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Axially chiral thioamides of acrylic acid: correlated and uncorrelated internal rotations

Margit Kuttenberger, Markus Frieser, Martin Hofweber and Albrecht Mannschreck *

Institut für Organische Chemie, Universität Regensburg, Universitätsstraße 31, D-93040 Regensburg, Germany

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Abstract

In acrylic thioamides (Scheme 1), two intramolecular motions are possible: thiocarbonyl–nitrogen (=C–N) and alkenyl–carbonyl (=C–C=) rotations. Since the two mobile molecular fragments can interact by steric and by resonance effects, we intended to demonstrate the existence of *correlated* in addition to the above *uncorrelated* motions. For each of the three thioamides chosen, at least two of the four stereoisomers were enriched by crystallization and by liquid chromatography on nonracemic sorbents. Thereby axial chirality of acrylic thioamides was proven for the first time. Thermal equilibrations were monitored quantitatively by time-dependent ^{1}H NMR spectroscopy in the presence of a nonracemic additive, a method which, to our knowledge, has not previously been described. These kinetic results were evaluated by a simulation program with reference to uncorrelated and correlated rotations (Figs. 4–6). We have shown that *all* of these motions occur in thioamide **14**. The enantiomers of thioamide **13** do not interconvert directly. However, *indirect*, two-step enantiomerizations in **13** have been proven one of the two steps consisting of correlated rotations. The latter are, therefore, possible in acrylic thioamides, a class of compounds which differ considerably from the molecules for which correlated motions were hitherto known.

1. Introduction

Intramolecular motions of many types have been investigated in considerable detail during the last thirty years.[1,2] In the case of the occurrence of several such processes in the same molecule, these will often occur independently of each other, i.e. they will be uncorrelated. However, some molecular systems are known in which certain motions are coupled, i.e. they are correlated. This field of research has been pioneered by Mislow and his coworkers. It comprises mainly molecular propellers[3,4] (1,1,1-triaryl compounds) and bis(triptycyl)methanes.[3] For many such systems, clear-cut evidence in favor of correlation or non-correlation has been obtained.

* Corresponding author. Fax: (941) 943 4617.

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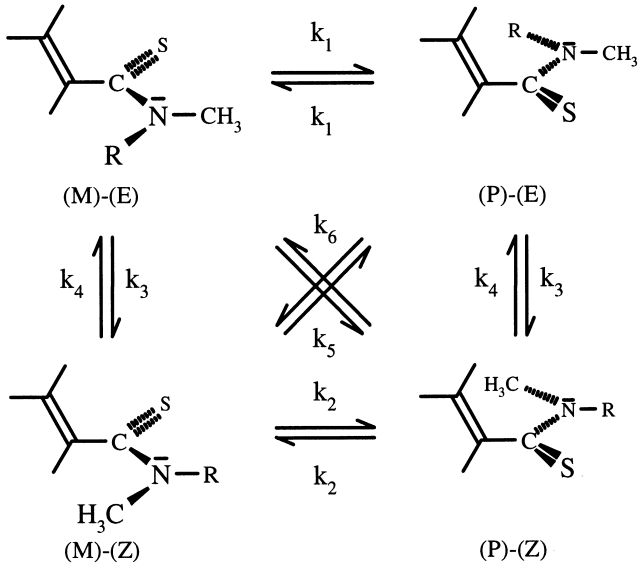
We asked the question whether such correlations may occur more frequently than hitherto supposed, particularly in cases where the mobile molecular fragments are sufficiently close to one another for interactions by steric and, possibly, by resonance effects. In some 2-(dialkylamino)-benzamides and thioamides, aryl–nitrogen and aryl–carbon rotations turned out to be uncorrelated, in others uncorrelated *and* correlated motions were both shown to be possible,[5] but further conclusions were not attainable.

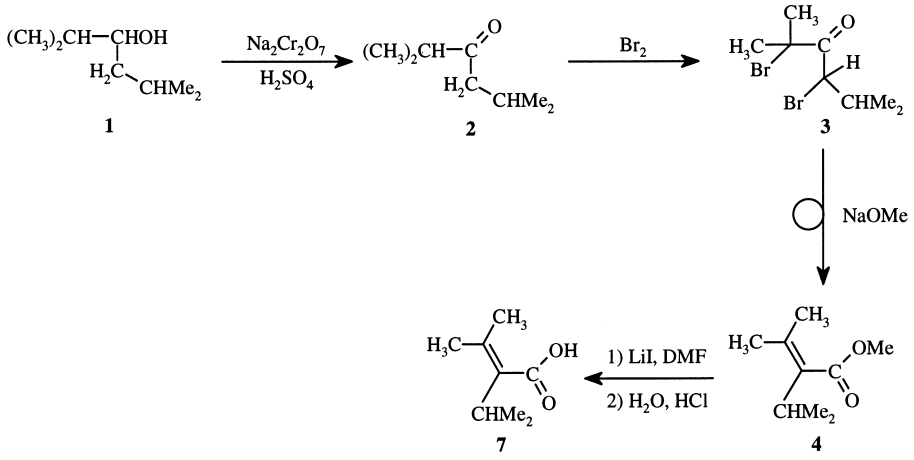
Therefore, we considered carbonyl–nitrogen (=C–N) and alkenyl–carbonyl (=C–C=) rotations in amides and thioamides (Scheme 1) of acrylic acids which could potentially use uncorrelated (k_1, k_2, k_3 and k_4) or correlated (k_5 and k_6) pathways. Their mobile fragments, the alkenyl, thiocarbonyl and amino groups, are indeed close to one another and interact sterically and by π overlap in the respective ground (Scheme 1) and transition states of the above two types of rotation. Because of the amide resonance, these molecules show[6] the usual[1,2] diastereomers (*E*) and (*Z*) (Scheme 1, R≠CH_3) and their =C–N interconversions. In addition, we demonstrated[6,7] for the first time that acrylic thioamides consist of enantiomers (M) and (P) (Scheme 1, R=CH_3) which exhibit =C–C= interconversions. The detection of this type of axial chirality in solution at room temperature requires that the C=C fragment and the nitrogen atom bear substituents other than hydrogen, i.e. some steric hindrance is required. In this respect, acrylic thioamides resemble axially chiral 1,3-dienes[8] and oxalic dithioamides.[9] In a similar way, 1-naphthoic analogues can also be considered. The 1-naphthyl group has the same symmetry properties as the alkenyl moiety which means that the stereostructural and kinetic situation[10] fits Scheme 1. For 1-naphthoic *N,N*-dimethylthioamide,[11] enantiomers were detected in solution at room temperature and they showed =C–C= interconversion.[12]



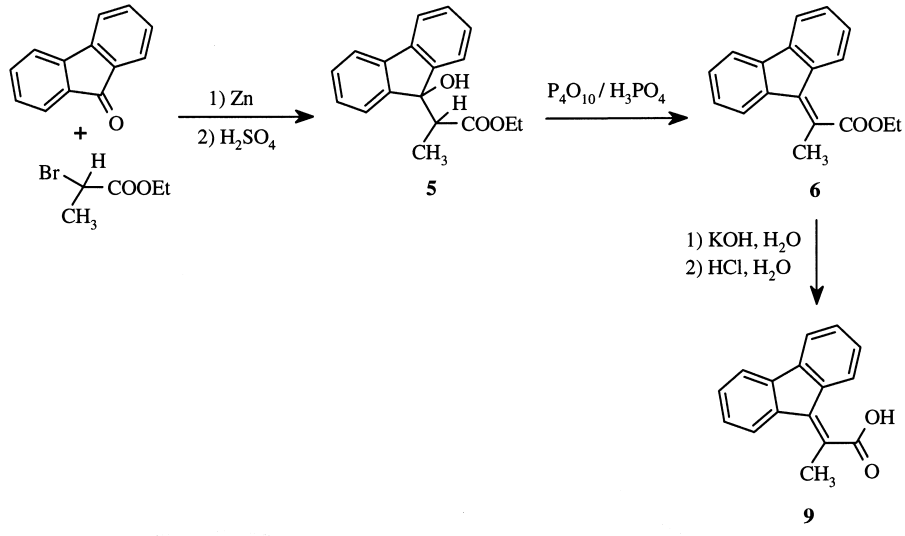
Scheme 1.

