Reinvestigation of the Reaction of PhenacylMalononitrile with Hydrazines under Solvent Conditions

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Nueva investigación de la reacción de fenacilmalononitrilo con hidrazinas en disolución

Nova investigació de la reacció de fenacilmalononitril amb hidrazines en dissolució

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RESUMEN

El fenacilmalononitrilo 3 reacciona con hidrato de hidrazina en dioxano a reflujo para dar el derivado de iminopiridazina 6 y el derivado de pirazolo[3,4-*c*]piridazina 7. El compuesto 3 reacciona también con fenilhidrazina en etanol a reflujo rindiendo el derivado de iminopiridazina 11 junto con el derivado de fenilhidrazona 12. El compuesto 12 cicla para dar el derivado de pirazolo[3,4-*c*]piridazina 13 por reflujo con etóxido sódico.

Palabras clave: **Fenacilmalononitrilo. 3,5-diamino-4-fenacilpirazolas. Aminopiridazinas. Pirazolo[3,4-c]piridazinas.**

SUMMARY

Phenacylmalononitrile 3 reacts with hydrazine hydrate in refluxing dioxan to afford the iminopyridazine derivative 6 and the pyrazolo[3,4-c]pyridazine derivative 7. Compound 3 reacts also with phenylhydrazine in refluxing ethanol to afford the iminopyridazine derivative 11 along with the phenylhydrazone derivative 12. Compound 12 could be cyclized into the pyrazolo[3,4-*c*]pyridazine derivative 13 upon reflux with sodium ethoxide.

Key words: **Phenacylmalononitrile. 3,5-Diamino-4-phenacylpyrazoles. Aminopyridazines and pyrazolo[3,4-c]pyridazines.**

RESUM

El fenacilmalononitril 3 reacciona amb hidrat d'hidrazina en dioxà a reflux donant el derivat d'iminopiridazina 6 i el derivat de pirazolo[3,4-*c*]piridazina 7. El compost 3 reacciona també amb fenilhidrazina en etanol a reflux rendint el derivat d'iminopiridazina 11 junt amb el derivat de fenilhidrazona 12. El compost 12 ciclitza per donar el derivat de pirazolo[3,4-*c*]piridazina 13 per reflux amb etòxid sòdic.

Mots clau: Fenacilmalononitril. 3,5-diamino-4-fenacilpirazoles. Aminopiridazines. Pirazolo[3,4-c]piridazines.

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INTRODUCTION

In the past few years we have been involved in a program aimed at the synthesis of some new heterocyclic systems of biological interest to be tested as biodegradable agrochemicals[1-4]. In the context of this program we have previously reported a novel synthesis of phenacyl malononitrile **3** (Scheme 1) and its transformation into 3,5-diaminopyrazole derivatives **4a,b**[5]. This work was further elaborated and we could get a variety of compounds[6-8]. During a routine literature search, we have been faced by a paper published by Elnagdi *et. al*.[9] claiming that they invented the reaction of phenacyl bromide with malononitrile in presence of sodium hydroxide to give higher yield of phenacyl malononitrile **3** ignoring that this reaction is well known in the literature[10]. They claimed also that the reaction of **3** with hydrazine hydrate afforded compounds **4a** and **5** (Scheme 1) (**2** & **5** in the original paper[9]); and with phenyl hydrazine to afford the phenylhydrazide **9** which was cyclized into **10** (Scheme 1) (**7** and **8** in the original paper[9]). The melting point cited in this paper for compound **4a** (their **2**) is 290-291 °C; while its reported mp. is 218-220 °C[5]. Structure **5** (their **5**) is not likely to be obtained from this reaction, but rather logic compound **6** (the intermediate **4** in their paper) should have been the final product since the hydrolysis of the imino group into a carbonyl group is not likely to occur so simply with water under the reaction conditions. The formation of the phenylhydrazide **9** (their **7**) seemed doubtful and even if this imaginary compound was true; its cyclization would not lead to the pyrazolone **10** (Scheme 1) (their **8**[9]; wrongly drawn); unless some mysterious rearrangement leading to transfer of the phenyl group from the terminal N to the next N is operating. The numbers of compounds **15** and **17** in their third scheme; should be **16** and **18**[9], Furthermore, in their structures **18a,b** (the ring C=O should be C-NH_2; and the molecular formulae are calculated on the wrong structures and the found analysis values are fabricated to fit with the calculated)[9]. Finally, in the experimental part the preparations and data for compounds **19** and **21** (in their paper [9]) are repeated twice, and the data are different in these repeated parts.

