Asian Journal of Chemistry Vol. 17, No. 3 (2005), 1889–1901

Heterocyclic Synthesis from the Reaction of Aryl Cyanate with Malonyl Chloride and Bromomalonyl Chloride

MOHAMMED A. SHEAT† and JASIM M.A. AL-RAWI*
Pharmacy Department, School of Health and Environment
La Trobe University, Bendigo VIC 3552, Australia
E-mail: j.al-rawi@bendigo.latrobe.edu.au; Fax: +(613)54447476

Substituted aromatic cyanate reacts with malonyl chloride to yield 7-chloro-2-aryloxy-4*H*,5H-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (**3**). Water reacts with 7-chloro-2-phenoxy-4*H*, 5*H*-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (**3a**), producing phenyl (6-chloro-4-hydroxy-2-oxo-2*H*-pyran-3-yl) carbonylcarbamate (**8**). Compound **3a** reacts with morpholine in the presence of anhydrous potassium carbonate to yield phenyl (4-hydroxy-6-morpholin-4-yl-2-oxo-2*H*-pyran-3-yl)carbonylcarbamate (**9**). Product **9** was also produced from the reaction of compound **8** with morpholine. Substituted aromatic cyanate induces the self-condensation of bromomalonyl chloride, yielding 3,5-dibromo-6-chloro-4-hydroxy-2-oxo-3,4-dihydro-2*H*-pyran-3-carboxylic acid chloride (intermediate **14**) which then cyclized and produced 6-bromo-7-chloro-2-aryloxy-4*H*,5H-pyrano- [3,2-*e*][1,3]oxazine-4,5-dione (4-pyrano-oxazine) (**15**) and not the expected 8-bromo-7-chloro-2-aryloxy-4*H*,5H-pyrano-[3,4-*e*][1,3] oxazine-4,5-dione (**16**).

Key Words: Synthesis, Aromatic cyanate, Malonyl chloride, Bromomalonyl chloride.

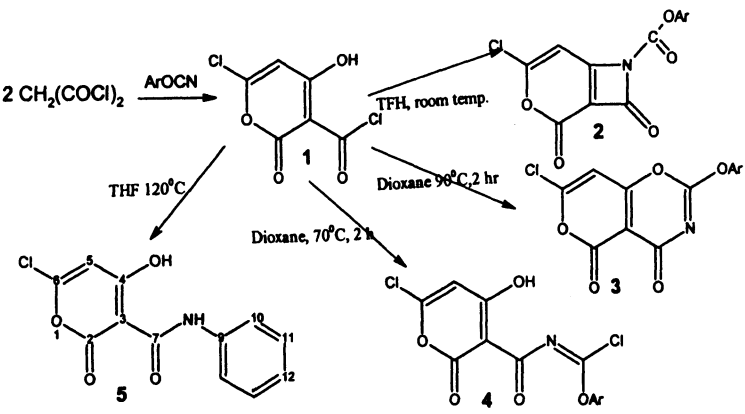
INTRODUCTION

Our ongoing interest in the synthesis and biological evaluations of the pyrano-oxazine prepared from the reaction of malonyl chloride and substituted malonyl chloride with weakly unsaturated organic base[1] led us to reinvestigate part of the study by Ried *et al.*[2] on the reaction of the aryl cyanate with malonyl chloride; this showed different products depending on the temperature and the solvent used in the reaction **(Scheme-1).**

RESULTS AND DISCUSSION

An attempt has been made by reacting two moles of malonyl chloride in dry dioxane with one mol of phenyl cyanate using the previously described procedure by Ried *et al.*[2] and yielded product **3a** with different physical and spectroscopic parameters and structural features from that previously proposed **3a** by Ried *et al.*[2] To optimize the condition for the above reaction many attempts were carried out, involving changing the mole ratio of the reactants, solvent, the time and the temperature of the reaction. The best reaction conditions were obtained

†Chemistry Department, College of Science, University of Mosul, Mosul, Iraq.



Ar = a. C_6H_5-. b. p-CH_3C6H4-,c. p-CH_3O-C_6H_4-, and d. m-CH_3O-C_6H_4-.

Scheme-1

by mixing malonyl chloride (2 mol) and phenyl cyanate (1 mol) in dry *n*-hexane, then heated with reflux at 60°C for *ca.* 2 h to yield a product which was identified as 7-chloro-2-phenoxy-4*H*,5H-pyrano[3,4-*e*][1,3] oxazine-4,5-dione **3a,** 55% yield, m.p. 207°C (proposed[2] **3a,** m.p. 168–170°C and 24% yield); this devolved method gave a better yield.

The spectroscopic data for compound **3a** are slightly different from that previously prepared by Ried *et al.*[2] The spectroscopic data of compound **3a** prepared here confirm the 2-pyrone and 1,3-oxazine moieties. IR ν_{max} (Nujol) 1800 and 1710 cm^{-1} are typical absorption for 2-pyrone and 1,3-oxazine carbonyl 5-C=O and 4-C=O respectively[1a–f] (the IR ν_{max}, KBr for the proposed[2] **3a,** 1800, 1740 cm^{-1}), while UV absorption λ_{max} (CH_3CN) 312 and 272 nm, ε 21.0×10^3 and 18.0×10^3 respectively, [λ_{max} ($CHCl_3$) for the proposed[2] **3a,** 331 and 278 nm, ε 21.4×10^3 and 24.8×10^3 respectively] (Table-1).

