SHORT PAPER

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Mechanism of stereoselective synthesis of push-pull (*Z*)-4-oxothiazolidine derivatives containing an exocyclic double bond. A MNDO-PM3 Study†

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Calculations using the MNDO-PM3 method were performed to elucidate the mechanism of stereoselective base-catalyzed reaction affording exclusively (*Z*)-2-alkylidene-4-oxothiazolidine push-pull derivatives from the corresponding α-mercapto esters and activated β-oxonitriles in ethanol as a solvent.

Keywords: MNDO-PM3, *Z*-2-alkylidene-4-oxothiazolidine

There is a considerable interest in synthetic and naturally occurring thiazolidine derivatives containing the exocyclic double bond, in part due to their broad range of biological activity[1] and, in part because they exhibit increasing enaminic reactivity toward electrophiles which can be exploited for the preparation of precursors leading to push-pull polyenes.[2-4] We have recently reported the first regioselective synthesis of 2-alkylidene-4-oxothiazolidine derivatives **3c–3g**[5a] (which resemble known pharmacological agents) from activated β-oxonitriles **1** and α-mercapto esters **2c–e** (R = CO_2Et), in ethanol at reflux temperature (Scheme 1).

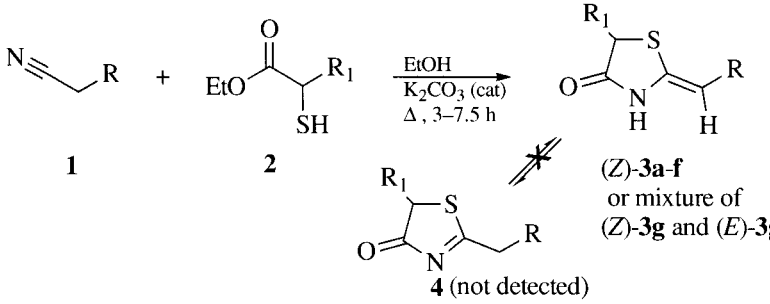
In order to explain the effect of solvent and an electron withdrawing group R on the stereochemical outcome in the synthesis of thiazolidinone derivatives **3** existing as enamino tautomers (no imino tautomers **4** were observed),[6] we have postulated the mechanistic pathway (Scheme 2) with a number of elementary steps, encompassing possible charged and neutral intermediates leading to products. Within this context and as an extension of our studies on 2-alkylidene-4-oxothiazolidine push-pull derivatives[2,5] we report a computational study on the model system **3a**,[5b] comprising of **1** (R =$NHCH_2CH_2Ph$) and **2** (R_1 = H) as precursors. Our objective has been the correlation of this study with the experimental results (Table 1) which indicate that, under given experimental conditions in ethanol as a solvent, the (*Z*)-isomer is exclusively formed in the specific case **3a**, and related cases **3b–f**, except in the case of **3g** (R = CN).

The first step in the addition-cyclization reaction sequence leading to **3a**, is an interaction between the highly nucleophilic mercapto group of the ester **2** (R1 = H) with the cyano group of *N*-(2-phenylethyl)cyanoacetamide (**1**) to generate non-isolable adduct **II** (R1 = H). Calculation of the potential energy surface for the addition process provides the evidence that the reaction proceeds with the simultaneous formation of the S–C and N–H bonds and the S–H bond cleavage (Fig. 1).

The decrease of the S–C and N–H distances occur at almost the same rate, with slight preference for the S–C interaction. Apparently, this can be ascribed to the greater polarisability of the S–C pair in comparison to the N–H pair.

In so far as the ring-formation process is concerned, a number of intermediates should be taken into account. As no intermediate has been isolated, extensive calculations were performed on all possible intermediates **II–V** (Scheme 2) in order to estimate their relative stabilities and tendency to cyclise into the thiazolidinone derivative **3a**. Thus, the cyclisation step, *e.g.* the nucleophilic attack of an imino- or enamino-nitrogen on the ester group was simulated from the anionic, noncharged, and zwitterionic intermediates **II–V**. Regarding the stereochemical control of the spontaneous intramolecular cyclization of intermediate **II**, it can be anticipated that two conformers are of major importance: (i) the precursor **II**-*syn* for the formation of the configurational isomer (*Z*)-**3a**, and (ii) the precursor **II**-*anti* for the isomer (*E*)-**3a** (Scheme 3).

