Reaction of 2-Bromo 2-Alkenoic Carbonyl Compounds with Amidines: Experimental and Theoretical (PM3) Studies of the Mechanism of Heterocyclisation into Dihydroimidazole and Pyrimidin-4(3*H*)-one

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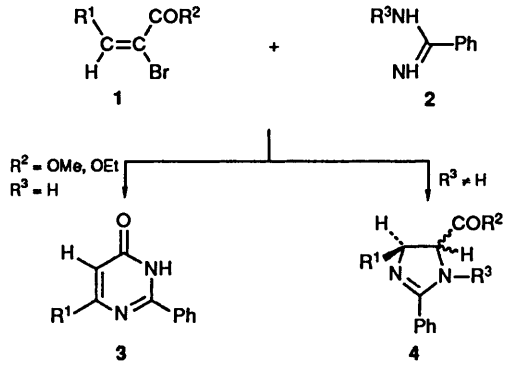
Different pathways have been considered to describe heterocyclisation between monosubstituted or unsubstituted amidines and 2-bromo 2-alkenoic carbonyl compounds, giving pyrimidin-4(3*H*)-one or dihydroimidazole heterocycles. Semi-empirical calculations (PM3) have been carried out on the reactants and intermediates. The transition states have been analysed. From both thermodynamic and kinetic arguments, it appears that a mechanism involving a pyrimidinone intermediate is more probable than one in which the intermediate is an aziridine. Solvent effects have been estimated and they do not seem to modify substantially these conclusions.

We have reported previously[1a,b] the reaction of 2-bromo 2-alkenoic carbonyl compounds **1**, with amidines **2**. When the substituent R^3 in the amidine was H and R^2 in the carbonyl compound was a leaving group, the pyrimidinone **3** was obtained exclusively (Scheme 1). In the literature[2-4] similar reactions have been reported to give **3**, when they have been carried out using an unsubstituted or mono *N*-substituted amidine. Several mechanisms may be advanced for the formation of functionalized dihydroimidazole **4** and pyrimidin-4-(3*H*)-one **3**. The condensation reaction of primary amines with ethyl 2-bromocinnamate[5,6] was considered as a good example, and allows us to propose a possible mechanism *via* an aziridine **6** or **6'**, then a 4-oxo-1,3-diazabicyclo[3.1.0]hex-2-ene **8** as intermediates (Scheme 2). In addition, the stereochemistry of **4** was consistent with the stereospecificity and regiospecificity observed in the rearrangement of aziridines[7,8] into 2-imidazolines or 2-oxazolines. Earlier observations[7,8] could also explain the formation of **4** when R^3 on the amidine is not H. Weiss *et al.*[9,10] have proposed a direct mechanism with a possible intermediate **7** (pathway b, Scheme 2) for this reaction. At the same time we proposed another mechanism,[1b] that followed pathway a, in Scheme 2. The latter clearly described an iminomethylaziridine intermediate **6** or **6'**, which rearranged *via* a 1,3-diazabicyclohexene **8** to give in a second step the product **3** (Scheme 2).

Elsewhere, on the basis of stereochemical results,[11] it was possible in a first approach to neglect a theoretical mechanism, involving a 1,3-amidine dipole as reactant. Also, the existence of such a highly reactive dipolar intermediate has never been encountered previously.[12,13]

Facing such a controversial situation it appeared necessary to undertake complementary experiments in order to display or isolate an aziridine intermediate during the course of the reaction. Two methods have been used: (i) ^{1}H NMR trapping experiments; and (ii) a similar chemical reaction pathway in which the same type of intermediates have been isolated previously.

In the meantime, because molecular modelling methods are becoming quite accessible for such molecules and are known to give reliable results, especially if one bears in mind the magnitude of the error bars entering their results, we decided to perform some quantum chemical computations to compare the possible reaction paths. Considering the size of the molecules, the choice of a semi-empirical method was necessary. The NDDO level of approximation seemed a reasonable choice. Owing to the fact that it is possible for some hydrogen bonds to play a role we selected the PM3 parametrization.[14] This choice will be discussed later.

