CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200902528

Ring-Opening/Ring-Closing Protocols from Nitrothiophenes: Six-Membered versus Unusual Eight-Membered Sulfur Heterocycles through Michael-Type Addition on Nitrobutadienes

Lara Bianchi,[a] Gianluca Giorgi,[b] Massimo Maccagno,[a] Giovanni Petrillo,[a] Fernando Sancassan,[a] Elda Severi,[a] Domenico Spinelli,[c] Marco Stenta,[c] and Cinzia Tavani*[a]

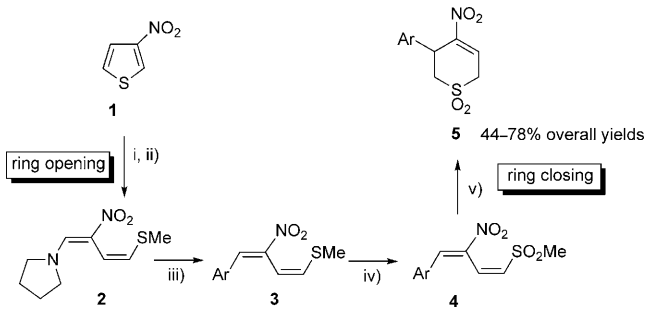
Dedicated to the Centenary of the Italian Chemical Society

Abstract: When Ar is a low-aromaticity homo- or heterosystem, the sulfonyl-stabilized anion of nitrobutadienes **4** (which derive from the initial ring opening of 3-nitrothiophene) undergoes a rather surprising addition onto the aromatic ring itself, thereby leading to the construction of an unusual eight-membered sulfur heterocycle condensed with the original Ar ring. The competitiveness of such a pathway with respect to the formation of the thiopyran ring (i.e., addition onto the nitrovinyl moiety) is favored at low temperatures, thus revealing its nature as a kinetically controlled process.

Keywords: fused-ring systems · medium-ring compounds · nitrothiophenes · ring expansion · sulfur heterocycles

Introduction

In the context of a long-running project on the synthetic exploitability of highly functionalized butadiene building blocks from nitrothiophenes,[1] we have recently shown that the initial ring opening of 3-nitrothiophene (**1**) with pyrrolidine/$AgNO_3$ in EtOH followed by MeI quenching can lead, after proper modifications of the functionalities of the resulting nitroenamine **2** (Scheme 1), to the thiopyran *S*,*S*-dioxides **5** in generally good yields.[2] The pivotal step of the overall ring-opening/ring-closing procedure is represented by an intramolecular Michael-type addition of a sulfonyl-stabilized carbanion onto the nitrovinyl moiety, followed by regioselective protonation of the resulting delocalized cyclic carbanion.[2]



Scheme 1. i) Pyrrolidine (2 mol equiv)/$AgNO_3$ (2 mol equiv), absolute EtOH, RT, overnight; ii) excess MeI, 0 °C to RT, 2 h; iii) ArMgBr (1.1 mol equiv), THF, −78 °C, 15–45 min, followed by acidic quenching; iv) *meta*-chloroperbenzoic acid (MCPBA; 2 mol equiv), CH_2Cl_2, RT; v) lithium hexamethyl disilazide (LHMDS; 1.1 mol equiv), THF, 0 °C, 4 h, followed by NH_4Cl quenching. Ar = Ph; *o*-, *m*-, *p*-MeC_6H_4; *p*-$MeOC_6H_4$; *p*-ClC_6H_4.

It is noteworthy that compounds **5** also promise significant pharmacological activity on the grounds of a concomitant presence of well-known pharmacophores such as a sulfur heterocycle, a sulfonyl, and a nitro group:[3] surely relevant are, in this respect, recently published results on the L-type calcium-entry blocker activity[4] or on the multidrug resistance (MDR) inhibition[5] of diltiazem analogues, as well as

[a] Dr. L. Bianchi, Dr. M. Maccagno, Prof. G. Petrillo, Prof. F. Sancassan, Dr. E. Severi, Dr. C. Tavani
Dipartimento di Chimica e Chimica Industriale
Genova University, Via Dodecaneso 31, 16146 Genova (Italy)
Fax: (+39) 010-353-6118
E-mail: tavani@chimica.unige.it

[b] Prof. G. Giorgi
Dipartimento di Chimica, Siena University
Via A. Moro, 53100 Siena (Italy)

[c] Prof. D. Spinelli, Dr. M. Stenta
Dipartimento di Chimica "G. Ciamician"
Bologna University, Via Selmi 2, 40126 Bologna (Italy)

even more recent ones[6] on the activity of multisubstituted thiochromans obtained from 3-nitrobenzo[*b*]thiophene by means of a protocol similar to that described herein.

The observations above have driven us to expand the applicability range of the system of Scheme 1 by, for example, pursuing the synthesis of heteroaryl derivatives of **5**. At any rate, in the course of this study, we have rather surprisingly observed the occurrence of a previously unrevealed competitive process that leads to unprecedented fused-ring derivatives characterized by the presence of an eight-membered sulfur heterocycle. Herein we report our rationalization of such an outcome as well as the identification of structural/experimental factors that affect the competition.

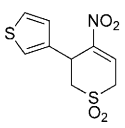
Results and Discussion

When the 3-thienyl derivative **4a** (Ar = 3-thienyl) was subjected to base-induced cyclization (Scheme 1, step v) in the experimental conditions previously reported,[2] the final reaction mixture revealed the presence of the expected thiopyran **5a** (Ar = 3-thienyl) only as a secondary product (ca. 24%: Table 1). Instead, a main product (48%) could be isolated, to which the thieno[2,3-*c*]thiocine structure **6a** could be assigned on the grounds of microanalytical and spectroscopic (MS, ^{1}H and ^{13}C NMR) evidence (see the Experimental Section). Definite structural confirmation was provided by a single-crystal X-ray determination (see the ORTEP drawing in Figure 1).