For some acrylic thioamides, the barriers $\Delta G^{\ddagger}$, corresponding to the rate constants k_1, k_2, k_3 and k_4 in Scheme 1, were known,[6,13] the considerable heights of which had required time-dependent measurements of concentrations during thermal equilibrations. Consequently, we planned to monitor the interconversion of the two diastereomers[14] quantitatively by NMR spectroscopy and to extend this technique to the enantiomers[15] by adding a nonracemic auxiliary. The choice of suitable compounds was limited by the following conditions: R≠CH_3 (Scheme 1) in order to create diastereomers; *both* diastereomers to be detectable in sufficient concentration after equilibration; significant enrichment of a single stereoisomer

to be possible, from which the equilibration can start; at least one NMR signal of each stereoisomer to be present during equilibration, suitable for quantitative measurement of the four intensities; the NMR signals to be assigned to the relative configurations, which requires the enrichment of *more* than one of the four stereoisomers. The syntheses given in Schemes 2–4 resulted in thioamides **13**–**15** as candidates for the present project, whereas a considerable number of further compounds[6,13] failed to meet the above conditions.

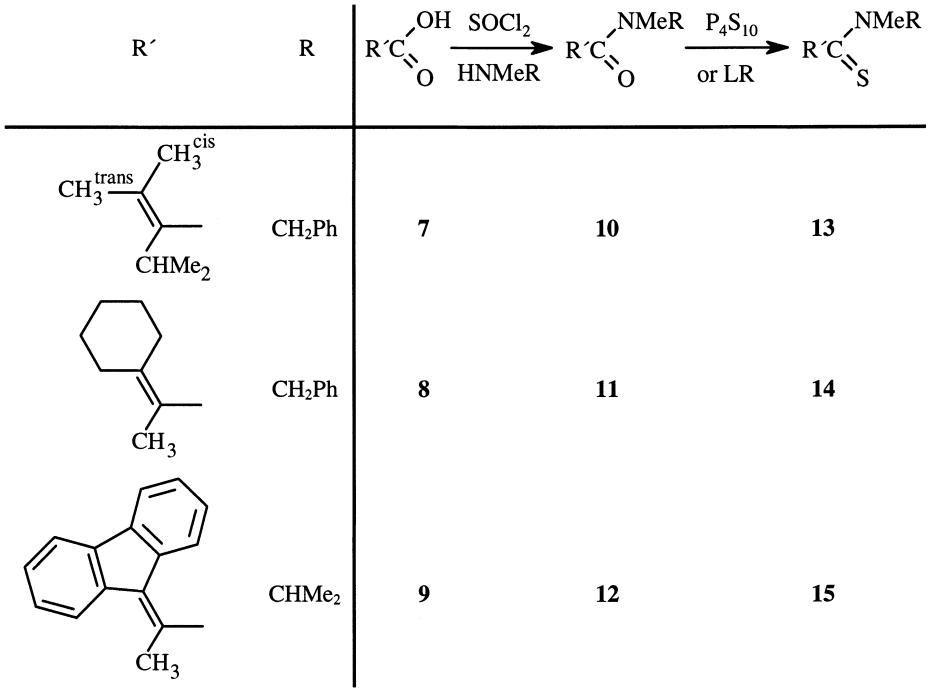


Scheme 2.

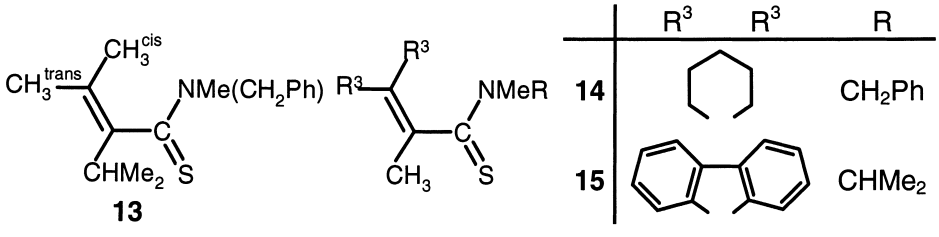


Scheme 3.

Therefore, we intended to enrich at least one stereoisomer of each of these three thioamides, to monitor the thermal equilibrations as suggested above and to evaluate the results with reference to the uncorrelated and correlated rotations indicated in Scheme 1.



Scheme 4. LR: Lawesson's reagent=2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide



2. Synthesis and separation of stereoisomers

Acids **7** (Scheme 2) and **9** (Scheme 3) were unknown, **8** was known. These were converted into **13**–**15** (Scheme 4) by general methods. In all cases, recrystallization yielded one of the two racemic diastereomers in pure form which was analyzed. For the three thioamides, analytical liquid chromatography (e.g. Fig. 1) on several nonracemic sorbents was performed. Semipreparative enrichment of enantiomers was obtained on microcrystalline triacetylcellulose[7] or tribenzoylcellulose.[16] These enantiomers were characterized by their enantiomeric purities, circular dichroism spectra, and, if possible, specific rotations. Only the samples to be used for the kinetics of stereoisomerization appear in the Experimental, i.e. (−)-(*E*)-**13**, (+)-(*E*)-**14**, and (+)-(*Z*)-**15**. (+)-(*E*)-**14** was a colorless oil, whereas melting points are given for the other two enriched enantiomers. Together with our earlier findings,[6,7] this is the first time that enantiomers of substituted acrylic thioamides have been described, i.e. that the axial chirality of this class of compounds is proven.

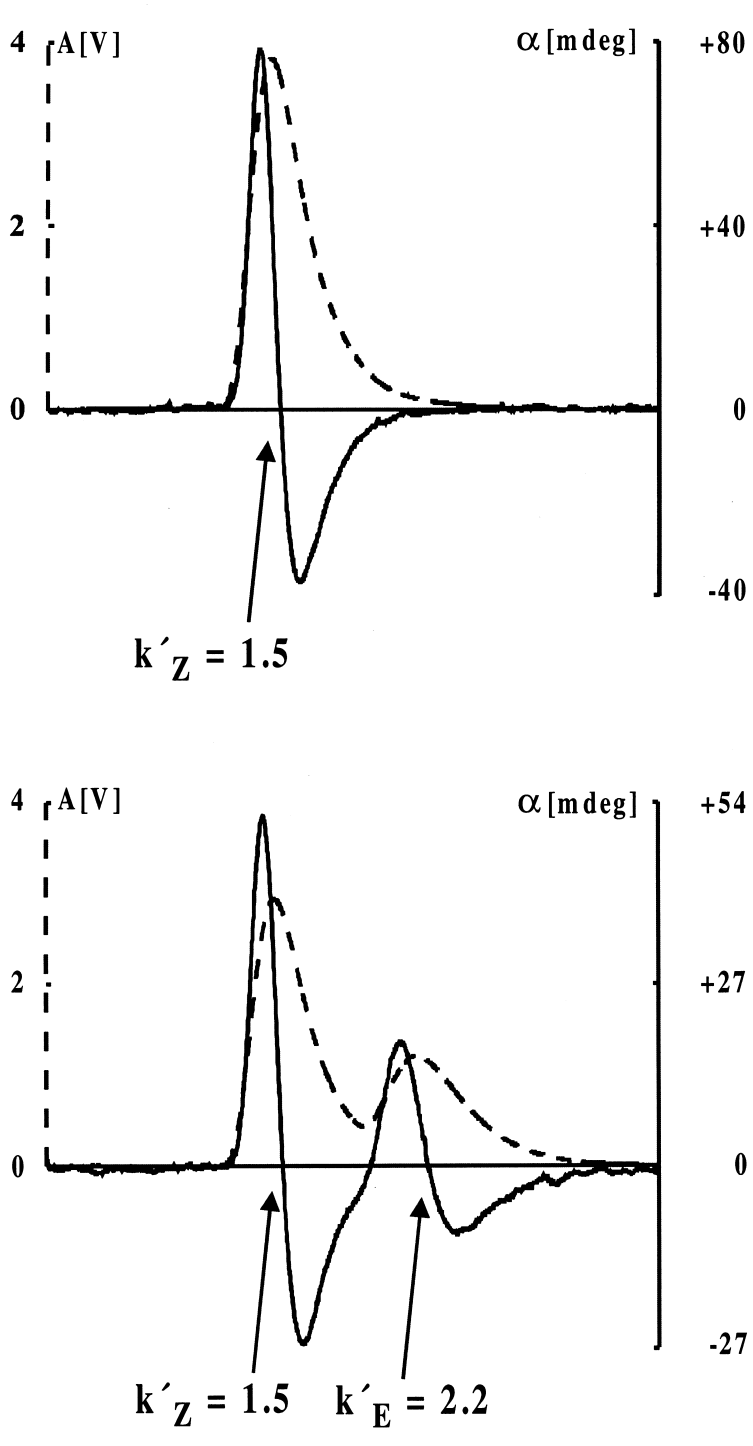
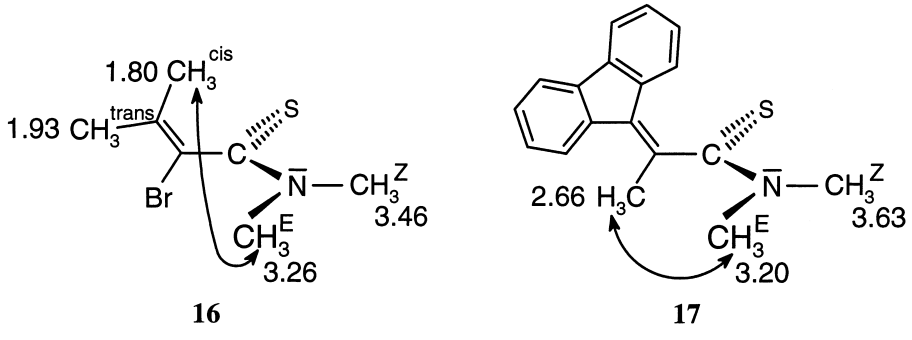