Calculated heats of formation of the **II**-*syn* and **II**-*anti* conformers in an absence of dielectric medium (Table 2), indicate that the latter is more stable by ~5 kcal/mol as a consequence of the intramolecular H-bonding between the optimally oriented imino group and carbonyl group from the amide moiety. The respective energies of other relevant species, such as the resonance-stabilised anionic species **III**, in *anti* or *syn* conformation, and neutral enamino intermediates **IV**, having the *E*- and *Z*-configurations, which lead to (*E*)- or (*Z*)-**3a** isomers respectively, are also given in Table 2. Calculations carried out for the imino type **II** and enamino type intermediate **IV** as



R	R_1
3a: $CONHCH_2CH_2Ph$	H
3b: COPh	H
3c: COPh	CO_2Et
3d: CONHPh	CO_2Et
3e: $CONHCH_2CH_2Ph$	CO_2Et
3f: CO_2Et	CO_2Et
3g: CN	CO_2Et

Scheme 1

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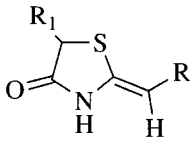
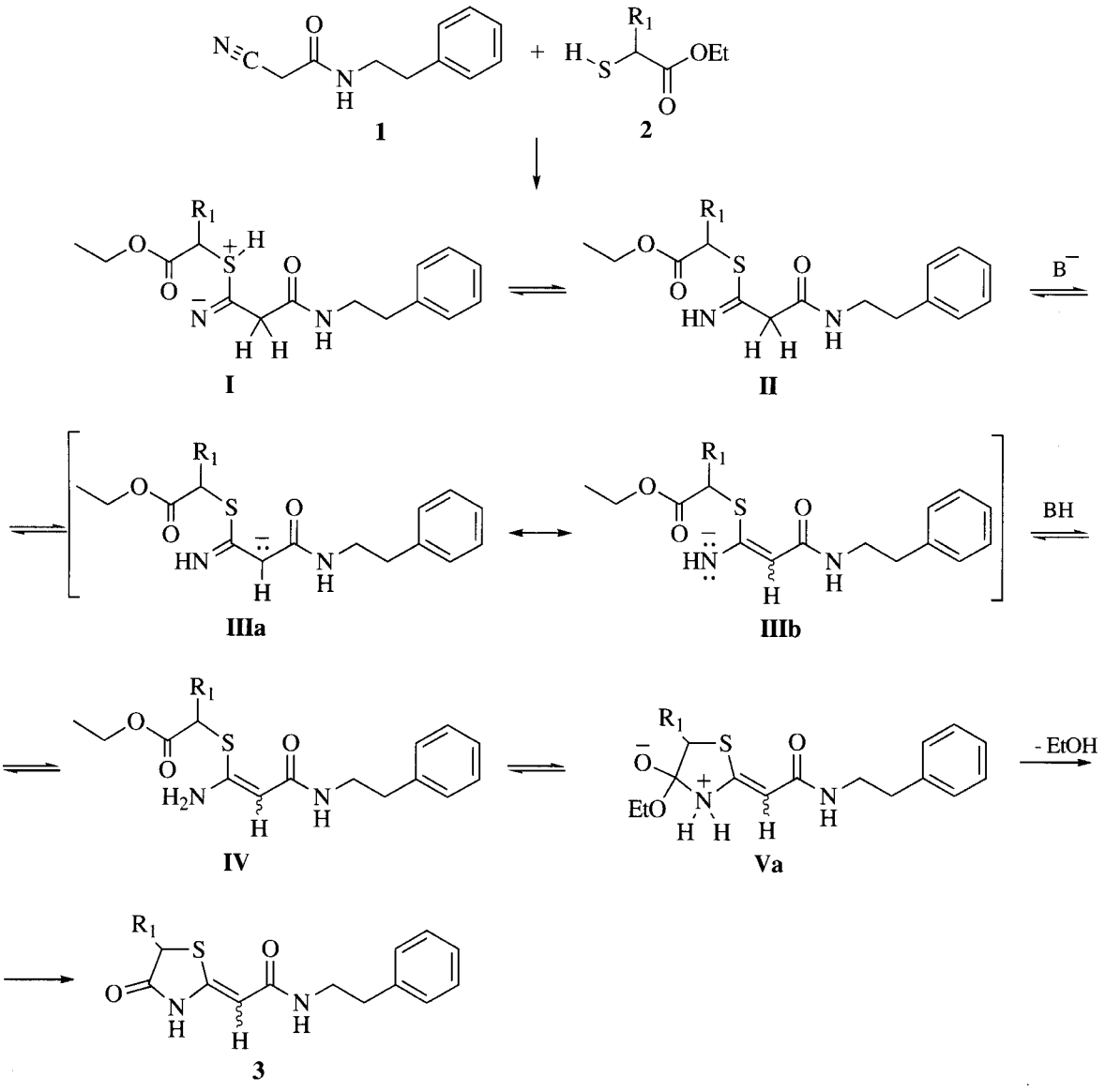
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Selected ^{1}H NMR chemical shifts of (*Z*)- and (*E*)-isomers **3a–g**[a] and *Z*/*E* isomerisation data

