Synthesis and Configuration of 4-Alkyl-2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide

Evelyne Grunder*, Gérard Leclerc [1] and Jean-Daniel Ehrhardt

Laboratoire de Pharmacologie Cardiovasculaire et Rénale, URA DO 589 CNRS, Université Louis Pasteur, Faculté de Médecine, 11 rue Humann, 67000 Strasbourg, France.

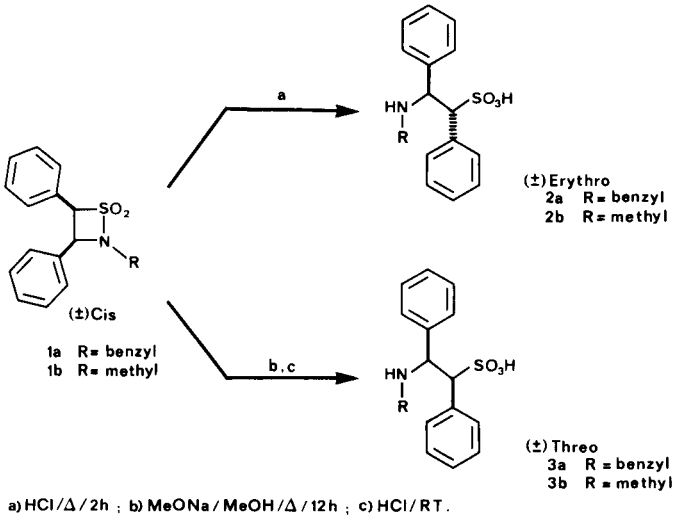
Received March 14, 1989

4-Alkyl-2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-dioxide **5**, **6** and **7** were obtained from 2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-dioxide **1** by reaction of its anion **4** with alkyl halides. *cis*- and *trans*-Configuration of the 4-alkylated products were determined by ^{1}H-nmr and NOE difference spectroscopy studies.

J. Heterocyclic Chem., **26**, 1781 (1989).

During our studies on substituted 2-aminoethanesulfonic acids as potential taurine analogs [2], we chose to investigate the use, as synthesis intermediates, of substituted 1,2-thiazetidine 1,1-dioxide, these heterocycles having been little studied before 1970 [3]. Recently, we reported the synthesis and the diastereoselective ring cleavage of (±)*cis*-2-benzyl-3,4-diphenyl-1,2-thiazetidine 1,1-dioxide **1a**, to obtain (±)*erythro*- or (±)*threo*-*N*-benzyl-1,2-diphenyl-2-aminoethanesulfonic acids **2a** and **3a**, as shown in Scheme I [4]. In the present work, we only used the *N*-methyl derivative **1b**.

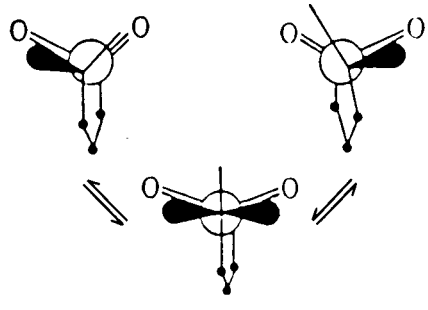
Scheme I



a) HCl/Δ/2h ; b) MeONa/MeOH/Δ/12h ; c) HCl/RT.

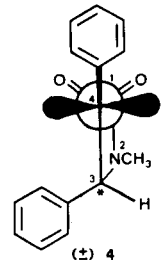
We have already shown that the basic hydrolysis of the sulfonamide bond involves an anionic intermediate (like **4**), so **1b** is transformed into the (±)*threo*- product with an inversion of configuration at C-4. In accordance with the results of Roitman and Cram [5] (Scheme IIa), and Gais *et al*, [6], the anion **4** is stabilized by high delocalisation of the charge on the 4-phenyl and the sulfonamide groups [7a-b] and is, therefore, nearly planar. A possible representation is given in Scheme IIb.

Scheme IIa



Anion of a cyclic sulfone

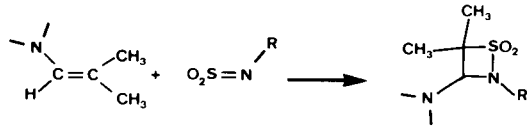
Scheme IIb



represents the orbitals occupied by the free electron pair.

