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1,3-Diphenylpropane-1,3-diamines, VIII. Reactions of Lithiated Oximes and Oxime Ethers with C=N-Electrophiles[#]

A. Kaiser and **W. Wiegrebe**

Institute of Pharmacy, University of Regensburg, D-93040 Regensburg, Germany

Summary. The reaction of lithiated acetophenone oximes and their O-methyl ethers with benzylideneamines affords (1,3-diphenyl-3-hydroxyimino-1-propyl)-amines or their O-methyl derivatives, respectively, which are precursors of 1,3-diphenylpropane-1,3-diamines.

Keywords. Lithiated oximes; Lithiated oxime ethers; N-Benzylideneamines; C=N-Electrophiles; 5-Aminoisoxazolines.

1,3-Diphenylpropan-1,3-diamine, 8. Mitt. Reaktionen lithiierter Oxime und Oximether mit C=N-Elektrophilen

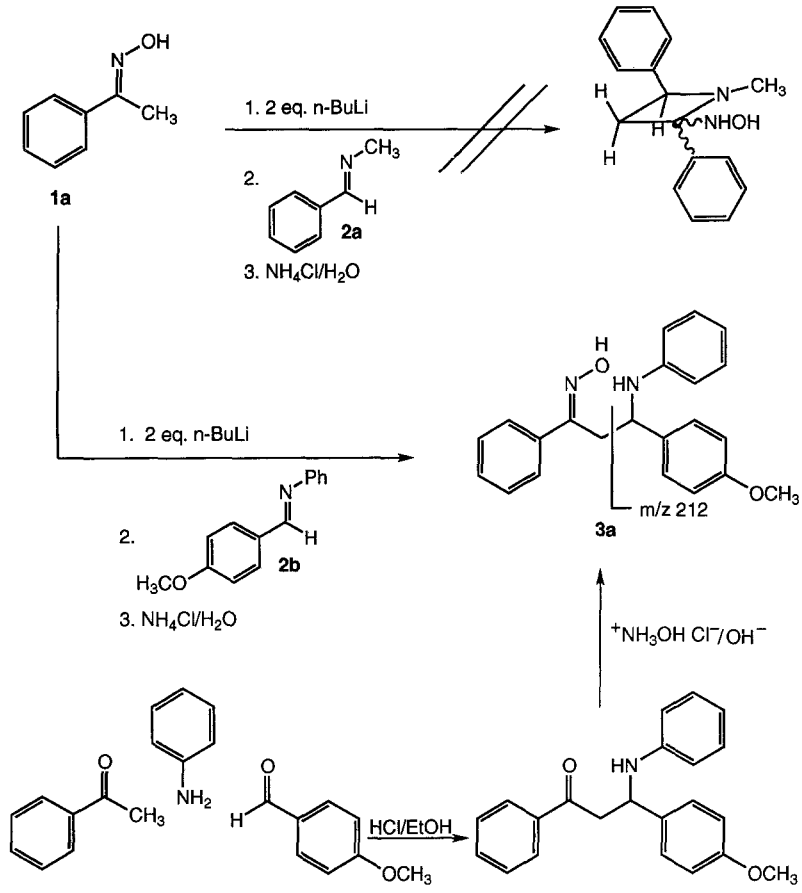
Zusammenfassung. Die Reaktion lithiierter Acetophenonoxime bzw. ihrer O-Methylether mit Benzylidenaminen führt zu (1,3-Diphenyl-3-hydroxyimino-1-propyl)-aminen bzw. zu deren O-Methylderivaten. Diese Verbindungen sind Vorstufen für 1,3-Diphenylpropan-1,3-diamine.

Introduction

In Part VII of this series concerning 1,3-diphenylpropane-1,3-diamines and their Pt(II) complexes [1], we have correlated *threo* diastereomers with racemates and *erythro* configurated compounds with *meso* forms by chemical transformations. The cytostatic effects of these complexes strongly depend on their stereochemistry [2]. The assignments *meso/rac* had in turn been established unequivocally [3].

Here we report our results which disprove *Gaudemar*'s results [4] concerning the formation of 2-hydroxyamino-azetidines by *n*-BuLi effected reaction of acetophenone oxime (**1a**) with N-methyl-benzaldehyde imine (**2a**) (Scheme 1). Moreover, we describe a new approach to precursors of the compounds mentioned in the series title. This turned out as necessary for diastereoselective and enantiospecific syntheses which will be dealt with in forthcoming papers.

[#] Dedicated with warm regards to Prof. Dr. Dr. h.c. mult. *H. Oelschläger*, Jena (Germany) on the occasion of his 75th birthday



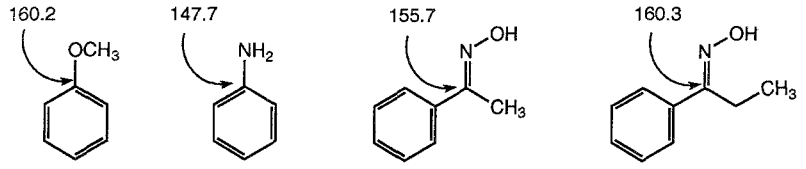
Scheme 1

Results and Discussion

Repeating *Gaudemar*'s experiment [4], we did not obtain an azetidine but recovered 90% of oxime **1a**; imine **2a** or benzaldehyde could not be detected. As a consequence, we checked the literature concerning 2-aminoazetidines. *Nomura et al.* [5] assume a 2-aminoazetidine intermediate to be generated in the formation of chalcone imines from enamines and imines in AcOH. *Aben et al.* [6] obtained 2-(pyrrolidin-1-yl)-azetidines from pertinent enamines and imines under high pressure by [2 + 2]-cycloaddition, which, however, collapse to the starting materials at atmospheric pressure. On the other hand, *Effenberger et al.* [7] have synthesized a 2-aminoazetidine with an electron-withdrawing substituent at the ring-N by [2 + 2]-cycloaddition of a morpholine-enamine and N-phenylsulfone-benzaldehyde imine. When ethyl N-(2,2,2-trichloro)-ethylidene carbamate was reduced to the corresponding trichloroethane derivative by branched *Grignard* reagents, this ethane derivative reacted with an excess of the ethylidene carbamate affording N-ethoxycarbonyl-2-(ethoxycarbonylamino)-3,3-dichloro-4-(trichloromethyl)-azetidine and HCl (*Kashima* [8]). 4-Amino-2-azetidinones (2-amino-β-lactams) can be obtained either from ketenes and amidines or from isocyanates and enamines [9, 10].

Considering these results, the formation of 2-hydroxyamino-azetidines (aminal like compounds) as reported by *Gaudemar* [4] became unlikely. In accordance with this supposition, the repetition of *Gaudemar*'s [4] addition of oxime **1a** to imine **2b** (Scheme 1) did not afford an azetidine but the precursor of a 1,3-diphenylpropane-1,3-diamine (**3a**). Its structure **3a** is corroborated by the following data:

a) In the ^{13}C NMR spectrum, oxime C-atoms resonate at 145–165 ppm [11, 12]. In this region, **3a** shows three resonances: the signal at 147.2 ppm is attributed to C-1 of the aniline group, the signals at 158.8 and 157.6 ppm stem from C=N–OH and =*C*–OCH_3. These associations agree with those shown in Scheme 2 [13, 14].



Scheme 2

As indicated, 2-hydroxyamino-azetidines are aminals and, therefore, should show resonances at 70–95 ppm [15–18]. In oxime **3a**, however, no signals can be found between 56.0 and 113.2 ppm.

b) The 70 eV mass spectrum of **3a** reveals a fragment ion at $m/z = 212$ (base peak; α- and benzylic cleavage).

c) At 90 MHz, the benzylic H of **3a** resonates as a multiplet at 4.43–4.73 ppm, which is simplified to a dd by H/D exchange. This exchange (NH *versus* ND) is reasonable for **3a**, whereas in the azetidine in question this exchange will not influence the signal of the benzylic H.

d) Independent *Mannich*-synthesis of **3a** from acetophenone, aniline, and *p*-methoxybenzaldehyde, followed by oximation of the pertinent 3-anilino-2,3-dihydrochalcone (Scheme 1) afforded a compound identical with **3a** obtained under *Gaudemar*'s condition [4] (Scheme 1).

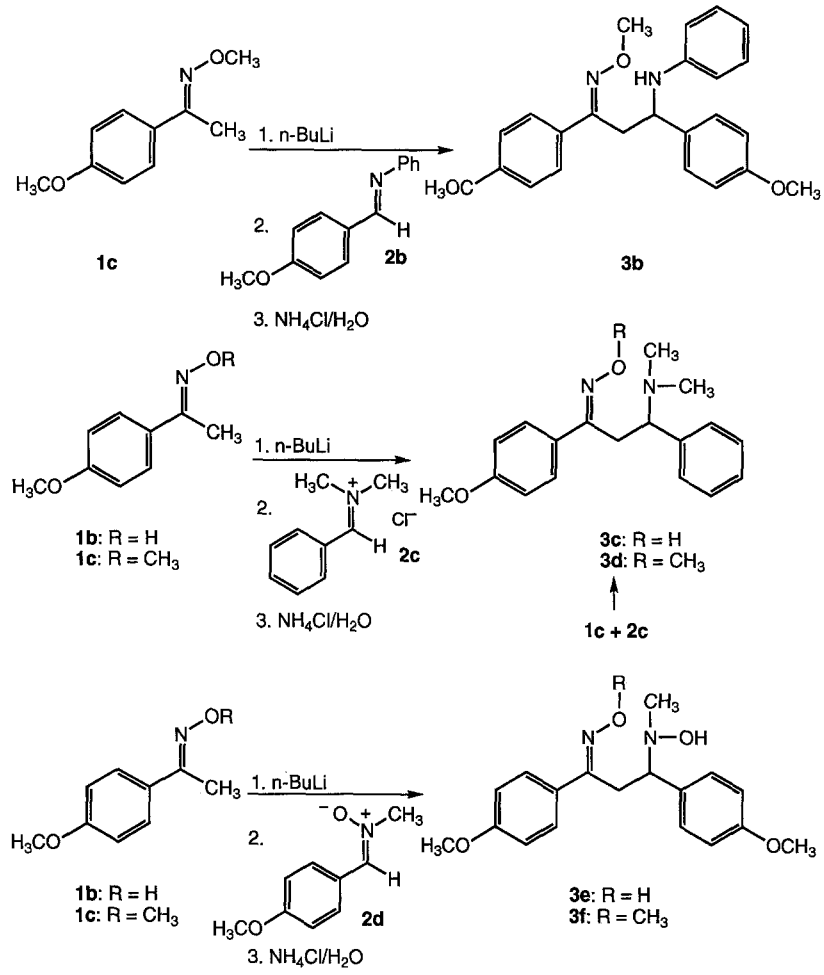
The reaction of the lithiated oxime ether (*E*)-**1c** with imine **2b** afforded the oxime ether **3b**, whereas the dianion of **1b** gave only 10% of oxime **3c** when being reacted with the iminium ion **2c** (Scheme 3). The metho-iodide of **3c** is known [19].