TABLE-1
IR (NUJOL, cm^{-1}) AND UV ABSORBANCES OF COMPOUNDS **3a–d**

Compd.	ν(HC=)	ν(C_5=O)	ν(C_4=O)	ν(C=C)	ν(C=N)	Aromatic skeletal stretching	λ_{max} (CH_3N) (nm)	$\varepsilon_{max} \times 10^3$
3a	3100 w	1800 s	1710 w	1660 s	1590 s	1610 s, 1590 m, 1500 w	312.0 272.0	21.0 18.0
3b	3100 w	1800 s	1700 w	1660 s	1590 s	1610 s, 1590 m, 1500 w	306.0 276.0	14.7 9.4
3c	3100 w	1800 s	1700 w	1660 s	1590 s	1610 s, 1590 m, 1500 w	304.0 274.0	11.0 9.0
3d	3100 w	1800 s	1700 w	1660 s	1590 s	1610 s, 1590 m, 1500 w	304.0 276.0	9.0 7.0

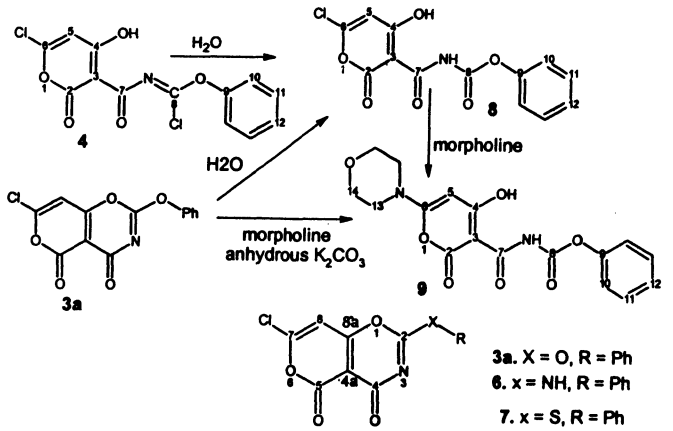
The ^{1}H NMR spectra of compound **3a–d** (Table-2) gave good evidence for the structure. It is worth noting that the compound **3a** prepared here is not soluble in chloroform while the **3a** previously proposed[2] was soluble in chloroform.

TABLE-2
^{1}H NMR δ CHEMICAL SHIFT ASSIGNMENTS OF COMPOUNDS **3a–d** IN CD_3NO_2

Compd.	Ar$\underline{CH_3}$, or $\underline{OCH_3}$	8-H	Ar
3a	—	6.7 (s, 1H)	7.2–7.7 (m, 5H)
3b	2.4 (s, 4-CH_3)	6.6 (s, 1H)	7.3 and 7.5 (AB, J_{AB} = 7.5 Hz, 4H)
3c	3.7 (s, 4-OCH_3)	6.4 (s, 1H)	6.9 and 7.05 (AB, J_{AB} = 8 Hz, 4H)
3d	3.8 (s, 3-OCH_3)	6.7 (s, 1H)	6.8–7 (m, 3H) and 7.2–7.5 (m, 1H)

Further proof for the structure of the pyrano-oxazine structure **3a** comes from its reaction with water in refluxed dichloromethane/acetone which gave phenyl (6-chloro-4-hydroxy-2-oxo-2H-pyran-3-yl)carbonylcarbamate **(8) (Scheme-2).** The physical and spectroscopic data of compound **8** are identical to the product previously prepared by Ried *et al.* [2] from the reaction of 2 moles of malonyl chloride with phenyl cyanate in dry dioxane at 70°C for 2 h **(Scheme-1).**

The analysis of the carbon-13 chemical shifts for compounds **3a–d** (Table-3) and compaction with previously analyzed carbon-13 chemical shifts of analogue compounds **6** (X = NH, R = Ph) and **7** (X = S, R = Ph)[1d] **(Scheme-2)** gave strong support for pyrano-oxazine structures.



Scheme-2

The carbon-13 spectra for compounds **6** and **7** were previously analyzed[1d] using direct, long-range carbon-proton coupling patterns and nitrogen-15 (at position-3) carbon coupling. Table-3 shows good agreement between the carbon-13 chemical shifts for the pyrano-oxazine rings of compounds **3a, 6** and **7.**

TABLE-3
^{13}C NMR SHIFT DATA (δ) FOR PYRANO-OXAZINES **3a–d** (in CD_3NO_2), **6** and **7** (in d_6DMSO)

Carbons	3a	3b	3c	3d	6*	7*
2	181.8	181.3	183.1	181.3	157.7	176.3
4	170.7	170.2	171.0	170.1	171.9	164.3
4a	156.9	156.5	159.1	156.5	157.8	154.7
5	151.5	149.3	153.0	152.3	154.4	152.3
7	93.9	93.0	93.4	93.0	87.2	92.6
8	104.5	104.1	105.5	104.1	108.1	112.4
8a	149.7	149.1	145.8	148.9	149.2	148.7
10	123.0	122.1	124.1	108.8	—	—
11	131.1	131.0	117.4	162.1	—	—
12	128.1	137.6	165.8	114.5	—	—
13	131.1	131.0	117.4	131.0	—	—
14	123.0	122.1	124.1	113.3	—	—
15	—	20.1	57.7	56.4	—	—
10	123.0	122.1	24.1	108.8	—	—

*^{13}C chemical shifts for compounds 6 and 7 are from reference **1d.**

The C-13 chemical shifts for the 2-pyrone ring of compound **5 (Scheme-1),** prepared according to the previously reported method[1c], are used to confirm the C-13 chemical shifts of compound **8,** which show very good agreement (Table-4).

