Tri- and Tetrasubstituted N-Phthalimidoaziridines in 1,3-Dipolar Cycloaddition Reactions

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Dedicated to Professor Manfred Hesse on the occasion of his 75th birthday

The thermal reactions of the 2,2,3-trisubstituted N-phthalimidoaziridine 1a with dimethyl acetylenedicarboxylate (DMAD), thioketones 4a–4d, and dimethyl azodicarboxylate (5) proceed even at room temperature leading to the five-membered cycloadducts 2a, 6–8, and 12, respectively, with retention of the spatial arrangement of the aziridine substituents, in contrast to the expectation based on the conservation of orbital symmetry in concerted reactions. The analogous reactions of the tetrasubstituted phthalimidooaziridine 1b with thioketones at 40°C lead to the 1,3-thiazolidine derivatives 10 and 11 as mixtures of diastereoisomers. These unexpected results may be explained by either the isomerization of the intermediate azomethine ylides or a non-concerted stepwise cycloaddition reaction of these ylides with the dipolarophiles. The structures of some adducts have been determined by X-ray crystallography.

Introduction. – As far back as in the sixties of the past century, the reaction of aziridines, e.g., A, with active dipolarophiles, e.g., a ≡ b, leading to five-membered N-containing heterocycles C was discovered [1–3] (Scheme 1). The process is considered to start with a thermally (conrotatory) or photochemically (disrotatory) induced cleavage of the aziridine C–C bond to give azomethine ylides B, which are named

Scheme 1

1) Part of the Ph.D. thesis of A. V. U., University of Saint-Petersburg, 2009; stay at the University of Zürich, July–September, 2005.
‘octet-stabilized 1,3-dipoles’ [4]. These reactive intermediates, which can be represented by various mesomeric structures, formally bear a positive charge on the N-atom and negative partial charges on both C-atoms, suggesting that the opening of aziridines A to azomethine ylides B should be accelerated by electron-withdrawing substituents, which are able to stabilize negative charges on the terminal C-atoms of the formed dipoles. This proposal is supported by experimental data [1–3][5][6]. The reactive 1,3-dipoles B subsequently undergo cycloaddition to dipolarophiles or stabilize via various other inter- or intramolecular transformations [3–8].

If both reactions of this process are concerted – the conrotatory C–C bond cleavage is thermally allowed according to the Woodward–Hoffmann rules [9], and the disrotatory one under photolysis conditions – and no stereoisomerization of the intermediate azomethine ylides B takes place, the adduct formation proceeds stereospecifically, and the spatial arrangement of the substituents of the product is determined by that of the starting compounds (see, e.g., [10]). However, sometimes these conditions are not fulfilled, and mixtures of stereo(and regio-)isomers resulted [3][5–7].

The number of publications on the cycloaddition of azomethine ylides generated from aziridines thermally or photochemically grows rapidly. More and more often, this transformation is used in the synthesis of complex natural and biologically active compounds [7][8]. The use of N-aminooaziridine derivatives could open a direct way to various N-aminoheterocycles; however, only a few examples were described by Foucaud et al. in the seventies and eighties of the past century [11]. It was shown that, upon heating (or even at room temperature!), some N-phthalimidoaziridines with three or four electron-withdrawing substituents in the presence of dipolarophiles give products, which can be considered as the result of inter- (pyrrolines, azetidines) or intramolecular (oxazolines, oxazoles) transformations of the corresponding azomethine ylides. Similar intramolecular transformations were also described for some N-succinimidoaziridines [12].

Nevertheless, all of the few known examples of [2 + 3] cycloadditions with N-phthalimidoazomethine ylides were carried out with a single dipolarophile, the very reactive dimethyl acetylenedicarboxylate (DMAD), and the reports are very scarce and partly contradictory. It was reported in the first communication [11a] that briefly boiling trans-aziridine 1a and DMAD in benzene gives a mixture of 2,5-dihydro-1H-pyrrole 2a (25%) as a single stereoisomer and oxazole 3 (65%), which can be considered as the product of a 1,5-dipolar electrocyclization of the intermediate acylazomethine ylide and its subsequent aromatization by loss of phthalimide (Scheme 2). If the same reaction was carried out at room temperature in CH2Cl2 for two weeks, the yield of 2,5-dihydro-1H-pyrrrole 2a, isolated again as a single stereoisomer (according to the 1H-NMR data), increased to 85%, and the yield of oxazole 3 decreased to 15% [11b]. But, in the latest article of the same group [11c], it was reported that boiling of the tetrasubstituted N-phthalimidoaziridine 1b in the presence of DMAD in CH2Cl2 led to the corresponding 2,5-dihydro-1H-pyrrrole 2b (84%) as a 1:1 mixture of diastereoisomers, and the authors affirmed that they had obtained a mixture of diastereoisomers of dihydropyrrrole 2a in the earlier described experiment [11b] too! Furthermore, no determination of the relative configuration of any of these 2,5-dihydro-1H-pyrrroles was carried out.
Meanwhile, we reported on the inter- [13–15] and intramolecular [16] cyclo-
addition of several 2,3-disubstituted N-phthalimidoaziridines to a number of dipolaro-
philes with C,C multiple bonds under forced thermolysis conditions (80 – 220°), which
proceeded in a stereospecific and diastereoselective manner. Therefore, the aim of the
present work was to investigate [2 + 3] cycloaddition reactions of N-phthalimidoaziri-
dines 1a and 1b, which are activated with three and four electron-withdrawing
substituents, respectively, to shed light on the spatial regularities of this process.

