New Data About the Reaction of Benzyolacetonitrile with Malononitrile and Its Self-condensation

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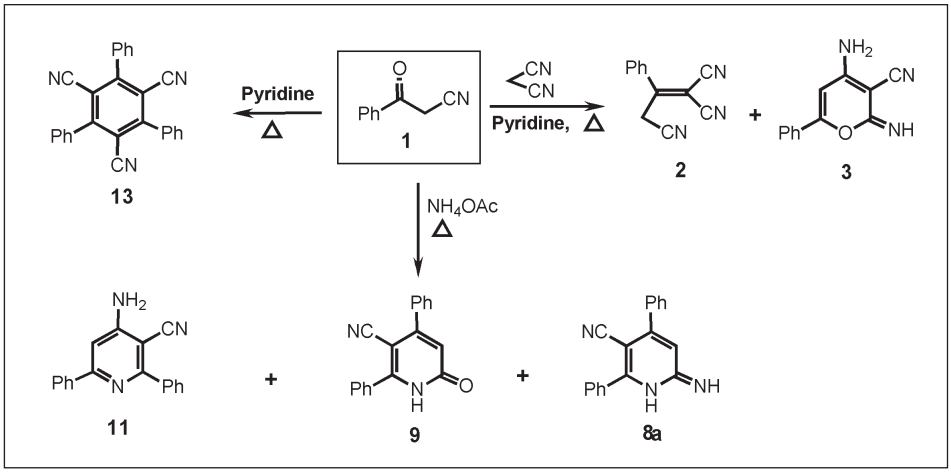

The reactions of benzoylacetonitrile with malononitrile in refluxing pyridine and its self condensation under fusion conditions in the presence of ammonium acetate and in refluxing pyridine were reinvestigated. New data were found and plausible mechanisms to account for the formation of the products are suggested.

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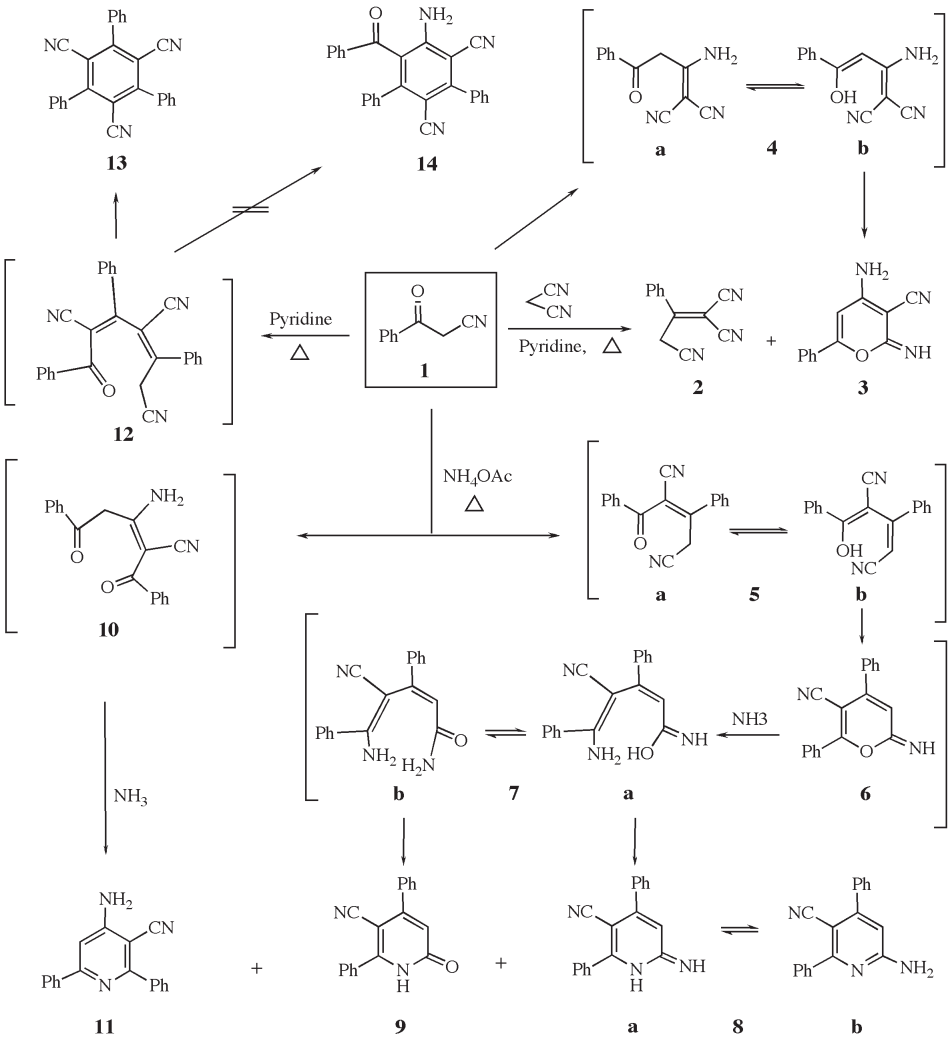
In the last few years we have been involved in a program aiming at the synthesis of functionally substituted heterocyclic compounds of expected biological activity to be used as biodegradable agrochemicals from laboratory available starting material [1-4]. During the present phase of our research some functionally substituted pyridazine derivatives were required for biological activity evaluation. Benzoylacetonitrile **1** seemed to be a good precursor to fulfill our objective *via* its condensation with malononitrile or its self-condensation to obtain the Knoevenagel condensation products **2** and **5a** respectively (Scheme 1). These two compounds, by virtue of their active methylene groups, can undergo azo coupling with different aromatic and heteroaromatic diazonium salts followed by cyclization to afford our target pyridazine derivatives. During our literature search we have found a complete research paper dealing with the preparations of the desired compounds [5]. Therefore we started to prepare some of these compounds following the same synthetic pathways described in this paper [5]. It should be stated that it was not intended to reinvestigate this work but rather to prepare the required compounds; however the new data encountered during our preparations seemed worth publishing and is reported in the present paper.

