# SYNTHESIS OF 2,4-DIARYLTHIO-5-*N*-ALKYL-*N*-PHENYLAMINOOXAZOLES. A NOVEL CLASS OF OXAZOLE DERIVATIVES

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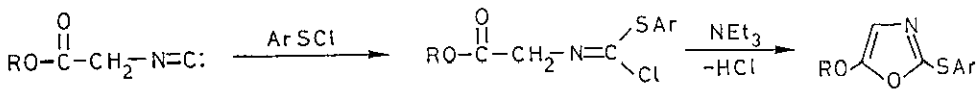
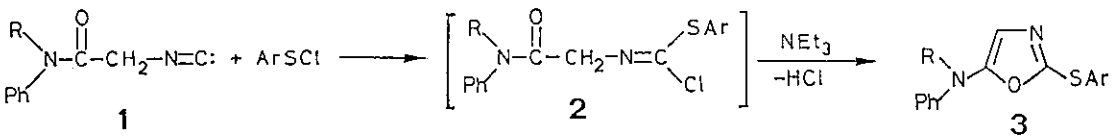
*Abstract* - The reaction between *N*-alkylisocyanoacetanilides, arylsulfenyl chlorides and $NEt_3$ afforded 2,4-diarylthio-5-*N*-alkyl-*N*-phenylaminooxazoles, a hitherto unknown class of oxazole derivatives.

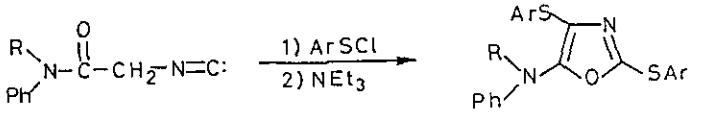
In a previous paper[1] we described the synthesis of 2-arylthio-5-alkoxyoxazoles by reacting alkyl isocyanoacetates with arylsulfenyl chlorides and triethylamine.



In continuation of our studies[1-5] on the reactivity of compounds containing -SCl groups towards isonitriles we attempted the synthesis of 2-arylthio-5-*N*-alkyl-*N*-phenylaminooxazoles starting from *N*-alkylisocyanoacetanilides and arylsulfenyl chlorides.



Although attempts to obtain compounds **3** by an one pot procedure failed, we noted an interesting behavior of isonitriles **1** towards arylsulfenyl chlorides. In fact the reaction between **1** and arylsulfenyl chlorides afforded 2,4-diarylthio-5-*N*-alkyl-*N*-phenyl-aminooxazoles **4**, a hitherto unknown class of oxazoles derivatives.



