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Synthesis of 3-(1-Adamantyl)pyrazole and 3,5-Di(1-adamantyl)pyrazole in a Microwave Oven

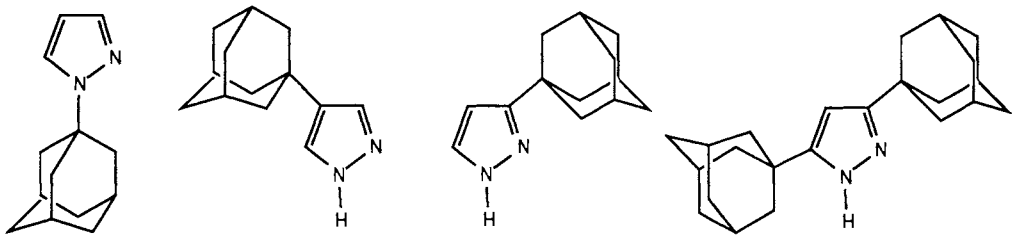
Isabelle FORFAR,* Pilar CABILDO, Rosa María CLARAMUNT and José ELGUERO
Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED & CSIC,
Ciudad Universitaria, 28040 Madrid, Spain

An extraordinary inversion of the regioselectivity in the reaction of C-adamantylation of pyrazoles by 1-bromoadamantane was observed when the autoclave vessel was replaced by a microwave oven. In these last conditions mono and disubstituted 3(5)-(1-adamantyl) pyrazoles were obtained.

Pyrazoles bearing 1-adamantyl substituents are interesting compounds for several reasons: the high lipophilicity of the adamantyl residue [π_{Ad} = 3.49] strongly affects the biological response,[1] the extreme polarizability of the substituent [σ_α = -0.95] modifies the acid-base properties in the gas phase,[2] and the plasticity of adamantane confers special physical properties to the resulting crystals .[3]

Of the three possible positions of a substituent in a pyrazole ring, 1, 4 and 3(5), the synthesis of 1-(1-adamantyl)-pyrazoles, for instance **1**, is straightforward either by *N*-adamantylation or by reaction of *N*-adamantylhydrazine with β-dicarbonyl compounds.[4]

On the other hand, 3,5-disubstituted 4-(1-adamantyl)pyrazoles are easy to prepare from β-diketones such as acetylacetone, by *C*-adamantylation followed by reaction with hydrazine.[5] This procedure cannot be used starting from malonaldehyde and, consequently, 4-(1-adamantyl)pyrazole itself **2** has to be prepared in a four-step procedure from 1-adamantylcarboxaldehyde with a low total yield.[6] However, we have recently reported that 4-(1-adamantyl)pyrazoles, like **2**, can be obtained very easily by *C*-adamantylation of pyrazoles.[7]



1 **2** **3** **4**

Finally, the unknown 3(5)-(1-adamantyl)pyrazoles, for instance **3**, cannot be prepared by any of the preceding procedures. We have discovered that changing the reaction conditions from an autoclave to a microwave (MW) oven produces a surprising inversion of the regioselectivity: from pure **2** without traces of **3** obtained in an autoclave[7] we have obtained pure **3** without traces of **2** in the MW oven.[8a] If the relative amounts of reagents are changed from 1:6 (1-bromoadamantane/pyrazole) to 1:1, then 3,5-di(1-adamantyl)pyrazole **4** is obtained.[8b] For these syntheses to succeed is of paramount importance that the teflon vessel is perfectly closed. A decrease in the internal pressure results in the formation of large quantities of **1**. The same result occurs when the MW power is decreased from 600 W to 440 W.

A final comment concerning the mechanism of these adamantylations follows. The only related reaction in pyrazole chemistry, which affords 1, 4 or 3(5) isomers depending on the experimental conditions , is nitration. In this case also, 1-nitro, 4-nitro and 3(5)-nitropyrazoles are obtained, the last ones by [1,5]sigmatropic shift from 1-nitro derivatives.[9] We think that the mechanisms involved in the adamantylation of pyrazole may change depending on the temperatures and pressures used. However, nitration and adamantylation do not follow the same paths: 1-(1-adamantyl)pyrazole **1** does not isomerize into 3(5)-(1-adamantyl)pyrazole **3** in the MW oven.

The three main conclusions of this work are: i) the dramatic effect that experimental conditions (heating a sealed tube or introducing it in a MW oven) produces on a simple reaction; ii) that 3(5)-(1-adamantyl)pyrazoles, previously unknown, can be easily prepared from commercial products; iii) that probably the reaction is general and may be used to C-adamantylate other heterocycles, for instance, 1,2,4-triazoles.

