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Reactions with Arylhydrazones of α-Cyanoketones: Synthesis of New α-Arylhydrazononitriles

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New α-arylhydrazononitriles were prepared by reaction of the hydrazide **1** and the amidrazone **2** with nucleophilic reagents. β-Bifunctional reagents were condensed with **1** and **2** to yield new heterocyclic hydrazonitriles.

Reaktionen mit Arylhydrazonen von α-Cyanoketonen: Synthese einiger neuer α-Arylhydrazonitrile

Einige neue α-Arylhydrazonitrile werden durch Umsetzung der Hydrazide **1** und der Amidrazone **2** mit Nucleophilen hergestellt. Bifunktionelle Reagentien werden ebenfalls mit **1** und **2** kondensiert, um einige neue heterozyklische Hydrazonitrile zu gewinnen.

The considerable biological activity of arylhydrazono-α-cyanoketones as antituberculotic agents and oxidative phosphorylation inhibitors[1–5] recently have stimulated interest in the synthesis and chemistry of these compounds. In continuation of previous work[6–8], we report the utility of the recently synthesised compounds **1** and **2** for the syntheses of several, otherwise difficult to prepare α-arylhydrazononitriles.

Thus, compound **1** reacted with acetyl and benzoyl chlorides to yield the acetyl and benzoyl derivatives **3a** and **3b.** In contrast, compound **2** reacted with acetyl chloride to yield 1-acetyl-4-(2-methylphenylhydrazono)-3,5-diaminopyrazole hydrochloride **(4)** which could be converted into **5** by action of ammonium hydroxide. The ready deacylation of this compound on basification is similar to the reported deacylation of N-acylpyrazoles when treated under similar conditions[9,10].

When compound **2** was reacted with benzoyl chloride, a product with the possible structures **6** or isomeric **7** was obtained. Structure **6** could be excluded based on formation of **8** on hydrolysis of **7** by the action of acetic/hydrochloric acids mixture. Attempts to synthesise **4** from methylphenylhydrazonomesoxalonitrile **(9)** and benzoylhydrazine were unsuccessful.

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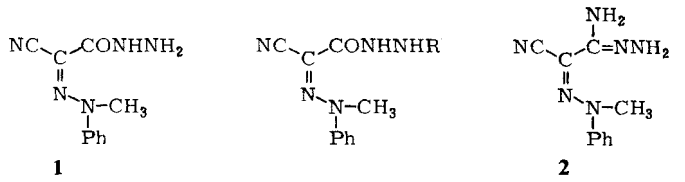
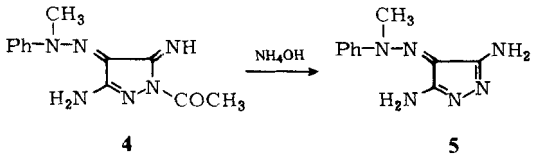
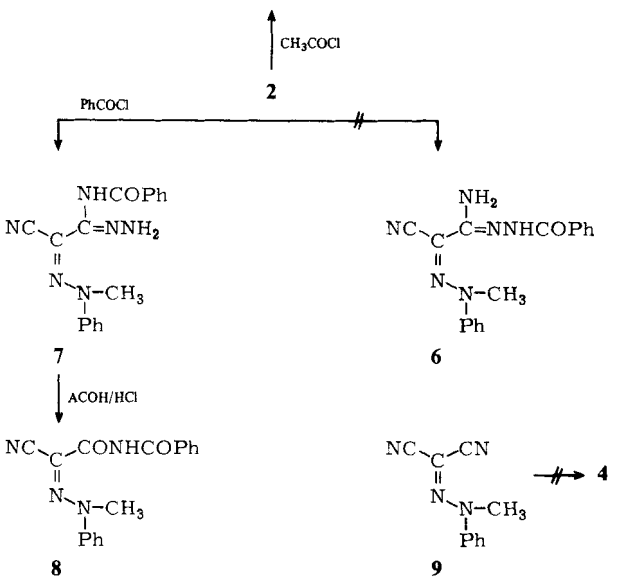


