Reactions with the Arylhydrazones of α -Cyanoketones: Utility of Arylhydrazonomesoxalonitriles for the Synthesis of Azoles and Azolines

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Z. Naturforsch. **35b**, 485–489 (1980); received February 13/July 30, 1979

Arylhydrazones, α -Cyanoketones

The arylhydrazonomesoxalonitriles derivatives **1a–c** were utilised for the synthesis of several new pyrimidine, pyridines, triazine and isoxazole derivatives.

Compound **1a** reacted with alkyl halides to yield the N-alkyl derivatives **12a, b**. The latter reacted with hydrazines to yield the amidrazones **13a, b**.

The coupling reaction of aryl diazonium salts with malononitriles has been reported to afford arylhydrazonomesoxalonitrile [1]. Although the activity of these compounds as oxidative phosphorylation inhibitors [2–5] has received considerable attention, only very little emphasis was placed on the chemical reactivity of this class of compounds [6, 7]. In previous work, from this laboratory we have demonstrated the usefulness of these products as precursors for synthesis of 3,5-diaminopyrazole derivatives [8–10]. In continuation of previous work we report here the results of our investigations aiming to explore the potential utility of these derivatives as intermediates in heterocyclic synthesis.

1a reacts with thiourea to yield the diamino-pyrimidine derivative **2**. Compound **2** ($\text{Ar} = \text{C}_6\text{H}_5$) was converted into the aminopyrimidine hydrochloride (**3a**) on treatment with acetic acid-hydrochloric acid. Similar to **1a**, compound **1b** reacted with thiourea to yield a product which on boiling for a short period with acetic acid-hydrochloric acid, afforded the hydrochloride **3b**.

Compound **1a** reacted with urea to yield a product which could be converted into the hydrochloride **4** on treatment with acetic acid-hydrochloric acid mixture.

Compounds **1a–c**, reacted with malononitriles to yield products for which structures **5** or possible isomeric **6** seemed possible on the basis of analytical and spectral data. In order to establish the structure of the product obtained by the reaction of **1** with

malononitrile, 2-amino-1,1,3-tricyanopropene was coupled with benzene diazonium chloride to afford a product which was considered to have structure **6**. The latter when boiled for a short period in DMF afforded a product identical in all respects with the product of reaction of **1a** with malononitrile thus establishing structure **5** for the latter product [11].

The IR spectra of **5a, b** revealed a broad CN absorption in the region $2180\text{--}2200\text{ cm}^{-1}$ this large frequency shift may be attributed to the presence of amino and imino groups adjacent to the cyano function. Baldwin [12] has reported CN absorption for O-aminonitriles in the range $2160\text{--}2200\text{ cm}^{-1}$.

Compounds **1a, b** reacted with benzoyl isothiocyanate or with ethoxycarbonyl isothiocyanate to yield the amino-1,2,4-triazine derivatives **7a, b**. When **1c** was similarly treated, the amide **7** was the only isolable product. The formation of **7a, b** from the reaction of **1a, c** with isothiocyanates might be assumed to proceed via addition of the reagent to the hydrazone nitrogen to form the intermediate thiourea derivative **9**. The latter then cyclises into the triazine derivative **10** which loses a benzoyl or ethoxycarbonyl isothiocyanate to yield the final isolable **7a, b**. In reaction with **1b**, a longer reflux time was needed for complete reaction and it seems that traces of moisture in the reaction medium effects partial hydrolysis of the cyano group to yield the amide. The formation of 4-amino-1-aryl-1,2,4-triazines in this reaction may be considered as a new simple route for the synthesis of 1-aryl-4-amino-1,2,4-triazin-6-thione [13].

Compound **1a** reacted with hydroxylamine hydrochloride in the presence of sodium carbonate to

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0340-5087/80/0400-0485/\$ 01.00/0

To a solution of sodium ethoxide (prepared from 5.0 g of sodium metal and 150 ml ethanol), compound **1a** (0.01 mole), and thiourea (0.1 mole) was added. The reaction mixture was refluxed for 10 h, then evaporated *in vacuo*. The remaining product was dissolved in water and acidified by addition of concentrated hydrochloric acid. The solid product, so formed, was collected by filtration and crystallised from dioxane.

