Regioselective Synthesis of 2-Imino-1,3-thiazolidin-4-ones by Treatment of *N*-(Anthracen-9-yl)-*N*′-ethylthiourea with Bromoacetic Acid Derivatives

Karel D. Klika,[a] Ladislav Janovec,[b] Ján Imrich,[b] Gejza Suchár,[b] Pavol Kristian,[b] Reijo Sillanpää,[c] and Kalevi Pihlaja*[a]

Keywords: NMR spectroscopy / Regioselectivity / Structure elucidation / Sulfur heterocycles

The reaction between *N*-(anthracen-9-yl)-*N*′-ethylthiourea (**1**) and methyl bromoacetate yielded mainly 2-[(anthracen-9-yl)imino]-3-ethyl-1,3-thiazolidin-4-one (**2**), together with some of the regioisomeric 3-(anthracen-9-yl)-2-ethylimino-1,3-thiazolidin-4-one (**3**). The structures of the products were elucidated by NMR techniques and, for **3**, X-ray crystallographic analysis. Treatment of **1** with bromoacetyl bromide again yielded **2** and **3**, but with a reversed product distribution ratio, thus providing an interesting and unexpected regioselectivity, depending on the electrophile selected. The underlying cause of the observed regioselectivity is a result of different reaction pathways taken by the two electrophiles. The number of possible products, including those resulting from ring-opening/ring-closing rearrangements is large (24 in total), and a simple lettered notation is introduced to handle the set of structures conveniently.

Introduction

Thiazolidinones have been known for a long time[1,2] and have been utilised for a diverse range of applications, including materials,[1,2] synthetic intermediates,[1] analysis,[2] dyes,[2] photography[2] etc. In addition, they also possess a wide range of biological activities[1,2] and this array of properties has resulted in a considerable number of reviews.[1−3] Interestingly, accounts of the thiazolidinones are overwhelmingly dominated by 4-thiazolidinones,[2,3] and 2-imino-4-thiazolidinones in particular are highly prevalent. There are many available methods for the synthesis of 2-imino-4-thiazolidinones, but the treatment of thioureas and variously substituted α-haloalkanoic acids or their derivatives (esters, acid halides, salts, amides, anhydrides or carbamates) is well known[1,2] and has been utilised extensively since the very first reports of this approach in 1873.[4,5] The use of α-haloalkanoyl halides appears to be rather limited, and the specific use of bromoacetyl bromide was only sporadic since its first report in 1959.[6] Even as long ago as 1877[7] it was recognised that unsymmetrically substituted thioureas should potentially give rise to two regioisomeric 2-imino-4-thiazolidinones on treatment with α-haloalkanoic acids or their derivatives.

Structures incorporating the acridine moiety have shown marked mutagenic,[8] antiviral[9] and antitumour[10−13] activities, and so are of prime interest for pharmaceutical applications. In our previous studies on acridine,[14−20] the particular susceptibility of C-9 in acridine to nucleophilic attack and the subsequent ready formation of a five-membered spiro ring was highlighted. To avoid spiro ring formation in the acridine series, it is necessary, aside obviously from having suitable nucleophilic centres available, to limit the bulkiness of R groups attached to such nucleophilic atoms, the formation of new, non-spiro rings being facilitated under these conditions.[18,19] However, we wished to preclude spiro ring formation altogether, in order to obtain a much more precise idea of the relative reactivities between the various nucleophilic centres present in the substrate, and so *N*-(anthracen-9-yl)-*N*′-ethylthiourea (**1**) was selected as a substrate in which the anthracene moiety was otherwise analogous to acridine. Potentially, new substrates incorporating anthracenyl groups might also possess desirable therapeutic attributes such as anticancer or antipsoriatic properties, and might in their own right represent an extension of our studies on biologically interesting acridines.

It thus seemed natural to combine these two entities, anthracenyl and thiazolidinone, together to produce potentially powerful biologically active compounds. If unsymmetrical thioureas were utilised, though, there would be a

[a] Structural Chemistry Group, Department of Chemistry, University of Turku,
Vatselankatu 2, 20014 Turku, Finland
Fax: (internat.) + 358-2/333-6750
E-mail: kpihlaja@utu.fi
[b] Department of Organic Chemistry, P. J. Šafárik University, 04167 Košice, Slovak Republic
[c] Department of Chemistry, University of Jyväskylä, 40500 Jyväskylä, Finland
Supporting information for this article is available on the WWW under http://www.eurjoc.com or from the author.

need for regioselective control, particularly for enhancing or retaining the bioactive properties of acridine, as the moiety could consequently be linked either through an amine or through an imine, with important electronic implications. We have serendipitously encountered such a methodology in quite a simple system, for it appears that the regioselectivity described here, despite the vast amount of research, had previously been overlooked. This may in part be due to the limited use of acid halides in thiazolidinone synthesis, combined with a similarly limited use of unsymmetrical thioureas, resulting in the process having eluded description until now. As an initial foray in this direction, an unsymmetrical thiourea (**1**) was treated with bromoacetic acid derivatives, resulting in unexpected regioisomeric control depending on the electrophile used.

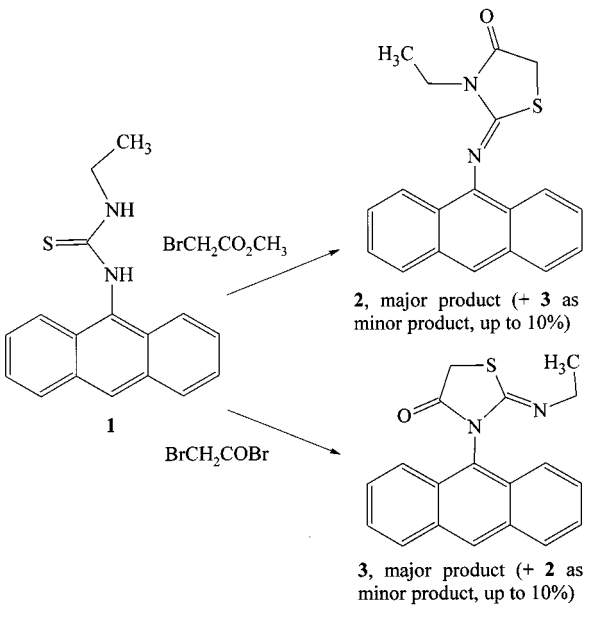
Results and Discussion

Treatment of thiourea **1** (see Scheme 1) with methyl bromoacetate yielded mainly 2-(anthracen-9-yl)imino-3-ethyl-1,3-thiazolidin-4-one (**2**), the cyclised product analogous to the non-spiro acridine products obtained in previous work.[18,19] In that study, thioureas containing various alkyl groups other than ethyl and acridinyl as the aromatic moiety were also treated with methyl bromoacetate, but under basic conditions (sodium methoxide), to yield either the spiro product or the thiazolidinone product. On treatment of **1** in this way, however, some of the regioisomeric product 3-(anthracen-9-yl)-2-ethylimino-1,3-thiazolidin-4-one (**3**) was also obtained as a minor product. Its counterpart in the acridine work[18,19] was not reported. Here the reaction proceeded either thermally or was accelerated by the addition of triethylamine. Upon treatment of **1** with bromoacetyl bromide, in contrast, **3** was obtained as the major product, together with a minor amount of **2**.

