

Evidence for a Robinson-like annelation during the reaction between *N*-(1-chloroalkyl)pyridinium chlorides and *N*-substituted enaminoesters

Jean Jacques Vanden Eynde^{*a}, Annie Mayence^a, Olga N. Kataeva^b, Igor A. Litvinov^b, and Ernst Anders^c

^a University of Mons-Hainaut, Organic Chemistry Laboratory, Place du Parc 20,B - 7000 Mons, Belgium E-mail: jjvde@umh.ac.be

^b A. E. Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences, A. E. Arbuzov str. 8, Kazan 420088, Russia

^c Institut für Organische Chemie und Makromolekulare Chemie der Friedrich-Schiller-Universität Jena, Humboldtstrasse 10, D - 07743 Jena, Germany

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Abstract

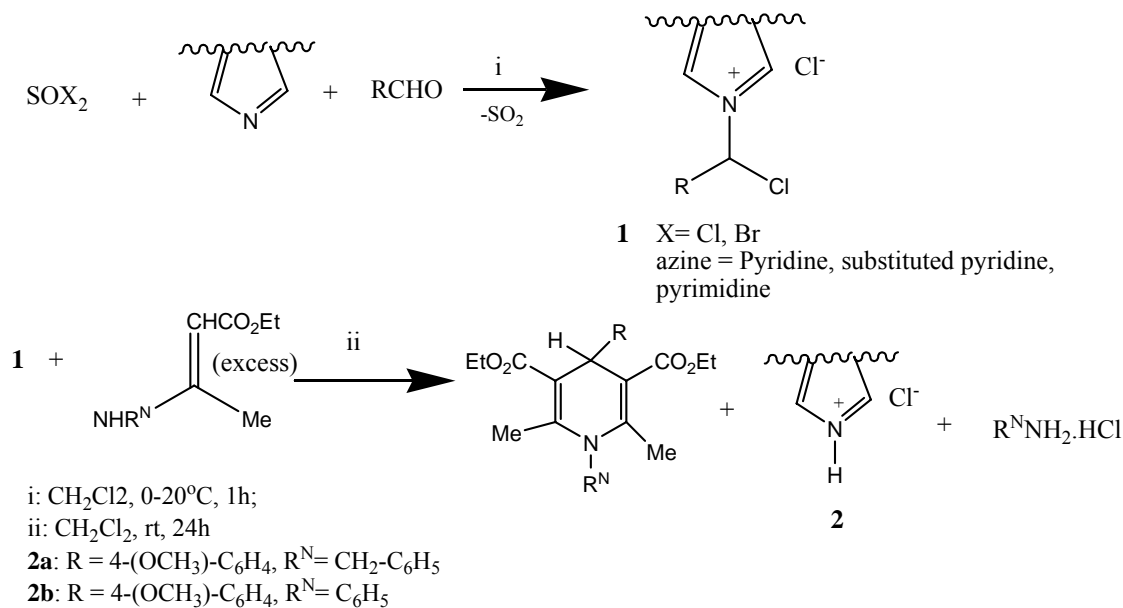
N-Benzyl 1,4-dihydropyridine **2a** and (\square) 2-benzylaminocyclohexa-1,3-diene **3** are obtained in satisfactory yields by reaction between *N*-(1-chlorobenzyl)pyridinium chloride and ethyl 3-benzylaminobut-2-enoate in dichloromethane at room temperature. Mechanistic and practical considerations are discussed. Compound **3** has been unequivocally characterized by X-ray single crystal diffraction.

Keywords: Robinson annelation, 1,4-dihydropyridines, enaminoesters, cyclohexa-1,3-dienes

Introduction

A decade ago, one of our research groups reported the first synthesis of *N*-(1-haloalkyl)azinium halides (**1**, Scheme 1) from a thionyl halide, an azine, and aldehydes.¹ Prepared *in situ*, these salts were then subjected to substitution reactions in which both the halogen atom and the azine could be replaced by various nucleophiles.² The reactivity of these salts makes them suitable as synthetic equivalents for the starting aldehydes. This has led to the development of new synthetic pathways for the synthesis of numerous heterocycles containing nitrogen. Among the target molecules, we focused our attention^{3, 4} on Hantzsch dihydropyridines of the nifedipine-type. They are compounds which belong to the most studied class of calcium channel modulators used in the clinical treatment of cardiovascular diseases.⁵ Whereas the *N*-unsubstituted derivatives (**2**, R^N = H) were obtained in excellent yields from **1** and enaminoesters, the results were disappointing in a few cases when we attempted to prepare the *N*-substituted analogs. For

example, derivative **2a** (R = 4-methoxyphenyl, R^N = benzyl, Scheme 1) was detected by NMR spectroscopy but it was not isolated. This finding led us to reinvestigate this particular reaction.



