Monatshefte für Chemie 116, 223—228 (1985)

Monatshefte für Chemie
Chemical Monthly

Studies on 3,5-Diaminopyrazole Derivatives

Nosrat Mustafa Abed*, Ebtisam Abdel Aziz Hafez, Nadia Sobhy Ibrahim, and **Mohamed Elsaid Mustafa**

Department of Chemistry, Faculty of Science,
Cairo University, Giza, A.R. Egypt

(Received 24 October 1983. Revised 2 February 1984. Accepted 17 February 1984)

The behaviour of 3,5-diamino-4-phenylazopyrazole toward a variety of reagents is reported. Several new 3,5-diaminopyrazole derivatives as well as amino derivatives of fused pyrazoles have been prepared.

(Keywords: Heterocyclic compounds; fused pyrazoles)

Untersuchungen an 3,5-Diaminopyrazol-Derivaten

Es wird über das Verhalten von 3,5-Diamino-4-phenylazopyrazol gegenüber verschiedenen Agentien berichtet. Es wurden sowohl einige neue 3,5-Diaminooyrazol-Derivate als auch einige Aminoderivate von kondensierten Pyrazolen dargestellt.

Introduction

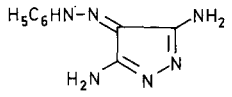
Aminopyrazoles are versatile reagents that have been extensively utilised as intermediates for synthesis of fused pyrazoles of potential biological activity[1—4]. In spite of enormous efforts in the chemistry of 5-aminopyrazoles, very little attention has been paid to the chemistry of 3,5-diaminopyrazoles. The difficulty to access to these pyrazole derivatives is probably the reason. Sometime ago, however, a new efficient synthesis of 3,5-diamino-4-phenylazopyrazole (**1**) has been reported by *Elnagdi* et al.[5]. The authors have also reported several chemical properties of this compound which proved to be different from other aminopyrazole derivatives. In order to explore further the chemistry of 3,5-diaminopyrazoles, the behaviour of **1** towards a variety of reagents has been investigated.

Results and Discussion

In previous reports it has been shown that 5-aminopyrazoles react with hydrazidic halides to yield either alkylation products or 3 + 2 cycloaddi-

tion products[6]. Now it has been found that **1** reacts with benzophenylhydrazonyl chloride (**2 a**) to yield a product of molecular formula $C_{22}H_{17}N_7$. The pyrazolo[5,1-c]-1,2,4-triazole structure was considered for the reaction product based on spectral data and its stability under conditions reported to effect decomposition or isomerisation of isomeric pyrazolo-[1,5-c]-1,2,3-triazoles[6]. The formation of **3** may be assumed to proceed either via alkylation of **1** and subsequent cyclization or via addition of the nitrile imine, formed by dehydrohalogenation of **2 a** to the double bond in **1**. We believe that the reaction proceeds most likely via the cycloaddition route as previously reported for a similar reaction; N-alkylated pyrazoles

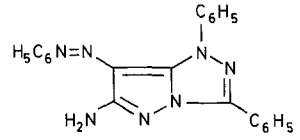
Scheme 1



1

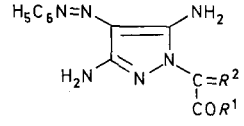
	R^1	R^2
2a	C_6H_5	$N-NHC_6H_5$
b	$COCH_3$	$N-NHC_6H_5$
c	$CONHC_6H_5$	$N-NHC_6H_4Cl-p$
d	$CO_2C_2H_5$	$OH-C-CH_3$

1 + 2a ⟶



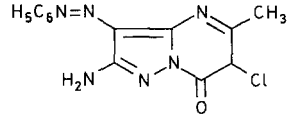
3

1 + 2b,c ⟶



	R^1	R^2
4a	CH_3	$N-NHC_6H_5$
b	NHC_6H_5	$N-NHC_6H_4Cl-p$

1 + 2d ⟶



5

of similar structure did not cyclise readily, if at all, into pyrazolo-1,2,4-triazoles under conditions similar to those utilised to effect reaction of **1** with **2a** or at even more drastic conditions[7,8]. Further evidence in support of this is also presented later in this paper.

