

Behaviour of 4-Arylhydrazono-3-phenyl-2-isoxazoline-5-thiones  
Toward Hydrazines, Grignard Reagents and Alkylating Agents

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Received July 18, 1983

The 4-arylhydrazono-3-phenyl-2-isoxazoline-5-thiones **2** react with hydrazines to yield the 5-hydrazones **3** and **5**. The reaction of **2** with Grignard reagent resulted in addition of the reagent to the thiocarbonyl group to yield **7**. Treatment of **2** with diazomethane effected *S*- and *N*-methylation beside 1,2,3-triazole derivative **11** obtained through isomerisation. The potassium salt of **2** react with alkyl halides to yield the *S*-alkyl derivatives **12**.

*J. Heterocyclic Chem.*, **21**, 253 (1984).

Although the chemistry of isoxazolin-5-ones was well reviewed [1,2] little has been reported for their thiocarbonyl analogues. Here we report the behaviour of 4-arylhydrazono-3-phenyl-2-isoxazoline-5-thiones **2a** and **2b** toward the action of some nucleophilic and alkylating agents. Compounds **2a** and **2b** were readily obtained by the action of phosphorus pentasulphide on 4-arylhydrazono-3-phenyl-2-isoxazolin-5-ones [3] **1a** and **1b** respectively. The structure of **2** was inferred from analytical and ir data; besides, oxidation of **2a** by hydrogen peroxide afforded the isoxazolinone derivative **1a**.

The reaction of **2a** and **2b** with hydrazine hydrate yielded 4-arylhydrazono-3-phenyl-2-isoxazoline-5-hydrazones **3a** and **3b** respectively. The structure assigned for compound **3** was based on analytical and ir data; besides, hydrolysis of **3a** by ethanolic hydrochloric acid afforded **1a**. Compound **3a** and **3b** condensed with benzaldehyde and/or ethyl acetoacetate to yield the azines **4a-d** respectively. Structure **4** was inferred from analytical and spectral data. The behaviour of **2** toward the action of phenylhydrazine was found to be dependent on the reaction conditions. Thus, fusion of **2a** or **2b** with phenylhydrazine afforded the 5-phenylhydrazone **5a** or **5b**, as inferred from analytical and spectral data. On the other hand, when the reaction between **2** and phenylhydrazine was carried out in refluxing ethanol, compound **6** was obtained together with **5**. The structure of **6** was assigned from analytical and spectral data.

The reaction of **2a** or **2b** with phenylmagnesium bromide afforded 4-aryldazo-3,5-diphenylisoxazoles **7a** or **7b**. The structure of **7** was assigned from analytical and ir data; besides, **7a** was obtained *via* another route, by the action of phenylmagnesium bromide on **1a** to afford the carbinol **8** which afforded **7a** when heated with acetic acid.

Subjecting **2a** or **2b** to the action of ethereal diazomethane resulted in the formation of three products which were separated by fractional crystallisation. Structures **9** and **10** were assigned for the two coloured products representing

the *S*-methyl and *N*-methyl derivatives respectively based on analytical and ir data. Besides, **9a** was obtained authentically *via* the action of methyl iodide on **2a** in ethanolic potassium hydroxide solution. Structure **11** assigned for the third product, which is colourless, was inferred from analytical and ir data; moreover, hydrolysis of **11a** with ethanolic hydrochloric acid afforded 2,5-diphenyl-1,2,3-triazol-4-carboxylic acid [4]. The formation of **11** is expected