The aziridines 1a and 1b were obtained by oxidative /C28phthalimidoaziridination/C29 of
the corresponding unsaturated compounds [17][18]. As far as this reaction occurs
completely stereospecifically, the trans configuration of compound 1a follows from the
(E) configuration of the starting acrylate, which was established by its NOESY
spectrum (see Exper. Part). The trans configuration of 1b is in agreement with the non-
equivalence of the two MeO groups in the 1H-NMR spectrum as a result of the well-
known slow inversion of the ring N-atom in N-aminoaziridine derivatives [19].

2. Results and Discussion. – 2.1. Reaction of Aziridine 1a with DMAD. First, we
have repeated the reaction of 1a with DMAD [11]. Preliminary microscale (ca.
35 μmol) experiments in benzene and in CH2Cl2 were performed at room temperature.
The 1H- and 13C-NMR spectra of the reaction mixture, recorded immediately after the
reaction had ceased, revealed the presence of 2,5-dihydro-1H-pyrrole 2a, as a single
stereoisomer, and of oxazole 3 in a ratio of ca. 1:1 in both cases (Scheme 3). The
separation of the mixture by chromatography on silica gave ca. 60% of 2a, but only
traces (ca. 5%) of oxazole 3a, indicating the low stability of the latter under the
separation conditions.

Scheme 2

\[ \text{R}^1 \quad \text{N} \quad \text{CO}_2\text{Me} \quad \text{CN} \quad \xrightarrow{\text{DMAD} \quad \Delta} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{N} \quad \text{CO}_2\text{Me} \quad \text{CN} \quad + \quad \text{Ph} \quad \text{N} \quad \text{CO}_2\text{Me} \]

\[ \text{a} \quad \text{R}^1 = \text{Ph}, \text{R}^2 = \text{H} \]
\[ \text{b} \quad \text{R}^1 = \text{CO}_2\text{Me}, \text{R}^2 = \text{CN} \]

Scheme 3

\[ \text{R}^1 \quad \text{N} \quad \text{CO}_2\text{Me} \quad \text{CN} \quad \xrightarrow{\text{DMAD} \quad \text{Benzene, r.t.}} \quad \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \quad \text{N} \quad \text{CO}_2\text{Me} \]

\[ (+ 3) \]

\[ \text{Ph} \quad \text{N} \quad \text{CO}_2\text{Me} \]

\[ 1a \]

\[ 2a \]
The preparative-scale reaction of 1a with DMAD in benzene at room temperature gave, after column chromatography, only 2a in 60% yield. Its melting point and 1H-NMR spectrum were in a good agreement with the data published earlier [11b], and its structure was unambiguously established as the trans-isomer (rel-(2R,5R)-isomer) by X-ray crystallography (Fig. 1). Concerning its 13C-NMR spectrum, it should be noted that all signals of the phthalimide C-atoms are broad or even cannot be detected (N−C=O) in the spectrum. This indicates slow rotation of this substituent about the sterically crowded N−N bond.

The crystal structure of 2a clearly shows that the Ph and C≡N groups have the same relative configuration (cis orientation) as in the starting aziridine 1a. This result was unexpected taking into account our experience with 2,3-disubstituted N-phthalimidoaziridines [13–16]: we have shown that the thermal ring opening of these aziridines to give N-phthalimidoazomethine ylides always proceeded stereospecifically, in full agreement with the Woodward–Hoffmann rules, as a conrotatory process, and it led to the reverse spatial arrangement of the aziridine substituents in the final cycloadducts. In contrast, the reaction of 1a with DMAD unequivocally led to 2a with retention of the relative configuration!

With the aim of investigating the general character of this change of the stereochemical outcome of this process by going from disubstituted N-phthalimidoaziridines to the thermally less stable three- and tetrasubstituted 1a and 1b, we have carried out reactions with very active dipolarophiles, i.e., thioketones 4a–4d, and, in the case of 1a, also with dimethyl azodicarboxylate (5).
2.2. Reactions of Aziridines 1a and 1b with Thioketones 4a – 4d. All reactions of 1a with the deeply colored thioketones 4 were carried out in the same manner as described above with DMAD, i.e., by stirring a solution of the reagents in dry benzene under Ar at room temperature for several days. The progress of the reactions was followed by TLC. In addition, the intense color of the initial reaction mixtures faded or disappeared completely indicating the completion of the reaction.

The reaction of 1a with bis(4-methoxyphenyl)methanethione (4a) after 6 d gave the 1,3-thiazolidine 6 (85%) as a single regio- and diastereoisomer (Scheme 4). The product appeared to be a heat-sensitive compound, and decomposed completely by recrystallization from MeOH or by the determination of the melting point. Suitable crystals of 6 were obtained from CH₂Cl₂/hexane, and the structure was determined by single-crystal X-ray diffraction (Fig. 2). It shows the conservation of the spatial arrangement of the aziridine substituents in the cycloadduct, i.e., the trans-isomer 1a yielded the trans-isomer 6.