Entry		(*Z*)-C(2′)H /ppm	(*E*)-C(2′)H[c] /ppm	Yield[b] /%	Configuration of isolated products	*Z*/*E* Ratio after equilibration
1	**3a** (DMSO-d_6)[a]	5.61		63	*Z*	No isomerisation
2	**3b** (Me_2CO-d_6)[a]	6.96	6.61	58	*Z*	76/24
3	**3c** ($CDCl_3$)[a]	6.85	6.32	48	*Z*	11/89; 76/24 in Me_2CO-d_6
4	**3d** (DMSO-d_6)[a]	5.79	5.36	43	*Z*	No isomerisation
5	**3e** ($CDCl_3$)[a]	5.54	4.90	42	*Z*	22/78; 52/46 in Me_2CO-d_6
6	**3f**($CDCl_3$)[a]	5.90	5.12	70	*Z*	10/90
7	**3g** (DMSO-d_6)[b]	4.93	4.87	70	*Z*/*E*	Not investigated

[a]All reactions carried out in ethanol. [b](*Z*)-isomers as exclusive products, except for R = CN when the mixture of both isomers is isolated. [c]*E*-isomers detected in the *Z*/*E* mixtures during the isomerization process.



Scheme 2

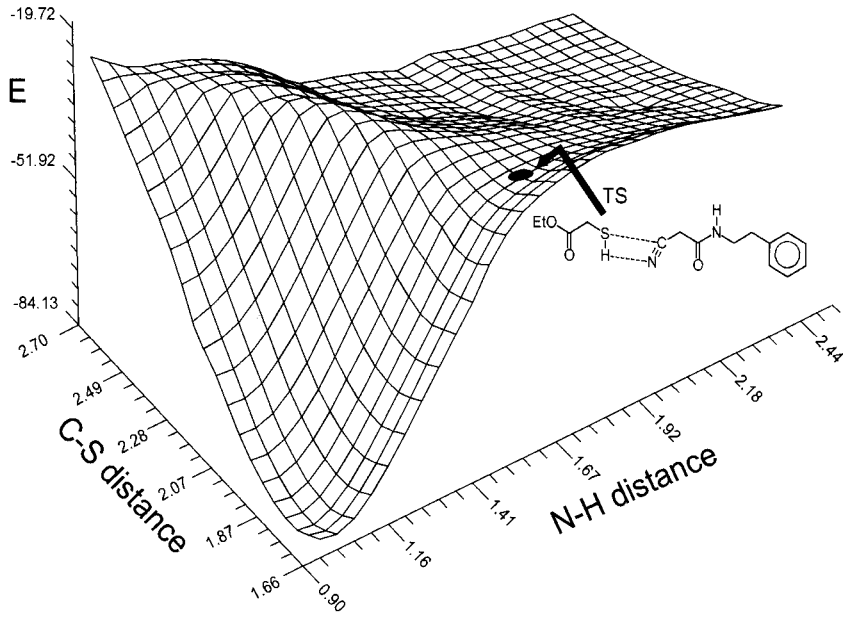
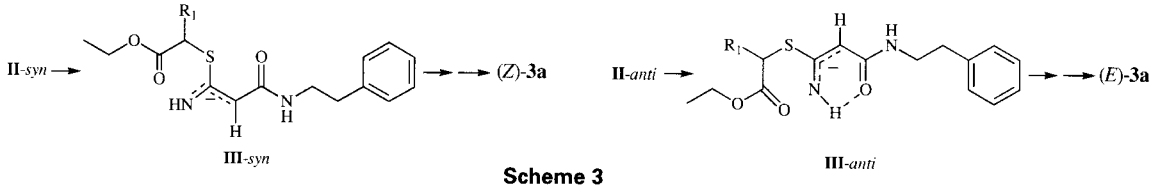
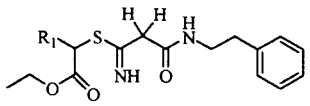
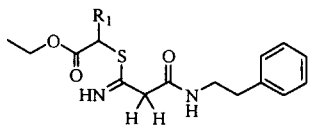
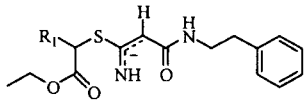
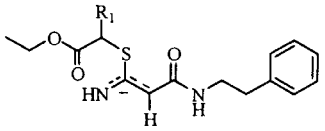
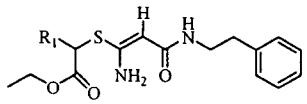
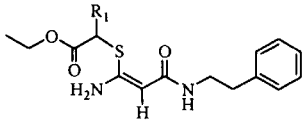
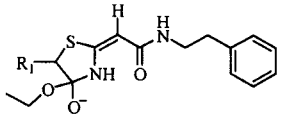
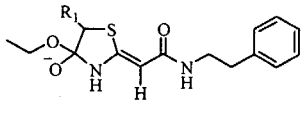