**1a,b** **4a-h**

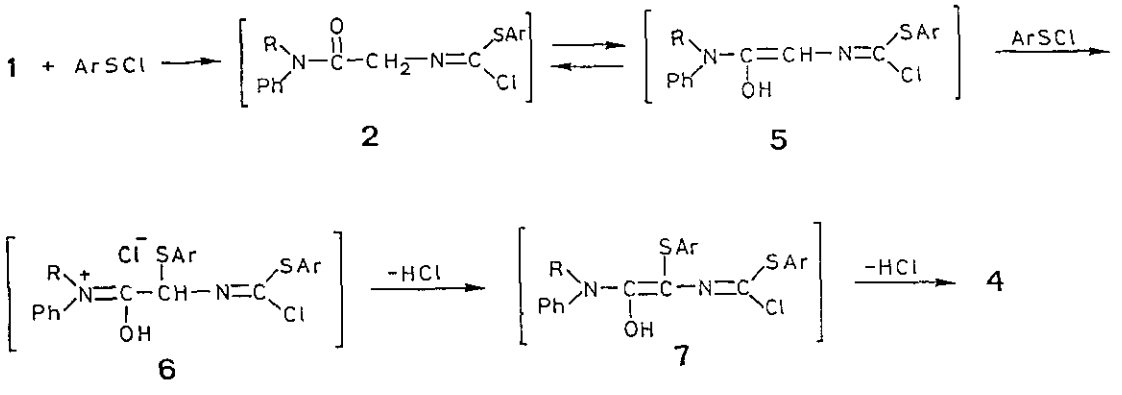
**1a** R = Me

**1b** R = Et

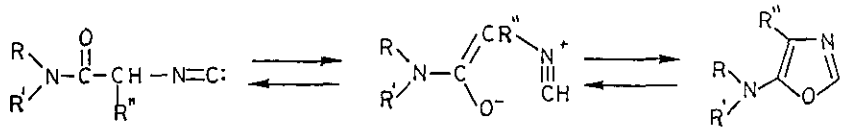
| | | | | | |
|---|---|---|---|---|---|
| **4a** | R = Me | Ar = 4-chlorophenyl | **4e** | R = Me | Ar = 2-nitro-4-chlorophenyl |
| **4b** | R = Et | Ar = 4-chlorophenyl | **4f** | R = Et | Ar = 2-nitro-4-chlorophenyl |
| **4c** | R = Me | Ar = 2-nitrophenyl | **4g** | R = Me | Ar = 2,4-dinitrophenyl |
| **4d** | R = Et | Ar = 2-nitrophenyl | **4h** | R = Et | Ar = 2,4-dinitrophenyl |

A possible reaction pathway is reported in the scheme.

**Scheme**



The formation of intermediates **2** appears to be reasonable because of the high reactivity of isonitriles towards sulfenyl chlorides[6]. The enolization of compounds **2** to **5** can be explained on the basis of the behavior of *N*-alkylisocyanoacetamides. In fact these compounds, on heating, undergo a ring-closure reaction to oxazoles, through an enolic intermediate[7].



The formation of intermediates **6** appears to be reasonable due to the high reactivity of sulfenyl chlorides towards the enamino moiety[8,9].

We believe that the different behavior of alkyl isocyanoacetates and isocyanoacetanilides towards arylsulfenyl chlorides must be related to the degree of enolization of their carbonyl groups. Whereas isocyanoacetanilides can be isomerized to 5-aminooxazoles in high yields, the less enolizable ethyl isocyanoacetate affords 5-ethoxyoxazole in only 5% yield[10].

The low degree of enolization of alkyl isocyanoacetates agrees with the fact that their adducts with arylsulfenyl chlorides can be isolated and are rather stable. Furthermore the cyclization of the above adducts to oxazoles only takes place upon treatment with a base[1].

On the present synthesis some remarks can be made. Attempts to isolate reaction intermediates failed, probably because of their tendency to cyclize. In fact compounds **4** were obtained even in the absence of $NEt_3$, although in lower yields. In earlier experiments, that were carried out by employing a molar *ratio* 1:ArSCl:$NEt_3$ = 1:1:1, compounds **4** were obtained in low yields. As expected, compounds **4** were obtained in good yields by performing the reactions with a molar *ratio* 1:ArSCl:$NEt_3$ = 1:2:2.

## EXPERIMENTAL

Melting points are uncorrected. The $^1$H-nmr spectra were recorded with a Varian VX 300 apparatus for DMSO-$d_6$ solutions, chemical shifts are reported in ppm (δ) from TMS. The mass spectra were recorded with a Kratos MS 80 instrument at 70 eV.

**_N_-Methylisocyanoacetanilide 1a**

Chloroacetyl chloride (90.35 g, 800 mmol) was slowly dropped into an ice-cooled and well-stirred solution of *N*-methylaniline (171.46 g, 1600 mmol) in $Et_2O$ (400 ml). The reaction mixture was filtered and the collected solid was washed with water and air-dried to give *N*-methylchloroacetanilide (126 g). A further crop (15 g) was obtained by evaporating the ethereal solution. Total yield 141 g (96 %), mp 65-67 °C from petroleum ether 40-70 °C. *Anal.* Calcd for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.73; H, 5.52; N, 7.55. The above material (120 g, 653 mmol) was slurried with DMF (600 ml) and 133.2 g (719 mmol) of potassium phthalimide. The mixture was heated at 75-80 °C for 2.5 h and then placed into a beaker containing 500 g of crushed ice and 700 ml of water. The resulting suspension was filtered and the solid was washed again with water and then dried to give *N*-(*N*-phenyl-*N*- methylcarbamoylmethyl)phthalimide (160 g, 83 %), mp 177-179 °C from EtOH. *Anal.* Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.42; H, 4.70; N, 9.43. The above material (110 g, 374 mmol) was slurried with EtOH (1 l) and hydrazine hydrate (18.72 g, 374 mmol) in a flask fitted with an efficient mechanical stirrer. The mixture was refluxed for 2.5 h and then cooled and filtered. The filtrate was evaporated to dryness and the residue stirred with 2*N* HCl (650 ml) and filtered. The filtrate was evaporated to dryness and the residue treated with 25 % NaOH (165 ml) and extracted with two portions of benzene (150 ml). The organic phase was dried over $MgSO_4$ and benzene was removed. The residue was distilled under reduced pressure to give *amino-N-methylacetanilide (43 g, 70 %), bp 106-108 °C,0.1 mm/Hg. Anal. Calcd for* $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06.