TABLE-4
^{13}C NMR δ CHEMICAL SHIFT ASSIGNMENT OF COMPOUNDS **5, 8, 9** AND **13**

Carbon	5*	8	9	13
2	168.5	168.0	168.9	168.9
3	156.0	149.4	148.1	149.7
4	180.0	179.7	179.3	182.1
5	104.5	102.9	78.3	103.1
6	91.5	91.4	84.0	129.1
7	163.0	161.0	160.9	165.7
8	—	147.3	149.7	160.4
9	136.5	155.3	158.7	66.7
10	126.1	120.9	121.1	14.1
11	129.5	129.2	129.1	62.2
12	122.0	126.0	125.7	14.1

*Compound **5** was prepared according to the procedure published elsewhere [1c]

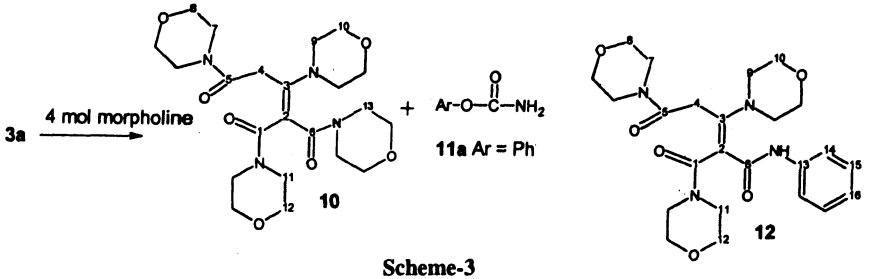
It is worth mentioning that product **5** prepared by Ried *et al.*[2] showed different melting point, IR and UV from what we prepared earlier[1c].

Compound **8** was also obtained in 15% yield from the filtrate (mother liquor, of the reaction of 2 moles of malonyl chloride and one mole of phenyl cyanate, which produced compound **3a**.

Compound **8** in this instance could come from the action of humidity on the dissolved compound of the monocyclic phenyl (6-chloro-4-hydroxy-2-oxo-2*H*-pyran-3-yl)carbonylchloridimidocarbonate **(4) (Scheme-2).** Compound **8** did not react further with 4 moles of water under reflux for 20 h in dichloromethane/acetone.

Reactions of compound 7-chloro-2-phenoxy pyrano-oxazine (3a) with morpholine: Previously, it was found that the thio-analogue of **3a** (compound **7, Scheme-2**) reacts with primary, secondary, aliphatic or aromatic amines[1f] as follows:

First, the 2-phenylthio group is replaced by an amino moiety, then the 7-chloro atom is replaced by the amine molecule and in this step amine hydrochloride is formed which attacks the oxazine ring[1e] at position **8a** opening it. Then another amine molecule opens the 2-pyrone ring, attacking at the 5-C=O group. Similarly, compound **3a** was allowed to react with morpholine and a mixture of products was obtained, no matter what the molar ratio of the morpholine to compound **3a** was used. However, the best yield (16%) of pure product was obtained when the morpholine-mole ratio was 4 to 1 moles of compound **3a** and 2-morpholinocarbonyl-3-morpholino-glutaconoyl dimorpholide **(10)** was obtained. The 2-phenoxy group in **3a** is much more difficult to be replaced by amine in the first step. Consequently, the 7-chloro atom in compound **3a** is the first to be replaced and leads to the formation of amine hydrochloride. This leads to the attack at position **8a** and opens the oxazine ring, then the 2-pyrone ring. Finally, a molecule of morpholine attacks the carbamate residue after opening the oxazine ring at the 4-C=O nitrogen bond, releasing $PhOC(O)NH_2$ **11a (Scheme-3).**

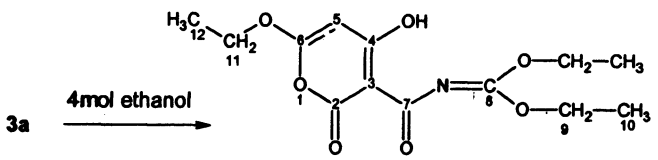


Scheme-3

The structure of compound **10** was verified by analysis of the spectroscopic data of IR, ^1H and ^{13}C NMR. The previously analyzed carbon-13 spectrum of compound **12**[1a] **(Scheme-3)** was used to confirm the C-13 chemical shifts of product **10**. When compound **3a** was allowed to react with 1 mole of morpholine which replace the chlorine at position 7 and liberated hydrogen chloride, then 0.5

mol of the morpholine would be used up by the liberated hydrogen chloride so the reaction resulting in a mixture of products. To overcome this problem anhydrous potassium carbonate was used to neutralize the hydrogen chloride evolved, so the product of the reaction of 1 mole of morpholine and excess anhydrous potassium carbonate is phenyl (4-hydroxy-6-morpholin-4-yl-2-oxo-2*H*-pyran-3-yl)carbonylcarbamate (**9**) **(Scheme-2).** This was because the morpholine first replaces the 7-chloro-atom, liberating hydrogen chloride which then reacted with K_2CO_3, and formed CO_2, KCl and H_2O. The water molecule then attacks the 7-morpholino pyrano-oxazine compound at C-8a producing compound **9 (Scheme-2).** Compound **9** also resulted from the reaction of compound **8** with 2 mole of morpholine.