All these discrepancies raised the doubt in the factual accuracy of this work. Therefore it was decided to reinvestigate the most significant reactions, and the data encountered seemed worth to publish.

RESULTS AND DISCUSSION

In our hands the reaction of **3** with hydrazine hydrate was repeated in refluxing dioxan (the same reaction conditions of Elnagdi *et. al.*[9]), and we could isolate two products with melting points 233 °C and 292 °C (233 & 290 as described by Elnagdi *et. al.*[9]). Based on the analytical and spectral data the lower mp. product (233 °C) was found to be the tetrahydropyridazine imine structure **6** (Scheme 1) (the intermediate **4** in the original paper[9]). The ^1H and ^{13}C NMR data given for structure **5** in ref.[9] better fits to the iminopyridazine structure **6** (Scheme 1) since the ^{13}C signal at δ = 159.79 ppm is most probably due to the C=NH rather than the C=O which should appear at much lower field (below 175 ppm), and also the stretching frequency in the IR spectrum given at υ = 1630 cm^{-1} is very low to a lactam carbonyl group and better fits to C=NH[11]; and even they stated in their paper that the IR spectrum showed two band at υ3250 and 3200 cm^{-1} and assigned them to two NH which is applicable to our structure **6** rather than their structure **5**. The analyses seem to be put as required by their wrong structure **5**.

The higher mp. product (292 °C) showed a molecular ion peak in the mass spectrum at m/z 213. The IR spectrum of this product showed no carbonyl absorptions and the presence of only amino absorption bands at υ3320-3150 cm^{-1}. The ^1H NMR spectrum of this product revealed a singlet (2H) at δ 3.7 ppm, an aromatic multiplet (8H) at δ 7.3-7.9 ppm and a singlet (1H) at δ 10.35 ppm. On the basis of these data the pyrazolo[3,4-*c*]pyridazine structure **7** was assigned.

It seems that in refluxing dioxan two competitive reactions are working: 1st is the condensation of hydrazine hydrate with the carbonyl group of **3** followed by addition of the hydrazone NH_2 to one of the cyano groups to afford **6**. 2nd is the cycloaddition of hydrazine to the two cyano groups of **3** to afford the 4-phenacyl-3,5-diaminopyrazole **4a** which undergoes an *insitu* condensation with hydrazine hydrate to afford the hydrazone intermediate **8** (Scheme 1), which in its role undergoes cyclization with elimination of ammonia via the nucleophilic attack of the hydrazone NH_2 on the ring amino group to give **7**. Compound **7** has also been previously reported to be obtained from the reaction of **4a** with hydrazine hydrate (lit. mp. 293 °C)[8].

Thus it evident that the pyrazole derivative **4a** (scheme 1) (no. **2** in ref.[9]) is not isolated from this reaction under these reaction conditions. The wrong assignment given by Elnagdi *et. al.*[9] has serious consequences for some other reactions involved in their paper and based on the their claimed **2**; for example structures **13-21** are all doubtful.

