The Synthesis and Nucleophilic Substitution of Haloxanthones

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Received January 3, 2000

Acylation reaction of *m*-cresol with 2,6-dihalobenzoic acid in the presence of methansulfonic acid and subsequently, cyclization of the obtained *o*-hydroxybenzophenones with K_2CO_3/dimethyl formamide, afforded haloxanthones **4** and **5** in high yields. Aromatic nucleophilic substitution of the resulted haloxanthones with *O*-, *N*- and *S*-nucleophiles are studied in a comparative manner, and various new *O*-, *N*- and *S*-substituted xanthones have obtained.

J. Heterocyclic Chem., **38**, 617 (2001).

Introduction.

Xanthones are one of the most important natural occuring compounds. Beside a wide variety of chemical and industrial applications, synthetic derivatives of xanthones as well as naturally occuring derivatives have been used for medical purposes [1-7]. The biological and photochemical behaviour of this family of xanthone derivatives made these substances attractive for synthetic studies [8,9].

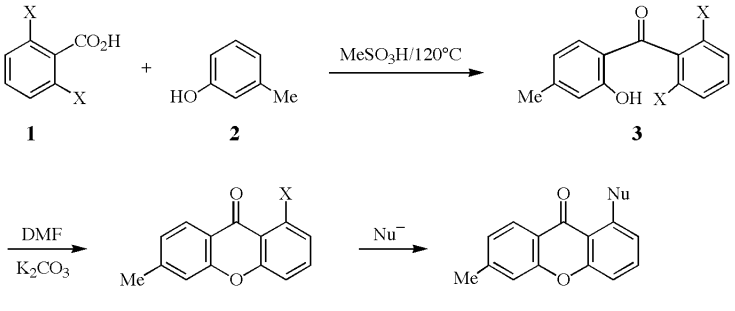
Nucleophilic substitution of aromatic halo groups has attracted increasing attention in recent years for both theoretical [10] and synthetic reasons [11-15]. Possibility to run such reactions in dipolar media in high concentrations with short reaction times and excellent yields has prompted their introduction into industrial processes [16]. However, the functions are displaced by nucleophiles in dipolar aprotic solvents [11-15]. The S_NAr reaction proceeds with decreasing facility in the series of F, NO_2 >> Cl > Br > I, so that for practical purposes, bromine and iodine displacement are lacking in synthetic utility [17]. Recently, nucleophilic aromatic substitution of some nitro derivatives of benzophenones and xanthones were studied in dipolar aprotic solvents [18-21]. To the best of our knowledge, there is no report about direct nucleophilic substitution of the corresponding halo derivatives. In this paper we report our preliminary results concerning the nucleophilic aromatic substitution of the two new chloro and fluoro substituted xanthones **4** and **5** in a comparative manner (Scheme 1).

Results and Discussion

Acylation reaction of *m*-cresol (**2**) with 2,6-dihalobenzoic acid was carried out in anhydrous methansulfonic acid and benzophenones **3a** and **3b** were obtained in 60% and 70% yields respectively. Among the various reported methods for cyclization of *o,o'*-halohydroxybenzophenones [22-27] which we tried, none of them were successful, and in all cases a mixture of unreacted benzophenone and haloxanthone were obtained. In order to improve the yields and purity of haloxanthone, we refluxed the benzophenone **3** in dimethyl formamide (DMF) with K_2CO_3 and 1-halo-6-methylxanthone **4** (X = F)and **5** (X = Cl) were obtained in quantitative yields.

Generally, in direct nucleophilic aromatic substitution, fluorides are anticipated to be the most reactive halide, and substitution of the chloro groups requires more vigorous conditions [11,12,28,29]. However, reaction of xanthone **4** (X = F) with sodium methoxide in methanol produced the new 1-methoxy-6-methylxanthone (**6**) in 95% yield, whereas chloro substituted xanthone **5** (X = Cl) gave the same product in 40% yield. When the latter reaction was carried out in DMF, the yield was increased to 65%, and the use of Cu(1) [14,15] as a catalyst, did not improve the reaction time and yield.