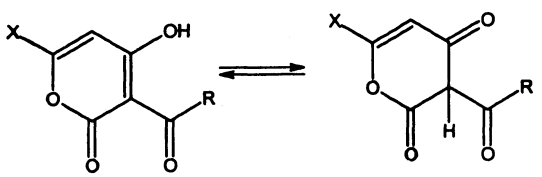
Reaction of 7-chloro-2-phenoxy pyrano-oxazine (3a) with 4 moles of absolute ethanol: Compound **3a** was allowed to react with 4 moles of absolute ethanol and ethyl(4,6-diethoxy-2-oxo-2*H*-pyran-3-yl)carbonylcarbamate (**13**) was obtained **(Scheme-4).**



Scheme-4

The ethanol reaction sequences with compound **3a** could be as follows:

The first molecule of ethanol attacks at position 7 and replaces the chlorine atom, resulting in the generation of hydrogen chloride. The hydrogen chloride then protonates the oxygen of the 4-C=O, thus leading to the attack of a second molecule of ethanol at C-2 and opening the oxazine ring (breaking the bond between O-1 and C-2). The replacement of the phenoxy group by an ethanol molecule could take place before or after the opening of the oxazine ring. The low field C-13 chemical shift of C-4 in compounds **5, 8, 9** and **13**, *ca.* 180 ppm (Table-4) could be as a result of the ketone form contribution in the enol-ketone tautomerization **(Scheme-5).**

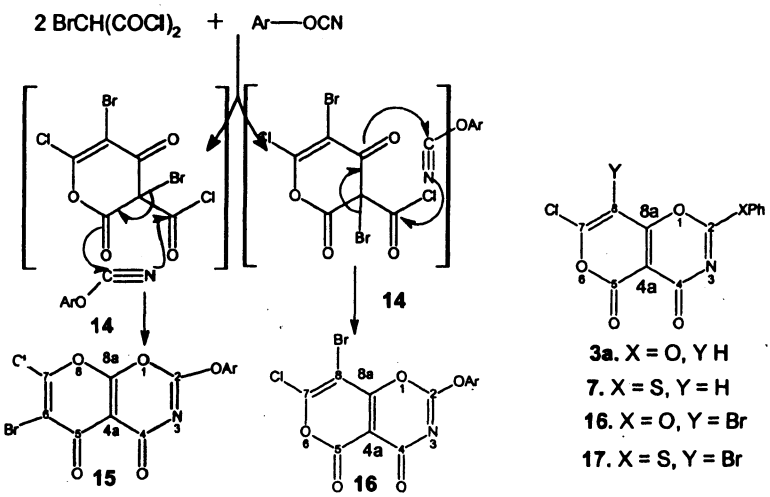


5 X = Cl, R = PhNH
8 X = Cl, R = PhOC(O)NH
9 X = Morpholine, R = PhOC(O)NH
13 X = CH_3CH_2O, R = ($CH_3CH_2O)_2$ C = N

Scheme-5

Reaction of 2 moles of bromomalonyl chloride with 1 mole phenyl cyanate: Previously[1b], aryl thiocyanate induced self-condensation of two molecules of bromomalonyl chloride producing intermediate **14 (Scheme-6).** Intermediate **14** then undergoes 3-debromination either before cyclization with the phenyl thiocyanate or concurrent with that process producing compound **17 (Scheme-6).** Chloride ion or thiocyanate could be responsible for abstraction of the bromonium ion.

Similarly, aryl cyanate also induced the self-condensation of two molecules of bromomalonyl chloride producing intermediate **14.** Evidently this latter undergoes 3-debromination, then cyclization to yield (8-bromo-7-chloro-2-aryloxy-4*H*, 5H-pyrano[3,4-*e*][1,3] oxazine-4,5-dione) **(16),** the oxygen analogue of compound 17 (Scheme-6).



Ar **a** = H, **b** = p-Me, **c** = m-MeO, and **d** = p-MeO.

Scheme-6

However, the structure of the product from the reaction of bromomalonyl chloride with aryl cyanate was not the 2-pyrano-1,3-oxazine **16** after the analysis of its spectroscopic data. Inspection of the UV absorption (Table-5) for compound **15a** and comparison with the 2-pyrono-1,3-oxazine (compounds **17, 7,** and **3a**) reveals that the compound is not **16a** (not 2-pyrano-1,3-oxazine). Similarly, comparing the IR absorption (Table-5) and C-13 chemical shifts (Table-6) confirms the structure of the products from the reaction of 2 moles of bromomalonyl chloride and aryl cyanate are 6-bromo-7-chloro-2-aryloxy-4*H*,5H-pyrano[3,2-*e*][1,3]oxazine-4,5-dione **15a–d** (a 4-pyrano-oxazine product). The arguments supporting the 4-pyrono-1,3-oxazine **16** and not 2-pyrano-oxazine **17** are cited as follows:

1. The absence of a lactone absorption band (*ca.* 1770 cm^{-1}) in the IR spectra compound **15** confirms 4-pyrano-1,3-oxazine[3a, b].

2. The UV spectra supported the structure of 4-pyrano-oxazine for compound **15** in that it showed two λ_{max} at 276 and 252 nm for the 4-pyrane and oxazine rings, while the previously reported[1b] 2-pyrano-oxazine **17** (thio-analogue) showed higher λ_{max} 364, 355, 304, 294 and 270 nm.

TABLE-5
IR (NUJOL, cm^{-1}) AND UV ABSORBANCES OF COMPOUNDS **16a–d** COMPARED WITH THAT OF COMPOUND **17**, **7** AND **3a** (in $CDCl_3$).

