Synthetic Methods

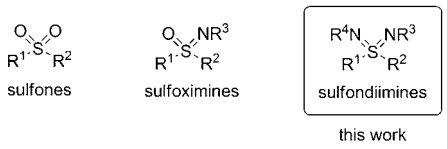
DOI: 10.1002/ange.201201296

Synthesis of Sulfondiimines by *N*-Chlorosuccinimide-Mediated Oxidative Imination of Sulfiliminium Salts**

*Mathieu Candy, Carole Guyon, Stefanie Mersmann, Jia-Rong Chen, and Carsten Bolm**

Dedicated to Professor H.-J. Gais on the occasion of his 70th birthday

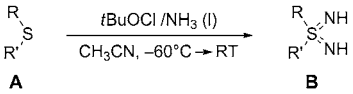
Sulfondiimines are aza analogues of sulfones and sulfoximines (Scheme 1),[1] and although they have been known for decades, only very few applications of these sulfur derivatives



Scheme 1. Structures of sulfones, sulfoximines, and sulfondiimines.

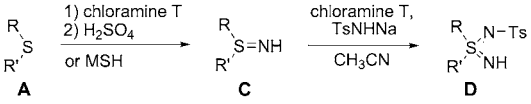
have been reported.[2–4] This observation is surprising with regard to the significant interest in oxygen-containing analogues of sulfondiimines that is best reflected by the large number of contributions on bioactive sulfoximine derivatives and their use in medicinal and crop-protection chemistry.[5–7] The difficult preparative access and the limited structural variety of sulfondiimines are probably the main reasons for their rare use. These restrictions are particularly true for chiral derivatives, which could be of interest for asymmetric synthesis and bio-related applications. Surprisingly, only three nonracemic sulfondiimines with chirality at the sulfur atom have been reported to date.[8]

The main synthetic contributions in this area date back to the 1970s when Haake and Oae developed preparative routes toward sulfondiimines, which are still the most efficient to date. Thus, N,N′-nonsubstituted sulfondiimines **B** can be obtained in moderate to good yields by treatment of the corresponding sulfides **A** with a chlorite source and an excess of liquid ammonia [Eq. (1)].[9] This method is efficient for the synthesis of S,S-dialkyl sulfondiimines but gives lower yields for S-alkyl-S-aryl and S,S-diaryl derivatives. N-Tosyl-N′H-S,S-



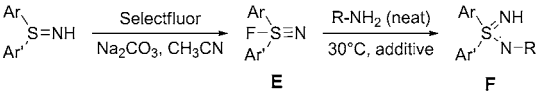
(1)

diaryl sulfondiimines **D** can be synthesized in good yields by treatment of the corresponding NH-sulfilimines[10] **C** with chloramine T [Eq. (2)].[11] However, because S,S-dialkyl or S-alkyl-S-aryl NH-sulfilimines are unstable, only poor yields and a very limited substrate scope have been reported.[8a,11,12]



(2)

More recently, Yoshimura described an alternative approach toward S,S-diaryl sulfondiimines **F**,[13] in which S-fluorothiazynes **E** react with primary amines [Eq. (3)]. However, this protocol appears to be restricted to the synthesis of S,S-diaryl sulfondiimines.



(3)

With the goal to overcome the current preparative limitations to structurally diverse and functionalized sulfondiimines, we decided to search for a more general synthetic route toward those interesting sulfur compounds. With respect to potential applications, chiral derivatives with an S-alkyl-S-aryl substitution pattern appeared particularly interesting as targets.

In the initial screening, sulfiliminium mesitylenesulfonate salt **1a** was used as starting material. This approach was inspired by the pioneering work of Georg and Haake, who utilized such salts for the preparation of N,N′-nonsubstituted diaryl and *sec*-alkyl aryl sulfondiimines **B**.[14] Compound **1a** was readily available from the corresponding sulfide by treatment with *O*-mesitylenesulfonyl hydroxylamine (MSH),[10c] and use of **1a** avoided commencing the synthetic route with the more sensitive *S*-methyl-*S*-phenyl sulfilimine **2**. Based on the work by Yoshimura, we expected that the addition of Selectfluor to **1a** would provide S-fluorothiazyne