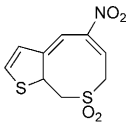
Table 1. Results from the cyclization of nitrobutadienes **4** by treatment with LHMDS in THF at 0 °C, followed by NH_4Cl quenching.

Substrate	Ar	Yield of **5** [%][a]	Yield of **6** [%][a]
4a	3-thienyl	24 (**5a**)[b]	48 (**6a**)[b]
4b	2-thienyl	22 (**5b**)	14 (**6b**), 25 (**6b′**), 16 (**6b″**)
4c	1-naphthyl	44 (**5c**)	40 (**6c**)
4d	2-naphthyl	42 (**5d**)	38 (**6d**)

[a] If not otherwise stated, yields were determined by quantitative ^{1}H NMR spectroscopic analysis on the crude final residue (1,4-bis(chloromethyl)benzene as internal standard). [b] Yield of the isolated, chromatographically pure compound.



5a



6a

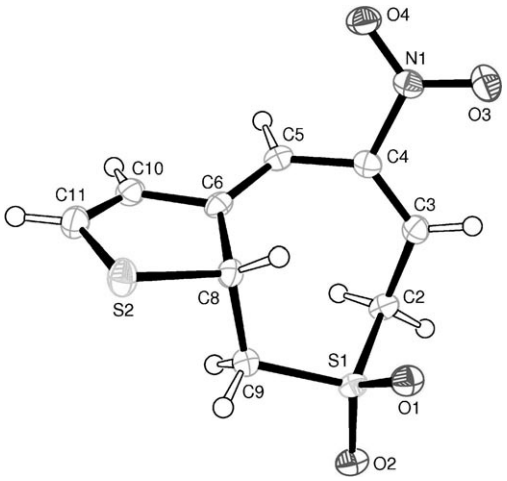
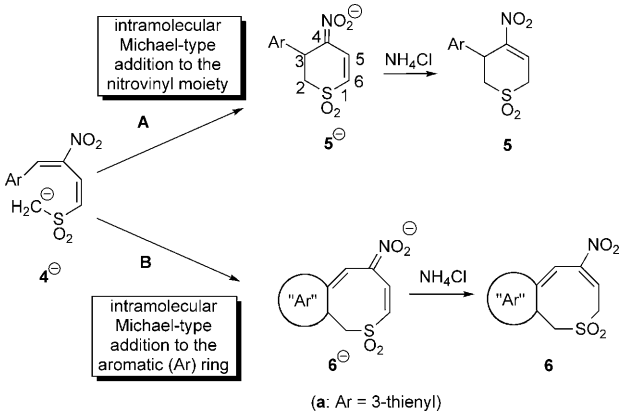


Figure 1. ORTEP drawing of the crystal structure of **6a**. Ellipsoids enclose 50% probability.

The most peculiar feature of **6a** is represented by the eight-membered sulfur heterocycle that has been built up at the expense of the aromaticity of the thiophene ring. Medium-sized heterocycles are in fact not very common in preparative organic chemistry but have recently experienced a renewed interest[7] thanks to their occurrence in natural products,[7b,c] and/or to foreseeable potentialities as biologically active moieties.[3a,7] Moreover, a special place is occupied within the field by medium-sized heterocycles fused to aryl rings.[7b,8] Accordingly, new synthetic methods have been developed that could bypass the thermodynamic obstacles to their construction. In particular, an intramolecular Heck protocol has been recently applied to dibenzothiocine *S*,*S*-dioxides,[7b] that is, to eight-membered sulfur heterocycles fused to an aryl ring that bear a close resemblance to the derivatives herein. Thus, the unexpected **4a** to **6a** ring closure described above seemed worthy of deeper exploration so as to better define its mechanistic and applicative contours.

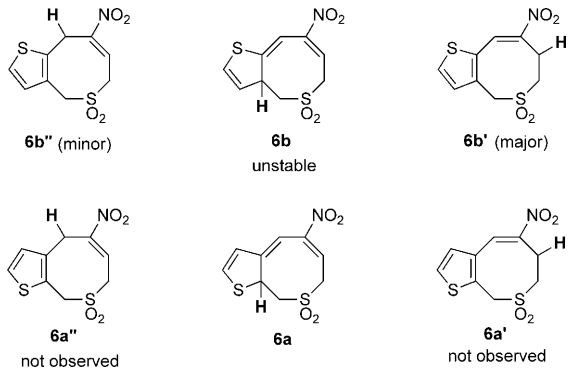
The formation of **6a** can be justified by means of a competitive intramolecular Michael-type addition of the initially formed $\mathbf{4}^-$ anion onto the aromatic system, followed by protonation of the resulting nitronate $\mathbf{6}^-$ (Scheme 2); quite reasonably, the competitiveness of this route with respect to the alternative cyclization to $\mathbf{5}^-$ is to be ascribed to the relatively low aromatic character of the thienyl (aromaticity index value (I_A) = 82)[9] with respect to the phenyl (I_A = 100)[9]



Scheme 2. Competitive formation of six- and eight-membered sulfur heterocycles by means of Michael-type intramolecular addition. "Ar" indicates a dihydroaromatic moiety.

moiety. Interestingly, protonation of the delocalized cyclic anion occurs in both cases at the carbon atom adjacent to sulfur (see the relevant discussion below).