	15a	**15b**	**15c**	**15d**	**17**[1b]	**7**[1f]	**3a**
ν(5-C=O)	1720 w	1720 w	1720 w	1720 w	1755	1755	1800 s
ν(4-C=O)	1650 m	1650 s	1650 s	1650 s	1720	1750	1710 w
ν(C=N)	1570 m	1580 s	1575 s	1575 m	1570	1590	1590 s
λ_{max} (CH_3CN) nm	260.0, 252.0	270.0, 269.0	275.0, 256.0	276.0, 268.0	364, 355, 304, 294, 270	347.0, 279.5	312.0, 272.0
$\varepsilon_{max} \times 10^3$	8.5, 15.0	4.1, 3.8	4.64, 2.74	4.3, 4.5	20.2, 20.0, 9.4, 10.0, 8.6	14.8, 10.7	21.0, 18.0

TABLE-6
^{13}C NMR δ CHEMICAL SHIFT ASSIGNMENTS OF COMPOUNDS **15a, b** AND **d** (in $CDCl_3$) COMPARED WITH THAT OF **3a**

Carbon	**3a**	**15a**	**15b**	**15d**
C-2	181.8	158.4	152.9	151.6
C-4	170.7	161.9	159.2	160.2
C-4a	156.9	129.6	131.0	129.7
C-5	151.5	162.4	162.4	160.4
C-6*/7	93.9	107.6	107.9	107.1
C-7*/8	104.5	117.2	117.4	118.5
C-8a	149.7	157.8	159.0	157.3
C-9	163.7	150.7	149.1	151.0
C-10	123.0	120.7	120.8	106.7
C-11	131.0	130.1	131.0	160.4
C-12	128.1	127.5	138.1	112.4
C-13	131.1	130.1	131.0	130.0
C-14	123.0	120.7	12.8	112.9
C-15	—	—	21.0	53.4

The ^{13}C NMR spectra assignment was in a better agreement for the structure of 4-pyrano-1,3-oxazine moieties for the product **15** and not 2-pyrano-1,3-oxazine **16**. The carbon-13 chemical shifts for the aryl groups in compounds **15(a, b, d)** were assigned by analogy to the aryl carbamates **11** (Ar = (a) Phenyl, (b) *p*-metylphenyl and (d) *m*-methoxy phenyl) (**Scheme-3** and Table-7). The carbon-13 chemical shifts of the 4-pyrano-1,3-oxazine showed distinct differences from that for 2-thio-2-pyrano-1,3-oxazine analogue **17**[1b] and **3a** (**Scheme-1** and Table-7).

TABLE-7
^{13}C NMR δ CHEMICAL SHIFT ASSIGNMENTS OF
COMPOUNDS **12a–d** IN THE INDICATED SOLVENTS

Carbon	12a	12b	12c	12d
C-1	154.8	155.4	154.0	154.6
C-2	151.1	149.7	145.4	152.2
C-3	121.8	121.9	123.0	107.9
C-4	129.1	129.8	114.5	160.0
C-5	124.7	134.6	157.2	110.5
C-6	129.1	129.8	114.5	129.5
C-7	121.8	121.9	123.0	114.0
C-8	—	20.7	55.6	55.1

EXPERIMENTAL

UV and IR spectra were obtained with Unicam SP 800B and SP 200 spectrometers, respectively. ^1H and ^{13}C NMR spectra ($SiMe_4$ as internal reference) were recorded on Bruker WH 90 DS FT NMR spectrometer. Microanalysis was performed on a Carlo-Erba Strumentazione elemental analyser MOD 1106.

Preparation of starting materials

Preparation of bromomalonic acid starting from malonic acid and bromine in acetic acid was done according to the published procedure[4]. The produced bromomalonic acid was recrystallized from a mixed solvent, acetone and benzene, into colourless crystals, 61%, m.p. 112°C; δ ^1H (d_6 acetone) 11.0 (b, OH), 5.2 (s, CH); δ ^{13}C (d_6 acetone) 43.2 (d, ^1J = 155 Hz, CH), 166.5 (d, ^2J = 7 Hz, C=O).

Malonyl chloride was prepared[5] using thionyl chloride and malonic acid; the pale yellow malonyl chloride distilled at reduced pressure (65%, bp. 51°C/21 mm Hg).

Bromomalonyl chloride was prepared[4] using thionyl chloride and bromomalonic acid; the pale yellow bromomalonyl chloride distilled at reduced pressure (70%, b.p. 43°C/0.8 mm Hg) and showed δ ^1H ($CDCl_3$) 5.62 (s, CH); δ ^{13}C ($CDCl_3$) 56.9 (d, ^1J = 165 Hz, CH), 162.7 (d, ^2J = 8 Hz, C=O).

Cyanogen bromide was prepared[6] using bromine and potassium cyanide (yield 94%).

The preparation of aryl cyanates was achieved starting from cyanogen bromide and freshly distilled phenol as per reported procedure[7]. The phenyl cyanate distilled at 55°C/0.4 mm Hg and gave 92% yield; *p*-methylphenyl cyanate distilled at 68°C/0.25 mm Hg and gave 96% yield; *p*-methoxyphenyl cyanate distilled at 85°C/0.2 mm Hg and gave 90% yield; *m*-methoxyphenyl cyanate distilled at 74°C/0.07 mm Hg and gave 94% yield; aryl carbamate was prepared[8] from the acid catalyzed hydrolysis of the corresponding aryl cyanate; phenyl carbamate (**11a**) gave 78% m.p. 145°C, ν_{max} (Nujol) 3420 m, 3340 m, 3290 m, 3200 w, 1710 s, 1600 w, 1500 sh cm^{-1}; δ ^1H ($CDCl_3$) 5.1 (b, NH_2) and 7–7.5 (m, 5H of Ph) ppm.

4-Methylphenyl carbamate (**11b**) gave 75% m.p. 161°C, ν_{max} (Nujol) 3420 m, 3340 m, 3290 m, 3200 w, 1715 s, 1600 sh, 1515 w cm^{-1}; δ ^1H ($CDCl_3$) 2.3 (s, CH_3), 5.0 (b, NH_2), 6.93 (d, J_{AB} = 8 Hz, 2H), 7.07(d, J_{AB} = 8 Hz, 2H) ppm.