The anion **4** may be a valuable synthesis intermediate, as its alkylation at C-4 could lead to new 4-alkyl-2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-dioxide. The few compounds of this class described in the literature were directly synthesized *via* cycloaddition of *N*-alkylsulfonylimides with nucleophilic olefins, as in Scheme III [8a,b].

Scheme III



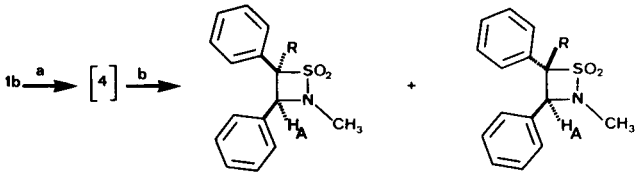
In this article, we report the synthesis of compounds **5** to **7** by reacting **4** with alkyl halides, as outlined in Scheme IV. The reactivity of **4** towards these different reagents is also examined. Compound **1b** was prepared by the cycloaddition of phenylsulfene with benzylidenemethylamine [9].

Results and Discussion.

Alkylation of **4** with Methyl Iodide.

The carbanion **4**, obtained from **1b** by reaction with 1

Scheme IV



5a R= methyl
6a R= iso-butyl
7a R= iso-propyl

5b R= methyl
6b R= iso-butyl
7b R= iso-propyl

a) NaH/THF/RT/12h ; b) 15 eq. RX/THF/RT/24-48h

equivalent of sodium hydride, was treated with 15 equivalents of methyl iodide to produce the two diastereoisomers **5a** and **5b**.

The presence of the second methyl group was confirmed by mass spectrometry. In particular, the molecular peak of **5a** and **5b** was $M^+ = 287$ instead of $M^+ = 273$ for the initial compound **1**. The purification of **5a** and **5b** required the use of high performance liquid chromatography (hplc) [10].

The assignment of the *cis*- and *trans*-configurations was based on their 200 MHz ^{1}H-nmr spectra. In the *trans*-isomer, the CH_3-C-4 bond is roughly perpendicular to the plane of the phenyl ring at C-3, which leads to an anisotropic effect in the ^{1}H-nmr spectrum; so the δ - values of "H_R" chemical shifts are lower than those of the *cis*-isomer [11a-b] (see Table I).

Table I

Partial ^{1}H-NMR [a] Data for *cis* and *trans*-4-Alkylated Thiazetidines

	δ H_A ppm		δ H_R ppm [b]	
Compound	*cis*-	*trans*-	*cis*-	*trans*-
5	4.32	4.71	2.22	1.59
6	4.08	4.58	2.71 - 2.24	2.21 - 1.81
7	7.70	/	3.99 - 3.89	/

[a] The ^{1}H-nmr data are 200 MHz spectra (deuteriochloroform). [b] H_R is (are) the first proton(s) of the alkyl chain at C-4.

Furthermore, the chemical shift of "H_A" was slightly shielded in the *trans*-isomer, in accordance with described results [12]. Since we only synthesized one isomer of **7**, ^{1}H-nmr study could not give us the configuration of the molecule, we decided to use the Nuclear Overhauser Effect.

In the case of molecules with analogous structures, the larger the NOE effect observed, the smaller the distance between the protons involved [13]. The structures of **5a** and **5b** were thus corroborated by NOE difference spectroscopy. In compound **5a**, irradiating H_A enhanced H_R, and irradiating H_R enhanced H_A, establishing a mutual dependence between H_A and H_R only compatible with the *cis*-configuration. Furthermore, in compound **5b**, irradiating H_A had no effect on H_R and irradiating H_R had a lesser effect on H_A than in **5a**, establishing that H_A and H_R are far from one another (see Table II).

Table II

Results of the Differential NOE Experiments for Derivatives **5a**, **5b**, **7a** at Room Temperature in Deuteriochloroform

			Observed NOE, % [a]	
	Compound	Irradiated Proton	H_A	H_R
5a	R = methyl	H_A	/	1.7
		H_R	7.8	/
5b	R = methyl	H_A	/	0
		H_R	2.1	/
7a	R = isopropyl	H_A	/	<1
		H_R	3.7	/

[a] The error is about 0.5%.