As a first, straightforward extension of the procedure, the base-assisted cyclization has been applied to the 2-thienyl derivative **4b**. Interestingly enough, the ^{1}H NMR spectroscopic analysis of the final crude product showed the signals of thiopyran **5b** (22%) besides those of three additional isomeric products (overall yield: 55%; A/B/C = 1.00:0.64:0.56): column chromatography allowed the isolation of the two more abundant isomers, which were identified as **6b′** (25%) and **6b″** (16%). To the third isomer (14%) structure **6b** was

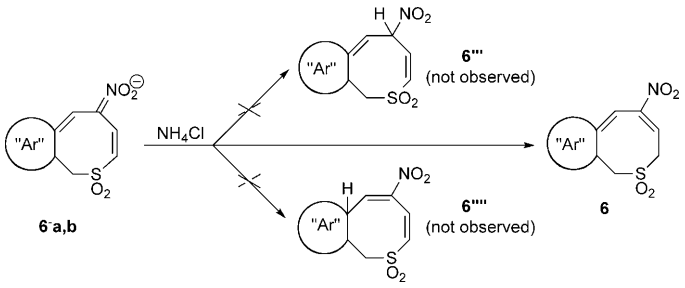


assigned on the grounds of ^{1}H NMR spectral analogies with **6a**; it could not be isolated, though, as during chromatography it underwent almost complete tautomerization to **6b′** and **6b″**: accordingly, the yields of the isolated "rearomatized" thiocines were somewhat higher than those (^{1}H NMR spectroscopy) reported in the table for the final mixture. It should be remarked in this regard that, at variance with **6b**, **6a** was found to be perfectly stable and no traces of "aromatized" products such as **6a′** or **6a″** were ever detected.

As a matter of fact, two relevant aspects, which are of undeniable interest both from a practical and a theoretical point of view, are represented by 1) the site of protonation of the nitronate (**5**$^-$ or **6**$^-$ for routes A and B of Scheme 2, respectively), which determines the π-electron distribution in the final heterocycle; and 2) the possibility of aromatization, by means of acid-catalyzed isomerization, of the initially formed heterocycle itself during quenching and/or workup.

The preferential protonation at C6 (cf. **5a**) of the thiopyran heterocycle (notwithstanding a higher Mulliken charge on C(NO_2) than on C(SO_2)) has been already discussed and justified on the grounds of a thermodynamically driven process towards a more stable product:[2] such an outcome is once more confirmed herein by the exclusive isolation of the naphthyl-substituted thiopyrans **5c** and **5d** (see below in the text and Scheme 4). On the other hand, the protonation of **6**$^-$ presents some interesting facets that ought to be considered in light of the basic observation that the aromaticity of Ar is not recovered in the initially formed product.

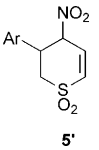
Actually, it is worth noting that **6**$^-$ can effectively delocalize its charge towards both the vinylsulfonyl moiety or the condensed "Ar" ring; accordingly, following the acidic quenching, the anion could in principle be protonated at least on three different positions, namely, at C(SO_2), at C(NO_2), or at the "bridging" C to give **6**, **6‴**, or **6⁗**, respectively (see Scheme 3).[10] Among these, only **6** is actually



Scheme 3. Possible protonation sites of **6**$^-$: C(SO_2) to give **6**, C(NO_2) to give **6‴**, or the "bridging" C to give **6⁗**.

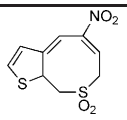
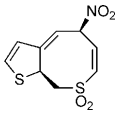
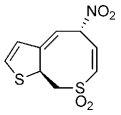
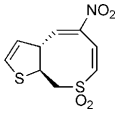
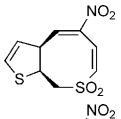
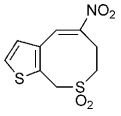
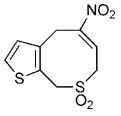
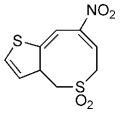
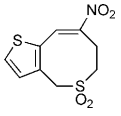
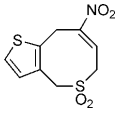
produced, in a way that parallels what has been observed[2] for the protonation of **5**$^-$, which only furnishes the more stable nitrovinyl derivative **5**—that is, protonation at C6 (see Scheme 2)—with no traces of the isomeric solfonylvinyl **5′**, that is, protonation at C4. The outcome is perfectly matched by the results of DFT calculations performed on the 3-thienyl system after geometry optimization (see the Experimental Section),[11] which assign to **6a** the lowest energy among the three conceivable products of C-protonation (Table 2, compare entry 1 with entries 2–5).

The successive point of interest is represented by the possibility of isomerization of the initially formed **6** during workup and/or purification, a possibility that has been actually experienced (see discussion above) for **6b** but not for **6a**. As a matter of fact, the rearomatization of **6b** to **6b′** (major) and **6b″** (minor) perfectly matches, in turn, the DFT calculations, which indicate **6b′** as the most stable tautomer; both **6b′** and **6b″** are much more stable than **6b** (Table 2, entries 8–10). An awkward result is provided, on the other hand, by the "3-thienyl" system, with **6a** unable to tautomerize despite a definitely lower calculated energy for both **6a′** and **6a″** (Table 2, entries 1, 6, and 7); such an outcome also contrasts somehow with the observed effective competitiveness played by the thiopyran ring formation (**5a**: ca. 24% at 0°C; see Table 1), which testifies to a definite reluctance of the thiophene ring to renounce to its aromaticity. A reason for the unexpected stability of **6a** could perhaps be found in the extended electron delocalization that encompasses the sulfur atom and three conjugated double bonds, and that might not be suitably accounted for by the DFT calculations.

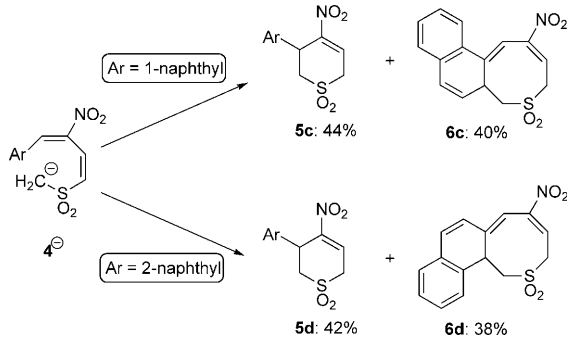


The base-assisted cyclization protocol has been extended to the two naphthyl derivatives **4c** and **4d** to better define the applicability range of the thiocine-ring formation in accordance with the aromaticity of the Ar moiety. It should be