Structural Elucidation

With three nucleophilic heteroatoms in **1** and with both methyl bromoacetate and bromoacetyl bromide possessing two electrophilic centres each, the possible number of initial products is moderate: $3 \times 2 = 6$. This could grow considerably, though, if product rearrangements such as ring-opening/ring-closing (RORC) processes were to occur. Thus, any one of the heteroatoms may be positioned endocyclic or exocyclic to the ring or located at any of the "heteroatom" positions of the ring. This raises the total number of possible isomers as potential products, which is given by the number of permutations from an ordered set of four: i.e. $4! = 24$. Interestingly, all 24 structures are interconvertible through RORC processes. Individual depictions of all of these structures is obviously cumbersome, and so in order to handle such an unwieldy set we have found it convenient to use a lettered notation system for the structures, in which adjacent letters (atoms or atom pairs for sp^2-hybridised atoms) represent adjacent positions in the ring, with the two terminal atoms completing the ring. Figure 1 illustrates this notation for four of these structures.

In this notation, atoms in italics indicate those atoms doubly bound to carbon atoms and thus exocyclic to the



Scheme 1. *N*-(Anthracen-9-yl)-*N'*-ethylthiourea (**1**), produced from the addition of ethylamine to anthracen-9-yl isothiocyanate,[28,29] yields mainly 2-(anthracen-9-yl)imino-3-ethyl-1,3-thiazolidin-4-one (**2**) together with a minor amount of the regioisomeric 3-(anthracen-9-yl)-2-ethylimino-1,3-thiazolidin-4-one (**3**) upon treatment with methyl bromoacetate; treatment of **1** with bromoacetyl bromide produces the same products but with a reversed product distribution ratio

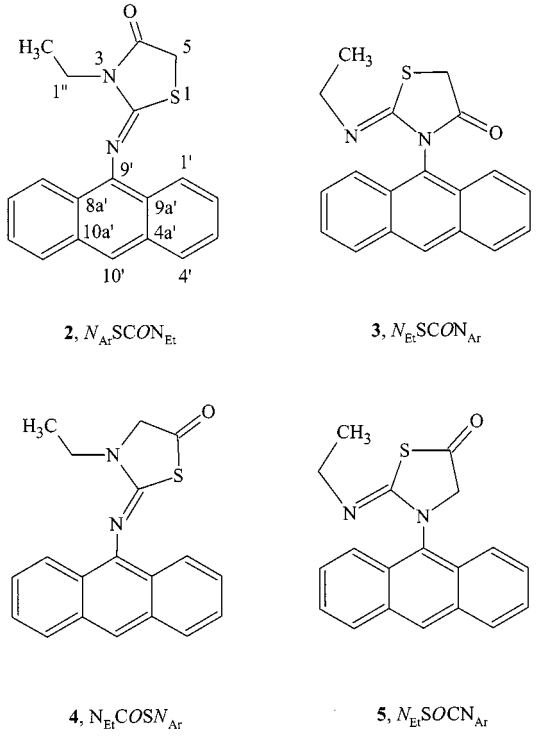


Figure 1. The structures of **2**–**5** together with the numbering system used and their lettered notation (explanation provided in the text)

ring; subscripts distinguishing the nitrogen atoms also indicate the substituent they bear. A RORC process results in the letter positions of two adjacent atoms being interchanged and also their state of hybridisation; moreover, any two adjacent letters can be interchanged except for the methylene carbon atom, which is "anchored". (The sp^2-hybridised carbon atoms of the ring are also anchored, and it is only the heteroatoms that are truly labile.) Thus, with this notation, it is clear to see that, from any one potential product, any of the other 23 structures could be generated. The distinct advantage of the lettered notation also quickly becomes evident: not only is it a convenient shorthand to indicate the structure, but the various permutations can quickly be systematically formulated with retention of the basic group relationships (chemical or NMR).

The structural elucidation of **2** and **3** and the assignment of the 1D ^1H, ^{13}C, and ^{15}N spectra was based on a fairly comprehensive package of 1D NOE difference (homo- and heteronuclear) and DEPT and 2D DQF COSY, CHSHF, FG HMBC (^1H-{^{13}C} and ^1H-{^{15}N}) experiments. Viable candidate structures were not limited to the six plausible initial structures; all 24 possible structures were considered.

From the ^{15}N NMR spectra of compound **2**, one sp^3- and one sp^2-hybridised nitrogen atom were found to be present and a $^1H\{^{15}N\}$ HMBC experiment indicated that the ethyl group was attached to the former, consistent with the observed chemical shifts of this group [^1H NMR: δ = 1.54 (CH_3), 4.21 (CH_2); ^{13}C NMR: δ = 38.5 (CH_2)]. As a consequence, the aryl group had to be attached to the sp^2-hybridised nitrogen atom, as duly reflected in the chemical shift of C-9′ (δ = 140.5). Thus, from the full set of 24 structures, only eight remained as candidates (that is, only eight notations contain the N_{Ar} and N_{Et} elements). A further four structures were eliminated by the resonance at δ = 171.6 (the most downfield carbon signal), since these four structures incorporated a thiocarbonyl group, the carbon atom of which should resonate downfield of δ = 180. Heteronuclear NOEs from the H-5 protons to the carbonyl carbon atom attested to the intact nature of the CH_2CO unit, eliminating two more structures, leaving just structures N_{Ar}SC*O*N_{Et} (**2**) and N_{Et}C*O*S*N*$_{Ar}$ (**4**). The selection of structure N_{Ar}SC*O*N_{Et} (**2**) over N_{Et}C*O*S*N*$_{Ar}$ (**4**) was based on a $^1H\{^{13}C\}$ HMBC experiment in which the methylene protons of the ethyl group (H-1′′ protons) were found to correlate to both the sp^2-hybridised carbon atoms of the heterocycle, which was incompatible with structure N_{Et}C*O*S*N*$_{Ar}$ (**4**) as the carbonyl carbon atom is four bonds distant. The carbonyl carbon atom, adjacent to the sulfur atom in structure N_{Et}C*O*S*N*$_{Ar}$ (**4**), would also be expected to resonate at significantly higher field, by several ppm, and the shift of C-5 (δ = 33.3) indicated that it was not bound to a nitrogen atom anyway. Indeed, the correlations between the H-1′′ protons and both C-4 and C-2 locked the relative positions of C-2, N-3 and C-4 in place, which thus determined the position of C-5 (relative to C-4), with the sulfur atom left as the final piece of the puzzle. Homonuclear NOEs indicated no great proximity of the ethyl group to H-1′/H-8′ in the anthracenyl moiety (1.6, 1.7% for the methylene and methyl protons, respectively), and irradiation of the methylene H-5 protons did not yield any discernible enhancement to any other hydrogen atoms, consistently with their distal relationship to all other protons.

