Reactions with Heterocyclic Diazonium Salts, II
Synthesis of Some New Pyrazolo[1,5-c]-as-triazines
and 1,2,4-Triazolo[1,5-c]-as-triazines

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Heterocyclic Diazonium Salts, Pyrazolo[1,5-c]-as-triazines

3-Phenylpyrazole-5-diazonium chloride (2) couples with benzoylacetonitrile and with phenacylthiocyanate to yield the corresponding hydrazone derivatives 8a, b. Whereas 3a cyclized into the pyrazolo[1,5-c]-as-triazine derivative (4a) upon treatment with concentrated sulphuric acid via elimination of water, treatment of 3b with the same reagent under the same conditions has resulted in elimination of thioicinic acid and the formation of the pyrazolo[1,5-c]-as-triazine derivative (4b).

Treatment of 2 with aqueous sodium acetate has afforded the corresponding 3-phenyl-5-diazoypyrazole (6). The latter reacted readily with dipolarophiles to yield pyrazolo-[1,5-c]-as-triazine derivatives. Pyrazolo[1,5-c]-as-triazines has also been formed upon treatment of 6 with active methylene compounds. The mechanism of reaction of 2 and 6 with active methylene compounds is discussed.

Diazotization of 5-amino-3-ethyl-1,2,4-triazole nitrate (7) has afforded the corresponding diazonium derivative which coupled with benzoylacetonitrile and with acetoacetanilide to yield the corresponding hydrazones 9a, b. The latter could be cyclised into 1,2,4-triazolo[1,5-c]-as-triazines by the action of concentrated sulphuric acid.

Diazotized 1H-aminoazoles are versatile reagents and their synthetic potentials has received considerable recent attention [1-5]. As a part of our program directed for development of new procedures for the synthesis of bridge-head azoles [6-12] we have previously [6, 11] reported the synthesis of a variety of pyrazolo[1,5-c]-as-triazines and pyrazolo-[1,5-c]-1,2,4-triazoles based on the coupling reaction of 3-phenylpyrazole-5-diazonium chloride with active methylene compounds. In continuation of this work we report here the results of our further investigation on the reaction of diazotized 1H-aminoazoles. The work has resulted, in addition to synthesis of several new pyrazolo[1,5-c]-as-triazines in clarification of the mechanistic pathways for reaction of diazotized 5-aminoazopyrazoles with active methylene compounds. Thus, diazotization of 5-amino-3-phenylpyrazole (1) has afforded 3-phenylpyrazole-5-diazonium chloride (2) which coupled with benzoylacetonitrile and with phenacylthiocyanate to yield the corresponding hydrazone derivatives 3a, b, respectively. The isolation of 3b from reaction of 2 and phenacylthiocyanate is in contrast to the recently reported spontaneous cyclization of the coupling products of aryl-diazonium salts with phenacylthiocyanate [13].

Compound 3a readily cyclised into the pyrazolo-[1,5-a]-as-triazine derivative (4a) upon treatment with concentrated sulphuric acid. On the other hand, when 3b was similarly treated, compound 4b, the structure of which was inferred from analytical and spectral data, was formed. The formation of 4b from 3b and concentrated sulphuric acid might be assumed to proceed via initial elimination of thioicinic acid leading to the formation of a resonance stabilised nitrie imine intermediate which cyclises then to afford the final reaction products (cf. Chart 1).

