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[6] Sr_4N_3 was synthesized by heating Sr_2N (prepared at 1120 K from the elements) in a molybdenum boat under a N_2 atmosphere (Messer Griesheim, given purity 99.999 %, purified by oxisorb-catridges, Messer Griesheim) for 6 h at 920 K in an autoclave.[5] An initial pressure of 8 bar (corresponding to a reaction pressure of 9 bar) led to nearly single-phase Sr_4N_3. The course of the reaction was steadily controlled by a pressure gauge.
[7] Neutron diffraction experiments were carried out on the powder diffractometer E9 at the reactor BER II of the HMI Berlin. Sr_4N_3 was placed under argon into a cylindrical vanadium container (diameter 8 mm, length 47 mm, wall thickness 0.15 mm) and was closed with a cap containing an indium seal. Crystal structure data derived from neutron diffraction experiments with the wavelength $\lambda = 1.7965$ Å in the range $2^\circ < 2\theta < 158^\circ$ at 298 K and 2 K: monoclinic, space group $C2/m$, $Z = 2$; 298 K: $a = 6.7070(4)$, $b = 3.8280(2)$, $c = 13.7625(8)$ Å, $\beta = 96.519(5)^\circ$, $V = 351.05(3)$ Å^3; Sr1 in (4*i*): $x = 0.413(1)$, $z = 0.1413(4)$; Sr2 in (4*i*): $x = 0.127(1)$, $z = 0.3406(3)$; N1 in (4*i*): $x = 0.775(1)$, $z = 0.2515(4)$; N2 in (4*i*): $x = 0.083(1)$, $z = 0.0217(6)$, occupancy factor = 0.5; $R_{profile} = 0.055$, $R_{Bragg} = 0.053$, number of observed reflections: 272. 2 K: $a = 6.6886(3)$, $b = 3.8173(2)$, $c = 13.7382(6)$ Å, $\beta = 96.447(3)^\circ$, $V = 348.55(3)$ Å^3; Sr1 in (4*i*): $x = 0.4133(7)$, $z = 0.1412(3)$; Sr2 in (4*i*): x = 0.1290(7), $z = 0.3413(3)$; N1 in (4*i*): $x = 0.7748(6)$, $z = 0.2483(3)$; N2 in (4*i*): $x = 0.0850(8)$, $z = 0.0234(4)$, occupancy factor = 0.5; $R_{profile} = 0.066$, $R_{Bragg} = 0.047$, number of observed reflections: 261. The refinements were carried out using the program Fullprof.[8] Further details on the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-412394 and CSD-412395.
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[9] The nonmetallic components N, O, H, C were quantitatively determined by the carrier-gas hot extraction or combustion technique (TC 436 DR/5, RH 404 and C200CHLH (LECO)): Sr_4N_3 (N_{exp} 10.86(8), N_{calcd} 10.71 wt %). Si_3N_4 was used as a calibration standard. Impurities of O, H, and C were not detected (limits of detection: C < 0.1; H < 0.005; O < 0.05 wt %). Using a temperature ramping from 500 – 1500 K, it was not only possible to determine the nitrogen content[2] in $Sr_4N_3 \mathrel{\hat{=}} (Sr^{+1.5})_4(Sr^{2+})_4[N^{3-}]_4\ [N_2^{2-}]$ but also to quantify the two different nitrogen species in the molar ratio of 2:1.
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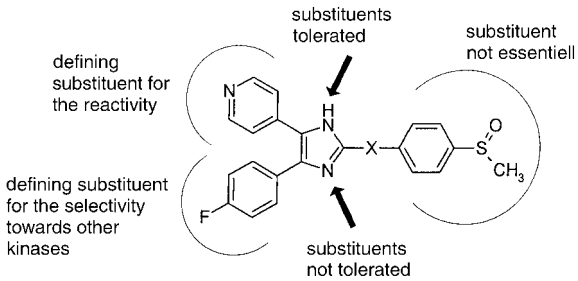
Ones, Thiones, and *N*-Oxides: An Exercise in Imidazole Chemistry**

Stefan Laufer,* Gerd Wagner, and Dunja Kotschenreuther

Dedicated to Prof. Dr. Wolfgang Wiegrebe on the occasion of his 70th birthday

The inhibition of the proinflammatory cytokines interleukin 1β (IL-1β) and tumor-necrosis factor α (TNF-α) has been recognized as a rewarding target for the development of tailor-made anti-inflammatory drugs.[1] Among the most promising small-molecular anticytokine agents are inhibitors of p38 MAP kinase, a serine/threonine-specific kinase involved in the biosynthesis and release of cytokines from immunocells.[2a] Like other potent inhibitors of p38 MAP kinase, our lead compound ML 3163 was derived from 5-(pyridin-4-yl)imidazole (SB 203580; Scheme 1), which