On the NMR timescale, the fluxional motion of the five-membered heterocycle and rotation about the N−aryl bond rendered the H-5 methylene protons equivalent to one another in **2**, while the nuclei in the anthracene moiety similarly each have equivalent counterparts, as defined by the mirror plane bisecting the plane of the anthracene moiety.

The same degree of time-averaged equivalence was also evident in **3**, with only 13 unique carbon atoms and 8 unique hydrogen atoms. Of the sp^3- and sp^2-hybridised nitrogen atoms present, the sp^2-hybridised nitrogen atom bore the ethyl group, as evidenced by the $^1H\{^{15}N\}$ HMBC spectrum and the chemical shifts of the ethyl group [^1H NMR: δ = 0.98 (CH_3), 3.29 (CH_2); ^{13}C NMR: δ = 47.2 (CH_2)]. The sp^3-hybridised nitrogen atom therefore had to bear the aryl group, and this was also evident from the upfield shift of the C-9′ signal (shifted by 13.3 ppm) and the downfield shifts of the C-9a′ and C-10′ signals relative to those of their counterparts in **2** (shifted by 6.2 and 6.4 ppm, respectively; the shifts of all other aromatic carbon signals were essentially unchanged). As a consequence, 16 of the 24 structures could be eliminated as candidate structures on this basis of N_{Et} and N_{Ar} elements. Similarly, once again, the lack of a very lowfield sp^2-carbon signal indicated that the sulfur atom was not exocyclic, eliminating a further four structures. Heteronuclear NOE measurements also indicated the intact nature of the acetyl unit, eliminating a further two structures and leaving just N_{Et}SC*O*N_{Ar} (**3**) and N_{Et}S*O*CN_{Ar} (**5**) for consideration. $^1H\{^{13}C\}$ HMBC was not able to distinguish between these two structures, since both might show a correlation between the H-1′′ protons and C-2, as was indeed observed, although this did in fact lock in the relative positions of the sulfur atom, C-2, and N-3 provided that no RORC processes were involved. Distinction between N_{Et}SC*O*N_{Ar} (**3**) and N_{Et}S*O*CN_{Ar} (**5**) was based on the similarity of the carbonyl carbon shift (C-4) to that in structure **2**, the difference between the two being only 0.2 ppm. Structure N_{Et}S*O*CN_{Ar} (**5**), with the sulfur atom adjacent to the carbonyl group, would also be expected to have the carbonyl carbon atom resonating at a higher field position, and the shift of the methylene C-5 signal (δ = 32.8) also indicated that it was not bound to a nitrogen atom. Thus, the structure of **3** was N_{Et}SC*O*N_{Ar}.

Homonuclear NOE measurements on **3** again showed no interaction between the H-5 protons and those of the ethyl group, consistent with either structure N_{Et}SC*O*N_{Ar} (**3**) or N_{Et}S*O*CN_{Ar} (**5**). Examination of molecular models indicated little spatial difference between the H-5 protons and H-1′/H-8′ in either structure, while both structures could conceivably accommodate the observed 1.2% enhancement of H-1′/H-8′ upon irradiation of the H-5 protons. Again, no great proximity of the ethyl group to the H-1′/H-8′ protons was indicated (0.4 and 0.5% for the methylene and methyl protons, respectively).

The elucidated structure of **3** was confirmed by X-ray crystallographic analysis, the pictorial result of which is presented in Figure 2.

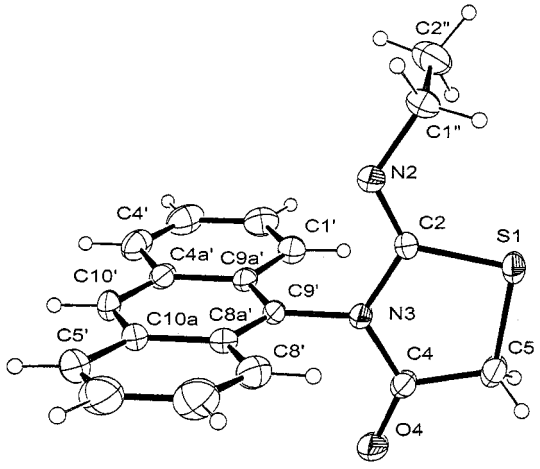


Figure 2. The X-ray crystallographic structure of **3**; the compound crystallised in the monoclinic space group *P*21/*c*

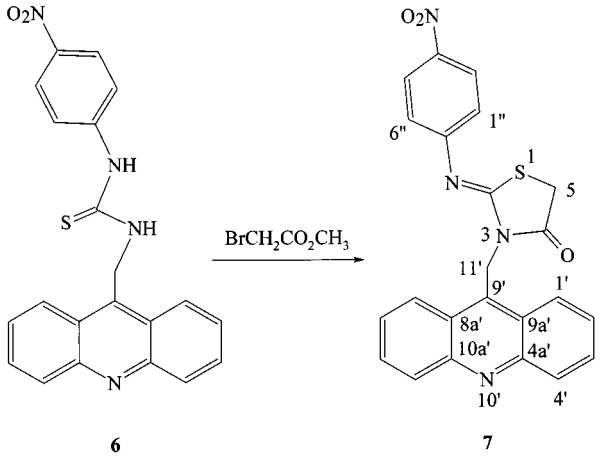
The outer rings of the anthracenyl moiety are slightly angled with respect to the inner ring (dihedral angles 2−4°), but each of the three individual ring planes is quite flat. The heterocycle, however, is surprisingly flat (rms deviation of the atoms from this plane: 0.01 Å) and N-2 and O-4 only deviate slightly in the same direction away from this plane (by 0.03 and 0.04 Å, respectively). The angle between the two planes defined by the heterocycle and by the anthracenyl segment is almost orthogonal at 83.4°. Thus, in contrast to similar structures, only "minimal" rapid fluxional mobility of the heterocycle and rotation about the N-3−C-9′ bond is required to render the geminal H-5 protons and nuclei pairs of the anthracenyl moiety equivalent in solution. Although the crystallographic depiction of **3** is enantiomeric, this achiral compound did not crystallise in an enantiomeric space group as has been observed for a similar acridine derivative[20] and both enantiomorphs are present in the crystal structure.

