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Note

Synthesis of substituted isoxazoles and 1,3,4-oxadiazoles

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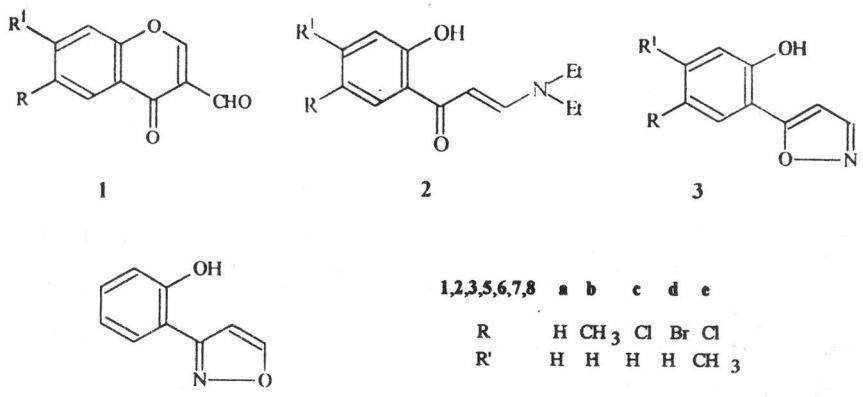
A few novel 5-(2′-hydroxyaryl)-isoxazoles **3** and 2-(aryloxymethyl)-3-mercapto-1,3,4-oxadiazoles **8** have been synthesized from the intermediate enamino ketones **2**, and tested for their herbicidal activity.

The enamino ketones **2a-e**[1,2] constitute an important class of synthon which can be elaborated to a wide variety of heterocyclic compounds[3]. These enamino ketones are readily derived from substituted 3-formylchromones **1a-e**[4] in one step by treating with diethylamine in refluxing ethanol. We report herein the synthesis of novel substituted isoxazoles **3a-e** and 1,3,4-oxadiazoles **8a-e** from the synthon **2**. Substituted isoxazoles and oxadiazoles in general are reported to possess antimicrobial, antiinflammatory and sedative activities[5-8].

As most of the compounds **2a-e**, **3a-e** and **8a-e** are reported for the first time, screening of their herbicidal activity has been undertaken with the help of Du Pont Agricultural Products, USA and the data indicate that they possess moderate activity.

The enamino ketone **2a** on treatment with hydroxylamine hydrochloride in refluxing glacial acetic acid gave 5-(*o*-hydroxyphenyl)isoxazole **3a**, mp 194-96 °C in 82% yield. Mass spectral fragmentation pattern [m/z 161 (M^+), 121, 93] confirms[9,10] that the product is 5-substituted isoxazole **3**, and not the 3-substituted compound **4** (cf. Figure 1), which is reported to be a liquid. Similar reaction of substituted enamino ketones **2b-e** gave the corresponding isoxazoles **3b-3** (Tables I and II). This constitutes an easy and elegant method of preparing exclusively 5-(*o*-hydroxyaryl)-isoxazoles **3** in better yields with less reaction period in comparison with earlier methods[11-13].

The enamino ketones **2a-e** on treatment with phenylhydrazine in ethanol gave the phenyl pyrazoles **5a-e**[14]. Reaction of **5** with ethyl bromoacetate in acetone-K_2CO_3 medium in the presence of phase transfer catalyst gave the aryloxy acetates **6a-e**. These esters were then reacted, without further purification, with hydrazine hydrate in aqueous alcohol to get the corresponding hydrazides **7a-e**. The oxadiazole



1 2 3

4

1,2,3,5,6,7,8	a	b	c	d	e
R	H	CH_3	Cl	Br	Cl
R'	H	H	H	H	CH_3

Figure 1

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Table I—Yields and elemental analyses of compounds **3a-e**, **7a-e** and **8a-e**