Scheme 1. Structural requirements for inhibition of p38 MAP kinase.

binds to the ATP-binding site of the p38 kinase,[2b] and has demonstrated efficacy in various models.[2c] In the development of pharmaceuticals, in addition to bioactivity, the issues of bioavailability and toxicity must be addressed. For example, further development of SB 203580 itself has been obstructed by its liver toxicity, which is caused by interaction with cytochrome P450 (P450).[2d] Therefore, it is of general interest to the medicinal chemist to have a straightforward synthetic methodology which provides access to a large number of bioactive candidate molecules.

Herein we describe such a versatile synthetic strategy for the ready preparation of numerous structurally diverse

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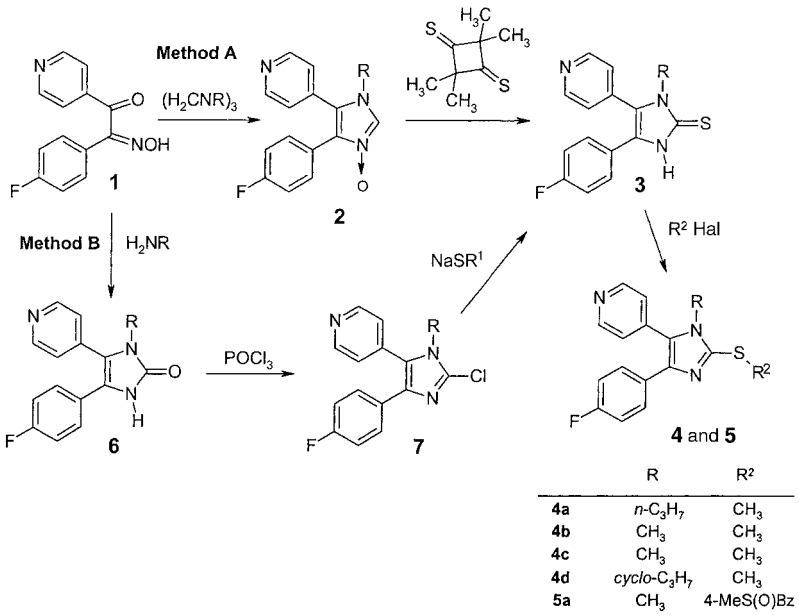
ML 3163 analogues. In this class of compounds (Scheme 1), substituents at the 4 and 5-position of the imidazole core are essential for efficient and selective inhibition of p38 MAP kinase,[2b,e,f] while substituents at the 1 and 2-position primarily serve to reduce interaction with P450 and to improve cell permeability. To find p38 MAP kinase inhibitors with enhanced cellular activity and diminished toxicity, we have developed a synthetic methodology which provides 1,2,4,5-tetrasubstituted imidazole derivatives, with maximum flexibility in the type of substituents. Most importantly, this synthetic route also allows for the regioselective placement of substituents at the imidazole nitrogen atom; the regiochemistry of substituents at the ring nitrogen atoms being decisive for inhibitory potency (Scheme 1).[2e,f] As a result of these efforts, several analogues of ML 3163 were identified as anticytokine agents well suited for further development. Moreover, this general method may be applied in the quest for novel ATP-competitive inhibitors for other kinases.

Synthetic approaches towards highly substituted imidazoles are few and often restricted to a fixed pattern of substitution.[3a–c] Preliminary experiments revealed that direct *N*-methylation of 5-(pyridin-4-yl)imidazoles by various methods predominantly yields the "wrong" regioisomer.[3d] To obtain tetrasubstituted imidazole derivatives of the desired regiochemistry, and to extend the scope of substituents at the 1-position beyond simple alkyl moieties, we attempted the introduction of N-substituents at an earlier synthetic stage. The synthesis of 4/5-alkyl/aryl-substituted imidazole-2-thiones with simple alkyl substituents at the 1-position has been reported, from the corresponding *N*-oxides.[4a] However, initial attempts to extend the scope of this reaction to the preparation of 5-(pyridin-4-yl)imidazole-2-thiones failed (Scheme 2, Method A). The required *N*-oxides **2** could not be synthesized from 1-(4-fluorophenyl)-2-(pyridin-4-yl)hydroximino-ethan-2-one (**1**) under acidic conditions. Compounds **2** were obtained in good yields only when **1** was treated with the appropriate triazinanes under neutral conditions.[4b] Unfortunately, this approach was not successful in the case of *N*-phenyl- or *N*-pyridinyltriazinanes (Scheme 2, R = Ph, 3-Pyr). Imidazole *N*-oxides **2** were converted into imidazole-2-thiones **3** by treatment with 2,2,4,4-tetramethylcylobutane-1,3-dithione.[4a] Here, a much wider array of different substituents in the 1-position was tolerated than previously reported;[4a] these included favorable functionalities for biological activity (R = cyclopropyl, 3-morpholinopropyl) or toxicity (R = tetramethylpiperidin-4-yl). Subsequent alkylation of imidazole-2-thiones **3**, according to the protocol we had applied in the preparation of ML 3163,[5] yielded the corresponding 2-alkylsulfanyl imidazoles **4** and **5**.

