Synthesis of Pyrazolo[3,2-*c*]-1,2,4-triazines from *N*-(5-Pyrazolyl)-α-ketohydrazidoyl Halides

Abdou O. Abdelhamid, Hamdi M. Hassaneen and Ahmad S. Shawali* [1]

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

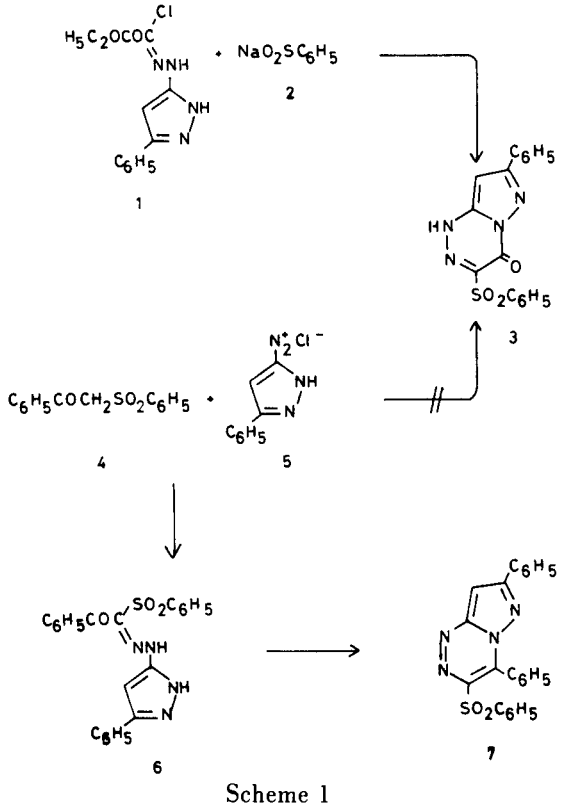
Received August 7, 1984

3-Phenylpyrazole-5-diazonium chloride (**5**) couples with benzenesulfonylacetone (**9a**), benzenesulfonylacetophenone (**9b**), ethyl benzenesulfonylacetate **9c**, and ethyl benzoylacetate (**12b**) in ethanol in the presence of sodium acetate at room temperature to afford the pyrazolo[3,2-*c*]-1,2,4-triazine derivatives **11a** and **11b** and the acyclic hydrazones **10c** and **13** respectively. The products **11a,b** and **10c** can also be obtained from the reaction of the corresponding hydrazidoyl halides **8a-c** with sodium benzenesulfinate in high yield. The hydrazones **10c** and **13** can be cyclised thermally or under the influence of acid into pyrazolo[3,2-*c*]-1,2,4-triazine derivatives **11c** and **14** respectively.

J. Heterocyclic Chem., **22**, 453 (1985).

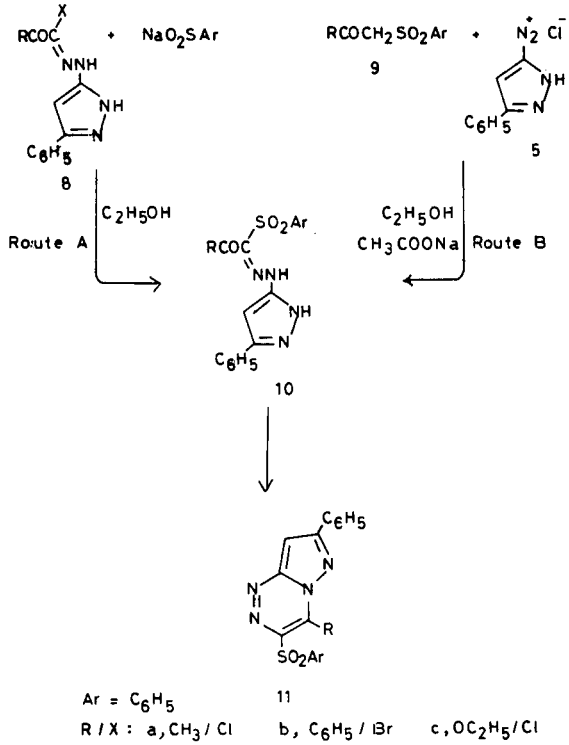
Introduction.