Table 2. Optimized DFT geometries and relative energies for the thienothiocines of Scheme 3. Geometries have been optimized by the DFT/B3LYP/DZVP method, using the Gaussian 03 suite of programs, and simulating the solvent (water) by means of the SCRF-CPCM implicit method.[10]

Entry	Product	Structure	Energy [hartree]	Relative energy [kcal mol^{-1}]
1	**6a**		−1500.240852	0.00
2	*syn*-**6a‴**		−1500.230617	6.42
3	*anti*-**6a‴**		−1500.222558	11.48
4	*trans*-**6a⁗**		−1500.225660	9.53
5	*cis*-**6a⁗**		−1500.221898	11.89
6	**6a′**		−1500.269452	−15.95
7	**6a″**		−1500.261852	−13.18
8	**6b**		−1500.238816	1.28
9	**6b′**		−1500.272289	−19.30
10	**6b″**		−1500.263228	−14.04

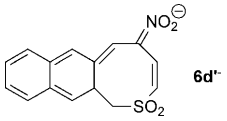
recalled that the aromaticity index for naphthalene ($I_A = 146$)[9] implies that in aromatic substitution on naphthalenes, whether electrophilic or nucleophilic, the aromaticity loss for the formation of the relevant transition states towards the addition complexes is much lower than in benzenes, a factor that must be considered the most important for the understanding of the higher reactivity of naphthalenes with respect to benzenes. The outcome for the two naphthyl derivatives, in the same experimental conditions adopted for **4a** and **4b**, is reported in Scheme 4; in both cases there is evidence of an almost perfect balance between route A and route B of Scheme 2. Interestingly enough, neither of the



Scheme 4. Results from the reaction of nitrobutadienes **4c** and **4d** with LHMDS at 0 °C, followed by acidic (NH_4Cl) quenching.

two isolable isomeric thiocines **6c** and **6d** showed any tendency to rearomatize, as experienced instead for **6b**.

It should also be pointed out that an alternative eight-membered ring closure in the case of the 2-naphthyl derivative (i.e., cyclization onto the Cβ carbon atom, eventually leading to naphtho[2,3-*c*]thiocines) would be energetically highly unfavorable as it would lead to a carbanion (**6d′**$^-$) with loss of aromaticity for both rings of the starting naphthalene moiety.



In the attempt to influence the competitiveness in favor of either heterocycle, thus making the procedure more synthetically useful, the base-induced cyclization has been performed at different temperatures and employed **4d** (Ar = 2-naphthyl) as the model substrate. The results collected in Table 3 highlight a significant enhancement of the competitiveness of route B (i.e., the thiocine derivative formation) with a decrease in temperature: at −78 °C the only resulting isolable product was **6d**, the absolute yield of which reaches a more than satisfactory value (70 %) at longer reaction times, which corresponds to a quantitative consumption of the substrate. The optimized conditions for the thiocine-ring formation ($T = -78$ °C, $t = 16$ h) were then extended to substrates **4a–c**, thereby obtaining in every instance the relevant thiocines as the sole reaction products in satisfactory overall yields (Table 3). This result allows us to

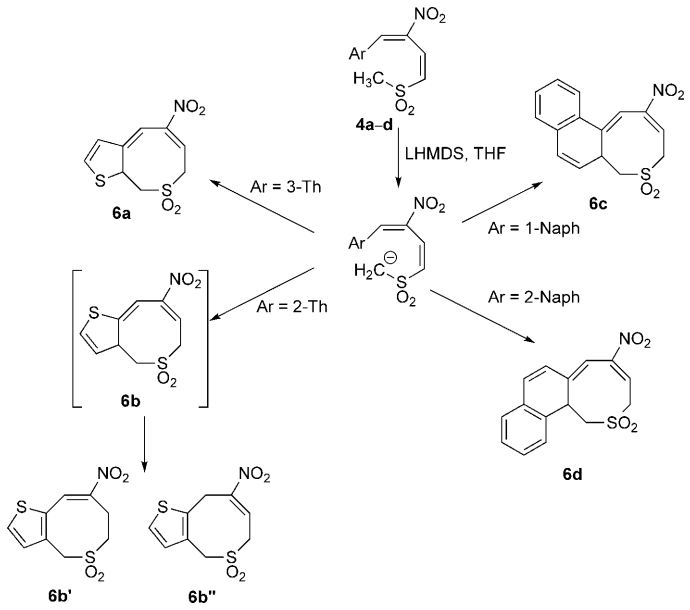
Table 3. Results of the base-induced cyclization of **4** at different temperatures.

	T [°C]	t [h]	Yield of **5** [%][a]	Yield of **6** [%]
4a	−78	16	traces	73[b]
4b	−78	16	–	≈2 (**6b**),[a] 33 (**6b′**),[b] 31 (**6b″**)[b]
4c	−78	16	–	70[b]
4d	0	4	40	40[a]
4d	−30	4	23	66[a]
4d	−60	4	10	70[a]
4d	−78	4	–	4[b]
4d	−78	16	–	70[b]

[a] Yield determined by quantitative ^{1}H NMR spectroscopic analysis on the crude final residue (1,4-bis(chloromethyl)benzene as internal standard). [b] Yield of the isolated, chromatographically pure compound.

say that the thiocine route appears to be the kinetically favored process.

A picture of the new thiocine derivatives obtained from 3-nitrothiophene as detailed herein is shown in Scheme 5.



Scheme 5. General procedure for the synthesis of new thiocine derivatives **6a–d** from 3-nitrothiophene (Th = thienyl; Naph = naphthyl).

Conclusion

The interest of the results herein is, in our opinion, multifaceted, as it encompasses both practical and theoretical aspects.

From a synthetic point of view, it must be remarked that the overall procedure from 3-nitrothiophene represents a very simple path to obtain new thiocine derivatives (Scheme 5), the possible biological activity of which is presently under investigation and will be reported in due time.