1 **2**

3a: R = $COCH_3$
b: R = COPh
c: R = $COCH_2COCH_3$
d: R = $CO_2C_2H_5$



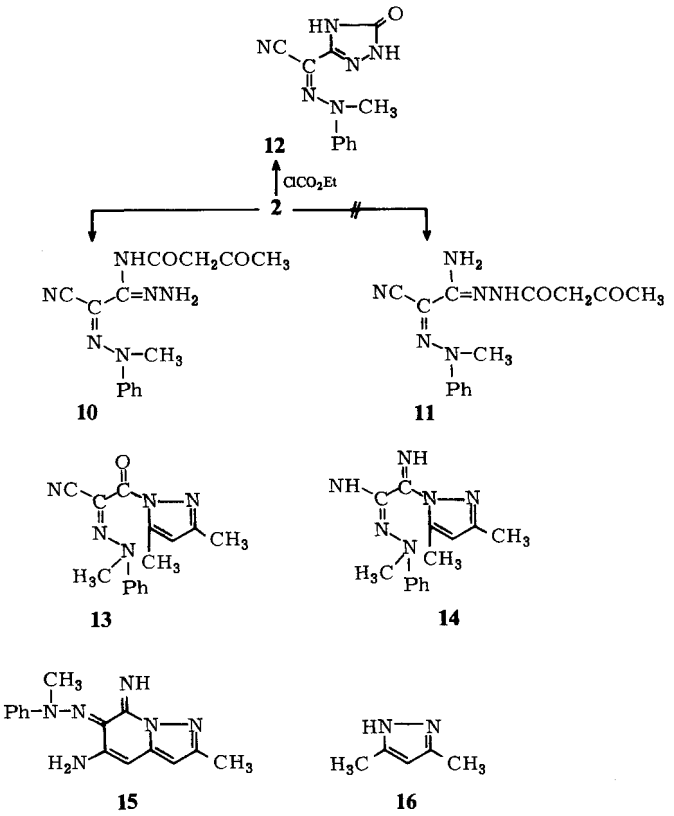
4 **5**



7 **6** **8** **9**

Similar to its behaviour towards the action of benzoyl chloride, compound **1** was reacted with ethyl acetoacetate and ethyl chloroformate to yield the acyl derivatives **3c** and **3d.** Also, compound **2** reacted with ethyl acetoacetate to yield a product for which structure **10** seemed more likely than the isomeric **11** based on analogy to the established behaviour of **2** with acylation agents. However, we are not in a position to exclude completely the isomeric structure **11.**

On the other hand, **2** reacted with ethyl chloroformate to yield the 1,2,4-triazol derivative **12.**

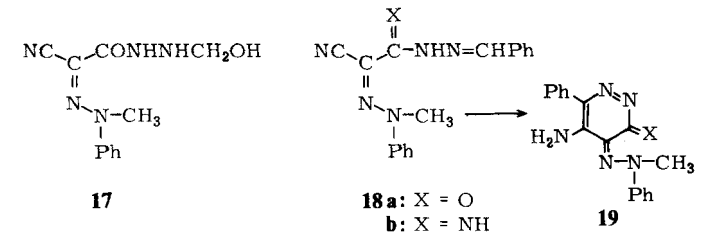


In contrast to the behaviour of **1** and **2** towards the action of ethyl acetoacetate, compound **1** reacted with acetylacetone to yield the pyrazole derivative **13.** Also, compound **2** reacted with the same reagent to yield a product for which the pyrazole structure **14** was suggested. Attempts to convert **14** into the cyclic compound **15** or to hydrolyse **13** or **14** into the pyrazole **16** were unsuccessful.

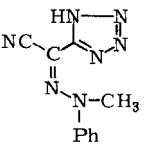
Compound **1** reacted with formaldehyde in methanol containing piperidine to yield the hydroxymethyl derivative **17.** On the other hand, benzaldehyde reacted with **1** and **2** to yield the *Schiff*'s bases **18a** and **18b** resp.. Attempts to cyclise **18a** and **18b** into **19** under a variety of conditions were unsuccessful.

The semicarbazide and thiosemicarbazide derivatives **20a, b** could be obtained via the reaction of **1** with phenylisocyanate and phenylisothiocyanate.