Scheme 4

The ¹H-NMR spectrum of 6 in (D₆)benzene displays a low-field signal at 7.21 ppm for the single H-atom of the thiazolidine ring, which serves as an indication that this H-atom is at C(2). It could be also noted that the change of the solvent from CDCl₃ to (D₆)benzene causes a strong high-field shift of all signals of the phthalimide H-atoms: instead of the usual 7.7 – 8.0 ppm, the multiplet of H – C(b) appears at 7.1 – 7.2 ppm, and the signal of H – C(c) even at 6.6 – 6.7 ppm. The remarkable feature of the ¹³C-NMR spectrum of this sterically overcrowded compound (as well as of other polysubstituted 3-phthalimido-1,3-thiazolidines obtained in this work; see Exper. Part) is a doubling of all signals of the phthalimide C-atoms, which demonstrates the hindered rotation of this fragment about the N=C=N bond.

The analogous reaction of 1a and adamantane-2-thione (4b) in benzene was sluggish, and, after 16 d at room temperature, 60% of 4b were recovered (Scheme 5). The cycloadduct 7, which was expected on the basis of the experiment with 4a, was isolated in only 8% yield (calculated on consumed 4b). The main product of this reaction was thiazolidine 8 (23%), which could be considered as the result of secondary transformations of 7 with loss of the phthalimide unit. It is remarkable that both 7 and 8 were formed as single diastereoisomers. The relative configurations of both molecules were assumed to be trans taking into account the structures of 2a and 6, which were established by X-ray crystallography. It is essential to note that the reactions of the unsymmetrical 1a with also unsymmetrical dipolarophiles 4a and 4b, respectively, proceeded regioselectively affording 2-phenyl-1,3-thiazolidines exclusively.
Beside 7 and 8, a mixture of phthalimide (18%) and a third product 9 (23%) was isolated. The $^1$H-NMR spectrum of the latter displayed a singlet at 4.07 ppm (MeO) and a characteristic multiplet of the phthaloyl H-atoms at 7.85 – 8.10 ppm. The same product was isolated in pure form from the reaction of 1a with dimethyl azodicarboxylate (5; see Sect. 2.3). Its ESI-MS showed a quasimolecular-ion peak at $m/z$ 312 (100, $[M + Na + MeOH]^+$) that corresponds to the molecular weight of 257. Therefore, the product might be considered as being formed by loss of the benzylidene fragment from the starting aziridine 1a. Taking into account this information as well as the IR-, and $^1$H- and $^{13}$C-NMR spectra, we assume that this product has the structure of hydrazonoacetate 9 with unknown configuration of the C= N bond. Its formation could be explained as depicted in Scheme 6.
The formed 1,3-thiazolidine could undergo a \([2 + 3]\) cycloreversion under the reaction conditions or during the separation of the reaction mixture, which led to 9 and a thiocarbonyl ylide. This ylide apparently decomposed further, e.g., by hydrolysis, to give, in particular, benzaldehyde, whose presence in the mixture was indicated by its characteristic odor. It is worth mentioning that, after some time, the \(^1\)H- and \(^13\)C-NMR spectra of a solution of 9 showed a second set of signals, which perhaps belong to the second stereoisomer of this hydrazone (the ESI-MS of this mixture was identical with the previous one).

In the course of the analogous reaction of 1a with xanthenethione (4c), TLC control showed the weakening of the spots of the reagents and an increase of the intensity of the spot of a new product. But, all attempts to separate the mixture after the complete conversion of the starting compounds by CC on SiO\(_2\) failed, and only small amounts of 4c and its hydrolysis product, i.e., xanthone, were isolated. This may be the result of the instability of the corresponding 1,3-thiazolidine(s).

Under the same reaction conditions, the sterically crowded C=S bond of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (4d; formula not shown) was inert. The generated azomethine ylide underwent the known intramolecular 1,5-electrocyclization [11b][21], instead of the 1,3-dipolar cycloaddition, and after long stirring of a mixture of 1a and 4d in benzene and chromatographic workup, 1,3-oxazole 3 was obtained in low yield because of its low stability on silica. In addition, phthalimide was isolated.

Furthermore, the reactions of thioketones 4a–4d with aziridine 1b were carried out for 6–7 h in boiling CH\(_2\)Cl\(_2\) under Ar. Formation of cycloadducts was observed only in the cases of 4a and 4c. Both reactions gave a pair of diastereoisomeric 1,3-thiazolidines 10a/10b and 11a/11b, respectively (Scheme 7). We could separate the mixture 10a/10b and obtained both isomers in pure form (31 and 23\%), but from the mixture of 11a and 11b, which, according to the \(^1\)H-NMR spectrum of the reaction mixture, were present in a ca. 3:1 ratio, only 11a could be isolated in pure form.

The structures of 10a and 11a were established unequivocally by X-ray crystal-structure determinations (Figs. 3 and 4). In both cases, the molecule is trans-configured. In the case of 10a, the ester group at C(2) is disordered, and the two conformers differ by a ca. 180° rotation about the C(2)–C(6) bond.
It is remarkable that, in both cases, the main product is the ‘anomalous’ one with the same configuration of the substituents as in the starting aziridine 1b. It should be mentioned that the reaction of 1b with DMAD was reported to lead to the mixture of two diastereoisomers too, but in a ratio of ca. 1:1 [11d].