The effect of temperature on the competing cyclization pathways of Scheme 2 has once more highlighted the importance of such an experimental parameter on the occurrence of kinetically or thermodynamically controlled reaction routes. In particular, low temperatures significantly favor herein the eight-membered cyclization pathways, thereby allowing easy isolation of the thiocine derivatives in more than satisfactory yields. This is an outcome of undeniable advantage from the perspective of either the use of compounds **6** in synthesis or of their pharmacological evaluation.

From a theoretical point of view, the results obtained represent an advance in the general field of knowledge concerning the relationship between reactivity and aromaticity, thus marking the importance of the degree of aromaticity of the aryl substituent of nitrobutadienes **4** in affecting the course of the reaction. It must be stressed that when Ar is a substituted phenyl (such as those cited in Scheme 1) no significant chance is offered to the thiocine pathway, even at low temperatures, as has been independently ascertained.

The importance of the aromaticity factor shows up also in the exclusive formation of **6c** and **6d** in the case of the 1-naphthyl and of the 2-naphthyl derivatives, respectively, at −78 °C with no significant rearomatization detected. On the contrary, the thiophene ring experiences a definite driving force to rearomatize, at least (cf. the isolation of **6b′** and **6b″**) when the initially formed thiocine derivative does not present an extended delocalization (as in **6a**).

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded using a Varian GEMINI or a Mercury plus instrument at 200 or 300 MHz and 50 or 60 MHz, respectively; chemical shifts (TMS as internal reference) are reported as δ values (ppm); 1,4-bis(chloromethyl)benzene was used as internal standard in the quantitative determinations. ESIMS analyses were recorded using either an Agilent 1100 LC/MSD-SL ion trap mass spectrometer or a Micromass Z0MD Waters instrument. GC–MS was carried out using a HP-5971A instrument with an HP-1 column (12 m × 0.2 mm inside diameter, 0.33 μm film thickness), electron ionization at 70 eV, and a source temperature of about 170 °C. All analyses were performed with a constant He flow of 0.9 mL min^{-1}, and with an initial temperature of 70 °C, an initial time of 2 min, a rate 15 °C min^{-1}; final T = 280 °C, final t = 5 min, injection T = 200 °C, MS detector T = 280 °C. Retention times (t_R) are in min. HRMS analyses were recorded using a Finnigan MAT95XP apparatus. Melting points were determined using a Büchi 535 apparatus and are uncorrected.

X-ray crystallography: A single crystal of **6a** was submitted for X-ray data collection. A Bruker-Nonius FR591 rotating anode diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) was used for data collection. The structure was solved by direct methods implemented in the SHELXS-97 program.[12] The refinements were carried out by full-matrix anisotropic least-squares on F^2 for all reflections for non-hydrogen atoms by using the SHELXL-97 program.[13]

CCDC-747565 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Materials: Petroleum ether and light petroleum refer to the fractions with b.p. 40–60 °C and 80–100 °C, respectively. Silica gel 230–400 mesh was used for column chromatography. All solvents (petroleum ether, ethyl acetate, and dichloromethane) were distilled before use. Tetrahydrofuran (THF) was purified by standard methods and distilled over potassium benzophenone ketyl before use. All commercially available reagents were used as received. Compounds **4a–d** were prepared as previously reported.[14]

Base-induced cyclization of 4: In a flask, **4** (1 mmol) was dissolved under argon in THF (63 mL) at the appropriate temperature and lithium hexamethyl disilazide (LHMDS; 1 M, 1.1 mol equiv, 1.1 mL) was added by a syringe under magnetic stirring. After the reported reaction time, the mixture was poured into saturated aqueous NH_4Cl (150 mL), and extracted with dichloromethane (3 × 50 mL), with the organic extracts being then dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure. Because of instability of the reaction products on different chromatographic supports (silica gel or neutral Al_2O_3), in the case of **5b–d** and **6b** the reported yields have been determined by quantitative ^{1}H NMR spectroscopic analysis on crude final residues; all thiocines (except **6b**) could be easily isolated from the reactions carried out at −78 °C. Temperatures and reaction times are reported in Tables 1 and 3.

4-Nitro-3-(3-thienyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide (5a): Pale brown solid; m.p. 147–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.32 (dd, J = 14.8, 9.3 Hz, 1H), 3.53 (ddd, J = 14.8, 6.2, 3.2 Hz, 1H), 3.88 (dm, J = 18.3 Hz, 1H), 4.08 (dtd, J = 18.4, 3.3, 1.1 Hz, 1H), 5.08–4.96 (m, 1H), 6.96 (dd, J = 5.0, 1.4 Hz, 1H), 7.14 (ddd, J = 6.3, 3.3, 1.7 Hz, 1H), 7.18 (dd, J = 2.8, 1.3 Hz, 1H), 7.34 ppm (dd, J = 5.0, 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 37.93, 48.65, 53.27, 123.16, 124.32, 125.94, 127.56, 136.14, 151.56 ppm; HRMS: m/z: calcd for $C_9H_9NO_4S_2$: 258.9973; found: 258.9969.

5-Nitro-9,9a-dihydro-7*H*-1,8-dithiacyclopentacyclooctene 8,8-dioxide (6a): Yellow solid, m.p. 157–158 °C (dichloromethane/light petroleum); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.07 (app. dq, J = 15.2 Hz, 1H), 3.56 (dd, J = 15.2, 11.6 Hz, 1H), 4.00 (dd, J = 8.9, 1.7 Hz, 2H), 4.76 (app. dt, J = 11.6 Hz, 1H), 6.13 (d, J = 5.9 Hz, 1H), 6.35 (s, 1H), 6.98 (d, J = 5.9 Hz, 1H), 7.37 ppm (t, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 43.93, 53.86, 55.22, 113.10, 122.27, 124.25, 138.23, 153.01, 157.75 ppm; IR (Nujol): $\tilde{\nu}$ = 1618, 1529, 1410, 1308, 1281, 1264, 1129, 1095 cm^{-1}; ESIMS: m/z: 282 $[M+Na]^+$, 258 $[M-H]^-$; EIMS: m/z (%): 259 (6) $[M]^+$, 213 (11), 194 (14), 178 (11), 147 (100), 134 (65), 121 (18), 115 (36), 97 (15), 91 (12), 77 (14), 69 (16), 45 (20); HRMS: m/z: calcd for $C_9H_9NO_4S_2$: 258.9973; found: 258.9974.