4-Methoxyphenyl carbamate (**11c**) gave 80% m.p. 128°C, ν_{max} (Nujol) 3420 m, 3340 m, 3290 m, 3200 w, 1720 s, 1600 m, 1515 w cm^{-1}; δ ^1H ($CDCl_3$) 3.6 (s, OCH_3), 5.0 (m, NH_2), 6.76 (d, J_{AB} = 8.4 Hz, 2H), 6.92 (d, J_{AB} = 8.4 Hz, 2H) ppm.

3-Methoxyphenyl carbamate (**11d**) gave 82% m.p. 140°C, ν_{max} (Nujol) 3420 m, 3340 m, 3290 m, 3200 w, 1715 s, 1600 w, 1500 m cm^{-1}; δ ^1H ($CDCl_3$) 3.7 (s, OCH_3), 5.0 (b, NH_2), 6.5–6.8 and 7.0–7.4 (m, Ph, 4H).

Reaction of 2 moles of malonyl chloride with one mole of aryl cyanate

General procedure: Malonyl chloride (7.0 g, 0.0496 mol) was placed in dry *n*-hexane (60 mL) in a 100 mL round bottomed flask fitted with a serum cap, after cooling to 0°C in an ice bath with stirring; aryl cyanate (0.0248 mol) was added dropwise using a syringe. After the addition was completed, an air condenser with a calcium chloride tube was fitted and the mixture was stirred at 0°C for 10 min and then heated in an oil bath at 60°C for 1.5–2.5 h. After cooling and decanting the solvent, the residue was washed with dry *n*-hexane (50 mL). Recrystallization of the product from dry 1,2-dichloroethane (charcoal) gave pale yellow crystals of 7-chloro-2-aryloxy-4*H*,5H-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (**3a–d**).

Using the above general procedure the following 2-pyrano-1,3-oxazines **3a–d** were prepared:

1. 2 moles of malonyl chloride were allowed to react with 1 mole of phenyl cyanate at 60°C for 2 h and gave 7-chloro-2-phenoxy-4*H*,5H-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (**3a**), 55% yield, m.p. 207°C (decomposed) (found: C, 53.58; H, 2.04; N, 4.72; $C_{13}H_6NO_5Cl$ requires C, 53.51; H, 2.06; N, 4.80 %). The evaporation (left to evaporate in the open air at room temperature) of the combined n-hexane used as medium for the above reaction and washing the product gave a solid compound, recrystallized from acetone and identified as phenyl (6-chloro-4-hydroxy-2-oxo-2*H*-pyran-3-yl)carbonylcarbamate (**9**) (15%, m.p. 182–184°C, lit.[2] m.p. 182–184°C); ν_{max} (Nujol) 3230 w, 309 w, 2680 w, 1795 s, 1745 s, 1660 w, 1630 s, 1600 sh, 1555 m and 1515 m cm^{-1}; λ_{max} (CH_3CN) 306, 250 nm (ε = 16, 5.5 x 10^3); δ ^1H ($CDCl_3$) 6.3 (s, H-5), 7.1–7.7 (m, 5H of Ph), 11.1 (b, NH), 15.5 (b, OH) ppm.
2. Similarly, malonyl chloride (2 mol) and 4-methylphenyl cyanate (1 mol) at 60°C for 2.5 h gave 7-chloro-2-(4-methylphenoxy)-4*H*,5H-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (**3b**), 44% yield, m.p. 197°C (decomposed) (found: C, 54.83; H, 2.46; N, 4.59. $C_{14}H_8NO_5Cl$ requires C, 54.99; H, 2.62; N, 4.58%).
3. Similarly, malonyl chloride (2 mol) and 4-methoxyphenyl cyanate (1 mol) at 60°C for 1.5 h gave 7-chloro-2-(4-methoxyphenoxy)-4*H*,5H-pyrano-[3,4-*e*][1,3]oxazine-4,5-dione (**3c**), 44% yield, m.p. 213°C (decomposed), (found: C, 52.10; H, 2.49; N, 4.17; $C_{14}H_8NO_6Cl$ requires C, 52.25; H, 2.49; N, 4.35%).
4. Similarly, malonyl chloride (2 mol) and 3-methoxyphenyl cyanate (1 mol) at 60°C for 2 h gave 7-chloro-2-(3-methoxyphenoxy)-4*H*,5H-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (**3d**), 50% yield, m.p. 203°C (decomposed)

(found: C, 52.10; H, 2.34; N, 4.28. $C_{14}H_8NO_6Cl$ requires C, 52.25; H, 2.49; N, 4.35%).

Reactions with water

1. Compound **3a** (0.5 g, 0.00172 mol) was dissolved in dry dichloroethane (70 mL) with stirring and heating at 95°C. A solution of water (0.0619 g, 0.0344 mol) in dry acetone (10 mL) was added and the mixture was refluxed at 95°C for 1 h. Evaporation of the solvent to dryness under reduced pressure produced a solid product. Recrystallization from acetone (charcoal) gave a white powder (0.35 g, 66%, m.p. and mixed m.p. with compound **9** was 182–184°C). All the spectroscopic data are identical to phenyl (6-chloro-4-hydroxy-2-oxo-2*H*-pyran-3-yl)carbonylcarbamate **(8)**.
2. Compound **8** (0.5 g, 0.00172 mol) dissolved in dry dichloroethane (70 mL) with stirring and heating at 95°C. A solution of water (0.138 g, 0.0688 mol) in dry acetone (10 mL) was added and the mixture was refluxed at 95°C for 20 h. Evaporation of the solvent to dryness under reduced pressure produced a solid product and recrystallization from acetone (charcoal) gave a white powder of unreacted compound **8**.