Scheme 1

Experimental Section

General Procedures. IR spectra were recorded on a Perkin-Elmer FTIR 1760K spectrophotometer. NMR spectra were recorded on a Jeol JNP-PMX 60 spectrometer (60 MHz for ¹H at 1.4 T) or a Bruker AMX spectrometer (300 MHz for ¹H and 75 MHz for ¹³C at 7.0 T). Chemical shifts are given in ppm using TMS as internal reference. Melting points (uncorrected) were determined on a Electrothermal 9100 apparatus. Elemental analyses were carried out at the Station de Haute Belgique (Libramont-Chevigny, Belgium). Pyridine was kindly supplied by Reilly Chemicals (Tertre, Belgium). Thionyl chloride, 4-methoxybenzaldehyde, and solvents are commercially available (Acros Organics, Aldrich Co) and were used without further purification. Ethyl 3-benzylaminobut-2-enoate, ⁶ ethyl 3-phenylaminobut-2-enoate, ⁶ and **2b** ⁴ have been described in the literature.

General experimental procedure. A solution of thionyl chloride (0.9 mL; 12 mmol) in dichloromethane (25 mL) was cooled to 0 °C. Pyridine (1.0 mL; 12 mmol) was added dropwise followed by the addition of 4-methoxybenzaldehyde (1.2 mL; 10 mmol). The solution was allowed to warm up to room temperature. After confirmation ⁷ of the formation of the salt by NMR (1 hour), the enaminoester (40 mmol) was slowly added and the reaction mixture was stirred for 2 h (optimized reaction time). The precipitate, identified (NMR) as benzylamine

hydrochloride, was discarded. The filtrate was concentrated under reduced pressure, and the residue was precipitated by addition of ethanol. Concentration of the alcoholic solution afforded the excess of the enaminoester and pyridinium hydrochloride. The solid, composed by two products (TLC, NMR), could readily and efficiently be separated by treatment with ether.

Diethyl 1-benzyl-1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2a). M.p. (EtOH): 132-3 °C. IR (KBr): 1697; 1678; 1576; 1386; 1202; 1153 cm^{-1} . ^1H NMR (CDCl_3): 1.2 (6 H, q, 7 Hz); 2.4 (6 H, s); 3.7 (3 H, s); 4.1 (4 H, t, 7 Hz); 4.9 (2 H, s); 5.2 (1 H, s); 6.7-7.2 (9 H, m) ppm. ^{13}C NMR (CDCl_3): 15; 17; 38; 50; 56; 61; 108; 114; 126; 128; 129; 130; 138; 139; 149; 158; 169 ppm. $\text{C}_{27}\text{H}_{31}\text{NO}_5$ (449.55) Calc.: C, 72.14; H, 7.00; N, 3.12; Found: C, 71.82; H, 6.75; N, 2.72.

Diethyl 2-benzylamino-6-(4-methoxyphenyl)-4-methylcyclohexa-1,3-diene-1,5-dicarboxylate (3). M.p. (EtOH): 137-138 °C. IR (KBr): 3251; 1723; 1676; 1627; 1588; 1275; 1219 cm^{-1} . ^1H NMR (CDCl_3): 1.2 (3 H, q, 7 Hz); 1.3 (3 H, q; 7 Hz); 1.8 (3 H, s); 3.1 (1 H, s); 3.7 (3 H, s); 4.1 (4 H, m); 4.5 (2 H, s); 4.6 (1 H, s); 6.2 (1 H, s); 6.7-7.4 (9 H, m); 9.3 (1H, br) ppm. ^{13}C NMR (CDCl_3): 14; 15; 25; 40; 47; 53; 55; 59; 61; 88; 113; 118; 126; 127; 128; 129; 136; 139; 143; 154; 158; 170; 171 ppm. $\text{C}_{27}\text{H}_{31}\text{NO}_5$ (449.55) Calc.: C, 72.14; H, 7.00; N, 3.12; Found: C, 71.87; H, 7.42; N, 3.07.