On the other hand, 68% of oxime ether **3d** were obtained from **2c** and **1c**-anion. The reactions of **1b** and **1c** with the nitrone **2d** afforded the propane-1,3-diamine precursors **3e** and **3f**, respectively.

Deviating from the reaction of O-alkylated ketoxime (**1c**) the reaction of **1b**-dianion with (*E*)-4-methoxybenzaldehyde O-methyloxime **2e** did not lead to the methoxyamino-oxime **4a** but to the 5-amino-2-isoxazoline **5** (Scheme 4; for preparation of **4** and **4b**, *cf.* Scheme 7).

Barluenga [20] has transformed 4,4-disubstituted 4-aminoisoxazolines into 3-imino-oximes by $LiAlH_4$ as a base (1. step), followed by reduction of the imine moiety, leading to 3-amino-oximes (Scheme 5).

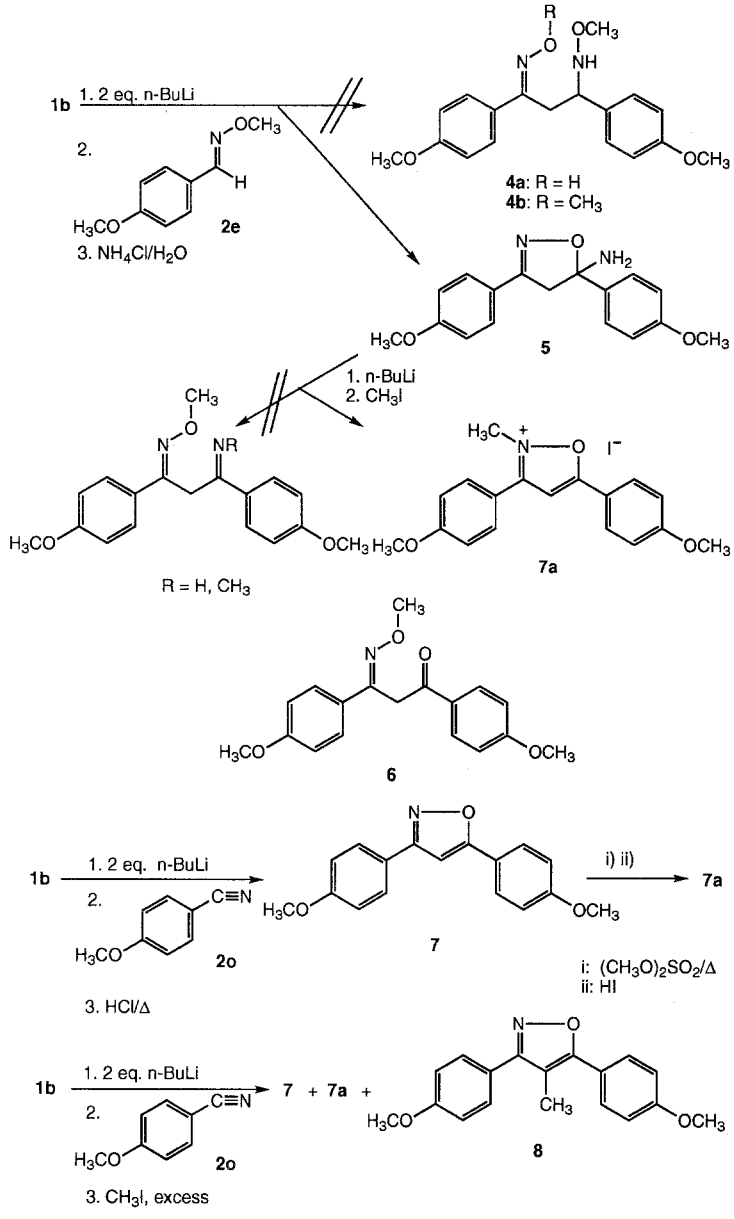
When we used this procedure, isoxazoline **5** afforded 34% of the amine-oxime **3h** (for **3h** see Scheme 8). So, 5-amino-3,5-diphenylisoxazolines are versatile precursors of 1,3-diphenylpropane-1,3-diamines.



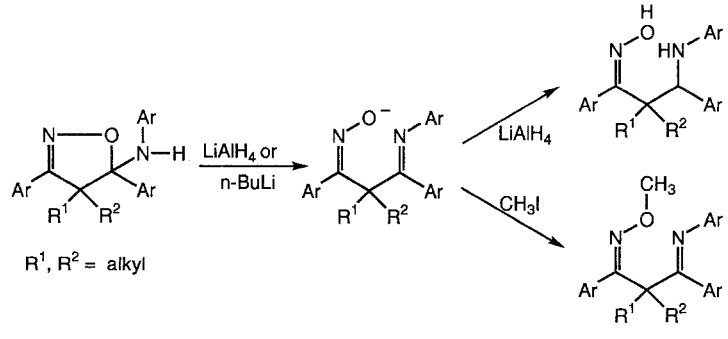
Scheme 3

In order to check the intermediacy of the pertinent 3-imino-oxime-O-anion (Scheme 5), isoxazoline **5** was treated with *n*-BuLi, followed by CH_3I for trapping the O-anion, but neither the 3-imino-oxime ether nor the methoxyimino-ketone **6** (Scheme 4) was identified as a product of hydrolyis in the product mixture (for independent synthesis of **6** *cf.* Scheme 6). Instead, we found 8% of the isoxazolium iodide **7a** which is probably produced by deprotonation at C-4 of **5** (aza-allylic position), followed by N-methylation of the ambident anion and subsequent loss of the exocyclic amino group. This hypothesis is corroborated by the formation of the 4-methylisoxazole **8** (Scheme 4). N-Methylation of the corresponding isoxazole **7** is excluded because **7** – independently prepared according to *Beam* [21, 22] (Scheme 4) – does not react with CH_3I at room temperature but needs more vigorous conditions to produce its metho-iodide **7a**.

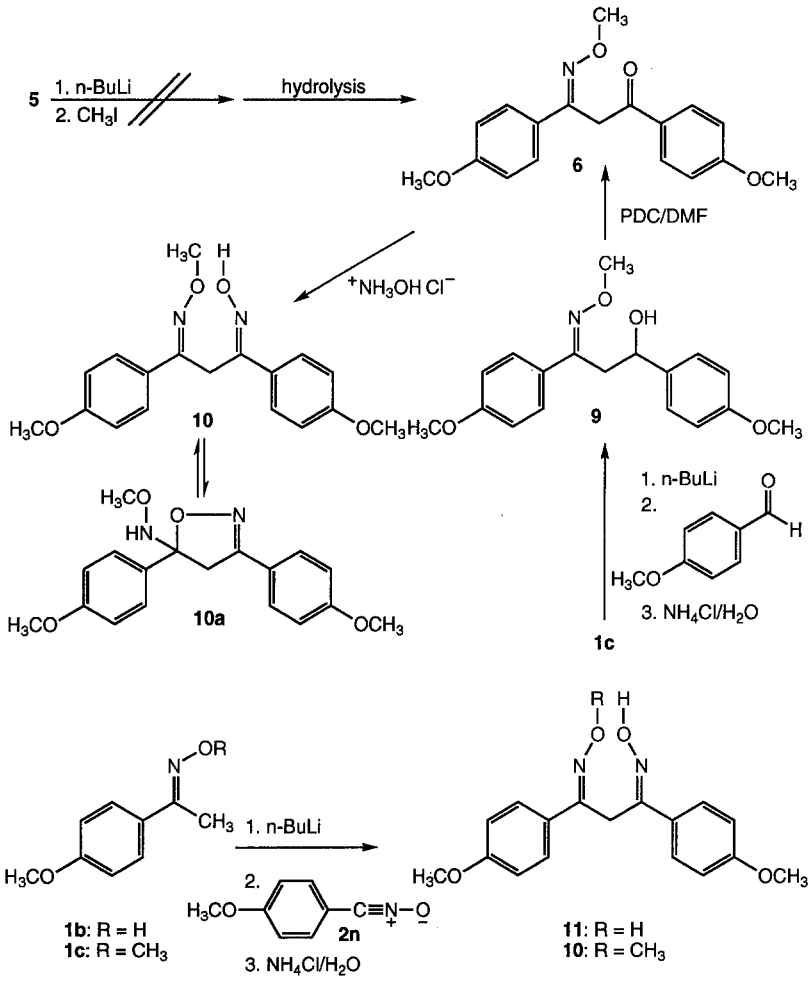
Methoxyimino ketone **6** was obtained by addition of **1c**-anion to 4-methoxybenzaldehyde and subsequent oxidation of carbinol **9**, following *Shatzmiller*'s procedure [23]. Oximation of **6** afforded the 1,3-diphenylpropane-1,3-diamine precursor **10** which can also be obtained from **1c**-anion and the nitrile oxide **2n**, whereas twofold lithiated **1b** affords the *bis*-oxime **11**. According to ^{13}C and ^{1}H NMR spectra in



Scheme 4



Scheme 5 (*Barluenga et al.* [20])



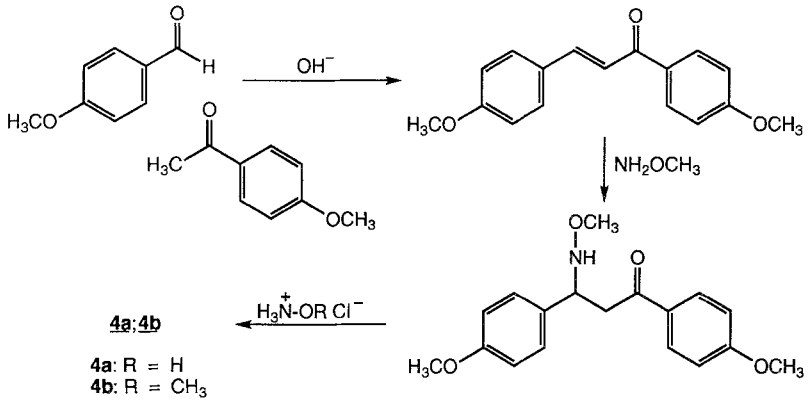
Scheme 6

$CDCl_3$, there is an equilibrium of the methoxyimino oxime **10** and about 30% of the methoxyaminoisoxazoline **10a**: C5 of **10a** resonates at 101.67 ppm (C5 of **5**: 98.88 ppm). In **10a**, the CH_2 protons are diastereotopic and form an AB system ($\delta_A = 3.70$; $\delta_B = 3.38$ ppm; $J_{AB} = 7.1$ Hz); in **5**, however, these protons are isochronous (s at 3.40 ppm). As compared with H_3CO–N= (**10**; 3.93 ppm), the resonance of H_3CO–NH is shifted to 3.60 ppm; in *E*- and *Z*-**4b**, these protons resonate at 3.40 ppm. *Ershov et al.* [24] have investigated this tautomerism, but they did not find it in (*E*, *E*)-1,3-diphenyl-1,3-propanedione dioxime. In accordance with this result, we did not observe this tautomerism in *DMSO*-d_6. Our results point towards the assumption that the base-catalyzed transformation of 5-aminoisoxazolines to 3-imino-oxime ethers seems to be restricted to 4,4-disubstituted 5-aminoisoxazolines as studied by *Barluenga* [20]: here the formation of the said 4-aza-allyl anion is impossible.