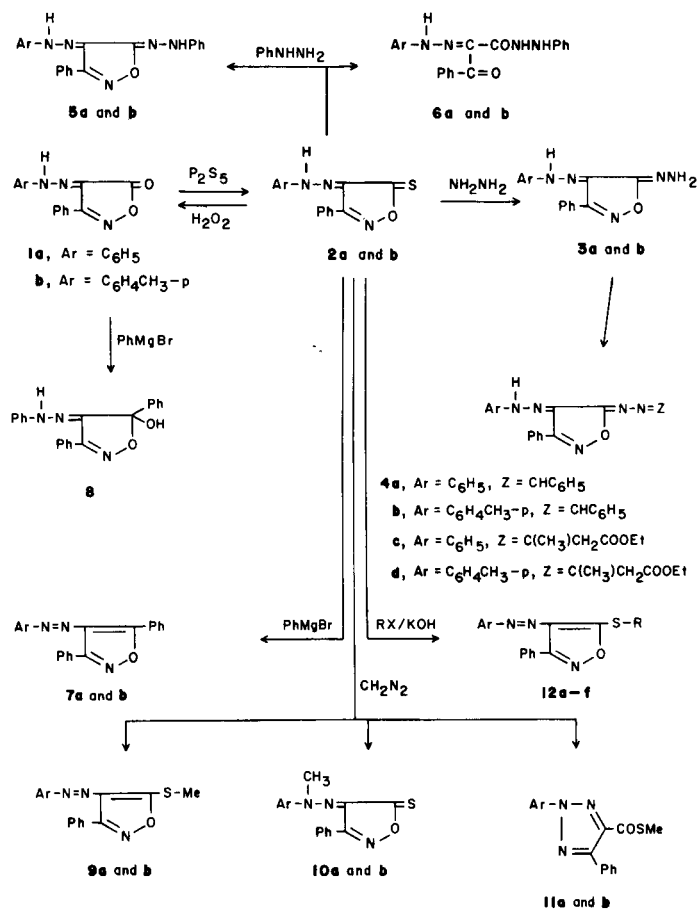


Table I

Analytical Data for **3a** and **b**, **4a-d**, **5a** and **b**, **6a** and **b** and **7a** and **b**

Compound	Mp °C	Yield %	Formula	Analyses Calcd./Found		
				C	H	N
<b>3a</b>	124	60	C <sub>15</sub> H <sub>13</sub> N <sub>5</sub> O	64.50	4.69	25.08
				64.19	4.66	25.11
<b>3b</b>	138	65	C <sub>16</sub> H <sub>15</sub> N <sub>5</sub> O	65.51	5.15	23.88
				65.70	5.15	23.78
<b>4a</b>	180	70	C <sub>22</sub> H <sub>17</sub> N <sub>5</sub> O	71.92	4.66	19.06
				71.85	4.71	19.13
<b>4b</b>	176	70	C <sub>23</sub> H <sub>19</sub> N <sub>5</sub> O	72.42	5.02	18.36
				72.63	5.08	18.00
<b>4c</b>	155	55	C <sub>21</sub> H <sub>21</sub> N <sub>5</sub> O <sub>3</sub>	64.43	5.41	17.89
				64.35	5.39	17.88
<b>4d</b>	173	60	C <sub>22</sub> H <sub>23</sub> N <sub>5</sub> O <sub>3</sub>	65.17	5.72	17.28
				65.33	5.81	17.41
<b>5a</b>	215	65	C <sub>21</sub> H <sub>17</sub> N <sub>5</sub> O	70.96	4.82	19.71
				70.73	4.88	19.80
<b>5b</b>	218	65	C <sub>22</sub> H <sub>19</sub> N <sub>5</sub> O	71.52	5.18	18.96
				71.35	5.16	18.77
<b>6a</b>	150	45	C <sub>21</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub>	70.37	5.06	15.63
				70.61	5.13	15.86
<b>6b</b>	156	50	C <sub>22</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub>	70.95	5.41	15.05
				70.98	5.39	15.11
<b>7a</b>	143	55	C <sub>21</sub> H <sub>15</sub> N <sub>5</sub> O	77.52	4.65	12.92
				77.41	4.50	13.30
<b>7b</b>	156	55	C <sub>22</sub> H <sub>17</sub> N <sub>5</sub> O	77.85	5.05	12.38
				77.70	5.10	12.40

to arise from a transformation analogous to the known isomerisation of 4-arylhydrazono-3-methyl-2-isoxazolin-5-ones by the action of diazomethane to 1,2,3-triazole derivatives [5].