The fact that alkylating **4** with methyl iodide yielded a 60/40 mixture of the *cis*- and *trans*-thiazetidines **5a** and **5b** (as shown in Table III), was not particularly surprising since the electrophile is supposed to approach the anion **4** preferentially from the less hindered side to yield the *cis*-isomer, Cram's product (as represented in Scheme V).

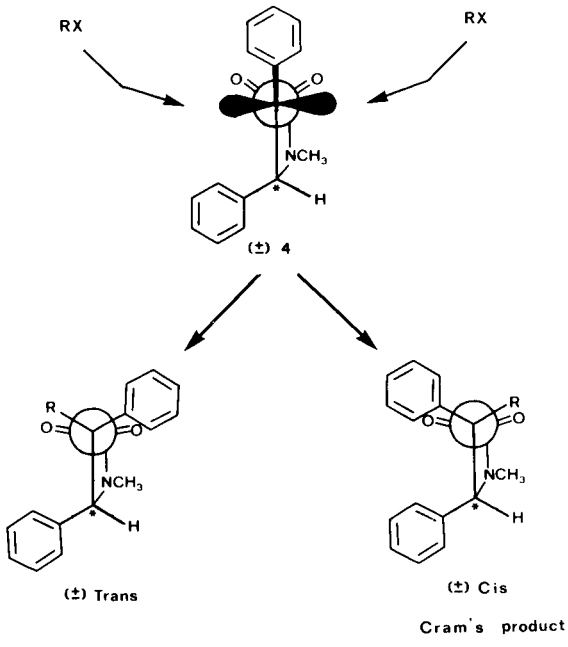
Table III

Experimental Results for the Reaction of [4] with Various Alkyl Halides

Entry	RX	Compound	Yield % [a]	Ratio a/b [b]
1	CH_3I	**5a + 5b**	67	60/40
2	$(CH_3)_2CHCH_2I$	**6a** [c]	< 5 [d]	/
3	$(CH_3)_2CHCH_2Br$	**6a + 6b**	52	65/35
4	$(CH_3)_2CHI$	/	0	/
5	$(CH_3)_2CHBr$	**7a**	26	100/0
6	$(CH_3)_3CBr$	/	0	/

[a] Purified by silica gel chromatography. [b] Diastereoisomer ratios were determined after silica gel column chromatography. [c] The compound **6b** was not detected by tlc, nmr or ms. [d] The compound **6a** was detected by ms and tlc.

Scheme V



In order to define the scope of this reaction further experiments were carried out with other electrophilic reagents (results are summarized in Table III).

Alkylation of **4** with Isobutyl Halides.

Anion **4** treated with 15 equivalents of isobutyl iodide produced only one diastereisomer **6a** at a very low yield. To check if this low yield was due to a steric effect of the iodide or the alkyl chain, we carried out the reaction with isobutyl bromide. Under these conditions, we obtained 52% of **6a** and **6b** in a ratio of 65/35. The presence of the isobutyl group in these compounds was confirmed by ms data. The assignment of the *cis*- and *trans*-configurations was based on their 200 MHz ^{1}H-nmr spectra, as for **5a** and **5b** (see Table I).

It is noteworthy that the preferentially formed diastereoisomer was again **6a**, the *cis*-isomer. The phenyl moiety at C-4 stabilized the anion **4** but also congested it; so, although Br^- is a weaker leaving group than I^-, isobutyl bromide was preferred in this reaction (yield = 52% versus < 5%). Isobutyl bromide can probably access to **4** much easier than isobutyl iodide because of the steric bulk of iodide.

Alkylation of **4** with Isopropyl Halides.

The reaction of **4** with isopropyl iodide did not produce either of the desired diastereoisomers, **7a**, and **7b** and the use of isopropyl bromide only gave **7a**. These results tally completely with those we obtained previously: - the preferred formed diastereoisomer is the Cram's one, *cis*-product; - alkyl iodide reagent have a worse accessibility to the anion **4** than alkyl bromide.