Isoxazoline **5** is also obtained from **1b**-dianion with 4-methoxybenzonitrile. We, therefore, conclude that **2e** loses MeOH affording this nitrile which in turn is attacked by **1b**-dianion. As a matter of fact we could identify 4-methoxybenzonitrile

by TLC and its IR spectrum in crude **5**. The formation of isoxazoline **5** is analogous to the well-known reactions of aldoxime ethers with organometallic compounds *via* the corresponding nitriles [25]. Elimination of alcohols from aldoxime ethers can be effected also with KNH_2/NH_3 [26] or with OH^- in water/dioxane [27].

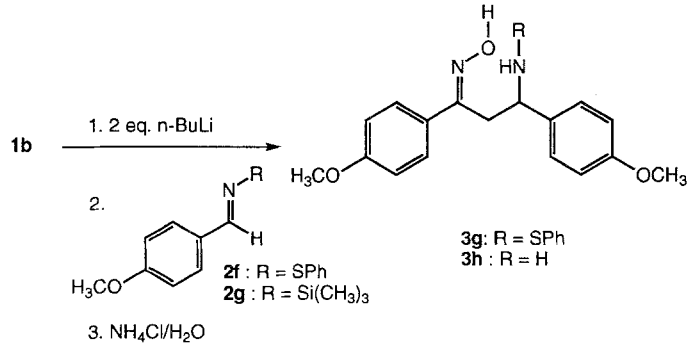
The crude material resulting from **1c**-anion and aldoxime ether **2e** contains also 4-methoxybenzonitrile, although in an useless, complex mixture, TLC runs of which did not show the presence of compound **4b** (Scheme 4) which had been synthesized according to Scheme 7. The oxime **4a** has been prepared analogously (for the 3-methoxyamino-propanone intermediate see *Blatt* [28]) (Scheme 7).



Scheme 7

Crude **4a** is free of stereoisomers, whereas (*E*)- and (*Z*)-isomers of **4b** could be separated by column chromatography. According to *Karabatsos* [29], we assigned the singlet of $NOCH_3$ at 3.90 ppm to the (*E*)-diastereomer and the singlet at 3.80 ppm – overlapping with that of the $C-OCH_3$ groups – to the (*Z*)-configurated compound.

The reactions with sulfen- and silylimines are characterized by the increased nucleophilicity of the oxime dianions. So, twofold lithiated **1b** affords the amine oximes **3g,h** when being reacted with the imines **2f, g** respectively (Scheme 8).

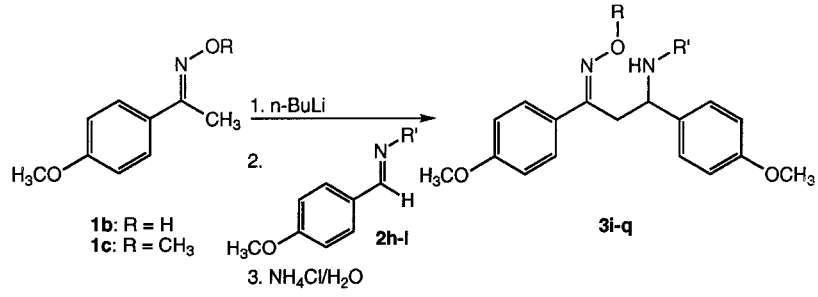


Scheme 8

On account of the lability of the N—S bond [30], **3g** was always deteriorated by **3h**. Therefore, **3g** was not further characterized, but intentionally converted to **3h** by short treatment with diluted HCl.

Reactions with acceptor substituted imines

In order to increase the electrophilicity of the imines, we used *Schiff* bases with an electron acceptor at the N atom for the reaction with lithiated oximes and their O-methyl derivatives, leading to oxime amides **3i–q** (Scheme 9).



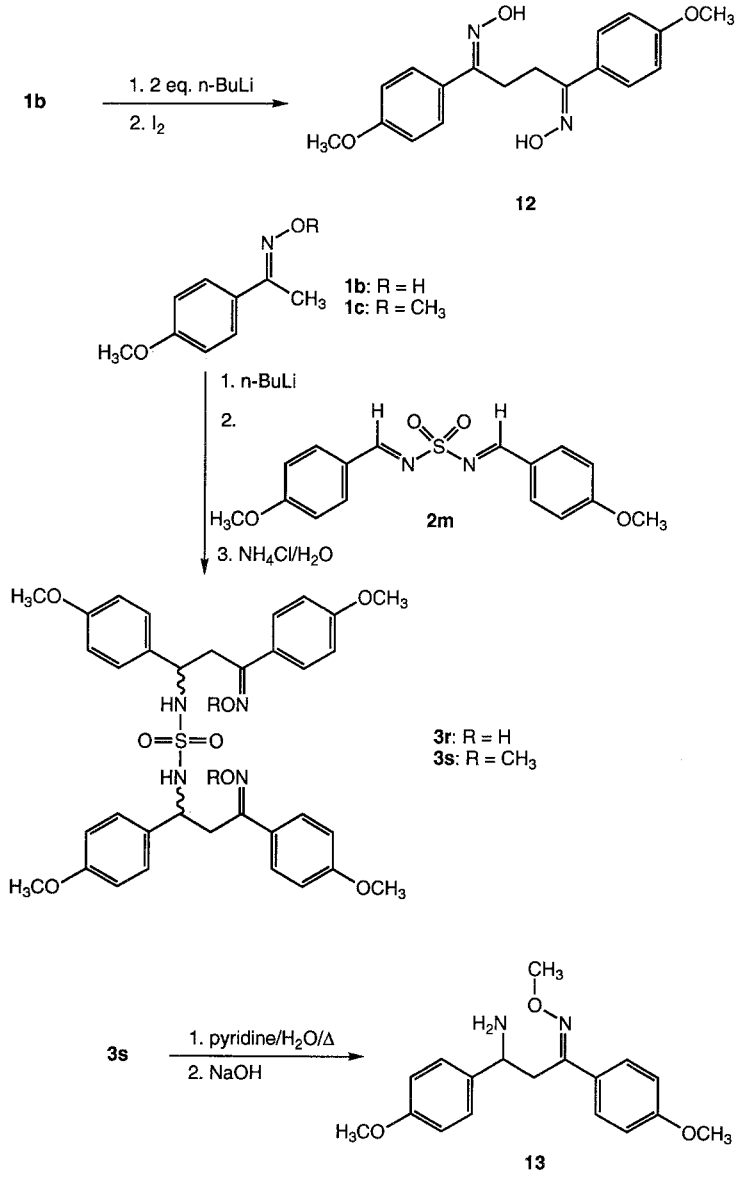
Educt	Product	R	R′
1c + 2h	**3i**	CH_3	$COCCl_3$
1b + 2i	**3j**	H	COPh
1c + 2i	**3k**	CH_3	COPh
1b + 2j	**3l**	H	$POPh_2$
1c + 2j	**3m**	CH_3	$POPh_2$
1b + 2k	**3n**	H	SOPh
1c + 2k	**3o**	CH_3	SOPh
1b + 2l	**3p**	H	SO_2Ph-4-Me
1c + 2l	**3q**	CH_3	SO_2Ph-4-Me

Scheme 9

As expected, the sulfineamides **3n** and **3o** arise as mixtures of diastereomers (broad, nonresolved multiplets in the ^1H NMR spectra of crude **3n** and **3o**). **3n** could not be separated; after recrystallization, **3o** is stereochemically pure as indicated by its sharp melting point, ^1H, and ^{13}C NMR spectra.

When **1b**-dianion was reacted with the N-trichloroacetylimine **2h**, we did not obtain an oxime amide but the 1,4-*bis*-(hydroxyimino)-butane derivative **12**. *Hauser* [31] has obtained the **12**-analogue without the methoxy groups in another context. Using *Shatzmiller*'s method [32, 33], we have dimerized **1b**-dianion oxidatively, affording the *bis*-oxime **12**. N,N′-*bis*-(4-methoxybenzylidene)-sulfamide **2m** reacts with two equivalents of **1b**-dianion or **1c**-anion, respectively, leading to the sulfamides **3r** and **3s** as mixtures of diastereomers. **3r** was separated into the racemate and the *meso* form by crystallization. These diastereomers were identified by separation of the racemic stereoisomer on a chiral HPLC column, whereas the *meso* form could not be separated under identic conditions; the racemate is less soluble

and shows a higher melting point than the *meso* form. Sulfamide **3s** was spilt into two molecules of the amine oxime ether **13** by heating in pyridine / water [34], most probably *via* the corresponding sulfimide [34]. Compound **13** was also obtained in 86% yield by OH^--catalyzed hydrolysis of trichloroacetamide **3i**.



Scheme 10

Experimental

Melting points: Büchi 510, uncorrected. IR spectra: Nicolet 510M FT-IR. ^{1}H NMR spectra: Varian EM 390 (90 MHz), Varian EM 60 (60 MHz), Bruker WM 250 (250 MHz), Bruker ARX 400 (400 MHz), *TMS* as int. standard; 90 MHz spectra, if not otherwise stated. MS: Varian MAT 112 S EI-MS (70 eV). TLC: SiO_2 Merck, No. 5554, silica 60 F254. Column chromatography (CC): SiO_2 Merck, No. 7734, silica 60 (70–230 mesh ASTM); solvents in *pro analysi* quality. *PE*: petroleŭm ether 40–60 °C. Mixture of

solvents in v/v. Drying: Na_2SO_4. Evaporation *in vacuo* at the rotary evaporator. Yields: colourless crystals if not stated otherwise.

