A theoretical study of the mechanism of rearrangement of dihydropyrimidines into pyrroles

A. de la Hoz[1] , I. Alkorta[2]* and J. Elguero[2]

[1]Departamento de Química Orgánica, Facultad de Química, Universidad de Castilla-La Mancha, Avda. Camilo José Cela, 10, E-13071 Ciudad Real, Spain. [2]Instituto de Química Médica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain

Estudio teórido del mecanismo de transposición de dihidropirimidinas a pirroles

Estudi teòric del mecanisme de transposició de dihidropirimidines a pirrols

RECEIVED: 24 OCTOBER 2016. REVISED: 23 NOVEMBER 2016. ACCEPTED: 29 NOVEMBER 2016

SUMMARY

Two possible mechanisms for the transformation of a 1,4-dihydropyrrolo[3,2-b]pyrrole derivative into a tetrasubstituted pyrrole have been studied theoretically and one of them has been found in reasonable accord with the experimental data. This mechanism is part of the very rare example of rearrangement of dihydropyrimidines into pyrroles.

Keywords: Pyrimidines, pyrroles, cycloreversion, CO extrusion, DFT calculations.

RESUMEN

Se han estudiado teóricamente dos posibles mecanismos para la transformación de un derivado del 1,4-dihidropirrolo [3,2-b]pirrol en un pirrol tetrasustituido; uno de ellos está en acuerdo razonable con los datos experimentales. Este mecanismo es una parte de uno más completo de transposición de dihidropirimidinas en pirroles, del cual hay muy pocos ejemplos.

Palabras clave: Pirimidinas; pirroles; cicloreversión; extrusión de CO; cálculos DFT.

RESUM

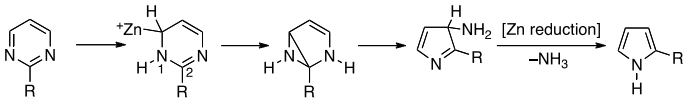
S'han estudiat teòricament dos possible mecanismes per a la transformació d'un derivat de 1,4-dihidropirrolo[3,2-b]pirrol en un pirrol tetrasustituit; un d'ells està en accord raonable amb les dades experimentals. Aquest mecanism és part d'un mes complet de transposició de dihidropirimidinas a pirrols, del qual hi ha molt pocs exemples.

Paraulas clau: Pirimidinas; pirrols; cicloreversió; exttrusió de CO; DFT calculs.

***Corresponding author: ibon@iqm.csic.es**

INTRODUCTION

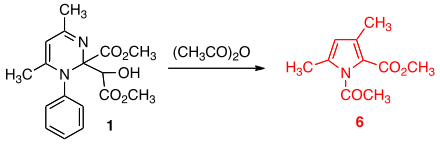
The field of heterocyclic rearrangements owes much to van der Plas and, particularly, to his two volumes on "Ring Transformations of Heterocycles" [1] where so many reactions are reported. If a search for transformation of pyrimidines into pyrroles is made, there is an entry in volume 2 sending to page 116, where there is nothing on this subject. However, in page 125 of the same volume, there is the following sentence "It has further been reported that arylpyrimidines by use of zinc and aqueous acetic acid are converted into pyrroles (ref. 453a). In the mechanism of this ring interconversion the site of the initial reduction attack by zinc is believed to be at the 1,6- rather than the 2,3-bond"[2,3]. One of the proposed mechanisms by Longridge and Thompson[3] is represented in Scheme 1. It may be observed that the mechanism involves a 2-substituted-1,6-dihydropyrimidine, although it was not isolated. The authors suggest that to prove the mechanism a dihydropyrimidine has to be synthesized and rearranged, they wrote: "Scheme 1 could be verified by synthesis of a dihydro compound and demonstrating that it will react to form a pyrrole under the required conditions. However compounds of this type have not been reported, possibly owing to their instability".