2.3. Reaction of Aziridine 1a with Dimethyl Azodicarboxylate (5). The reaction was carried out in benzene at room temperature for two weeks, and the products were

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Fig. 3. ORTEP Plot [20] of the molecular structure of one of the conformers of 10a (arbitrary numbering of atoms; 50% probability ellipsoids)
separated by column chromatography on SiO₂. In addition to phthalimide (41%), the expected trimethyl 3-cyano-5-phenyl-4-phthalimido-1,2,4-triazolidine-1,2,3-tricarboxylate (12; 12%) and 9 (4%) were isolated (Scheme 8). The identity of 9 with the product obtained from the reaction of 1a and 4b was established by the comparison of the 1H- and 13C-NMR spectra. The configuration of 12 was not determined, but, in analogy to products 2a and 6 of the other reactions with 1a, we propose the trans configuration for 12 too.

2.4. Mechanism of the Reactions. Because of the low thermal stability of the starting aziridines 1a and 1b, generally low yields of cycloadducts, and an appreciable sensitivity of the processes under consideration to steric factors, the mechanisms can be discussed only with great care.

First, it was established that the reactions of the trisubstituted aziridine 1a with DMAD, thioketones 4a and 4b, and dimethyl azodicarboxylate (5) occur in a
stereoselective way, affording only one of two possible diastereoisomers. Moreover, in two cases it has been shown by X-ray crystallography that the reaction proceeds with the conservation of the spatial arrangement of the aziridine substituents in the final cycloadducts 2a and 4. The same stereoselectivity, but to a far less extent, is observed for the reactions with the tetrasubstituted aziridine 1b. In addition, it can be noted that the cycloaddition of the ‘asymmetric’ aziridine 1a onto the C=S bond of thioketones occurs regioselectively, i.e., the S-atom is connected with the less substituted aziridine C-atom.

These observations can be explained in different ways. Provided that the opening of aziridines 1 to the corresponding azomethine ylides and the subsequent cycloaddition are concerted, the rate of the generation of the ylides must be significantly higher than the rate of their cycloaddition. In this case, the initially generated W-type (trans,trans) dipoles (or the less probable U-type (cis,cis) dipoles) have enough time to isomerize completely (or partially, if the cycloaddition rates for the stereoisomers are different) into the more stable S-type (trans,cis) dipoles, which are usually more active in the subsequent cycloadditions [3]. This mechanism is supported by the observation that the pure trans-aziridine 1b in solution, in the absence of a dipolarophile, is slowly transformed to a mixture of cis- and trans-stereoisomers already at room temperature, which can be explained as the result of the stereoisomerization of the intermediate ylide [11d].

On the other hand, one can assume that the cycloaddition of the tri- and tetrasubstituted azomethine ylides onto dipolarophiles is not concerted, but proceeds as a stepwise nucleophilic addition. In this case, the stereoselectivity of the whole transformation could be determined by the relative stability of the products, which is in agreement with our results too.

In principle, it is necessary to take into account a third possibility, namely that the S-atom of the C=S bond plays the role of an active nucleophilic centre. A priori, one cannot exclude that the reaction of thioketones with 1a and 1b could start with the attack of the S-atom onto one of the C-atoms of the electron-poor aziridine ring, leading to the opening of the three-membered ring and subsequent ring closure of the five-membered chain. Again, the stereoselectivity of the product formation should mainly be determined by steric factors. But, in this case, the opening of the aziridine should proceed by the cleavage of a C=N bond, and the following ring closure would give 1,3-thiazolidines with the thioketone-derived substituents at C(2), in contrast to the outcome of our experiments.

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Experimental Part

1. General. All reagents and solvents were of reagent-grade and were used without further purification unless otherwise specified. Column chromatography (CC): flash chromatography, Merck silica gel 60 (particle size 0.040–0.063 mm) packed in glass columns; for each chromatography, the eluting solvent was optimized by TLC. Anal. TLC: Macherey-Nagel POLYGRAM SIL G/UV 254 or ALUGRAM SIL G/UV 254. M.p.: Buchi B-540 apparatus; uncorrected. IR Spectra: Perkin-Elmer-1600 (FT-IR) spectrophotometer; in KBr; absorptions in cm$^{-1}$. $^1$H- (300 or 600 MHz) and $^1$H-decoupled
\(^1\)C-NMR (75.4 or 150.8 MHz) spectra: Bruker DPX-300, ARX-300 or AMX-600 instruments; in CDCl\(_3\) or (D\(_2\))benzene; \(\delta\) in ppm (TMS = 0 ppm), coupling constants \(J\) in Hz. ESI-MS: Finnigan TSQ-700 instrument. Elemental analyses were performed at the Institute of Organic Chemistry, University of Zurich.

_Bis(4-methoxyphenyl)methanethione (4a) [22], adamantane-2-thione (4b) [23], 9H-xanthen-9-thione (4c) [24], and 2,2,4,4-tetramethyl-1-thioxocyclobutanone (4d) [25]_ were prepared by thionation of the corresponding ketones according to literature procedures. _Dimethyl acetylenedicarboxylate (DMAD) and dimethyl azodicarboxylate (5)_ were commercially available (Fluka).