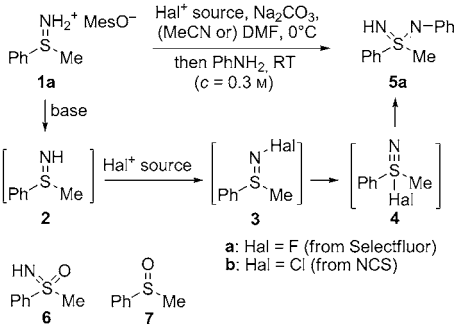
[*] Dr. M. Candy, C. Guyon, S. Mersmann, Prof. Dr. J.-R. Chen, Prof. Dr. C. Bolm
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52056 Aachen (Germany)
E-mail: carsten.bolm@oc.rwth-aachen.de

[**] This work was supported by the Fonds der Chemischen Industrie and the Excellence Initiative of the German federal and state governments (Seed Funds at RWTH Aachen University). M.C. and J.-R.C. acknowledge support by the Alexander von Humboldt foundation. We also thank Prof. Dr. M. Rueping and C. Vermeeren for performing the enantiomer separation by preparative supercritical fluid chromatography.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201296.

4a, which we hoped to convert into sulfondiimine **5a** by treatment with aniline. Because all attempts to isolate **4a** failed, a one-pot reaction sequence was envisaged. Thus, **1a** was first treated with the oxidizing agent (Selectfluor) in acetonitrile in the presence of a base (Na_2CO_3), and aniline was added after five hours. As hypothesized, this protocol led indeed to the formation of sulfondiimine **5a**, albeit with varying amounts of sulfoximine **6** and sulfoxide **7** as by-products [Eq. (4)]. After significant optimization of the reaction conditions (solvent, base, reaction time, etc.)[15] sulfondiimine **5a** could finally be isolated in 42% yield.

this work:

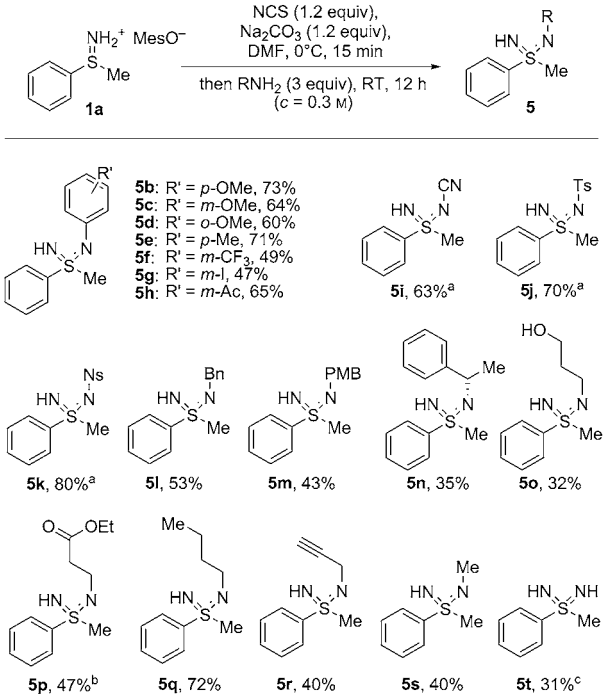


(4)

Considering the role of Selectfluor as oxidant and F^+ source, other Hal^+ transfer agents were tested next. Whereas *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) were less effective or even ineffective,[15] the use of *N*-chlorosuccinimide (NCS) significantly improved the yield of sulfondiimine **5a**, and the amounts of by-products were reduced. In this case, halogenated intermediates, such as **3b** or **4b**, could not be isolated. Compared to the reaction sequence with Selectfluor, the halogenation step with NCS appeared to be much faster (15 min versus 5 h), whereas the amine substitution needed more time (12 h versus 1 h). Furthermore, the amount of both Na_2CO_3 and Hal^+ transfer agents could be reduced to 1.2 equivalents by using NCS (compared to 5 and 2 equivalents, respectively, with Selectfluor). Now, sulfondiimine **5a** was obtained in 75% yield from the reaction in DMF and by using Na_2CO_3 as base, even on multigram scale.