Scheme 1



4) X = F
5) X = Cl

6) Nu^- = - OMe
7) Nu- = - OEt
8) Nu- = - OPr
9) Nu- = - $O(CH_2CH_2O)_2H$
10) Nu- = -$NHCH_2CH_2NH_2$
11) Nu^- = -$NH(CH_2CH_2NH)_2H$

The use of pyridine and deimthyl sulfoxide (DMSO) were not found to be superior solvents than DMF, though reaction of xanthone **5** (X = Cl) with sodium methoxide in pyridine or DMSO, afforded compound **6** in 68 and 55% yields respectively. Similarly, reaction of xanthone **4** (X = F) with sodium in ethanol or propanol afforded xanthones **7** and **8** in 95 and 85% yields respectively, while xanthone **5** (X = Cl) reacted with sodium ethoxide or sodium propoxide in DMF to produced new compounds **7** and **8** in 65 and 60% yields respectively.

Subsequently, reaction of xanthone **4** with sodium and diethylene glycol in DMF afforded new xanthone **9** with an ethylenoxy side chain in 92% yield, while reaction of chloroxanthone **5** under similar conditions produced xanthone **9** in 80% yield, and an enhancement of the yield was observed for nuucleophilic substitution of the chloro group by diethylene glycol. As well as 1-chloroanthraquinone [11,12,30,31], the chloro group of xanthone **5** is more readily substituted by diethylene glycol than the simple aliphatic alcohols. This enhancement in the rate of substituation reaction of **5** may result from nucleophilicity enhancement of diethylene glycol by either complexation of the cation with nucleophile, or a self-solvation process which deaggregates the alloxide [12,31].

Reaction of xanthone **4** with ethylenediamine or diethylenetriamine in DMF afforded 1-[(2-aminoethyl)amino]-6-methylxanthone (**10**) or 1-[2-(2-aminoethyl)aminoethylamino]-6-methylxanthone (**11**) in 88 and 92% yields respectively. Compound **11** was also obtained from chloroxanthone **5** under the above mentioned conditions in 65% yield, but refluxing of compound **5** and diethylenetriamine with K_2CO_3 in DMF, produced xanthone **11** in quantitative yield.

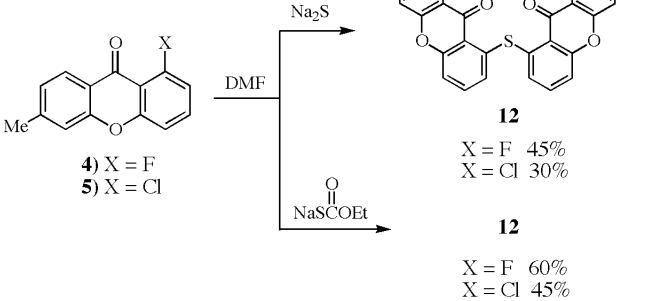
When xanthone **4** was refluxed with Na_2S [32] or sodium thioxanthate in DMF, di(6-methylxanthono) sulfide (**12**) was obtained in 45 and 60% yields respectively (Scheme 2).

In 1979 Gorvin [21] found that 3,6-dinitroxanthone is produced from 2,2',4,4'-tetranitro benzophenone by a variety of reagents, either by an ionic route, (in the presence of OH^- or ONO^- in DMSO), or by what appears to be a Nef-type hydroxyldenitration reaction proceeding through an anion-radical (copper in pyridine, potassium cyanide in DMSO are used). In most cases the 4-hydroxy-2,2',4'-trinitrobenzophenone is formed in approximately equal amount (15-38%). Therefore, in an attempt to find a short route to the new substituted xanthones **6-8**, the nucleophilic substitution of halobenzophenones **3a** and **3b** were studied.

Although, cyclization of dihalohydroxy benzophenones is a more favorable intramolecular nucleophilic substitution and restricted to non or less nucleophilic bases, both intra and intermolecular nucleophilic substitution may occur. Thus, reaction of benzophenone **3a** with nucleophilic bases such as sodium in methanol, ethanol and propanol produced preferentially alkoxy substituted xanthones **6-8** and no substituted benzophenones were obtained (Scheme 3). A similar but slower reaction with alkoxides occurred for chloro substituted benzophenone **3b**. In both cases, the reactions with nucleophiles were not completed and a mixture of unreacted benzophenone together with substituted xanthone were identified. In the case of benzophenone **3b**, chloroxanthone **5** was also obtained in addition to the above mentioned compounds (Table 1). When nucleophilic reactions were carried out in DMF, all yields were increased in about 10%.