2. Preparation of 1-Phthalimidoaziridines 1a and 1b. 2.1. Methyl (E)-2-Cyano-3-phenylprop-2-enoate was prepared from PhCHO and NCCH\(_2\)COOMe on basic Al\(_2\)O\(_3\) according to [11b]. 2.2. Dimethyl trans-2-Cyano-3-phenyl-1-phthalimidoaziridine-2-carboxylate (1a). N-Aminophthalimide (486 mg, 3 mmol) and Ph(OAc)\(_2\) (1.33 g, 3 mmol) were added portionwise (10–15 mg) within 40 min to a stirred suspension of dry K\(_2\)CO\(_3\) (1.3 g, 9.4 mmol) in a soln. of methyl (E)-2-cyano-3-phenylprop-2-enoate (561 mg, 3 mmol) in dry CH\(_2\)Cl\(_2\) (40 ml) at 0 °C. After the completion of the addition, the stirring was continued for 30 min. The mixture was filtered through a short plug of SiO\(_2\), which was washed with CH\(_2\)Cl\(_2\) (50 ml). The solvent was evaporated in vacuo. The oily residue was mixed with Et\(_2\)O (5 ml) and left overnight at −4 °C. White crystals of 1a were separated by filtration. Yield: 720 mg (69%). M.p. 165–166° ([17]: 165°).

2.3. Dimethyl trans-2,3-Dicyano-1-phthalimidoaziridine-2,3-dicarboxylate (1b). As described in 2.2, N-aminophthalimide (486 mg, 3 mmol), Ph(OAc)\(_2\) (1.33 g, 3 mmol), K\(_2\)CO\(_3\) (1.3 g, 9.4 mmol), and dimethyl (2E)-2,3-dicyanobut-2-enedioate [27] (582 mg, 3 mmol) gave 365 mg (34%) of 1b. M.p. 114–116° ([15]: 130°). \(\text{H-NMR (CDCl}_3\): 3.18 (s, 2 MeO); 6.55–6.65 (m, 2 H, Ph); 7.00–7.10 (m, 4 H, Ph). \(\text{H-NMR (CDCl}_3\): 4.02, 4.10 (2s, 2 MeO); 7.80–8.00 (m, 4 H, Ph).}

3. Reactions of 1a with Dipolarophiles. 3.1. Reaction with DMAD. Trimethyl trans-2-Cyano-2,5-dihydro-5-phenyl-1-phthalimidino-1H-pyrole-2,3,4-tricarboxylate (2a) was obtained from 1a and DMAD according to [11b] (1/3 scale) in dry benzene under Ar within 7 d at r.t. The solvent was evaporated in vacuo, and the residue was separated by CC (hexane/AcOEt, gradient). Yield: 60%. M.p. 202–203° ([11b]: 208°).

3.2. Reactions with Thioketones. General Procedure. A soln. of 1a (347 mg, 1 mmol) and the thioketone (1 mmol) in dry benzene (10 ml) was stirred at r.t. under Ar, until 1a disappeared in the mixture (TLC control). The solvent was evaporated in vacuo, the residue was treated with hexane/AcOEt 1:1 (10 ml), and the precipitated phthalimide was filtered off. The filtrate was evaporated in vacuo, and the residue was separated by CC on SiO\(_2\) (45 g) with hexane/AcOEt (gradient elution).

3.2.1. Reaction of 1a with 4a. Methyl trans-4-Cyano-5,5-bis(4-methoxyphenyl)-2-phenyl-3-phthalimido-1,3-thiazolidine-4-carboxylate (6). After 6 d at r.t., the mixture of 1a and 4a was diluted with AcOEt (40 ml) and filtered through a short plug of SiO\(_2\), which was washed with AcOEt (50 ml). The solvent was evaporated in vacuo, and the residue was diluted with Et\(_2\)O (3 ml). The precipitate formed was filtered and dried. Yield: 513 mg (85%) of 6. M.p. 149–150° (dec.). IR (KBr): 3067, 3036, 3002 (C\(_\text{arom}\), H); 2953, 2935, 2836 (OC–H); 1793, 1758 (NC–O); 1737 (OC=O); 1607, 1580, 1509, 1457, 1550, 1297, 1254, 1206, 1186. \(\text{H-NMR (CDCl}_3\): 3.28 (s, 2 MeO); 3.38 (s, MeO); 6.59–6.69 (m, 2 H – C(c), Ph); 6.70–7.06 (AA' of AA' BB', \(J = 8.7, 9.3, 4\) arom. H\(_\text{ar}\)); 6.79 (t, \(J = 7.5, 1\) H\(_\text{ar}\), Ph); 6.91 (t, \(J = 7.5, 2\) H\(_\text{ar}\), Ph); 7.10–7.20 (m, 2 H – C(b), Ph); 7.21 (s, H – C(5)); 7.77 (d, \(J = 7.2, 2\) H\(_\text{ar}\), Ph); 7.93, 8.48 (BB' of
3.2.3. Reaction of 1a with Adamantane-2-thione (4b). Reaction time 16 d. The separation of the mixture provided 100 mg (60%) of 4b. 110 mg of a mixture (molar ratio 2:1) of phthalimide (calculated: 65 mg, 44%) and methyl 2-cyano-2-(phthaloylhydrazono)acetate (9; calc.: 45 mg, 18%), 85 mg (23%) of methyl trans-4-cyano-2-phenyl-3-phthalimidospiro[1,3-thiazolidine-5,2-tricyclo[3.3.1.13,7]decane]-4-carboxylate (8), and 40 mg (8%) of methyl trans-4-cyano-2-phenyl-3-phthalimidospiro[1,3-thiazolidine-5,2-tricyclo[3.3.1.13,7]decane]-4-carboxylate (7).