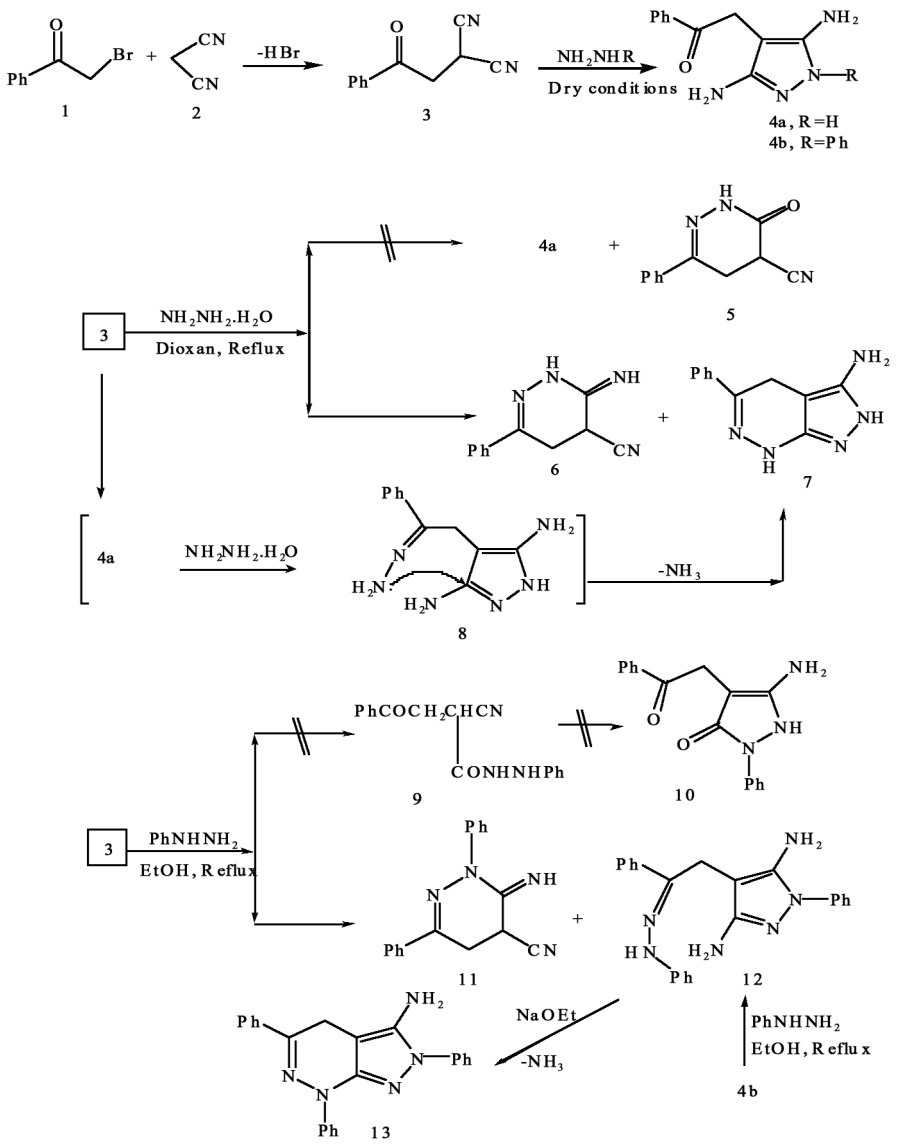
The reaction of **3** with phenyl hydrazine in refluxing ethanol was also claimed to afford the phenylhydrazide **9** as the only product, which was cyclized to the pyrazolone **10** (scheme 1); (**7, 8** in the original paper[9]; **8** is wrongly drawn). In our hands this reaction also afforded two products: The first product with mp. 177 °C showed analyses and spectra that suggested the tetrahydropyridazine imine structure **11** to be assigned to it (Scheme 1; *cf.* experimental; not isolated by Elnagdi *et. al.*[9]).

The second product is a yellow crystalline product of mp. 200 °C (this perhaps what happened with Elnagdi *et. al.*; mp.199-200 °C[9]): This product showed a molecular ion peak in the mass spectrum at m/z 382. The IR spectrum of this product did not show any carbonyl absorption bands. The ^1H NMR spectrum revealed only a singlet (2H) at δ 2.85 ppm, a multiplet (17H) at δ 6.55-7.85 ppm assignable to three phenyl rings and NH_2 protons and two singlets at 8.15 and 10.45 ppm (2H & 1H; D_2O exchangeable due to NH_2 & hydrazone NH respectively). Based on these spectral as well as analytical data the phenyl hydrazone structure **12** was assigned to this product.

It is assumed that phenacylmalononitrile **3** reacts with phenyl hydrazine in refluxing 96% ethanol (the same reaction conditions described by Elnagdi *et. al.*[9]) following the same route as its reaction with hydrazine hydrate to afford **11** and the 3,5-diaminopyrazole derivative **4b**, which undergoes an *insitu* condensation with phenyl hydrazine to give the corresponding phenyl hydrazone **12**.

To confirm this hypothesis the 3,5-diaminopyrazole derivative **4b** was prepared separately as described before[5] and allowed to react with phenyl hydrazine in refluxing ethanol for 2h, the obtained product was found to match completely with compound **12**.