Previously we have reported [11] that 2 reacts with acrylonitrile, ethyl acrylate and with dimethyl acetylene-dicarboxylate to yield the pyrazolo[1,5-c]-as-triazine derivatives 5a, b and 4c, respectively. Intermediacy of 3-phenyl-5-diazoypyrazole (6) has been suggested to account for the formation of these products. Now, we would like to report the isolation of 6 as well as its reactions with dipolarophiles [13]. Thus, when 2 was treated with aqueous sodium acetate solution it was converted almost quantitatively into the diazobetaine 6. The latter was stable at room temperature but exploded when heated at 145 °C. Compound 6 decomposed on
boiling in ethanol or in benzene. The nature of the decomposition products will be a subject for a separate communication. When compound 6 was treated with acrylonitrile ethyl acrylate or with dimethyl acetylenedicarboxylate, products identical in all aspects with those previously formed on treatment of 2 with the same reagents were formed in excellent yields. Compound 6 readily added less reactive dipolarophiles namely chalcone and methyl cinnamate to yield the pyrazolo[1,5-c]as-triazine derivatives 5c, d, respectively.

Compound 6 reacted with benzoylacetonitrile, ethyl acetoacetate, 3-iminobutyronitrile, ethyl cyanoacetate and with malononitrile to yield the pyrazolo[1,5-c]as-triazine derivatives 4a, d-g. Under similar conditions compound 6 failed to react with phenacylthiocyanate.

In an attempt to prepare authentic specimen of 4f via cyclization of the hydrazone 7, recently synthesised via coupling of 2 with ethyl cyanoacetate, it has been found that the latter (7) is only formed when the coupling is performed in presence of an excess of acetic acid as has been described for its synthesis. Coupling of 2 and ethyl cyanoacetate in less acidic media using the experimental procedure recently reported by us [11] has resulted in the direct formation of 4f. This result clearly indicate that the accepted assumption [15] that the acid eliminated during the coupling reaction is responsible, by catalysing cyclisation of a hypothetically formed hydrazones, for the inability of several authors to isolate acyclic intermediates for the coupling reaction of diazotized 1H-aminoazoles with certain active methylene compounds. It seems to us most probable that the formation of cyclic or acyclic products from the coupling reaction with active methylene compounds with diazotized aminoazoles is determined by the mechanistic pathway for the reaction. Thus, reagents affording directly cyclic products react, most likely, with the diazonium compound, which under the coupling condition is expected to exist in equilibrium with the diazobetaiene, via a 1,3-dipolar cyclo addition. On the other hand, the formation of hydrazones results from a usual coupling reaction.

In order to gain further information of the mechanism of coupling of diazotized 5-amino-pyrazoles with active methylene compounds a re-investigation of the behavior of 2 toward a variety of active methylene compounds was undertaken. It has been found that 2 reacts with ethyl acetoacetate and with 3-iminobutyronitrile under a variety of basic, neutral and acidic conditions to yield pyrazolo[1,5-c]as-triazine derivatives (4d, e). The same products were obtained on treatment of 6 with the same reagents in ethanolic solutions. On the other hand, benzoylacetonitrile, ethyl cyanoacetate and malononitrile afforded the respective hydrazones when the coupling reaction was performed in faintly acidic medium. In neutral and in basic media the cyclic pyrazolo[1,5-c]as-triazines (4a, f, g) were the only isolable reaction products. Compounds 4a, f, g were also formed from the reaction of 6 with the same reagents in ethanolic solutions. Phenacylthiocyanate did not react with 2 in basic or in neutral media. However in acidic solutions the acyclic hydrazones 3b was the only obtainable product. These results are in good agreement with the suggested mechanism of reaction of 2 with active methylene compounds.

As an extention of our work an investigation of the behavior of 5-amino-3-ethyl-1,2,4-triazole (8) on diazotization was undertaken. Similar to literature attempted diazotization of 8 in the presence of hydrochloric acid resulted in the formation of the corresponding chloro derivative 9. On the other
hand, diazotization of 8 in the presence of nitric acid has generated the corresponding diazonium salt in solution. Although attempted isolation of the latter has resulted in its decomposition, evidence for the formation of the diazonium salt was obtained via coupling with benzoylacetonitrile and with acetoacetanilide to yield the corresponding hydrazones 10a, b. Attempted coupling of ethylacetoacetate, ethyl cyanoacetate or with 3-iminobutyronitrile under similar conditions were unsuccessful.