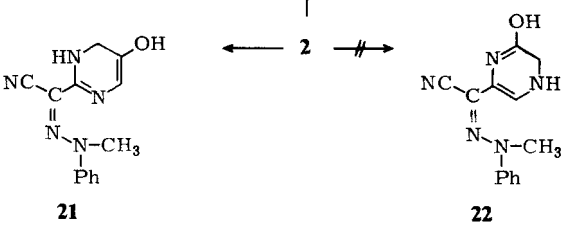
It was found that the amidrazone **2** could be utilised for the synthesis of 1,2,4-triazine derivatives with arylhydrazononitrile moiety. Thus, when **2** was reacted with ethyl chloroacetate, a product was isolated for which structures **21** or **22** seemed possible. Structure **21** was established for the reaction product based on the nonidentity of this product with a sample of **22** prepared via the action of ethyl hydrazinoacetate on **8**. The 1,2,4-tetrazine derivative **23** was synthesised via the action of nitrous acid on the amidrazone derivative **2**.



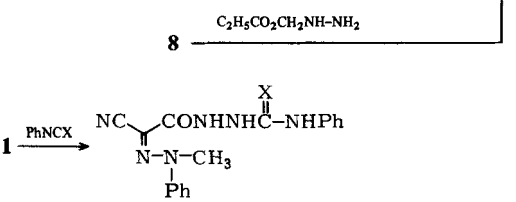
17 **18a**: X = O; **b**: X = NH **19**



23



21 **22**



20a: X = O

20b: X = S

Experimental Part

MP: uncorr.. *IR spectra* (KBr): Pye Unicam SP 1100. *^{1}H-NMR spectra:* EM-390-90 MHz DMSO, TMS int. stand., chemical shifts: δ = (ppm). *Analytical data:* the analytical data unit at Cairo Univ..

Methylphenylhydrazonocyanoglyoxalic acid N-acylhydrazides **3a, b**

A solution of 0.01 mole of **2** in 80 ml pyridine was treated with 0.01 mole of the appropriate acid chloride. The reaction mixture was refluxed for 2 h and then evaporated i. vac. The remaining product was triturated with water, and the resulting solid product was crystallized from ethanol (tables 1, 2).

1-Acetyl-3-amino-5-imino-4-methylphenylhydrazonopyrazole hydrochloride **(4)**

A solution of 0.01 mole of **2** in 100 ml pyridine was treated with 0.01 mole acetyl chloride. The reaction mixture was kept for 3 h at room temp., and the resulting solid product was crystallized from ethanol (tables 1, 2).

4-Methylphenylhydrazono-3,5-diaminopyrazole **(5)**

A suspension of 5 g **4** in 20 ml water was treated with 10 ml 20 % ammonium hydroxide and stirred at room temp. for 1 h. The resulting solid product was washed with water carefully and crystallized from ethanol (tables 1 and 2).

Methylphenylhydrazonobenzoylamidrazonylacetonitrile **(7)**

A solution of 0.01 mole of **2** in 100 ml pyridine was treated with 0.01 mole benzoyl chloride. The reaction mixture was kept at room temp. and then evaporated i. vac. till most of the pyridine was evaporated. The remaining solid product was crystallized from ethanol (tables 1 and 2).

Reaction of **7** *with acetic acid/hydrochloric acid mixture*

A solution of 5 g of **7** in 15 ml of acetic acid and 5 ml hydrochloric acid was refluxed for 3 h and then evaporated i. vac. The remaining product was triturated with water, and crystallized from ethanol (tables 1 and 2).

Reaction of **1** *and* **2** *with*

a) Ethyl acetoacetate: A solution of each of 0.01 mole of **1** and **2** in 100 ml ethanol was treated with 0.01 mole ethyl acetoacetate. The reaction mixture was heated under reflux for 2 h, then evaporated i. vac. The resulting solid product was crystallized from ethanol (tables 1 and 2).

b) Ethyl chloroformate: A solution of 0.01 mole of **1** in 100 ml acetone was treated with 0.01 mole of ethyl chloroformate. The reaction mixture was refluxed for 3 h, then evaporated i. vac. The resulting solid product was crystallized from ethanol (tables 1 and 2).

c) Acetylacetone: A mixture of each of 0.01 mole of **1** and **2** was treated with 0.01 mole acetylacetone and heated at 100° (bath temp) for 2 h, and then triturated with benzene/petroleum ether mixture. The resulting solid product was crystallized from ethanol (tables 1 and 2).