Fig. 1. Analytical liquid chromatogram of 0.6 mg of **14**. Microcrystalline tribenzoylcellulose, MeOH, flow rate 0.5 ml/min, pressure 24 bar. k′: Retention factor. A: Absorbance in V at 320 nm. α: Rotation angle at 405 nm. Top: Soon after dissolution of crystals of (±)-(*Z*)-**14**. Bottom: Equilibrium mixture after keeping the above sample at 50°C for 1 h

3. Assignment of the stereoisomers to ^{1}H NMR signals

NOE effects in the model thioamides **16**[6] and **17**[6] (Scheme 5) served to assign the ^{1}H NMR CH_3 shifts to the positions of these groups. Transfer of this information to **13**, **14** and **15** resulted in assignments of shifts to the diastereomers (*E*) and (*Z*), given in the Experimental. These were in agreement with benzene-induced shifts carried out for (*E*)- and (*Z*)-**14** and further acrylic thioamides. For (*E*)- and (*Z*)-**15**, the assignments in $CDCl_3$ solution had to be transferred to a d_8-toluene solution because a solvent boiling at a higher temperature than does $CDCl_3$ was required for the equilibrations (see below). This transfer took into account d_8-toluene-induced shifts and resulted in the δ-values for **15** in d_8-toluene in the Experimental. The addition of 6.0 equiv. of (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol **18** renders the *enantiomers* visible in the ^{1}H NMR spectra (e.g. Fig. 2) in addition to the two diastereomers. The corresponding assignments (Table 1) resulted from one or more of the following pieces of information. (*E*) and (*Z*) were assigned via relative signal intensities after equilibration (see K-values in Figs. 4–6) and their comparison with the known intensities in the absence of (+)-(*S*)-**18**; thus, the major diastereomer is (*Z*) in the cases of **13** and **14** and (*E*) in the case of **15**. All enantiomers in equilibrium showed ^{1}H NMR peaks with *equal* intensities. (In the presence of a nonracemic additive, unequal intensities have been observed occasionally.[17–19]) For **14** and **15**, all four stereoisomers were enriched preparatively and examined by ^{1}H NMR in the presence of (+)-(*S*)-**18**, by circular dichroism and by polarimetry which provided the assignments in Table 1. For **13**, (+)- and (−)-(*E*) were enriched preparatively and analyzed as above. The low abundance of (±)-(*Z*)-**13** after synthesis rendered preparative enrichments difficult but analytical HPLC with polarimetric detection resulted in the required information.



Scheme 5. NOE effects are indicated by arrows, ^{1}H NMR shifts in $CDCl_3$ at 21°C by numbers close to protons. Only one of the enantiomers is shown

4. Equilibration of stereoisomers, monitored by signal intensities in enantioselective ^{1}H NMR

The enriched enantiomers mentioned above were equilibrated at suitable temperatures, i.e. at 21–90°C, depending upon the substituents of the substrate molecules, in the presence of 6.0 equiv. of (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol **18**. To our knowledge, the application of this technique has not yet been described. Soon after dissolution, the extent of enrichment was determined by ^{1}H NMR signal intensities (e.g. in Fig. 2, top). The end of the isomerizations (cf. Fig. 2, bottom) was attained after 6–137 h, depending upon the substrate. During this period, 15 further measurements of intensities were carried out, i.e. the relative concentrations of the stereoisomers were monitored quantitatively as a function of

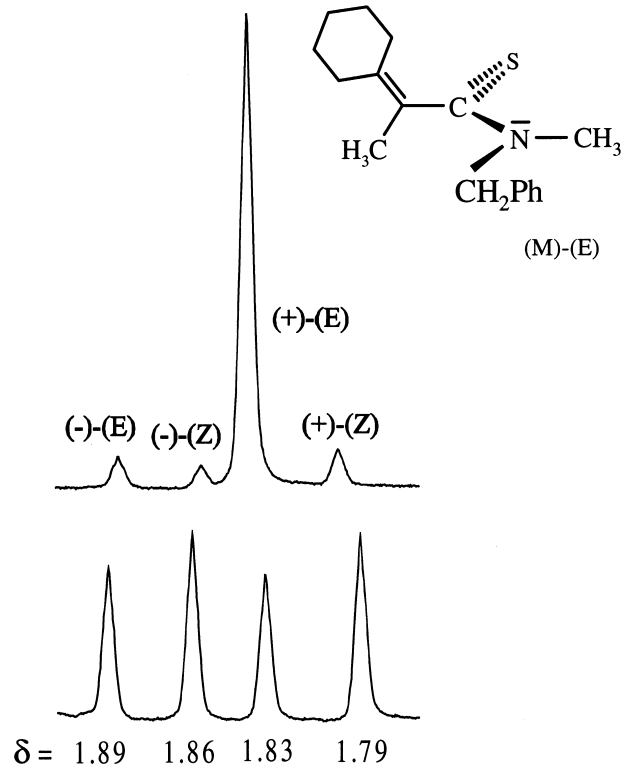


Fig. 2. ^{1}H NMR at 400 MHz of the =C–CH_3 groups for the stereoisomers of **14** in $CDCl_3$ in the presence of 6.0 equiv. of (+)-(*S*)-**18**. The formula of *one* of the stereoisomers is shown. See Fig. 3 for relative concentrations. Top: Soon after dissolution of a sample, containing enriched (+)-(*E*)-**14**. Bottom: Equilibrium mixture after keeping the above sample at 21°C for several days

Table 1
Assignments of stereoisomers to NMR shifts δ of =CCH_3 protons in the presence of 6.0 equiv. of (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol (**18**). In the case of **13**, *cis* =CCH_3 (Scheme 4) was chosen. Signs of polarimetric rotation refer to 436 nm

	Solvent	T	δ			
		°C	Assignment			
13	$CDCl_3$	55	1.62	1.59	1.56	1.51
			(+)-(E)	(-)-(E)	(+)-(Z)	(-)-(Z)
14	$CDCl_3$	21	1.89	1.86	1.83	1.79
			(-)-(E)	(-)-(Z)	(+)-(E)	(+)-(Z)
15	d_8-toluene	21	2.34	2.32	2.19	2.17
			(-)-(E)	(+)-(E)	(+)-(Z)	(-)-(Z)