Data of 7. M.p. 201–202°. IR (KBr): 3063, 3030, 3010 (v(C-H)), 2914, 2861 (C-H), 1795 (OC=O), 1738 (OC=O), 1608, 1456, 1353, 1211. 1H-NMR (CDCl3): 1.65–2.35 (m, 11 H, Ad); 2.69 (d, J = 12.3, 1 H, Ad); 3.06 (s, 1 H, Ad); 3.39 (d, J = 12.3, 2 H, Ad); 4.00 (s, MeO); 6.38 (s, H-C(2)); 7.10–7.40 (m, 2 H, C(1)); 7.40–7.60 (m, 2 H); 7.60–7.90 (m, 4 H, Ph); 10.78 (1H). 13C-NMR (CDCl3): 26.04, 26.61, 34.31, 34.63, 36.19, 36.76, 37.07, 37.38 (2C); 53.87 (MeO); 65.60, 67.39, 75.32 (C(2), C(4), C(5)); 116.55 (CN); 123.51, 124.24 (2 C(b), Ph); 128.48, 129.47 (5 arom. C); 129.20, 129.29 (2 C(a), Ph); 134.62, 134.84 (2 C(c), Ph); 135.98 (C(o)); 164.56, 167.66, 167.52 (3 CO). ESI-MS: m/z 312 (100, [M + Na]+). Anal. calc. for C19H15N2O2S (512.62): C 67.82, H 5.30, N 8.18, S 6.24; found: C 67.12, H 5.17, N 7.91, S 6.13.

Data of 8. M.p. 142–143°. IR (KBr): 3310 (v(NH)), 3064, 3030, 2986 (C-H), 2855 (C-H), 1665, 1494, 1475, 1457, 1441, 1262. 1H-NMR (CDCl3): 1.45–2.40 (m, 13 H, Ad); 2.68 (s, 1 H, Ad); 3.70 (br. s, NH); 3.91 (s, MeO); 5.67 (s, H-C(2)); 7.30–7.45 (m, 2 H, C(1)); 7.45–7.55 (m, 2 H, Ph). 13C-NMR (CDCl3): 25.90, 26.58, 33.58, 34.39, 36.41, 37.42, 38.10, 39.43, 41.08 (Ad); 54.40 (MeO); 66.85, 75.05, 75.59 (C(2), C(4), C(5)); 115.52 (CN); 127.71, 128.94 (C(2), C(o)); 129.14 (C(4), C(5)); 153.77 (C(6), C(8)); 167.13 (CO). ESI-MS: m/z 391 (100, [M + Na]+). 346 (5), 225 (42).

Data of 9 (mixture with phthalimide). 1H-NMR (CDCl3): 4.07 (s, MeO): 7.85–8.10 (m, 4 H, Ph). 3.2.3. Reaction of 1a with 9H-Xanthene-9-thione (4c). The reaction was followed by TLC. After 7 d, starting material 1a (R, 0.3, hexane/AcOEt 2:1 (v/v)) had almost disappeared, and a new product with Rf 0.35 has formed. After CC on SiO2, only 4c (135 mg, 64%) and traces of xanthone were obtained. 3.2.4. Reaction of 1a with 2,2,4,4-Tetramethyl-3-thioxocyclobutanone (4d). After 7 d, CC on SiO2 gave starting material 4d (64 mg, 41%), phthalimide (75 mg, 51%), and 5-methoxy-2-phenyl-1,3-oxazole-4-carbonitrile (3). Yield: 45 mg (23%). M.p. 106–107° (116°). 1H-NMR (CDCl3): 3.40 (s, MeO); 7.40–7.55 (m, 3 arom. H); 7.60–7.90 (m, 2 arom. H). 13C-NMR (CDCl3): 60.03 (MeO): 88.86 (C(4)); 112.89 (CN); 125.66 (C(o)); 125.66, 128.95 (C(2), C(5)); 131.05 (C(1)); 152.26 (C(2), C(5)); 164.49 (C(3)).

3.3. Reaction of 1a with 5. Reaction time 2 weeks. After CC, phthalimide (60 mg, 41%), trimethyl-3-cyano-5-phenyl-4-phthalimido-1,2,4-triazolidine-1,2,3-tricarboxylate (12; 60 mg, 12%), and 9 (10 mg, 4%) were isolated.

Methyl 2-Cyano-2-(phthaloylhydrazono)acetate (9). M.p. 201–202°. IR (KBr): 3087 (C=O), 2963 (OC=O), 1795, 1765 (NC=O), 1714 (OC=O), 1600, 1570, 1466, 1441, 1363, 1344, 1251. 1H-NMR (CDCl3): 4.07 (s, MeO); 7.85–8.10 (m, 4 H, Ph). 13C-NMR (CDCl3): 54.82 (MeO); 109.78 (CN); 125.46 (2 C(b), Ph); 130.33 (2 C(a), Ph); 133.56 (2 C(c), Ph); 136.11 (C=N); 158.70 (COO); 161.25 (CON). ESI-MS: m/z 312 (100, [M + Na + MeOH]+). 285 (19).