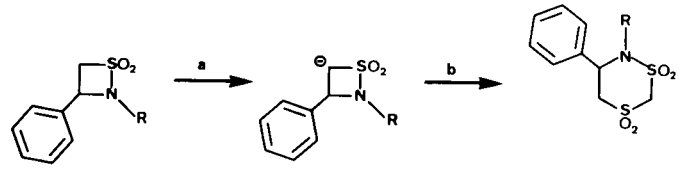
The structure of **7a** was determined by ir, ms, ^{1}H-nmr data, NOE difference spectroscopy and microanalysis (*cf*, Experimental). Nevertheless, the 200 MHz ^{1}H-nmr spectrum was unexpected since the chemical shift of H_A was δ = 7.70 ppm instead of nearly 4-5 ppm (for the other products described). The strong shielding effect might be explained by a cumulative anisotropy of the doublet of the nitrogen atom, the isopropyl and the two phenyl groups. The assignment of the **7a** configuration was based on its NOE difference spectra (Trade II). Irradiating H_R enhanced H_A and irradiating H_A enhanced H_R, establishing a *cis*-configuration as in the case of **5a**.

No alkylation of anion **4** was obtained with *t*-butyl bromide which confirms the importance of the already mentioned steric effect.

Remark.

Meyle and Otto [14] described the formation of 2,4,1-dithiazine 2,2,4,4-tetroxide during the 4-alkylation of 2-alkyl-3-phenyl-1,2-thiazetidine 1,1-dioxide (see Scheme VI); we did not observe the formation of any such compound; the 4-phenyl group may prevent the self condensation by stabilization of the anion **4** and/or by a steric effect.

Scheme VI



a) BuLi/-78°C ; b) HCl,H_2O

In conclusion, our experiments indicate that, within the limits discussed in this paper, 4-alkyl-2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-dioxide can be easily prepared. Moreover, to the best of our knowledge, this is the first configuration study of 2-methyl-3,4,4-tri-substituted-1,2-thiazetidine 1,1-dioxide.

These compounds may be suitable precursors for 1,1,2-tri-substituted-2-aminoethanesulfonic acids; these taurine analogs will be tested in our laboratory for their pharmacological properties.

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained with either a Perkin Elmer R24-B (60 MHz) or a Bruker WP 200-SY spectrometer; chemical shifts are reported in δ units, with tetramethylsilane as the internal standard. Mass spectra were recorded on a LKB 2091. Infrared spectra were run on a Philips PU 9716 spectrophotometer. The main bands are described by their frequency (cm^{-1}) and relative intensity (weak, medium, strong). Melting points were

determined on a Kofler hot bench and are uncorrected. Elemental analyses (C, H, N) were performed by the "Service de microanalyses du CNRS à l'Institut de Chimie de Strasbourg".

(±)*cis*-2-Methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide **1b**.

This compound was prepared by the cycloaddition of phenylsulfene and *N*-benzylidenemethylamine according to established procedures [9] and purified by silica gel column chromatography with hexane/diethyl ether (6:4) as eluent, followed by recrystallization from diisopropyl ether, mp 140°; ir (chloroform): γ 2850 (m, C-C aromatic), 1305-1130 (s, SO_2), 945 (m, C-C ring); ^{1}H-nmr (deuteriochloroform): 60 MHz δ 7.3-7.2 (m, 10H, aromatic H), 5.7-4.7 (AB system, 2H, J_{AB}^3 = 9 Hz, N-CH_B-CH_A-S), 2.9 (s, 3H, N-CH_3); ms: m/z 273 (34, M$^+$), 209 (21, M-SO_2), 208 (100, M-SO_2-H), 194 (27, M-SO_2-CH_3).

Anal. Calcd. for $C_{15}H_{15}O_2NS$: C, 65.91; H, 5.53; N, 5.12. Found: C, 66.10; H, 5.39; N, 5.05.

Synthesis of (±)*cis*- and (±) *trans*-4-Alkyl-2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide Derivatives: **5**, **6** and **7**. General Procedure.

To a solution of **1b** (200 mg, 0.73 mmole) in dry THF (5 ml) was added sodium hydride, 60% in oil (32 mg, 0.80 mmole). After stirring at room temperature under nitrogen, alkyl halides (RX, 15 equivalent) in dry THF (5 ml) were added to the solution. The resulting mixture was stirred at room temperature for 24 to 48 hours, after which the precipitate was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel column chromatography with hexane/diethyl ether (60/40) as eluent. Yields are reported for pure product.