However, the yield and rate of chloro-displacement by nucleophiles was lower than the flouro-displacement, therefore, cyclization and nucleophilic substitution of ben-

Scheme 2



Scheme 3

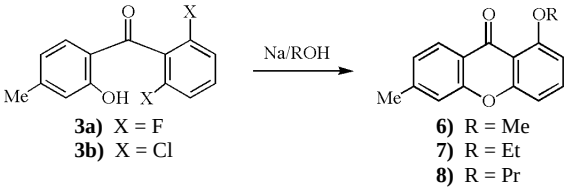


Table 1

Reaction of Halobenzophenones with some Alkoxides

Benzophenone	Conditions	Time (h)	Product(s) (%)	Yield (%)
3a	Na/MeOH/reflux	5	**6**	70
3b	Na/MeOH/reflux	10	**5**(20)/**6**(30)	50
3a	Na/EtOH/reflux	6	**7**	60
3b	Na/EtOH/reflux	10	**5**(25/)**7**(30)	55
3a	Na/PrOH/reflux	8	**8**	55
3b	Na/PrOH/reflux	10	**5**(30)/**8**(25)	55
3a	NaOMe/DMF/reflux	5	**6**	80
3b	NaOMe/DMF/reflux	10	**5**(30)/**6**(40)	70
3b	NaOMe/DMF/Cu	10	**6**	65
3b	NaOMe/DMSO/Cu	10	**6**	55
3b	NaOMe/Pyridine/Cu	10	**6**	60
3a	NaOEt/DMF	6	**7**	70

zophenone **3b** was re-examined in the presence of copper powder [17,18,21]. The copper assisted nucleophilic reaction involves a mechanism in which halogen displacement usually proceeds with decreasing rate of the reaction in the series I>Br>Cl>>F. Reaction of benzophenone **3b** with sodium methoxide in DMF in the presence of copper powder produced 1-methoxy-6-methylxanthone **6** in 65% yield. The same reactions in DMSO or pyridine afforded compound **6** in 55 and 60% yields respectively (Table 1).

It is remarkable that, the presence of copper powder did not affect the reaction of fluorobenzophenone **3a** with sodium alkoxides, so that compounds **6** and **7** were obtained in 80 and 70% yields from the reaction of **3a** with sodium methoxide or ethoxide in DMF respectively. An increase of the yields (~20%) was also observed in the copper-assisted reaction of **3b** with sodium ethoxide and propyloxide in DMF.

The preferential formation of alkoxy substituted xanthones during the reaction of benzophenones **3a** and **3b** with alkoxides, suggests that firstly an intramolecular displacement of one halo group occurred and the corresponding haloxanthones were produced. Then, these haloxanthones undergo a subsequent intermolecular nucleophilic substitution with alkoxides to give the alkoxy substituted xanthones **6**-**8**.

Conclusion.

In conclusion, we have found that methanesulfonic acid offers a convenient method for synthesis of halo substituted benzophenones which are easily converted into the halo substituted xanthones in the presence of K_2CO_3 in DMF. Nucleophilic aromatic substitution of these haloxanthones afforded a range of new substituted heterocyclic compounds in high yield and purity which are not available through other synthetic methods. In addition, the simplicity and convenience of this procedure make this new method a highly useful technique in organic synthesis.

EXPERIMENTAL

Solvents, reagents, and chemicals were obtained from Merck and Fluka chemical companies. Melting points were determined in open capillary tubes in a Buchi 510 circulating oil melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 781 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker Advance DPX FT 250 MHz, Jeol-EX 90Q (FT 90 MHz) and Hitachi R-245 (60 MHz) for solutions in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as internal standard. Mass spectra (MS) were obtained by a GCMS-QP 1000 EX at 20 and/or 70 ev. UV spectra were recorded on a UV/Vis spectrometer PU 8750. TLC were carried out on silica gel 60F-254 analytical sheets obtained from Merck chemical company. Column chromatography was carried out on the short column of silica gel 60 mesh in glass columns using 15-30 g of silica gel per one gram of crude mixture. Elemental analyses were performed at the National Oil Co. of Iran at Tehran Research Center.