Reaction of **1** *with formaldehyde*

A solution of 0.01 mole of **1** in 100 ml ethanol was treated with 0.01 mole formaldehyde and some drops of piperidine. The reaction mixture was left overnight at room temp.. The resulting crystals were recrystallized from ethanol (tables 1 and 2).

Reaction of **1** *and* **2** *with benzaldehyde*

A solution of 0.01 mole of each of **1** and **2** in 100 ml ethanol was treated with 0.01 mole benzaldehyde and 1 ml piperidine. The reaction mixture was refluxed for 2 h and then poured into cold water. The solid product so formed was crystallized from ethanol (tables 1 and 2).

Reaction of **1** *with isocyanate and isothiocyanate*

A solution of 0.01 mole of **1** in 100 ml acetone was treated with 0.01 mole of phenylisocyanate or phenyl isothiocyanate. The reaction mixture was refluxed for 2 h, then evaporated i. vac. The remaining product was triturated with ethanol (tables 1 and 2).

Table 1: *Newly synthesised compounds*

Compd.	M.P. (°C)	Yield %	Mol. Form Mol. Wt.	Found Calcd. C		Analysis H		N	
3a	180	70	$C_{12}H_{13}N_5O_2$ (259)	55.5	55.6	5.5	5.1	26.9	27.1
3b	212	70	$C_{17}H_{15}N_5O_2$ (321)	63.3	63.5	4.9	4.7	21.6	21.8
3c	110	50	$C_{14}H_{15}N_5O_3$ (301)	55.8	55.8	5.2	5.0	22.9	23.2
3d	181	70	$C_{13}H_{15}N_5O_3$ (289)	54.0	54.0	5.2	5.2	23.8	24.2
4	169	65	$C_{12}H_{15}N_6OCl$ (294.5)	48.9	48.9	4.9	5.0	28.8	28.5
5	300	80	$C_{10}H_{12}N_6$ (216)	54.9	55.4	5.4	5.5	38.6	38.9
7	186	60	$C_{17}H_{16}N_6O$ (320)	64.2	63.7	5.2	5.0	26.9	26.3
8	98	50	$C_{17}H_{14}N_4O_2$ (306)	66.4	66.7	4.8	4.6	17.9	18.3
10	108	40	$C_{14}H_{16}N_6O_2$ (300)	55.8	56.0	5.5	5.3	27.8	28.0
12	175	75	$C_{11}H_{10}N_6O_2$ (242)	54.3	54.5	4.3	4.1	34.5	34.7
13	95	50	$C_{15}H_{15}N_5O$ (281)	63.9	64.0	5.2	5.3	24.5	24.9
14	140	45	$C_{15}H_{16}N_6$ (280)	64.8	64.3	5.3	5.7	30.0	30.0
17	125	70	$C_{11}H_{13}N_5O_2$ (247)	53.4	53.4	5.2	5.3	27.9	28.3
18a	195	60	$C_{17}H_{15}N_5O$ (305)	67.1	66.9	4.8	5.0	22.4	22.9
18b	215	70	$C_{17}H_{16}N_6$ (304)	67.5	67.1	5.4	5.3	27.9	27.6
20a	225	80	$C_{17}H_{16}N_6O_2$ (336)	60.9	60.7	4.6	4.8	24.6	25.0
20b	210	70	$C_{17}H_{16}N_6OS$ (352)	58.0	58.0	4.3	4.5	23.6	23.9
21	111	65	$C_{12}H_{12}N_6O$ (256)	56.2	56.3	4.8	4.7	32.6	32.8

Table 1:

Compd.	M.P. (°C)	Yield %	Mol. Form Mol. Wt.	Found Calcd. C		H		N	
22	183	80	$C_{12}H_{12}N_6O$ (256)	56.4	56.3	4.5	4.7	32.5	32.8
23	209	80	$C_{10}H_9N_7$ (227)	52.7	52.9	4.0	4.0	42.9	43.1