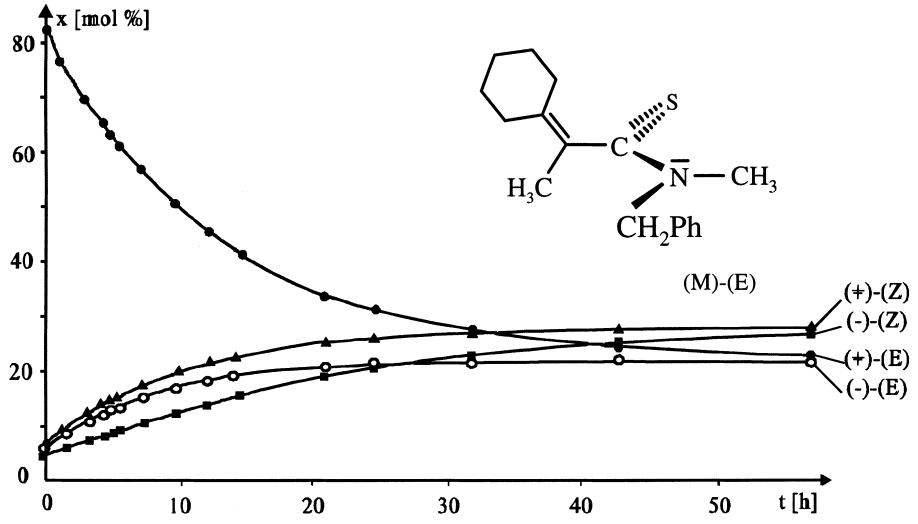


Fig. 3. Relative concentrations *x* of the stereoisomers of **14** in $CDCl_3$ in the presence of 6.0 equiv. of (+)-(*S*)-**18** as a function of time *t*. The formula of *one* of the stereoisomers is shown. Points represent ^{1}H NMR measurements (cf. Fig. 2), curves were obtained by computer simulation of the experiments (see text)

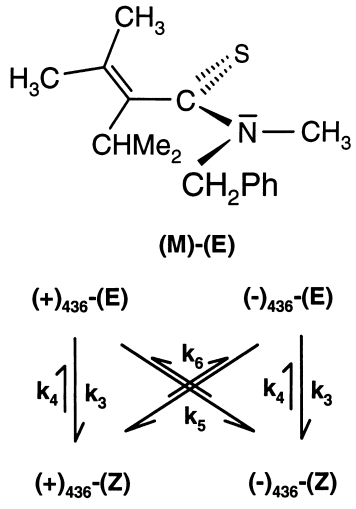
time (e.g. the points in Fig. 3). Table 1 shows the protons chosen for these measurements as well as their ^{1}H NMR shifts.

5. Individual rates of stereoisomerization, obtained by computer simulation of the experimental equilibrations

The relative concentrations of stereoisomers as a function of time (e.g. the points in Fig. 3) cannot be transformed analytically into the six rate constants given in Scheme 1. However, methods[20] are known to obtain k_1–k_6 via a first simulation of the experimental equilibrations by the use of six preliminary rate constants and their subsequent iterative improvement via an improved fit between simulation and experiment. For this procedure, we chose the program SimFit (Nonlinear Curve-*Fit*ting by Dynamic *Sim*ulation), written by von Kiedrowski.[21,22] It furnishes final k-values and their standard deviations Δk (Figs. 4–6) as well as the corresponding relative concentrations as a function of time (e.g. the curves in Fig. 3), as early as the program is unable to provide further improvement of the fit. In addition, SimFit gives the R-factor of the final simulation. All reasonable alternative kinetic possibilities were tried, without success, as sets of preliminary rate constants, in addition to the sets of k-values in Figs. 4–6. The kinetic schemes in these figures are simplified by the fact mentioned above that all enantiomers in equilibrium showed ^{1}H NMR peaks with *equal* intensities. The legends give equilibrium constants K between (*E*)- and (*Z*)-stereoisomers which were obtained at the end of the isomerizations. The errors of the barriers $\Delta G^{\ddagger}$ in Figs. 4–6 were calculated by propagation of Δk (see above) and ΔT (see Experimental).

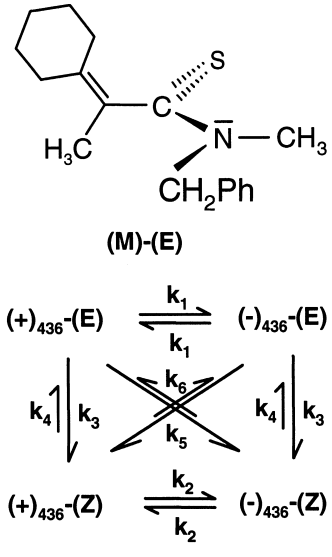
For thioamide **14**, a simulation without k_5 and k_6, i.e. the correlated rotations, showed clear-cut graphic deviations from the experimental points in Fig. 3 and an R-factor of 1.8%. Participation of all six rate constants resulted in a better graphic fit (Fig. 3), an R-factor of only 0.8% and the k-values of Fig. 5.

For thioamide **13**, participation of all six rate constants yielded extremely low values for k_1 and k_2



	10^{-6} s^{-1}	kJ mol^{-1}	
k_3	132.0 ± 0.4	105.0 ± 0.7	$\Delta G^{\neq}_3$
k_4	44.0 ± 0.4	108.0 ± 0.7	$\Delta G^{\neq}_4$
k_5	14.5 ± 0.1	111.0 ± 0.7	$\Delta G^{\neq}_5$
k_6	4.8 ± 0.1	114.0 ± 0.7	$\Delta G^{\neq}_6$

Fig. 4. k- and $\Delta G^{\ddagger}$-values for rotations in **13** [$CDCl_3$, 55°C, 6.0 equiv. of (+)-(*S*)-**18**]. K=0.33±0.02=$k_4/k_3=k_6/k_5$

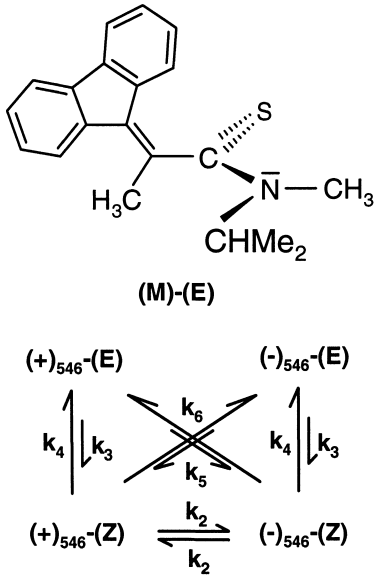


	10^{-6} s^{-1}	kJ mol^{-1}	
k_1	7.8 ± 0.1	100.7 ± 0.8	$\Delta G^{\neq}_1$
k_2	7.0 ± 0.1	100.9 ± 0.8	$\Delta G^{\neq}_2$
k_3	8.3 ± 0.1	100.5 ± 0.8	$\Delta G^{\neq}_3$
k_4	6.5 ± 0.1	101.1 ± 0.8	$\Delta G^{\neq}_4$
k_5	2.8 ± 0.1	103.2 ± 0.8	$\Delta G^{\neq}_5$
k_6	2.2 ± 0.1	103.8 ± 0.8	$\Delta G^{\neq}_6$

Fig. 5. k- and $\Delta G^{\ddagger}$-values for rotations in **14** [$CDCl_3$, 21°C, 6.0 equiv. of (+)-(*S*)-**18**]. K=0.79±0.03=$k_4/k_3=k_6/k_5$

which are due to the enantiomerizations by =C–C= rotations. When these motions were forbidden completely ($k_1=k_2=0$), the R-factor dropped tremendously to 0.8%, resulting in the k-values of Fig. 4.