Found: C, 65.75; H, 7.29; N, 17.12. The above material (41 g, 250 mmol) was mixed with xylene (160 ml) and formic acid (23.02 g, 500 mmol). The resulting solution was refluxed for 4.5 h in a Dean-Stark apparatus and then cooled and filtered to give formamido-*N*-methylacetanilide (44.2 g, 92 %), mp 102-103 °C from toluene. *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.42; H, 6.33; N, 14.64. A solution of $POCl_3$ (18.4 g, 120 mmol) in $CH_2Cl_2$ (20 ml) was slowly dropped into a well-stirred solution of the above material (19.2 g, 100 mmol) and $NEt_3$ (40.35 g, 400 mmol) in $CH_2Cl_2$ (280 ml) maintaining the temperature at -10 °C. The reaction mixture was allowed to stand until the temperature rose to 10 °C and then stirred with a solution of $Na_2CO_3$ (33.9 g, 308 mmol) in water (180 ml). The resulting mixture was filtered and the phases separated. The organic layer was washed with water (200 ml) and the resulting emulsion was filtered through Celite 545 (Fluka) and the phases separated. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The residue was dissolved in EtOH and this solution was refluxed with charcoal and filtered. The filtrate was evaporated to dryness and the residue was recrystallized from isopropyl ether to give *N*-methylisocyanoacetanilide (12 g, 69 %), mp 85-86 °C. An analytical sample was obtained from hexane,mp 86-87 °C. *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.65; H, 5.91; N, 16.27.

*N*-Ethylisocyanoacetanilide (**1b**) was prepared according to ref. 7.

**2,4-Diarylthio-5-*N*-alkyl-*N*-phenylaminooxazoles 4a-h**

General Procedure: *N*-Alkylisocyanoacetanilide 1 (10 mmol) in $CH_2Cl_2$ (20 ml) was added to a solution of the appropriate sulfenyl chloride (20 mmol) in $CH_2Cl_2$ (30 ml) maintaining the temperature at -50 °C. The resulting solution was allowed to react at room temperature for 1 h and then cooled at -40 °C and treated with the calculated amount of $NEt_3$ (20 mmol). The resulting solution was allowed to react at room temperature for 1 h and then evaporated to dryness. The residue was stirred with a little EtOH and filtered to give **4**.

**4a**: mp 81-82 °C from EtOH; 48 % yield; $^1$H-nmr: 7.62-6.81 (m, 13H, aromatic protons), 3.20 (s, 3H, $CH_3$); ms: $[M]^+$ m/z 459 (19 %), $[MePhNC_2O]^+$ m/z 146 (100 %), $[4\text{-}ClC_6H_4S]^+$ m/z 143 (30 %), $[MePhNCO]^+$ m/z 134 (58 %), $[MePhN]^+$ m/z 106 (50 %). *Anal.* Calcd for $C_{22}H_{16}N_2OCl_2S_2$: C, 57.51; H, 3.51; N, 6.09. Found: C, 57.45; H, 3.39; N, 6.02.

**4b**: mp 76-77 °C from EtOH; 45 % yield; $^1$H-nmr: 7.60-6.80 (m, 13H, aromatic protons), 3.78-3.71 (q, $J$=0.7 Hz, 2H, $CH_2$), 1.16- 1.11 (t, $J$=0.7 Hz, 3H, $CH_3$); ms: $[M]^+$ m/z 473 (25 %), $[EtPhNC_2O]^+$ m/z 160 (100 %), $[EtPhNCO]^+$ m/z 148 (43 %), $[4\text{-}ClC_6H_4S]^+$ m/z 143 (20 %), $[EtPhN]^+$ m/z 120 (91 %). *Anal.* Calcd for $C_{23}H_{18}N_2OCl_2S_2$: C, 58.35; H, 3.83; N, 5.91. Found: C, 58.48; H, 3.80; N, 6.10.

**4c**: mp 144-145 °C from DMF/EtOH; 75 % yield; $^1$H-nmr: 8.46-7.00 (m, 13H, aromatic protons), 3.36 (s, 3H, $CH_3$); ms: $[M]^+$ m/z 480 (4 %), $[2\text{-}NO_2C_6H_4S]^+$ m/z 154 (8 %), $[MePhNC_2O]^+$ m/z 146 (7 %), $[MePhNCO]^+$ m/z 134 (73 %), $[MePhN]^+$ m/z 106 (100 %). *Anal.* Calcd for $C_{22}H_{16}N_4O_5S_2$: C, 54.99; H, 3.35; N, 11.66. Found: C, 55.12; H, 3.40; N, 11.81.