Scheme 1. *The Longridge-Thompson mechanism of ring-contraction of pyrimidines into pyrroles.*

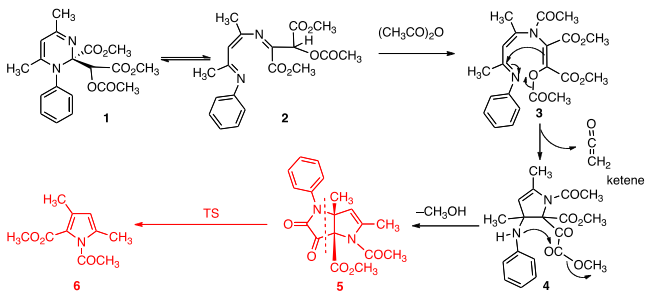
This work has been cited in several reviews[4,5,6,7] because it is related to the transformation of pyrimidin-2-ones to pyrroles[8,9,10,11]. The reaction has been successfully applied to the preparation of 4-cyanopyrroles[12].

In 1989 we reported (Scheme 2) the transformation of an isolated 1,2-dihydropyrimidine **1** into a pyrrole **6**[13].



Scheme 2. The 1989 ring transformation.

To explain the experimental results, we proposed the mechanism represented in Scheme 3.



Scheme 3. The proposed mechanism.

Since this ring contraction remains the only unambiguous reported example of a transformation of a dihydropyrimidine into pyrrole and since pyrimidine is one of the most important ring systems in medicinal chemistry[14], we decided to explore theoretically one part of the mechanism of Fig. 1, i.e. the transformation of the 3a,6a-dihydropyrrolo[3,2-b]pyrrole derivative **5** into the pyrrole derivative **6**.

COMPUTATIONAL DETAILS

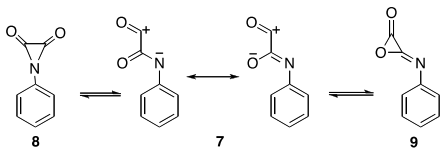
The geometry of the molecules has been fully optimized with the hybrid HF/DFT[15,16,17] computational method B3LYP and the 6-31G(d) basis set[18]. (posar el 18 en superindex). Frequency calculations have been carried out at the same computational level to verify that the structures obtained correspond to energy minima (number of imaginary frequencies = 0) or to transition states (TS, number of imaginary frequencies = 1). All the calculations have been carried out with the Gaussian-09 package[19].

RESULTS AND DISCUSSION

We have considered two possible mechanisms:

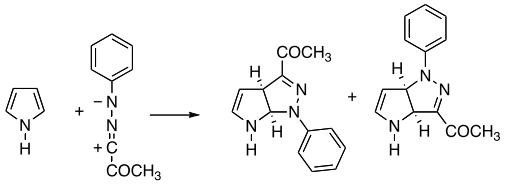
i. Retrocycloaddition.

The isomerization **5** → **6** is formally the reversed part of a 1,3-dipolar cycloaddition of the 1,3-dipole **7** [1-oxoethan-1-ylium)(phenyl)amide or (Z)-1-oxo-N-phenylethan-1-yliumimidate] on the pyrrole **6** (Scheme 4).



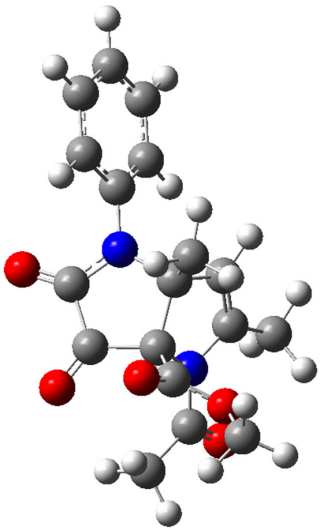
Scheme 4. *Compounds of general formula $C_8H_5NO_2$.*

Cycloaddition of dipoles on pyrroles are very uncommon and the main results were due to Ruccia, Vivona and Cusmano[20,21,22] (Scheme 5). Recently, it was reported the [3+2] dipolar cycloaddition reaction of nitrones and benzonitrile oxide with the electron-rich N-vinylpyrrole[23,24,25].



Scheme 5. *Addition of C-acetyl-N-phenylnitrilimine to pyrrole itself.*

We have calculated the minimum energy structures of compounds **5** and **6** (Fig. 1 and Fig. 2).



