SOME NOVEL OBSERVATIONS ON THE REACTION OF 1-HYDRAZINOPHTHALAZINE WITH POLYCARBONYL COMPOUNDS

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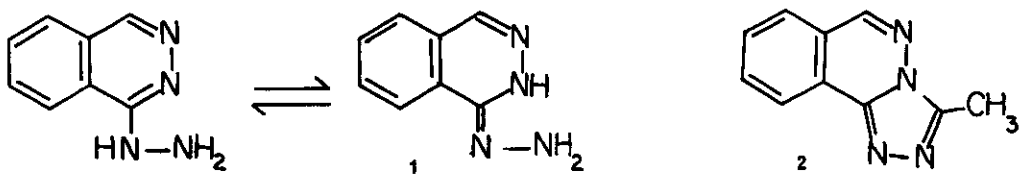
Abstract —— The reaction of 1-hydrazinophthalazine (1) with polycarbonyl compounds depends on the acid and acidity of the reaction as well as on the structure of the carbonyl components.

The reaction of 1-hydrazinophthalazine (1) with carbonyl compounds, especially concerning its role in human metabolism involving its reactions with the Krebs cycle carbonyl compounds, is an intensely researched field.[1-17] In continuing our interest in this particular area and in the view of a number of discrepancies in the literature concerning the structure assignments of reaction products of 1 with certain carbonyl compounds we reinvestigated in more detail the reaction of 1 with 1,3-dicarbonyl compounds. Thus, Druey and Ringier[4] reported that 1 gave 3-methyl-s-triazolo[3,4-a]phthalazine (2) in high yield on treatment with ethyl acetoacetate. More recently it was reported that 1 reacts with certain 1,3-dicarbonyl compounds including ethyl acetoacetate, acetylacetone, and benzoylacetone, to give 1-(substituted pyrazol-1-yl)phthalazine derivatives with potential hypotensive action.[12]