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References

1) M. E. Gonzalez, B. Alarcon, P. Cabildo, R. M. Claramunt, D. Sanz, and J. Elguero, *Eur. J. Med. Chem.*, **20**, 359 (1985); R. M. Claramunt, D. Sanz, J. Elguero, J. Alvarez-Builla, and F. Gago, *Il Farmaco Ed. Sci.*, **42**, 915 (1987).

2) R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, **17**, 159 (1990); C. Hansch, A. Leo, and R. W. Taft, *Chem. Rev.* , **91**, 165 (1991); R. Notario, M. Herreros, A. El Hammadi, J-L. M. Abboud, I. Forfar, R. M. Claramunt, and J. Elguero, *J. Phys. Org. Chem.*, **1994**, in press.

3) M. Foulon, T. Belgrand, C. Gors, and M. More, *Acta Crystallogr.*, **B45**, 404 (1989); Y. Huang, D. F. R.Gilson, I. S. Butler, and F. Morin, *J. Phys. Chem.*, **95**, 2151 (1991).

4) P. Cabildo, R. M. Claramunt, and J. Elguero, *J. Heterocycl. Chem.*, **21**, 249 (1984); P. Cabildo, R. M. Claramunt, D. Sanz, M. C. Foces-Foces, F. H. Cano, J. Catalán, and J. Elguero, *Tetrahedron*, **41**, 473 (1985); P. Cabildo, R. M. Claramunt, D. Sanz, M. C. Foces-Foces, F. H. Cano, J. P. Fayet, M. C. Vertut, and J. Elguero, *J. Heterocycl. Chem.*, **23**, 1045 (1986).

5) A. Gonzalez, J. Marquet, and M. Moreno-Mañas, *Tetrahedron*, **42**, 4253 (1986).

6) C. Reichardt and E. U. Würthwein, *Z. Naturforsch.*, **37b**, 1187 (1982).

7) P. Cabildo, R. M. Claramunt, I. Forfar, and J. Elguero, *Tetrahedron Lett.*, **35**, 183 (1994); P.Cabildo, R. M. Claramunt, I. Forfar, C. Foces-Foces, A. L. Llamas-Saiz, and J. Elguero, *Heterocycles*, **37**, 1623 (1994).

8) a) *Preparation of 3(5)-(1-adamantyl)pyrazole* **3**. A fine powdered mixture of 2.5 mmol of 1-bromoadamantane and 15 mmol of pyrazole is placed in a teflon autoclave (4781 Parr microwave bomb of 23 ml), which, in turn, is put in a digestion bomb. The whole system is irradiated during 3 min at 600 W in the microwave oven (Panasonic NN 5352). After cooling, the mixture is disolved in dichloromethane and chromatographed over silica gel (eluent: dichloromethane/ethanol 9:1). Yield 44%. Mp 135-138 °C. R_f = 0.58 (dichloromethane/ ethanol 9:1) (A small amount (6%) of **4** is also present). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.08 (d, J = 1.9 Hz, 1 H, 4-H), 7.49 (d, J = 1.9 Hz, 1 H, 5-H), 1.78 (s, 6 H, Hδ Ad), 1.95 (s, 6 H, Hβ Ad), 2.07 (s, 3 H, Hγ Ad). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 156.0 (br, C-3), 135.3 (br, C-5), 100.10 (C-4), 28.22 (3 C, Cγ), 32.90 (1 C, Cα), 36.43 (3 C, Cδ), 42.31 (3 C, Cβ). b) *Preparation of 3,5-di(1-adamantyl)pyrazole* **4**. The only difference from the preceding procedure is the relative amounts of reagents, in this case 5 mmol of bromoadamantane and 5 mmol of pyrazole. With the same purification work up a 48% yield of **4** is obtained (no presence of **3**). Mp 338-340 °C (water-ethanol). R_f = 0.72 (dichloromethane/ethanol 9:1). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.08 (1 H, 4-H), 1.78 (s, 6 H, Hδ Ad), 1.95 (s, 6 H, Hβ Ad), 2.10 (s, 3 H, Hγ Ad), 11.41 (br, NH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 157.24 (br, C-3 and C-5), 95.60 (C-4), 28.34 (6 C, Cγ), 33.16 (2 C, Cα), 36.57 (6 C, Cδ), 42.50 (6 C, Cβ).

9) J. Elguero, in Pyrazoles and their Benzo Derivatives, *Comprehensive Heterocyclic Chemistry*, **5**, 270 (1984).

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