In contrast to its behaviour toward **2a**, compound **1** reacted with **2b** and **2c** to yield the acyclic amidrazones **4a, b**. The structure assigned for the reaction product is well documented by ^{1}H-NMR which revealed signals for two NH_2, thus excluding the possible reaction of **1** and **2** to yield products derived from reaction with the exocyclic amino group. Compounds **4a, b** could not be cyclised under a variety of reaction conditions into the corresponding imidazo[1,2-b]-pyrazoles or into pyrazolo[5,1-c]-1,2,4-triazoles. This findings support the conclusion that compound **3** is formed via a 3 + 2 cycloaddition sequence and not through alkylation and cyclisation.

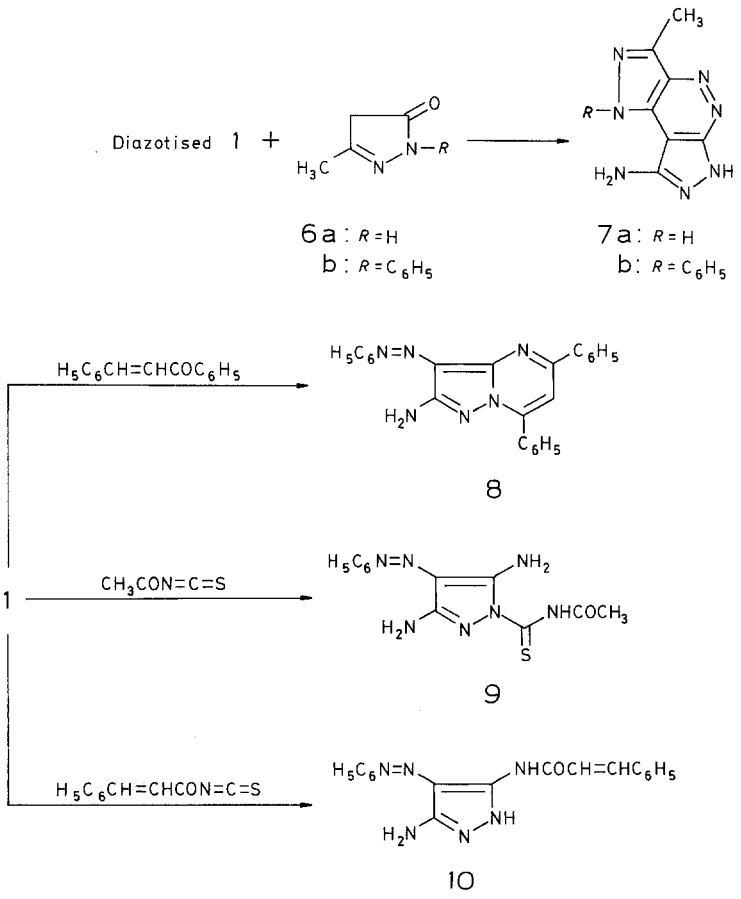
Compound **1** reacted also with **2d** to yield the pyrazolo[1,5-a]-pyrimidine derivative **5**. Compound **5** is assumed to be also formed via intermediate formation of the condensation product similar to those previously described one for reaction of aminopyrazoles with β-keto esters[1], which looses ethanol to yield **5**. However, the possibility that **5** is formed via other intermediates followed by cyclisation cannot be ruled out.

Diazotised aminopyrazoles have been shown to react with active methylene reagents to yield either cycloadducts or coupling products depending on the experimental conditions[9,10]. The mechanism of the formation of the cycloadducts has been a matter of long debate. Some authors suggest a novel 7 + 2 cycloaddition sequence[11]. Others believe in a 3 + 2 cycloaddition sequence followed by rearrangement. However, intermediates suggested by the latter authors have not yet been isolated. Now, it has been found that diazotised **1** reacts with the 2-pyrazolin-5-one derivatives **6a, b** to yield the cycloadducts **7a, b**. These adducts are believed to be formed via addition of 3-amino-5-diazo-4-phenylazopyrazole, formed via addition of **1** to the double bond in the enolate of **6a, b** followed by elimination of water and the arylazo group. Diazotised **1** has been reported to react with activated double bond systems to yield addition products which could be cyclised into a variety of fused azoles. Elimination of the arylazo group in this reaction finds parallelism to previously reported arylazo group decoupling of the arylazo function in **1**[12,13].

