Reactions With Heterocyclic Diazonium Salts. Synthesis of Several New Azolylhydrazones

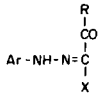
Ebtissam Abdel Aziz Hafez, Nosrat Mustafa Abed, Ibrahim Ahmed Elsakka, and Mohamed Hilmy Elnagdi*

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

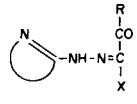
Several new stable azolylhydrazones could be synthesized *via* coupling of diazotised cyclic amidines with active methylene reagents. The obtained compounds were utilised for synthesis of several, otherwise not readily accessible fused azoles.

J. Heterocyclic Chem., **20**, 285 (1983).

The chemistry of the hydrazones of α-diketones and their functional derivatives (I) has received considerable attention (1-3).



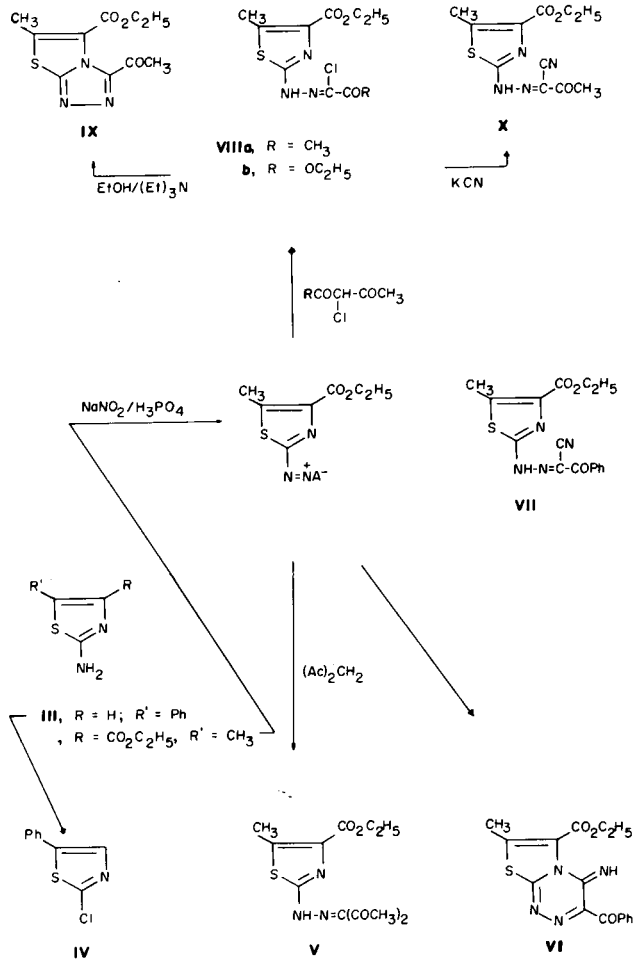
I



II

In previous work we have reported the synthesis and chemical reactivity of a variety of compounds of type I (4-6). In continuation to this work it seemed of value to synthesize heterocyclic hydrazones of the type II in order to establish their chemical and biological activities. Our previous reported attempted preparation of such compounds *via* coupling of diazotised aminopyrazoles with active methylene reagents has led, either to the formation of pyrazolo[1,5-*c*]-*as*-triazines or to the formation of acyclic hydrazones which spontaneously cyclised to pyrazolo-[1,5-*c*]-*as*-triazines under a variety of mild reaction conditions (7). Only few examples of compounds of type II could be obtained from these reactions. It occurred to us that it may be possible to isolate acyclic hydrazones from diazotised cyclic amidines whose cyclization into fused triazines would be hindered by loss of aromaticity of the heterocyclic ring. 2-Aminothiazoles III were chosen as typical compounds of this type. Thus, 2-amino-5-phenylthiazole (IIIa) was prepared following the reported procedure for its preparation (7). Diazotisation in presence of hydrochloric acid has afforded the corresponding 2-chloro derivative IV. On the other hand, in presence of oxyacids unstable diazonium salts were apparently obtained. However, these readily decomposed under the coupling reaction conditions and no coupling products could be obtained.

In contrast to the behaviour of IIIa, compound IIIb could be diazotised in presence of phosphoric acid. The diazonium salt could be successfully coupled with acetylacetone to yield the corresponding hydrazone derivative V. However, with benzoylacetonitrile and under a variety of coupling reaction conditions the thiazolo[2,3-*c*]-*as*-triazine derivative VI was the only isolable product. The



hydrazone VII could not be isolated.