Reaction Mechanism

Although **2** and **3** represent structures from the set of six initial products, it cannot be totally ruled out that they result from rearrangements, and the two structures are indeed related to one another by a single RORC process, giving rise to the possibility that the product profiles are to some degree thermodynamically controlled. However, whilst both reactions yielded mixtures, neither reaction appeared to tend towards equilibrium and there was no indication of reversibility or rearrangements occurring in either reaction. The product distributions therefore in all likelihood represent the kinetic profiles of the respective reactions.

Monitoring of the reactions by NMR provided some insight. The reaction between **1** and methyl bromoacetate (in $CDCl_3$) in the absence of base, which required raised temperatures to go to completion, proceeded to give a stable intermediate (ca. 70%), in all likelihood the *S*-[(methoxycarbonyl)methyl]isothiourea hydrobromide, together with some product **2** (ca. 13%) and remaining starting material (**1**; ca. 17%). Upon addition of triethylamine (3 equiv.), the intermediate cyclised to yield **2**, with discernible detection of a minor quantity of **3**. The reaction with bromoacetyl bromide yielded similar observations of an intermediate, whilst the final product proportions were of course reversed.

When the ethyl substituent in **1** was varied (*n*-butyl, *s*-butyl, *tert*-butyl, etc.) and the various substrates were treated with methyl bromoacetate, the thiazolidinone product analogous to **2** in each case predominated, typically in the range of 90−99%, with the thiazolidinone analogous to **3** representing the remainder. To ensure that the course of the reaction was not due to something peculiar to the anthracenyl moiety, the reaction between *N*′-ethyl-*N*-phenylthiourea and bromoacetyl bromide was also examined, and again the product analogous to structure **3** was obtained as the major product. In conjunction with the acridine studies, a similar reaction between *N*-[(acridin-9-yl)-methyl]-*N*′-(4-nitrophenyl)thiourea (**6**) and methyl bromoacetate was also examined, in order to observe whether spiro ring formation occurred. It did not, and, as expected in view of the previous examples, reaction as a result of attack by the *N*-[(acridin-9-yl)methyl] nitrogen atom dominated the product profile to yield the major product, 3-[(acridin-9-yl)methyl]-2-(4-nitrophenyl)imino-1,3-thiazolidin-4-one (**7**), the product analogous to **2** (see Scheme 2). In previous work with acridines utilising thioureas[18,19] with different alkyl groups (benzyl, ethyl,[21] isopropyl, 2-furanylmethyl, cyclohexyl, *n*-butyl or *tert*-butyl) on one nitrogen atom and the acridinyl moiety on the other, either the cyclised product analogous to **2** or the spiro ring product (preferred with increasing size of the alkyl substituent) was always produced upon treatment with methyl bromoacetate in the presence of sodium methoxide as the base. No pres-



6 **7**

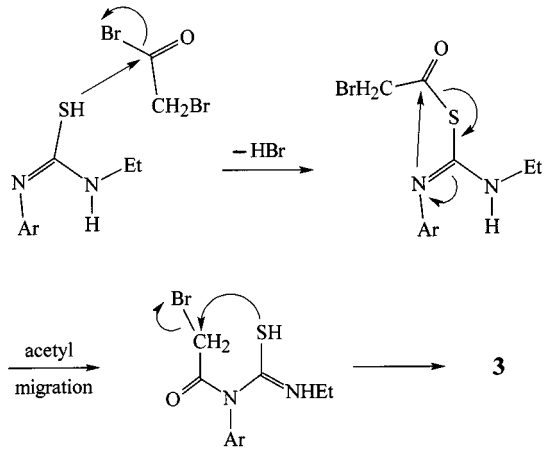
Scheme 2. The reaction between *N*-[(acridin-9-yl)methyl]-*N*′-(4-nitrophenyl)thiourea (**6**) and methyl bromoacetate was performed to see whether spiro ring formation occurred; it did not, and reaction as a result of attack by the *N*-[(acridin-9-yl)methyl] nitrogen atom dominated the product profile to yield the major product, 3-[(acridin-9-yl)methyl]-2-(4-nitrophenyl)imino-1,3-thiazolidin-4-one (**7**)

ence of any minor component analogous to **3** was reported. With bromacetyl bromide, however, the major product resulting from treatment[21] with *N*-(acridin-9-yl)-*N′*-ethylthiourea was the one analogous to compound **3**. Literature reports all appear to follow the analogous route to **2**, since α-haloalkanoyl halides have not been in common use or, if used, then unsymmetrical thioureas were not utilised and any regioselectivity was precluded.

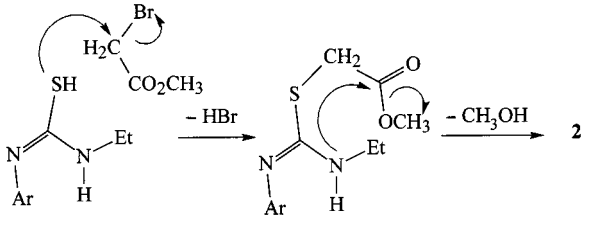
Finally, it was found that both reactions could be either thermally or base-catalysed to yield the respective ring-closed products. This, together with all of the above, suggests the conclusion that the course of the reactions is effectively reagent-dependent and essentially independent of conditions of the reaction, factors such as pH, for example. The results of these reactions, though initially representing something of a quandary with regard to the unexpected shift in product preference, are readily amenable to explanation and the disparity in product ratios can be accounted for on the basis of different mechanisms for the two reagents.