Subjecting the potassium salts of **2a** and **2b** to the action of alkylating agents such as, phenacyl bromide, ethyl bromoacetate and chloroacetamide afforded the corresponding S-alkyl derivatives **12a-f**. The structure of **12a-f** was inferred from analytical and ir data; besides, ethanolic hydrochloric acid hydrolysis of **12a** afforded 4-phenylhydrazono-3-phenyl-2-isoxazolin-5-one (**1a**).

## EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) using a Pye-Unicam IR 20. The <sup>1</sup>H-nmr were recorded on a Varian A-60 spectrometer in deuteriochloroform using TMS as an internal indicator and chemical shifts are expressed as δ ppm.

4-Arylhudrazono-3-phenyl-2-isoxazolin-5-thiones **2a** or **2b**.

To a solution of each of **1a** or **1b** (10 g) in 100 ml of dioxan was added phosphorus pentasulphide (10 g) and the reaction mixture was heated on a water bath for two hours with continuous stirring. The mixture was then filtered and the filtrate was left to evaporate. The solid so obtained was crystallised from ethanol to yield **2a** or **2b** respectively.

Compound **2a** formed red crystals, yield 60%, mp 160°; ir: 3250 cm<sup>-1</sup> (NH) and 1600 cm<sup>-1</sup> (C=C).

Table II

Analytical Data for the Alkyl Derivatives **9-12**

Compound	Mp °C	Yield %	Formula	Analyses Calcd./Found			S
				C	H	N	
<b>9a</b>	98	45	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> OS	65.08	4.44	14.23	10.84
				64.90	4.39	14.31	10.70
<b>9b</b>	101	40	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> OS	66.01	4.89	13.59	10.34
				66.70	4.80	13.44	10.70
<b>10a</b>	80	10	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> OS	65.08	4.44	14.23	10.84
				65.31	4.40	14.21	10.88
<b>10b</b>	85	10	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> OS	66.01	4.89	13.59	10.34
				66.30	4.87	13.71	10.20
<b>11a</b>	120	20	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> OS	65.08	4.44	14.23	10.84
				65.51	4.36	14.55	11.13
<b>11b</b>	125	25	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> OS	66.01	4.89	13.59	10.34
				66.50	4.67	13.80	10.30
<b>12a</b>	138	70	C <sub>23</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	69.16	4.29	10.52	8.00
				68.68	4.34	10.46	7.91
<b>12b</b>	157	68	C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S	69.72	4.63	10.16	7.74
				70.13	4.60	10.34	7.22
<b>12c</b>	106	80	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S	62.12	4.66	11.44	8.71
				62.43	4.70	11.30	8.66
<b>12d</b>	115	80	C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S	62.98	5.02	11.02	8.39
				63.40	4.91	11.11	8.20
<b>12e</b>	194	65	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S	60.35	4.17	16.56	9.46
				60.41	4.20	16.58	9.18
<b>12f</b>	165	65	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> S	61.36	4.58	15.90	9.08
				60.98	4.61	16.11	8.80

*Anal.* Calcd. for  $C_{15}H_{11}N_3OS$ : C, 64.05; H, 3.94; N, 14.94; S, 11.38. Found: C, 64.1; H, 3.9; N, 14.8; S, 11.2.

Compound **2b** formed red crystals, yield 65%, mp 162°; ir: 3200  $cm^{-1}$  (NH) and 1600  $cm^{-1}$  (C=C).

*Anal.* Calcd. for  $C_{16}H_{13}N_3OS$ : C, 65.08; H, 4.44; N, 14.23; S, 10.84. Found: C, 65.2; H, 4.4; N, 14.4; S, 10.8

#### Action of Hydrazine Hydrate and/or Phenylhydrazine on **2a** or **2b**.

To each of **2a** or **2b** (1.0 g) hydrazine hydrate and/or phenylhydrazine (1.0 ml) was added and the mixture was heated on a water bath for 30 minutes. The reaction mixture was then treated with ethanol and the solid so obtained was filtered off.

4-Arylhydrazono-3-phenyl-2-isoxazoline-5-hydrazones **3a** or **3b** formed yellow crystals from ethanol, yield 60% and are listed in Table I. The ir spectrum of **3a** showed absorption at 3400 and 3360  $cm^{-1}$  (NH<sub>2</sub>) and 3200  $cm^{-1}$  (NH).