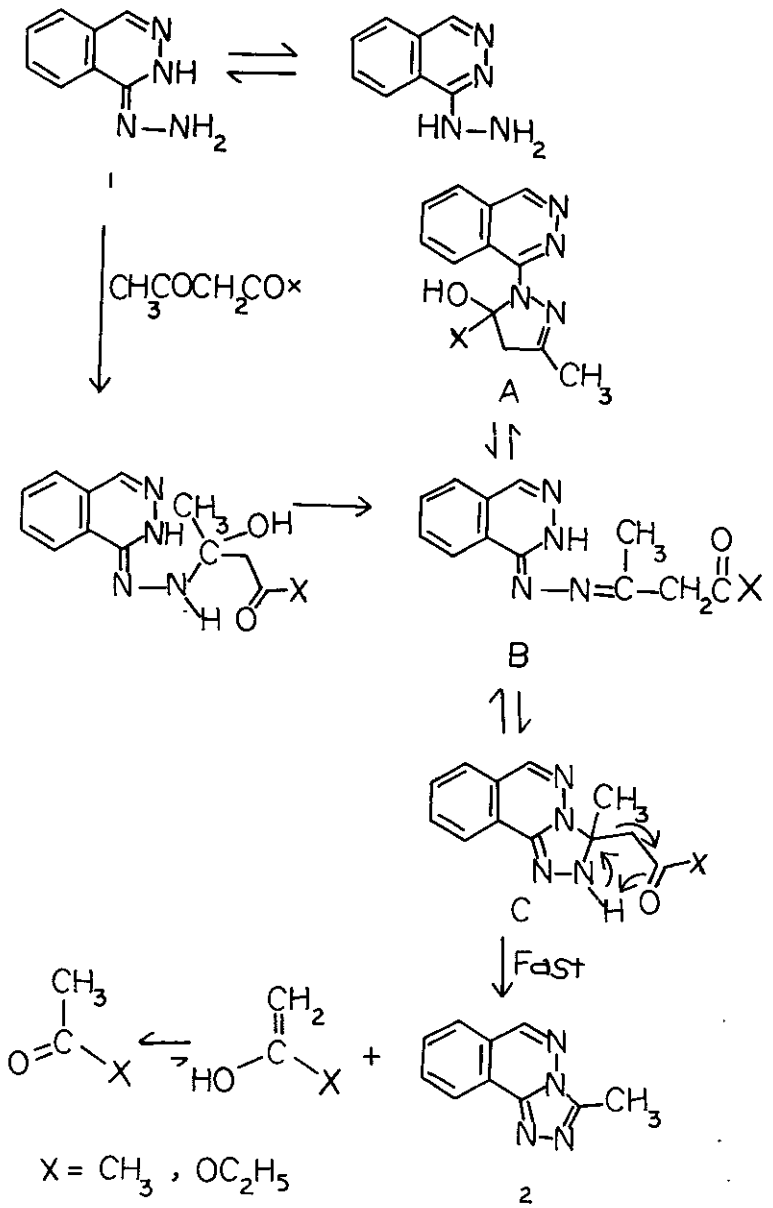


In order to clarify this discrepancy, we reinvestigated the reaction of 1 with these carbonyl compounds under the reported condition as well as in methanolic solution and obtained in every case 2.[14,15] In addition to our findings, there existed an earlier report by Johnson et al.[11] who reported in 1977 a synthesis of 1-(3,4-dimethyl pyrazol-1-yl)phthalazine (3) using 1-HCl instead of 1 with acetylacetone.

In this report, we wish to communicate some new findings on the mechanism through which this ring transformation occurs and shed light on some factors that have an influence on the structure of the reaction products. In a typical reaction, 1 as its free base was heated with CH_3COCH_2COX (X=OEt, CH_3) species in methanolic solution (0.025M) at 67°C. The progress of the reaction was monitored by uv-spectroscopy.

Bathochromic shift of the absorption bands from 265 and 274 nm of 1 to 274 and 282 ($X=CH_3$) or 272 and 281 nm ($X=OEt$), respectively, was observed from the beginning of the experiments. These new bands were found to

Scheme I



reach maximum absorption values after approximate 40 min. The reaction mixture was then super-cooled by a dry ice-acetone bath and the intermediates were isolated. They were identified as a mixture of two tautomeric forms, namely 5-hydroxypyrazoline A and the ketoimine B (Scheme I) as evidenced by their ^{1}H-nmr spectra[18] which displayed two different methylene groups (see Table I). Structure determination of these intermediates was unambiguously established by means of ^{13}C-nmr spectroscopy. The spectra exhibit two different CH_2 groups at δ37.823 and 44.878 ppm (t) (X=OEt). The ester carbonyl carbon and the tertiary carbon atoms are responsible for signals at δ170.067 (s) and 169.895 (s) for tautomers B and A, respectively (X=OEt, Scheme I).

A plausible explanation for this transformation is to assume that the cyclization proceeds very fast via the intermediate[15] C (Scheme I). This reaction must be very rapid because, according to the uv-spectroscopic monitoring of the progress of the reaction, no new curve indicating a buildup of an intermediate was observed. The buildup of 2 according to uv-evidence again was fast.

Table I

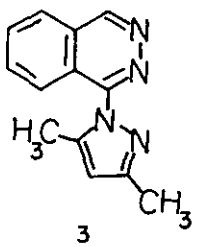
^{1}H-nmr Spectra[(a)] *of the Intermediates Isolated from the Reaction of Hydralazine 1 with* CH_3COCH_2COX

X	X	^{1}H-nmr (δ) (Deuterochloroform) CH_3	CH_2	ArH	NH OH
CH_3		2.121(s) 1 2.146(s) 1 2.195(s) 2 (b)	3.87(s) 67 A 4.204(s) 35 B	7.411-7.58 (m) 8.326 (s) 8.52 (s)	10.44(s) A 10.55(s) B
CH_3CH_2O	1.210(t) 1.263(t) 4.154(q) 4.184(q)	2.186(s) 2.258(s)	3.426(s) 47 A 3.702(s) 53 B	7.361-7.405 (m) 7.511-7.553 (m) 7.742 (s) 7.752 (s) 8.250-8.334 (m)	10.587(s) 10.757(s)

a) Concentration of ~0.2 mole/l.

b) Since 4 peaks for the mixture A and B are expected, it was found that 2 peaks have practically the same chemical shift and overlap each other at δ2.195.