For thioamide **15**, participation of all six rate constants yielded a very low value for k_1 which is due to the enantiomerization by =C–C= rotation in the diastereomer (*E*)-**15**. When this motion was forbidden completely ($k_1=0$), two sets of k-values resulted: (a) the set given in Fig. 6 with small values for k_5 and k_6 which are due to the correlated rotations, with acceptable graphic fit and with an R-factor of 1.5%; and (b) a second set with $k_5=k_6=0$, with a less perfect graphic fit and with an R-factor of 1.7%. This means that some extent of correlated rotations is probable in the case of **15**. A possible coupling between the two processes in Fig. 6 has been discussed[23] for a thiobenzamide and for a corresponding non-thioamide.[24]



	10^{-6} s^{-1}	kJ mol^{-1}	
k_2	10.3 ± 0.6	124.4 ± 0.4	$\Delta G^{\neq}_2$
k_3	76.0 ± 0.5	118.3 ± 0.2	$\Delta G^{\neq}_3$
k_4	103.4 ± 0.6	117.4 ± 0.2	$\Delta G^{\neq}_4$
k_5	1.7 ± 0.3	129.8 ± 0.7	$\Delta G^{\neq}_5$
k_6	2.3 ± 0.5	128.9 ± 0.8	$\Delta G^{\neq}_6$

Fig. 6. k- and $\Delta G^{\ddagger}$-values for rotations in **15** [d_8-toluene, 90.5°C, 6.0 equiv. of (+)-(*S*)-**18**]. K=1.36±0.04=$k_4/k_3=k_6/k_5$

6. Discussion of the barriers to stereoisomerizations

We did not find a way to measure the individual barriers in the *absence* of a nonracemic auxiliary. Therefore, these cannot be compared with the $\Delta G^{\ddagger}$-values in Figs. 4–6 which were determined in the *presence* of (+)-(*S*)-**18**. Somewhat more limited information about the influence of this additive upon barriers can be obtained in the following way, exemplified for thioamide **14**. Crystalline (±)-(*Z*)-**14** undergoes a slow (*E*)/(*Z*) equilibration[14] at 24°C after dissolution in $CDCl_3$ in the absence of an auxiliary. Monitoring of ^{1}H NMR signals as a function of time results[14] in $\Delta G^{\ddagger}$=98.4±0.7, (*E*)→(*Z*), and 99.3±0.8 kJ mol^{-1}, (*Z*)→(*E*).[13] The corresponding values, referring to the presence of (+)-(*S*)-**18**, were determined from the data in Fig. 3 by summing up the relative concentrations of (+)- and (−)-(*E*) as well as the ones of (+)- and (−)-(*Z*). These united (*E*) and united (*Z*) concentrations were treated as an (*E*)/(*Z*) equilibration[14] as above, resulting[14] in $\Delta G^{\ddagger}$=99.9±0.7, (*E*)→(*Z*), and 100.5±0.8 kJ mol^{-1}, (*Z*)→(*E*)[13] at 21°C in $CDCl_3$. This means that the presence of the additive increased the above barriers by approx. 1 kJ mol^{-1}. For thioamide **13**, the increase was even less, for **15** no change of barriers by (+)-(*S*)-**18** was observed within error limits.[13] Similar results had been obtained for related systems,[25] showing again that the influence of nonracemic alcohols upon the $\Delta G^{\ddagger}$-values must not be taken into account in the following semiquantitative discussion of Figs. 4–6.

All the barriers for uncorrelated rotations, corresponding to k_1, k_2, k_3 and k_4 in **14** amount to ca. 101 kJ mol^{-1} (Fig. 5), whereas $\Delta G^{\ddagger}_5$ and $\Delta G^{\ddagger}_6$ are close to 103 kJ mol^{-1}. This means that the four independent motions occur more frequently than the two correlated ones, although the existence of the latter has been demonstrated beyond doubt in the above section on individual rates.

In that section, it has also been stated that some extent of correlated rotations is probable in **15** (Fig. 6). The corresponding values $\Delta G^{\ddagger}_5$ and $\Delta G^{\ddagger}_6$ are as high as ca. 129 kJ mol^{-1}, i.e. these motions occur much less frequently than the observed uncorrelated rotations ($\Delta G^{\ddagger}_2$, $\Delta G^{\ddagger}_3$ and $\Delta G^{\ddagger}_4$). According to our experimental results, the enantiomers of (*E*)-**15** do not interconvert directly, which means that the barrier to =C–C= rotation ($\Delta G^{\ddagger}_1$) must be very high. The two possible transition states for this motion would be close to planar; in these, the voluminous N–$CHMe_2$ substituent would meet either the =C–CH_3

group or an ortho-proton of the fluorenylidene moiety (cf. formula in Fig. 6). Such repulsions are less severe in the corresponding transition states of the diastereomer (*Z*)-**15**, in which the smaller N–CH_3 substituent interacts with the =C–CH_3 group or the fluorenylidene moiety.

In **13**, the enantiomers of (*E*)-**13** again do not interconvert, but unlike the situation in **15**, this is true for (*Z*)-**13** too (Fig. 4). The four possible transition states of =C–C= rotation would be close to planar and would experience severe repulsion of substituents (cf. formula in Fig. 4). In spite of the absence of direct enantiomerizations ($\Delta G^{\ddagger}_1$ and $\Delta G^{\ddagger}_2$), *indirect* ones do occur. They are two-step processes, e.g. via the $\Delta G^{\ddagger}_3$ and the $\Delta G^{\ddagger}_6$ barriers, $\Delta G^{\ddagger}_3$ representing the uncorrelated =C–N motion and $\Delta G^{\ddagger}_6$ the correlated rotations.

Independent semiquantitative support for some enantiomerization process comes from thermal transformation of (−)-(*E*)-**13** into a mixture of all four stereoisomers, i.e. from equilibration. The latter was monitored by polarimetry, i.e. by the dependence of the angle α of rotation upon time t. For (−)-(*E*)-**13** in $CHCl_3$ at 55°C, this procedure gives an α/t dependence developing towards α=0, the approximate first-order evaluation of which results in $\Delta G^{\ddagger}$=112.7 kJ mol^{-1}. A curvature of this α/t dependence clearly indicates the occurrence of a faster and a slower process. We do not see an easy way to evaluate such measurements quantitatively but conclude that they are in agreement with the above two-step enantiomerization and with the facts given in Fig. 4, i.e. with correlation. Similar experiments and conclusions were performed for **14** and **15**.

Semiempirical calculations[26] by the AM1, PM3 and MINDO3 methods for 2,3-dimethyl-2-butenoic *N*-benzyl-*N*-methylthioamide as a model molecule resulted in the energy surfaces for the =C–N and the =C–C= rotations corresponding to Scheme 1. All transition states were confirmed. Full theoretical support of all experimental results would require more sophisticated methods applied to the molecules **13** and **14** themselves.

For the first time, we have proven the above combined rotations in thioamides of acrylic acid. Thus, the known examples[3,4] of correlated motions have now been extended to a completely different class of compounds.

7. Experimental

7.1. General methods

Column chromatography was carried out on ICN silica gel 60 F_{254} (63–200 μm). ^{1}H NMR spectra were recorded on Bruker AW-80, AC-250 or ARX-400 instruments at 31, 24 or 21°C with tetramethylsilane (δ=0 ppm) as an internal standard. Temperatures were determined by samples of 1,2-ethanediol.[27] The NR^E and NR^Z groups in amides and thioamides were assigned by benzene-induced shifts[28,29] and/or NOE. IR spectra were measured on Beckmann Acculab 1, UV spectra on Hitachi U 2000, mass spectra (MS) on Finnigan (MAT 90, 70 eV) or Varian (MAT CH 5, 70 eV) spectrometers. The enrichments of stereoisomers were performed by liquid chromatography[30,31] on microcrystalline triacetylcellulose[7] (TAC) for **13** and **14** in EtOH/H_2O 96/4 at 22°C and on microcrystalline tribenzoylcellulose[16] (TBC) for **15** in MeOH at 22°C. See lit.[32] for the definition of the retention factor k′. Diastereomeric purities were measured via ^{1}H NMR spectroscopy. Enantiomeric purities [P] were either determined by liquid chromatography on nonracemic sorbents or via ^{1}H NMR in the presence of 6.0 equiv. of (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol **18**. Specific rotations [α_0] were measured for enriched stereoisomers at 21°C on a Perkin–Elmer 241 polarimeter at certain wavelengths. Similarly, circular dichroism was recorded on a Jasco J-40 A dichrograph, differential absorption coefficients $\Delta\varepsilon_0$ of maxima being given

in l mol^{-1} cm^{-1}. $[\alpha_0]$ and $\Delta\varepsilon_0$ are calculated for [P]=100%. Melting points were determined on a Büchi SMP-530 apparatus and are not corrected. (+)-(*E*)-**14** was stereoisomerized and analyzed in the probe head of an NMR spectrometer at (21±2)°C. The isomerization of (−)-(*E*)-**13** at 55°C was monitored in this way only during the first half-life time; they were continued in a thermostat (ΔT=±0.5°C), i.e. after certain time intervals the sample was cooled rapidly to 0°C (in order to quench the equilibration) and analyzed by ^{1}H NMR at 21°C. In the case of (+)-(*Z*)-**15**, the latter procedure was performed in a thermostat at (90.5±0.5)°C, starting from the beginning of the isomerization. After several further half-life times, all four samples were brought to equilibrium by thermostatting. All ^{1}H NMR analyses included intensities and spectra; no decomposition products were detected.