Preparation of Halo Substituted Benzophenones **3a** and **3b** General Procedure.

To a well stirring solution of anhydrous methansulfonic acid (3 ml) were added halo substituted benzoic acid (0.01 mole) and *m*-cresol (0.01 mole, 1.08 g), and heated at 120 °C for 8 hours. Then the mixture was added to crushed ice (400 g) and the benzophenone was isolated either by filtration, or by extraction with $CHCl_3$ (3 × 100 ml). In the latter cases, the organic layer was washed with 10% sodium bicarbonate (3 × 50 ml), water (2 × 100 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under reduced pressure to give benzophenones **3a** and **3b**.

2,6-Difluoro-2'-hydroxy-4'-methylbenzophenone (**3a**).

Compound **3a** was obtained by following the general procedure with 2,6-difluorobenzoic acid and *m*-cresol in 60% yield as white solids; mp 100-103 °C (from ethanol 60%); R_f = 0.85 (CCl_4/MeOH-95:5); IR(KBr): 3300-2700(b, OH), 1645(s, C=O), 1610, 1580 (s,Ar), 1490(m), 1310(s), 1250(s), 1030(s), 800 cm^{-1}(s); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.32 (s,3H, -CH_3), 6.75 (d, 1H, J = 8.14 Hz, H-5'), 6.85 (s, 1H, H-3'), 7.25 (td, 2H, J_1 = 8.59 Hz, J_2 = 2.64 Hz, H-3 + H-5), 7.39 (d, 1H, J = 8.10 Hz, H-6'), 7.68 (m, 1H, H-4),11.07 (s,1H, OH); ^{13}C NMR (DMSO-d_6, 62.89 MHz): δ 21.77, 112.56, 118.84, 119.60, 121.38, 132.16, 133.18, 149.19, 156.82, 160.89, 190.78. UV(MeOH) λ 236(ε_{max}=11000), 267 nm (ε=8000); MS:m/z(EI) =248 (M^+,43), 247(20), 229(76), 228(28), 141(52), 135(100, base peak), 134(24), 113(33), 99(13), 77(57%).

Anal Calcd. for $C_{14}H_{10}O_2F_2$: C, 67.74; H, 4.03. Found C, 67.63; H, 3.92.

2,6-Dichloro-2'-hydroxy-4'-methylbenzophenone (**3b**).

Compound **3b** was obtained by following the general procedure with 2,6-dichlorobenzoic acid and *m*-cresol in 70% yield as white solids; mp 131-133 °C (from ethanol 60%); R_f = 0.8(CCl_4/MeOH-95:5); IR(KBr): 3200-2800 (b,OH), 1640(s, C=O), 1595, 1575(s,Ar), 1480(m), 1335(s), 1230(m), 1020(w), 800 cm^{-1} (s); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.35(s, 3H, -CH_3), 6.74(d, 1H, J = 8.2 Hz, H-5'), 6.86 (s, 1H, H-3'), 7.27 (t, 1H, J = 8.1 Hz, H-4), 7.57 (m, 3H, H-3+H-5+H-6'), 11.14 (s,1H, OH); ^{13}C NMR(DMSO-d_6, 62.89 MHz): δ 21.86, 118.00, 118.38, 121.60, 128.74, 130.68, 131.99, 137.72, 149.47, 161.61, 194.61; UV(MeOH) λ 271 nm(ε_{max}=10000); MS:m/z (EI) =283 (M^++2, 30), 281(M^+,22), 280(20), 247(30), 246(12), 245(100, base peak), 210(48), 209(10), 175(8), 173(15), 153(8), 152(10), 135(82), 107(26), 77(70%).

Anal. Calcd. for $C_{14}H_{10}O_2Cl_2$: C, 59.79; H, 3.56. Found C, 59.94; H, 3.85.

1-Fluoro-6-methylxanthone (**4**).