Data of 12. M.p. 209–210°. IR (KBr): 3066, 3009 (C=O), 2985, 2958 (C–H), 1799 (NC=O), 1750 (OC=O), 1610, 1443, 1371, 1332, 1284, 1213. 1H-NMR (CDCl3, 600 MHz): 3.79, 3.90, 3.94 (3s, 3 MeO); 6.55 (s, H-C(5)); 7.30–7.40 (m, 2 H, C(1)); 7.69–7.75 (m, 2 H); 7.75–7.88 (m, 4 H, Ph). 13C-NMR (CDCl3, 150.8 MHz): 54.54, 54.58, 55.09 (3 MeO); 65.97 (C(3)); 80.13 (br. s, C(5)); 111.33 (br. s, CN); 124.32 (2 C(b), Ph); 127.72, 128.81 (2 C, C(2)); 129.04 (C(4), Ph); 129.86 (2 C(a), Ph); 133.78 (br. s, C(o)); 135.17 (2 C(c), Ph); 161.20 (COO); 165.07 (br. s, CON). ESI-MS: m/z 548 (7, [M + Na + MeOH]+), 552 (17, [M + K]+), 516 (100, [M + Na]+). 432 (10), 259 (14).
4. Reactions of 1b with Thioketones. General Procedure. A soln. of 1b (354 mg, 1 mmol) and the thioketone (1 mmol) in dry CH₂Cl₂ (5 ml) was heated under reflux with stirring under Ar, until 1b disappeared (TLC control). The solvent was evaporated in vacuo, and the residue was separated by CC on SiO₂ (45 g) with hexane/AcOEt (gradient elution).

4.1. Reaction of 1b with 4a. After 6 h under reflux, the mixture was left overnight at r.t. After CC on SiO₂, 4a (80 mg, 31%) and 1b (30 mg, 9%) were isolated as well as dimethyl trans-2,4-dicyano-5,5-bis(4-methoxyphenyl)-3-phthalimido-1,3-thiazolidine-2,4-dicarboxylate (10a; 187 mg, 31%) and dimethyl cis-2,4-dicyano-5,5-bis(4-methoxyphenyl)-3-phthalimido-1,3-thiazolidine-2,4-dicarboxylate (10b; 143 mg, 23%). Taking into account the recovered 4a, the total yield of the two adducts is 78%.

**Data of 10a.** M.p. 222–223° (dec). IR (KBr): 3079, 3008 (C=C−H); 1980, 1775 (NC=C=O); 1750 (OC=O); 1607, 1511, 1466, 1434, 1351, 1299, 1258, 1218, 1188; 1H-NMR (CDCl₃): 3.20, 3.22, 3.23, 3.63 (4s, 4 MeO); 6.60, 6.90 (AA' of AA'BB', J = 9.0, 9.3, 4 H); 6.71, 6.77 (2t, J = 7.2, 2 H − C(c), PiN); 7.15 (1 H − C(b), PiN); 7.36 (d, J = 6.6, 1 H − C(b), PiN); 7.55, 8.13 (BB' of AA'BB', J = 9.0, 9.3, 4 H); 131.30, 131.58, 131.73 (C(2'), C(5')); 115.38 (CN); 123.62, 123.73 (2 C(C), 2 PiN); 129.25, 129.37 (2 C(4), C(8)); 130.95, 131.08 (4 C(C); 134.87, 134.93 (2 C(C), PiN); 135.20 (br., 2 C(C)); 135.70, 163.50, 163.85, 165.01, 165.40 (2 COO, 2 CON). ESI-MS: 667 [M + Na + MeOH]+, 635 (100, [M + Na]+), 377 (26), 258 (7). Anal. calc. for C₂₃H₁₄N₄O₈S (612.61): C 60.78, H 3.95, N 9.15, S 5.23; found: C 60.71, H 4.06, N 8.94, S 5.17.

Suitable crystals for the X-ray crystal-structure determination were obtained by CH₃Cl/hexane/benzene by slow evaporation of the solvent.

**Data of 10b.** M.p. 208–209° (dec). IR (KBr): 3070, 3038, 3000 (C=C−H); 1980, 1979 (OC=O); 1607, 1580, 1511, 1467, 1434, 1359, 1309, 1259, 1217, 1187; 1H-NMR (CDCl₃): 3.20, 3.21, 3.23, 3.25 (4s, 4 MeO); 6.54, 7.01 (AA' of AA'BB', J = 9.0, 9.3, H); 6.70–6.85 (m, 2 H − C(c), PiN); 7.25–7.40 (m, 2 H − C(b), PiN); 7.53, 8.30 (BB' of AA'BB', J = 9.0, 4 H); 131.30, 131.58, 131.73 (C(2'), C(5')); 115.38 (CN); 124.03, 124.34 (2 C(C), PiN); 128.84, 128.90, 129.12, 137.44 (2 C(C), 2 PiN, 2 C(2)); 130.95, 131.08 (4 C(C); 134.87, 134.93 (2 C(C), PiN); 135.20 (br., 2 C(C)); 135.70, 163.50, 163.85, 165.01, 165.40 (2 COO, 2 CON). ESI-MS: 635 (100, [M + Na]+), 377 (29), 258 (7). Anal. calc. for C₂₃H₁₄N₄O₈S (612.61): C 60.78, H 3.95, N 9.15, S 5.23; found: C 60.69, H 4.11, N 8.91, S 5.32.