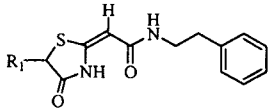
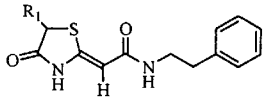
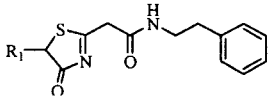
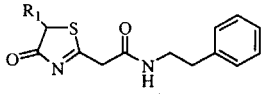


Fig. 1 Two-dimensional potential energy surface for the addition of -SH to -C ≡ N group (distances are given in Å, and energy in kcal/mol).



Scheme 3

Table 2 Calculated heats of formation (/kcal/mol) of intermediate structures anticipated in the cyclization step leading to thiazolidinone **3a** (R = H).

II-*anti*[a]		−87.756	**II**-*syn*[a]		−82.782
III-*anti*		−122.087	**III**-*syn*		−115.126
IV-*E*		−88.2684	**IV**-*Z*		−86.136
V-*E*[b]		−120.876	**V**-*Z*[b]		−116.550
(*E*)-**3a**		−36.580	(*Z*)-**3a**		−33.170
4a-*anti*		−29.832	**4a**-*syn*		−27.109
	TS for cyclisation step **III**-*anti* → **V**-*E*	−114.583		TS for cyclisation step **III**-*syn* → **V**-*Z*	−108.766

[a]**II**-*syn*: sulfur and the carbonyl group in *synperiplanar* orientation (the molecule is viewed along the C(2*)-C(2) bond); **II**-*anti*: the same groups in *antiperiplanar* orientation. [b]Intermediate **Va** from neutral acyclic species **IV** (Scheme 2) was not considered.

