4-Arylazo-3,5-diaminoisoxazole: Synthesis and Some Chemical Reactions

Ezzat Mohamed Zayed* and Said Ahmed Soliman Ghozlan

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

Z. Naturforsch. 40b, 1727–1730 (1985); received April 15/August 16, 1985

4-Arylazo-3,5-diaminoisoxazole. Synthesis

Several new isoxazole derivatives were prepared from the newly synthesized 4-arylazo-3,5-diaminoisoxazole.

α,β-Unsaturated nitriles have been extensively utilized for the synthesis of aminoisoxazoles [1, 2], many of which have been found to exhibit biological activities [3, 4]. It was reported [5] that arylhydrozonomesoxalonitrile (1) reacts with hydroxylamine hydrochloride in the presence of sodium carbonate in refluxing ethanol to yield 5-amino-3-hydroxy-4-phenylazoisoxazole. Up to our knowledge no convenient method for preparing 4-arylazo-3,5-diaminoisoxazole (2) has been reported.

In the present paper we report on the synthesis of 2 using 1 as starting material. Investigations on the newly synthesized compound 2 were made aiming to explore its utility in the synthesis of isoxazole derivatives of expected biological activities. The results offer a new efficient route for the synthesis of isoxazole-pyrimidines and imidazo-isoxazole derivatives.

Compound 1 reacted with hydroxylamine at room temperature to give 2 in 75% yield. The structure of 2 was inferred from the correct analytical and spectral data. As a typical example 1H NMR of 2a revealed a singlet for one amino group at δ 6.1 and a multiplet for one NH2 and phenyl protons at δ 7.2–7.8 ppm.

Compound 2a was converted into the diacetamido derivative 3 on treatment with acetic anhydride. The structure of compound 3 was established via inspection of analytical and spectral data.

Compound 2a reacted with an excess of acrylonitrile in aqueous pyridine to yield a mixture of two products, the analytical data of each indicated the addition of two moles of the reagent. Two theoretically possible isomeric structures were, thus, considered for each of the two reaction products (cf. structures 4a, b and 5a, b). The IR spectra of the reaction products revealed a ring CO band at 1710 cm⁻¹. If these products have structures 5a and 5b, CO absorption at lower frequency (ca. 1660 cm⁻¹) is to be expected.
anticipated [5]. Thus, the cyanoethylation products were identified as 4a and 4b. On the other hand, when the reaction of 2a with acrylonitrile was conducted in pyridine compound 6 was isolated which on treatment with acetic acid – hydrochloric acid mixture 4b was obtained (m.p. and mixed m.p.).

5-Amino-3-phenylisoxazole has been reported to react with α-cyanochalcones to afford the isoxazolo[4,3-b]-pyrimidines [6]. In a similar manner compound 2a reacted with benzaldehyde acetoacetate to give the isoxazolo[3,4-a]-pyrimidine derivative 7.

Compound 2a reacted also with α-bromoacetophenone to yield a product of molecular formula C_{17}H_{13}N_{5}O. Two structures seemed possible (cf. structure 8 and 9). Structure 8 was established for the reaction product based on 1H NMR which revealed only one multiplet at δ 7.3–8.4 ppm. If this product is the isomeric 9, imidazole CH should have appeared at higher field [7].

The isoxazole derivative 10 was obtained on treatment of 2a with 2 moles of acetylacetone. Structure 10 was inferred from both analytical and spectral data (cf. Experimental Part).

When 2a was treated with benzoyl isothiocyanate a mixture of 11 and 12 was isolated. Also the corresponding isoxazolyl thiourea derivative 13 was obtained when 2a was treated with ethoxycarbonyl isothiocyanate. Trials to effect cyclization of compounds 11 and 13 were unsuccessful. Structures 11, 12 and 13 were proposed based on analytical and spectral data (cf. Experimental Part).

**Experimental**

All melting points are uncorrected. IR spectra were measured (KBr) on a Pye-unicam SP 1000. 1H NMR were measured in DMSO on a Varian A 60 MHz using TMS as internal standard and chemical shifts are expressed as δ ppm.

**4-Arylazo-3,5-diaminoisoxazole (2)**

To a solution of 0.01 mol of arylhydrazono mesoxalonitrile [8] (1) in 30 ml of 10% NaOH was added gradually a solution of 0.01 mol hydroxylamine hydrochloride in 10 ml water while stirring. The reaction was stirred for 2 h at room temperature and then left overnight. The crystalline aryl-
Azoisoxazole 2 was filtered, washed with water till the filtrate is neutral to litmus and crystallized from dilute methanol.

Compound 2a formed yellow crystals, m.p. 131 °C; yield 75%. IR: 1570 (N=N), 3400 and 3500 cm$^{-1}$ (NH$_2$). $^1$H NMR: $\delta$ (ppm) = 6.1 (s, 2H, NH$_2$), 7.2–7.8 (m, 7H, C$_6$H$_5$, NH$_2$).

$$\text{C}_9\text{H}_9\text{N}_5\text{O}$$
Calcd C 53.2 H 4.4 N 34.5,
Found C 53.0 H 4.5 N 34.8.