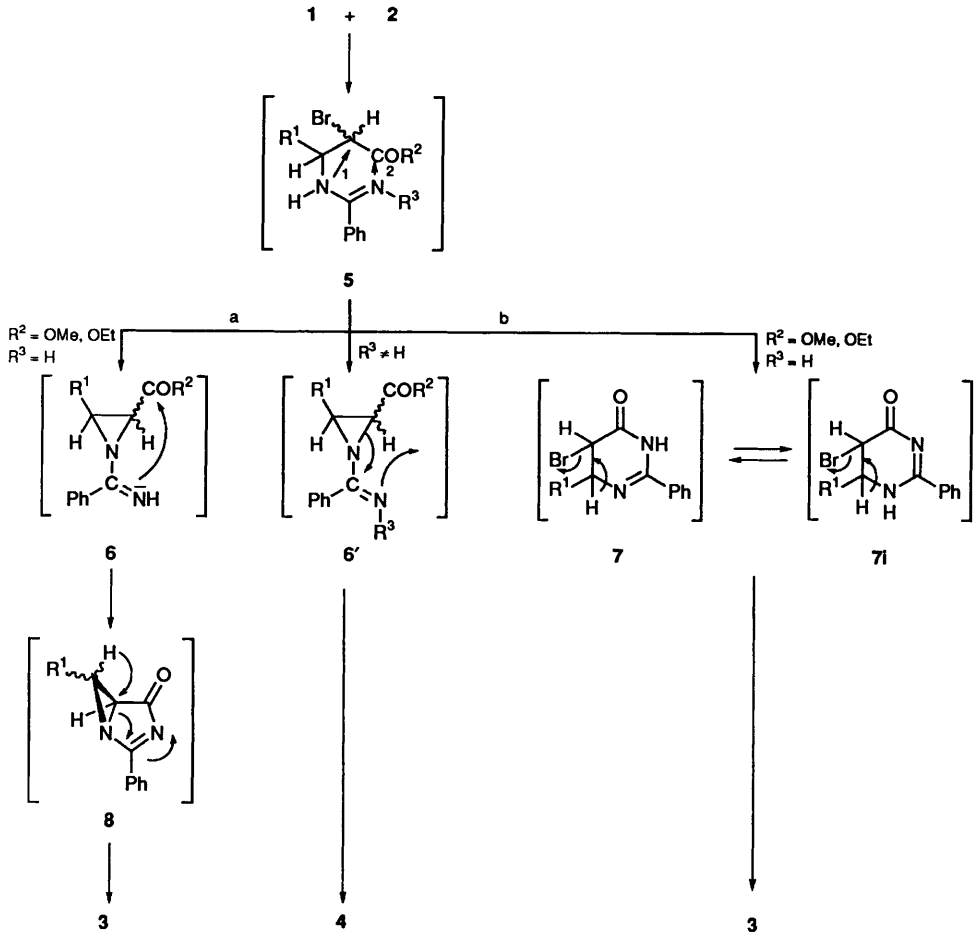


Scheme 1

Experimental

IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer as 2% KBr discs or neat; ^{1}H NMR on a Bruker AC 200 FT NMR spectrometer (200.132 MHz); and MS on a Nermag R-10-10C EI instrument at 70 eV.

Ethyl 2-Bromo-3-cyanoamino-2-methylbutanoate **13**.—A mixture of ethyl tiglate **9** (3.20 g, 2.5 mmol), cyanamide **11** (4.20 g, 100 mmol) and *N*-bromosuccinimide (NBS) **10** (5.34 g, 30 mmol) in CH_2Cl_2 (100 cm^3) was stirred in the dark for 1 h at 5 °C, and then for four days at room temp. The resulting suspension was filtered, and the filtrate was washed with distilled water (900 cm^3), dried (anhyd. Na_2SO_4) and evaporated to dryness. The crude product was purified by