A second general synthesis of imidazole-2-thiones had to be devised to provide *N*-aryl and *N*-pyridinylimidazole derivatives. This synthetic pathway was based on the conversion of imidazole-2-ones into imidazole-2-thiones via 2-chloroimidazoles (Scheme 2, Method B). According to Lettau, simple *N*-aryl imidazole-2-ones can be prepared from the corresponding α-hydroximinoketones.[6] However, this method has been limited to imidazole-2-ones bearing at least one simple alkyl substituent at the 4 or 5-position, and was unsuitable for the preparation of 4,5-diphenyl-imidazole-2-ones.[6] We managed to overcome these restrictions and application of this strategy afforded 4,5-diphenylimidazole-2-ones as well as the 5-(pyridin-4-yl)imidazole-2-ones **6**. However, under the reaction conditions reported by Lettau, only the starting material was recovered.[6] A change in the solvent from ethanol to acetonitrile or glacial acetic acid gave the imidazole-2-ones **6** in moderate to high yields. A wide range of different substituents at position 1 was tolerated, including alkyl, cycloalkyl, aryl, heteroaryl, and substituted alkyl, for example, 3-chloropropyl. The latter compound (**6**, R = 3-chloropropyl) served to generate further analogues by nucleophilic modification of the side-chain (e.g. **6**, R = 3-morpholinopropyl).



	R	R²
4a	*n*-C_3H_7	CH_3
4b	CH_3	CH_3
4c	CH_3	CH_3
4d	*cyclo*-C_3H_7	CH_3
5a	CH_3	4-MeS(O)Bz

Scheme 2. Preparation of imidazole-2-thiones from imidazole-*N*-oxides (Method A) or imidazole-2-ones (Method B). The imidazole derivative **4c** has a 2-acetylaminopyridinyl group in the 5-position, in place of the shown pyridinyl group.

As immediate synthetic precursors for imidazole-2-thiones, we required the corresponding 2-chloroimidazoles **7** which were readily obtained by chlorination of imidazole-2-ones **6** with phosphorylchloride (Scheme 2).[7a] The conversion of chloro-substituted (hetero)aromatics into the corresponding aromatic thiols by nucleophilic substitution has been described for electron-deficient polychlorobenzoles, 4-chloropyridine, and 2- and 4-chloroquinolines.[7b] Much to our surprise, this approach was also successful in the case of the electron-rich 2-chloro-5-(pyridin-4-yl)imidazoles **7**. When compounds **7** were reacted with sodium (4-chlorophenyl)methanethiolate (4.5 equiv), the corresponding imidazole-2-thiones **3** formed in good to moderate yields. This reaction proceeds in two consecutive steps (Scheme 3): First, nucleophilic aromatic substitution affords the 2-(4-chlorobenzylsulfanyl)imidazole. Second, nucleophilic aliphatic substitution effects the cleavage of these thioethers. Bis-