It has been found that **1** reacts with chalcone to yield a product of molecular formula $C_{24}H_{18}N_6$. The ^{1}H-NMR of the reaction product revealed the absence of signals for the CH protons at a field higher than 7 ppm, thus structure **8** was suggested for this product. Compound **8** is assumed to be formed via its intermediate dihydropyrimidine derivatives which readily undergo oxidation into the final isolable **8**.

Whereas **1** reacted with acetylisothiocyanate to yield the thiocarbamoyl derivative **9**, cinnamoylisothiocyanate reacted with **1** under the same reaction conditions to yield the cinnamoyl derivative **10**. Compound **10** is believed to be formed via the intermediate N-thiocarbamoyl derivative of **1**. Similar phenomena have been previously observed and rationalised for by *Elnagdi* et al.[14].

Scheme 2



Experimental

All melting points are uncorrected. IR spectra were recorded on a Beckman spectrophotometer, ^{1}H-NMR on a Varian EM-390-90 MHz spectrometer. The microanalyses were performed by the microanalytical unit at Cairo University. The experimental C, H, N values agreed well with the molecular formulas given below.

Reaction of **1** *with* **2a** *and* **2b**

Equimolecular amounts of **1** (0.01 mol) and the appropriate hydrazidic halide **2a** (0.01 mol) or **2b** (0.01 mol) in dry dioxane (50 ml) was refluxed for 5 h in presence of triethylamine (0.01 mol). Dioxane was evaporated *in vacuo* and the product so formed was collected by filtration and crystallised from the proper solvent.

3 was crystallised from acetic acid; m.p. 238 °C; yield 60%. IR: 3 420, 3 320 (NH_2), 1 610 (δ NH_2 and C=N). ^{1}H-NMR: 7.16 (s, 2 H, NH_2), 7.25–8.22 (m, 15 H, aromatic protons). $C_{22}H_{17}N_7$ (379).

4a was crystallised from *DMF*; m.p. 205 °C; yield 65%. IR: 3 340 (NH_2), 1 660 (C=O), 1 660 (C=O), 1 600 (C=N and δ NH_2). $C_{18}H_{18}N_8O$ (362).

Reaction of **1** *with* **2c** *and* **2d**

To a solution of **1** (0.01 mol) in ethanol (30 ml), **2c** (0.01 mol) or **2d** (0.01 mol) and triethylamine (0.01 mol) were added. The reaction mixture was refluxed for 5 h. Ethanol was evaporated *in vacuo* and the remaining solid product was collected by filtration and crystallised from the proper solvent.

4b was crystallised from *DMF*; m.p. 245 °C, yield 80%. IR: 3 460, 3 420, 3 380, 3 360 (NH_2 and NH); 1 680 (C=O); 1 600 (δ NH_2 and δ NH). ^{1}H-NMR: 7.28–7.72 (m, 17 H, phenyl protons, NH_2 and NH), 7.82 (s, br, 2 H, NH_2), 9.28 (s, 1 H, NH). $C_{23}H_{20}N_9OCl$ (473.5).

5 was crystallised from ethanol; m.p. 280 °C; yield 55%. IR: 3 480, 3 380 (NH_2), 1 680 (C=O), 1 640 (C=C), 1 600 (C=N and δ NH_2). ^{1}H-NMR: 2.46 (s, 3 H, CH_3), 4.18 (s, 1 H, CH), 6.92 (s, br, 2 H, NH_2), 7.33–7.88 (m, 5 H, phenyl protons). $C_{13}H_{11}N_6OCl$ (302.5).

Reaction of Diazotised **1** *with* **6a** *and* **6b**

An ice-cold solution of diazotised **1**, prepared from 0.01 mol of **1** and the appropriate amounts of sodium nitrite and hydrochloric acid, was added to an ethanolic solution of **6a** (0.01 mol) or **6b** (0.01 mol), respectively. The solid product was collected by filtration and crystallised from the proper solvent.

