



Theoretical study of the regiospecific synthesis of pyrazole-5-carboxylate from unsymmetrical enaminodiketones

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INTRODUCTION

The synthesis of pyrazoles has been the subject of consistent interest because of the wide applications for such heterocycles.¹ Nevertheless the synthesis of such compounds with unsymmetrical 1,3-dicarbonyl substrates often produces a regioisomeric mixture of pyrazoles with generally poor selectivity. However, Rosa and co-workers reported the regiospecific synthesis of pyrazole-5-carboxylates from unsymmetrical enaminodiketones.² Thus, considering the application of pyrazoles and the regiospecificity of the reactions presented by Rosa, we conducted a detailed theoretical investigation of the structure of the reagents, products and possible transition states in the reactions (Figure 1).

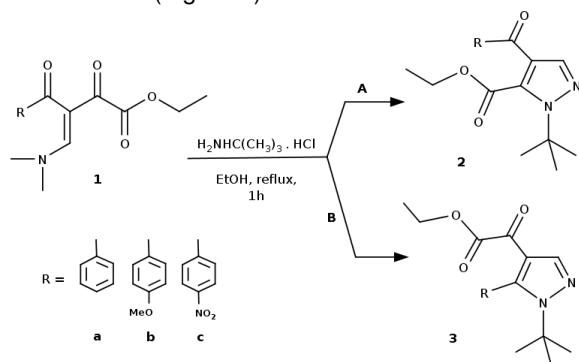


Figure 1. Enaminodiketones (1) and possible pyrazoles (2-3) from reaction with *tert*-butylhydrazine hydrochloride.²

RESULTS AND DISCUSSION

Geometries of the reactant, transition states and products of the reaction studied were optimized at M06-2X/6-31++G(d,p) level in ethanol (IEF-PCM) using the Gaussian 09. The optimized geometries were characterized as a minimum or transition state and the ZPE energies for all structures were determined (Table 1). All transition states were proved by applying the IRC methodology.

Rosa and co-workers observed the formation of only pyrazole 2 (cyclization A). The study of the transition states for the two cyclizations revealed that compounds 2a-c are the most stable (thermodynamic products). Whereas for cyclization B, 1a-c are the more stable structures.

Table 1. Relative energies (kcal mol⁻¹) for compounds a-c.

	a		b		c	
	A	B	A	B	A	B
Reac.	4.55	0.00	5.37	0.00	4.93	3.03
TS	14.18	9.47	14.96	10.54	10.89	10.99
Prod.	0.90	4.17	2.17	5.70	0.00	3.64
ΔE [‡]	9.64	9.47	9.59	10.54	5.95	7.95

*M062X/6-31++G(d,p) // IEF-PCM (ethanol)

For a and b, the TSB was more stable than TSA. For c both TSs have similar energies. The activation energies for 2a and 3a are very close and the OCH₃ introduction in the aromatic ring raised the activation energies of 3b (cyclization B) when compared with 3a but doesn't give much difference for cyclization A. On the other hand, the NO₂ introduction in the aromatic ring gives the smallest activation energies for both cyclizations.

The relative stability of TSB over TSA for a and b could be explained by the orientation of the TSB that permit a hydrogen bond between the protonated carbonyl with the ester carbonyl. For the TSA, this kind of interaction was observed only to compound c and helps to explain the higher stability of this TS. NBO analyzes showed that the LP_O → δ*_{O-H} for compound a was only 4.08 kcal mol⁻¹ in TSA but 33.87 kcal mol⁻¹ for TSB. The energy difference between 2a-c and 3a-c could be associated with the higher hyperconjugative orbital interactions in 2a-c due to the presence of a carbonyl between the aromatic ring and the pyrazole.

CONCLUSION

The regiospecific formation of the pyrazoles 2a-c (cyclization A) could be explained with the thermodynamic data once these products are more stable than the pyrazoles 3a-c.

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