We then reacted 1-HCl with acetylacetone as reported by Johnson[11] et al. In accordance with these authors, we isolated 3 (mp 108°C) in a practical quantitative yield.



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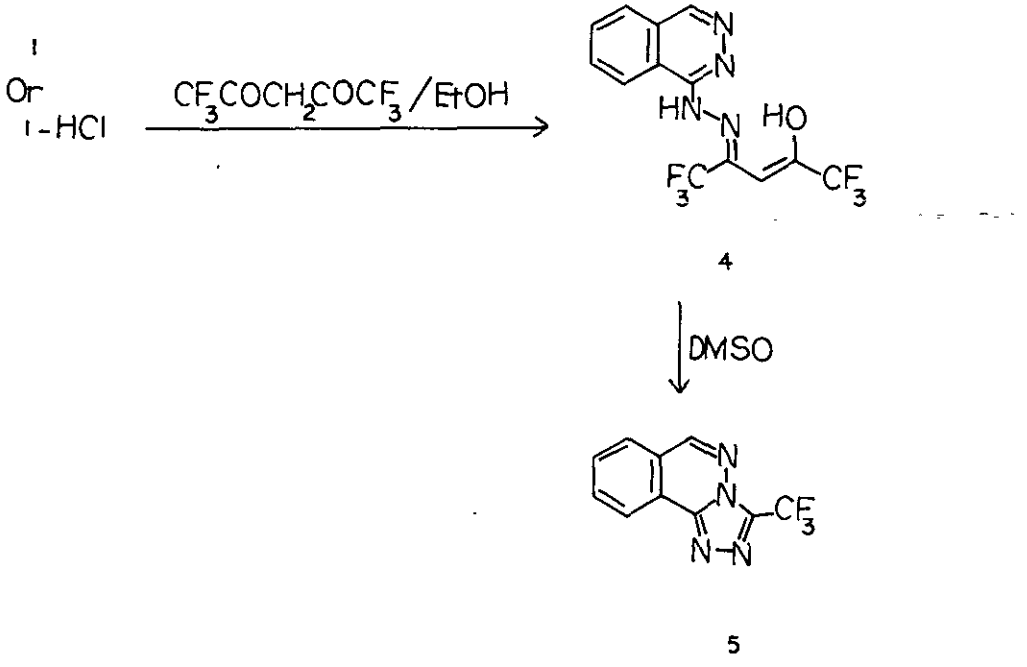
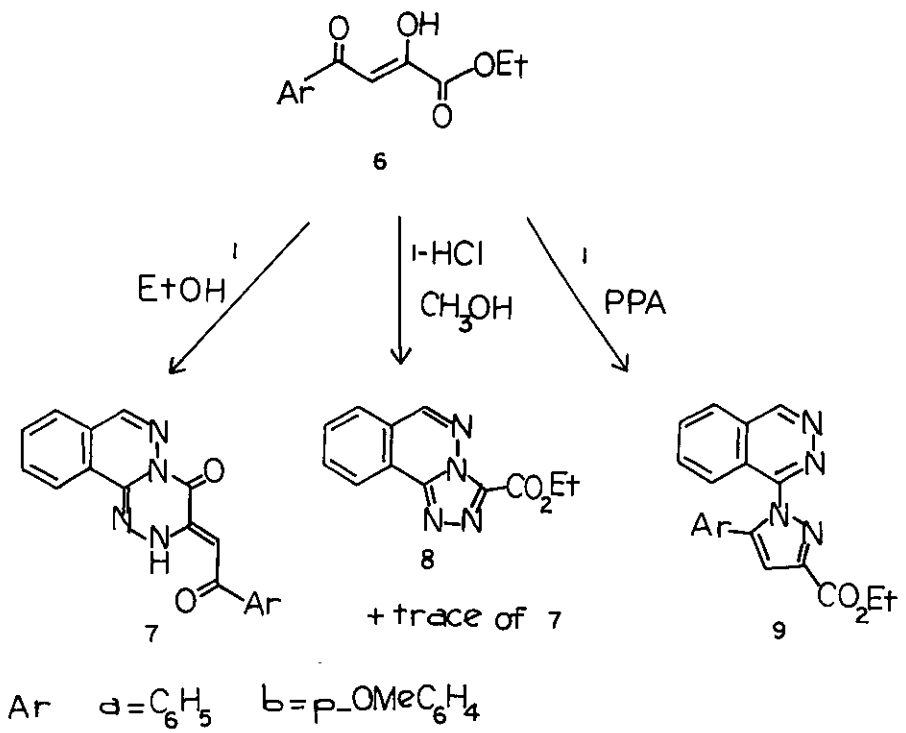
However, in contrast to that reaction, 1 or 1-HCl reacted with hexafluoroacetone in methanolic medium to the intermediate 4 (mp 174-176°C), which could be cyclized to 3-trifluoromethyl-s-triazolo[3,4-a]phthalazine(5) by heating it for a few min in dimethyl sulfoxide solution (Scheme II). The enolimine structure of 4 is based on its analytical and spectral data. ^{1}H-nmr spectrum in dimethyl sulfoxide showed signals at δ5.293 (s, 1H, =CH), 8.193, 8.460, 8.946 (m,m,s, 5H, ArH), 13.493 (s, 1H, NH) and 17.427 (s, 1H, OH). Moreover, ^{13}C-nmr evidence corroborates on this assignment. The spectrum exhibited the olefinic carbon atom at δ83.146 (^{1}J=157.5 Hz) and in accordance with the structure there was no signal in the carbonyl frequency region.