X-Ray structure determination. Table 1 lists the experimental conditions and the final refinement parameters for **3**. Stability of the crystals and of the experimental conditions was checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering two standards. Linear decay correction was applied, total loss of intensity being equal to 7%. No absorption correction was necessary. Corrections for Lorentz and polarization effects were applied. The phase problem was solved by direct methods using program SIR.⁸ The structure was developed by difference-Fourier calculations interspersed with cycles of full-matrix least-squares refinements. All hydrogen atoms were located from difference Fourier maps and refined isotropically with fixed thermal parameters. Interestingly the selected crystal had noncentrosymmetrical space group, thus only one enantiomer was present. Its absolute configuration, determined *via* anomalous dispersion effects, was found to be C3_S , C4_R with the probability of 90% according to the Hamilton test⁹: for direct structure $R=0.05554$, $R_w=0.06335$, number of variables 391, number of reflections in least-squares 1902, max. $|\Phi| = 0.07$, goodness of fit 2.099, for inverse structure $R=0.05558$, $R_w=0.06339$, max. $|\Phi| = 0.13$, goodness of fit 2.101. All calculations were carried out on Alpha Station 200 using programs MOLEN.¹⁰ The drawing of the molecule was made using the program PLATON.¹¹ Crystallographic data (excluding structure factors) for the structure **3** reported in this paper have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 137227. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44 1223 336 033; E-mail : deposit@ccdc.cam.ac.uk).

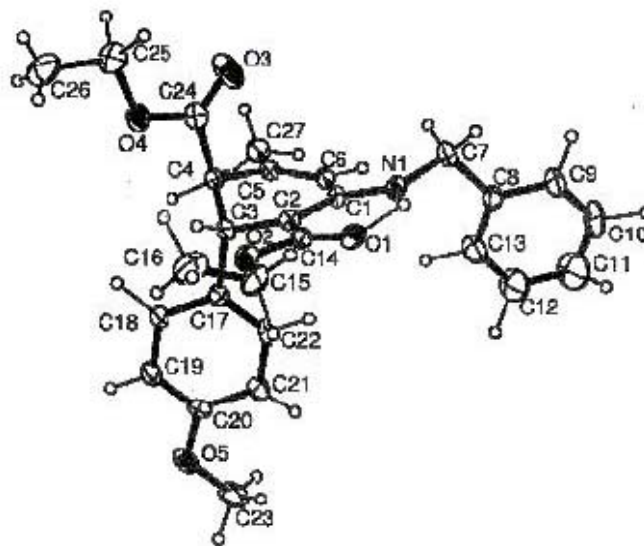
Table 1. Crystal data and structure refinement parameters for the X-ray analysis of **3**

Molecular Formula	C ₂₇ H ₃₁ NO ₅
Crystal color, shape	Colorless, prism
Approx. Crystal dimensions, mm	0.1 × 0.2 × 0.5
Formula weight	449.55
Temperature, °C	20
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
Cell constants	
a, Å	8.279(3)
b, Å	15.517(5)
c, Å	18.958(7)
Z	4
V, Å ³	2435 (2)
μ _{calc.} , cm ⁻¹	6.44
ρ _{calc.} , g · cm ⁻³	1.23
F(000)	960
Radiation	Cu K α (λ = 1.54178 Å)
Diffractometer	Enraf-Nonius CAD4
2θ range, deg.	152
Scan type	ω / 2θ
h, k, l range collected	0 → 10, -19 → 0, 0 → 23
Reflections collected	2853
Reflections observed, F ² ≥ 3σ (F ²)	2006
No. of reflections in least-squares	1902
No. of parameters	391
Goodness-of-fit	2.1
$R = \sum \Delta F / \sum F_o$	0.056
$R_w = [\sum w (\Delta F)^2 / \sum w F_o^2]^{1/2}$	0.063
Weighting scheme	$4F_o^2 / (\sigma(I)^2 + (0.04F_o^2))^2$