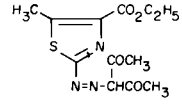
Diazotised IIIb also coupled with the α-chloro derivatives of acetylacetone and of ethyl acetoacetate to yield the corresponding coupling products VIIIa,b. The formation of VIIIa,b from this reaction is assumed to proceed *via* coupling with the active hydrogen in the α-chloroketo derivatives followed by a Japp-Klingmann acyl group removal.

Compound V is potentially tautomeric (*cf.* forms A-D). In order to establish one of these potentially tautomeric structures for the synthesised hydrazones their ir spectra

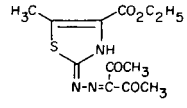
Table 1

List of the Newly Prepared Compounds

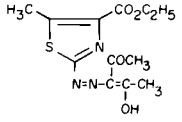
Compound	Crystallization Solvent	Mp °C	Yield %	Formula	Analysis Calcd./Found C	H	N	S
V	Ethanol	110	60	$C_{12}H_{15}N_3O_4S$	48.48	5.05	14.14	10.77
					48.12	4.91	13.78	11.10
VI	Ethanol	230	55	$C_{16}H_{14}N_4O_3S$	56.14	4.12	16.37	9.34
					56.30	4.30	16.17	9.60
VIIIa	Ethanol	145	60	$C_{10}H_{12}ClN_3O_3S$	41.45	4.14	14.50	11.05
					41.40	4.20	14.31	11.40
VIIIb	Ethanol	150	58	$C_{11}H_{14}ClN_3O_4S$	41.31	4.38	13.14	10.01
					41.60	4.21	12.97	9.78
IX	Ethanol	282	55	$C_{10}H_{11}N_3O_3S$	47.43	4.34	16.60	12.64
					47.71	4.20	16.68	12.48
X	Ethanol	247	50	$C_{11}H_{12}N_4O_3S$	47.14	4.28	20.00	11.42
					47.14	4.28	19.89	11.10
XII	Ethanol	216	50	$C_{17}H_{13}N_7O$	61.6	3.9		
					61.4	4.3		
XIII	DMF/Water	270	55	$C_{17}H_{15}N_7O_2$	58.4	4.3		
					58.4	4.2		
XIVa	Ethanol	125	60	$C_{17}H_{15}N_9$	59.1	4.3	36.6	
					58.9	4.3	37.0	
XIVb	Ethanol	255	55	$C_{23}H_{19}N_9$	65.5	4.5	29.9	
					65.6	4.3	30.2	
XVI	Ethanol	263	60	$C_{17}H_{15}N_7O_5S$	47.5	3.4		
					47.7	3.3		
XVIII	Ethanol	192	70	$C_{19}H_{22}N_4O_5$	59.9	5.7		
					59.5	5.5		
XIX	Ethanol	185	80	$C_{12}H_9ClN_4$	58.7	3.6	22.8	
					58.5	4.0	22.8	
XXII	Ethanol/Water	220	52	$C_{12}H_{10}N_4O$	63.7	4.4		
					63.8	4.3		
XXIII	Ethanol	130	45	$C_{18}H_{14}N_4S$	67.9	4.4		
					67.7	4.4		



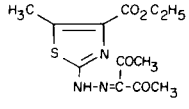
A



B



C



D

were examined. The ir spectra of V revealed its CO absorptions at frequencies almost similar to the corresponding aryl counter analogues and di α,β-unsaturated acetylacetone. The absence of an absorption for the OH group in these compounds rules out structure C. Moreover the absence of a CH proton in the ^{1}H-nmr spectra of these compounds excludes possible azo structure A. Thus the hydrazone structure D or the azine B might be suggested for these products. Although B cannot be excluded based on the available data, it seems to us least likely based on analogy to the well established structure of heterocyclic hydrazones of similar structure (8).

The chemical behaviour of VIIIa has been investigated.