In our hands compound **1** reacts with malononitrile in refluxing pyridine (see experimental) to afford two products (tlc analysis). The first product (brown; mp. 83 °C) showed a molecular ion peak in the mass spectrum at m/z=193. The IR spectrum of this product showed three cyano absorption bands at ν = 2220, 2215 and 2205 cm^{-1}. The ^1H nmr spectrum revealed only two signals at δ = 3.1 (s, 2H) and 7.2-7.52 (m, 5H) ppm. Based on these data the condensation product **2** was assigned to this product (structure **2** in the original paper [5], mp 80 °C and no nmr data given). The second product (mp. 236 °C) showed a molecular ion peak in its mass spectrum at m/z = 211. The ir spectrum of this product showed absorption bands at ν = 3420-3160 and 2210 cm^{-1} attributable to NH, NH_2 and CN groups. The ^1H nmr spectrum of this compound showed signals at δ = 6.85 (s, 1H), 7.15 (br.s, 2H, exchangeable), 7.18-7.52 (m, 5H) and 9.85 (s, 1H, exchangeable). Based on these data the pyran structure **3** was assigned to this product (not mentioned in the original paper [5], most likely not separated by the authors).

To account for the formation of these two products from **1** and malononitrile the reactants apparently undergo two competitive reactions. A Knoevenagel condensation reaction which leads directly to compound **2**; and a Michael addition of the active methylene of malononitrile to the cyano function of **1** will lead to the tautomerized intermediate **4a/4b** which undergoes a *6-exo-dig* cyclization [6] to afford the iminopyran **3** as shown in Scheme 1.

On the other hand, Elnagdi *et. al.* [5] claimed that they could successfully dimerize compound **1** and assigned

Scheme 1



structure **5a** (Scheme 1) for the product (structure **7** in their paper; it is a self condensation product and not a dimer as they called it). It should be mentioned that the authors have provided all possible evidence in their discussion that this product exists predominantly (in both solid state and in solution) in the dienol form **5b** (structure **8** in their paper), however all the reactions provided after, and the spectral data given contradict this conclusion and are based on structure **5a** (**7** in the original paper) as the predominant one. This contradiction caused some doubt in the factual accuracy of this work; and therefore we have turned our aim from the preparation of the compounds to the reinvestigation of this work.