4-Arylhydrazono-3-phenyl-2-isoxazolin-5-phenylhydrazones **5a** or **5b** formed orange crystals from ethanol-dioxan mixture, yield 65% and are listed in Table I. The ir spectrum of **5a** showed absorption at 3300 and 3250  $cm^{-1}$  (NH).

#### Action of Benzaldehyde and/or Ethyl Acetoacetate on **3a** or **3b** to Give the Azines **4a-d**.

To a solution of **3a** or **3b** (1.0 g) in 20 ml of ethanol was added an equimolecular amount of benzaldehyde and/or ethyl acetoacetate. The reaction mixture was refluxed for 2 hours. The solid product that separated on cooling was filtered off and recrystallised from ethanol. Compounds **4a-d** are orange coloured and are listed in Table I. The ir spectrum of **4a** showed absorption at 3200  $cm^{-1}$  (NH) and 1620  $cm^{-1}$  (C=N).

The ir spectrum of **4c** showed absorption at 3200  $cm^{-1}$  (NH), 1700  $cm^{-1}$  (C=O) and 1620  $cm^{-1}$  (C=N); <sup>1</sup>H-nmr: 12 (br, 1H, NH), 8.3-7.3 (m, 10H, Ar), 4.4-4.1 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.7 (s, 2H, -CH<sub>2</sub>COOEt), 2.5 (s, 3H, CH<sub>3</sub>) and 1.4 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>).

#### Action of Phenylhydrazine on **2a** or **2b** in Boiling Ethanol to Afford the Arylhydrazones of Benzoylacetic Phenylhydrazides **6a** or **6b**.

To a solution of each of **2a** or **2b** (1.0 g) in ethanol (100 ml) was added 1.0 ml of phenylhydrazine, the reaction mixture was boiled under reflux for one hour and the solid that separated while hot was filtered off and crystallised from ethanol-dioxan mixture; proved to be identical (mp and mixed mp) with **5a** or **5b**. Cooling of the filtrate afforded yellow solid which was filtered off and crystallised from ethanol. The  $\alpha$ -arylhydrazonobenzoylacetic phenylhydrazides **6a** or **6b** are listed in Table I. The ir spectrum of **6a** showed absorption at 3300 and 3200  $cm^{-1}$  (NH), 1700 and 1680  $cm^{-1}$  (C=O) and 1620  $cm^{-1}$  (C=N).

#### Action of Phenylmagnesium Bromide on **2a** or **2b** to Yield 4-Arylazo-3,5-diphenylisoxazoles **7a** or **7b**.

A suspension of each of **2a** or **2b** (2.0 g) in 100 ml of dry ether was added to phenylmagnesium bromide solution (prepared from 9.0 g bromobenzene and 1.0 g magnesium in 100 ml ether). The reaction mixture was kept at room temperature for 15 minutes, then decomposed by cold saturated ammonium chloride solution. The ethereal layer was worked out to give **7a** or **7b** which formed orange crystals from acetic acid, yield 55%, and are listed in Table I. Compound **7a** was found to be identical with an authentic sample [6].

#### Action of Phenylmagnesium Bromide on **1a** to Give 4-Phenylhydrazono-3,5-diphenyl-5-hydroxy-2-isoxazoline **8**.

The reaction between phenylmagnesium bromide and **1a** following the same procedure described above afforded **8**. The carbinol **8** formed colourless crystals from petroleum ether, mp 135°, yield 65%; ir: 3500  $cm^{-1}$  (OH), 3200  $cm^{-1}$  (NH).

*Anal.* Calcd. for  $C_{21}H_{17}N_3O_2$ : C, 73.45; H, 4.99; N, 12.24. Found: C, 73.6; H, 4.91; N, 12.36.

#### Action of Acetic Acid on **8** to Afford 4-Phenylazo-3,5-diphenylisoxazole.

A solution of **8** (1.0 g) in glacial acetic acid (20 ml) was refluxed for 15 minutes then left to cool. The solid that separated was filtered off and recrystallised from acetic acid. The orange coloured product mp 143°, proved to be identical (mp and mixed mp) with **7a**.