Table 2: *IR. and ^{1}H-NMR-spectra of selected compounds*

Compd.	IR, (cm^{-1}) Selected bands	^{1}H-NMR, δ = (ppm)
3a	3410, 3280 (NH), 2290 (CH_3) 2220 (CN), 1710 and 1650 (2CO)	2.25 (s, 3H, $COCH_3$), 3.65 (s, 1H, NH), 4.2 (br, 5H, NCH_3 and CH_2), 6.1 (s, 2H, NH_2) and 7.0–7.9 (m, 5H, C_6H_5)
3c	3400, 3050 (NH), 2220 (CN), 1770 (acetyl CO), 1710 (CO) and 1660 (hydrazide CO)	2.49 (s, 3H, $COCH_3$), 3.4 (s, 2H, CH_2), 4.0 (s, 3H, NCH_3), 7.0–8.1 (m, 5H, Ph), 9.6 (s, 1H, NH) and 10.2 (s, 1H, NH).
5	3400, 3320, 3200 (NH_2) and 1650–1620 (NH_2 and C=N)	
14	3450, 3360 (NH_2), 2220 (CN) and 1670 (NH_2)	2.1, 2.3 (dd, 6H, $2CH_3$), 4.15 (s, 3H, NCH_3, 5.2 (s, 1H, pyrazole CH), 6.1 (br, 1H, NH) and 7.0–7.0 (m, 5H, Ph).
17	3500, 3200 (chelated OH), 2220 (CN), 1680–1640 (CO)	4.1 (s, 5H, NCH_3 and CH_2), 5.2 (br, 1H, OH) and 7.0–7.0 (m, 5H, Ph).
18a	3350–3260, 3050 (NH), 2220 (CN), 1660–1640 (CO and C=N)	4.12 (s, 3H, NCH_3), 7.0–7.9 (m, 6H, CHPh) and 8.5 (s, 1H, NH).
18b	3410–3100 (NH), 3/50, 2290 (CH- and CH_3), 2220 (CN) and 1650 (CN)	4.13 (s, 3H, NCH_3), 6.5 (s, 1H, NH), 7.1–8.0 (m, 6H, CHPh) and 8.5 (s, 1H, NH).
20a	3380 (NH), 2220 (CN), 1760 (CO) and 1670–1650 (hydrazide CO).	
21	3550–3400 (chelated OH), 3000, 2290 (CH_2 and CH_3) and 2200 (CN).	
22	3450–3000 (NH and OH), 2290-(CH_3), 2220 (CN) and 1640 (C=N)	2.45 (s, 2H, triazole CH_2), 3.5 (br, 2H, NH and OH), 4.1 (s, 3H, NCH_3) and 7.0–7.9 (m, 5H, Ph).
23	2222 2220 (CN).	

3-Methylphenylhydrazonocyanomethyl-6-hydroxy-4-dihydro-1,2,4-triazine **(21)**

A solution of 0.01 mole of **2** in 100 ml ethanol was treated with 0.01 mole ethyl chloroacetate. The reaction mixture was refluxed for 3 h then left to cool to room temp. and poured into water. The solid product so formed was crystallized from ethanol (tables 1 and 2).

3-Methylphenylhydrazonocyanomethyl-5-hydroxy-1,6-dihydro-1,2,4-triazine **(22)**

A solution of ethylhydrazinoacetate (prepared from 0.01 mole of ethylhydrazinoacetate hydrochloride and the appropriate amount of $NaHCO_3$ in 20 ml ethanol) was treated with 0.01 mole of **8** and refluxed for 7 h. The reaction mixture was evaporated i. vac. and the resulting product was triturated with water and crystallized from ethanol (tables 1 and 2).

5-Methylphenylhydrazonocyanomethyl-1,2,4-tetrazole **(23)**

A solution of 0.01 mole of **2** in 100 ml ethanol was treated with 10 ml 37.5 % hydrochloric acid. The solution was cooled to 0°, then treated gradually, while stirring, with a saturated solution of 0.7 g of sodium nitrite. After complete addition of the nitrite solution, the solid product formed, was crystallized from ethanol (tables 1 and 2).

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