Materials: The data of most cpds. of type **1** and **2** are known. In many cases, however, these molecules were prepared according to protocols given for analogous cpds. for sake of higher yields, facilitated work-up, *etc.* O-Methylhydroxylamine and its hydrochloride: Ref. [35]; **1a**: Ref. [36]; **1b**: Ref. [37], prepared according to Ref. [38]; (**E**)-**1c**: Ref. [39], prepared according to Ref. [38]; **2a**: Ref. [40], prepared according to Ref. [41]; **2b**: Ref. [42]; **2c**: Ref. [43], Et_2O was used instead of *THF*, **2c** was used as a suspension in Et_2O for further reactions; **2d**: Ref. [44]; **2e**: Ref. [45], prepared according to Ref. [38], the *E*/*Z*-isomers were separated by CC on SiO_2 with *PE*/Et_2O 8:2; **2f**: prepared according to Ref. [47] and purified by CC (*PE*/Et_2O 8:2) and by recrystallization from 2-propanol; **2g**: Ref. [43].

N-(4-Methoxybenzylidene)-trichloroacetamide (**2h**): prepared according to Ref. [48]. Mp.: 75 °C (Et_2O); IR (KBr): $\nu = 1700\ cm^{-1}$ (C=O); ^1H NMR ($CDCl_3$): $\delta = 3.90$ (s; 3 H, OCH_3), 7.02, 7.95 (AA',BB', $J_{AB} = 9$ Hz, 4 H arom), 8.83 (s; 1 H, HC=N) ppm; $C_{10}H_8Cl_3NO_2$ (280.5); calcd.: C 42.81, H 2.87, N 4.99; found: C 42.85, H 2.90, N 5.01.

2i: Ref. [48], prepared according to Ref. [49]; **2j**: Ref. [50], prepared according to Ref. [51].

N-(4-Methoxybenzylidene)-benzenesulfinamide (**2k**): *cf.* Ref. [46], prepared according to Ref. [52]. Mp.: 122–123 °C (toluene); IR (KBr): $\nu = 1021\ cm^{-1}$ (S=O); ^1H NMR ($CDCl_3$): $\delta = 3.85$ (s; 3 H, OCH_3), 6.82–7.08 (m; 2 H arom), 7.34–7.92 (m; 7 H arom), 8.72 (s; 1 H, HC=N) ppm; $C_{14}H_{13}NO_2S$ (259.3); calcd.: C 64.84, H 5.05, N 5.40; found: C 64.78, H 4.92, N 5.44.

21: Ref. [53]; **2m**: Ref. [54]; **2n**: Ref. [55], *THF* was used instead of Et_2O; **2n** was not isolated, the solution obtained after filtration ($Et_3N \cdot HCl$) was used directly in order to prevent dimerization [55]; **2o**: Ref. [56].

General procedure I (lithiated oximes **1a** *and* **1b**)

At 0 °C, 14.0 ml of a 1.6 m solution of *n*-BuLi in hexane are added within 3 min to a solution of 10 mmol oxime in absol. *THF* under N_2. After stirring for 1 h at 0 °C, a solution of 10 mmol of the C=N-electrophile in 20–30 ml of absol. *THF* is added. For reaction times, deviations, *etc.*, see individual compounds. For work-up, 15 ml of half-satd. NH_4Cl solution are added. The organic phase is separated, the aqueous phase is extracted twice with 30 ml of EtOAc, the combined org. phases are washed twice with 15 ml of satd. NaCl solution, dried, evaporated, and the residue is dried at the oil pump at room temp.

General procedure II (lithiated oxime **1c**)

At −78 °C, 7.0 ml of a 1.6 ml solution of *n*-BuLi in hexane are added within 3 min to a solution of 10 mmol **1c** in 20 ml of absol. *THF* under N_2. After stirring for 40 min at −78 °C, a solution of 10 mmol of the C=N-electrophile in 20–30 ml of absol. *THF* is added. For work-up, see general procedure I.

(E)-3-(4-Methoxyphenyl)-1-phenyl-3-(phenylamino)-1-propanone oxime (**3a**)

Procedure I; after addition of **2b**, stirring is continued under reflux for 1 h. The yellow oil of **3a** is dissolved in 7 ml of EtOH for crystallization, recrystallization at −20 °C. 1.39 g (39%); mp.: 150 °C; IR (KBr): $\nu = 3417$ (NH and OH), 1603 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.85$–3.10 (m, 1 H, *H*CH), 3.38–3.60 (m, 1 H, HC*H*), 3.73 (s, 3 H, OCH_3), 4.43–4.90 (m, 2 H, CHN and NH; H/D exch., after exchange 4.43–4.73, dd), 6.27–7.67 (m, 14 H, H arom), 9.50 (s, 1 H, OH, H/D exch.) ppm; ^{13}C NMR ($CDCl_3$): δ (50 MHz) = 35.6 (C2), 55.2, 56.0 (C3 and OCH_3), 113.2, 114.1, 117.0, 126.5, 127.1, 128.7, 128.9, 129.6, 135.2, 135.5 (C arom), 147.2 (C–NH arom), 157.6, 158.8 (Cl and C–OCH_3 arom) ppm; MS (70 eV): *m/z* (%) = 346 (2) [M^+], 253 (4) [M–$PhNH_2$], 252 (8), 212 (100) [MeOPhCHNHPh]; $C_{22}H_{22}N_2O_2$ (346.4); calcd.: C 76.27, H 6.40, N 8.09; found: C 76.21, H 6.59, N 8.20.

Preparation of **3a** *by oximation of 3-(4-methoxyphenyl)-1-phenyl-3-phenylamino-1-propanone* [57]

At 0 °C a solution of 6.0 g (107 mmol) KOH in 25 ml MeOH is added drop by drop to 2.1 g (30.2 mmol) hydroxylammonium chloride in 30 ml of MeOH, followed by addition of the said 3-phenylamino-1-propanone. After stirring at room temp. for 10 min, the mixture is heated to reflux for 15 min. After cooling, 4 g of NH_4Cl are added, MeOH is removed *in vacuo*, the remaining material is mixed with 30 ml of water and extracted three times with 30 ml of EtOAc. The organic phase is washed twice with 20 ml of satd. NaCl solution, dried, and the solvent is evaporated. After drying at the oil pump, the oily residue is dissolved in 3 ml of warm EtOH for crystallization. The crystals are recrystallized at first from 6 ml of toluene, then from 3 ml of EtOH; data: see above.

(E)-1,3-bis-(4-methoxyphenyl)-3-(phenylamino)-1-propanone O-methyloxime (**3b**)

Procedure II; after addition of **2b**, the solution is allowed to reach room temp. for 8 h. The dark brown oil is purified by twofold CC (1. Et_2O/PE 1:1; 2.CH_2Cl_2). Weakly yellow oil; 2.52 g (64%); IR (Film): $\nu = 3405$ (NH), 1605 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.77$–3.03 (m; 1 H, *H*CH), 3.30–3.63 (m; 1 H, HC*H*), 3.77 (s; 3 H, OCH_3), 3.83 (s; 3 H, OCH_3), 4.07 (s; 3 H, $NOCH_3$), 4.37–4.53 (m, 1 H, CHN), 4.87 (s; br., 1 H, NH, H/D exch.), 6.33–7.70 (m; 13 H arom); $C_{24}H_{26}N_2O_3$ (390.5); calcd.: C 73.82, H 6.71, N 7.18; found: C 73.86, H 6.58, N 7.32.

(E)-3-Dimethylamino-1-(4-methoxyphenyl)-3-phenyl-1-propanone oxime (**3c**)

Procedure I; after addition of the suspension of the iminium chloride **2c**, the mixture is stirred for 30 min. Then, 10 ml of water are added, the organic solvent is evaporated, 100 ml of 2 *N* HCl are added, and the aqueous phase is extracted three times with 50 ml Et_2O. The acidic phase is alkalized by solid Na_2CO_3, extracted three times with EtOAc, and the organic phase is washed with satd. NaCl solution, dried, and evaporated. For crystallization, the yellow oil is dissolved in 4 ml of 2-propanol. Recrystallization from 1.5 ml of EtOH yields 0.29 g (10%). Mp.: 151 °C; IR (KBr): $\nu = 3400$–2200 (OH), 1609 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.26$ (s; 6 H, $N(CH_3)_2$), 3.17–3.55 (m; 2 H, CH_2), 3.60–3.87 (m; 1 H, CHN, overlap with OCH_3), 3.78 (s; 3 H, OCH_3), 6.70–6.90 (m; 2 H arom), 7.16–7.40 (m;7 H arom), 10.33 (s; br., 1 H, OH, H/D exch.) ppm; $C_{18}H_{22}N_2O_2$ (298.4); calcd.: C 72.45, H 7.43, N 9.39; found: C 72.52, H 7.47, N 9.44.

(E)-3-Dimethylamino-1-(4-methoxyphenyl)-3-phenyl-1-propanone O-methyloxime (**3d**)

Procedure II; after addition of the suspension of **2c**, stirring is continued at −78 °C for 25 min. For work-up, see **3c**. **3d** is purified by CC (CH_2Cl_2/MeOH 9:1). Weakly yellow oil; 2.10 g (68%); IR (film): $\nu = 1609$ cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.17$ (s; 6 H, $N(CH_3)_2$), 3.07–3.65 (m; 3 H, CH_2 and CHN), 3.77 (s; 3 H, OCH_3), 3.85 (s; 3 H, $NOCH_3$), 6.70–6.90 (m; 2 H arom), 7.10–7.37 (m; 7 H arom) ppm; $C_{19}H_{24}N_2O_2$ (312.4); calcd.: C 73.08, H 7.68, N 8.96; found: C 73.12, H 7.40, N 9.08.

(E)-3-(N-Hydroxy-N-methylamino)-1,3-bis-(4-methoxyphenyl)-1-propanone oxime (**3e**)

Procedure I; after addition of **2d**, stirring is continued for 2 h at 0 °C and for 2 h at room temp. The yellow oil is dissolved in 10 ml of MeOH for crystallization. Recrystallization from 20 ml of CH_3NO_2 affords 2.32 g (70%). Mp.: 143 °C; IR (KBr): $\nu = 3230$ (br, OH and NH), 1607 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): $\delta = 2.27$ (s; 3 H, NCH_3), 3.20–3.43 (m; 2 H, CH_2), 3.57–3.83 (m; 1 H, CHN, overlap with OCH_3), 3.70 (s; 3 H, OCH_3), 3.80 (s; 3 H, OCH_3), 6.67–7.50 (m; 8 H arom), 7.90 (s; 1 H,OH, H/D exch.), 10.83 (s; 1 H, OH, H/D exch.) ppm; $C_{18}H_{22}N_2O_4$ (330.4); calcd.: C 65.44, H 6.71, N 8.48; found: C 65.42, H 6.65, N 8.61.