Recently an ambiguous product namely 3-benzenesulfonyl-7-phenylpyrazolo[3,2-*c*]-1,2,4-triazine-4(1*H*)-one (**3**) was claimed to be obtained in 75% yield from coupling of 3-phenyl-5-aminopyrazole (**5**) to benzenesulfonylacetophenone (**4**) (Scheme 1) [2]. It was also claimed that this same product can be prepared by the reaction of the hydrazidoyl chloride **1** with sodium benzenesulfinate (**2**). As



Scheme 1

coupling of **5** with keto sulfone **4** is expected to yield the hydrazone derivative **6** which upon cyclization (by the loss of the elements of water would yield 3-benzenesulfonyl-4,7-diphenylpyrazolo[3,2-*c*]-1,2,4-triazine (**7**) (Scheme 1) [3-6], the identity of the products from these reactions has to be reinvestigated. Accordingly, we have studied the reactions between each of the three α-ketohydrazidoyl halides **1** and **8a,b** with sodium benzenesulfinate in ethanol. Also, the reactions between the diazonium salt **5** and the β-ketosulfones **9a-c** were studied and the products obtained from both routes were compared (Scheme 2).



Scheme 2

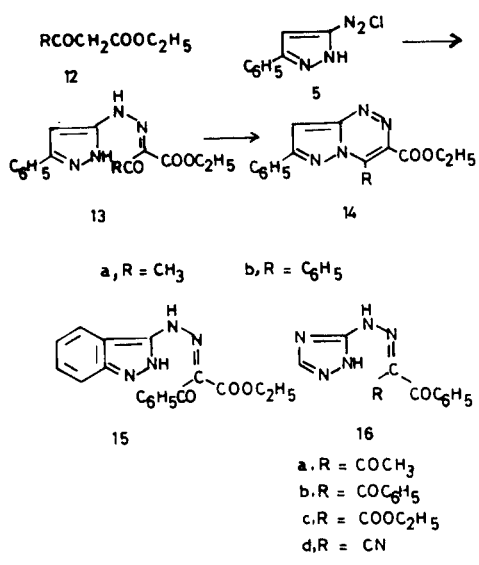
Results and Discussion.

Treatment of *C*-acetylhydrazidoyl chloride **8a** (prepared from coupling of the diazonium salt **5** to α-chloroacetylacetone [2]) with sodium benzenesulfinate in ethanol af-

forded a product which gave analytical and spectral data in accord with its formulation as 3-benzenesulfonyl-4-methyl-7-phenylpyrazolo[3,2-*c*]-1,2,4-triazine (**11a**). For example, its infrared spectrum revealed the absence of bands due to C=O and NH groups. The reaction of *C*-benzoylhydrazidoyl bromide **8b** (prepared from coupling of **5** with phenacyldimethylsulfonium bromide) with sodium benzenesulfinate afford 3-benzenesulfonyl-4,7-diphenylpyrazolo[3,2-*c*]-1,2,4-triazine (**11b**) in 70% yield. The structure of **11b** follows from its spectral and elemental analysis data (see Experimental). These results indicate that the intermediate hydrazones **10a,b** undergo cyclization as soon as they are formed to afford the corresponding pyrazolotriazine derivatives **11a,b** respectively. In support of this is the fact that the products **11a,b** were also obtained directly by coupling of diazotized 3-phenyl-5-aminopyrazole **5** to the β-keto sulfones **9a,b** respectively (Scheme 2).

Next, the reaction of ethoxycarbonylhydrazidoyl chloride (**1**) with sodium benzenesulfinate was reinvestigated. In our hands, treatment of **1** with sodium benzenesulfinate in ethanol at room temperature yielded a product which gave analytical data consistent with the formula $C_{19}H_{18}N_4O_4S$. Its infrared spectrum reveals bands at 3220 (NH), 1690 (CO), 1350 and 1150 (SO_2) cm^{-1}. On the basis of these data, the product was assigned the structure **10c**. The low frequency of the ester carbonyl group might be attributed to the possible intramolecular hydrogen bonding and α,β-unsaturation [7]. The structure of **10c** was further evidenced by its alternate synthesis from coupling of ethyl benzenesulfonylacetate (**9c**) with **5**. Thus, treatment of **9c** with **5** in ethanol in the presence of sodium acetate yielded the acyclic hydrazone **10c** whose structure follows its spectral and elemental analyses. In support of this is the fact that **9c** is known to couple with diazotized aromatic amines to give the corresponding arylhydrazone derivatives of ethyl 2-oxo-2-benzenesulfonylacetate [7]. Brief heating of **10c** obtained from either route A or B (Scheme 2) in an oil bath at 200° yielded **3**. The latter can be obtained directly from **8c** by refluxing it with sodium benzenesulfinate in ethanol.