Compound 2b formed yellow crystals, m.p. 158 °C; yield 76%. IR: 1560 (N=N), 3390 and 3460 cm$^{-1}$ (NH$_2$).

$$\text{C}_{10}\text{H}_{11}\text{N}_5\text{O}_2$$
Calcd C 55.3 H 5.1 N 32.3,
Found C 55.0 H 5.0 N 32.5.

Compound 2c formed brownish crystals, m.p. 148 °C; yield 76%. IR: 1560 (N=N), 3330 and 3420 cm$^{-1}$ (NH$_2$).

$$\text{C}_{10}\text{H}_{11}\text{N}_5\text{O}_2$$
Calcd C 51.5 H 4.7 N 30.0,
Found C 51.6 H 4.5 N 29.8.

3,5-Diacetamido-4-phenylazoisoxazole (3)

2.0 g of compound 2a was dissolved in 4 ml acetic anhydride. The reaction is exothermic. After all the solid had dissolved, 50 ml ether was added and the mixture left at room temperature for complete precipitation. The solid product, so formed, was filtered off, crystallized from ethanol and the product was identified as 3.

Compound 3 formed brownish crystals, m.p. 173 °C; yield 80%. IR: 3300 (NH) and 1700 cm$^{-1}$ (CO).

$$\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}_3$$
Calcd C 54.4 H 4.5 N 24.4,
Found C 54.2 H 4.4 N 24.6.

Reaction of 2a with excess acrylonitrile in pyridine-water mixture (4a, 4b)

A solution of 2.0 g of 2a in 40 ml pyridine and 20 ml water was treated with 2.0 ml acrylonitrile. The reaction mixture was refluxed for 4 h and then evaporated in vacuo. The remaining solid product was triturated with ethanol, collected by filtration and identified as 4a. Compound 4a formed yellow crystals, m.p. 150 °C; yield 60%. IR: 1710 (CO), 2250 (CN), 3370 and 3420 cm$^{-1}$ (NH$_2$).

$$\text{C}_{15}\text{H}_{17}\text{N}_4\text{O}_3$$
Calcd C 62.4 H 5.0,
Found C 62.5 H 5.2.

Action of acetic acid-hydrochloric acid mixture on 6 (4b)

A solution of 1.0 g of 6 in 20 ml acetic acid was treated with 1 ml hydrochloric acid (37.5%). The reaction mixture was refluxed for 1 h and then evaporated in vacuo. The remaining solid product was triturated with water, collected by filtration and crystallized from ethanol. The product was identified as 4b (m.p. and mixed m.p.).

2-Amino-3-phenylazo[2,3-a]-pyrimidine derivative (7)

To a solution of 2.0 g of 2a in 50 ml ethanol was added 2.0 g benzylidene ethylcyanoacetate and 0.5 ml triethylamine. The reaction mixture was refluxed for 3 h and then evaporated in vacuo. The solid product was triturated with methanol, collected by filtration and crystallized from dil. ethanol. The solid product was identified as 7.

$$\text{C}_{21}\text{H}_{20}\text{N}_6\text{O}_3$$
Calcd C 62.4 H 5.0,
Found C 62.5 H 5.2.
**Imidazo-isoxazole derivative (8)**

To a solution of 2.0 g of 2a in 30 ml ethanol was added 2.0 g w-bromoacetophenone. The reaction mixture was refluxed for 3 h and then the solvent was removed *in vacuo*. The solid product, so formed, was crystallized from dioxan and identified as 8.

Compound 8 formed pale yellow crystals, m.p. 260 °C; yield 60%. IR: 1690 (C=N), 3300 and 3480 cm⁻¹ (NH₂). ¹H NMR: δ (ppm) = 7.3–8.4 (m, 7H, C₆H₅ and NH₂).

![Chemical formula](image)

**Reaction of 2a with acetylacetone (10)**

A solution of 2a (2.0 g) in ethanol (50 ml) was treated with conc. HCl (1.7 ml) and acetylacetone (2.6 ml). The reaction mixture was stirred for 15 min and then treated with 5% aqueous sodium hydrogen carbonate. The solid was filtered off and washed well with water, crystallized from dioxan and identified as 10.

Compound 10 formed golden yellow crystals, m.p. 202 °C; yield 73%. IR: 1660 (CO), 3200 and 3400 cm⁻¹ (NH).

![Chemical formula](image)

**Reaction of 2a with isothiocyanates: general procedure**

A solution of 0.1 mol of 2a in 50 ml acetone was added to a solution of the isothiocyanate derivative (prepared from 0.12 mol of NH₄SCN and the appropriate quantity of benzoyl chloride or ethyl chloroformate as has been previously described [6]) and was refluxed for 3 h then evaporated *in vacuo*. The remaining solid product was then triturated with water. The product of benzoylisothiocyanate was treated with hot alcohol and the solid product remained was crystallized from acetic acid and was identified as 11.

Compound 11 formed yellow crystals, m.p. >300 °C; yield 60%. IR: 1670 (CO), 3300 and 3420 cm⁻¹ (NH₂).

![Chemical formula](image)

Thanks are due to Miss Mona Hassan Mohamed for carrying out the experimental work.

---