(±)*cis*-2,4-Dimethyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide **5a**.

This compound was obtained as a colorless oil in 41% yield; ir (chloroform): γ 3100-2800 (m, C-C aromatic), 1300-1150 (s, SO_2), 960 (m, C-C ring); ^{1}H-nmr (deuteriochloroform): 200 MHz δ 7.36-7.10 (m, 10H, aromatic H), 4.32 (s, 1H, N-CH-), 2.82 (s, 3H, N-CH_3), 2.22 (s, 3H, CH_3); ms: m/z 287 (70, M$^+$), 222 (100, M-SO_2-H), 208 (19, M-SO_2-CH_3), 168 (23, M-[Ph-CH=N-CH_3]).

Anal. Calcd. for $C_{13}H_{17}O_2NS$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.95; H, 6.01; N, 4.84.

(±)*trans*-2,4-Dimethyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide **5b**.

This compound was obtained in 26% yield after recrystallization from hexane/ethyl acetate (90/10), mp 127°; ir (chloroform): γ 3110-2830 (m, C-C aromatic), 1300-1140 (s, SO_2), 950 (m, C-C ring); ^{1}H-nmr (deuteriochloroform): 200 MHz δ 7.6-7.3 (m, 10H, aromatic H), 4.71 (s, 1H, N-CH-), 2.79 (s, 3H, N-CH_3), 1.59 (s, 3H, CH_3-C-4); ms: m/z 287 (44, M$^+$), 222 (100, M-SO_2-H), 208 (48, M-SO_2-CH_3), 168 (44, M-[Ph-CH=N-CH_3]).

Anal. Calcd. for $C_{16}H_{17}O_2NS$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.95; H, 6.00; N, 4.86.

(±)*cis*-4-Isobutyl-2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide **6a**.

We did not find any recrystallization solvent for this compound, so we applied a second silica gel chromatography using hexane/diethyl ether (80/20) as eluent, the yield was 35%, mp 98°; ir (chloroform): γ 2910 (m, C-C aromatic), 1290-1140 (s, SO_2), 980 (m, C-C ring); ^{1}H-nmr (deuteriochloroform): 200 MHz δ 7.43-6.90 (m, 10H, aromatic H), 4.08 (s, 1H, N-CH-), 2.71-2.24 (m, H, CH_2-C-4), 2.66 (s, 3H, N-CH_3), 1.44-1.31 (m, 1H, CH), 0.93-0.83 (dd, 6H, 2CH_3); ms: m/z 329 (72, M$^+$), 286 (100, M-[$(CH_3)_2$-CH], 264 (23, M-SO_2-H), 250 (9, M-SO_2-CH_3), 222 (9, M-SO_2-CH[CH_3]$_2$).

Anal. Calcd. for $C_{19}H_{23}O_2NS$: C, 69.27; H, 7.04; N, 4.25. Found: C, 69.30; H, 6.95; N, 4.22.

(±)*trans*-4-Isobutyl-2-methyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide **6b**.

This compound was obtained as a colorless oil in 21% yield; ir (chloroform): γ 2910 (m, C-C aromatic), 1310-1150 (s, SO_2), 980 (m, C-C ring); ^{1}H-nmr (deuteriochloroform): 200 MHz δ 7.69-7.27 (m, 10H, aromatic H), 4.58 (s, 1H, N-CH-), 2.67 (s, 3H, N-CH_3), 2.21-1.81 (m, 2H, CH_2-C-4), 1.04-0.99 (m, 1H, CH), 0.39-0.35 (d, 3H, CH_3), 0.19-0.15 (d, 3H, CH_3); ms: m/z 329 (3, M$^+$), 286 (5, M-[$(CH_3)_2$-CH], 265 (100, M-SO_2), 264 (28, M-SO_2-H), 222 (41, M-SO_2-CH[CH_3]$_2$).

Anal. Calcd. for $C_{19}H_{23}O_2NS$: C, 69.27; H, 7.04; N, 4.25. Found: C, 68.90; H, 6.96; N, 4.22.

(±)*cis*-2-methyl-4-isopropyl-3,4-diphenyl-1,2-thiazetidine 1,1-Dioxide **7a**.