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\begin{align*}
\text{KHN}^+ & \text{Cl}^- \quad \text{NaN}_2/\text{HCl} \\
\text{K} & \text{C}_2\text{H}_5 \\
\text{H} & \text{N}^+ \text{R} \\
\text{R} & = \text{C}_6\text{H}_5, \text{X} = \text{CN} \\
\text{10a} & : \text{R} = \text{C}_6\text{H}_5, \text{X} = \text{CN} \\
\text{10b} & : \text{R} = \text{CH}_3, \text{X} = \text{CONHPh} \\
\text{11,12} & : \text{R} = \text{C}_5\text{H}_5, \text{X} = \text{CN} \\
\text{11,12} & : \text{R} = \text{CH}_3, \text{X} = \text{CONHPh} \\
\end{align*}
\]

Compounds 10a, b were readily cyclised by the action of concentrated sulphuric acid to yield products that can be formulated as the 1,2,4-triazolo[1,5-c]-as-triazines (11a, b) or the isomeric 1,2,4-triazolo[3,4-c]-as-triazines (12a, b). Although we have not now evidence in favour of any of the two isomeric structures, structure 11 seems most likely based on analogy to the behaviour of triazolylhydrazones on cyclisation [1].

Experimental

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer model 337 spectrophotometer.

2-(3-Phenylpyrazol-5-yl)hydrazono-3-oxo-3-phenylproionitrile (3a)

A solution of benzyloacetonitrile (0.1 mol) in ethanol (100 ml) was treated with a suspension of sodium acetate (10.0 g in 50 ml of water). A suspension of 3-phenylpyrazol-5-diazonium chloride (2) (prepared by diazotization of 0.1 mol of 1 in the presence of hydrochloric acid-acetic acid mixture as has been recently described [6]) was added with stirring to this solution. The reaction mixture was kept at room temperature for two hours and the solid product, so formed, was collected by filtration. Recrystallisation from ethanol afforded analytically pure sample of 3a as brown crystals, m. p. 235 °C, yield 80%. IR: 1640 cm⁻¹ (conjugated CO), 2220 cm⁻¹ (conjugated CN) and 3300–3380 cm⁻¹ (NH). C₁₃H₁₂O₃N₃

Found C 68.69 H 4.11 N 22.29, Caled C 68.56 H 4.16 N 22.21.

1-Phenyl-2-thiocyanatoglyoxalate-2-(3-phenylpyrazol-5-yl)hydrazone (3b)

Phenacylthiocyanate (0.1 mol) was coupled with 2 using the experimental procedure described above for the preparation of 3a. The reaction product was crystallised from ethanol.

Compound 3b, brown crystals, m. p. 185 °C, yield 75%. IR: 1650 cm⁻¹ (conjugated CO) and 3300–3420 cm⁻¹ (NH). C₁₈H₁₂O₃N₃S


Cyclisation of 3a, b by concentrated sulphuric acid

A mixture of each of 3a, b (3.0 g) and concentrated sulphuric acid (2.0 ml) was warmed on water-bath for 30 minutes then left to stand overnight at room temperature. The mixture was then diluted with water, neutralised by addition of ammonia and the resulting product was collected by filtration and crystallised from ethanol.

Compound 4a formed colourless crystals, m. p. 206 °C, yield 55%. IR: 1640 cm⁻¹ (N=N) and 2220 cm⁻¹ (conjugated CN). C₁₈H₁₁N₅

Found C 72.69 H 3.61 N 23.29, Caled C 72.72 H 3.70 N 23.56.

Compound 4b formed colourless crystals, m. p. 110 °C, yield 48%. C₁₇H₁₂N₄

Found C 74.98 H 4.43 N 20.49, Caled C 75.00 H 4.47 N 20.58.