On treatment with methyl bromoacetate, an expected result is obtained (see Scheme 3). The sulfur atom attacks the α-carbon atom to form the intermediate *S*-[(methoxycarbonyl)methyl]isothiourea hydrobromide; this reaction is well known[1,2] and follows an intuitive course. After this, competition between the two nitrogen atoms for intramolecular attack on the carbonyl carbon atom and elimination of a methoxide ion occurs. The nitrogen atom bearing the ethyl group, a better nucleophile than that bearing the anthracenyl group, dominates the product profile. The tautomeric equilibrium also favours the former nitrogen atom being in the amino form, with the latter one in the imino form. Thus, product **2** is, not surprisingly, highly favoured and it is perhaps unexpected to observe any **3** at all. Because the HBr produced in the first instance must be slowly removed thermally, when base is not used, to permit reaction by the amine nitrogen atom, the presence of **3** may thus be a result of slow attack by the imine nitrogen atom. One also cannot discount the contribution of the cyclic sulfonium ion (neighbouring group effect, vide infra), which may enhance the rate of formation of **3**.

On treatment with bromoacetyl bromide, the reaction course is very different. The reaction between thioureas and acyl halides is known to give the *S*-bound carbonyl product,[22–24] and the sulfur atom should in this instance react with the more reactive of the electrophiles (the carbonyl carbon atom) to form the acetylisothiouronium halide. Rearrangement of the acetyl group onto the nitrogen atom ($S \rightarrow N$ migration) is also known to occur and has been studied in depth kinetically.[22–24] The $S \rightarrow N$ migration[22–25] occurs through the imine as the neutral species and is therefore accelerated by base, but can occur thermally. The imine nitrogen atom may be the preferred target for geometric reasons, but it is this step that accounts for the reversed product distributions, as the nitrogen atom bearing the anthracenyl group is strongly favoured to be in the imine form and consequently becomes bound to the carbonyl carbon atom. Finally, the sulfur atom attacks the α-carbon atom, displacing a bromide ion, and forms the thiazolidinone ring. This sequence is outlined in Scheme 4.



Scheme 4. The reaction course followed on treatment of thiourea **1** with bromoacetyl bromide; initially the sulfur atom combines with the more reactive acid bromide group to form the isothiouronium ion,[22–24] which subsequently isomerises by $S \rightarrow N$ acetyl migration;[22–25] the migration occurs through the imine[22] and so the reaction profile is dominated by the imine equilibrium, which heavily favours the nitrogen atom bearing the anthracenyl group; subsequent nucleophilic intramolecular attack by the sulfur atom on the α-carbon atom effects cyclisation and yields the product



Scheme 3. The reaction course followed on treatment of thiourea **1** with methyl bromoacetate; the initial *S*-[(methoxycarbonyl)methyl]isothiourea hydrobromide formed undergoes subsequent competitive nucleophilic intramolecular attack by the two nitrogen atoms to yield the products; the nitrogen atom bearing the ethyl group dominates the reaction profile

Although the regioselectivity for bromoacetyl bromide might appear to be good, it is actually poor in comparison to the results of Kaválek,[23] who reported effectively exclusive regioselectivity in a comparison between *N*-methyl-*N′*-phenyl-disubstituted thiourea and *N′*-phenyl-monosubstituted thiourea (in both cases the benzoyl/acetyl group preferentially migrated from the sulfur atom to the nitrogen atom bearing the phenyl moiety). This was a kinetic result, as they were also able, subsequent to this, to effect $N' \rightarrow N$ migration of the benzoyl or acetyl group to yield the thermodynamic product, showing that this is also a facile reaction. If the product distribution were determined solely by the imine equilibrium, then almost exclusive formation of **3** would be expected. Of course, isomerisation after the $S \rightarrow$

N migration[23] − i.e., $N \rightarrow N'$ migration of the acetyl group − could occur. Alternatively, the less than exclusive regioselectivity could be the result of a contribution from the cyclic sulfonium ion produced by the sulfur atom displacing the α-bromine atom prior to any $S \rightarrow N$ migration. It is not clear whether this pathway would enhance or impede the regioselectivity, but given the likely state of the imine equilibrium it may be inferred that it would inhibit regioselectivity. From this intermediate, either the alkyl-bearing (producing **2**) or the aryl-bearing nitrogen atom (affording **3**) could attack the carbonyl carbon atom. Figure 3 depicts attack of the aryl-bearing nitrogen atom as an imine to yield **3**, which equates to a heteroatom vinylcyclopropane-to-cyclopentene rearrangement followed by deprotonation.

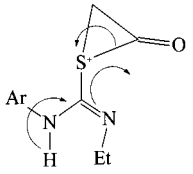


Figure 3. The reaction profile of thiourea **1** with bromoacetyl bromide may be distorted by a reactive intermediate resulting from the sulfur atom participating through the neighbouring group effect to yield the sulfonium ion by ejection of the α-bromide ion prior to any $S \rightarrow N$ acetyl migration; either nitrogen atom could effectively compete with the alkyl-bearing nitrogen atom preferred, but the sequence in the reaction depicted is equivalent to a heteroatom vinylcyclopropane-to-cyclopentene rearrangement

Conclusion

In conclusion, we have characterised and determined the structures of distinct products resulting from the reaction between *N*-(anthracen-9-yl)-*N*′-ethylthiourea and methyl bromoacetate, which yields mainly **2** together with some of the regioisomeric product **3**. In contrast, treatment with bromoacetyl bromide again yields **2** and **3**, but with a reversed product distribution ratio, thus providing an interesting and unexpected regioselectivity depending on the selected electrophile. As a result, a very desirable situation in which regioselectivity is available through reagent selection is at hand. However, the regioselectivity is also dependent on the substituents on the thiourea (alkyl and aryl), which also biases the imine equilibrium for the reaction with bromoacetyl bromide. The underlying cause of this divergence is the different reaction pathways taken by the two reagents.

In addition, a methodical and systematic approach to structural analysis incorporating a lettered notation to describe the products, which would readily lend itself to automated and computational methods, is demonstrated. The reactions themselves also hold considerable promise for production of a variety of regioisomeric thiazolidinone products that may possess considerable therapeutic potential.