(E)-3-(N-Hydroxy-N-methylamino)-1,3-bis-(4-methoxyphenyl)-1-propanone O-methyloxime (**3f**)

Procedure II; after addition of **2d**, the mixture is allowed to warm to 0 °C for 5 h. The crude yellow oil of **3f** crystallizes at the oil pump. Recrystallization from 11 ml of MeOH yields 2.10 g (61%). Mp.: 111 °C; IR (KBr): $\nu = 3190$ (br, OH), 1609 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.37$ (s; 3 H, NCH_3), 2.87–3.22 (m; 1 H, *H*CH), 3.52–3.97 (m; 2 H, HC*H* and CHN, overlap with OCH_3), 3.77 (s; 3 H, OCH_3), 3.80 (s; 3 H, OCH_3); 3.92 (s; 3 H, $NOCH_3$), 6.27 (s; br, 1 H, OH, H/D exch.), 6.67–6.93 (m; 4 H arom), 7.07–7.28 (m; 2 H arom), 7.37–7.57 (m; 2 H arom) ppm; $C_{19}H_{24}N_2O_4$ (344.4); calcd.: C 66.26, H 7.02, N 8.14; found: C 66.34, H 6.92, N 8.20.

(E)-N-(3-Hydroxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-benzenesulfenamide (**3g**)

Procedure I; after addition of **2f**, the mixture is stirred for 30 min at 0 °C and for 1.5 h at room temp. Purification of oily yellow **3g** by CC (CH_2Cl_2/EtOAc 9.5:0.5) affords 0.74 g (18%) of a yellow oil.
Hydrolysis of **3g** to **3h**: The solution of crude **3g** in 25 ml of Et_2O is extracted four times with 10 ml of 2 *N* HCl; the HCl phase is alkalized by solid Na_2CO_3 and extracted three times with 20 ml EtOAc. The organic phase is washed with 10 ml of satd. NaCl solution, dried, and evaporated; pale yellow solid, 0.38 g (64%) (see **3h**).

(E)-3-Amino-1,3-bis-(4-methoxyphenyl)-1-propanone oxime (**3h**)

a) Procedure I; after addition of **2g**, stirring is continued for 1 h at 0 °C and for 1 h at 20 °C. Then, 20 ml of half satd. NH_4Cl solution are added, the organic solvent is evaporated, and 100 ml of 2 *N* HCl are added. The aqueous phase is extracted with Et_2O (3 × 50 ml), alkalized by 22 g solid anhydrous Na_2CO_3, and extracted with EtOAc (3 × 40 ml). The EtOAc phase is washed twice with satd. NaCl solution, dried, and evaporated. The residue is crystallized from 15 ml of EtOH. 1.53 g (51%); mp.: 145 °C; IR (KBr): $\nu = 3342$, 3292 (br, OH and NH), 1609 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): $\delta = 2.88$–3.13 (m; 2 H, CH_2), 3.72 (s; 3 H, OCH_3), 3.77 (s; 3 H, OCH_3, 4.05–4.36 (m; 1 H, CHN), 4.60 (s; br, 3 H, NH_2 and OH, H/D exch.), 6.70–7.60 (m; 8 H arom) ppm; $C_{17}H_{20}N_2O_3$ (300.4); calcd.: C 67.98, H 6.71, N 9.33; found: C 67.88, H 6.59, N 9.32.
b) From 5-aminoisoxazoline **5**: A solution of 1.49 g (5 mmol) **5** in 20 ml of absol. *THF* is slowly mixed with 0.8 g (21 mmol) $LiAlH_4$ at 0 °C, stirred at 20 °C for 14 h, and carefully treated with 30 ml of 1 *N* NaOH. The *THF* phase is separated, the aqueous phase is extracted with Et_2O (2 × 40 ml), the combined organic phase is washed with satd. NaCl solution (2 × 15 ml), dried and evaporated. The residue is purified by CC (CH_2Cl_2/MeOH 9:1). Data: see *a*).

(E)-N-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-trichloroacetamide (**3i**)

Procedure II; the solution of **2h** is cooled to −78 °C before adding it to **1c**-anion in one portion. The mixture is stirred for 25 min at −78 °C. Oily yellow **3i** (4.71 g) crystallizes at the oil pump. The crude material is suspended in 20 ml of Et_2O. After crystallization at −20 °C, the crystals are recrystallized from 75 ml of Et_2O at −20 °C. 2.50 g (54%); mp.: 101 °C; IR (KBr): $\nu = 332a$ (NH), 1709 (C=O), 1609 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$); $\delta = 2.78$–3.05 (m; 1 H, *H*CH), 3.43–3.67 (m; 1 H, HC*H*), 3.78 (s; 3 H, OCH_3), 3.83 (s; 3 H, OCH_3), 4.05 (s; 3 H, $NOCH_3$), 4.77–5.13 (m; 1 H, CHN), 6.80–7.67 (m; 8 H arom), 7.92 (s, br, 1 H, NH, H/D exch.) ppm; $C_{20}H_{21}Cl_3N_2O_4$ (459.8); calcd.: C 52.25, H 4.60, N 6.10; found: C 52.18, H 4.66, N 6.17.

(E)-N-(3-Hydroxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-benzamide (**3j**)

Procedure I; after addition of **2i**, the mixture is stirred for 1 h at 0 °C. Oily yellow **3j** (4.05 g) is recrystallized from 23 ml of nitromethane. 2.59 g (64%); mp.: 197 °C; IR (KBr): $\nu = 3300$ (br, OH and

NH), 1636 (C=O), 1611 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): $\delta = 3.15–3.42$ (m, 2 H, CH_2), 3.72 (s; 3 H, OCH_3), 3.78 (s; 3 H, OCH_3), 5.20–5.57 (m, 1 H, CHN), 6.77–7.80 (m; 13 H arom), 8.67 (d; $J = 9$ Hz, 1 H, NH, H/D exch.), 11.40 (s; 1 H, OH, H/D exch.) ppm; $C_{24}H_{24}N_2O_4$ (404.5); calcd.: C 71.27, H 5.98, N 6.93; found: C 71.29, H 6.02, N 7.03.

(E)-N-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)1-propyl)-benzamide (**3k**)

Procedure II; after addition of **2i**, the mixture is stirred for 1 h at −78 °C and 20 min at room temp. Oily yellow **3k** crystallizes at the oil pump. Recrystallization from 8 ml of 2-propanol yields 2.72 g (65%). Mp.: 137 °C; IR (Br): $\nu = 3350$ (NH), 1634 (C=O), 1613 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.83–3.10$ (m; 1 H, *H*CH), 3.40–3.67 (m; 1 H, HC*H*), 3.77 (s; 3 H, OCH_3), 3.83 (s; 3 H, OCH_3), 4.05 (s; 3 H, $NOCH_3$), 5.03–5.40 (m; 1 H, CHN), 6.75–7.80 (m; 13 H arom and 1 H, NH, H/D exch.) ppm; $C_{25}H_{26}N_2O_4$ (418.5); calcd.: C 71.75, H 6.26, N 6.69; found: C 71.75, H 6.33, N 6.74.

(E)-N-(3-Hydroxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-diphenylphosphineamide (**3l**)

Procedure I; after addition of **2j**, stirring for 1 h at 0 °C. Oily **3l** is dissolved in 18 ml of warm EtOH and crystallizes overnight at 4 °C. The crystals are dissolved in 60 ml of hot dioxane. After cooling, 180 ml of Et_2O and seed crystals are added. Crystallization at −20 °C affords 3.62 g (72%). Mp.: 208 °C; IR (KBr): $\nu = 3220$ (br, OH and NH), 1605 (C=N and C=C), 1180 cm^{-1} (P=O); ^1H NMR (*DMSO*-d_6): $\delta = 3.00–3.46$ (m; 2 H, CH_2), 3.70 (s; 3 H, OCH_3), 3.80 (s; 3 H, OCH_3), 4.13–4.60 (m; 1 H, CHN), 5.73–6.07 (m; 1 H, NH, H/D exch.), 6.66–7.83 (m; 18 H arom), 11.00 (s; 1 H, OH, H/D exch.) ppm; $C_{29}H_{29}N_2O_4P$ (500.5); calcd.: C 69.59, H 5.84, N 5.62; found: C 69.40, H 5.95, N 5.71.

(E)-N-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-diphenylphosphineamide (**3m**)

Procedure II; after addition of **2j**, the mixture is allowed to warm to 0 °C within 6 h. Then, NH_4Cl solution is added and the organic phase is removed *in vacuo*. 20 ml of water are added; the crystals are recrystallized from 25 ml EtOH. 4.10 g (82%); mp.: 187 °C; IR (KBr): $\nu = 3210$ (NH), 1609 (C=N) and C=C), 1180 cm^{-1} (P=O); ^1H NMR ($CDCl_3$): $\delta = 2.87–3.20$ (m; 1 H, *H*CH), 3.30–3.63 (m; 1 H, HC*H*), 3.70–4.10 (m; 1 H, NH, H/D exch., overlap with OCH_3), 3.77 (s; 3 H, OCH_3), 3.82 (s; 6 H, 2 OCH_3), 4.22–4.67 (m; 1 H, CHN), 6.70–7.93 (m; 18 H arom) ppm; $C_{30}H_{31}N_2O_4P$ (514.6); calcd.: C 70.03, H 6.07, N 5.45; found: C 69.81, H 6.19, N 5.48.

(E)-N-(3-Hydroxyimino-1,3-bis(4-methoxyphenyl)-1-propyl)-benzenesulfineamide (**3n**), *mixture of diastereomers*

Procedure I; after addition of **2k**, the mixture is stirred for 1 h. Oily yellow **3n** is purified but not separated by CC (CH_2Cl_2/EtOAc 9:1, then CH_2Cl_2/EtOAC 1:1). Colourless, viscous oil; 2.92 g (69%); IR (film): $\nu = 3220$ (br, OH and NH), 1609 (C=N and C=C), 1032 cm^{-1} (S=O); ^1H NMR ($CDCl_3$): $\delta = 2.93–3.33$ (m; 2 H, CH_2), 3.67–3.87 (m; 6 H, 2 OCH_3), 4.53–5.05 (m; 1 H, CHN), 5.10–5.40 (m; 1 H, NH, H/D exch.), 6.55–7.80 (m; 13 H arom), 9.63 (s; br, 1 H, OH, H/D exch.) ppm; $C_{23}H_{24}N_2O_4S$ (424.5); calcd.: C 65.07, H 5.70, N 6.60; found: C 64.90, H 5.72, N 6.47.