3-Phenyl-5-diazo pyrazole (6)

A suspension of 2 (2.0 g) in water (50 ml) was treated with sodium acetate solution (prepared by dissolving 3 g of anhydrous sodium acetate in 100 ml of water). The reaction mixture was stirred at room temperature for four hours. The solid product, so formed, was collected by filtration and washed several times with cold water (till the washing were free from chloride ions). The product so obtained afforded correct analytical and ¹H NMR data.

Compound 6, buff powder, explodes at 145 °C, IR: 2175 cm⁻¹ (diazo band), ¹H NMR: 7.0 (s, 1H, pyrazole CH) and 7.4–7.8 (m, 5H, C₆H₅).
C₈H₆N₄

Found C 63.55 H 3.11 N 33.09,
Calcd C 63.52 H 3.55 N 32.93.

Reaction of 6 with activated double bond systems

A suspension of 6 (0.1 mol) in ethanol (100 ml) was treated with the appropriate activated double bond reagent (0.12 mol). The reaction mixture was left to stand in a refrigerator for 24 hours, then poured onto water. The solid product, so formed, was collected by filtration and crystallised.

The product obtained from reaction of 6 with acrylonitrile, ethyl acrylate and dimethyl acetylene dicarboxylate proved to be identical in all aspects with the recently prepared 5a,b and 4c [11] respectively.

Compound 5c, formed colourless crystals from ethanol, m.p. 135 °C, yield 60%.

C₈H₁₂ON₆

Found C 56.50 H 5.55 N 31.00,
Calcd C 56.50 H 5.45 N 31.00.

Compound 10b formed yellow crystals from ethanol, m.p. 149 °C, yield 55%.

C₉H₁₀O₂N₈

Found C 62.72 H 4.10 N 33.75,
Calcd C 62.69 H 4.03 N 33.78.

C₁₂H₁₄O₂N₆

Found C 59.56 H 5.00 N 27.44,
Calcd C 59.50 H 5.00 N 27.39.

C₁₅H₁₉O₂N₈

Found C 59.20 H 5.46 N 28.00,
Calcd C 59.56 H 5.00 N 29.77.

The reaction of 6 with active methylene compounds

A suspension of 6 (0.1 mol) in ethanol (100 ml) was treated with the appropriate active methylene compound (0.1 mol). The reaction mixture was stirred for six hours then evaporated in vacuo. The remaining product was triturated with water and the resulting solid was collected by filtration and crystallised. The reaction products with activated methylene compounds were identified (m.p. and mixed m.p.) as 4a,d-g, respectively.

a,β-Diozo-2-ethyl-1,2,4-triazole-5-yl-a-hydrazono-hydrocinnaminitrile (10a,b)

A solution of 8 (0.01 mol) in concentrated nitric acid (5 ml, 65%) and water (10 ml) was treated with continual stirring by a solution of sodium nitrite (0.7 g dissolved in the least amount of water). The resulting solution was then added to a solution of the appropriate active methylene compound (0.01 mol) in ethanol-water mixture (50 ml, 75%) saturated with sodium acetate. The mixture was then left in a refrigerator for six hours. The solid product, so obtained was collected by filtration and crystallised.

Compound 10a formed orange crystals, from ethanol, m.p. 197 °C, yield 62%.

C₁₂H₁₄ON₆

Found C 57.90 H 4.80 N 31.00,
Calcd C 58.20 H 4.51 N 31.33.

Compound 10b formed yellow crystals from ethanol, m.p. 165 °C, yield 62%.

C₁₃H₁₉O₂N₈

Found C 62.72 H 4.10 N 33.75,
Calcd C 62.39 H 4.03 N 33.58.

C₁₅H₁₄O₂N₆

Found C 59.20 H 5.46 N 28.00,
Calcd C 59.56 H 5.00 N 29.77.

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[14] Up to our knowledge, with the exception of our earlier report (ref. [11]), only one report has dealt with the reactivity of 5-diazopyrazoles as dipolarophiles (ref. [5]).