Compd	R	R′	Yield (%)	mp °C	Mol. formula (Mol. wt)	Calcd (Found) (%) C	H	N
3a	H	H	82	194-96	$C_9H_7NO_2$ (161.16)	67.07 (67.17	4.38 4.29)	8.69 8.74)
3b	CH_3	H	80	176-78	$C_{10}H_9NO_2$ (175.19)	68.56 (68.47	5.18 5.28	8.00 7.97
3c	Cl	H	86	206-08	$C_9H_6ClNO_2$ (195.61)	55.26 (55.19	3.09 3.12	7.16 7.19
3d	Br	H	83	214-19	$C_9H_6BrNO_2$ (240.06)	45.03 (45.11	2.52 2.46	5.84 5.91)
3e	Cl	CH_3	80	236-39	$C_{10}H_8ClNO_2$ (209.63)	57.30 (57.43	3.84 3.89	6.68 6.51)
7a	H	H	74	115-17	$C_{17}H_{16}N_4O_2$ (308.34)	66.22 (66.28	5.23 5.30	18.17 18.24)
7b	CH_3	H	71	120-22	$C_{18}H_{18}N_4O_2$ (322.37)	67.06 (66.98)	5.63 5.74	17.38 17.43)
7c	Cl	H	76	127-29	$C_{17}H_{15}ClN_4O_2$ (342.79)	59-56 (59.55	4.41 4.51	16.35 16.33)
7d	Br	H	81	152-55	$C_{17}H_{15}BrN_4O_2$ (387.23)	52.73 (52.82)	3.90 3.86	14.47 14.53)
7e	Cl	CH_3	70	162-67	$C_{18}H_{17}ClN_4O_2$ (356.81)	60.59 (60.66	4.80 4.86	15.70 15.61)
8a	H	H	72	210-12	$C_{18}H_{14}N_4O_2S$ (350.34)	61.70 61.83	4.03 4.04	15.99 16.06)
8b	CH_3	H	75	180-82	$C_{19}H_{16}N_4O_2S$ (364.41)	62.62 (62.71	4.43 4.35	15.38 15.29)
8c	Cl	H	78	168-70	$C_{18}H_{13}ClN_4O_2S$ (384.83)	56.18 (56.04	3.40 3.48	14.56 14.62)
8d	Br	H	80	140-42	$C_{18}H_{13}BrN_4O_2S$ (429.29)	50.36 (50.44	3.05 3.00	13.05 13.01)
8e	Cl	CH_3	67	214-16	$C_{19}H_{15}ClN_4O_2S$ (398.86)	57.21 (57.14	3.79 3.86	14.05 14.15)

Table II—^{1}H NMR data of compounds **3a-e**, **7a-e** and **8a-e** (chemical shifts δ, ppm; *J* values in Hz)

Compd	^{1}H NMR ($CDCl_3$, DMSO-d_6)
3a	6.80-6.97 (m, 3H), 7.16 (s, 1H), 7.77 (d, 1H, *J*=6.08), 8.24 (d, 1H, *J*=4.6), 9.92 (s, 1H).
3b	2.34 (s, 3H), 6.86 (s, 1H), 6.94 (d, 1H, *J*=5.26), 7.04 (s, 1H), 7.68 (d, 1H, *J*=3.16), 8.30 (d, 1H, *J*=9.20), 9.78 (bs, 1H)
3c	6.83 (s, 1H), 6.96 (s, 1H), 7.11 (d, 1H, *J*=6.80), 7.72 (d, 1H, *J*=4.21), 8.25 (s, 1H), 10.20 (bs, 1H)
3d	6.85 (s,1H), 6.93 (d, 1H, *J*=2.1), 7.28 (d, 1H, *J*=7.08), 7.86 (d, 1H, *J*=3.15), 8.30 (d, 1H, *J*=1.57), 10.40 (bs, 1H)
3e	2.28 (s,3H), 6.78 (s, 1H), 6.86 (d, 1H, *J*=2.94), 7.69 (s, 1H), 8.25 (d, 1H, *J*=4.5), 10.12 (bs, 1H)
7a	3.66 (bs, 3H), 4.15 (s, 2H), 6.44 (s, 1H), 6.73 (d, 2H, *J*=9.1), 7.09 (d, 1H, *J*=8.63), 7.32 (s,5H), 7.38 (d, 2H, *J*=13.6), 7.75 (s,1H)
7b	1.55 (s, 3H), 2.29 (s, 3H), 4.08 (s, 2H), 6.38 (d, 1H, *J*=4.5), 6.57 (d, 1H, *J*=2.27), 7.26 (s, 5H), 7.72 (d, 1H, *J*=11.4)
7c	3.73 (d, 3H), 4.15 (s, 2H), 6.53 (d, 1H, *J*=1.36), 6.73 (d, 1H, *J*=1.5), 7.32-7.48 (m, 7H), 7.84 (d, 1H, *J*=9.5)
7d	2.43 (s, 3H), 4.12 (s, 2H), 6.41 (s, 1H), 6.57 (d, 1H, *J*=9.1), 7.28-7.40 (m, 6H), 7.50 (s, 1H), 7.73 (s, 1H)
7e	2.32 (s, 3H), 3.6 (bs, 3H), 4.12 (s, 2H), 6.45 (s, 1H), 6.63 (d, 1H, *J*=9.1), 7.25-7.46 (m, 5H), 7.54 (bs, 1H), 7.74 (q, 1H)
8a	4.59 (s, 2H), 6.44 (d, 1H, *J*=3.77), 6.89 (d, 1H, *J*=7.59), 7.05 (d, 1H, *J*=7.56), 7.15-7.38 (m, 7H), 7.65 (d, 1H, *J*=2.0), 14.19 (bs, 1H)
8b	2.32 (s,3H), 4.54 (s, 2H), 6.43 (d, 1H, *J*=4.52), 6.84 (d, 1H, *J*=9.18), 7.16 (s, 2H), 7.28 (m, 5H), 7.64 (s, 1H), 14.18 (s, 1H)
8c	4.56(s,2H), 6.46 (d, 1H, *J*=1.0), 6.91 (d, 1H, *J*=9.1), 7.18-7.41 (m, 5H), 7.71 (d, 1H, *J*=10.0), 14.7 (s, 1H)
8d	4.52 (s,2H), 6.45 (d,1H, *J*=1.25), 6.90 (d, 1H, *J*=9.25), 7.16-7.42 (m, 5H), 7.69 (d, 1H, *J*=9.75), 14.76 (s, 1H)
8e	7.25 (s,3H), 4.44(s, 2H), 6.38 (d, 1H, *J*=3.1), 6.78 (s, 1H), 7.19 (m, 5H), 7.44 (s, 1H), 7.6 (d, 1H, *J*=3.4), 14.16 (bs, 1H *J* = 13.15), 10.12 (bs, 1H)

