Tetrahedron Letters,Vol.29,No.46,pp 6001-6004,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

HETEROCYCLE FORMATION FROM 1,3-DINITROALKANES. A NOVEL PYRAZOLE SYNTHESIS

F. Cabrera Escribano, M.P. Derri Alcántara and A. Gómez-Sánchez*

Instituto de la Grasa y sus Derivados, CSIC, and Departamento de Química Orgánica, Universidad de Sevilla, Apartado de Correos No. 553, 41071-Seville, Spain

Summary.- 1,3-Dinitroalkanes, obtained in almost quantitative yields by Michael additions of nitroalkanes to nitro-olefins, react with hydrazines affording pyrazoles, in most cases in high yields.

Aliphatic nitro compounds have proved to be useful starting materials in organic synthesis.[1] When the nitro compounds are properly substituted they can cyclize, yielding heterocyclic compounds.[1,2] 1,3-Dinitroalkanes can be viewed as synthetic equivalents for 1,3-dicarbonyl compounds through a Nef, or equivalent, reaction, and therefore could be ultimately converted into azole heterocycles. Application of the Nef reaction under the usual conditions (NaOH; conc. H_2SO_4) to 1,3-dinitroalkanes gives only trace amounts of the anticipated dione,[3] although the yields can be increased (up to 40%) using a secondary amine as the base.[4] We now find that 1,3-dinitroalkanes react with hydrazines giving rise to pyrazoles.

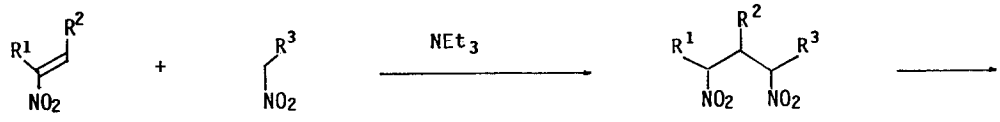
The 1,3-dinitroalkanes **3b,c** and **3e** were prepared by treatment of the appropiate nitro-olefin (**1a,b** and **1d**) and an excess of nitroethane (used as solvent) at room temperature in the presence of a catalytic amount of triethylamine. Evaporation of the reaction mixture gave an almost quantitative yield of the corresponding adduct pure enough to be used in the next step. Purification (and separation of the different stereoisomers) could be achieved by chromatography or fractional crystallization.[5] Treatment of these adducts with a ten-fold excess of hydrazine or methylhydrazine in ethanol solution then afforded the pyrazoles **4b-f** and **4h** (Scheme 1 and Table 1). A typical example is as follows:

A solution of 2,4-dinitro-3-phenylpentane (**3c**; 0.24 g) in ethanol (10 mL) containing hydrazine hydrate (0.5 mL) was stirred at room temperature for 24 hr. Evaporation of the mixture and recrystallization of the residue from EtOH-H_2O 1:4, gave 2,4-dimethyl-3-phenylpyrazole (**4e**, 0.12 g), m.p. 131-132°C.

The intermediate 1,3-dinitroalkanes need not be isolated; for example **4e** was obtained in better yield by the reaction of 2-nitro-1-phenylpropene (**1b**) and nitroethane followed by treatment with hydrazine hydrate. This one-pot procedure was adopted to prepare 4-phenylpyrazole (**4a**), 3,4,5-trimethylpyrazole (**4g**) and 4-(2'-furyl)-3,5-dimethylpyrazole (**4i**); the corresponding dinitroalkanes (**3a,d** and **3f**) were not isolated. The procedure is as follows:

A mixture of the nitro-olefin **1** (1 mmol), the nitroalkane **2** (10 mL) and Et_3N (0.5 mL) was allowed to stand at room temperature until complete transformation of **1** had taken place (t.l.c., 2-24 hr). The solvent was removed by evaporation, and the residue, dissolved in ethanol (10 mL), was stirred with hydrazine hydrate (10 mL) for the period of time and at the temperature indicated in Table 1. Evaporation of the mixture, and purification of the residue by crystallization or column chromatography (silica-gel, hexane-EtOAc 4:1) afforded the pyrazole **4**.

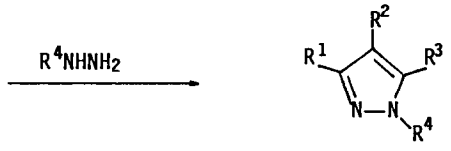
SCHEME 1



1 2 3

	R^1	R^2		R^3
a	H	Ph	**a**	H
b	Me	Ph	**b**	Me
c	Me	Me		
d	Me	p-MeO-C_6H_4		
e	Me	2-Furyl		

	R^1	R^2	R^3
a	H	Ph	H
b	H	Ph	Me
c	Me	Ph	Me
d	Me	Me	Me
e	Me	p-MeO-C_6H_4	Me
f	Me	2-Furyl	Me



4

	R^1	R^2	R^3	R^4
a	H	Ph	H	H
b	H	Ph	Me	H
c	H	Ph	Me	Me
d	Me	Ph	H	Me
e	Me	Ph	Me	H
f	Me	Ph	Me	Me
g	Me	Me	Me	H
h	Me	p-MeO-C_6H_4	Me	H
i	Me	2-Furyl	Me	H