Results and Discussion

At the end of the procedure described in the experimental section, the expected 1,4-dihydropyridine **2**, as indicated by the spectral data,⁴ was isolated in 36% yield by evaporation of the ether solution. The ether-insoluble derivative (**3**) has the same molecular weight (m/z =

449) as **2** and was isolated in 29% yield. Its IR spectrum reveals the presence of a secondary amine (3251 cm^{-1}) and a (non conjugated) carbonyl group (1723 cm^{-1}). The ^1H NMR spectrum is indicative of an unsymmetrical and complex product with two non equivalent ester functions. In the ^{13}C NMR spectrum, 23 signals are detected. To establish the structure of **3**, a sample was investigated by X-ray single crystal diffraction. Compound **3** can be described as diethyl 2-benzylamino-6-(4-methoxyphenyl)-4-methylcyclohexa-1,3-diene-1,5-dicarboxylate.



The central unsaturated 6-membered ring adopts an unsymmetrical boat conformation, which is determined by two planar fragments twisted around the single bond C1-C6. The bond lengths in the ring (Table 2) reveal the "classical" trends usually observed for unsaturated systems: two double bonds C1-C2 and C5-C6 are nearly coplanar and elongated, while the single bond in between is shortened. The $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^2)$ bonds are shorter than the $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ bonds. The methoxybenzyl group at C3 is twisted around the C3-C17 bond by 25° to avoid steric interactions with the central 6-membered ring and the neighboring ethoxycarbonyl substituent at C2. This ethoxycarbonyl group forms a conjugated planar fragment $\text{C1}=\text{C2}\text{-C14}=\text{O1}$, the central single C2-C14 bond in this fragment is with $1.425(5)\text{ \AA}$ short and double bonds are elongated. In particular, the C14=O1 bond ($1.223(4)\text{ \AA}$) is 0.03 \AA longer than the C=O bond of the second ethoxycarbonyl substituent which exhibits a skew position with the torsion angle O3-C24-C4-C5 being -22.8° . The N-H bond of the benzylamino substituent is in an eclipsed position respective to the C1=C2 bond of the central ring. This permits a strong intramolecular hydrogen bond with formation of a 6-membered cycle. The parameters of the hydrogen bond are as follows: N1-H1...O1, N1-H1 $1.05(4)$, H1...O1 $1.86(5)\text{ \AA}$, $\angle\text{N1-H1...O1 } 127^\circ$.

Table 2. Principal geometrical parameters in compound **3**

Bond lengths in Å		Valence and torsion angles	
C1-C2	1.382(5)	C6C1C2	120.1(3)
C2-C3	1.521(5)	C1C2C3	118.3(3)
C3-C4	1.534(5)	C2C3C4	110.6(3)
C4-C5	1.518(5)	C3C4C5	112.0(3)
C5-C6	1.327(5)	C4C5C6	118.9(3)
C1-N1	1.354(4)	C5C6C1	122.3(3)
N1-C7	1.459(5)	C6C1C2C3	3.9(5)
C14=O1	1.223(4)	C1C2C3C4	-35.1(4)
C14-O2	1.353(5)	C2C3C4C5	47.6(4)
C14-C2	1.425(5)	C3C4C5C6	-31.6(5)
C3-C17	1.535(5)	C4C5C6C1	-0.8(6)
C24=O3	1.192(5)	C5C6C1C2	16.1(6)
C24-O4	1.331(5)	C1N1C7C8	-101.1(4)
C24-C4	1.516(5)	N1C7C8C13	38.4(5)