The reluctance of the ester group in **10c** to participate spontaneously in cyclisative condensation is analogous to the behaviour of other related hydrazones such as **15** and **16** [4]. In addition, ethyl benzoylacetate, in our hands, unlike ethyl acetoacetate [10] coupled with the diazonium salt **5** in ethanol in the presence of sodium acetate and gave the acyclic hydrazone derivative **13b**. Treatment of the latter with concentrated sulfuric acid at room temperature afforded a product whose spectral properties and elemental analysis establish its identity as 3-ethoxycarbonyl-4,7-diphenylpyrazolo[3,2-*c*]-1,2,4-triazine (**14b**) (Scheme 3). The reluctance of the benzoyl group in **13b** to participate



Scheme 3

spontaneously in cyclisative condensation is also encountered in the reported hydrazones **15** [2,4,5] and **16** [4].

The results of the present work indicate that the reaction of α-ketohydrazidoyl halides having an *N*-bifunctional heterocyclic ring residue with nucleophiles and subsequent cyclisation of the resulting substitution products, either after isolation or *in situ*, provides the basis of a convenient procedure for the synthesis of fused azolotriazine derivatives. The application of this annelation process to the synthesis of systems other than pyrazolo]3,2-*c*]-1,2,4-triazine described in this work is still under investigation.

EXPERIMENTAL

All melting points are uncorrected. The infrared spectra in nujol were recorded on a Perkin-Elmer model 710B spectrophotometer. The pmr spectra were obtained with a Varian T60-A instrument in chloroform-d and dimethylsulfoxide-d_6 using tetramethylsilane as the internal reference. Elemental analyses were carried out at the microanalytical laboratory, Faculty of Science, University of Cairo, Egypt. The mass spectra were obtained with Perkin-Elmer RMU-6E spectrometer at 70 eV. 3-Phenyl-5-aminopyrazole [8], benzenesulfonylacetone [11], benzenesulfonylacetophenone [12], ethyl benzenesulfonylacetate [9], and the hydrazidoyl halides **8a,c** [2] were prepared according to the procedures described in literature.

Preparation of Pyrazolo[3,2-*c*]-1,2,4-triazine Derivatives **11a,b** and the Hydrazone **10c**.

Method A.

Equivalent amounts of the appropriate hydrazidoyl halide **8** (0.005 mole) and sodium benzenesulfinate (**2**) (0.005 mole) in ethanol (50 ml) were heated gently on a water bath till a clear solution was obtained. Then the mixture was left overnight at room temperature. The solid that precipitated was collected, washed with water, dried and then crystallized. In this manner the following compounds were prepared.

Compound **11a** was obtained in 75% yield, mp 285° (*N,N*-dimethylformamide); ms: M^+ m/e 350; pmr (dimethylsulfoxide-d_6): 3.05 (s, 3H, CH_3), 7.0-8.2 (m, 11H, ArH) ppm; ir (nujol): 1350, 1155 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.98. Found: C, 61.69; H, 3.95; N, 15.77.

Compound **11b** was obtained in 78% yield, mp 329° (*N,N*-dimethylformamide); ms: M^+ m/e 412; ir (nujol): 1345, 1155 (SO_2) cm^{-1}.

Anal. Calcd. for $C_{23}H_{16}N_4O_2S$: C, 66.97; H, 3.91; N, 13.58. Found: C, 66.82; H, 3.78; N, 13.50.

Compound **10c** was obtained in 83% yield, mp 187° (methanol); ms: M^+ m/e 398; ir (nujol): 1670 (α,β-unsaturated, hydrogen bonded ester CO), 1370, 1150 (SO_2) cm^{-1}, 3300, 3150 (NH) cm^{-1}; pmr (deuterated chloroform): 1.77 (t, 3H, J = 7.0 Hz, CH_3CH_2O), 4.37 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.37 (s, 1H, pyrazole C_4H), 7.1-8.0 (m, 10H, ArH), 12.2 (s, 1H, NH) ppm.

Method B.