In our hands we could isolate three novel heterocyclic compounds from the fusion of **1** with ammonium acetate at 120 °C (the same reaction conditions as described in ref. [5]). On the basis of the analytical and spectral data of these three products, the pyridine structures **8a**, **9** and **11** were assigned to these compounds (*cf.* experimental). To account for the formation of these three products from **1**, again it is assumed that compound **1** undergoes two competitive reactions: A Knoevenagel self-condensation of two molecules of **1** to afford the tautomeric pair **5a/5b,** which undergoes a *6-exo-dig* cyclization [6] to afford the iminopyran **6** (as shown in Scheme 1). In presence of ammonium acetate and under fusion conditions compound **6** is apparently attacked by ammonia and the ring is opened to afford the acyclic tautomeric pair **7a/7b**. Recyclization of **7a** through loss of water will lead to the iminopyridine **8a**, which can in principle tautomerize to the amino pyridine **8b**, however all data suggest the imino structure **8a**; while recyclization of **7b** *via* reelimination of ammonia leads to the 2-pyridone derivative **9**. Compound **8a** has been previously described in the literature [7].

The other possible direction is a Michael addition of the active methylene of one molecule of **1** to the cyano function of another to afford the 1,5-dione intermediate **10**, which is transformed into the pyridine derivative **11** under

the effect of ammonia [8]. All the reactions described on the claimed structure **5a** (**7** in the original paper [5]) and all the structures derived from it and the spectral data presented to support these structures seem to be imaginary and fabricated.

Refluxing compound **1** in pyridine we could isolate a dark yellow compound. Elnagdi *et. al.* [5] claimed that this compound is the so called trimer and assigned structure **14** (structure **6** in the original paper), however our isolated product had the same melting point as mentioned [5] but the ir spectrum of this product did not show any absorption bands that can be attributed to amino or carbonyl functions and only one strong cyano absorption band is revealed (*cf.* experimental). Furthermore the ^{1}H nmr spectrum of this product showed only an aromatic multiplet. Mass spectral measurements showed that this compound has a molecular weight of 381, which is consistent with three molecules of **1** losing three molecules of water. On the basis of these data it was assumed that three molecules of **1** underwent three condensations with each other to afford **13** presumably *via* the intermediacy of **12** (Scheme 1). It should be mentioned that Elnagdi *et. al.* [5] had established their structure **14** (**6** in the original paper) based on the inactivity of the product toward reagents expected to effect ready condensation (*e.g.*, with hydrazine and hydroxylamine). Contrary to this structure **14** should undergo such condensations by its claimed carbonyl group and our structure **13** better fits with this statement. A conclusive evidence of structure **13** was obtained from the ^{13}C nmr of this product which showed only seven signals at δ = 110.2 (s), 115.9 (s), 127.2 (d), 128.5 (d), 129.9 (d), 137.1 (s), 150.1 (s) ppm, which is applicable with structure **13** beside the correct elemental analysis (*cf.* experimental). If the structure was **14** (claimed **6**) a carbonyl signal would have appeared in the ^{13}C nmr of this product at δ below 180 ppm similar to that of benzophenone [9]. The claimed path from **5a** to **14** (**7** to **6** in the original paper [5]) is not real since neither compound exists.

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H and ^{13}C-nmr spectra were recorded on a Varian Gemini 300 MHz spectrometer in deuterated DMSO using TMS as internal standard and chemical shifts are expressed in δ (ppm) values. Assignments were made by correlation of the off-resonance decoupled ^{13}C-nmr spectra and determination of the ^{1}H chemical shifts. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV). Elemental analyses were carried out by the Microanalytical Center at Cairo University. The reactions were followed by tlc carried out on a silica gel aluminium sheets using petroleum ether- ethyl acetate as eluent.

The Reaction of Benzoylacetonitrile (**1**) with Malononitrile.

To a solution of benzoylacetonitrile **1** (4.35 g, 30 mmol) in *ca.* 30 ml of pyridine was added malononitrile (1.98 g, 30 mmol) and the reaction mixture was refluxed at its boiling point for 3 h then left to cool to room temperature. The reaction mixture was then poured on ice cold water whereby a brown precipitate appeared, which was filtered off and recrystallized from ethanol / DMF and identified as **2**. The mother liquor was acidified with ice cold HCl till just neutral (pH paper) at which point a yellow crystalline product is formed, collected by filtration, recrystallized from ethanol and identified as **3**. The overall yield of the reaction is *ca.* 80% with a ratio of 2:1 respectively.

2-Cyano-3-phenylpent-2-enedinitrile **(2)**.

Brown powder, yield 3.15 g (~54 %); mp. 83-84 °C(lit. 80 °C) [5]. (EtOH / DMF);. Ir: 2220, 2215 and 2205 cm^{-1} (3 CN); ^{1}H nmr: 3.1 (s, 2H) and 7.2-7.52 (m, 5H); ms: m/z 193 (molecular ion).