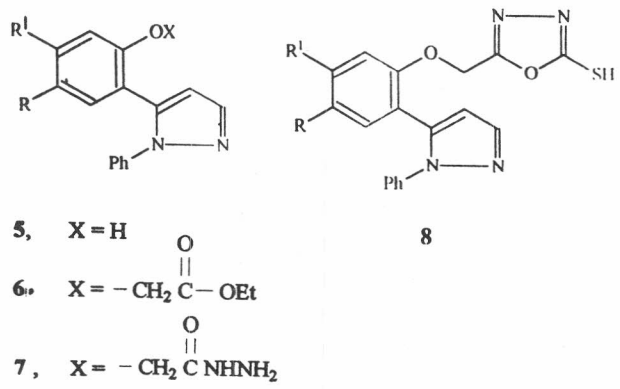

Figure 2

ring is now built by reacting **7** with CS_2 and KOH in aqueous ethanol to get the title compounds **8a-e** (Figure 2; Tables I and II).

Experimental Section

General. Melting points are uncorrected. ^1H NMR spectra were determined on a Varian Gemini 200 MHz spectrometer (internal $SiMe_4$). Mass spectra were recorded on a VG micromass 70-70H instrument. IR spectra were recorded on a Perkin-Elmer 1605 instrument. Thin layer chromatography was performed on Merck silica gel 60 F250 precoated plates (0.2mm).

5-(2′-Hydroxyaryl)isoxazoles 3a-e (Tables I,II). Equimolar mixture of substituted enamino ketones **2a-e** (10 mmoles) and hydroxylamine hydrochloride (10 mmoles) in glacial acetic acid (5 mL) was refluxed for 1-2 hr. It was cooled to room temperature and poured onto crushed ice to give light yellow solid which was recrystallized from ethanol to afford colorless crystals of **3a-e**; the yields are given in Table I.

Aryloxyacetyl hydrazones 7a-e (Tables I, II). A mixture of aryloxyphenyl pyrazoles **5a-e** (12 mmoles), ethyl bromoacetate (14 mmoles), K_2CO_3 (10g) and TBA HSO_4(2 mmoles) was taken in acetone and refluxed for 5-7 hr. Solvent was then evaporated and the resulting aryloxy acetates **6** reacted without further purification with hydrazine hydrate (15 mmoles) by refluxing in aqueous ethanol for 30 min. The resulting solid was recrystallized from ethanol to get **7a-e** as colourless crystals; the yields are given in Table I.

2-(Aryloxymethyl)-5-mercapto-1,3,4-oxadiazoles 8a-e (Tables I,II). A mixture of the hydrazides **7a-e** (15 mmoles), carbon disulfide (18 mmoles) and potassium hydroxide (18 mmoles) was refluxed in aqueous ethanol (10 mL) for 4-6 hr and cooled. The resulting crystalline solid was filtered, and recrystallized from ethanol to give **8a-e** as colorless crystals; the yields are given in Table I.

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