Scheme II



In an earlier paper[16] we reported that 1 as the free base reacted with ethyl benzoylpyruvate (6) to yield 3-(2-oxo-2-phenylethyl)-4H-as-triazino[3,4a]phthalazin-4-one (7), and when 1-HCl was applied, 3-carboxy-s-triazolo-[3,4-a]phthalazine, (8), was obtained in 51% yield. We now find that heating a mixture of equimolar amounts of 1 and 6a in 10 parts of polyphosphoric acid (PPA) for 20 min, quenching the mixture with water, neutralizing with $NaHCO_3$ and extracting with chloroform yielded, after drying (Na_2SO_4) and evaporating the solvent, an oil, which solidified and was identified as 1-(phthalazin-1-yl)-3-ethoxycarbonyl-5-phenylpyrazole, 9a, mp 149-150°C (MeOH, 50%); ir(KBr) 1720 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ1.5 (t, 3H, $-OCH_2\underline{CH_3}$), 4.5 (q, 2H, $O-\underline{CH_2}CH_3$), 7.23, 7.9, 9.6 (s, m, s, 11H, aromatic H); MS: m/z 344 (60), 316 (22), 272 (36), 245 (13), 244 (17), 243 (22), 116 (25), 115 (30), 114(36), 103 (13), 102 (60), 101 (26), 77 (100). R_f = 0.4 (EtOAc). Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.65; H, 4.76; N, 16.38.

Analogously was obtained 1-(phthalazin-1-yl)-3-ethoxycarbonyl-5-(4-methoxyphenyl)pyrazole (9b) from 1 and ethyl 4-methoxybenzoylpyruvate (6b), mp 175°C (MeOH, 55%); ir(KBr) 1729 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ1.5 (t, 3H, $-OCH_2\underline{CH_3}$), 3.8 (s, 3H, $OC\underline{H_3}$) 4.5 (q, 2H, $OC\underline{H_2}CH_3$), 6.8, 7.3 (dd, 4H, aromatic H), 7.2 (s, 1H, proton of the 4 position of pyrazole ring), 9.6 (m, 5H, phthalazine ring protons); Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.84; N, 14.97. Found: C, 67.39; H, 14.92; N, 15.04. These results obtained so far can be summarized as follows.



Thus, the conditions, especially acidity as well as the nature of the polycarbonyl compounds have a profound influence on the course of annelation reactions involving 1. Further studies in this area are in progress.

ACKNOWLEDGEMENTS

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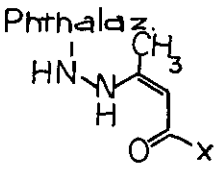
18. The presence of tautomer D was not detected in these cases (see ref. 14).



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