Experimental Section

General: NMR spectra were acquired with a JEOL Alpha 500 NMR spectrometer operating at 500.16 MHz for ^{1}H, 125.78 MHz for ^{13}C and 50.69 MHz for ^{15}N. The spectra were recorded at 35 °C and both ^{1}H and ^{13}C spectra were referenced internally to tetramethylsilane ($\delta = 0$ for both), whilst ^{15}N spectra were referenced externally to 90% nitromethane in CD_3NO_2 ($\delta = 0$). ^{15}N chemical shifts reported to two decimal places were observed directly, whilst shifts reported at lower precision were observed indirectly. Detailed experimental conditions have been described elsewhere previously.[20] 1D spectra consisted of normal proton and carbon, nitrogen (acquired with INEPT optimised on an $^{n}J_{HN}$ value of 2 Hz), DEPT 135°, and NOE difference measurements; 2D spectra are comprised of DQF COSY, CHSHF (^{1}H-{^{13}C} with partial homonuclear decoupling in *f*1 and optimised on a $^{1}J_{HC}$ coupling of 145 Hz) and HMBC (^{1}H-{^{13}C}, ^{1}H-{^{15}N}, both optimised on a long-range coupling of 8 Hz for both $^{n}J_{HC}$ and $^{n}J_{HN}$). Spectral widths and resolution were appropriately optimised from the 1D spectra and generally processed with zero-filling (×2, ×4) and exponential weighting (plus a 2π/3-shifted sinebell function for the absolute-value mode spectra) applied in both dimensions prior to Fourier transformation. Spin analysis was performed with PERCH software[26] for the extraction of ^{1}H chemical shifts and $^{1}H-^{1}H$ coupling constants. Mass spectra were acquired with a VG ZabSpec instrument for EI^{+} measurements including metastable ion analysis with a direct insert probe. The X-ray structure of compound **3** was determined by essentially the same methodology as prescribed in ref.[27] and according to the principles outlined in the references therein (29−33). CCDC-172657 (excluding structure factors) for **3** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

***N*-(Anthracen-9-yl)-*N*′-ethylthiourea (1):** Ethylamine (19 mg, 0.42 mmol, or the equivalent alkylamine for other derivatives) was added to a solution of anthracen-9-yl isothiocyanate[28,29] (100 mg, 0.42 mmol) in dichloromethane (10 mL), and the reaction mixture was stirred until completion as monitored by TLC. The solvent was then removed in vacuo, followed by the addition of diethyl ether (10 mL). The product **1** was filtered off, washed repeatedly with diethyl ether and dried. M.p. 193−195 °C, yield 106 mg (90%).

2-(Anthracen-9-yl)imino-3-ethyl-1,3-thiazolidin-4-one (2): Methyl bromoacetate (50 mg, 0.32 mmol) was added to a solution of **1** (91 mg; 0.32 mmol, or proportionately for other various alkyl-substituted derivatives) in dichloromethane (10 mL) and the reaction mixture was stirred for 2 h. Subsequently, two approaches could be taken: a) The solvent and unchanged methyl bromoacetate were removed in vacuo at temperatures up to 100 °C. The residue was then taken up in methanol (5 mL), and water (3.5 mL) was added. The precipitate that formed was filtered off, washed with methanol/water (5:3) and dried. Column chromatography provided analytically pure crystals of **2**, m.p. 193−195 °C, yield 48 mg (46%). Treatment of the filtrate with an excess of water provided 26 mg of a mixture of **2** (81%) and **3** (19%) by ^{1}H NMR. The total proportion of **2** to **3** was 93:7. b) Alternatively, the solvent was evaporated in vacuo at room temperature and the residue was taken up in dichloromethane (10 mL). Triethylamine (97 mg, 0.96 mmol) was added to this solution, and the mixture was stirred for 1 h, after which the precipite of triethylammonium bromide that had formed was filtered off. The solvent was evaporated and the product **2** was

recrystallised from dichloromethane/*n*-heptane, yield 77 mg (75%). $C_{19}H_{16}N_2OS$ (320.415): calcd. C 71.23, H 5.03, N 8.74, S 10.01; found C 71.40, H 4.93, N 8.85, S 10.19. LRMS: *m/z* (%) = 320 (100) [$M^{+\cdot}$], , 223 (2), 219 (7), 218 (17), 217 (7), 205 (2), 204 (6), 203 (8), 191 (7), 190 (13), 179 (1), 178 (2). ^{1}H NMR ($CDCl_3$): δ = 1.54 (t, $^3J_{H\text{-}2''H\text{-}1''}$ = 7.1 Hz, 3 H, H-2′′), 3.72 (s, 2 H, H-5), 4.21 (q, $^3J_{H\text{-}1''H\text{-}2''}$ = 7.1 Hz, 2 H, H-1′′), 7.41 (higher order ddd, $^3J_{H\text{-}2'H\text{-}1'}$ = 8.8, $^3J_{H\text{-}2'H\text{-}3'}$ = 6.5, $^4J_{H\text{-}2'H\text{-}4'}$ = 1.2 Hz, 2 H, H-2′ and H-7′), 7.45 (higher order ddd, $^3J_{H\text{-}3'H\text{-}4'}$ = 8.5, $^3J_{H\text{-}3'H\text{-}2'}$ = 6.5, $^4J_{H\text{-}3'H\text{-}1'}$ = 1.2 Hz, 2 H, H-3′ and H-6′), 7.88 (m, $^3J_{H\text{-}1'H\text{-}2'}$ = 8.8, $^4J_{H\text{-}1'H\text{-}3'}$ = 1.2, $^5J_{H\text{-}1'H\text{-}10'}$ = 1.0, $^5J_{H\text{-}1'H\text{-}4'}$ = 0.8 Hz, 2 H, H-1′ and H-8′), 7.98 (m, $^3J_{H\text{-}4'H\text{-}3'}$ = 8.5, $^4J_{H\text{-}4'H\text{-}2'}$ = 1.2, $^5J_{H\text{-}4'H\text{-}1'}$ = 0.8, $^4J_{H\text{-}4'H\text{-}10'}$ = 0.6 Hz, 2 H, H-4′ and H-5′), 8.22 (br. s, $^5J_{H\text{-}10'H\text{-}1'}$ = $^5J_{H\text{-}10'H\text{-}8'}$ = 1.0, $^4J_{H\text{-}10'H\text{-}4'}$ = $^4J_{H\text{-}10'H\text{-}5'}$ = 0.6 Hz, 1 H, H-10′). ^{13}C NMR ($CDCl_3$): δ = 13.1 (q, C-2′′), 33.3 (t, C-5), 38.5 (t, C-1′′), 122.3 (2 × s, C-8a′ and C-9a′), 122.7 (s, C-10′), 123.4 (2 × d, C-1′ and C-8′), 125.1 (2 × d, C-2′ and C-7′), 125.5 (2 × d, C-3′ and C-6′), 128.6 (2 × d, C-4′ and C-5′), 132.0 (2 × s, C-4a′ and C-10a′), 140.5 (s, C-9′), 156.5 (s, C-2), 171.6 (s, C-4). ^{15}N NMR ($CDCl_3$): δ = −128.0 (s, N-2), −216.9 (s, N-3).

