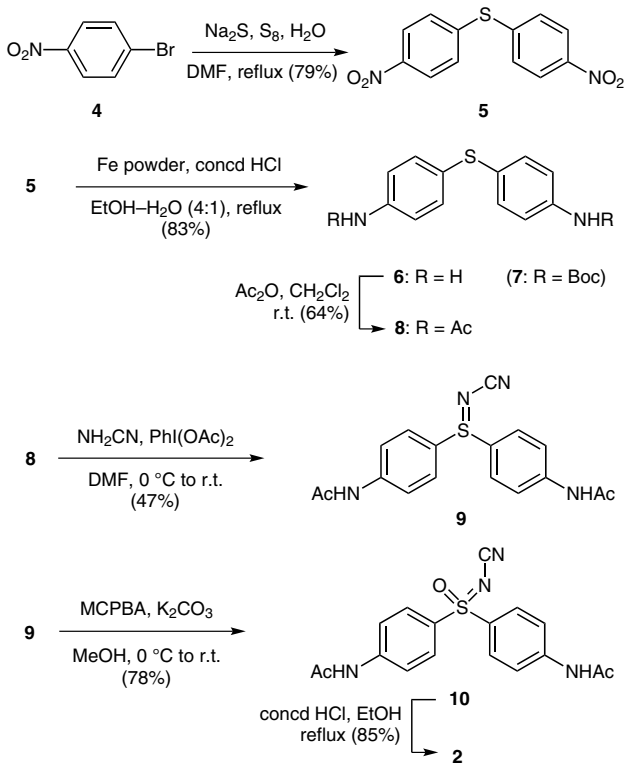
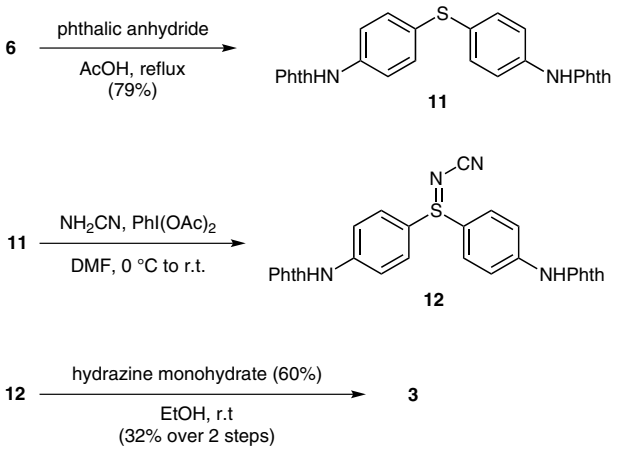


Scheme 1 Synthesis of sulfoximine **2**



Scheme 2 Synthesis of sulfilimine **3**

worthy that the sulfilimine core remained intact under these hydrolysis conditions.

Next, the biological properties of sulfoximine **2** and sulfilimine **3** were evaluated. Considering the effect of DAPSON on inflammatory events and to allow a direct comparison, the following enzyme and radioligand binding assays were initially selected: cyclooxygenase (COX-1 and COX-2), leukotriene (BLT; LTB_4), and tumor necrose factor (TNF; non-selective); Table 1 summarizes the results.[11]

To our great disappointment, neither sulfoximine **2** nor sulfilimine **3** (10 μM concentrations) showed significant

Table 1 Biological Properties of Sulfoximine **2** and Sulfilimine **3**[11]

Entry	Assay	Inhibition (%)[a]	
		Sulfoximine **2**	Sulfilimine **3**
1	COX-1	6	9
2	COX-2	4	4
3	LTB_4	–14	11
4	TNF	– 6	–3

[a] Using 10 μM inhibitor concentration. For details see the Supporting Information.

effects in the enzyme or radioligand binding assays. Apparently, even the comparatively minor one-atom modification [SO_2 versus SO(NH) for **2**] of the sulfonyl core had a major influence on the biological properties. The results with **3** were less surprising considering the significant property change associated with the sulfonyl-to-N-cyano sulfimidoyl switch (sulfone **1** vs. *N*-cyano sulfilimine **3**).

Being aware of current studies that revealed anticancer activities of DAPSON derivatives,[12] we decided to submit compounds **2** and **3** for an anticancer screening within the Developmental Therapeutics Program of the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI) at the National Institutes of Health, USA.[13] In the full NCI 60 cell panel representing leukemia, melanoma, and cancers of the lung, colon, CNS, ovarian, renal, prostate, and breast, **2** and **3** were applied at a single dose (10 μM).[14] Unfortunately, the observed antiproliferative activities on cell growth were not significant enough to progress the initial study.

Because several effects in DAPSON therapies have been attributed to the formation and presence of metabolites (such as N-hydroxylamines of **1**),[3,4,15] it remains to be seen if the reported core modifications also affect those activities due to altered oxidation potentials of the sulfur-bridged aniline moieties.

In summary, we have prepared two structural analogues of DAPSON (**1**) and studied their biological behavior with respect to COX-1/2 inhibitions, LTB_4 and TNF bindings, and anticancer activities. Neither sulfoximine **2** nor sulfilimine **3** showed significant blocking or binding potencies. The antiproliferative activities on cancer cell growth were not significant.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **General procedure for the synthesis of *N*-cyano sulfoximine from the corresponding sulfide:** *Step 1*: To a solution of sulfide (1 mmol) and NH_2CN (63.0 mg, 1.5 mmol) in DMF (5 mL), $PhI(OAc)_2$ (354.3 mg, 1.1 mmol) was added. The reaction was stirred at 0 °C for 30 min and then warmed to r.t. (substrate conversion was monitored by TLC). When the starting material was no longer consumed, the reaction mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with sat. $NaHCO_3$, H_2O, and brine, and dried over $MgSO_4$. The purified sulfilimine was obtained by silica gel column chromatography. *Step 2*: To a stirring solution of *N*-cyanosulfilimine (1 mmol) in MeOH (10 mL) was added K_2CO_3 (414.6 mg, 3.0 mmol) and MCPBA (258.9 mg, 1.5 mmol) at 0 °C. The mixture was stirred at room temperature until the starting material was consumed (ca. 6 h). The solvent was then removed under reduced pressure, H_2O (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried over $MgSO_4$, and column chromatography (silica gel) provided the purified *N*-cyano sulfoximine.

(11) These assays were performed by Ricerca Biosciences, Chicago, USA. Methods: (a) COX-1: human platelets (source); 100 μM arachidonic acid (substrate); EIA quantification of PGE_2 (quantification method). (b) COX-2: human recombinant insect Sf21 cells (source); 0.3 μM arachidonic acid (substrate); EIA quantification of PGE_2 (quantification method). (c) LTB_4: human U937 cells (source); 0.2 nM [^{3}H] LTB_4 (ligand); radioligand binding (quantification method). (d) TNF: human U937 cells (source); 0.028 nM [^{125}I] TNF-α (ligand); radioligand binding (quantification method). For details see the Supporting Information.

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