Scheme 2

column chromatography on silica gel with $CHCl_3$–MeOH (80:20, v/v) as the eluent to yield **13** (186 mg, 30%) (Found: C, 38.5; H, 5.2; N, 11.2 $C_8H_{13}BrN_2O_2$ requires C, 38.6; H, 5.2; N, 11.4%); ν_{max}/cm^{-1} 3500 (NH), 2200 (C=N) and 1700 (C=O); δ_H(200 MHz; C_6D_6) 0.88 (3 H, t, *J* 7.10, *Me*CH_2), 1.11 (3 H, s, 2-Me), 1.23 (3 H, d, *J* 6.40, 4-H_3), 3.90 (2 H, q, *J* 7.10, MeCH_2) and 4.30 (1 H, q, *J* 6.40, 3-H); *m/z* 249 (M^+, 30%), 222 (M^+ + −27, 100), 207 (M^+ − 42, 72), 180 (21), 175 (55), 169 (84), 152 (17), 141 (52), 136 (11), 123 (31), 113 (68) and 108 (47).

Theoretical.—Computations were performed by the PM3 method,[14] and the CHIMISTE[15,16] and GEOMOS[17] packages. We computed the energies of the various molecules which occur in the different possible reaction paths both for isolated species and in solution. The effect of solvent was simulated by a dielectric continuum in a self consistent reaction field approach using a deformable ellipsoidal cavity[18,19] surrounded by dielectric continuum of dielectric permittivity $\varepsilon = 4.8$,[20] for $CHCl_3$. The transition states were located with the help of the procedure in the MOPAC package.[21] The modelling of the reaction paths was performed on a set of compounds in which the phenyl ring was replaced by a methyl group in order to reduce the size of the computations.

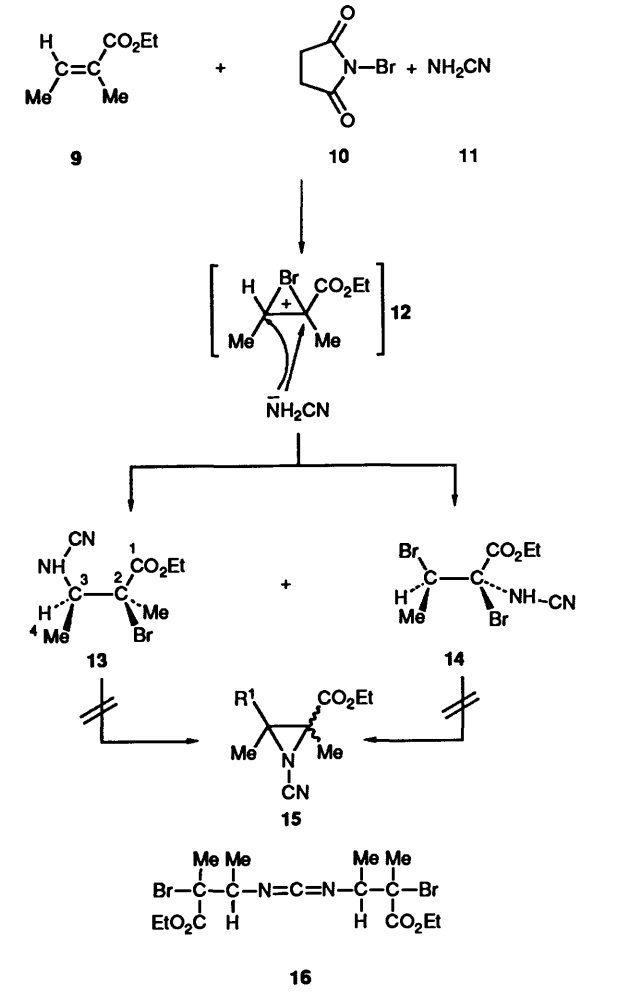
Results and Discussion

Clearly, isolation of the assumed intermediates would be the best proof of any proposed mechanism. Unfortunately, this was unsuccessful under normal or modified reaction conditions (*e.g.* low temperature ^1H NMR trapping experiments). This failure was not surprising, because it is known from other cases, that these unstable species were particularly difficult to observe or to isolate.[22–25] With simple unfunctionalized alkenes, Jung *et al.*[26,27] obtained a Michael adduct, which was cyclised into an *N*-cyanoaziridine with NBS and cyanamide, and was transformed into an *N*-imidoylaziridine and rearranged into a 2-oxazoline.