4-Nitro-3-(2-thienyl)-3,6-dihydro-2*H*-thiopyran 1,1-dioxide (5b): The compound was obtained at 0 °C in an admixture with **6b** (77% in all) and the relative yield was estimated by ^{1}H NMR spectroscopy (22%). Only a few representative signals could be attributed. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.40 (dd, J = 14.8, 9.6 Hz, 1H), 3.62 (ddd, J = 14.8, 6.2, 3.3 Hz, 1H), 3.89 (dm, J = 18.2 Hz, 1H), 4.10 (dtd, J = 18.4, 3.3, 1.0 Hz, 1H), 5.12–5.24 (m, 1H), 7.15 ppm (ddd, J = 6.5, 3.2, 1.8 Hz, 1H).

8-Nitro-3a,6-dihydro-4*H*-1,5-dithiacyclopentacyclooctene 5,5-dioxide (6b): Compound **6b** was present in minor amounts (ca. 14% at 0 °C; <2% at −78 °C) in the final crude mixture together with **6b′** and **6b″**. It was too unstable to allow isolation by chromatography; the ^{1}H NMR spectrum was thus deduced from the spectrum of the crude. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 2.66 (dm, J = 15.2 Hz, 1H), 3.07 (dd, J = 15.2, 10.8 Hz, 1H), 3.86–4.15 (m, 2H), 4.20 (dq, J = 10.8 Hz, 1H), 5.59 (dd, J = 6.3, 3.0 Hz, 1H), 6.42 (dd, J = 6.3, 1.5 Hz, 1H), 6.52 (s, 1H), 7.36 ppm (t, J = 9.0 Hz, 1H).

8-Nitro-6,7-dihydro-4*H*-1,5-dithiacyclopentacyclooctene 5,5-dioxide (6b′): Yellow solid; m.p. 217–218 °C (dichloromethane/light petroleum); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.20–3.25 (m, 2H), 3.32–3.37 (m, 2H), 4.26 (s, 2H), 7.19 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 5.1 Hz, 1H), 8.24 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 23.78, 46.77, 52.76, 128.06, 131.07, 132.78, 133.28, 134.04, 151.23 ppm; IR (Nujol): $\tilde{\nu}$ = 1640, 1513, 1320, 1280, 1206, 1133, 1108, 1061 cm^{-1}; GC–EIMS: t_R = 12.98 min; m/z (%): 259 (10) $[M]^+$, 134 (100), 149 (84), 147 (51), 115 (48), 45 (47), 69 (28), 77 (27), 39 (25), 121 (24), 51 (24), 97 (23), 65 (22), 91 (21), 213 (18), 105 (16), 30 (10), 58 (9), 178 (6), 165 (5); ESIMS: m/z: 282 $[M+Na]^+$, 258 $[M-H]^-$; HRMS: m/z: calcd for $C_9H_9NO_4S_2$: 258.9973; found: 258.9971.

8-Nitro-6,9-dihydro-4*H*-1,5-dithiacyclopentacyclooctene 5,5-dioxide (6b″): White solid; m.p. 233–234 °C (dichloromethane/light petroleum); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.71 (d, J = 9.3 Hz, 2H), 4.37 (s, 2H), 4.45 (s, 2H), 7.08 (d, J = 5.1 Hz, 1H), 7.30–7.37 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 27.30, 51.53, 55.35, 125.21, 125.45, 128.92, 131.91, 138.20, 157.21 ppm; IR (Nujol): $\tilde{\nu}$ = 1311, 1272, 1189, 1128, 1114 cm^{-1}; GC–EIMS: t_R = 12.75 min; m/z (%): 259 (2) $[M]^+$, 111 (100), 147 (53), 53 (51), 84 (47), 45 (42), 64 (30), 97 (25), 39 (24), 115 (22), 134 (21), 69 (21), 51 (20), 77 (18), 58 (18), 55 (18), 48 (16), 121 (14), 178 (13), 103 (9), 91 (8), 30 (7), 195 (6), 157 (2); ESIMS: m/z: 282 $[M+Na]^+$, 258 $[M-H]^-$; HRMS: m/z: calcd for $C_9H_9NO_4S_2$: 258.9973; found: 258.9974.

3-(1-Naphthyl)-4-nitro-3,6-dihydro-2*H*-thiopyran 1,1-dioxide (5c): The compound was obtained from the reaction at 0 °C in an admixture with **6c** (84% in all) and the relative yield (44%) was estimated by ^{1}H NMR spectroscopy. Only a few representative signals could be attributed. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.39 (dd, J = 14.7, 9.6 Hz, 1H), 3.68 (ddd, J = 14.7, 6.3, 3.5 Hz, 1H), 3.97 (dm, J = 18.0 Hz, 1H), 4.19 (dt, J = 18.0, 3.0 Hz, 1H), 5.72 ppm (m, 1H).