Application of the optimized conditions to reactions between **1a** and various primary amines (including sulfonamides) led to an array of N-monosubstituted sulfondiimines (Scheme 2). To our delight, the functional-group tolerance was excellent, and most products were formed in satisfying yields (31–80%), in particular considering the complexity and substrate sensitivity of the one-pot reaction. Aniline derivatives that bear either electron-donating or electron-withdrawing groups generally gave the corresponding sulfondiimines (**5b–h**) in good yields (47–71%).

Noteworthy, in these reactions, both iodo and acetyl substituents on the aniline core were tolerated (**5g** and **5h**). Also, less nucleophilic amino derivatives, such as cyanamide, nosyl or tosyl amide, reacted well, although in these cases the corresponding sodium salts had to be used (**5i–k**). N-Benzyl derivatives were obtained in moderate yields (**5l–n**).

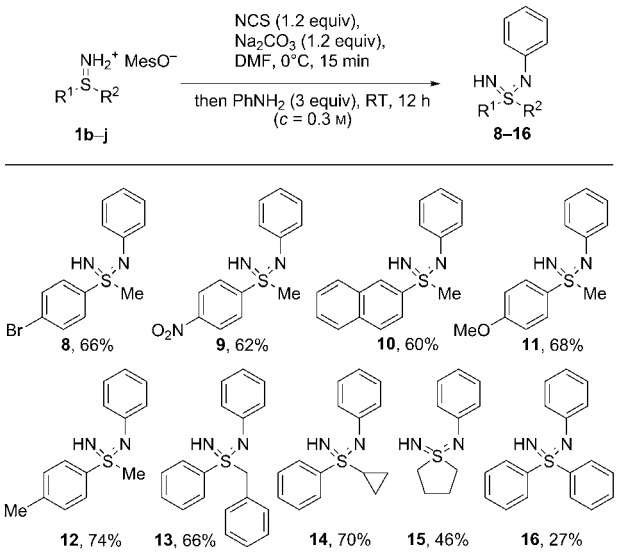


Scheme 2. Amine substrate scope. Yields after column chromatography. [a] Use of the corresponding sodium salt (RNHNa) of the amine. [b] Use of the HCl salt of the corresponding amine and 4.2 equiv of Na_2CO_3. [c] Use of hexamethyldisilylamine (HMDS) as amino source and 4.2 equiv of Na_2CO_3. Bn = benzyl, DMF = *N*,*N*-dimethylformamide, Mes = 2,4,6-trimethylphenylsulfonyl, Ns = 4-nitrobenzenesulfonyl, PMB = *p*-methoxybenzyl, Ts = 4-toluenesulfonyl.

With enantiopure α-methylbenzylamine, the reaction gave a separable 1:1 mixture of diastereomers of **5n** in 35% yield. The high functional-group tolerance in reactions with aliphatic amines (**5o–s**) is noteworthy; products with a free hydroxy, a carboxy, and an alkynyl moiety were obtained. Finally, N,N′-nonsubstituted sulfondiimine **5t** was prepared in 31% yield by using HMDS as a masked source of ammonia. Considering the initially mentioned sulfone–sulfoximine–sulfondiimine analogy, the straightforward access to this product might be of relevance for subsequent developments in medicinal and crop-protection chemistry.

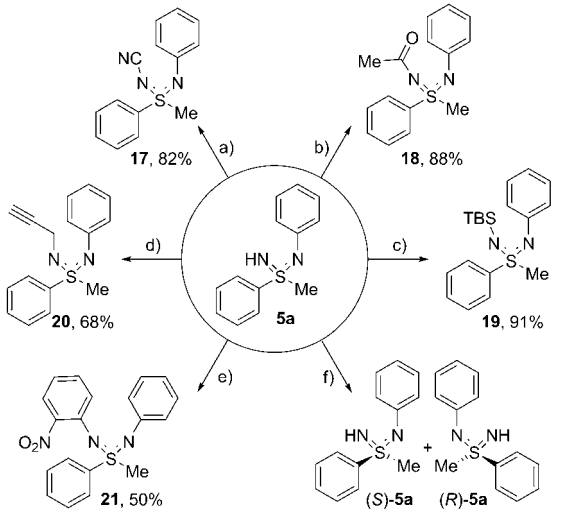
Next, the sulfiliminium salt was varied by using aniline as nucleophile in the imination step (Scheme 3). A wide range of synthetically challenging S-alkyl-S-aryl sulfondiimines (**8–14**) was obtained in good yields (up to 74%). Various substituents on the aryl group were tolerated, and electron-rich substrates gave the best results (**11** and **12**). Sulfiliminium salts derived from benzyl phenyl sulfide and cyclopropyl phenyl sulfide afforded the corresponding products in 66 and 70% yield, respectively. As representatives for dialkyl and diaryl derivatives, **15** and **16** were prepared starting from tetrahydrothiophene and diphenyl sulfide, respectively. Although in these cases the yields were low (46 and 27%), the results confirmed that substrates with those substitution patterns were also suitable starting materials in the newly devised protocol.