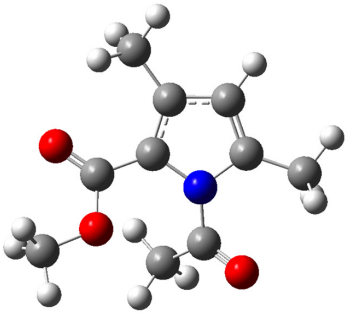


Fig. 1 *(compound* **5***) left;* **Fig. 2** *(compound* **6***) right.*

However, when the 1,3-dipole **7** was optimized, it spontaneously decomposes into isocyanatobenzene (or phenyl isocyanate) and carbon(II) oxide (or carbon monoxide). We have considered the possibility that the dipole **7** was stabilized by forming 1-phenylaziridine-2,3-dione (**8**) or (Z)-3-(phenylimino)oxiran-2-one (**9**). Isomer **8** is much more stable than **9** (43.9 kJ·mol^{-1}) and it has been isolated and characterized[26]. However, the energy balance is unfavorable, **5** being more stable than the sum of **6** and **8** by 100.8 kJ·mol^{-1}.

ii. CO extrusion.

Since compound **5** decomposes into three compounds, **6** plus phenyl isocyanate, Fig. 3 (**10**) and carbon monoxide, Fig. 4 (**11**) (both in their minimum energy structures), the reaction can be considered to belong to the group of CO extrusion reactions[27,28]. An FVP experiment of extrusion of CO from a compound related to **5** (a pyrrole-2,3-dione) has been reported[29]. Fig. 5 is the structure of the TS.

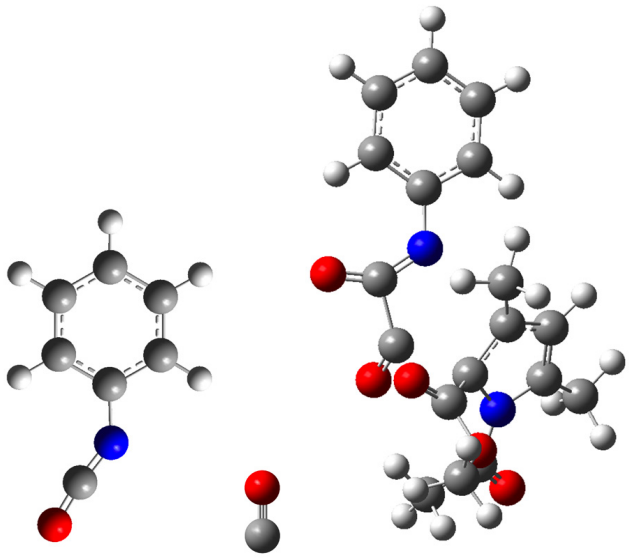


Fig. 3 *(compound* ***10****) left;* **Fig. 4** *(compound* ***11****) middle;* **Fig. 5** *(TS) right.*

The energy values are gathered in Table 1.

Table 1. *Energy values (absolute in hartress, relative in kJ·mol–1) of the mechanism* ***5*** *→* ***6*** *+* ***10*** *+* ***11****.*

Comp.	E	Erel	E+ZPE	Erel+ZPE	G	ΔG
5	–1182.3727	0.0	–1182.0351	0.0	–1182.0896	0.0
TS	–1182.3110	161.9	–1181.9785	148.6	–1182.0357	141.5
6	–669.3311	–1.0	–669.1117	–24.9	–669.1539	–127.9
10	–399.7325		–399.6284		–399.6608	
11	–113.3095		–113.3044		–113.3236	

The inclusion of the ZPE and even more the use of free energies strongly favors the fragments compared to the bicycle to the point that the transition state for the forward reaction is reduced to 13.6 kJ·mol^{-1}: this justifies the spontaneous **5** → **6** exoergonic reaction.

CONCLUSIONS

Computational chemistry can shed light on complex mechanisms as two recent reviews report [30,31]. Our present contribution justifies the spontaneous formation of pyrrole **6** from the bicyclic derivative **5**. Although the whole mechanism depicted in Scheme 3 still remains incomplete, at least, part of it is now firmly supported.

ACKNOWLEDGEMENTS

This work has been supported by the Spanish Ministerio de Economía y Competitividad (CTQ2015-63997-C2-2-P) and Comunidad Autónoma de Madrid (S2013/MIT-2841, Fotocarbon). Computer, storage and other resources from the CTI (CSIC) are gratefully acknowledged. We are greatly indebted to Professors Fernando Cossío (Universidad del País Vasco UPV/EHU, Química Orgánica I) and José Ignacio García (Instituto de Síntesis Química y Catálisis Homogénea, Universidad de Zaragoza-CSIC) for useful discussions about the mechanisms.