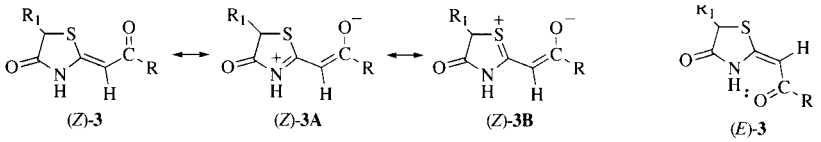
well (formed under basic conditions from the former), with or without simulation of a dielectric continuum, failed to produce any minimum along the course of the simulated cyclisation.

According to the calculations, the anionic intermediate **III**, depicted by the resonance structures **III**-*syn* and **III**-*anti* undergoes the cyclization most easily, whereas the **III**-*anti* conformer, giving rise to (*E*)-**3a**, is ~7 kcal/mol more stable *in vacuum* than its *syn* analogue. In addition, the product **3a** as an enamine tautomer, is more populated than the endocyclic imine **4a**, which is in full agreement with our experimental findings (Scheme 1) and the reported structure characterisation of numerous push-pull 2-nitroenamines. The overall reactivity profile related to the formation of (*E*)-**3a** and (*Z*)-**3a** depends on the conformation adopted by enamino species **III**-*anti* and **III**-*syn*. Since the stereochemistry of the *anti*-**III** intermediate is presumably retained throughout the proposed reaction path, the origin of the stereoselectivity in the absence of solvent, favouring the (*E*)-**3a** isomer over the (*Z*)-**3a** analog, reflects the greater thermodynamic stability of *anti*-**III** *versus* *syn*-**III** conformations.

In comparison to (1) the predominant enamine structure and (2) *E*-configuration of derivatives **3** as two main points inferred from the computational studies, Table 1 lists relevant experimental results in addition-cyclization reactions carried out in ethanol (Scheme 1). In each case, with one exception (entry 7, R=CN), a single diastereoisomer **3a-f** was produced, *e.g.* the one having exclusively the *Z*-configuration. When they were subjected to *Z*/*E* isomerisation, monitored by dynamic ^{1}H NMR spectroscopy in the solvents of different polarities, the corresponding *E*-counterparts were produced in different ratios.[5a] The *Z*-isomers **3a–f** are highly favoured in the polar DMSO (entries 1 and 4), mixtures of both isomers, enriched in the *Z*-isomer, are present in less polar acetone (entries 2, 3 and 5) and the *E*-isomers are major species in the weakly polar chloroform (entries 3, 5 and 6). Obviously, intermolecular H-bonding of the *Z*-isomers **3a–f** with polar acetone, DMSO, or ethanol *via* increasing contribution of dipolar resonance form (*Z*)-**3A** (Scheme 4) and strong electrostatic interactions present in (*Z*)-**3B** providing the strongest stabilisation, is actually the driving force that induces exclusive formation of the (*Z*)-isomers in ethanol.

The *Z*/*E* isomerisation is the stereochemical consequence, resulting from the change of the polar solvent to nonpolar solvent ($CDCl_3$). In other words, intermolecular H-bonding is then suppressed to various extent depending on the dielectric constant of the solvent used, due to the favorable and stabilising effect of intramolecular H-bonding in the isomer (*E*)-**3**. Introduction of cyano group in **3g**, incapable of intramolecular hydrogen bond formation, led to the formation of both isomers in approximately equal amounts.