7.2. General procedures

(A) *Acrylic amides*. $SOCl_2$ (11 mmol) in dry ether was added dropwise to the solution of an acid (10 mmol) and pyridine (12 mmol) in dry ether over a period of 20 min at 0°C. After additional stirring over a period of 4 h at room temperature, colorless pyridinium chloride precipitated and was filtered off. A solution of benzylmethylamine (25 mmol) in dry ether was added dropwise at 0°C and the mixture was stirred for 1 h at room temperature. The precipitate was removed and the filtrate washed with H_2O, dil. HCl, Na_2CO_3, H_2O and dried (Na_2SO_4). After removing the solvent, the remaining oil was characterized and subjected to thionation.

(B) *Acrylic thioamides.* The amide (10 mmol) in dry pyridine (40 ml) was refluxed with P_4S_{10} (3.5 mmol) over a period of 20 h. Monitoring of the reaction by thin-layer chromatography showed the completeness of the reaction. The mixture was cooled and the solvent removed. The residue was extracted several times with hot petroleum ether (PE) 40/60 (3×50 ml), the solvent removed and this second residue recrystallized or purified by column chromatography.

7.3. Compounds used

Compounds **1**,[33] **3**,[34] **4**[34] and **8**[35] (Schemes 2–4) were prepared as described in the literature.

*7.4. 2,5-Dimethylhexan-3-one **2***

A solution of $Na_2Cr_2O_7$ (2.0 g, 6.7 mmol) in sulfuric acid (1.5 ml) and H_2O (10 ml) was added gradually to 2,5-dimethylhexan-3-ol **1** (2.6 g, 20 mmol) in ether at 0°C and stirred for 2.5 h at room temperature. The water layer was separated, extracted twice with ether and the combined organic phases were washed with sat. $NaHCO_3$ solution, water and dried (Na_2SO_4). Evaporation of the ether afforded pure **2** (2.3 g, 90%) as a colorless liquid, b.p. 64°C /6400 Pa (lit.[36] 67°C/6400 Pa). IR (film): 2960, 2930, 2870 (C–H), 1700 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ 0.90 (6H, d, ^3J=6.5 Hz, –CH(CH_3)$_2$), 1.05 (6H, d, ^3J=6.5 Hz, –CH(CH_3)$_2$), 2.3 (2H, m, –CO–CH_2–CH), 2.30 (1H, h, ^3J=6.5 Hz, –CH(CH_3)$_2$), 2.60 (1H, h, ^3J=6.5 Hz, –CH (CH_3)$_2$).

*7.5. Ethyl 2-(9-hydroxyfluoren-9-yl)-propanoate **5***

20% of a solution of 9-fluorenone (40.0 g, 222 mmol) and ethyl 2-bromopropanoate (28.0 g, 155 mmol) and a small crystal of iodine[37] in 75 ml of abs. toluene were refluxed under vigorous stirring in the presence of zinc powder (12.1 g, 185 mmol) which had been previously activated by washing it with hot NaOH (25%), H_2O, dil. acetic acid, H_2O, ethanol, acetone and ether and finally by drying it over

KOH. The remaining 80% of the above solution was added dropwise over a period of 30 min. After 8 h of additional stirring, the mixture was allowed to cool to room temperature and then poured into ice-cold H_2SO_4 (10%, 92 ml). The mixture was filtered, extracted with ether and the organic layer was washed with dil. H_2SO_4 (5%, 2×100 ml), Na_2CO_3 (10%, 2×100 ml) and H_2O, then dried (Na_2SO_4) and the solvent removed. The remaining oil was twice submitted to column chromatography (PE/MeOH 11/1, last fraction). Slightly orange oil (39.4 g, 90%). IR (film): 3700–3200 (O–H), 3060, 3040, 3020 (C_{ar}–H), 2980, 2870 (C_{al}–H), 1720, 1700 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 0.80 (3H, d, ^3J=7.1 Hz, –CH–CH_3), 1.22 (3H, t, ^3J=7.0 Hz, –O–CH_2–CH_3), 3.19 (1H, q, ^3J=7.1 Hz, C*H*–CH_3), 4.20 (2H, q, ^3J=7.0 Hz, –O–CH_2–CH_3), 7.0–7.6 (8H, m, CH_{arom}).

7.6. Ethyl 2-fluoren-9-ylidenepropanoate **6**

A solution of ethyl 2-(9-hydroxyfluoren-9-yl)-propanoate (**5**) (38.32 g, 136 mmol) in dry toluene (170 ml) was added to a cold solution of P_4O_{10} (38.00 g, 134 mmol) in H_3PO_4 (85%, 380 g) and refluxed for 4 h. The mixture was washed with water (300 ml), the aqueous layer was extracted with ether and the combined organic phases were washed with NaCl (5%). While removing the solvent slowly, a brown oil and colorless crystals precipitated and were filtered off. Further evaporation afforded an orange oil that crystallized after addition of ether (5 ml). The product was filtered and dried in vacuo at 40°C for 4 h to give yellow crystals (23.69 g, 66%), m.p. 78.5–80.5°C. IR (KBr): 3070 (C_{ar}–H), 2990, 2910 (C_{al}–H), 1710 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 1.45 (3H, t, ^3J=7.0 Hz, –O–CH_2–CH_3), 2.55 (3H, s, =C–CH_3), 4.40 (2H, q, ^3J=7.0 Hz, –O–CH_2–CH_3), 7.5 (8H, m, CH_{arom}).

7.7. 2-Isopropyl-3-methyl-2-butenoic acid **7**

The ester **4** (10.5 g, 67 mmol) and LiI (45.0 g, 336 mmol) were heated in dry DMF under an N_2 atmosphere for 30 h. The reaction mixture was poured into water (50 ml), acidified with hydrochloric acid and extracted thrice with ether. After purification by column chromatography (PE/ethyl acetate (EA) 1/1, first fraction), evaporation of the ether afforded pure **7** (6.9 g, 72%) as a colorless liquid. ^1H NMR ($CDCl_3$): δ 1.13 (6H, d, ^3J=7.0 Hz, –CH(CH_3)$_2$), 1.78 (3H, s, =C–CH_3), 1.87 (3H, s, =C–CH_3), 2.85 (1H, h, ^3J=7.0 Hz, –C*H*(CH_3)$_2$), 10.2–10.4 (1H, br, COO*H*). IR (film): 3400–2800 (O–H), 2960, 2930, 2870 (C–H), 1680 cm^{-1} (C=O). MS (70 eV): *m*/*z*=142 (61, M^+), 127 (100, M^+-CH_3), 97 (79, M^+-COOH).