We therefore decided to reproduce (Scheme 3) similar experiments with unsaturated carbonyl compounds instead of the alkenes. Our first attempt failed with carbonyl compounds possessing an acidic C(O)*H*. The use of ethyl tiglate **9** avoided this problem and allowed the formation of the desired Michael adducts **13** and **14**, with **13** as the major and only characterized product. Also, a by-product of carbodiimide structure **16** similar to those described in the paper of Young[26] was obtained. Unfortunately, the cyclisation of **13** into *N*-cyanoaziridine **15** failed and only decomposition of the starting material was observed.

In order to further analyse the mechanism, we made some semi-empirical quantum chemical computations on the two paths a and b (Scheme 2).

Relative stability of the possible intermediates. Intermediates **6**, **6'**, **7** and **8** correspond to a minimum of the potential energy surface. Their PM3 energies are given in Table 1 together with the energies of the leaving molecules, and their geometries are presented in Fig. 1. These results show that the reaction leading to the pyrimidinone intermediate **7** should be exothermic (ΔE = −53.5 kJ mol^{-1}) although the aziridine intermediates **6** and **6'** should be obtained by an endothermic process (ΔE = +142 and +147 kJ mol^{-1} respectively), in the case of isolated species. The role of solvent does not seem to modify substantially these conclusions if HBr is solvated in the molecular form. In reality



Scheme 3

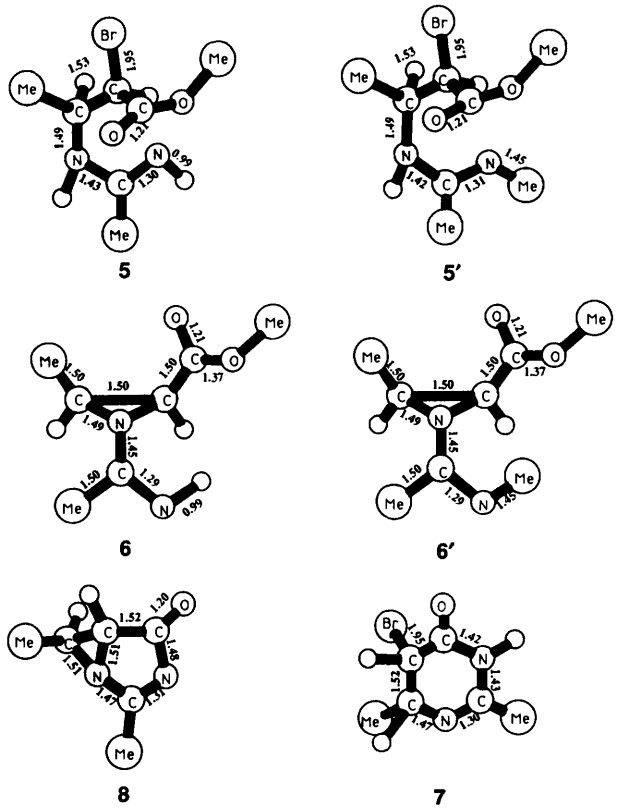


Fig. 1 Geometries (in Å) of the intermediates **5**–**8** (unlabelled circles = H)

Table 1 PM3 energies of intermediates **5**–**8** in a vacuum and in $CHCl_3$

Molecule	E/kJ mol^{-1} vacuum	$CHCl_3$
5 (R^2 = OMe, R^3 = H)	−221 502.6	−221 523.2
5' (R^2 = OMe, R^3 = Me)	−235 930.7	−235 940.9
6	−185 774.9	−185 804.8
6'	−200 198.1	−200 217.3
HBr	−355 85.8	−355 89.8
7	−175 805.8	−175 814.9
8	−140 004.3	−140 021.6
MeOH	−457 50.4	−457 56.8
3	−140 174.1	−140 190.6
4	−200 316.2	−200 346.0