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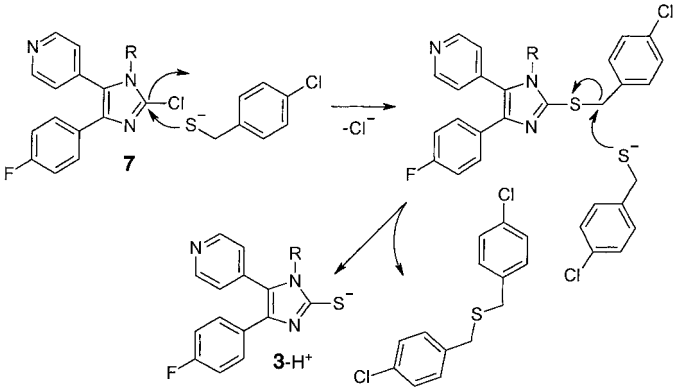
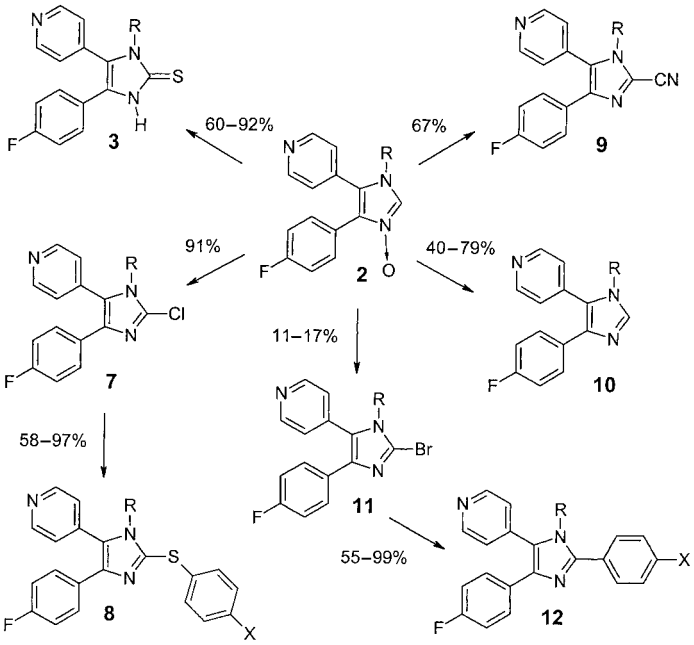


Scheme 3. Proposed mechanism for the conversion of 2-chloroimidazoles into imidazole-2-thiones, by treatment with (4-chorophenyl)methanethiolate.

(4-chlorobenzyl)sulfide could be identified by GC–MS as the elimination product of the second step. This observation strongly supports the proposed mechanism. However, this reaction failed in the presence of sterically demanding substituents at the 1-position of 2-chloroimidazoles **7** (R = 2-dimethylaminoethyl, tetramethylpiperidin-4-yl, 3-morpholinopropyl). In one case, 2-(4-chlorobenzylsulfanyl)imidazole was isolated in a very low yield, which indicates that nucleophilic aromatic substitution indeed takes place during the first reaction step. This result prompted us to investigate the general applicability of this reaction to the preparation of imidazolyl sulfides. Compound **7a** (R = propyl) was treated with a reduced amount (2.2 equiv) of sodium (4-chlorophenyl)methanethiolate, to halt the reaction at the level of the corresponding 2-(4-chlorobenzylsulfanyl)imidazole. However, examination of the crude product by GC–MS did not reveal the expected sulfide, but a 4:5 ratio of **7**:**3a** (R = propyl). This result suggests that nucleophilic heteroaromatic substitution is the rate-limiting step in this reaction scheme. Replacement of sodium (4-chlorophenyl)methanethiolate with three equivalents of sodium ethanethiolate afforded ethylsulfanylimidazole as the only product (yield 74%). We reasoned that cleavage of the imidazolyl sulfides by nucleophilic aliphatic substitution (step 2) is favored by activating substituents such as a benzyl group, while a simple alkyl group is not sufficient. This finding led us to the synthesis of phenylimidazolyl sulfides **8**, which are not readily accessible by other methods. Treatment of **7** with thiophenol derivatives (2.5 equiv) gave the corresponding phenylimidazolylsulfides **8** in good yields (Scheme 4). Apart from this additional benefit, the strategy of preparing **3** from **6** (Scheme 2, Method B) was complementary to the imidazole-*N*-oxide pathway (Scheme 2, Method A) for two reasons: 1) While Method A fails in the case of (hetero)aromatic amines, these substituents are readily introduced by Method B, and 2) the problems which are encountered with Method B in the case of sterically demanding substituents at the 1-position do not occur in Method A.

During the course of our work directed at the regioselective synthesis of the 1-substituted imidazole-2-thiones **3** via the imidazole-*N*-oxides **2** (Scheme 2, Method A), it became apparent that these *N*-oxides are extremely useful intermediates



Scheme 4. The scope of synthetic transformations of 5-pyridin-4-yl-imidazole-*N*-oxides. In the case of **7**, **8**, and **9**, only the derivatives with R = propyl were synthesized.