(E)-N-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-benzenesulfineamide (**3o**)

Procedure II; after addition of **2k**, the mixture is allowed to warm to 0 °C within 6 h. Oily yellow **3o** is dissolved in 35 ml of Et_2O; crystallization takes place first at 4 °C, then at −20 °C. After three recrystallizations at −20 °C 1.48 g (34%) **3o** are obtained. Mp.: 112 °C; IR (KBr): $\nu = 3160$ (NH), 1611 (C=N and C=C), 1040 cm^{-1} (S=O); 250 MHz ^1H NMR ($CDCl_3$): $\delta = 3.00–3.30$ (m; 2 H, CH_2), 3.79 (s; 9 H, 2 OCH_3 and $NOCH_3$), 4.63–4.78 (m; 2 H, CHN und NH, H/D exch.), 6.76–6.92 (m; 4 H arom),

7.24–7.38 (m; 4 H arom), 7.43–7.53 (m; 3 H arom), 7.62–7.73 (m; 2 H arom) ppm; ^{13}C NMR ($CDCl_3$): δ (62.9 MHz) = 35.4 (C-2), 55.2, 55.3, 55.3 (3 OCH_3), 61.7 (C-3), 113.9, 114.0, 125.5, 127.6, 127.8, 128.5, 128.8, 130.9, 133.3 (C-arom), 145.5 (C-S arom), 154.7 (C-1), 159.3 (C-OCH_3 arom), 160.5 (C-OCH_3 arom) ppm; $C_{24}H_{26}N_2O_4$ (438.6); calcd.: C 65.73, H 5.98, N 6.39; found: C 65.87, H 6.11, N 6.49.

(E)-N-(3-Hydroxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-toluenesulfonamide (**3p**)

Procedure I; after addition of **2l**, stirring is continued for 1 h at 0 °C. Purification is effected by CC (CH_2Cl_2/EtOAc 9:1). Oily **3p** crystallizes at the oil pump. It is suspended in 125 ml of water, boiled for 30 min, sucked off while still hot and recrystallized from 6 ml of EtOH. 2.66 g (58%); mp.: 140 °C; IR (KBr): ν = 3300 (br, OH and NH), 1607 (C=N and C=C), 1156, 1324 cm^{-1} (S=O); ^1H NMR ($CDCl_3$): δ = 2.28 (s; 3 H, $ArCH_3$), 2.65–2.93 (m; 1 H, *H*CH), 3.28–3.67 (m; 1 H, HC*H*), 3.73 (s; 3 H, OCH_3), 3.82 (s; 3 H, OCH_3), 4.32–4.65 (m; 1 H, CHN), 6.07 (d; J = 6 Hz, 1 H, NH, H/D exch.), 6.67–7.60 (m; 12 H arom), 9.27 (s; br, 1 H, OH, H/D exch.) ppm; $C_{24}H_{26}N_2O_5S$ (454.6); calcd.: C 63.42, H 5.77, N 6.16; found: C 63.16, H 5.77, N 6.18.

(E)-N-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-toluenesulfonamide (**3q**)

Procedure II; after addition of **2l**, the mixture is stirred for 2 h at −78 °C and 30 min at room temp.The yellow oil (4.19 g) is dissolved in 10 ml of 2-propanol. Crystallization at 4 °C and recrystallization from 43 ml of EtOH yields 2.77 g (59%). Mp.: 141 °C; IR (KBr): ν = 3295 (NH), 1611 (C=N and C=C), 1333, 1160 cm^{-1} (S=O); ^1H NMR ($CDCl_3$): δ = 2.28 (s; 3 H, $ArCH_3$), 2.60–2.87 (m; 1 H, *H*CH), 3.15–3.52 (m; 1 H, HC*H*), 3.72 (s; 3 H, OCH_3), 3.78 (s; 3 H, OCH_3). 3.93 (s; 3 H, OCH_3), 4.25–4.55 (m, 1 H, CHN), 5.73 (d; J = 6 Hz, 1 H, NH, H/D exch.), 6.63–7.55 (m; 12 H arom) ppm; $C_{25}H_{28}N_2O_5S$ (468.6); calcd.: C 64.08, H 6.02, N 5.98; found: C 64.03, H 6.05, N 6.03.

meso and rac (E,E)-N,N'-bis-(3-Hydroxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-sulfamide (*meso*-**3r**; *rac*-**3r**)

Procedure I; 1.66 g (5 mmol) finely powdered **2m** are added to the solution of **1b**-dianion. After stirring for 20 min at 0 °C and 1.5 h at room temp., the yellow oil is purified by CC (CH_2Cl_2 / acetone 9:1, then CH_2Cl_2 / acetone 8:2). The foam is dissolved in 7 ml of MeOH. After standing first at room temp. and then at −20 °C, the mixture is filtered and the residue (1.03 g) is boiled with 10 ml of MeOH. The remaining crystals are recrystallized from 30 ml of nitromethane: *rac*-**3r**, crystals, 0.67 g (20%). According to HPLC analysis, *rac*-**3r** contains only 1% of *meso*-**3r**. Mp.: 187 °C (decomp.); IR (KBr): ν = 3280 (br, OH and NH), 1609 (C=N and C=C), 1304, 1180, 1157 cm^{-1} (S=O); ^1H NMR (*DMSO*-d_6): δ = 3.03–3.43 (m; 4 H, 2 CH_2), 3.67 (s; 6 H, 2 OCH_3), 3.75 (s; 6 H, 2 OCH_3), 4.27–4.73 (m, 2 H, 2 CHN), 6.50–7.03 (m; 12 H arom), 7.20–7.53 (m; 4 H arom and 2 H, 2 NH, H/D exch.), 11.05 (s; 2 H, 2 OH, H/D exch.) ppm; $C_{34}H_{38}N_4O_8S$ (662.8); calcd.: C 61.62, H 5.78, N 8.46; found: C 61.74, H 5.79, N 8.68.

The filtrate obtained after boiling with MeOH (*vide supra*) is evaporated. After three crystallizations from CH_2Cl_2, 0.17 g (5%) of *meso*-**3r** are obtained containing 2% of *rac*-**3r** (HPLC). Mp.: 93 °C; IR (KBr): ν = 3276 (br, OH and NH), 1609 (C=N and C=C), 1302, 1179, 1152 cm^{-1} (S=O); ^1H NMR ($CDCl_3$): δ = 2.70–3.03 (m; 2 H, CH_2), 3.15–3.53 (m; 2 H, CH_2), 3.70 (s; 6 H, 2 OCH_3), 3.77 (s; 6 H, 2 OCH_3), 4.43–4.72 (m; 2 H, 2 CHN), 5.30 (d; J = 6 Hz, 2 H, 2 NH, H/D exch.), 6.60–7.12 (m; 12 H arom), 7.30–7.50 (m; 4 H arom), 9.87 (d; 2 H, 2 OH, H/D exch.) ppm; $C_{34}H_{38}N_4O_8S$ (662.8); calcd.: C 61.62, H 5.78, N 8.46; found: C 61.46, H 5.82, N 8.42.

HPLC conditions: LiChrospher 100 RP 18/II (Merck); acetonitrile/water 100%, lowered down to 35% of acetonitrile; flow: 2 ml/min. HPLC devices: Spectra Physics 8700 (Rheodyne injection system); detection at 254 nm (Spectra Physics 8300); integration: Spectra Physics 4000.

(E,E)-N,N'-bis-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-sulfamide (**3s**), *mixture of diastereomers*

Procedure II; 1.66 g (5 mmol) finely powdered **2m** are added to the solution of **1c**-anion. The mixture was allowed to warm up to 0 °C within 6 h. Dark-brown oily **3s** is purified by CC (CH_2Cl_2 / EtOAc 9.5:0.5). Colourless viscous oil; 2.29 g (66%); IR (KBr): ν = 3280 (br, NH), 1611 (C=N and C=C), 1306, 1179, 1154 cm^{-1} (S=O); ^1H NMR ($CDCl_3$): δ (ppm) = 2.73–3.40 (m; 4 H, 2 CH_2), 3.63–3.93 (m; 18 H, 6 OCH_3), 4.25–4.60 (m, 2 H, 2 CHN), 4.90–5.12 (m, 2 H, NH, H/D exch.), 6.55–7.10 (m; 12 H arom), 7.27–7.53 (m; 4 H arom); $C_{36}H_{42}N_4O_8S$ (690.8); calcd.: C 62.59, H 6.13, N 8.11; found: C 62.40, H 6.12, N 8.03.

(E)-3-Methoxyamino-1,3-bis-(4-methoxyphenyl)-1-propanone oxime (**4a**) *and (E)-and (Z)-3-Methoxyamino-1,3-bis-(4-methoxyphenyl)-1-propanone O-methyloximes* ((*E*)-**4b** and (*Z*)-**4b**)

a) 3-Methoxyamino-1,3-bis-(4-methoxyphenyl)-1-propanone: To a solution of 5.36 g (20 mmole) (*E*)-4,4'-dimethoxychalcone [3b] in 20 ml of absol. EtOH/absol. *THF* (1:1), a solution of 2.08 g (66 mmol) O-methylhydroxylamine in 2 ml of absol. EtOH is added. After 48 h at 50 °C, the solvent is distilled off and the residue is purified by CC (CH_2Cl_2 / EtOAc 9:1). Colourless oil; 5.47 g (87%); IR (film): ν = 3259 (NH), 1672 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ = 3.00–3.60 (m; 2 H, CH_2, overlap with $NOCH_3$), 3.38 (s; 3 H, $NOCH_3$), 3.75 (s; 3 H, OCH_3), 3.83 (s; 3 H, OCH_3), 4.46–4.73 (m; 1 H, CHN), 6.10 (s; 1 H, NH, H/D exch.), 6.76–7.00 (m; 4 H arom), 7.20–7.47 (m; 2 H arom), 7.78–8.00 (m; 2 H arom) ppm; $C_{18}H_{21}NO_4$ (315.4); calcd.: C 68.55, H 6.71, N 4.44; found: C 68.53, H 6.67, N 4.54.

b) Formation of **4a**: 1.58 g (5 mmol) 3-methoxyamino-1,3-*bis*-(4-methoxyphenyl)-1-propanone and 3.48 g hydroxylammonium chloride are stirred in 20 ml of EtOH for 24 h at 20 °C. After dilution with 120 ml of water, the mixture is extracted four times with 20 ml of EtOAc. The organic phase is washed twice with 20 ml of satd. NaCl solution, dried, and evaporated. The remaining oil is dissolved in Et_2O for crystallization; recrystallization from 15 ml of 2-propanol. Crystals; 1.19 g (72%); mp.: 145–147 °C; IR (KBr): ν = 3500–2500 (OH and NH), 1611 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): δ = 2.93–3.17 (m; 2 H, CH_2), 3.30 (s, 3 H, $NHOCH_3$), 3.72 (s; 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.10–4.38 (m; 1 H, CHN), 6.70–7.53 (m; 8 H arom and 1 H, NH, H/D exch.), 10.98 (s; 1 H, OH, H/D exch.) ppm; $C_{18}H_{22}N_2O_4$ (330.4); calcd.: C 65.44, H 6.71, N 8.48; found: C 65.19, H 6.77, N 8.51.

c) Formation of **4b** *((E)- and (Z)- diastereomers)*: 1.58 g (5 mmol) 3-methoxyamino-1,3-*bis*-(4-methoxyphenyl)-1-propanone and 0.84 g (10 mmol) O-methylhydroxylammonium chloride in 20 ml of EtOH are stirred for 24 h at room temp. After dilution with 60 ml of water, the mixture is extracted four times with 20 ml of EtOAc. The EtOAc phase is washed twice with 10 ml of satd. NaCl solution, dried, and evaporated. The diastereomers are separated by CC (CH_2Cl_2 / EtOAc 9:1).