This compound was obtained in 26% yield after recrystallization from petroleum ether/ethyl acetate (95/5), mp 112°; ir (chloroform): γ 2915 (m, C-C aromatic), 1310-1130 (s, SO_2), 960 (s, C-C ring); ^{1}H-nmr (deuteriochloroform): 200 MHz δ 7.70 (s, 1H, CH), 7.41-7.02 (m, 10H, aromatic H), 3.99-3.89 (m, 1H, CH-C-4), 2.54 (s, 3H, N-CH_3), 0.97-0.94 (d 6H, 2[CH_3]); ms: m/z 315 (100, M$^+$), 300 (75, M-CH_3) 251 (5, M-SO_2), 250 (16, M-SO_2-H), 236 (16, M-SO_2-CH_3).

Anal. Calcd. for $C_{19}H_{23}O_2NS$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.39; H, 6.62; N, 4.47.

Differential NOE Experiments.

The nuclear Overhauser enhancement experiments were also run at 200 MHz by irradiating the desired signals for 5 seconds and acquiring for 3.3 seconds the spectrum with the decoupler turned off, so that coupled spectra were obtained. A control experiment was created by setting the irradiation away from any signal. The acquisitions were carried out in groups of 8 for each irradiated signal. Each transient was separated by a relaxation delay of 3.7 seconds. The cycle was repeated 100 times, thus resulting in 800 accumulations for each spectrum. The FID's (Free Induction Decay) were Fournier transformed. The spectra obtained in this way were subtracted from the control, yielding the NOE difference spectrum.

Acknowledgement.

We wish to thank Dr. J. P. Kintzinger and R. Graff for helpful discussions of the nmr data. Evelyne Grunder was recipient of a Ministry Research Technology Fellowship (MRT).

REFERENCES AND NOTES

[1] Present address: Université de Grenoble I, Faculté de Pharmacie, 38240 Meylan, France.

[2] For a biological update on taurine see: C. E. Wright, H. H. Tallan and Y. Y. Lin, *Ann. Rev. Biochem.*, **55**, 427 (1986) and references therein.

[3] A. Champseix, J. Chanet, A. Etienne, A. Le Berre, J. C. Masson, C, Napierala and R. Vessiere, *Bull. Soc. Chim. France*, 463 (1984) and references therein.

[4] E. Grunder and G. Leclerc, *Synthesis*, 135 (1989).

[5] J. N. Roitman and D. J. Cram, *J. Am. Chem. Soc.*, **93**, 2225 (1971).

[6] H. J. Gais, J. Vollhardt, G. Hellmann, H. Paulus and H. J. Lindner, *Tetrahedron Letters*, 1259 (1988).

[7a] E. Gypi, W. Eckhardt and C. A. Gros, *Tetrahedron Letters*, 3627 (1973).

[7b] J. Mathieu, "Formation of C-C Bonds" Vol **1**, J. Weill-Raynal, eds, Georg Thieme Publishers, Stuttgart, 1973, p 77.

[8a] G. M. Atkins and E. M. Burgess, *J. Am. Chem. Soc.*, **94**, 6135 (1972).

[8b] T. Nagai, T. Shingaki, M. Inagaki and T. Ohshima, *Bull. Chem. Soc. Japan*, **52**, 1102 (1979).

[9] T. Hiraoka and T. Kobayashi, *Bull. Chem. Soc. Japan*, **48**, 480 (1975).

[10] We found hexane/ether (6/4) or cyclohexane/diethyl acetate (9/1) the best eluents to separate *cis*- and *trans*-diastereoisomers. Preparative hplc was used: system Modul-prep, Jobin-Yvon; silica gel (Merck) Lichroprep, Si60 Art, 13905, 180 g for 220 mg of crude product.

[11a] H. Gunther, "NMR Spectroscopy", J. Wiley and Sons, 1980, p 77 and 380.

[11b] C. W. Haigh and R. B. Mallion, *Org. Magn. Reson.*, **4**, 203 (1972).

[12] L. A. Carpino, *J. Am. Chem. Soc.*, **84**, 2196 (1962).

[13] J. K. M. Sanders and J. D. Mersh, *Progr. NMR Spectros.*, **15**, 353 (1982).

[14] E. Meyle and H. H. Otto, *J. Chem. Soc., Chem. Commum.*, 1084 (1984).