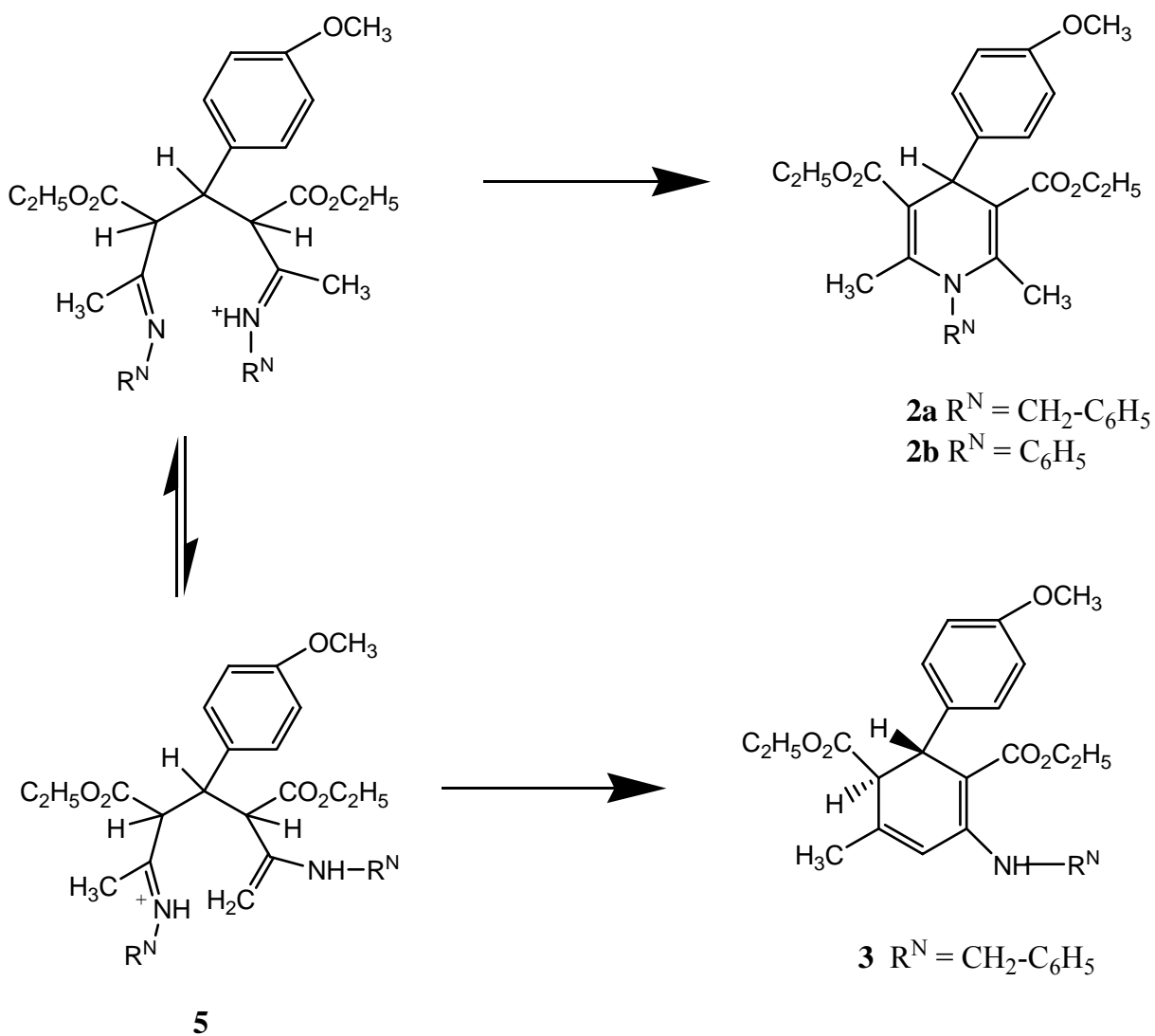
Since the molecule **3** contains a lot of C-H groups and O acceptors, one may expect intermolecular C-H...O interactions present in a vast number of crystal structures.¹² However, we did not observe C-H...O intermolecular contacts shorter than 2.6 Å. Moreover, there are many short intramolecular C-H...O contacts (Table 3), in which the H and O atoms are usually separated by three or four covalent bonds. The C - H contacts, treated as weak hydrogen bonds, are considered to play a significant role in crystal packing and molecular conformations.¹³⁻¹⁵ Many short contacts in molecule **3**, listed in Table 3, are imposed by the inherent geometry of the corresponding fragments. However, observed deviations of geometrical parameters from their "ideal" values tend to bring H and O atoms closer for most of the detected contacts. It should be mentioned that the positions of the hydrogen atoms were refined with sufficient accuracy in this structure, thus the deviation of the C-C-H bond angles from the tetrahedral value to 100(2)° or even less may therefore be indicative of hydrogen bond formation.