(*E*)-**4b**: pale yellow oil; 0.63 g (36%); IR (film): ν = 3249 (NH), 1611 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): δ (ppm) = 2.83–3.33 (m; 2 H, CH_2), 3.40 (s; 3 H, $NHOCH_3$), 3.80 (s; 6 H, 2 OCH_3), 3.90 (s; 3 H, $NOCH_3$), 4.13–4.43 (m; 1 H, CHN), 5.70 (s; 1 H, NH, H/D exch.), 6.70–7.00 (m; 4 H arom), 7.17–7.60 (m; 4 H arom); $C_{19}H_{24}N_2O_4$ (344.4); calcd.: C 66.26, N 7.02, N 8.13; found; C 66.28, H 7.16, N 8.21.

(*Z*)-**4b**: pale yellow oil; 0.18 g (10%); IR (film): ν = 3253 (NH), 1609 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): δ = 2.60–3.22 (m; 2 H, CH_2), 3.40 (s; 3 H, $NHOCH_3$), 3.80 (s; 9 H, 2 OCH_3 and $NOCH_3$), 4.00–4.25 (m; 1 H, CHN), 6.03 (s; 1 H, NH, H/D exch.), 6.77–7.00 (m; 4 H arom), 7.13–7.50 (m; 4 H arom) ppm; $C_{19}H_{24}N_2O_4$ (344.4); calcd.: C 66.26, H 7.02, N 8.13; found: C 66.33, H 7.05, N 8.19.

5-Amino-3,5-bis-(4-methoxyphenyl)-2-isoxazoline (**5**)

Procedure I from **1b**-dianion; after addition of 4-methoxybenzonitrile, the mixture is stirred at room temp. for 1.5 h. Then, 25 ml of water are added. After work-up, the orange coloured oil partially crystallizes at the oil pump and is mixed with 6 ml of absol. Et_2O. After cooling overnight, the crystals

are recrystallized from 20 ml of EtOH. 1.82 g (61%); mp.: 120 °C; IR (KBr): $\nu = 3388$, 3328 (NH), 1609 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.42$ (s; 2 H, NH_2, H/D exch.), 3.37 (s; 2 H, CH_2), 3.77 (s; 6 H, 2 OCH_3), 6.77–7.00 (m; 4 H arom), 7.47–7.67 (m; 4 H arom) ppm; ^{13}C NMR ($CDCl_3$): δ (62.9 MHz) = 48.5 (C-4), 55.3 (OCH_3), 55.4 (OCH_3), 98.9 (C-5), 113.7, 114.2, 122.5, 127.1, 127.9, 135.0 (C-arom), 155.6 (C-3), 159.5 (C–OCH_3 arom), 161.0 (C–OCH_3 arom) ppm; $C_{17}H_{18}N_2O_3$ (298.4); calcd.: C 68.44, H 6.08, N 9.39; found: C 68.21, H 6.28, N 9.44.

(E)-3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-1-propanone (**6**)

At 0 °C, a solution of 3.15 g (10 mmol) **9** (see below) in 20 ml of *DMF* is mixed with 7.52 g (20 mmol) pyridinium dichromate. After stirring for 5 h at room temp., 150 ml of water are added and the mixture is extracted by Et_2O (5 × 50 ml). The ether phase is washed with 30 ml of 2 *N* HCl, satd. solution of $NaHCO_3$ (2 × 30 ml), and satd. NaCl solution (2 × 30 ml), dried, and evaporated. The residue is crystallized from 4 ml of EtOH. 2.34 g (75%); mp.: 82 °C; IR (KBr): $\nu = 1669$ (C=O), 1607 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.78$ (s; 3 H, OCH_3), 3.85 (s; 3 H, OCH_3), 3.95 (s; 3 H, $NOCH_3$), 4.33 (s; 2 H, CH_2), 6.77–7.03 (m; 4 H arom), 7.50–7.70 (m; 2 H arom), 7.78–8.10 (m; 2 H arom) ppm; $C_{18}H_{19}NO_4$ (313.4); calcd.: C 68.99, H 6.11, N 4.47; found: C 69.05, H 6.16, N 4.79.

3,5-bis-(4-Methoxyphenyl)-isoxazole (**7**)

Prepared analogously to **5** with the following modification: instead of addition of 25 ml of water, the mixture is refluxed for 1 h with 30 ml of water and 10 ml of conc. HCl, neutralized with solid Na_2CO_3, separated, and the organic phase is evaporated. The residue is washed with water (3 × 20 ml), dried, and crystallized from EtOAc at −20 °C. 1.41 g (50%), for analytical data *cf.* Ref. [58].

7-*Metho-iodide* (**7a**)

a) From aminoisoxazole **5**: At 0 °C, 2.0 ml of *n*-BuLi (1.6 molar in hexane) are added to a solution of 0.75 g (2.5 mmol) **5** in 20 ml of absol. *THF* under N_2. After stirring for 1 h at 0 °C, the anion is stirred with 0.2 ml (0.45 g, 3 mmol) of CH_3I for 5 days at room temp. and subsequently for 10 min with 5 ml of 2 *N* HCl, diluted with 20 ml of water, weakly alkalized with solid Na_2CO_3, and filtered. The residue is crystallized from 5 ml of MeOH at −20 °C. Pale yellow crystals; 86 mg (8%); mp.: 174 °C (decomp.); IR (KBr): $\nu = 3060$ (CH), 1607, 1591 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): $\delta = 3.90$ (s; 6 H, 2 OCH_3), 4.41 (s; 3 H, NCH_3), 7.16–7.40 (m; 4 H arom), 7.83–8.20 (m; 5 H arom) ppm; $C_{18}H_{18}INO_3$ (423.3); calcd.: C 51.05, H 4.29, N 3.31; found: C 51.07, H 4.34, N 3.40.

b) From isoxazole **7**: 1.49 g (5 mmol) **7** are heated at 100 °C with 6.75 g (5.1 ml, 40 mmol) dimethyl sulfate for 4 h. After cooling, 12.5 ml of HI (28%) are added, the mixture is stirred for 5 min, the lower phase is separated, mixed with 3 ml of MeOH and cooled first to 4 °C, then to −20 °C; brown crystals, 90 mg (4%); for data, see *a*).

3,5-bis-(4-Methoxyphenyl)-4-methylisoxazole (**8**)

Prepared analogously to **5**, but instead of water 6.2 ml (14.2 g, 100 mmol) CH_3I are added. The mixture is stirred for 6 days at room temp., poured on 100 ml of EtOAc and 100 ml of water, stirred vigorously for 10 min, filtered and crystallized from 14 ml of MeOH. Yield: 0.47 g (11%) **7a**. The organic phase of the filtrate is washed with 30 ml of satd. NaCl solution and evaporated. The residue is mixed with 18 ml of MeOH and filtered after 4 h to afford 0.62 g of a mixture of **8** and **7**. After four recrystallizations from MeOH 0.10 g (5%) of **8** are obtained. Mp.: 136–137 °C; IR (KBr): $\nu = 1603$, 1513 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.25$ (s; 3 H, isoxazole-CH_3), 3.85 (s; 6H, 2OCH_3), 6.90–7.13 (m; 4 H arom), 7.55–7.78 (m; 4 H arom) ppm; $C_{18}H_{17}NO_3$ (295.3); calcd.: C 73.20, H 5.80, N 4.74; found: C 72.92; H 5.74, N 4.77.

(E)-3-Hydroxy-1,3-bis-(4-methoxyphenyl)-1-propanone O-methyloxime (**9**)

Procedure II; 1.36 g (10 mmol) of 4-methoxybenzaldehyde in 10 ml of absol. *THF* are added to **1c**-anion at −78 °C. After stirring for 20 min at −78 °C, the mixture is worked up according to Procedure I. Yellow oil, purification by CC (1. CH_2Cl_2, 2. CH_2Cl_2 / EtOAc 9:1); colourless oil, 2.52 g (80%). IR (film): $\nu = 3430$ (br, OH), 1611 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.63$ (s; 1 H, OH, H/D exch.), 2.88–3.40 (m; 2 H, CH_2), 3.77 (s; 6 H, 2 OCH_3), 3.97 (s; 3 H, $NOCH_3$), 4.86–5.10 (m; 1 H, CH), 6.77–6.97 (m; 4 H arom), 7.20–7.67 (m; 4 H arom) ppm; $C_{18}H_{21}NO_4$ (315.4); calcd.: C 68.55, H 6.71, N 4.44; found: C 68.80, H 6.36, N 4.19.

(E,E)-1-(N-Methoxyimino)-1,3-bis-(4-methoxyphenyl)-3-propanone oxime (**10**)

a) From 4-methoxybenzonitrile oxide (**2n**): Procedure II; the mixture of 1.49 g (10 mmol) nitrile oxide and **1c**-anion is stirred for 2 h at −78 °C. Usual work up; the crude oxime **10** is recrystallized from 24 ml of benzene. 2.49 g (76%); mp.: 146 °C; IR (KBr): $\nu = 3233$ (br, OH), 1609 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): $\delta = 3.73$ (s; 6 H, 2 OCH_3), 3.93 (s; 3H, $NOCH_3$), 4.22 (s; 2 H, CH_2), 6.75–6.97 (m; 4 H arom), 7.33–7.58 (m; 4 H arom), 11.45 (s; 1 H, OH, H/D exch.) ppm; $C_{18}H_{20}N_2O_4$ (328.4); calcd.: C 65.84, H 6.14, N 8.53; found: C 65.91, H 6.26, N 8.53.

b) From ketone **6**: At room temp., 1.57 g (5 mmol) **6** are stirred with 2.1 g (30 mmol) $H_2NOH \cdot HCl$ in 7 ml of pyridine for 72 h. The mixture is poured onto 150 ml of 2 *N* HCl and 50 g ice and immediately extracted with 150 ml of EtOAc; the extract is instantly washed with 30 ml of satd. $NaHCO_3$ solution and 30 ml of satd. NaCl solution, dried, and evaporated. The residue is crystallized from 20 ml of EtOH. Crystals; 0.85 g (62%); data: see *a*). **10** prepared from ketone **6** contains small quantities of isoxazole **7** which cannot be removed by recrystallization from benzene. Therefore, EtOH is used.