#### Action of Diazomethane on **2a** or **2b**.

To a cold suspension of **2a** or **2b** (2.0 g) in ether (50 ml) was added an excess of cold ethereal solution of diazomethane (prepared from 15.0 g nitrosomethylurea) and the reaction mixture was kept overnight in a refrigerator. The oily residue obtained upon evaporation of ether was extracted with methanol. The solid which remained undissolved was collected by filtration and crystallised from ethanol to give the 1,2,3-triazole derivatives **11a** or **11b** as colourless crystals listed in Table II. The methanol extract on evaporation, afforded an oily residue which was triturated with petroleum ether, the solid product so obtained was filtered off and crystallised from methanol to give the *S*-methyl derivatives **9a** or **9b** as yellow crystals listed in Table II. The petroleum extract on slow evaporation, gave the *N*-methyl derivatives **10a** or **10b** as orange crystals from petroleum ether (bp 40-60°) listed in Table II.

The ir spectrum of 4-phenylazo-5-methylthio-3-phenylisoxazole **9a** showed absorption at 1620  $cm^{-1}$  (C=N) and 1590  $cm^{-1}$  (N=N).

The ir spectrum of 4-*N*-methylphenylhydrazono-3-phenyl-2-isoxazolin-5-thione **10a** showed absorption at 1620  $cm^{-1}$  (C=N).

The ir spectrum of 2,5-diphenyl-1,2,3-triazole-4-methylthiocarboxylate **11a** showed absorption at 1700  $cm^{-1}$  (C=O) and 1620  $cm^{-1}$  (C=N).

#### 4-Arylazo-5-alkylthio-3-phenylisoxazoles **12a-f**.

##### General procedure.

A solution of each of **2a** or **2b** (2.0 g) in 20 ml of ethanolic potassium hydroxide (10%) was refluxed for 20 minutes, then to the solution was added an equimolecular amount of either phenacyl bromide, ethyl bromoacetate or chloroacetamide. The reaction mixture was refluxed for 20 minutes then allowed to cool. The solid that separated was filtered off, washed with water and then recrystallised from ethanol. 4-Arylazo-5-alkylthio-3-phenylisoxazoles **12a-f** are all yellow coloured and are listed in Table II.

The ir spectrum of **12a** as an example of the *S*-phenacyl derivatives showed absorption at 1710  $cm^{-1}$  (C=O) and 1620  $cm^{-1}$  (C=N).

The ir spectrum of **12c** as an example of the *S*-acetate derivatives showed absorption at 1720  $cm^{-1}$  (C=O) and 1630  $cm^{-1}$  (C=N).

The ir spectrum of **12e** as an example of the *S*-acetamide derivatives showed absorption at 3400 and 3380  $cm^{-1}$  (NH<sub>2</sub>), 1680  $cm^{-1}$  (C=O) and 1620  $cm^{-1}$  (C=N).

#### Action of Methyl Iodide on **2a** to Give **9a**.

Treatment of **2a** with methyl iodide under the same reaction conditions described above afforded **9a** as proved by mp and mixed mp determination.

#### Action of Ethanolic Hydrochloric Acid on **11a** to Give 2,5-Diphenyl-1,2,3-triazole-4-carboxylic Acid.

A suspension of **11a** (1.0 g) in a solution of ethanol (15 ml) and hydrochloric acid (5 ml) was heated under reflux for two hours, then allowed to cool. The reaction mixture was diluted with water and the solid product that separated was filtered off and crystallised from methanol to afford crystals of mp 208°, which proved to be identical (mp and mixed mp) with 2,5-diphenyl-1,2,3-triazole-4-carboxylic acid [4].

#### Action of Ethanolic Hydrochloric Acid on Each of **3a**, **12a**, **12c**, and/or **12e** to Give **1a**.

Subjecting each of **3a**, **12a**, **12c** and/or **12e** to the action of ethanolic hydrochloric acid as described above, afforded in each case 4-phenylhydrazono-3-phenyl-2-isoxazolin-5-one (**1a**).

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