Table 3. Short intramolecular C-H...O contacts in compound **3**

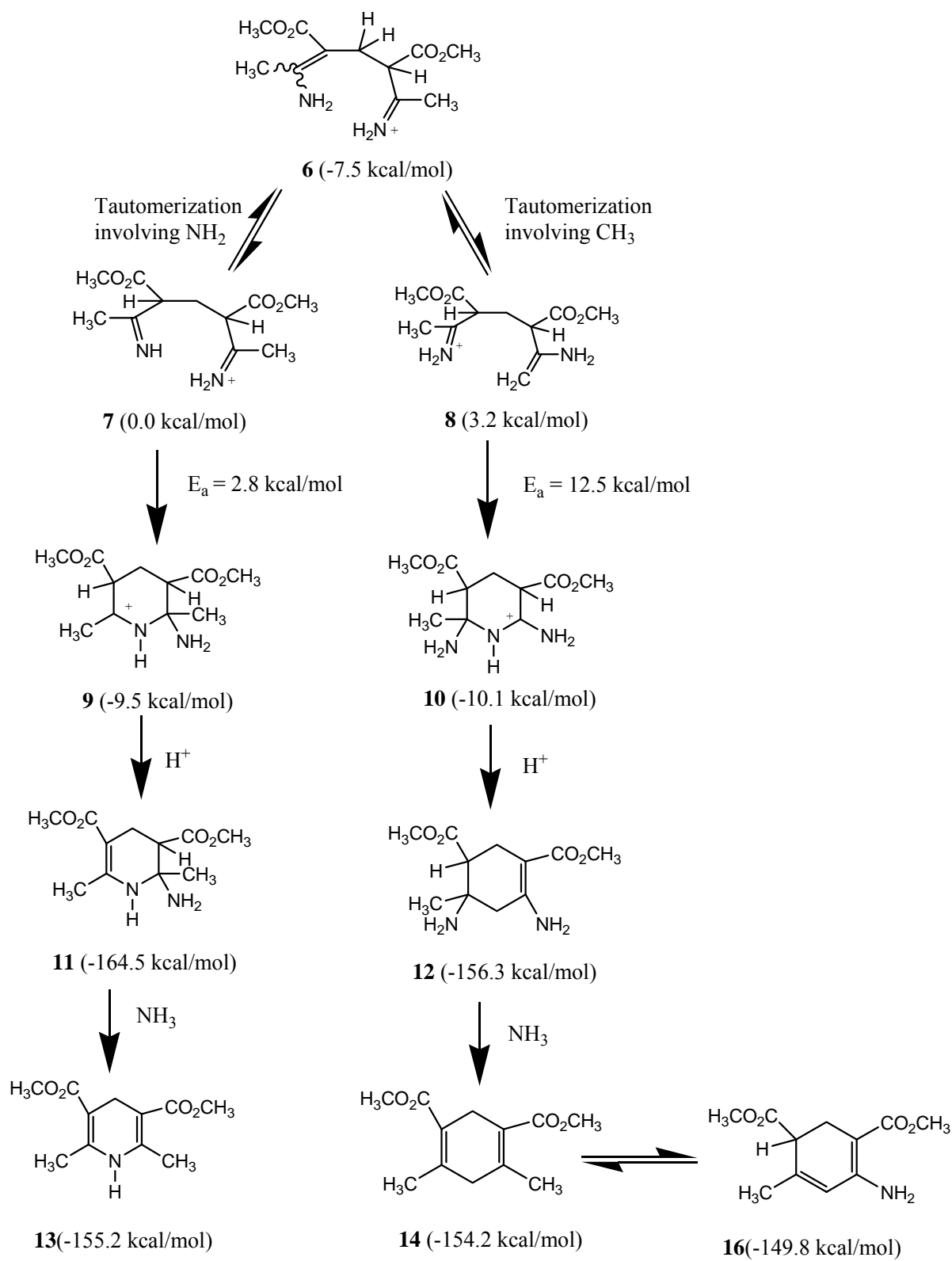
Short contacts in Å		Angles at hydrogen atoms in deg.	
O1...H152	2.43	C15-H152...O1	89
O2...H162	2.43	C16-H162...O2	75
O2...H3	2.39	C3-H3...O2	106
O3...H251	2.34	C25-H251...O3	94
O4...H4	2.37	C4-H4...O4	78
O4...H263	2.35	C26-H263...O4	77

The torsion angle H-C(CO₂Et)-C(Ar)-H is estimated to be - 74.7° in the solid phase, a result that is comparable to the value that can be calculated¹⁶ from the NMR data by the equations of Karplus (³J H-H < 1 Hz). This indicates a *trans* arrangement of the hydrogen atoms and characterizes a considerable flattening of the cycle.