(E,E)-1,3-bis-(4-Methoxyphenyl)-propane-1,3-dione dioxime (**11**)

Procedure I; after addition of **2n**, the solution is stirred for 30 min at 0 °C. The crude product (2.6 g) is dissolved in 6 ml of *DMF* by gentle warming; after cooling to room temp., 80 ml of Et_2O are added in portions. After standing at −20 °C, crystals of dioxime **11** separate. 1.67 g (53%); mp.: 186 °C (MeOH); IR (KBr): $\nu = 3200$ (br, OH), 1609 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): $\delta = 3.73$ (s; 6 H, 2 OCH_3), 4.25 (s; 2 H, CH_2), 6.73, 7.48 (AA'BB'', $J_{AB} = 9$ Hz, 8 H arom), 11.09 (s; 1 H, OH, H/D exch.) ppm; $C_{17}H_{18}N_2O_4$ (314.4); calcd.: C 64.96, H 5.77, N 8.91; found: C 65.00, H 5.83, N 8.90.

Oxidative dimerization of **1b**-*dianion to 1,4-bis-(4-methoxyphenyl)-1,4-butandione dioxime* (**12**)

Lithiated **1b** (Procedure I) is treated with 3.06 g (12 mmol) I_2 in 10 ml of absol. *THF* at 0 °C. After 3 min, 10 ml of satd. NH_4Cl solution are added, the organic phase is separated, washed twice with $Na_2S_2O_3$ solution and satd. NaCl solution, dried, evaporated, and the residue is recrystallized from 12 ml of dioxane. Crystals; 0.46 g (28%); mp.: 210 °C; IR (KBr): $\nu = 3185$ (br, OH), 1605 cm^{-1} (C=N and C=C); ^1H NMR (*DMSO*-d_6): $\delta = 2.85$ (s; 4 H, CH_2CH_2), 3.80 (s; 6 H, 2 OCH_3), 6.95, 7.67 (AA'BB', $J_{AB} = 9$ Hz, 8 H arom), 11.20 (s; 2 H, 2 OH, H/D exch.) ppm; $C_{18}H_{20}N_2O_4$ (328.4); calcd.: C 65.84, H 6.14, N 8.53; found: C 65.68, H 6.12, N 8.49.

(E)-3-Amino-1,3-bis-(4-methoxyphenyl)-1-propanone O-methyloxime (**13**)

a) By hydrolysis of **3s**: 1.73 g (2.5 mmol) **3s** are refluxed in pyridine / water (19:1) for 4 h. After evaporation, the residue is mixed with 20 ml of 2 *N* NaOH and extracted with EtOAc (4 × 20 ml). The EtOAc phase is washed with satd. NaCl solution (2 × 20 ml), dried, concentrated, and purified by CC (CH_2Cl_2 / MeOH 9:1). Yellow oil; 1.29 g (82%); IR (film): $\nu = 3376$ (NH), 1609 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 1.58$ (s; 2 H, NH_2, H/D exch.), 2.78–3.35 (m; 2 H, CH_2), 3.77 (s; 3 H, OCH_3), 3.82

(s; 3 H, OCH_3), 3.93 (s; 3 H, $NOCH_3$), 4.15–4.37 (m; 1 H, CHN), 6.77–7.00 (m; 4 H arom), 7.20–7.67 (m; 4 H arom) ppm; $C_{18}H_{22}N_2O_3$ (314.4); calcd.: C 68.77, H 7.05, N 8.91; found: C 68.72, H 7.18, N 8.63.

b) By hydrolysis of **3i**: At room temp., 2.3 g (5 mmol) **3i** are stirred with 50 ml of 10% ethanolic KOH for 6 h. 7 g NH_4Cl are added, the solvent is removed, the residue is diluted with 30 ml of water, extracted with EtOAc, and worked up (see *a*); 1.35 g (86%).

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References

[1] Kaiser A, Wiegrebe W (1995) Sci Pharm (in press)
[2] Kammermeier T, Wiegrebe W (1995) Arch Pharm (Weinheim) **328**: 409
[3a] Kammermeier T, Wiegrebe W (1994) Arch Pharm (Weinheim) **327**: 697
[3b] Lee GS, Kammermeier T, Kaiser A, Eibler E, Wiegrebe W (1991) Arch Pharm (Weinheim) **324**: 177
[4] Bellassoued M, Chtara R, Dardoize F, Gaudemar M (1983) Synthesis **1983**: 951
[5] Nomura Y, Kimura M, Shibata T, Takeuchi Y, Tomoda S (1982) Bull Chem Soc Jpn **55**: 3343
[6] Aben RWM, Smit R, Scheeren JW (1987) J Org Chem **52**: 365
[7] Effenberger F, Maier R (1966) Angew Chem **78**: 389
[8] Kashima C, Aoki Y, Omote Y (1975) J Chem Soc Perkin Trans 1 **1975**: 2511
[9] Backes J (1991) In: Klamann D (ed) Methoden der Organischen Chemie (Houben-Weyl), vol. E 16b. Thieme, Stuttgart New York, pp 298, 456, 506
[10] Tennant G (1979) In: Sutherland IO (ed) Comprehensive Organic Chemistry, vol 2. Pergamon Press, Oxford, pp 499, 526
[11] Levy GC, Lichter RL, Nelson GL (1980) Carbon-13-nuclear Magnetic Resonance Spectroscopy, 2nd edn. John Wiley & Sons, New York, pp 161, 163
[12] Silverstein RM, Bassler GC, Morril TC (1991) Spectrometric Identification of Organic Compounds, 5th edn. John Wiley & Sons, New York, p 245
[13] Hesse M, Meier H, Zeeh B (1991) Spektroskopische Methoden in der Organischen Chemie, 4. Aufl. Thieme, Stuttgart New York pp 185, 186
[14] Sterk H, Steininger H (1974) Z Naturforsch **29a**: 1685
[15] Kalinowski H-O, Berger S, Braun S (1984) ^{13}C NMR Spektroskopie. Thieme, Stuttgart New York, pp 317, 318
[16] Mellor JM, Pathirana R, Smith NM (1988) J Chem Soc Perkin Trans 1 **1988**: 2501
[17] Brady WT, Shieh CH (1985) J Heterocycl Chem **22**: 357
[18] Aversa MC, Ferlazzo A, Giannetto P, Kohnke FH (1986) Synthesis **1986**: 230
[19] MacConnaill RJ, Scott FL, Hegarty AF (1972) Tetrahedron Lett **1972**: 1217
[20] Barluenga J, Jardon J, Gotor V (1986) J Chem Res (S) **1986**: 464
[21] Beam CF, Foote RS, Hauser CR (1972) J Heterocycl Chem **9**: 183
[22] Murthy MSR, Rao DV, Rao EV (1983) Indian J Pharm Sci **45**: 131; Chem Abstr (1984) **100**: 120938s
[23] Shatzmiller S, Bahar E, Bercovici S, Cohen A, Verdorn G (1990) Synthesis **1990**: 502
[24] Ershov AY, Yakimovich SI, Zelenin KN, Zerova IV (1988) Zh Org Khim **24**: 2287; Chem Abstr (1989) **111**: 56749d
[25] Volkmann RA (1991) In: Schreiber SL (ed) Comprehensive Organic Synthesis, vol 1. Pergamon Press, Oxford, p 385
[26] Vermillion G, Hauser CR (1941) J Org Chem **6**: 507

[27] Hegarty AF, Tuohey PJ (1980) J Chem Soc Perkin Trans 2 **1980**: 1313
[28] Blatt AH (1939) J Am Chem Soc **61**: 3494
[29] Karabatsos GJ, Hsi N (1967) Tetrahedron **23**: 1079
[30] Davis FA, Mancinelli PA (1977) J Org Chem **42**: 398
[31] Henoch FE, Hampton KG, Hauser CR (1969) J Am Chem Soc **91**: 676
[32] Shatzmiller S, Menashke N, Shalom E, Bahar E (1991) Liebigs Ann Chem **1991**: 1259 and lit. cited there
[33] Shatzmiller S, Lidor R, Bahar E, Goldberg I (1991) Liebigs Ann Chem **1991**: 851 and lit. cited there
[34] Davis FA, Giangiordano MA, Starner WE (1986) Tetrahedron Lett **27**: 3957
[35] Fujii T, Wu CC, Yamada S-i (1967) Chem Pharm Bull **15**: 345
[36] Gattermann L, Wieland T, Sucrow W (1982) Die Praxis des organischen Chemikers, 43. Aufl. Walter de Gruyter, Berlin New York, p 348
[37] v. Auwers K, Lechner M, Bundesmann H (1925) Ber Dtsch Chem Ges **58**: 36
[38] Shriner RL, Fuson RC, Curtin DY, Morril TC (1980) The Systematic Identification of Organic Compounds, 6th edn. John Wiley & Sons, New York p 181
[39] Johnson JE, Silk NM, Arfan M (1982) J Org Chem **47**: 1958
[40] Cromwell NH, Babson RD, Harris CE (1943) J Am Chem Soc **65**: 312 and lit. cited there
[41] Roelofsen DP, v. Bekkum H (1972) Recl Trav Chim Pays-Bas **91**: 605
[42] Ott H (1904) Sitzungsber Akad Wiss Wien, Math Naturwiss Kl Abt 2B **113**: 1279
[43] Betschart C, Schmidt B, Seebach D (1988) Helv Chim Acta **71**: 1999
[44] Brady OL, Dunn FP, Goldstein RF (1926) J Chem Soc **1926**: 2386
[45] Lindemann H, Tschang K-T (1927) Ber Dtsch Chem Ges **60**: 1725
[46] Almog J, Barton DHR, Magnus PD, Norris RK (1974) J Chem Soc Perkin Trans 1 **1974**: 853
[47] Davis FA, Slegeir WAR, Evans S, Schwartz A, Goff DL, Palmer R (1973) J Org Chem **38**: 2809
[48] Kupfer R, Meier S, Würthwein E-U (1984) Synthesis **1984**: 688
[49] Breuer SW, Bernath T, Ben-Ishai D (1967) Tetrahedron **23**: 2869
[50] Jennings WB, Lovely CJ (1991) Tetrahedron **47**: 5561
[51] Krzyzanowska B, Stec WJ (1978) Synthesis **1978**: 521
[52] Davis FA, Friedmann AJ, Kluger EW (1974) J Am Chem Soc **96**: 5000
[53] Albrecht R, Kresze G, Mlakar B (1964) Chem Ber **97**: 483
[54] Knollmüller M, Reich KR (1975) Monatsh Chem **106**: 1095
[55] Barbaro G, Battaglia A, Dondoni A (1970) J Chem Soc (B) **1970**: 588
[56] Olah GA, Keuni T (1979) Synthesis **1979**: 112
[57] Lin Y, Huangshu L, Junhua Z, Xiujuan X (1991) Synthesis **1991**: 717
[58] Murthy MSR, Rao DV, Rao EV (1983) Indian J Pharm Sci **45**: 13; Chem Abstr (1984) **100**: 120938s

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