As a final note, the potential energy diagram for the cyclization step of **III** to the tetrahedral intermediate **V** (Fig. 2) also supports the experimental findings. The right-hand side of the diagram corresponds to the **III**-*anti* and **III**-*syn* (less stable) intermediates and the energy minima to the **V**-*E* and **V**-*Z* isomers, respectively. The curves obtained for the cyclisation process in an absence of solvent, again shows the preferential formation of (*E*)-isomer as thermodynamically more stable one. The greater stabilisation of *anti*-structure **III** stems from intramolecular hydrogen bond (Scheme 3). The *syn*-isomer **III** is not prone to this type of intramolecular stabilization. The computed activation barrier for the cycliszation (or ring-opening) process is rather low (6.4 *vs.* 7.5 kcal/mol for *syn* and *anti*



Scheme 4

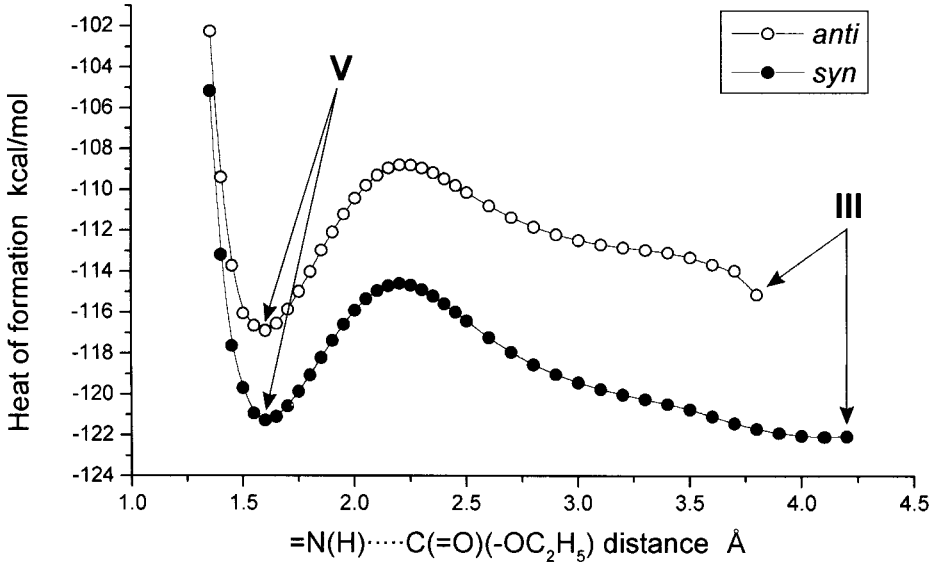


Fig. 2 Potential energy curves for the cyclization of III-*syn* and III-*anti* intermediates to cyclic species V-*Z* and V-*E*.

isomers, respectively), which accounts for the easy interconversion of isomers depending on the solvent used (Tables 1 and 2).

In summary, our calculations indicate that a key structural feature in the most reactive anionic intermediates **III**-*anti*, transition states and in 2-alkylidene-4-oxothiazolidines **3a–f**, responsible for the preferential formation of *E*-configurated derivatives from the α-mercapto esters and activated β-oxonitriles in the absence of dielectric medium, or in apolar solvent ($CDCl_3$), is the resonance-assisted formation of intramolecular hydrogen bonding. The experimental results regarding the exclusive formation of Z-isomers **3a–f** in polar ethanol (or DMSO) can be interpretated on the basis of the strong solute-solvent interactions via the solvent-exposed NH group, thus eliminating completely the existence of chelates, having the NH intramolecularly bonded to carbonyl group in the case of *E*-isomers.

Experimental

General procedure for the preparation of push-pull 4-oxothiazolidine derivatives **3a–f**:[5a,b]

CAUTION: *All reactions involving a-mercapto esters 2, due to the unpleasant odour, should be carried out in a well-ventilated fume hood.*

To a stirred suspension of activated β-oxonitrile **1a–g** (3 mmol) (Scheme 1) and α-mercapto ester **2** (~1% molar excess) in 5–10 ml of absolute ethanol, a catalytic amount of K_2CO_3 was added (reagents for the starting compounds **1** and **2** which were obtained by standard procedures, were purchased from commercial suppliers). The mixture was brought to reflux and reaction mixture was stirred for 3–7.5 h. The reaction mixture was cooled down to room temperature and separated solid was filtered, washed with ethanol and recrystallized from 96% ethanol to provide the final product **3a–g** in 42–70% yield. The structural assignments of all isolated products were made on the basis of spectroscopic data (IR, ^1H and ^{13}C NMR, MS, UV) and elemental analysis. Compound **3b** (m.p. 225°C; lit.[5c] 224°C) was prepared as described in the literature.