7.8. 2-Fluoren-9-ylidenepropanoic acid **9**

To a solution of **6** (23.7 g, 89.5 mmol) in isopropanol (380 ml), water (330 ml) and toluene (40 ml) was added a solution of KOH (10.8 g, 193 mmol) in 40 ml of isopropanol/water (1/1, 40 ml). After 4 h of reflux and removal of the solvent, water (1000 ml) was added and by-products were extracted with PE (2.42 g of **6** could be reisolated from this extract by crystallization). The aqueous phase was acidified with hydrochloric acid and extracted twice with ether. After evaporation of the ether a yellow–brown solid remained. Recrystallization from $CHCl_3$/PE afforded **9** (15.6 g, 74%) as yellow needles, m.p. 179.5–183°C. IR (KBr): 3600–3000 (O–H), 3080, 3030 (C_{ar}–H), 2930, 2900 (C_{al}–H) 1680 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 2.60 (3H, s, =C–CH_3), 7.0–8.0 (8H, m, CH_{arom}), O*H*-signal could not be detected.

*7.9. (*E,Z*)-2-Isopropyl-3-methyl-2-butenoic* N-*benzyl*-N-*methylamide* ***10***

Reaction of **7** yielded (*E,Z*)-**10** according to method A. The residue was purified by column chromatography (SiO_2; PE/EA 3/1). Evaporation of the solvents afforded pure **10** as a slightly orange oil [75%, $K_{E/Z}$ (24°C)=0.3]. IR (film): 3040, 3000 (C_{ar}–H), 2940, 2900 (C_{al}–H), 2840 (NC–H), 1610 cm^{-1} (C=O). MS (70 eV): *m*/*z*=245 (40, M^+), 230 (100, M^+-CH_3). (*E*)-**10**: ^{1}H NMR ($CDCl_3$): δ 1.03 (3H, d, ^3J=7.0 Hz, –CH–CH_3), 1.20 (3H, d, ^3J=7.0 Hz, –CH–CH_3), 1.69 (3H, s, *cis*[38] =C–CH_3), 1.73 (3H, s, *trans*[38] =C–CH_3), 2.84 (1H, h, ^3J=7.0 Hz, –CH(CH_3)$_2$), 2.89 (3H, s, NCH_3), 4.51 (1H, d, $^2J_{AB}$=15.5 Hz, NCH_AH$_B$, 7.2–7.3 (5H, m, CH_{arom}). (*Z*)-**10**: ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, d, ^3J=6.9 Hz, –CH–CH_3), 1.21 (3H, d, ^3J=6.9 Hz, CH–CH_3), 1.58 (3H, s, *cis*[38] =C–CH_3), 1.71 (3H, s, *trans*[38] =C–CH_3), 2.84 (3H, s, NCH_3), 2.84 (1H, h, ^3J=6.9 Hz, –CH(CH_3)$_2$), 4.61/4.71 (2H, d/d, $^2J_{AB}$=14.4 Hz, NC$H_A H_B$), 7.2–7.3 (5H, m, CH_{arom}).

*7.10. (*E,Z*)-2-Cyclohexylidenepropanoic* N-*benzyl*-N-*methylamide* ***11***

Reaction of **8** yielded (*E,Z*)-**11** according to method A as a slightly yellow oil [81%, $K_{E/Z}$ (31°C)=0.7]. IR (film): 3070, 3040 (C_{ar}–H), 2940 (C_{al}–H), 2860 (NC–H), 1630 cm^{-1} (C=O). (*E*)-**11**: ^{1}H NMR ($CDCl_3$): δ 1.50 (6H, m, –CH_2–(CH_2)$_3$–CH_2–), 1.85 (3H, s, =C–CH_3), 2.15 (4H, m, –CH_2–(CH_2)$_3$–CH_2–), 2.89 (3H, s, NCH_3), 4.40 (2H, br, NCH_2), 7.2 (5H, m, CH_{arom}). (*Z*)-**11**: ^{1}H NMR ($CDCl_3$): δ 1.50 (6H, m, –CH_2–(CH_2)$_3$–CH_2–), 1.85 (3H, s, =C–CH_3), 2.15 (4H, m, –CH_2–(CH_2)$_3$–CH_2–), 2.82 (3H, s, NCH_3), 4.60 (2H, s, NCH_2), 7.2 (5H, m, CH_{arom}).

*7.11. (*Z*)-2-Fluoren-9-ylidenepropanoic* N-*isopropyl*-N-*methylamide* ***12***

Reaction of **9** with isopropylmethylamine according to method A yielded pure (*Z*)-**12** (59%), according to ^{1}H NMR ($CDCl_3$). M.p. 114–120°C after recrystallization from CH_2Cl_2/n-hexane. IR (KBr): 3060 (C_{ar}–H), 2980, 2930 (C_{al}–H), 2870 (NC–H), 1615 cm^{-1} (C=O). Thermal equilibration yielded (*E,Z*)-**12** [$K_{E/Z}$ (24°C)=1.44]. (*E*)-**12**: ^{1}H NMR ($CDCl_3$): δ 0.92 (3H, d, ^3J=6.6 Hz, –CH–CH_3), 1.19 (3H, d, ^3J=6.6 Hz, –CH–CH_3), 2.58 (3H, s, =C–CH_3), 3.02 (3H, s, NCH_3), 4.07 (1H, h, ^3J=6.6 Hz, NCH), 7.2–7.9 (8H, m, Ar–*H*). (*Z*)-**12**: ^{1}H NMR ($CDCl_3$): 1.22 (3H, d, ^3J=6.8 Hz, –CH–CH_3), 1.27 (3H, d, ^3J=6.8 Hz, –CH–CH_3), 2.56 (3H, s, =C–CH_3), 2.75 (3H, s, NCH_3), 5.12 (1H, h, ^3J =6.8 Hz, NCH), 7.2–7.9 (8H, m, Ar–*H*).

*7.12. (±)-(*E*)-2-Isopropyl-3-methyl-2-butenoic* N-*benzyl*-N-*methylthioamide* ***13***

Reaction of (*E,Z*)-**10** yielded (±)-(*E*)-**13** according to method B. The residue was purified by column chromatography (PE/EA 2/1). Recrystallization from PE 40/60 afforded pure (±)-(*E*)-**13** (30%) as colorless crystals, m.p. 100–103°C. ^{1}H NMR ($CDCl_3$): δ 1.09 (3H, d, ^3J=7.0 Hz, –CH–CH_3), 1.32 (3H, d, ^3J=7.0 Hz, –CH–CH_3), 1.65 (3H, s, *cis*[38] =C–CH_3), 1.75 (3H, s, *trans*[38] =C–CH_3), 2.85 (1H, h, ^3J=7.0 Hz, –CH(CH_3)$_2$), 3.33 (3H, s, NCH_3), 4.77/4.85 (2H, d/d, $^2J_{AB}$=15.3 Hz, NC$H_A H_B$), 7.3 (5H, m, CH_{arom}). IR (KBr): 3060, 3030 (C_{ar}–H), 2960, 2930 (C_{al}–H), 2870 (NC–H), 1200 cm^{-1} (C=S). UV (MeOH) λ_{max}/nm (log ε_{max}): 227 (4.00), 280 (4.10). MS (70 eV): *m*/*z*=261 (60, M^+), 246 (100, M^+-CH_3). Anal. calcd for $C_{16}H_{23}NS$ (261.5): C 73.49, H 8.88, N 5.36; found: C 73.14, H 8.88, N 5.37%.

7.13. (±)-(Z)-2-Isopropyl-3-methyl-2-butenoic N-*benzyl*-N-*methylthioamide* ***13***

Signals of the ^{1}H NMR of (±)-(*Z*)-**13** were taken from the spectrum of an equilibrium mixture. ^{1}H NMR ($CDCl_3$): δ 1.01 (3H, d, ^3J=6.9 Hz, –CH–CH_3), 1.36 (3H, d, ^3J=6.9 Hz, –CH–CH_3), 1.60 (3H, s, *cis*[38] =C–CH_3), 1.73 (3H, s, *trans*[38] =C–CH_3), 2.83 (1H, h, ^3J=6.9 Hz, –CH(CH_3)$_2$), 3.05 (3H, s, NCH_3), 5.27/5.44 (2H, d/d, $^2J_{AB}$=14.1 Hz, NCH_AH_B), 7.3 (5H, m, CH_{arom}).