We can rule out the interconversion between **2** and **3** as being responsible for the formation of **3** since a mixture of **2** and **3** does not change slightest when the reaction time is modified (2 h to 24 h) nor is affected when the temperature is raised to the reflux point of the solvent (acetonitrile or chlorobenzene). We therefore suggest (Scheme 2) – supported by semiempirical calculations, *vide infra* – that the cationic intermediate **4**, resulting from the interaction between the pyridinium salt and two molecules of the enaminoester, is the key intermediate in the formation of both **2** and **3**. Heterocyclization could yield compound **2**, whereas an imine-enamine tautomerization¹⁷ should be responsible for the formation of **3** *via* a Robinson-like annelation. In agreement with such a mechanism, preparation of a cyclohexadiene should be disfavored when starting from ethyl 3-phenylaminobut-2-enoate because of the poor electron-donating effect of the nitrogen atom in the enamine form **5**. This was experimentally verified. The reaction with **1** affords the 1,4-dihydropyridine **2b** as the only product (25% yield, hydrolysis of the enaminoester is the limiting side-reaction).



Scheme 2



Scheme 3

The proposed mechanistic pathways have been simulated by the semiempirical PM3¹⁸ method (Scheme 3).¹⁹ The initial step is the formation of **6**, which is obtained from the interaction between of **1** (R = H) and two molecules of the model enaminoester, MeCO₂C(H)=C(Me)NH₂.²⁰ Compound **6** allows tautomerization in two directions: a) formation of **7**, which contains a nucleophilic imine group; and b) formation of **8**, which exhibits an enamine moiety. Both structures are quite similar in energy, **8** turns out to be just 3 kcal/mol more energetic than **7**. The latter is responsible for the formation of **9** and the further steps which lead to **13**. The alternative route (*via* **10** and **12**) to yield **14** and **15** depends on the availability and nucleophilicity of the enamine C-atom. Furthermore, the activation barrier for the cyclization reaction **7** → **9** ($E_a = 2.8$ kcal/mol) is lower than for the alternative pathway **8** → **10** ($E_a = 12.5$ kcal/mol). Both barriers can be surmounted under the applied reaction conditions. These semiempirical results allow the following general interpretation: the formation of the dihydropyridine **13** is the dominant feature of our cyclization reactions. Nevertheless and as already mentioned, structures **7** and **8** do not differ significantly in energy. Therefore, the second channel remains open, depending on subtle sterical and electronical effects of the substituents R and R^N. For example, bulky substituents R^N (e.g. CH₂C₆H₅) at both nitrogens of **7** will hinder the ring closure reaction more efficiently than in case of the counterpart, the **8** to **10** cyclization.

Conclusions

As reported by some research groups, aminocyclohexadienes with different double bonds locations have been obtained¹⁷ in low yields, but as major product besides N-substituted 1,4-dihydropyridines, by the interaction between 2-(hetero)arylmethylene-3-oxobutanoates and 3-benzylaminobut-2-enoates. In contrast, the multi-component reaction described here constitutes a convenient method for the preparation, in fairly acceptable yields, of both a 2-benzylaminocyclohexa-1,3-diene **3** and the isomeric N-benzyl 1,4-dihydropyridine **2b**, whose separation is not a tedious process. Our results therefore constitute a novel example of the efficiency and advantages of using N-(1-haloalkyl)azinium halides instead of the starting aldehydes in a procedure that is characterized by its simplicity. The detection and isolation of **3** also enable us to explain the variations of yields previously observed⁴ during the preparation of other N-substituted 1,4-dihydropyridines from N-(1-haloalkyl)pyridinium chlorides and N-substituted enaminoesters.

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19. More detailed information (geometrical and energetical parameters, additional calculations) can be obtained from the authors on request.
20. The formation of compound **6** can be rationalized by a well-balanced influence of stereoelectronic effects and the nucleofugicity of the pyridine moiety in **1**. Cf. ref. 2.