A solution of 5-diazo-3-phenylpyrazole (**5**) (0.01 mole) in ethanol (5 ml) was added to a stirred solution of the appropriate benzenesulfonylketone **9a,b** or ethyl benzenesulfonylacetate (**9c**) (0.01 mole) in ethanol (50 ml) containing sodium acetate trihydrate (0.01 mole) at 0°C. The reaction mixture was stirred for 3 hours. The separated product was filtered and crystallized. The products obtained from **9a,b** and **9c** (80-90% yield) were identical in all respects (mp, mixed mp, spectra) with **11a,b** and **10c** respectively (Method A).

Reaction of **5** with ethyl benzoylacetate when carried out following this same procedure gave compound **13b** in 80% yield. The product **13b** had mp 161° (ethanol); ms: M^+ m/e 362; ir (nujol): 1708 (ester CO), 1698 (benzoyl CO), 3210 (NH) cm^{-1}; pmr (dimethylsulfoxide-d_6): δ 1.7 (t, 3H, J = 7 Hz, CH_3CH_2O), 4.32 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.4-7.9 (m, 11H, ArH, pyrazole CH), 11.8 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.00; N, 15.46. Found: C, 66.15; H, 4.88; N, 15.21.

3-Phenylsulfonyl-7-phenylpyrazolo[3,2-*c*]-1,2,4-triazin-4(1*H*)-one (**3**).

Compound **10c** (0.5 g), was heated in a tube in an oil bath at 200° for 15 minutes then cooled. The solid was collected and crystallized from dimethylformamide to give **3** in 81% yield, mp 337°; ir (nujol): 1680 (CO), 1351, 1150 (SO_2), 3210 (NH) cm^{-1}; ms: M^+ m/e 352; pmr (dimethylsulfoxide-d_6): 6.4-7.0 (m, ArH, NH) ppm.

Anal. Calcd. for $C_{17}H_{12}N_4O_3S$: C, 57.94; H, 3.43; N, 15.90. Found: C, 57.72; H, 3.42; N, 15.74.

3-Ethoxycarbonyl-4,7-diphenylpyrazolo[3,2-*c*]-1,2,4-triazine (**14b**).

Compound **13b** (0.5 g), was dissolved in concentrated sulfuric acid (5 ml) at room temperature and left for 24 hours. The reaction mixture was poured on ice-cold water and the precipitated solid was collected and crystallized from ethanol. Compound **14b** was obtained in 81% yield and had mp 178°; ms: M^+ m/e 344; ir (nujol): 1708 (CO) cm^{-1}; pmr (deutrated chloroform): 1.8 (t, 3H, J = 7 Hz, CH_3CH_2O), 4.4 (q, 2H, J = 7 Hz, CH_3CH_2O), 6.4 (s, 1H, pyrazole 4CH), 7.0-8.5 (m, 10H, ArH) ppm.

Anal. Calcd. for $C_{26}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.60; H, 4.45; N, 15.81.

REFERENCES AND NOTES

[1] Author to whom correspondence would be addressed. Present address: Department of Chemistry, Faculty of Science, King Abdulaziz University, P. O. Box 9028; Jeddah 21413, Saudi Arabia.

[2] M. H. Elnagdi, M. R. H. Elmoghayar, E. M. Kandeel and M. K. A. Ibrahim, *J. Heterocyclic Chem.*, **14**, 227 (1977).

[3] G. Tennant and R. J. S. Vevers, *J. Chem. Soc., Perkin Trans. I*, 421 (1976).

[4] D. Fortuna, B. Stanovnik and M. Tisler, *J. Org. Chem.*, **39**, 1833 (1974).

[5] G. R. Bedford, F. C. Cooper, M. W. Partridge and M. F. G. Stevens, *J. Chem. Soc.*, 5901 (1963).

[6] R. Allmann, T. Debaedemacker, W. Grahn and C. Reichardt, *Chem. Ber.*, **137**, 1555 (1974).

[7] A. S. Shawali, M. I. Ali, M. M. Naoum and A. L. Elansari, *Tetrahedron*, **28**, 3805 (1972).

[8] A. Takamizawa and Y. Hamashima, *Yakugaku Zasshi*, **84**, 1113 (1964); *Chem. Abstr.*, **62**, 5276 (1965).

[9] J. L. Huppaiz, *Aust. J. Chem.*, **24**, 653 (1971).

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

[11] R. Otto and W. Otto, *J. Prakt. Chem.*, **36**, 401 (1887).

[12] J. Troger and O. Beck, *J. Prakt. Chem.*, **87**, 289 (1931).