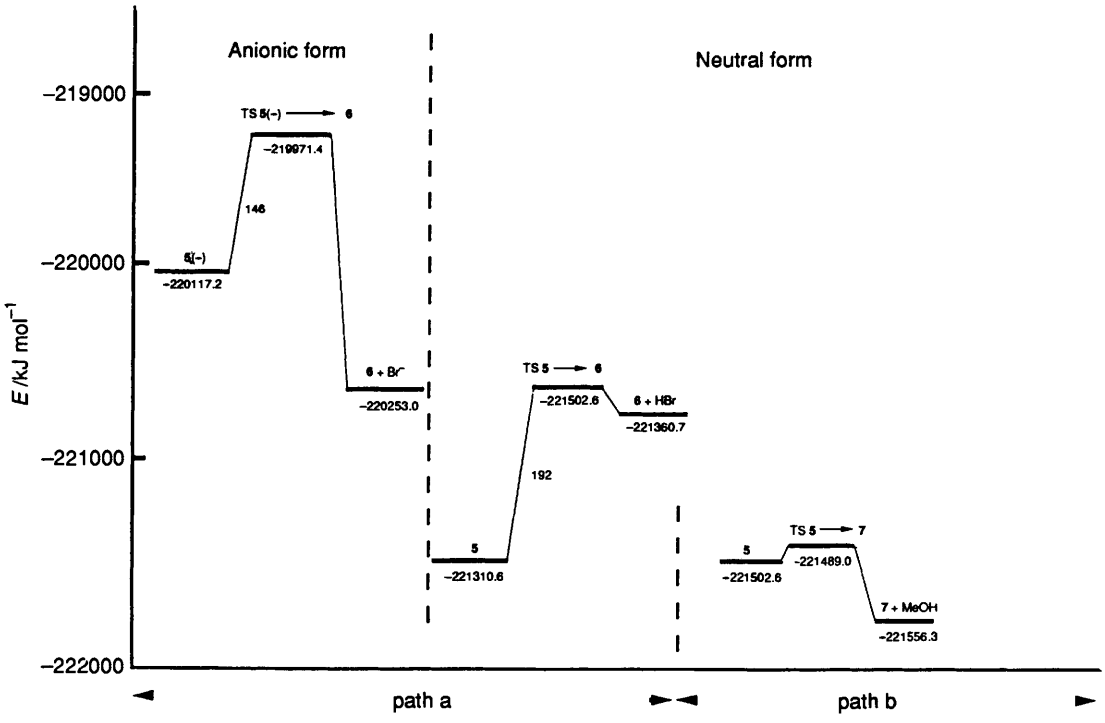
Table 2 PM3 energies of neutral and anionic transition states in a vacuum from neutral and anionic intermediates, **5** and **5'** to **6**, **6'** and **7**[a]

State	Molecule	E/kJ mol^{-1}
Starting intermediates	**5**	−221 502.6
(R^2 = OMe, R^3 = H)	**5**(−)	−220 117.2
(R^2 = OMe, R^3 = Me)	**5'**	−235 930.7
	5'(−)	−234 545.8
Final intermediates	**6**	−185 774.9
	6'	−200 198.1
	7	−175 805.9
Leaving molecules	HBr	−35 585.8
	MeOH	−45 750.4
Transition states	**5**→**6**	−221 310.6
	5(−)→**6**	−219 971.4
	5'→**6'**	−235 902.4
	5'(−)→**6'**	−234 602.2
	5→**7**	−221 489.0

[a] As references: the energies of starting intermediates and final intermediates **5**, **5'**, **6**, **6'** and **7**.

the reaction occurs in a basic medium and we observe the formation of an amine bromohydrate either with **2** or with an added amine, such as triethylamine. The heat of formation of this bromohydrate in solution is evaluated by our model as $\Delta H = -1023.3$ kJ mol^{-1}. The dissociation of HBr into H^+ and Br^- in the gas phase[28] requires *ca.* 1350 kJ mol^{-1} and the solvation enthalpy of Br^- was evaluated by means of the Born eqn.[29] to be −281.9 kJ mol^{-1}. It therefore appears that the formation of a bromohydrate in a solvent does not modify substantially the energetics of the reaction found in the gas phase.