In order to evaluate the reactivity of the N-monosubstituted sulfondiimines, several transformations were studied by



Scheme 3. Scope of the sulfiliminium salts. Yields after column chromatography.

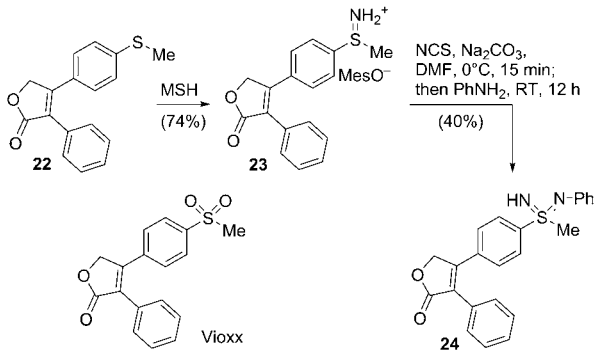
using **5a** as representative substrate (Scheme 4). Under common reaction conditions, **5a** could be cyanated,[16] acylated, silylated, alkylated, and arylated to give the corresponding N,N′-disubstituted sulfondiimines **17**–**21** in good to high yields. All transformations involved the presence of an adequate base in combination with a suitable organohalide. A copper catalyst[17,18] was applied for the conversion of **5a** into N-arylated compound **21** and, to the best of our knowledge, this transformation represents the first reported Ullmann-type cross-coupling reaction of a sulfondiimine.



Scheme 4. Derivatization of sulfondiimine **5a**. a) BrCN, NEt_3, CH_2Cl_2, RT; b) Ac_2O, DMAP (10 mol%), NEt_3, CH_2Cl_2 RT; c) KH, TBSCl, THF, 0°C→RT. d) KH, propargyl bromide, THF, 0°C→RT; e) 2-nitroiodobenzene, K_2CO_3, CuI (10 mol%), DMEDA (20 mol%), toluene, 90°C, 12 h; f) preparative SFC using a chiral stationary phase. DMAP = 4-dimethylaminopyridine, DMEDA = *N*,*N*′-dimethylethylenediamine, TBS = *tert*-butyldimethylsilyl.

With respect to potential applications in asymmetric synthesis and bioactivity studies, access to enantiopure sulfondiimine derivatives and configurational integrity under standard conditions had to be ensured. Along those lines, a resolution of **5a** by preparative supercritical fluid chromatography (SFC) using a chiral stationary phase was established, which efficiently provided both enantiomers. Their absolute configurations were unambiguously determined by comparing calculated and measured ECD spectra.[15] To the best of our knowledge, these are the first enantiopure sulfondiimines that bear a stereogenic center at the sulfur atom.

Considering the recent success of the sulfone-to-sulfoximine switch in medicinal chemistry,[6] and with the intention to demonstrate the applicability of the newly devised protocol for the preparation of sulfondiimines in a more complex context, the synthesis of Vioxx analogue **24** was targeted. Starting from the corresponding sulfide **22**, the imination with MSH proceeded smoothly and led to sulfiliminium salt **23** in 74% yield (Scheme 5). To our delight, the sensitive butenolide moiety was tolerated and sulfondiimine **24** was obtained in 40% yield by using the standard conditions.[19]



Scheme 5. Synthesis of a sulfondiimine-based Vioxx analogue.