11-Nitro-6a,9-dihydro-7*H*-8-thiacycloocta[*a*]naphthalene 8,8-dioxide (6c): Yellow solid; m.p. 215 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.74 (app. dt, J = 15.3, 1.2 Hz, 1H), 3.12 (dd, J = 15.3, 10.2 Hz, 1H), 3.80–4.10 (m, 3H), 5.90 (dd, J = 9.3, 5.7 Hz, 1H), 6.55 (d, J = 9.3 Hz, 1H), 6.75 (s, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.31–7.53 (m (2H; Ar) and t (J = 9.0 Hz, 1H) partially overlapped), 7.57 ppm (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 33.75, 50.63, 53.65, 116.77, 125.78, 126.50, 127.27, 127.66, 127.69, 128.94, 130.10, 131.26, 132.58, 148.87, 152.09 ppm; IR (Nujol): $\tilde{\nu}$ = 1655, 1616, 1515, 1321, 1293, 1253, 1173, 1130, 1096 cm^{-1}; GC–EIMS: t_R = 15.72 min; m/z (%): 303 (22) $[M]^+$, 178 (100), 165 (61), 192 (56), 152 (29), 96 (16), 139 (14), 115 (14), 89 (13), 76 (13), 222 (11), 128 (7), 63 (10), 70 (6), 39 (5), 30 (5), 82 (4), 51 (4); ESIMS: m/z: 326 $[M+Na]^+$, 302 $[M-H]^-$; HRMS: m/z: calcd for $C_{15}H_{13}NO_4S$: 303.0565; found: 303.0567.

3-(2-Naphthyl)-4-nitro-3,6-dihydro-2*H*-thiopyran 1,1-dioxide (5d): The compound was obtained from the reaction at 0 °C in an admixture with **6d** (80% in all) and the relative yield (42%) was estimated by ^{1}H NMR spectroscopy. Only a few representative signals could be attributed. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.39 (dd, J = 14.9, 10.2 Hz, 1H), 3.59 (ddd, J = 14.9, 6.3, 3.6 Hz, 1H), 3.92 (dm, J = 18.3 Hz, 1H), 4.18 (dt, J = 18.3, 3.0 Hz, 1H), 5.02 ppm (m, 1H).

8-Nitro-12,12a-dihydro-10*H*-11-thiacycloocta[*a*]naphthalene 11,11-dioxide (6d): Yellow solid; m.p. 170 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.81 (app. dt, J = 15.0, 1.2 Hz, 1H), 3.45 (dd, J = 15.0, 10.0 Hz, 1H), 3.86 (dd, J = 14.4, 9.0 Hz, 1H), 4.00 (ddd, J = 14.4, 8.4, 2.7 Hz, 1H), 4.41 (d, J = 10.0 Hz, 1H), 6.34 (s, 1H), 6.40 (d, J = 9.6 Hz, 1H), 6.73 (d, J = 9.6 Hz, 1H), 7.11–7.32 (m, 4H), 7.48 ppm (app. t, J = 9.0, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 37.03, 53.47, 56.81, 117.48, 125.52, 125.71, 127.51, 127.89, 128.33, 129.83, 130.79, 132.69, 135.99, 148.77, 151.58 ppm; IR (Nujol): $\tilde{\nu}$ = 1707, 1666, 1616, 1519, 1313, 1286, 1262, 1182, 1156, 1137, 1119, 1097 cm^{-1}; GC–EIMS: t_R = 15.81; m/z (%): 303 (15) $[M]^+$, 178 (100), 165 (57), 192 (35), 152 (29), 95 (22), 83 (20), 222 (19), 115 (19), 76 (19), 141 (18), 139 (16), 89 (16), 63 (16), 128 (9), 239 (7), 51 (7), 39 (7), 30 (7), 70 (5); ESIMS: m/z: 326 $[M+Na]^+$, 302 $[M-H]^-$; HRMS: m/z: calcd for $C_{15}H_{13}NO_4S$: 303.0565; found: 303.0562.

Acknowledgements

Financial support was provided by grants from the University of Genova and University of Bologna and from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, PRIN-2004031418_001 and 2005034305_001). Generous funding by Compagnia di San Paolo, Torino (Italy) for the purchase of NMR spectroscopic equipment is gratefully acknowledged. Dr. Carlo Scapolla is also gratefully acknowledged for performing ESIMS and HRMS analyses.

[1] L. Bianchi, M. Maccagno, G. Petrillo, E. Rizzato, F. Sancassan, E. Severi, D. Spinelli, C. Tavani, M. Viale in *Targets in Heterocyclic Systems: Chemistry and Properties, Vol. 11* (Eds.: O. A. Attanasi, D. Spinelli), Società Chimica Italiana, Roma, **2007**, pp. 1–20. L. Bianchi, M. Maccagno, G. Petrillo, F. Sancassan, D. Spinelli, C. Tavani in *Targets in Heterocyclic Systems: Chemistry and Properties, Vol. 10* (Eds. O. A. Attanasi, D. Spinelli), Società Chimica Italiana, Roma, **2006**, pp. 1–23. L. Bianchi, C. Dell'Erba, M. Maccagno, S. Morganti, G. Petrillo, E. Rizzato, F. Sancassan, E. Severi, D. Spinelli, C. Tavani, *Arkivoc* **2006**, *vii*, 169–185. C. Dell'Erba, M. Novi, G. Petrillo, C. Tavani in *Topics in Heterocyclic Systems: Synthesis Reactions and Properties, Vol. 1* (Eds.: O. A. Attanasi, D. Spinelli), Research Signpost, Trivandrum, **1996**, pp. 1–12.

[2] L. Bianchi, M. Maccagno, G. Petrillo, E. Rizzato, F. Sancassan, E. Severi, D. Spinelli, M. Stenta, A. Galatini, C. Tavani, *Tetrahedron* **2009**, *65*, 336–343.

[3] a) L. C. Bouchez, M. Turks, S. Reddy Dubbaka, F. Fonquerne, C. Craita, S. Laclef, P. Vogel, *Tetrahedron* **2005**, *61*, 11473–11487, and references therein; b) Several drugs showing different therapeutic approaches contain the nitrogroup: from nifedipine and nicardipine (L-type calcium channel blockers) to clonazepan, nimetazepan, and nitrazepan (anticonvulsant); from nitrofurantoin (bacteriocidal) to metronidazole and tinidazole (antiparasitic) and to tolcapone, entacapone, and dantrolene sodium (spasmolitic); and so on. Recently, some of us have observed that some nitro- and dinitronaphthylbutadienes show promising antitumor activity. See, for example: M. Viale, G. Petrillo, M. Maccagno, P. Castagnola, C. Aiello, C. Cordazzo, M. A. Mariggiò, S. A. Jadhav, L. Bianchi, G. Leto, E. Rizzato, A. Poggi, D. Spinelli, *Eur. J. Pharmacol.* **2008**, *588*, 47–51, and references therein; c) J. A. Upcroft, L. A. Dunn, J. M. Wright, K. Benakli, P. Upcroft, P. Vanelle, *Antimicrob. Agents Chemother.* **2006**, *50*, 344–347; d) M. D. Crozet. C. Botta, M. Gasquet, C. Curti, V. Rémusat, S. Hutter, O. Chapelle, N. Azas, M. De Méo, P. Vanelle, *J. Med. Chem.* **2009**, *52*, 653–659.