**4d**: mp 151-152 °C from DMF/EtOH; 72 % yield; $^1$H-nmr: 8.46-6.46 (m, 13H, aromatic protons), 3.92-3.85 (q, $J$=0.7 Hz, 2H, $CH_2$), 1.18-1.13 (t, $J$=0.7 Hz, 3H, $CH_3$); ms: $[M]^+$ m/z 494 (5 %), $[EtPhNC_2O]^+$ m/z 160 (4 %), $[2\text{-}NO_2C_6H_4S]^+$ m/z 154 (5

%), $[EtPhNCO]^+$ m/z 148 (39 %), $[EtPhN]^+$ 120 (100 %). *Anal.* Calcd for $C_{23}H_{18}N_4O_5S_2$: C, 55.86; H, 3.67; N, 11.33. Found: C, 55.94; H, 3.76; N, 11.42.

**4e**: mp 132-133 °C from DMF/EtOH; 80 % yield; $^1$H-nmr: 8.42-6.96 (m, 11H, aromatic protons), 3.37 (s, 3H, $CH_3$); ms: $[M]^+$ m/z 549 (1 %), $[2\text{-}NO_2\text{-}4\text{-}ClC_6H_3S]^+$ m/z 188 (54 %), $[MePhNC_2O]^+$ m/z 146 (3 %), $[MePhNCO]^+$ m/z 134 (50 %), $[MePhN]^+$ m/z 106 (100 %). *Anal.* Calcd for $C_{22}H_{14}N_4O_5Cl_2S_2$: C, 48.10; H, 2.57; N, 10.20. Found: C, 48.21; H, 2.59; N, 10.08.

**4f**: mp 144-145 °C from DMF/EtOH; 77 % yield; $^1$H-nmr: 8.41-6.94 (m, 11H, aromatic protons), 3.90-3.83 (q, $J$=0.7 Hz, 2H, $CH_2$), 1.19-1.14 (t, $J$=0.7 Hz, 3H, $CH_3$); ms: $[M]^+$ m/z 563 (1 %), $[2\text{-}NO_2\text{-}4\text{-}ClC_6H_3S]^+$ m/z 188 (100 %), $[EtPhNC_2O]^+$ m/z 160 (5 %), $[EtPhNCO]^+$ m/z 148 (14 %), $[EtPhN]^+$ m/z 120 (40 %). *Anal.* Calcd for $C_{23}H_{16}N_4O_5Cl_2S_2$: C, 49.03; H, 2.86; N, 9.94. Found: C, 49.11; H, 2.78; N, 9.91.

**4g**: mp 181-182 °C from DMF; 72 % yield; $^1$H-nmr: 9.00-7.10 (m, 11H, aromatic protons), 3.42 (s, 3H, $CH_3$); ms: $[M]^+$ m/z 570 (1 %), $[2\text{-}NO_2\text{-}4\text{-}NO_2C_6H_3S]^+$ m/z 199 (100 %), $[MePhNC_2O]^+$ m/z 146 (2 %), $[MePhNCO]^+$ m/z 134 (24 %), $[MePhN]^+$ m/z 106 (55 %). *Anal.* Calcd for $C_{22}H_{14}N_6O_9S_2$: C, 46.32; H, 2.47; N, 14.73. Found: C, 46.51; H, 2.54; N, 14.69.

**4h**: mp 190-191 °C from DMF/EtOH; 70 % yield; $^1$H-nmr: 8.98-7.10 (m, 11H, aromatic protons), 3.85-3.78 (q, $J$=0.7 Hz, 2H, $CH_2$), 1.16-1.11 (t, $J$=0.7 Hz, 3H, $CH_3$); ms: $[M]^+$ m/z 584 (1 %), $[2\text{-}NO_2\text{-}4\text{-}NO_2C_6H_3S]^+$ m/z 199 (47 %), $[EtPhNC_2O]^+$ m/z 160 (3 %), $[EtPhNCO]^+$ m/z 148 (22 %), $[EtPhN]^+$ m/z 120 (100 %). *Anal.* Calcd for $C_{23}H_{16}N_6O_9S_2$: C, 47.26; H, 2.77; N, 14.38. Found: C, 47.38; H, 2.81; N, 14.52.

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