Reaction path b appears to be favoured from a thermodynamic point of view. Nevertheless, owing to the fact that **6** and **7** are reaction intermediates, reaction path a can still be kinetically favoured—this is the reason why we computed the transition state of the various paths. In the case of path a in which departure of HBr is assisted by a second molecule, we chose to analyse two extreme situations: (i) the reaction occurring with HBr as a leaving molecule; or (ii) the reaction occurring on an anionic form **5**(−) corresponding to the deprotonated Michael adducts **5**. For path b we found that starting from the tautomer intermediate **7i** the transition state is 13.6 kJ mol^{-1} above the reactants. In the case of path a, the barrier is much higher in both situation (i) and (ii): 192 and 146 kJ mol^{-1}, respectively. All the results are summarized in Table 2 and Scheme 4. The corresponding anionic and neutral transition states geometries are shown in Fig. 2. Although the actual transition state in the assisted departure of HBr is probably below these two extreme cases, it cannot be below the intermediate products which are 142 kJ mol^{-1} above the reactants. In



Scheme 4

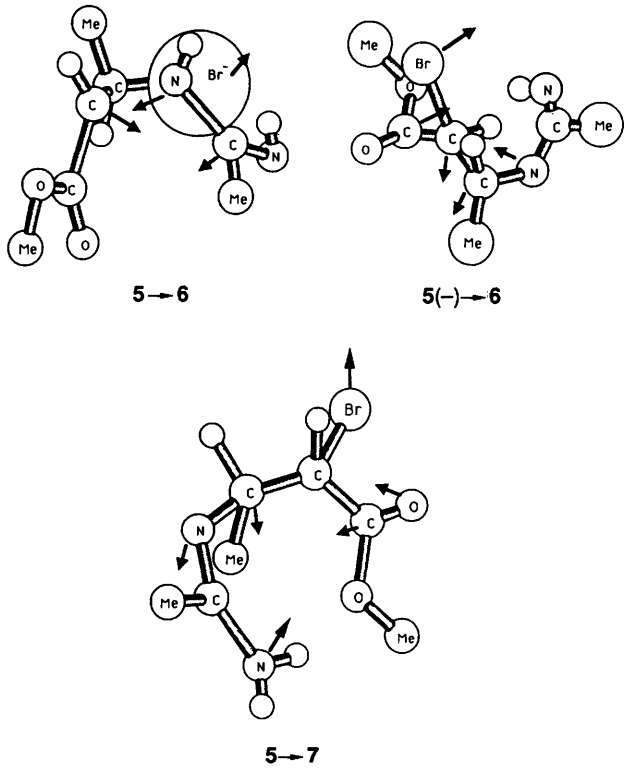


Fig. 2 Transition state geometries of paths a and b (unlabelled circles = H)

conclusion, it appears that the difference between the two paths both from the thermodynamic and the kinetic point of view are in favour of path b.

In addition, one notices that the differences between the two possible reaction paths are so large that the conclusions can hardly be modified by considering the error bars inherent in the semi-empirical method, which can be estimated to be less than 10 kJ mol^{-1} on activation energies. Similarly the conclusions are not expected to depend on the parametrization of the method. In this respect, MNDO[30] or AM1[31] results do not differ significantly from the PM3 ones, although these results suggest that the existence of an aziridine intermediate **6'** may be also improbable in the formation of imidazoline **4** from the methylated *vs.* alkylated compound **5'**. The heterocyclisation in this case probably follows other pathways which will be studied elsewhere.

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