TABLE 1

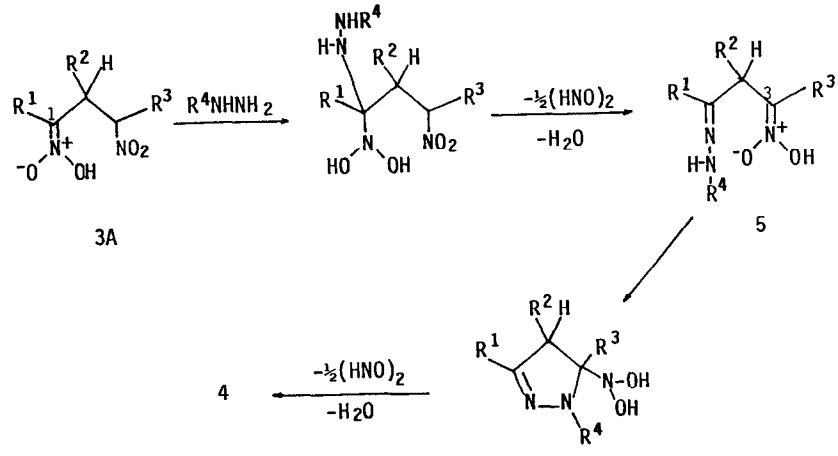
Compound	Yield (%)[a]	M.p. (°C) Obs.	M.p. (°C) Lit.	Reaction time[b]
4a	(38)	229-230	228[6]	2 weeks[c]
4b	56	140-142	140-142[7]	24 h
4c + 4d	62	syrup	-----[8]	18 h
4e	65 (71)	131-132	131-132[9]	24 h
4f	30[d]	34-35	35-37[10]	8 h
4g	(77)	138-139	137-138[11]	12 h
4h	68	153-155		18 h
4i	(58)	125-126		3 h

[a]In brackets, yield by the one-pot procedure. [b]At room temperature unless otherwise indicated. [c]At 80°C. [d]A mixture of products resulted, from which **4f** was isolated.

The efficiency of the reaction depended on the nature of the substituents R^1-R^4, being the lowest for R^1=R^3=H; furthermore, the reactions with hydrazine hydrate were slower than the reactions with methylhydrazine. In the experiments using phenylhydrazine long reaction times were required for the complete transformation of the dinitroalkanes, and complex mixtures of products resulted.

The pyrazole-forming reaction may be viewed as a stepwise hydrazinolysis process initiated by the nucleophilic attack of hydrazine on the electron-deficient C-1 of the nitronic acid **3A**, followed by dehydration and elimination of the elements of hyponitrous acid (HNO) (Scheme 2). Subsequent intramolecular attack of the amino group of the resulting hydrazone **5** on C-3, and elimination again of H_2O and HNO, would then yield the pyrazole **4**.

SCHEME 2



The procedure described here affords substituted pyrazoles, including 4-arylpyrazoles, from easily available starting materials, and complements the classical procedure using 1,3-dicarbonyl compounds, which is better suited for the preparation of 4-alkylpyrazoles.

The scope and mechanism of this reaction is being further investigated.

Acknowledgment: The authors thank the Comisión Asesora de Investigación Científica y Técnica and the Consejo Superior de Investigaciones Científicas of Spain for financial support.

REFERENCES AND NOTES

1. D. Seebach, E.W. Colvin, F. Lehr and T. Weller, Chimia, **1979**, 33, 1.
2. R. Fernández-Fernández, J. Galán and A. Gómez-Sánchez, J. Chem. Res. (M), **1987**, 1748, and references therein.
3. H.R. Snyder and W.E. Hamlin, J. Am. Chem. Soc., **1950**, 72, 5082.
4. M. Lagranée, C. R. Seances Acad. Sci. Serie C, **1977**, 153.
5. The reaction of 2-nitrostyrene (**1a**) and nitroethane (**2b**) yielded (95%) a mixture of the two (+,-) pairs of 1,3-dinitro-2-phenylbutane (**3b**), which were separated by fractional crystallization from EtOH; the most insoluble form (yield 48%) had m.p. 80-81°; concentration of the mother liquors afforded the second (+,-) pair, m.p. 44-46°, (19% after recrystallization from EtOH). 2,4-Dinitro-3-phenylpentane (**3c**) was obtained (98%), as a mixture of stereoisomers, from 2-nitro-1-phenylpropene (**1b**) and nitroethane (**2b**); fractional crystallization from EtOH afforded a meso-form (50%), m.p. 176-179°; evaporation of the mother liquors and chromatography of the residue afforded the (+,-) pair (28%), m.p. 98-100°. The reaction of 2-nitro-1-(4'-methoxyphenyl)propene (**1d**) and nitroethane (**2b**) gave (80%) 2,4-dinitro-3-(4'-methoxyphenyl)pentane (**3e**) as a mixture of stereoisomers; recrystallization from EtOH afforded (22%) a meso-form, m.p. 153-154°; evaporation of the mother liquors and chromatography of the residue, yielded (20%) a (+,-) pair, m.p. 55-56°.
   New compounds gave correct elemental analyses and had spectral properties consistent with the assigned structures.
6. H.V. Pechmann and E. Burkard, Ber., **1900**, 33, 3596.
7. J.A. Moore and C.L. Habraken, J. Org. Chem., **1965**, 30, 1889.
8. C.L. Habraken and J.A. Moore, ibid., **1965**, 30, 1892.
9. G. Fukata, Y. Kawazoe and T. Taguchi, Tetrahedron Lett., **1973**, 15, 1199.
10. F. Cohen-Fernandes and C.L. Habraken, Rec. Trav. Chim. Pays-Bass, **1967**, 86, 1249.
11. L. Knorr and B. Oettinger, Liebigs Ann. Chem., **1894**, 279, 244.

(Received in UK 22 September 1988)