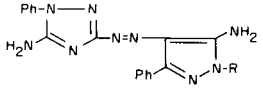
Table 2

Infrared Data of Some of the Newly Prepared Compounds

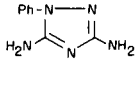
Compound	IR, cm^{-1} (Selected bands)
V	broad band at 3400 (NH) and 1720, 1695 and 1665 (two acetyl and ester CO)
VII	1710 and 1660 (benzoyl and ester CO)
X	2210 (conjugated CN) and 1700 (acetyl and ester CO)
XII	3460-3140 (NH_2 and NH), 2230 (CN) and 1640-1630 (CH_2 deformation and CO)
XIII	3400-3000 (chelated NH) and 1670 (NH_2 deformation)
XIVa	3440-2500 (chelated NH) and 1640 (NH_2 deformation)
XIVb	3400, 3300, 3100 (NH), 1640 (NH_2 deformation) and 1620 (C=N)
XVIII	3390, 3295 (NH), 1740 and 1720 (CO) and 1620 (C=N)

It has been found that VIIIa when refluxed with ethanol in the presence of triethylamine cyclised into the thiazolotriazole derivative IX. On the other hand, when VIIIa was treated with potassium cyanide in refluxing acetone the cyano derivative X was obtained.

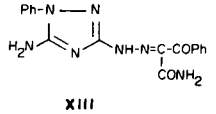
In continuation to this work, 3,5-diamino-1-phenyl-1,2,4-triazole (XI) could be diazotised by the action of nitrous acid. However, the resulting diazonium salt was highly inactive in the coupling reaction, thus, it decomposed before coupling with active methylene reagents like acetylacetone, ethyl acetoacetate and ethyl cyanoacetate. With malononitrile a coupling product was obtained, but this product decomposed readily on attempted crystallisation and we were unable to obtain an analytically pure sample of this product. A stable hydrazone was obtained on a coupling diazotised XI with benzoylacetonitrile. Attempted cyclisation of this hydrazone XII by the action of acetic acid-hydrochloric acid mixture has resulted in the formation of the amide XIII. Hydrazines reacted with XII to yield the pyrazol-4-ylazo-1,2,4-triazole derivatives XIVa,b. When compound XII was treated with sodium ethoxide in refluxing ethanol, benzoylacetonitrile was the only isolable product. Compound XII cyclised by the action of concentrated sulphuric acid into a triazoltriazine derivative which can be formulated as XV or XVI.



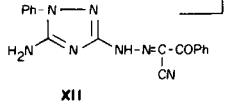
XIV a, R = H
b, R = C_6H_5



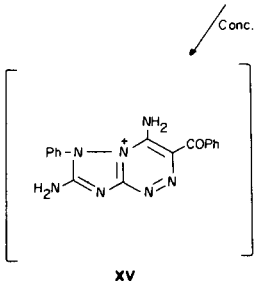
XI



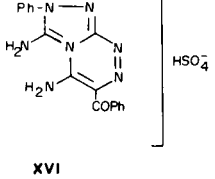
XIII



XII



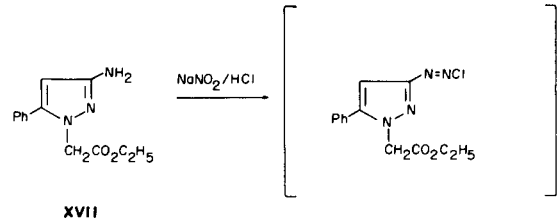
XV



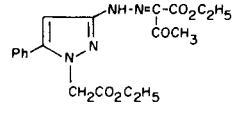
XVI

In addition, the behaviour of the aminopyrazole derivative XVII was investigated. Thus diazotised XVII reacted with ethyl acetoacetate to yield the hydrazone XVIII. Compound XVIII could not be cyclized into a pyrazolo-[1,5-*e*]-*as*-triazine derivative under a variety of conditions utilized previously to effect cyclization of the coupling products of 5-amino-1-unsubstituted pyrazoles into pyrazolo[1,5-*a*]-*as*-triazine derivatives.

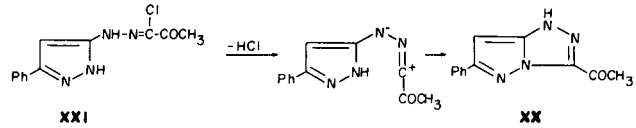
In previous work from this laboratory we have reported the synthesis of the pryazolo[1,5-*c*]-*as*-triazine XIX and the pyrazolo[1,5-*c*]1,2,4-triazole derivative XX *via* cyclization of the hydrazone XXI in protic and aprotic media, respectively. Although XX and XXII are isomeric and are expected to give very similar spectral data, the structure assignment was based on the assumption that in aprotic media, compound XXI loses hydrogen chloride to yield a nitrile imine intermediate which then cyclises into XX. The formation of XXII in protic media was assumed to proceed *via* routes *a* or *b*. Now we would like to report the synthesis of XX from the pyrazolo[1,5-*c*]-*as*-triazine intermediate, thus establishing its structure. It has been found