Refluxing compound **12** in ethanol with sodium ethoxide afforded a new compound of mp. 222 °C. The IR spectrum of this product did not show any carbonyl absorption bands. The ^1H NMR spectrum revealed only a singlet (2H) at δ 3.45 ppm and a multiplet (17H) at δ 7.35-7.85 ppm assignable to three phenyl rings and NH_2 protons. Based on these spectral as well as analytical data the pyrazolo[3,4-*c*]pyridazine derivative **13** was assigned to this product (this perhaps what happened with Elnagdi *et. al.*[9], but they failed to interpret the



Scheme 1

results). It should be clarified that the intermediate hydrazone **8** could not be isolated but undergoes insitu cyclization into **7**; while the phenyl hydrazone **12** could be separated and then cyclized into **13** upon reflux with sodium ethoxide. This perhaps may be due to the steric factors as well as the strong nucleophilicity of the hydrazone NH_2 rather than the phenyl hydrazone NHPh which needed more drastic conditions to accomplish its cyclization.

The ^{13}C NMR data of compound **13** confirmed its structure. It revealed a one C(t) at δ 16.35 ppm attributable to the pyridazine ring CH_2 and no signals below δ 160 ppm that can be attributed to carbonyl carbons (*cf.* experimental). A structure like **10** (Scheme 1) (**8** in ref.[9]) should have revealed the methylene carbon at ca. δ 35 ppm and two carbonyl carbons at ca. δ 165 and 195 ppm for the ring carbonyl and the side chain carbonyl respectively[11].

It is worth to mention that the products of this last reaction depend on the molar ratio of phenyl hydrazine and the time of the reaction. Thus when the reaction was carried out with 1:1 molar ratios of **1** and phenyl hydrazine and refluxed for 1h; low yield of **11** and **12** was obtained along with the pyrazole derivative **4b**, but when repeated using three fold excess of phenyl hydrazine and the reflux time was extended to 2h, both **11** and **12** were obtained in better yields.

The analytical and spectral data cited in ref.[9] for compounds **9** and **10** (Scheme 1) (their **7** and **8**) seem to be fabricated to coincide with these structures.

It has also been claimed that the reaction of phenacyl bromide **1** with ethyl cyanoacetate led only to the dialkylation product[9]. In our hands when phenacyl bromide **1** was allowed to react with ethyl cyanoacetate in presence of sodium hydroxide (as described by Elnagdi *et. al.*[9]) only unidentifiable tarry product was obtained. However the reactions of **1** with ethyl cyanoacetate in presence of piperidine and with the sodium salt of ethyl cyanoacetate were previously reported by us[6].

CONCLUSION

The reaction of phenacylmalononitrile with hydrazine hydrate and phenyl hydrazine is reinvestigated under solvent reaction conditions. Some wrong structures and claimed results could be corrected.

Experimental Section

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H-and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70ev). Elemental analyses were carried out by the Microanalytical Centre at Cairo University.

The reaction of phenacyl-malononitrile 3 with hydrazine hydrate:

A solution of **3** (1.85 g; 0.01 mole) and hydrazine hydrate (0.01 mole) in 100 ml of dioxan was refluxed for 2h. The reaction mixture was allowed to cool to room temperature. The solid precipitate was filtered off, boiled in ethanol and where a part dissolved, filtered while hot and left to recrystallize, it was identified as **6**. The insoluble part was recrystallized from DMF/dioxan mixture (1:1) and identified as **7**.

3-Imino-6-phenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile 6:

Pale yellow crystals (0.9 g, 45%) m.p. 233-234 °C (EtOH): IR: ν_{max} (KBr) = 3280-3220 (NH), 2222 (CN); ^{1}H NMR (DMSO-d_6): δ = 3.2 (m, 2H, CH_2), 4.6(dd, 1H, CH), 7.3-7.7 (m, 6H, Ph + ring NH) and 11.5 ppm (s, 1H, imine NH). MS [EI, 70 eV]: *m/z* = [M^+] (198). Analysis for $C_{11}H_{10}N_4$: calcd. C 66.65, H 5.08, N 28.26; found C 66.30, H 5.30, N 27.90.

5-Phenyl-4,7-dihydro-2H-pyrazolo[3,4-c]pyridazin-3-ylamine 7:

Yellow crystalline solid, (0.85 g, 40%) mp 290-291 °C (DMF/dioxan 1:1). IR: ν_{max} (KBr) 3380-3190 (br., NH_2 & NH); ^{1}H NMR (DMSO-d_6): δ = 2.8 (s, 2H, ring CH_2), 5.15 (s, 2H, NH_2), 7.25-7.6 ppm (m, 6H, Ph+NH), 12.35 (s, 1H, pyrazole NH). MS [EI, 70 eV]: *m/z* = [M^+] (213). Analysis for $C_{11}H_{11}N_5$: calcd. C 61.96, H 5.20, N 32.84; found C 62.10, H 5.10, N 32.50.