7a was crystallised from acetic acid; m.p. > 300 °C; yield 80%. IR: 3 400–3 250 (NH_2 and NH), 1 660 (C=C), 1 625 (δ NH_2 and NH). ^{1}H-NMR: 2.68 (s, 3 H, CH_3), 7.88 (s, br, 2 H, NH_2). $C_7H_7N_7$ (189).

7b was crystallised from ethanol; m.p. 170 °C; yield 70%. IR: 3 400–3 200 (NH_2), 1 650 (C=C), 1 590 (δ NH_2). $C_{13}H_{11}N_7$ (265).

Reaction of **1** *with Chalcone*

To a solution of **1** (0.01 mol) in ethanol (30 ml), chalcone (0.01 mol) and piperidine (0.1 ml) were added. The reaction mixture was refluxed for 5 h.

Compound **8**, so formed, was collected by filtration and crystallised from ethanol; m.p. 300 °C; yield 60%. IR: 3 410, 3 280 (NH_2), 1 620 (C=N and δ NH_2). ^{1}H-NMR: 7.38–8.32 (m, 6 H, CH and phenyl protons), 8.42 (s, br, 2 H, NH_2). $C_{24}H_{18}N_6$ (390).

Formation of **9** *and* **10**

To a solution of **1** (0.01 mol) in dry dioxane (50 ml) the appropriate isothiocyanate (0.01 ml) was added. The reaction mixture was refluxed for 3 h, then poured onto water. The solid product was collected by filtration and crystallised from the proper solvent.

9 was crystallised from *DMF*; m.p. 170 °C; yield 50%. IR: 3420 (NH_2), 1710 (C=O), 1610 (δNH_2). $C_{12}H_{13}N_7OS$ (303).

10 was crystallised from ethanol, m.p. 235 °C; yield 55%. IR: 3420, 3300, 3280 (NH_2 and NH), 1660 (C=O), 1610 (C=N, N=N, δNH_2 and δNH). $C_{18}H_{16}N_6O$ (332).

References

[1] For a review see: *Elnagdi M. H., Abdel Galil F. M., Riad B. Y., Elgemeie G. E. H.*, Heterocycles **20**, in press.

[2] *Kobe J., Robins R. K., O'Briens D. E.*, J. Heterocyclic Chem. **11**, 99 (1974).

[3] *Vogel A., Troxler F.*, Helv. Chim. Acta **58**, 761 (1975).

[4] *Elnagdi M. H., Hafez E. A. A., Elfahham H. A., Kandeel E. M.*, J. Heterocyclic Chem. **17**, 73 (1980).

[5] *Elnagdi M. H., Abdoula S. O.*, J. Prakt. Chem. **315**, 1009 (1973).

[6] *Elfahham H. A., Sadek K. U., Elgemeie G. E. H., Elnagdi M. H.*, J. Chem. Soc. Perkin I **1982**, 2663.

[7] *Elfahham H. A., Sadek K. U., Elgemeie G. E. H., Elnagdi M. H.*, Chem. Lett. **1982**, 119.

[8] *Elgemeie G. E. H., Elfahham H. A., Ghoslan S. A., Elnagdi M. H.*, Bull. Chem. Soc. Japan, in press.

[9] *Elnagdi M. H., Abdou S., Zayed E. M.*, Heterocycles **19**, 559 (1982).

[10] *El-Kashef H. S., Sadek K. U., Elnagdi M. H.*, J. Chem. and Engineering Data **27**, 103 (1982).

[11] *Ege G., Gilbert K.*, Tetrahedron Lett. **1979**, 1567.

[12] *Elnagdi M. H., Kandeel E. M., Zayed E. M., Kandeel Z. E.*, J. Heterocyclic Chem. **14**, 155 (1977).

[13] *Elnagdi M. H., Kandeel E. M., Zayed E. M., Kandeel Z. E.*, J. Prakt. Chem. **320**, 533 (1978).

[14] *Fahmy S. M., Kandeel E. M., Elsayed E. R., Elnagdi M. H.*, Heterocyclic Chem. **15**, 1291 (1978).