SUPPLEMENTARY DATA

Supplementary data associated with this article can obtained from the authors on request.

REFERENCES

1. H. C. van der Plas, Ring Transformations of Heterocycles, Vols. 1 and 2, Academic Press, London, 1973.
2. T. W. Thompson, Chem. Commun., 532 (1968).

3. J. L. Longridge, T. W. Thompson, J. Chem. Soc. C, 1658 (1970).
4. S. K. Robev, Khim. Geterotsikl. Soedin., 1587 (1981).
5. A. L. Weis, Adv. Heterocycl. Chem., **38**, 1 (1985).
6. A. L. Weis, H. C. van der Plas, Heterocycles, **24**, 1433 (1986).
7. U. Joshi, M. Pipelier, S. Naud, D. Dubreuil, Curr. Org. Chem., **9**, 261 (2005).
8. E. Bullock, R. A. Carter, B. Gregory, D. C. Shields, J. Chem. Soc., Chem. Commun., 657 (1972).
9. J. Ashby, D.Griffiths, J. Chem. Soc., Perkin Trans. 1, 657 (1075).
10. E. Bullock, R. A. Carter, R. M. Cochrane, B. Gregory, D. C. Shields, Can. J. Chem., **55**, 895 (1977).
11. C. O. Kappe, Tetrahedron, **49**, 6937 (1993).
12. S. Robev, Tetrahedron Lett., **19**, 1163 (1978).
13. A. M. de la Hoz, J. Elguero, C. Pardo, Heterocycles, **29**, 1951 (1989).
14. R. D. Taylor, M. MacCoss, A .D. G. Lawson, J. Med. Chem., **57**, 5845 (2014).
15. A. D. Becke, Phys. Rev. A, **38**, 3098 (1988).
16. A. D. Becke, J. Chem. Phys., **98**, 5648 (1993).
17. C. Lee, W. Yang, R. G. Parr, Phys. Rev. B, **37,** 785 (1988).
18. P. A. Hariharan, J. A. Pople, Theor. Chim. Acta, 2**8**, 213 (1973).
19. Gaussian 09, Revision A.1. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
20. M. Ruccia, N. Vivona, G. Cusmano, Tetrahedron Lett., **13**, (1972) 4703.
21. M. Ruccia, N. Vivona, G. Cusmano, G. Macaluso, J. Heterocycl. Chem., **15**, (1978) 1485.
22. A. S. Shawali, M. M. Edrees, Arkivoc, **ix**, 292 (2006).
23. A. P. Molchanov, R. S. Savinkov, A. V. Stepakov, G. L. Starova, R. R. Kostikov, V. S. Barnakova, A. V. Ivanov, Synthesis, **46**, 771 (2014).
24. M. M. Efremova, A. P. Molchanov, A. V. Stepakov, R. R. Kostikov, V. S. Shcherbakova, A. V. Ivanov, Tetrahedron, **71**, (2015) 2071.
25. L. R. Domingo, S. Emamian, M. Salami, M. Ríos-Gutiérrez, J. Phys. Org. Chem.,29, 368 (2016)
26. F. Risi, L. Pizzala, M. Carles, P. Verlaque, J. P. Aycard, J. Org. Chem., **61**, 666 (1996).
27. A. Obenhuber, K. Ruhland, Organometallics, **30**, 171 (2011).
28. C. Schulten, G. von Frantzius, G. Schnakenburg, A. Espinosa, R. Streubel, Chem. Sci., **3**, 2526 (2012).
29. S. Ebner, B. Wallfisch, J. Andraos, I. Aitbaev, M. Kislewsky, P. V. Bernhardt, G. Kollenz, C. Wentrup, Org. Biomol. Chem., **1**, 2550 (2003).
30. D. Balcells, E. Clot, O. Eisenstein, A. Nova, L. Perrin, Acc. Chem. Res., **49**, 1070 (2016).
31. T. Sperger, I. A. Sanhueza, F. Schoenebeck, Acc. Chem. Res., **49**, 1311 (2016)