In summary, a mild and general method for the synthesis of sulfondiimines was developed and allows the preparation of a wide variety of functionalized products, including synthetically challenging S-aryl-S-alkyl derivatives. N,N′-Disubstituted sulfondiimines can be obtained from the corresponding N-monosubstituted derivatives by straightforward chemical modifications. A representative chiral product was resolved, and the absolute configurations of the enantiomers were determined by spectroscopic and theoretical means. Finally, the applicability of the method was demonstrated by the synthesis of a sulfondiimine-based Vioxx analogue.

Experimental Section

General procedure for the oxidative imination of sulfiliminium salts [see Eq. (4)]: The sulfiliminium salt (1 mmol, 1 equiv) was dissolved in dry DMF (3 mL) and cooled to 0°C in an oven dry flask under an argon atmosphere. Na_2CO_3 (127 mg, 1.2 mmol, 1.2 equiv) was added, followed by NCS (160 mg, 1.2 mmol, 1.2 equiv), and the reaction mixture was stirred for 15 min at 0°C. The amine (3 mmol, 3 equiv)

was added and the reaction mixture was stirred at room temperature for 12 h. Water (15 mL) was added, the product was extracted with CH_2Cl_2 (3×15 mL), and the combined organic layers were washed with brine (1×10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography.

Received: February 16, 2012
Published online: March 20, 2012

Keywords: imination · *N*-chlorosuccinimide · sulfiliminium salts · sulfondiimines · synthetic methods

[1] a) J. A. Cogliano, G. L. Braude, *J. Org. Chem.* **1964**, *29*, 1397; for reviews, see: b) M. Haake in *Topics in Sulfur Chemistry*, *Vol. 1* (Eds.: A. Senning), Thieme, Stuttgart, **1976**, p. 185; c) M. Haake in *Houben-Weyl*, *Methoden der Organischen Chemie*, *Vol. 2*, Thieme, Stuttgart, **1985**, p. 1321; d) N. Furukawa, K. Akutagawa, S. Oae, *Phosphorus Sulfur Relat. Elem.* **1984**, *20*, 1.

[2] For applications of sulfondiimines in heterocyclic chemistry, see: a) W. Ried, R. Pauli, *Chem. Ber.* **1984**, *117*, 2779; b) W. Ried, R. Pauli, *Chem. Ber.* **1985**, *118*, 2561; c) W. Ried, M. A. Jacobi, *Chem. Ber.* **1988**, *121*, 383; d) M. Haake, H. Holz, *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, *153–154*, 407; e) W. E. Diederich, M. Haake, *J. Org. Chem.* **2003**, *68*, 3817.

[3] For the incorporation of sulfondiimines in pseudopeptides, see: J. Dehli, C. Bolm, *Synthesis* **2005**, 1058.

[4] For sulfondiimines in methods development, see: a) G. I. Georg, S. A. Pfeifer, M. Haake, *Tetrahedron Lett.* **1985**, *26*, 2739; b) T. Yoshimura, T. Fujie, T. Fujii, *Tetrahedron Lett.* **2007**, *48*, 427.

[5] For a summary, see: C. Worch, A. C. Mayer, C. Bolm, in *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**, p. 209.

[6] For selected examples in medicinal chemistry, see: a) M. Kahraman, S. Sinishtaj, P. M. Dolan, T. W. Kensler, S. Peleg, U. Saha, S. S. Chuang, G. Bernstein, B. Korczak, G. H. Posner, *J. Med. Chem.* **2004**, *47*, 6854; b) A. Raza, Y. Y. Sham, R. Vince, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5406; c) D. P. Walker, M. P. Zawistoski, M. A. McGlynn, J.-C. Li, D. W. Kung, P. C. Bonnette, A. Baumann, L. Buckbinder, J. A. Houser, J. Boer, A. Mistry, S. Han, L. Xing, A. Guzman-Perez, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3253; d) K. Takahashi, R. Tatsunami, T. Oba, Y. Tampo, *Biol. Pharm. Bull.* **2010**, *33*, 556; e) S.-J. Park, H. Buschmann, C. Bolm, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4888.