[4] E. Carosati, G. Cruciani, A. Chiarini, R. Budriesi, P. Ioan, R. Spisani, D. Spinelli, B. Cosimelli, F. Fusi, M. Frosini, R. Matucci, F. Gasparrini, A. Ciogli, P. J. Stephens, F. J. Devlin, *J. Med. Chem.* **2006**, *49*, 5206–5216.

[5] M. Viale, C. Cordazzo, B. Cosimelli, D. de Torero, P. Castagnola, C. Aiello, E. Severi, G. Petrillo, M. Cianfruglia, D. Spinelli, *J. Med. Chem.* **2009**, *52*, 259–266.

[6] R. Budriesi, A. Chiarini, G. Petrillo, D. Spinelli, et al., unpublished results.

[7] a) M. Lautens, E. Fillion, M. Sampat, *J. Org. Chem.* **1997**, *62*, 7080–7081; b) L. A. Arnold, W. Luo, R. K. Guy, *Org. Lett.* **2004**, *6*, 3005–3007; c) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007, and references therein; d) P. Arya, S. Couve-Bonnaire, P. Durieux, D. Laforce, R. Kumar, D. M. Leek, *J. Comb. Chem.* **2004**, *6*, 735–745; e) M. M. Krayushkin, M. A. Kalik, L. G. Vorontsova, E. Y. Zvezdina, M. G. Kurella, *Russ. Chem. Bull.* **1993**, *42*, 1204–1208.

[8] N. Dieltiens, C. V. Stevens, K. Masschelein, G. Hennebel, S. Van der Jeught, *Tetrahedron* **2008**, *64*, 4295–4303; L. G. Voskressensky, A. V. Listratova, T. N. Borisova, S. A. Kovaleva, R. S. Borisov, A. V. Varlamov, *Tetrahedron* **2008**, *64*, 10443–10452; M. K. Parai, Shagufta, A. K. Srivastava, M. Kassack, G. Panda, *Tetrahedron* **2008**, *64*, 9962–9976; E. Yu. Shinkevich, M. S. Novikov, A. F. Khlebnikov, R. R. Kostikov, J. Kopf, J. Magull, *Russ. J. Org. Chem.* **2007**, *43*, 1065–1079; H. S. Lee, S. H. Kim, S. Gowrisankar, J. N. Kim, *Tetrahedron* **2008**, *64*, 7183–7190; N. Mont, V. P. Mehta, P. Appukkuttan, T. Beryozkina, S. Toppet, K. Van Hecke, L. Van Meervelt, A. Voet, M. DeMaeyer, E. Van der Eycken, *J. Org. Chem.* **2008**, *73*, 7509–7516; K. Koriatopoulou, N. Karousis, G. Varvounis, *Tetrahedron* **2008**, *64*, 10009–10013.

[9] C. W. Bird, *Tetrahedron* **1992**, *48*, 335–340, and references therein. See also: A. T. Balaban, D. C. Oniciu, A. R. Katritzky, *Chem. Rev.* **2004**, *104*, 2777–2812.

[10] a) As a matter of fact, kinetically controlled protonation at a nitronate oxygen atom should conceivably initially occur:[10b] a thermodynamically driven tautomerization of the resulting nitronic acid to the observed **6** would anyway immediately follow; b) M. Sato, Y. Kitamura, N. Yoshimura, H. Yamataka, *J. Org. Chem.* **2009**, *74*, 1268–1274.

[11] a) DFT calculations have been carried out using the Gaussian 03 series of programs. The structures of the various minima points have been fully optimized with the gradient method. After gas-phase optimization, single-point calculations in solution were performed. The correctness of such a methodology was checked by means of a full-optimization calculation considering the solvent. In each case the solvent ($\varepsilon = 46.7$) was treated with the SCRF-CPCM method. The calculations were performed using the DFT level and the B3LYP functional available in Gaussian 03. All atoms were assigned the double-ζ DZVP basis set; b) Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**; c) R. Cammi, B. Mennucci, J. Tomasi, *J. Phys. Chem. A* **2000**, *104*, 5631–5637; d) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995–2001; e) The DZVP basis set is a local spin density (LSD)-optimized basis set of double-ζ quality in the valence shell plus polarization functions; f) N. Godbout, D. R. Salahub, J. Andzelm, E. Wimmer, *Can. J. Chem.* **1992**, *70*, 560–571; g) K. L. Schuchardt, B. T. Didier, T. Elsethagen, L. Sun, V. Gurumoorthi, J. Chase, J. Li, T. L. Windus, *J. Chem. Inf. Model.* **2007**, *47*, 1045–1052.

[12] SHELXS-97, Rel. 97-2, A program for automatic solution of crystal structures, G. M. Sheldrick, Göttingen University, Göttingen, **1997**.

[13] SHELXL-97, Rel. 97-2, A program for crystal structure refinement, G. M. Sheldrick, Göttingen University, Göttingen, **1997**.

[14] L. Bianchi, C. Dell′Erba, M. Maccagno, G. Petrillo, E. Rizzato, F. Sancassan, E. Severi, C. Tavani, *J. Org. Chem.* **2005**, *70*, 8734–8738.

Received: October 30, 2009
Published online: December 18, 2009