3-(Anthracen-9-yl)-2-ethylimino-1,3-thiazolidin-4-one (3): (a) Bromoacetyl bromide (85 mg, 0.43 mmol) was added to a solution of **1** (119 mg, 0.43 mmol) in dichloromethane (10 mL) and the reaction mixture was stirred for 4 h. The precipitate that formed was filtered off and washed with dichloromethane. It was then suspended in dichloromethane (20 mL), followed by addition of an excess of solid $NaHCO_3$, and stirred for 12 h. The new precipitate that formed was filtered off and washed successively with dichloromethane, methanol and finally water. The sample was dried and column-chromatographed to provide analytically pure crystals of **3**, m.p. 282−285 °C, yield 40 mg (38%). Heating of the solid intermediate on a water bath without base also provided **3** after several hours. (b) Alternatively, a solution of bromoacetyl bromide (85 mg, 0.43 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of **1** (119 mg, 0.43 mmol) in dry benzene (10 mL) and the reaction mixture was stirred for 1 h. The precipitate that formed was filtered off, washed with dry benzene, dried in vacuo to remove traces of bromoacetyl bromide, and then suspended in dry benzene (20 mL). Triethylamine (130 mg, 1.29 mmol) was added to this suspension and the mixture was stirred for 1 h. The precipitate of triethylammonium bromide that had formed was filtered off, and the filtrate was then concentrated to dryness. The product was recrystallised from chloroform/*n*-heptane to provide analytically pure crystals of **3**, yield 96 mg (70%). $C_{19}H_{16}N_2OS$ (320.415): calcd. C 71.22, H 5.03, N 8.74, S 10.01; found C 70.90, H 4.93, N 8.79, S 10.03. LRMS: *m/z* (%) = 320 (42) [$M^{+\cdot}$], , 223 (24, metastable ion analysis did not indicate that this ion emanated directly from the parent molecular ion), 219 (7), 218 (6), 217 (5), 205 (17), 204 (24), 203 (7), 191 (16), 190 (17), 179 (16), 178 (100). ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, $^3J_{H\text{-}2''H\text{-}1''}$ = 7.2 Hz, 3 H, H-2′′), 3.29 (q, $^3J_{H\text{-}1''H\text{-}2''}$ = 7.2 Hz, 2 H, H-1′′), 4.24 (s, 2 H, H-5), 7.47 (higher order ddd, $^3J_{H\text{-}3'H\text{-}4'}$ = 8.5, $^3J_{H\text{-}3'H\text{-}2'}$ = 6.6, $^4J_{H\text{-}3'H\text{-}1'}$ = 1.1 Hz, 2 H, H-3′ and H-6′), 7.51 (higher order ddd, $^3J_{H\text{-}2'H\text{-}1'}$ = 8.8, $^3J_{H\text{-}2'H\text{-}3'}$ = 6.6, $^4J_{H\text{-}2'H\text{-}4'}$ = 1.2 Hz, 2 H, H-2′ and H-7′), 7.73 (m, $^3J_{H\text{-}1'H\text{-}2'}$ = 8.8, $^4J_{H\text{-}1'H\text{-}3'}$ = 1.1, $^5J_{H\text{-}1'H\text{-}10'}$ = 1.0, $^5J_{H\text{-}1'H\text{-}4'}$ = 0.8 Hz, 2 H, H-1′ and H-8′), 8.05 (m, $^3J_{H\text{-}4'H\text{-}3'}$ = 8.5, $^4J_{H\text{-}4'H\text{-}2'}$ = 1.2, $^5J_{H\text{-}4'H\text{-}1'}$ = 0.8, $^4J_{H\text{-}4'H\text{-}10'}$ = 0.6 Hz, 2 H, H-4′ and H-5′), 8.55 (br. s, $^5J_{H\text{-}10'H\text{-}1'}$ = $^5J_{H\text{-}10'H\text{-}8'}$ = 1.0, $^4J_{H\text{-}10'H\text{-}4'}$ = $^4J_{H\text{-}10'H\text{-}5'}$ = 0.6 Hz, 1 H, H-10′). ^{13}C NMR ($CDCl_3$): δ = 15.0 (q, C-2′′), 32.8 (t, C-5), 47.2 (t, C-1′′), 122.3 (2 × d, C-1′ and C-8′), 125.5 (2 × d, C-3′ and C-6′), 127.20 (s, C-9′), 127.22 (2 × d, C-2′ and C-7′), 128.5 (2 × s, C-8a′ and C-9a′), 129.0 (2 × d, C-4′ and C-5′), 129.1 (s, C-10′), 131.9 (2 × s, C-4a′ and C-10a′), 151.0 (s, C-2), 171.4 (s, C-4). ^{15}N NMR ($CDCl_3$): δ = −120.3 (s, N-2), −222.4 (s, N-3).

***N*-[(Acridin-9-yl)methyl]-*N*′-(4-nitrophenyl)thiourea (6):** The reagent was prepared similarly as above for **1**, by treatment of 4-nitroaniline (58 mg, 0.42 mmol) with (acridin-9-yl)methyl isothiocyanate (106 mg, 0.42 mmol), yield 150 mg (92%).