Compound **2a** formed a yellow crystals, m.p. 245 °C; yield 70% IR: 1620 cm^{-1} (δNH_2) and a broad band 3200–3300 (νNH).

$\text{C}_{10}\text{H}_{10}\text{N}_6\text{S}$

Calcd C 48.7 H 4.06 S 13.00,
Found C 48.3 H 4.01 S 12.4.

When **2a** was refluxed for a short period with acetic acid and hydrochloric acid compound **3a** was formed in quantitative yield.

Compound **3a** formed yellow crystals; m.p. 265 °C; yield 80% IR: 1620–1650 (δNH_2 and CO), 3300 and 3420 cm^{-1} (νNH_2).

$\text{C}_{10}\text{H}_{10}\text{N}_5\text{ClSO}$

Calcd C 42.3 H 3.5 S 11.3,
Found C 42.3 H 3.2 S 11.2.

Compound **3b** could be prepared *via* treatment of **1b** with thiourea under the same conditions and boiling the resulting reaction product for a short period with acetic acid and hydrochloric acid.

Compound **3** formed yellow crystals; m.p. 245 °C; yield 98%.

$\text{C}_{10}\text{H}_9\text{N}_5\text{Cl}_2\text{SO}$

Calcd C 37.7 H 2.8 S 10.0,
Found C 37.5 H 2.8 S 10.0.

4-Amino-6-hydroxy-5-phenylhydrazono-2,5-dihydropyrimidin-2-one-hydrochloride (**4**)

To a solution of sodium ethoxide (prepared from 5.0 g of sodium metal and 150 ml of absolute ethanol), compound **1a** (0.1 mole) and urea (0.1 mole) were added. The reaction mixture was refluxed for 30 h then evaporated *in vacuo*. The remaining product was dissolved in water and acidified by the addition of concentrated hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from acetic acid containing 1% concentrated hydrochloric acid.

Compound **4** formed yellow crystals: m.p. > 300 °C; yield 70%. IR: 1640–1660 cm^{-1} (CO and δNH_2); 1725 cm^{-1} (CO) and 2500–3340 cm^{-1} (chelated OH and NH groups).

$\text{C}_{10}\text{H}_{10}\text{N}_5\text{O}_2\text{Cl}$

Calcd C 44.8 H 3.7 N 26.1,
Found C 44.5 H 4.1 N 25.5.

4-Amino-aryl-3,5-dicyano-6-aminopyridazines (**5a, b**)

To a solution of **1a, c** (0.01 mole) in pyridine (30 ml) malononitrile (0.7 g) was added. The reaction mixture was refluxed for 10 h then cooled and poured into water. The solid product, so formed, was collected by filtration and crystallised from DMF.

Compound **5a** formed brown crystals; m.p. > 300 °C; yield 80%. IR: 1630 ($\text{C}=\text{N}$ and δNH_2); 2180–2190 cm^{-1} (conjugated CN and 2900–3400 (chelated NH vibrations).

$\text{C}_{12}\text{H}_8\text{N}_6$

Calcd C 61.0 H 3.3,
Found C 60.9 H 3.2.

Compound **5a** was also obtained in 70% yield *via* cyclization of **6** (see latter) by refluxing in DMF for 10 min and on working up the reaction mixture.

Compound **5b** formed brown crystals: m.p. > 300 °C; yield 75%. IR: 1630–1660 ($\text{C}=\text{N}$ and δNH_2); 2200 and 2220 (two conjugated CN) and 2900–3360 (chelated NH vibration).

$\text{C}_{12}\text{H}_7\text{N}_6\text{Cl}$

Calcd C 53.2 H 2.5,
Found C 53.0 H 2.6.