in the synthesis of structurally diverse 5-(pyridin-4-yl)imidazole derivatives modified at the 2-position (Scheme 4). Compound **2a** (R = propyl) was converted into the imidazole-2-carbonitrile **9** with trimethylsilylcarbonitrile.[8a] Deoxygenation of **2** with PCl_3 yielded the imidazole **10** with only a hydrogen atom in the 2-position.[8b] This method provides an alternative pathway for the synthesis of known p38 MAP kinase inhibitors such as SB 210313 (**10**, R = 3-morpholinopropyl).[2f] As with the corresponding imidazole-2-ones **6**, the imidazole-1*N*-oxide **2a** (R = propyl) was chlorinated with phosphorylchloride to give the 2-chloroimidazole **7a**.[8b] Furthermore, bromination of several *N*-oxides **2** with phosphoryl bromide led to the 2-bromoimidazole derivatives **11**. The crude product of these reactions was a mixture of **10** and **11**, which was separated by column chromatography. Although **11** was obtained in only moderate yields, this approach was the most successful attempt in the preparation of 2-bromo-5-(pyridin-4-yl)imidazole. Alternative methods, for example, treatment of **10** with *N*-bromosuccinimide in acetonitrile, treatment of **10** with Br_2, or reaction of **6** with $SOBr_2$, afforded only traces of **11**. The 2-bromoimidazoles **11** were suitable synthetic precursors for the 1-substituted 2-aryl imidazoles **12**, as **11** underwent nearly quantitative Suzuki coupling with different boronic acids.[8c] The synthetic importance of **11** in this reaction is underlined by the failure of the corresponding 2-chloroimidazoles **7** to provide 2-aryl imidazoles under Suzuki conditions.

The above synthetic methodology enabled us to prepare a plethora of highly diverse and highly substituted imidazole derivatives from a comparatively small number of starting compounds. In the p38 MAP kinase assay, analogues **4b–d** exceeded the reference compound ML 3163 in biological potency (Table 1). These compounds also efficiently inhibited cytokine release from human monocytes because of their

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Table 1. Inhibition of p38 MAP kinase, cytokine release, and cytochrome P450 isoforms by selected compounds.

Compound	$IC_{50} \pm SEM$ [μM][a] p38	TNF-α	IL-1β	Inhibition [%] of P450 isoforms[b] 2D6	3A4
SB 203580	0.29 ± 0.03 (7)	0.59 ± 0.09 (21)	0.037 ± 0.006 (20)	73.1	76.6
ML 3163	4.0 ± 1.0	1.1 ± 0.4 (4)	0.38 ± 0.13 (4)	71.8	87.1
4b	2.2 (1)	2.2 ± 0.9	0.45 ± 0.03	7.8	28.3
4c	0.50 (1)	0.51 ± 0.24 (4)	0.11 ± 0.03 (4)	13.4	16.5
4d	2.2 (1)	1.1 ± 0.3	0.38 ± 0.04	0.7	28.8

[a] Tests were carried out in duplicate, except where the number in brackets denotes otherwise. SEM = Standard error of measurement. [b] Results are from one experiment each, carried out at a test-compound concentration of 10 μM in phosphate buffer (pH 7.4) with DMSO (0.1%).

favorable cell-penetration properties. In the whole-blood assay, IC_{50} values (μM) for the most active derivatives **4b** (TNF-α: 5.6 ± 0.95, IL-1β: 1.5 ± 0.7), **4c** (TNF-α: 0.51 ± 0.24, IL-1β: 0.11 ± 0.03), and **4d** (TNF-α: 5.1 ± 0.4, IL-1β: 1.1 ± 0.7) were lower than those of lead compound ML 3163 (TNF-α: 20.3 ± 4.8, IL-1β: 2.78 ± 0.13), and close to the nanomolar range. Finally, the most promising results came from the toxicity screen, in which **4b–d** (Table 1) only moderately interacted with those P450 isoforms most important for drug metabolism.[9] This profile gives **4b–d** a clear advantage over both SB 203580 and ML 3163, and makes them strong candidates for further development as anti-inflammatory drugs.

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Tetrafunctional Photoaffinity Labels Based on Nakanishi's *m*-Nitroalkoxy-Substituted Phenyltrifluoromethyldiazirine**

Mohammed Daghish, Lothar Hennig, Matthias Findeisen, Sabine Giesa, Frank Schumer, Horst Hennig, Annette G. Beck-Sickinger, and Peter Welzel*

Photoaffinity labeling has been demonstrated to be a remarkably efficient method for studying the interactions of biologically significant compounds (ligands) with their target macromolecules.[1] The method allows the identification of the targets (for example, binding proteins) and, also the binding domain within the target protein. An appropriate photoaffinity-labeling compound should contain three structural elements:

a) a ligand which directs the label to the binding site on the protein,
b) a photolabile group for attaching to the protein,
c) an indicator that allows the identification of the labeled peptides after enzymatic digestion of the labeled protein.

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