[7] For selected examples in crop-protection chemistry, see: a) O. García Mancheño, J. Dallimore, A. Plant, C. Bolm, *Adv. Synth. Catal.* **2010**, *352*, 309; b) Y. Zhu, M. R. Loso, G. B. Watson, T. C. Sparks, R. B. Rogers, J. X. Huang, B. C. Gerwick, J. M. Babcock, D. Kelley, V. B. Hegde, B. M. Nugent, J. M. Renga, I. Denholm, K. Gorman, G. J. DeBoer, J. Hasler, T. Meade, J. D. Thomas, *J. Agric. Food Chem.* **2011**, *59*, 2950; c) J. M. Babcock, B. G. Gerwick, J. X. Huang, M. R. Loso, G. Nakamura, S. P. Nolting, R. B. Rogers, T. C. Sparks, J. Thomas, G. B. Watson, Y. Zuh, *Pest Manage. Sci.* **2011**, *67*, 328.

[8] a) B. W. Christensen, A. J. Kjær, *Chem. Soc. Chem. Commun.* **1975**, 784; b) M. F. Müller-Kalben, diploma thesis, University of Bonn, **1969**; c) For a separation of enantiomers of a cyclic derivative by HPLC, see: G. Blaschke, *J. Liq. Chromatogr.* **1986**, *9*, 341.

[9] a) R. Appel, H. W. Fehlhaber, D. Hänssgen, R. Schöllhorn, *Chem. Ber.* **1966**, *99*, 3108; b) R. G. Laughlin, W. Yellin, *J. Am. Chem. Soc.* **1967**, *89*, 2435; c) M. Haake, *Tetrahedron Lett.* **1970**, *11*, 4449.

[10] For the most useful methods for the synthesis of *NH*-Sulfilimines see: a) Y. Tamura, K. Sumoto, J. Minamikawa, M. Ikeda, *Tetrahedron Lett.* **1972**, *13*, 4137; b) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, M. Ikeda, *J. Org. Chem.* **1973**, *38*, 1239; c) Y. Tamura, H. Matsushima, J. Minamikawa, M. Ikeda, K. Sumoto, *Tetrahedron* **1975**, *31*, 3035; d) N. Furukawa, T. Omata, T. Yoshimura, T. Aida, S. Oae, *Tetrahedron Lett.* **1972**, *13*, 1619; e) T. Yoshimura, T. Omata, N. Furukawa, S. Oae, *J. Org. Chem.* **1976**, *41*, 1728; f) C. Urban, Y. Macé, F. Cadoret, J.-C. Blazejewski, E. Magnier, *Adv. Synth. Catal.* **2010**, *352*, 2805.

[11] a) N. Furukawa, T. Omata, S. Oae, *J. Chem. Soc. Chem. Commun.* **1973**, 590; b) N. Furukawa, K. Akutugawa, T. Yoshimura, T. Akasaka, S. Oae, *Synthesis* **1979**, 289.

[12] R. Appel, J. Kohnke, *Chem. Ber.* **1971**, *104*, 2023.

[13] a) T. Yoshimura, H. Kita, K. Takeuchi, E. Takata, K. Hasegawa, C. Shimasaki, E. Tsukurimichi, *Chem. Lett.* **1992**, *21*, 1433; b) T. Fujii, S. Asai, T. Okada, W. Hao, H. Morita, T. Yoshimura, *Tetrahedron Lett.* **2003**, *44*, 6203; c) T. Yoshimura, H. Ishikawa, T. Fujie, E. Takata, R. Miyatake, H. Kita, E. Tsukurimichi, *Synthesis* **2008**, 1835.

[14] G. Georg, M. Haake, *Synthesis* **1983**, 919.

[15] For details see the Supporting Information.

[16] R. Appel, G. Vollmer, *Chem. Ber.* **1970**, *103*, 2555.

[17] For N-arylations of sulfoximines under those conditions, see: J. Sedelmeier, C. Bolm, *J. Org. Chem.* **2005**, *70*, 6904.

[18] For N-arylations of sulfondiimines by nucleophilic substitution of activated aryl halides, see: W. Ried, R. Pauli, *Liebigs Ann. Chem.* **1986**, 384.

[19] Attempts to prepare the N,N′-nonsubstituted analogue of **24** are currently in progress and shall be reported in combination with results from bioactivity studies in due course.