*7.14. (−)$_{436}$-(*E*)-2-Isopropyl-3-methyl-2-butenoic* N-*benzyl*-N-*methylthioamide* ***13***

Semipreparative enrichment of the stereoisomer was performed by liquid chromatography on TAC/EtOH, flow rate 3.5 ml/min, 4 bar, with k′=0.4, yielding colorless crystals, m.p. 102–103.5°C. $[P]_{LC}$=85±5%; $[\alpha_0]_{436}$=−405±60, $[\alpha_0]_{405}$=0, $[\alpha_0]_{365}$=+565±80 (MeOH, 24°C, c=0.1 g/l); CD (MeOH, 24°C) λ_{max}/nm (Δε): 273 (−3.6), 365 (−2.8).

7.15. (±)-(Z)-2-Cyclohexylidenepropanoic N-*benzyl*-N-*methylthioamide* ***14***

Reaction of (*E,Z*)-**11** yielded (±)-(*Z*)-**14** as colorless crystals (65%), m.p. 73.5–75.5°C, according to method B. ^{1}H NMR ($CDCl_3$): δ 1.60 (6H, m, –CH_2–(CH_2)$_3$–CH_2–), 1.91 (3H, s, =C–CH_3), 2.10 (4H, m, –CH_2–(CH_2)$_3$–CH_2–), 3.10 (3H, s, NCH_3), 5.28/5.39 (2H, d/d, $^2J_{AB}$=14.3 Hz, NCH_AH_B), 7.3 (5H, m, CH_{arom}). IR (film): 3080, 3040 (C_{ar}–H), 2970, 2940 (C_{al}–H), 2870 cm^{-1} (NC–H). UV (EtOH) λ_{max}/nm (log ε_{max}): 225 (4.00), 280 (4.06). Anal. calcd for $C_{17}H_{23}NS$ (273.5): C 52.35, H 5.42, N 4.70; found: C 52.15, H 5.69, N 4.53%.

*7.16. (±)-(*E*)-2-Cyclohexylidenepropanoic* N-*benzyl*-N-*methylthioamide* ***14***

Signals of the ^{1}H NMR of (±)-(*E*)-**14** were taken from the spectrum of an equilibrium mixture. ^{1}H NMR ($CDCl_3$): δ 1.60 (6H, m, –CH_2–(CH_2)$_3$–CH_2–), 1.95 (3H, s, =C–CH_3), 2.10 (4H, m, –CH_2–(CH_2)$_3$–CH_2–), 3.33 (3H, s, NCH_3), 4.60/5.07 (2H, d/d, $^2J_{AB}$=15.2 Hz, NCH_AH_B), 7.3 (5H, m, CH_{arom}).

*7.17. (+)$_{436}$-(*E*)-2-Cyclohexylidenepropanoic* N-*benzyl*-N-*methylthioamide* ***14***

Semipreparative enrichment of the stereoisomer was performed by liquid chromatography of an equilibrium mixture on TAC/EtOH, flow rate 3.5 ml/min, 4 bar, with k′=0.6, yielding a colorless oil. $[P]_{NMR}$=85±3%; because of the rapid interconversion of the isomers, only circular dichroism could be obtained (non-calibrated on-line measurement[39,40]); CD (24°C, TBC/MeOH, flow rate 1.0 ml/min, 38 bar) λ_{max}/nm (ΔA): 275 (+5.8), 304 (0.0), 370 (+2.7).

*7.18. (*E,Z*)-2-Fluoren-9-ylidenepropanoic* N-*isopropyl*-N-*methylthioamide* ***15***

The amide **12** (10 mmol) in dry toluene (200 ml) was refluxed with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, 20 mmol) until thin-layer chromatography showed the completeness of the reaction (after 15 h). The cold mixture was filtered and the solvent removed. Purification by column chromatography (CH_2Cl_2/toluene 1/4) and crystallization from the eluent afforded (*E,Z*)-**15** [36%, $K_{E/Z}$ (105°C)=1.38] as yellow crystals, m.p. 101–131°C. IR (KBr): 3100, 3060 (C_{ar}–H), 2980, 2930 (C_{al}–H), 2880 (NC–H), 1110 cm^{-1} (C=S). UV (MeOH) λ_{max}/nm (log ε_{max}):

232 (4.60), 250 (4.49), 258 (4.55), 275 (4.25), 303 (4.02), 321 nm (4.07). MS (70 eV): *m*/*z*=307 (77, M^+), 292 (79, M^+-CH_3), 165 (100, [fluorene]$^+$). Anal. calcd for $C_{20}H_{21}NS$ (307.5): C 78.14, H 6.89, N 4.56; found: C 78.05, H 6.78, N 4.68%.

7.19. (±)-(Z)-2-Fluoren-9-ylidenepropanoic N-*isopropyl*-N-*methylthioamide* ***15***

Recrystallization of one portion of (*E,Z*)-**15** from PE yielded long (up to 12 mm) bent needles aggregated to feathers, m.p. 149–150.5°C with a content of 100% (*Z*)-**15**. IR (KBr): identical with the spectrum of (*E,Z*)-**15**. ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, d, ^3J=6.8 Hz, –CH–C*H*$_3$), 1.36 (3H, d, ^3J=6.8 Hz, –CH–C*H*$_3$), 2.62 (3H, s, =C–C*H*$_3$), 2.95 (3H, s, NC*H*$_3$), 5.99 (1H, h, ^3J=6.8 Hz, NC*H*), 7.2–7.8 (8H, m, Ar–*H*). ^{1}H NMR (d_8-toluene): δ 0.84 (3H, d, ^3J=6.8 Hz, –CH–C*H*$_3$), 0.92 (3H, d, ^3J=6.8 Hz, –CH–C*H*$_3$), 2.25 (3H, s, =C–C*H*$_3$), 2.34 (3H, s, NC*H*$_3$), 6.01 (1H, h, ^3J=6.8 Hz, NC*H*), 7.0–7.9 (8H, m, Ar–*H*).

7.20. (±)-(E)-2-Fluoren-9-ylidenepropanoic N-*isopropyl*-N-*methylthioamide* ***15***

One portion of (*E,Z*)-**15** was equilibrated in xylene at 140°C for 2 h to increase the content of (*E*)-**15**. Enrichment by column chromatography (toluene), followed by recrystallization from CH_2Cl_2/n-hexane 1/4 and afterwards from ether/n-hexane (1/2) afforded yellow needles, m.p. 136–138°C with a content of 96% (*E*)-**15**. IR (KBr): identical with the spectrum of (*E,Z*)-**15**. ^{1}H NMR ($CDCl_3$): δ 0.97 (3H, d, ^3J=6.6 Hz, –CH–C*H*$_3$), 1.22 (3H, d, ^3J=6.6 Hz, –CH–C*H*$_3$), 2.66 (3H, s, =C–C*H*$_3$), 3.43 (3H, s, NC*H*$_3$), 4.50 (1H, h, ^3J=6.6 Hz, NC*H*), 7.0–7.9 (8H, m, Ar–*H*). ^{1}H NMR (d_8-toluene): δ 0.42 (3H, d, ^3J=6.6 Hz, –CH–C*H*$_3$), 0.55 (3H, d, ^3J=6.6 Hz, –CH–C*H*$_3$), 2.39 (3H, s, =C–C*H*$_3$), 3.03 (3H, s, NC*H*$_3$), 4.06 (1H, h, ^3J=6.6 Hz, NC*H*), 7.0–7.9 (8H, m, Ar–*H*).

7.21. (+)$_{436}$-(Z)-2-Fluoren-9-ylidenepropanoic N-*isopropyl*-N-*methylthioamide* ***15***

Semipreparative enrichment of the stereoisomer was performed by liquid chromatography on TBC/MeOH, flow rate 3.5 ml/min, 2 bar, with k'=2.0, yielding a light yellow solid, m.p. 140–146°C. $[P]_{NMR}$=88±3%; $[\alpha_0]_{546}$=−135±24, $[\alpha_0]_{436}$=+470±70, $[\alpha_0]_{405}$=+1610±210 (MeOH, 22°C, c=0.4 g/l); CD (MeOH, 24°C) λ_{max}/nm (Δε): 235 (+7.9), 259 (+1.0), 277 (−16.5), 365 (+2.6).

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