4.2. Reaction of 1b with 4c. After 7 h under reflux, the mixture was left at r.t. overnight. After CC on SiO₂, 4c (95 mg, 45%), dimethyl trans-2,4-dicyano-3-phthalimidospiro[1,3-thiazolidine-5,9-xanthene]-2,4-dicarboxylate (11a; 50 mg, 9%), and a mixture (ca. 2:1) of 11a and dimethyl cis-2,4-dicyano-3-phthalimidospiro[1,3-thiazolidine-5,9-xanthene]-2,4-dicarboxylate (11b; 180 mg, 32%) were isolated. Taking into account the recovered 4c, the total yield of the two adducts is ca. 75%.

**Data of 11a.** M.p. 195–196° (dec). IR (KBr): 3038, 3072 (C=C−H); 1954, 2927, 2847 (C−H); 1803, 1772 (NC=C=O); 1749 (OC=O), 1748, 1475, 1445, 1361, 1315, 1286, 1246, 1220; 1H-NMR (CDCl₃): 3.41, 4.10 (2x, 2 MeO); 7.10–7.26 (m, H − C(4')); 7.36–7.53 (m, H − C(2',3',6,7')); 7.70–8.00 (m, H − (1,8'); 2 H − C(c), PiN); 8.55–8.35 (m, 1 H − C(b), PiN); 8.60 (d, J = 7.8, 1 H − C(b), PiN); 131.30, 131.58, 131.73 (C(2'), C(5')); 115.38 (CN); 124.03, 124.34 (2 C(C), PiN); 128.84, 128.90, 129.12, 137.44 (2 C(C), 2 PiN, 2 C(2)); 130.95, 131.08 (4 C(C); 134.87, 134.93 (2 C(C), PiN); 135.20 (br., 2 C(C), PiN); 150.80, 152.87 (C(4a'), C(10a')); 161.04, 163.61 (2 COO). The signals of the phthalimido CO(N) and C(a) atoms could not be detected because of a strong broadening. ESI-MS: 589 (100, [M + Na]+), 546(b), 539(b), 377(b), 258(b), 213(b).

Suitable crystals for the X-ray crystal-structure determination were obtained from CH₂Cl₂/hexane by slow evaporation of the solvent.

**Data of 11b.** (in a mixture with 11a.) 1H-NMR (CDCl₃): 3.40, 3.97 (2x, 2 MeO); 7.15–7.32, 7.40–7.56 (2m, H − C(2−7')); 7.70–7.95 (m, H − C(1,8'); 2 H − C(c), PiN); 8.25, 8.53 (2d, J = 9.6, 9.3, 2 H − C(b), PiN); 131.30, 131.58, 131.73, 132.50 (C(2'), C(3'), C(6'), C(7')); 135.21 (2 C(C), PiN); 152.10, 152.48 (C(4a'), C(10a')); 162.46, 162.75 (2 COO). The signals of the phthalimido CO(N) and C(a) atoms could not be detected because of a strong broadening. Probably, some signals overlapped with the signals of the main stereoisomer.
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$^a$ $w^{-1} = a^2(F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2F_c^2)/3.$

5. X-Ray Crystal-Structure Determination of 2a, 6, 10a, and 11a (Table and Figs. 1–4).

All measurements were performed on a Nonius KappaCCD diffractometer [28] using graphite-monochromated MoKα radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given in the Table, and views of the molecules are shown in Figs. 1–4. Data reduction was performed with HKL Denzo and Scalepack [29]. The intensities were corrected for Lorentz and polarization effects, and, in the cases of 6, 10a, and 11a, an absorption correction based on the multi-scan method [30] was applied. Equivalent reflections were merged. The structures were solved by direct methods using SIR92 [31], which revealed the positions of all non-H-atoms. In the case of 10a, the asymmetric unit contains one molecule of 10a plus one molecule of CH₂Cl₂.

The CH₂Cl₂ molecule is disordered. Two sets of overlapping positions were defined for the atoms of CH₂Cl₂, and the site occupation factor of the major position refined to 0.509(8). One of the ester groups of 10a is disordered through a ca. 180° rotation of the parent C–C bond. This manifests itself in two positions being detected for the terminal Me group. These two positions were included in the model, and the site occupation factor of the major position refined to 0.510(6). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered atoms. Neighboring atoms within and between each conformation of the disordered CH₂Cl₂ molecule were restrained to have similar atomic displacement parameters. The non-H-atoms were refined anisotropically. All of the H-atoms in all of the structures were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 Ueq of its parent C-atom (1.5 Ueq for Me groups). The refinement of each structure was carried out on F² using full-matrix least-squares procedures, which minimized the function Σw(Fo² – Fc²)². Corrections for secondary extinction were applied in the cases of 6, 10a, and 11a, five, two, three, and three reflections, resp., whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from [32a], and the scattering factors for H-atoms were taken from [33]. Anomalous dispersion effects were those of [32c]. All calculations were performed using the SHELXL97 [35] program.

REFERENCES


CCDC-757763–757766 contain the supplementary crystallographic data for this work. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.