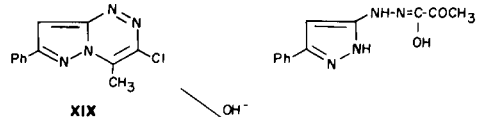
XVII



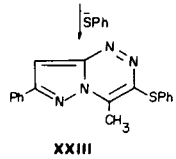
XVIII



XXI XX



XIX XXII



XXIII

that XXI cyclises readily in the presence of sodium acetate to yield the 6-chloro-7-methyl-2-phenylpyrazolo[1,5-*c*]-*as*-triazine derivative XIX. The latter reacted with 5% sodium hydroxide solution to yield the pyrazolo[1,5-*c*]-*as*-triazine derivative XXII. Compound XIX also reacted with thiophenol to yield the 6-thiophenyl-7-methyl-2-phenylpyrazolo[1,5-*c*]-*as*-triazine derivative XXIII.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded (potassium bromide) on a Pye Unicam SP-1100 spectrophotometer. Elemental analysis (C, H, N) has been carried out by the Microanalytical Data Unit at Cairo University.

2-(4-Ethoxycarbonyl-5-methylthiazol-2-yl)hydrazonopentane-2,3,4-trione (V).

A solution of acetylacetone (0.1 mole) in ethanol (100 ml) was treated with anhydrous sodium acetate (0.2 mole) and then cooled at 0°. To this solution a solution of diazotised IIIb (prepared at 0° from 0.1 mole of IIIb, 50 ml of phosphoric acid (70%) and the appropriate quantity of sodium nitrite) was then added. The reaction mixture was stirred for one hour at 0° and then left in a refrigerator overnight. The solid product, so formed, was collected by filtration, purified by washing with water and crystallized from the proper solvent (*cf.* Tables 1 and 2).

6-Benzoyl-5-imino-3-ethoxycarbonyl-2-methylthiazolo[2,3-*c*]-1,2,4-triazine (VI).

Diazotised IIIb was coupled with benzoylacetonitrile using the experimental procedure previously described for the reaction of diazotised IIIb with acetylacetone. The reaction product was crystallized from the proper solvent (*cf.* Tables 1 and 2).

Ethyl 2-[(1-Chloroacetonylidene)hydrazino]-5-methyl-4-thiazolecarboxylate (VIIIa) and Ethyl 2-[Chloro(ethoxycarbonyl)methylene]hydrazino]-5-methyl-4-thiazolecarboxylate (VIIIb).

A solution of the α-chloro derivatives of acetylacetone and of the ethyl acetoacetate (0.1 mole) in ethanol (100 ml) was treated with anhydrous sodium acetate (0.2 mole) and then cooled to 0°. To this solution a solution of diazotised IIIb prepared at 0° from 0.1 mole of IIIb, 50 ml of phosphoric acid and the appropriate quantity of sodium nitrite) was then added. The reaction mixture was stirred for one hour at 0° and then left in a refrigerator overnight. The solid product, so formed, was collected by filtration and crystallized from the proper solvent (*cf.* Tables 1 and 2).

(a) Reaction of VIIIa With Ethanol-Triethylamine Mixture.

A solution of VIIIa (2.0 g) in ethanol (20 ml) was treated with triethylamine (5 ml). The reaction mixture was then refluxed for 3 hours and then evaporated under reduced pressure. The remaining solid product was then collected by filtration and crystallised from the proper solvent (*cf.* Tables 1 and 2).

(b) Reaction of VIIIa With Potassium Cyanide.

A solution of VIIIa (2.0 g) in acetone (50 ml) was treated with potassium cyanide (1.0 g). The reaction mixture was refluxed for two hours and then evaporated *in vacuo*. The remaining product was collected by filtration, washed several times with water and crystallised from the proper solvent (*cf.* Tables 1 and 2).

α-[(5-Amino-1-phenyl-1*H*-1,2,4-triazol-3-yl)hydrazino]-β-oxobenzenepropanenitrile (XII).

A solution of diazotised 3,5-diamino-1-phenyl-1,2,4-triazole XI (prepared by diazotising a cold solution of 5.5 g of XI in 4.5 ml of concentrated sulphuric acid with a solution of 1.3 g of sodium nitrite dissolved in the least amount of water) was added to a solution of benzoyl acetonitrile (5.0 g) in ethanol and sodium acetate (5.0 g). The solid product, formed on standing, was collected by filtration and crystallised from the proper solvent (*cf.* Tables 1 and 2).