Anal. Calcd. for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.5; H, 3.7; N, 21.8.

4-Amino-2-imino-6-phenyl-2*H*-pyran-3-carbonitrile (**3**).

Yellow crystalline solid, yield 1.5 g (~26 %); mp. 236-237 °C (EtOH); ir: 3420-3160 (NH & NH_2), 2210 cm^{-1} (CN); ^{1}H nmr: 6.85 (s, 1H, pyran 5-H); 7.15 (br. s, 2H, NH_2) and 7.18-7.52 (m, 5H, arom. H); 9.85 (s, 1H, NH); ms: m/z 211 (molecular ion).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.5; H, 4.6; N, 20.2.

The Self-condensation and Self-dimerization of (**1**).

Benzoylacetonitrile **1** (4.35 g, 30 mmol) was mixed with ammonium acetate (1.6 g, 30 mmol) in a dry round bottom flask. The reaction mixture was heated on an oil bath at 120 °C for 3 h after which it was allowed to cool to room temperature. The solid mass thus obtained was triturated with ethanol where it dissolved. The solution was poured onto ice-cold water and acidified with cold acetic acid till neutral. The solid precipitate thus obtained was collected by filtration and washed with cold water. The overall yield of the reaction is *ca.* 75%. TLC analysis showed that this reaction product contains three compounds, which were separated by column chromarography on silica gel with petroleum ether/ethyl acetate (4:1) as eluent. Compound **9** was collected first followed by **8a** and then **11**.

6-Imino-2,4-diphenyl-1,6-dihydropyridine-3-carbonitrile (**8a**).

Yellow crystals, yield 1.2 g (22 %); mp. 218-220 °C (EtOH/DMF) (lit. 217-218 °C, [7]); ir: 3410- 3280 (NH), and 2212 (CN), 1618 (C=N) cm^{-1}; ^{1}H nmr: 6.25 (s, 1H, CH); 7.2-7.8 (m, 10H, arom. H); 9.65 (s, 1H, NH); 11.2 (s, 1H, ring NH); ms: m/z 271 (molecular ion).

Anal. Calcd. For $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.5; H, 4.7; N, 15.2.

6-Oxo-2,4-diphenyl-1,6-dihydropyridine-3-carbonitrile (**9**).

Dark yellow crystals, yield 0.85 g (15 %); mp. 286-288 °C (EtOH / DMF); ir: 3350- 3280 (NH), and 2230 (CN), 1675 (C=O) cm^{-1}; ^{1}H nmr: 6.65 (s, 1H, CH); 7.1-7.8 (m, 10H, arom. H); 11.45 (s, 1H, ring NH); ms: m/z 272 (molecular ion).

Anal. Calcd. For $C_{18}H_{12}N_2$ O: C, 79.39; H, 4.44; N, 10.29. Found % C, 79.4; H, 4.7; N, 10.2.

4-Amino-2,6-diphenylnicotinonitrile **(11)**.

Brown fine crystals, yield 1.4 g (25 %); mp. 220-222 °C (EtOH / DMF); ir: 3430- 3285 (NH_2), and 2215 (CN), cm^{-1}; ^1H nmr: 6.9 (s, 1H, CH); 7.15 (br. s, 2H, NH_2); 7.25-8.0 (m, 10H, arom. H); ms: m/z 271 (molecular ion).

Anal. Calcd. For $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.4; H, 4.6; N, 15.3.

1,3,5-Tricyano-2,4,6-triphenylbenzene (**13**).

Benzoylacetonitrile **1** (4.35 g, 30 mmol) was refluxed in pyridine for 2 h and then left to cool to room temperature where a yellowish green crystalline product appeared. This product was collected by filtration and washed thoroughly with ethanol and recrystallized from ethanol/DMF to afford 3.5 g (yield= 80 % relative to **1**; 30 % relative to **13**) of pure compound **13**, mp. 283-284 °C (EtOH/DMF) (lit. mp 285 °C) [5]; ir: 2235 (CN); ^1H nmr: 7.15-7.6 (m, arom. H). ^{13}C nmr 110.2 (s), 115.9 (s), 127.2 (d), 128.5 (d), 129.9 (d), 137.1 (s), 150.1 (s); ms: m/z 381 (molecular ion).

Anal. Calcd. for $C_{27}H_{15}N_3$: C, 85.02; H, 3.96; N, 11.02. Found: C, 84.8; H, 4.1; N, 11.3.

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