Reactions with morpholine

1. **Compound 3a with 4 moles of morpholine:** In 100 mL round-bottomed flask, 0.4 g (0.0014 mol) of compound **3a** was dissolved in dry dichloroethane (60 mL) with heating and stirring at 95°C. A solution of morpholine (0.487 g, 0.0056 mol) in dry dichloroethane (5 mL) was added dropwise then the mixture was refluxed at 95°C for 5 min. After cooling in an ice bath for 1 h the mixture was filtered to remove the solid morpholine hydrochloride. The filtrate was evaporated to dryness under reduced pressure, then the resulting solid was recrystallized from benzene/ether (charcoal) and gave a pale yellow powder of 2-morpholinocarbonyl-3-morpholinoglutaconoyl dimorpholide **(10)** (0.1 g, 16%, m.p. 229–232°C) (found: C, 44.23; H, 6.00; N, 2.54; $C_{21}H_{34}N_4O_7$ requires C, 44.15; H, 5.93; N, 2.44%); IR (Nujol) 1690 s, 1675 s 1665 s, and 1640 sh cm^{-1}; δ ^1H NMR (d_6 acetone) 3.4–4.4 (m, 34H) ppm; δ ^{13}C NMR (d_6 DMSO), 163.8 (C-1), 117.0 (C-2), 156.2 (C-3), 94.3 (C-4), 161.6 (C-5), 164.2 (C-6), 45.5 (C-7), 65.0 (C-8), 46.4 (C-9), 65.0 (C-10), 42.9 (C-11), 65.8 (C-12), 42.9 (C-13), 65.8 (C-14) ppm.
2. **Compound 3a with one mole of morpholine:** In 100 mL round bottomed flask, 0.5 g (0.00172 mol) of compound **3a** was dissolved in dry dichloroethane (70 mL) with heating and stirring at 95°C. After the addition of 2 g of anhydrous potassium carbonate, a solution of morpholine (0.15 g, 0.00172 mol) in dry dichloroethane (5 mL) was added dropwise then the mixture was refluxed at 95°C for 5 min. After cooling in an ice bath the mixture was filtered to remove the solid potassium chloride. The filtrate was evaporated to dryness under reduced pressure, then the resulting solid was washed with ether and recrystallized from benzene (charcoal) to give white crystals of phenyl (4-hydroxy-6-morpholin-4-yl-2-oxo-2*H*-pyran-3-yl)carbonylcarbamate **(9)** (0.2 g, 33%, m.p. 259–261°C, decomposed)

(found: C, 56.82; H, 4.52; N, 7.82; $C_{17}H_{16}N_2O_7$ requires C, 56.67; H, 4.44; N, 7.78%); IR (Nujol) 324 w (NH, broad, hydrogen bonded, 2700 w (OH, very broad, H-bonded); 1790 s ν(2-C=O, H-bonded), 1710 s ν(8-C=O), 1660 s ν(7-C=O, H-bonded), 1620 s ν(C=C), 1530 s and 1500 s ν(aromatic ring stretching) cm^{-1}; δ ^1H NMR ($CDCl_3$) 3.4–3.65 (m, 4H, 2 CH_2N of the morpholine), 3.65–3.90 (m, 4H, $2CH_2O$, of the morpholine), 5.2 (s, 1 H, H-5), 7.1–7.6 (m, 5H, Ph), 11.2 (b, 1 H, NH), 14.7 (b, 1 H, OH) ppm.

3. **Compound 8 with one mole of morpholine:** In 100 mL round-bottomed flask, 0.5 g (0.00161 mol) of compound **8** was dissolved in dry dichloromethane (40 mL) with stirring. A solution of morpholine (0.28 g, 0.00322 mol) in dry dichloroethane (5 mL) was added, then the mixture was refluxed at 95°C for 10 min. After cooling in an ice bath the mixture was filtered. The filtrate was evaporated to dryness under reduced pressure, then the resulting solid was recrystallized from benzene (charcoal) to give white crystals of phenyl (4-hydroxy-6-morpholin-4-yl-2-oxo-2*H*-pyran-3-yl)carbonylcarbamate (**9**) (0.2 g, 34%, m.p. and mixed m.p. with the product from the above experiment was 259–261°C, decomposed). The spectroscopic result confirms that the products from this experiment and the above are identical.

Reaction with absolute ethanol

Compound **3a** (0.5 g, 0.00172 mol) was dissolved in dry dichloromethane (70 mL) with heating and stirring at 95°C, then absolute ethanol (0.316 g, 0.00688 mol) in dry dichloromethane (5.0 mL) was added and the mixture was refluxed for 1 h at 95°C. The mixture was cooled and the solvent then evaporated under reduced pressure to dryness. The product was recrystallized from dry CCl_4/ petroleum spirit (40–60°C) (charcoal) giving a pale yellow powder of diethyl (6-ethoxy-4-hydroxy-2-oxo-2*H*-pyran-3-yl)carbonylimidocarbonate **(13),** 32%, m.p. 102 (found: C, 52.17; H, 5.69; N, 4.68; $C_{13}H_{17}NO_7$ requires C, 52.32; H, 5.72; N, 4.71 %); IR (Nujol) 3200 w ν(OH), 1790 m ν(2-C=O), 1720 s ν(7-C=O, hydrogen bonded), 1625 s ν(N=C), cm^{-1}; δ ^1H NMR ($CDCl_3$) 1.2–1.6 (m, $3CH_3$), 4.1–4.5 (m, $3CH_2$), 5.4 (s, 1H, H-5), 10.8 (b, 1H, OH) ppm.