Method of calculation: In our work we used the MNDO-PM3 method that has proved to be reliable for investigating the molecular properties of molecules, ions,[7–9] and zwitterions.[10] The MOPAC program package, Version 7.01 was employed. The initial structures of compounds were generated by PC MODEL, version 4.0,[11] that involves an MMX force field[12] and were saved as MOPAC input files for MNDO-PM3 semiempirical calculations.[8] The geometries of all molecular species, corresponding to the energy minima in vacuum, were optimised by the PM3 method. The transition states for all reactions were explored using corresponding MOPAC facilities (TS, SADDLE). When needed, the structures obtained were refined by Bartel's method (Non-Linear Least Squares gradient minimization routine – NLLSQ), and further proved by vibrational analysis showing only one negative vibration. The simulation of polar medium was performed using the COSMO facility in the MOPAC program package.[13]

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References

1 K. Yoneda, A. Ota and Y. Kawashima, *Chem. Pharm. Bull.*, 1993, **41**, 876.
2 R. Marković, Z. Džambaski and M. Baranac, *Tetrahedron*, 2001, **57**, 5833.
3 J.V. Metzger, In *Comprehensive Heterocyclic Chemistry* A.R. Katritzky and C.W. Rees, (eds) Pergamon, Oxford, UK, 1984. Vol 6, Chapter 19, 236–330;
4 S. Rajappa, *Tetrahedron*, 1999, **55**, 7065.
5 (a) R. Marković and M. Baranac, *Heterocycles*, 1998, **48**, 893; (b) R. Marković, D. Ilić and M. Bokšan, *J. Serb. Chem. Soc.*, 1996, **61**, 1087; (c) G. Satzinger, *Liebigs Ann. Chem.*, 1978, 473.
6 (a) J.L. Chiara and J. Bellanato, *J. Chem. Soc. Perkin Trans. 2*, 1998, 1797; (b) O. Ceder, U. Stenhede, K.-I. Dahlquist, J.M. Waisvisz, M.G. van der Hoeven, *Acta Chem. Scand.*, 1973, **27**, 1914.
7 (a) J.J.P. Stewart, *J. Comp.-Aided Molec. Des.*, 1990, **4**, 1; (b) J.J.P. Stewart, *QCPE* # 455.
8 For PM3 parametrization of MNDO see: (a) J.J.P. Stewart, *J. Comp. Chem.*, 1989, **10**, 109; (b) J.J.P. Stewart, *J. Comp. Chem.*, 1989, **10**, 221.
9 (a) E. Bartoszak, Z. Degaszafran, M. Grundwaldwyspianska, M. Jaskolski and M. Szafran, *J. Chem. Soc., Faraday Trans.*, 1993, **89**, 2085; (b) P. Burk and I.A. Koppel, *Theor. Chim. Acta*, 1993, **86**, 417; (c) H. Zuilhof, L.B.J. Vertegaal, A. Vandergen and G. Lodder, *J. Org. Chem.*, 1993, **58**, 2804; (d) C.B. Aakeroy, *J. Mol. Struct. (Teochem.)*, 1993, **281**, 259; (e) M.W. Jurema and G.C. Shields, *J. Comp. Chem.*, 1993, **14**, 89.
10 T. Matsuoka and K. Harano, *Tetrahedron*, 1995, **51**, 6451.
11 Serena Software Box, Bloomington, IN 45402–3076
12 (a) J.J. Gajevski, K.E. Gilbert and J. McKelvey, *Adv. Mol. Model.*, 1990, **2**, 65; (b) U. Burket and N.L. Allinger, *Molecular Mechanics*, American Chemical Society, Washington, DC 1982.
13 (a) A. Klamt and G. Schüürmann, *J. Chem. Soc., Perkin Trans. 2*, 1993, 799; (b) C.J. Cramer and D.G. Truhlar: *Chem. Rev.*, 1999, **99**, 2161.