(a) Reaction of XII With Acetic Acid-Hydrochloric Acid Mixture.

A solution of XII (4 g) in acetic acid (20 ml) was treated with concentrated hydrochloric acid (3 ml, 37%). The reaction mixture was refluxed for three hours then poured into ice. The solid product, so formed, was collected by filtration and crystallised from the proper solvent (*cf.* Tables 1 and 2).

(b) Reaction of XII With Hydrazines.

A suspension of XII (3 g) in ethanol (30 ml) was treated with hydrazine hydrate (2.0 ml, 99%) or with phenylhydrazine (2.0 ml) and the reaction mixture was refluxed for three hours then evaporated *in vacuo*. The remaining product was triturated with water, the resulting solid product was collected by filtration and crystallised from the proper solvent (*cf.* Tables 1 and 2).

(c) Reaction of XII With Concentrated Sulphuric Acid.

Compound XII (5.0 g) was treated with concentrated sulphuric acid (4.0 ml) and the solution was left for thirty minutes at room temperature then poured into ice and neutralized by addition of ammonium hydroxide. The solid product formed on standing was collected by filtration and crystallised from the proper solvent (*cf.* Tables 1 and 2).

Reaction of Ethyl Acetoacetate With Diazotized XVII.

A solution of diazotized XVII (prepared from 0.01 mole of XVII and the appropriate quantities of hydrochloric acid and sodium nitrite) was added to a solution of ethyl acetoacetate (0.01 mole) in ethanol (100 ml) and sodium acetate (3.5 g). The reaction mixture was left for three hours, at room temperature and the resulting hydrazone was collected by filtration and crystallized from the proper solvent (*cf.* Tables 1 and 2).

6-Chloro-7-methyl-2-phenylpyrazolo[1,5-*c*]-*as*-triazine (XIX).

A solution of XXI (5.0 g) in ethanol (100 ml) was treated with a solution of sodium acetate (2 g) dissolved in the least amount of water. The reaction mixture was stirred at room temperature for one hour. The solid product, formed on standing, was collected by filtration and crystallised from the proper solvent (*cf.* Tables 1 and 2).

6-Hydroxy-7-methyl-2-phenylpyrazolo[1,5-*c*]-*as*-triazine (XXII).

A suspension of XIX (5.0 g) in sodium hydroxide solution (100 ml, 5%) was boiled under reflux for ten hours. The reaction mixture was evaporated till one quarter of its volume, cooled and neutralized by the addition of concentrated hydrochloric acid. The solid product, so formed, was collected by filtration and crystallised from the proper solvent. The resulting product was found to be identical with authentic specimen of XXII prepared after Elnagdi, *et al.* (8) (*cf.* Tables 1 and 2).

1-Methyl-2-phenyl-6-thiophenylpyrazolo[1,5-*c*]-*as*-triazine (XXIII).

A solution of XIX (0.1 mole) in pyridine (80 ml) was treated with thiophenol (0.1 mole). The reaction mixture was then heated under reflux for five hours and then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised from the proper solvent (*cf.* Tables 1 and 2).

REFERENCES AND NOTES

(1) Z. Stransky, L. Cap and J. Slouka, *Collect. Czech. Chem. Commun.*, **38**, 2712 (1975).

(2) B. Lythgoo, A. R. Todd and A. Topham, *J. Chem. Soc.*, 386 (1943).

(3) M. Sekiya, J. Suzuki and Y. Terao, *Chem. Pharm. Bull.*, **24**, 1331 (1976).

(4) E. M. Kandeel, K. U. Sadek and M. H. Elnagdi, *Z. Naturforsch.*, **35b**, 91 (1980).

(5) E. A. Hafez, M. A. E. Khalifa, S. K. A. Guda and M. H. Elnagdi, *ibid.*, **35b**, 485 (1980).

(6) M. H. Elnagdi, M. R. H. Elmoghayar, E. A. A. Hafez and H. A. Alnima, *J. Org. Chem.*, **40**, 2604 (1975).

(7) S. M. Fahmy, E. M. Kandeel, E. R. Elsayed and M. H. Elnagdi, *J. Heterocyclic Chem.*, **15**, 1291 (1978).

(8) M. H. Elnagdi, M. R. H. Elmoghayar. E. A. A. Hafez, D. H. Fleita and S. M. Fahmy, *J. Org. Chem.*, **41**, 3781 (1976).