The reaction of phenacyl-malononitrile 3 with phenyl hydrazine:

A solution of **3** (1.85 g; 0.01 mole) and phenyl hydrazine (0.02 mole) in 100 ml of ethanol was refluxed for 2h where a solid precipitate appeared. The reaction mixture was filtered off while hot. The filtrate was allowed to cool to room temperature where dark yellow product precipitates, filtered off and recrystallized from ethanol to afford dark yellow crystals which were identified as **11**. The insoluble part was dissolved in hot ethanol with few drops of DMF, left to cool in ice bath overnight where an orange yellow precipitate appeared, filtered off and identified as **12**.

3-Imino-2,6-diphenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile 11:

Dark yellow crystals (1.1 g, 40%) m.p. 177-178 °C (EtOH): IR: ν_{max} (KBr) = 3310 & 3290 (NH), 2218 (CN); ^{1}H NMR (DMSO-d_6): δ = 3.25 (m, 2H, CH_2), 4.45(dd, 1H, CH), 6.55-7.65 (m, 10H, 2Ph) and 11.8 ppm (s, 1H, imine NH). ^{13}C NMR: 23.10(t), 23.43(d), 115.24(s), 115.75(d), 119.11(d), 128.60(d), 129.13(d), 129.45(d), 130.52(d), 131.35(s), 146.35(s), 156.72(s), 162.12(s). MS: *m/z* = [M^+] (274). Analysis for $C_{17}H_{14}N_4$: calcd. C 74.43, H 5.14, N 20.42; found C 74.60, H 5.20, N 20.70.

1-Phenyl-4-[2-phenyl-2-(phenylhydrazono)-ethyl]-1H-pyrazole-3,5-diamine 12:

Orange crystalline solid, (1.3 g, 34%) mp 200-201 °C (EtOH/DMF). IR: ν_{max} (KBr) 3385-3195 (br., NH_2 & NH); ^{1}H NMR (DMSO-d_6): δ = 2.85 (s, 2H, CH_2), 6.55-7.85 (m, 17H, 3Ph+NH_2), 8.15 (s, 2H, NH_2), 10.45 (s, 1H, NH). MS: *m/z* = [M^+] (382). Analysis for $C_{23}H_{22}N_6$: calcd. C 72.23, H 5.80, N 21.97; found C 72.10, H 5.50, N 21.60.

Alternative preparation of 12:

A solution of 3,5-diamino-4-phenacyl-1-phenylpyrazole **4b** (1.46 g; 0.005 mole; prepared according to literature method[5]) and phenyl hydrazine (0.54 g; 0.005 mole) in 50 ml of ethanol was refluxed for 2h where a solid orange precipitate appeared. The reaction mixture was then left to cool to room temperature, filtered off and recrystallized from ethanol/ DMF to afford orange yellow crystals identical with those of **12** in all respects.

2,5,7-Triphenyl-4,7-dihydro-2H-pyrazolo[3,4-c]pyridazin-3-ylamine 13:

(Cyclization of 12)

To a solution of **12** (1.91 g; 0.005 mole) in absolute ethanol (50 ml) was added 5 ml of sodium ethoxide (0.5 g of Na metal dissolved in 20 ml of ethanol) and the reaction mixture was refluxed for 2h, then left to cool to room temperature and poured on ice cold water and acidified with few drops of conc. HCl till just neutral. The solid precipitate thus appeared was filtered off and washed thoroughly with cold water, dried and recrystallized from ethanol to afford **13** as pale yellow crystals (1.5 g; 82%); mp. 222-223 °C (EtOH). IR: ν_{max} (KBr) 3385-3225 (br., NH_2); ^{1}H NMR (DMSO-d_6): δ = 3.42 (s, 2H, CH_2), 6.45-7.85 (m, 17H, 3Ph+NH_2). ^{13}C NMR: 16.35(t), 92.10(s), 115.15(d), 118.75(d), 118.80(d), 126.63(d), 128.65(d), 129.12(d), 129.2(d), 129.35(d), 131.25(s), 131.55(d), 138.9(s), 145.65(s), 147.10(s), 155.65(s), 159.85(s). MS: *m/z* = [M^+] (365). Analysis for $C_{23}H_{19}N_5$: calcd. C 75.59, H 5.24, N 19.16; found C 75.20, H 5.50, N 19.60.

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