Reaction of two mole of bromomalonyl chloride with one mole aryl cyanate

General procedure: Bromomalonyl chloride (3.7 g, 0.0168 mol) was placed in dry toluene or carbon tetrachloride (30 mL) in a 100 mL round-bottomed flask fitted with a serum cap. After cooling to 0°C in an ice bath with stirring, aryl cyanate (0.0084 mol) was added dropwise using a syringe. After the addition was completed, an air condenser with a calcium chloride tube was fitted and the mixture was stirred at 0°C for 10 min, and then heated in an oil bath at 75°C for 10–20 min. After cooling and decanting the solvent, the residue was washed with dry n-hexane (50 mL). Recrystallization of the product from the indicated dry solvent (charcoal) gave 6-bromo-7-chloro-2-aryloxy-4*H*,5H-pyrano[3,2-*e*][1,3] oxazine-4,5-dione-(4-pyrano-oxazine) **15a–d.**

Using the above general procedure the following 4-pyrano-1,3-oxazines **(15a–d)** were prepared:

1. 2 moles of bromomalonyl chloride were allowed to react with 1 mole of phenyl cyanate in dry toluene at 75°C for 15 min to yield a product which recrystallized from dry toluene (charcoal) and gave white crystals of 6-bromo-7-chloro-2-phenyloxy-4*H*,5H-pyrano[3,2-*e*][1,3]oxazine-4,5-di one(4-pyrano-oxazine) **(15a)**, 32% yield, m.p. 182–184°C (decomposed) (found: C, 42.20; H, 1.29; N, 3.68; $C_{13}H_5NO_5$ BrCl requires C, 42.11; H, 1.35; N, 3.78%).
2. 2 moles of bromomalonyl chloride were allowed to react with one mole of 4-methylphenyl cyanate in dry CCl_4 at 75°C for 10 min to yield a product which recrystallized from dry CCl_4 (charcoal) and gave pale yellow crystals of 6-bromo-7-chloro-2-(4-methylphenyloxy)-4*H*,5H-pyrano[3,2-*e*]- [1,3] oxazine-4,5-dione(4-pyrono-1,3-oxazine) **(15b)**, 28% yield, m.p. 188–190°C (decomposed) (found: C, 43.51; H, 1.71; N, 3.52; $C_{14}H_7NO_5BrCl$ requires C, 43.69; H, 1.82; N, 3.64%).
3. 2 moles of bromomalonyl chloride were allowed to react with 1 mole of 4-methoxyphenyl cyanate in dry CCl_4 at 75°C for 15 min to yield a product which recrystallized from dry CCl_4 (charcoal) and gave a pale yellow crystals of 6-bromo-7-chloro-2-(4-methoxyphenyloxy)-4*H*,5H-pyrano[3,2-*e*][1,3]oxazine-4,5-dione(4-pyrano-oxazine) **(15c)**, 30% yield, m.p. 168–170°C (decomposed) (found: C, 41.72; H, 1.62; N, 3.38. $C_{14}H_7NO_6BrCl$ requires C, 41.94; H, 1.74; N, 3.49%).
4. 2 moles of bromomalonyl chloride were allowed to react with 1 mole of 3-methoxyphenyl cyanate in dry CCl_4 at 75°C for 20 min to yield a product which recrystallized from dry CCl_4/ether (charcoal) and gave yellow crystals of 6-bromo-7-chloro-2-(3-methoxyphenyloxy)-4*H*, 5H-pyrano[3,2-*e*][1,3]oxazine-4,5-dione(4-pyrano-oxazine) **15d**, 27% yield, m.p. 156–158°C (found: C, 41.84; H, 1.71; N, 3.41; $C_{14}H_7NO_6BrCl$ requires C, 41.94; H, 1.74; N, 3.49%).

REFERENCES

1. (a) J.M.A. Al-Rawi and A.H.T. Mahmood, *J. Prakt. Chem.*, **330**, 859 (1988); (b) J.M.A. Al-Rawi, R.Y. David and J.A. Elvidge, *J. Chem. Soc. Perkin Trans. 1*, 2499 (1982); (c) M.S. Al-Ajely, J.M.A. Al-Rawi and J.A. Elvidge, *J. Chem. Soc. Perkin Trans. 1*, 1575 (1982); (d) J.M.A. Al-Rawi and J.A. Elvidge, *J. Chem. Soc. Perkin Trans. 1*, 2536 (1977); (e) J.M.A. Al-Rawi and J.A. Elvidge, *J. Chem. Soc. Perkin Trans. 1*, 2462 (1976); (f) J.M.A. Al-Rawi and J.A. Elvidge, *J. Chem. Soc. Perkin Trans. 1*, 2432 (1973); (g) A.H. Al-Mousawi, J.M.A. Al-Rawi and M.S. Al-Ajely, *Arab Gulf J. Scint. Res.*, **9**, 1 (1991).
2. W. Ried, J. Nenninger and J.W. Bats, *Chem. Ber.*, **118**, 1371 (1985).
3. (a) L.J. Bellamy, The Infrared Spectra of Complex Molecules, Chapman & Hall, London, 3rd Edn. (1978); (b) K. Nakanishi, Infrared Absorption Spectroscopy-Practical, 2nd Edn. (1964).
4. O. Lutz, *Chem. Ber.*, **35**, 2549 (1902).
5. R. Chittaranjan, *Org. Synth.*, **20**, 33 (1953).
6. E. Schulek and I.G. Molnar, *M.K. Lapja.*,**4**, 735 (1949); *Chem. Abstr.*, **45**, 969 (1951).
7. E. Grigat and R. Puetter, *Chem. Ber.*, **97**, 3012 (1964).
8. D. Martin, *Chem. Ber.*, **97**, 2689 (1964).

(*Received*: 23 October 2004; *Accepted:* 16 April 2005) AJC-4183