Compound **5c** formed brown crystals; m.p. > 300 °C; yield 86%.

$\text{C}_{13}\text{H}_{10}\text{N}_6$

Calcd C 62.4 H 4.0,
Found C 62.4 H 4.6.

2-Amino-1,1,3-tricyano-3-phenylhydrazono-propene (**6a**)

To a solution of (0.1 mole) 2-amino-1,1,3-tricyanopropene (prepared *via* dimerization of malononitrile as has been described in literature [15]) in ethanol (100 ml), 5.0 g of anhydrous sodium acetate was added. The solution was then treated with a solution of 0.1 mole of benzene diazonium chloride (prepared from 0.1 mole aniline and the appropriate quantities of hydrochloric acid and sodium nitrite). The reaction mixture was stirred for 1 h and the resulting solid product was collected by filtration and purified by washing with hot ethanol.

Compound **6a** formed brown crystals: m.p. above 300 °C, yield 80%. IR: 1600 cm^{-1} ($-\text{N}=\text{N}-$), 1640 cm^{-1} ($>\text{C}=\text{C}<\text{N}<$) and 2220 (conjugated CN).

$\text{C}_{12}\text{H}_8\text{N}_6$

Calcd C 61.01 H 3.38 N 35.59,
Found C 60.88 H 3.34 N 35.40.

1-Aryl-4-amino-3-cyano-1,6-dihydro-1,2,4-triazin-6-thione (**7a, b**)

To a solution of benzoyl isothiocyanate (prepared from 7.5 g of ammonium thiocyanate and the appropriate quantitatively of benzoyl chloride as has been previously described) [9] in pyridine 100 ml, 0.1 mole of each of **1a, b** was added. The reaction mixture was refluxed for 24 h, evaporated *in vacuo* the reaction mixture was then washed with water and the resulting solid product was collected by filtration and crystallised from pyridine.

Compound **7a** formed brown crystals: m.p. 220 °C; yield 70%. IR: 1640–1660 cm^{-1} (δNH_2) 2200 cm^{-1} (CN); 2500–3340 cm^{-1} (chelated NH vibrations).

C₁₀H₇N₅S

Calcd	C 52.4	H 3.1	S 13.9,
Found	C 52.8	H 3.2	S 14.0.

Compound **7b** formed yellow crystals from AcOH and HCl mixture, m.p. 235 °C; yield 70%.

C₁₀H₆N₅SCl

Calcd	C 45.4	H 2.2	S 12.1,
Found	C 45.3	H 2.2	S 12.0.

Compounds **7a, b** were also obtained in 80% yield when **1a, b** were treated with ethoxycarbonyliso-thiocyanate under similar conditions.

1-Aryl-4-carboxyamido-3-cyano-6-trioxo-1,6-dihydro-1,2,4-triazine (8)

Compound **8** was prepared refluxed, **1c** with equivalent quantity of benzoyl isothiocyanate and the reaction mixture was refluxed for 48 h then treated as has been described above.

Compound **8** formed yellow crystals: m.p. > 300 °C; yield 70%. IR: 1660 cm⁻¹ (CO) and 3100 cm⁻¹~3400 cm⁻¹ (NH vibrations).

C₁₁H₁₁ON₅S

Calcd	C 50.6	H 4.2	N 26.8	S 12.2,
Found	C 51.0	H 4.2	N 26.2	S 11.9.

5-Amino-3-hydroxy-4-phenylazoisoxazole (11)

A solution of **1a** (0.1 mole) in ethanol (150 ml) was treated with hydroxylamine hydrochloride (0.1 mole) and sodium carbonate (0.1 equivalent). The reaction mixture was refluxed for 3 h, then left to cool. The solid product, formed on standing, was collected by filtration, washed several times with water and then crystallised from ethanol.

Compound **6** formed yellow crystals: m.p. 245 °C; yield 80%.