3-[(Acridin-9-yl)methyl]-2-(4-nitrophenyl)imino-1,3-thiazolidin-4-one (7): Compound **7** was prepared similarly as above for **2**, by treatment of methyl bromoacetate (50 mg, 0.32 mmol) with **6** (124 mg, 0.32 mmol), with CH_3ONa as the base, yield 119 mg (87%). ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 2 H, H-5), 5.98 (s, 2 H, H-11′), 6.79 (BB′ part of AA′BB′ system, $^3J_{H\text{-}AH\text{-}B}$ = 8.8, $^4J_{H\text{-}BH\text{-}B'}$ = 2.7, $^5J_{H\text{-}AH\text{-}B'}$ = 0.4 Hz, 2 H, H-2′′ and H-6′′), 7.57 (ddd, $^3J_{H\text{-}2'H\text{-}1'}$ = 8.9, $^3J_{H\text{-}2'H\text{-}3'}$ = 6.5, $^4J_{H\text{-}2'H\text{-}4'}$ = 1.3 Hz, 2 H, H-2′ and H-7′), 7.77 (ddd, $^3J_{H\text{-}3'H\text{-}4'}$ = 8.8, $^3J_{H\text{-}3'H\text{-}2'}$ = 6.5, $^4J_{H\text{-}3'H\text{-}1'}$ = 1.3 Hz, 2 H, H-3′ and H-6′), 8.12 (AA′ part of AA′BB′ system, $^3J_{H\text{-}AH\text{-}B}$ = 8.8, $^4J_{H\text{-}AH\text{-}A'}$ = 2.3, $^5J_{H\text{-}AH\text{-}B'}$ = 0.4 Hz, 2 H, H-3′′ and H-5′′), 8.25 (ddd, $^3J_{H\text{-}4'H\text{-}3'}$ = 8.8, $^4J_{H\text{-}4'H\text{-}2'}$ = 1.3, $^5J_{H\text{-}4'H\text{-}1'}$ = 0.7, Hz, 2 H, H-4′ and H-5′), 8.54 (ddd, $^3J_{H\text{-}1'H\text{-}2'}$ = 8.9, $^4J_{H\text{-}1'H\text{-}3'}$ = 1.3, $^5J_{H\text{-}1'H\text{-}4'}$ = 0.7, Hz, 2 H, H-1′ and H-8′). ^{13}C NMR ($CDCl_3$): δ = 32.6 (t, C-5), 39.7 (t, C-11′), 121.4 (2 × d, C-2′′ and C-6′′), 124.6 (2 × d, C-1′ and C-8′), 125.2 (2 × d, C-3′′ and C-5′′), 125.9 (2 × s, C-8a′ and C-9a′), 126.3 (2 × d, C-2′ and C-7′), 129.7 (2 × d, C-3′ and C-6′), 130.6 (2 × d, C-4′ and C-5′), 137.1 (s, C-9′), 144.7 (s, C-4′′), 148.8 (2 × s, C-4a′ and C-10a′), 152.8 (s, C-1′′), 155.0 (s, C-2), 171.1 (s, C-4). ^{15}N NMR ($CDCl_3$): δ = −13 (s, NO_2), −76 (s, N-10′), −122 (s, N-2), −219 (s, N-3).

Supporting Information: Full listing of all 24 potential structures (see also footnote on the first page of this article).

Acknowledgments

Financial support from the Slovak grant agency VEGA, grant no. 1/6077/1999 (L. J., J. I., G. S., and P. K.); the Slovak Ministry of Education, International project SK-FIN (L. J., J. I., G. S., and P. K.); and the Academy of Finland, grant no. 4284 (K. P.), is gratefully acknowledged.

[1] S. P. Singh, S. S. Parmar, K. Raman, V. I. Stenberg, *Chem. Rev.* **1981**, *81*, 175.
[2] F. C. Brown, *Chem. Rev.* **1961**, *61*, 463.
[3] G. R. Newkome, A. Nayak, *Adv. Heterocycl. Chem.* **1979**, *25*, 83.
[4] R. Maly, *Justus Liebigs Ann. Chem.* **1873**, *168*, 133.
[5] J. Volhard, *Justus Liebigs Ann Chem.* **1873**, *166*, 383.
[6] G. S. Skinner, J. S. Elmslie, J. D. Gabbert, *J. Am. Chem. Soc.* **1959**, *81*, 3756.
[7] P. J. Meyer, *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1965.
[8] H. Tomosaka, K. Anzai, E. Hasegawa, T. Horigome, S. Omata, *Biosci. Biotechnol. Biochem.* **1996**, *60*, 4714.
[9] S. R. Kirk, N. W. Luedtke, Y. Tor, *J. Am. Chem. Soc.* **2000**, *122*, 980.
[10] S. A. Gamage, G. W. Rewcastle, G. J. Atwell, B. C. Baguley, W. A. Denny, *Anti-Cancer Drug Design* **1992**, *7*, 403.
[11] D. P. Figgitt, W. A. Denny, S. A. Gamage, R. K. Ralph, *Anti-Cancer Drug Design* **1994**, *9*, 199.
[12] C. H. Freudenreich, K. N. Kreuzer, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 11007.
[13] I. Antonini, P. Polucci, T. C. Jenkins, L. R. Kelland, E. Menta, N. Pescalli, B. Stefanska, J. Mazerski, S. Martelli, *J. Med. Chem.* **1997**, *40*, 3749.
[14] J. Bernát, P. Kristian, J. Imrich, D. Mazagová, J. Černák, T. Bušová, J. Lipkowski, *Synth. Commun.* **1995**, *25*, 3973.
[15] P. Kristian, J. Bernát, J. Imrich, I. Danihel, G. Suchár, I.

Chomča, S. Hočová, T. Bušová, J. Guspanová, A. Linden, *Molecules* **1996**, *1*, 191.
[16] J. Bernát, I. Chomča, P. Kristian, G. Voss, *Synth. Commun.* **1998**, *28*, 4171.
[17] J. Bernát, I. Chomča, P. Kristian, K. Pihlaja, K. D. Klika, J. Imrich, *Heterocycles* **1999**, *51*, 137.
[18] P. Kristian, I. Chomča, J. Bernát, J. Imrich, *Chem. Papers* **1999**, *53*, 49.
[19] P. Kristian, S. Hamulaková, J. Bernát, J. Imrich, G. Voss, T. Bušová, *Heterocycles* **1998**, *49*, 197.
[20] K. D. Klika, J. Bernát, J. Imrich, I. Chomča, R. Sillanpää, K. Pihlaja, *J. Org. Chem.* **2001**, *66*, 4416.
[21] P. Kristian, J. Bernát, J. Imrich, unpublished results.
[22] R. F. Pratt, T. C. Bruice, *J. Am. Chem. Soc.* **1972**, *94*, 2823.
[23] J. Kaválek, J. Jirman, V. Štěrba, *Collect. Czech. Chem. C* **1985**, *50*, 766.
[24] J. Kaválek, J. Novák, V. Štěrba, *Collect. Czech. Chem. C* **1982**, *47*, 2702.
[25] R. F. Pratt, T. C. Bruice, *Biochemistry* **1971**, *10*, 3178.
[26] See for example: R. Laatikainen, M. Niemitz, U. Weber, J. Sundelin, T. Hassinen, J. Vepsäläinen, *J. Magn. Reson. Ser. A* **1996**, *120*, 1; or the program website at http://www. uku.fi/perch.html
[27] J. Liimatainen, A. Lehtonen, R. Sillanpää, *Polyhedron* **2000**, *19*, 1133.
[28] C. Grundmann, J. M. Dean, *J. Org. Chem.* **1965**, *30*, 2809.
[29] W. O. Foye, J. M. Kauffman, *J. Org. Chem.* **1966**, *31*, 2417.

Received October 24, 2001
[O01514]