C₉H₈N₄O₂

Calcd	C 52.9	H 3.9	N 27.4,
Found	C 52.5	H 3.8	N 26.9.

N-Methyl-phenylazomalononitrile (13a)

To a solution of 1.7 g (0.01 mole) of phenylazomalononitrile in 50 ml acetone, was added 1.4 g (0.01 mole) methyl iodide and 2 g of anhydrous potassium carbonate. The reaction mixture was refluxed for 90 min, then evaporated *in vacuo*. The solid product so formed was collected by filtration and crystallised from methanol.

Compound **13a** formed yellow crystals, m.p. 100 °C; yield 80%. IR: 2200 and 2220 cm⁻¹ (two CN), 1590 cm⁻¹ (δ C=N).

C₁₀H₈N₄

Calcd	C 65.2	H 4.3,
Found	C 65.1	H 4.6.

This compound was found identical with authentic specimen [9].

N-Ethylarylazomalononitrile (13b, c)

Compounds **13b, c** were obtained in 80% yield *via* treatment of **2a, b** with equivalent quantity of ethyl iodine utilising the experiment conditions described above and refluxing the reaction mixture 15 h.

Compound **13b** formed colourless crystals: m.p. 65 °C. IR: 2620 (C=N); 2200 and 2210 cm⁻¹ (two conjugated CN).

C₁₁H₁₀N₄

Calcd	C 66.6	H 5.05	N 28.2,
Found	C 66.6	H 5.00	N 28.1.

Compound **13c** formed colourless crystals; m.p. 65 °C. IR: 1620 cm⁻¹ (C=N); 2200 and 2220 cm⁻¹ (two conjugated CN).

C₁₁H₉N₄Cl

Calcd	C 56.7	H 3.8	N 24.1	Cl 15.2,
Found	C 56.5	H 3.7	N 23.9	Cl 15.1.

N-Alkylarylazocycanoacetamidrazone (14a-c)

A solution of 1.8 g (0.01 mole) of **13a-c**, in 50 ml ethanol, was treated with 0.5 g (0.01 mole) of hydrazine hydrate (98%). The reaction mixture was refluxed for 90 min, then evaporated *in vacuo*. The solid product so formed was collected by filtration and crystallised from ethanol.

Compound **14a** formed yellow needles, m.p. 140 °C, yield 75%. IR: 3400 and 3340 cm⁻¹ (σ NH₂ and NH), 2200 cm⁻¹ (δ CN), 1650 cm⁻¹ (C=N), and 1600 cm⁻¹ (δ NH₂).

C₁₁H₁₄N₆

Calcd	C 57.3	H 6.1	N 36.6,
Found	C 57.2	H 6.1	N 36.2.

Compound **14b** formed brown crystals; m.p. 85 °C; yield 70%. IR: 1610 cm⁻¹ (C=N), 1670 cm⁻¹ (δ NH₂); 2210 (CN) 3350 and 3460 cm⁻¹ (σ NH₂).

C₁₅H₁₄N₆

Calcd	C 64.7	H 5.0,
Found	C 64.5	H 5.1.

Compound **14c** formed brown crystals; m.p. 95 °C; yield 70%.

C₁₁H₁₃N₆Cl

Calcd	Cl 13.4,
Found	Cl 13.0.

Reaction of 14a with acetic acid

A solution of 1.7 g (0.01 mole) of **14a** in 50 ml acetic acid was refluxed for 30 min. The solvent was then evaluated *in vacuo*. The remaining product was triturated with water and the solid product so formed, was collected by filtration. Repeated crystallisation from methanol affected analytically pure sample.

Compound **10** formed greenish yellow crystals, m.p. 115 °C, yield 70%. IR: broad band at 3450 cm^{-1} (δNH), 2200 cm^{-1} (δCN), 1600 cm^{-1} (νNH).

$\text{C}_{20}\text{H}_{17}\text{N}_9$

Calcd	C 62.6	H 4.4	N 32.8,
Found	C 62.8	H 4.3	N 32.5.

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