A mixture of benzophenone **3a** (248 mg, 1 mmol) and k_2CO_3 (138 mg, 1 mmol) in DMF (10 ml) was refluxed for 1 hour. Then water (100 ml) was added and the product was extracted by $CHCl_3$ (3 × 50 ml). The organic layer washed with 10% sodium bicarbonate (3 × 50 ml) and water (3 × 50 ml), dried over Na_2SO_4 and evaporated to give a white solid in 98% yield; mp 125-126 °C (from ethanol 70%); R_f = 0.7 (CCl_4/MeOH-95:5); IR(KBr): 1670(s, C=O, γ-pyrone), 1610(s, Ar), 1480 (s), 1420(m), 1305(m), 1250(w), 1180(w), 1050(s), 800 cm^{-1}; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.38 (s, 3H, -CH_3), 7.14 (m, 2H, H-2 + H-7), 7.23 (s, 1H, H-5), 7.33 (d, 1H, J = 8.5 Hz, H-4), 7.40 (m, 1H, H-3), 7.88 (d, 1H, J = 8.1 Hz, H-8); ^{13}C NMR (DMSO-d_6,

62.89 MHz): δ 21.6, 111.1, 111.4, 114.4, 117.6, 119.6, 125.8, 126.1, 135.7, 146.9, 155.0, 156.7, 158.7, 163.5, 174.0; UV(MeOH) λ 237(ε_{max}=10000), 266(ε=6000), 335 nm(ε=300); MS: m/z (EI) = 228 (M^+, 100, base peak), 213(13), 209(15), 199(54), 170(15), 140(45), 135(26), 134(17), 113(15), 100(17), 99(15), 76(18%).

Anal. Calcd. for $C_{14}H_9O_2F$: C, 73.68; H, 3.95. Found C, 73.50; H, 4.16.

1-Chloro-6-methylxanthone (**5**).

Compound **5** was prepared from chlorosubstituted benzophenone **3b** by following the above mentioned procedure within 2 hours and isolated by similar work up in 97% yield; White plates (from CH_2Cl_2/light petroleum ether or EtOH 79%); mp 139-140 °C; R_f = 0.72 (CCl_4/MeOH-95:5); IR(KBr): 1665(s, C=O, γ-pyrone), 1610, 1600(s, Ar), 1450(s), 1320(m), 1240(w), 1180(m), 900(w), 800 cm^{-1}(s); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.40(s, 3H, -CH_3), 7.17(d, 1H, J = 8.1 Hz, H-7), 7.25(s, 1H, H-5), 7.40(d, 1H, J = 7.8 Hz, H-4), 7.49(d, 1H, J = 8.5 Hz, H-2), 7.69(t, 1H, J = 7.7 Hz,H-3), 7.9(d, 1H, J = 8.0 Hz, H-8); ^{13}C NMR (DMSO-d_6, 62.89 MHz): δ 21.7, 117.5, 118.0, 118.2, 119.7, 126.1, 126.2, 127.3, 132.9, 134.9, 146.8, 154.6, 157.4, 174.6; UV(MeOH) λ 239 (ε_{max}=9500), 270(ε=5000), 340 nm (ε=3500); MS:m/z (EI) = 247 (M^++2, 30), 245(M^+, 100, base peak), 211(10), 210(50), 173(12), 152(10), 145(10), 135(82), 109(15), 107(26), 85(9), 81(9), 77(68%).

Anal. Calcd. for $C_{14}H_9O_2Cl$: C, 68.57; H, 3.67. Found C, 68.40; H, 3.45.

Nucleophilic Substitution of Haloxanthones **4** and **5**.

Preparation of Alkoxyxanthones (**6-8**).

General Procedure A: By F-Displacement.

To a well stirring solution of sodium (100 mg, 4 mmol) in alcohol (10 ml) was added xanthone **4** or benzophenone **3a** (0.001 mol) and heated at reflux temperature. The cold reaction mixture was poured onto crushed ice (100 g) and extracted with chloroform (3 × 50 ml). The organic layer was washed with water (2 x 50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated to give the corresponding alkoxysubstituted xanthones **6-8** in good yields.

General Procedure B: By Cl-Displacement.

A mixture of xanthone **5** or benzophenone **3b** (0.001 mol) and sodium alkoxide (0.01 mol) in dry DMF (10 ml) was refluxed. Then the reaction mixture was added to crushed ice (100 g) and the product was isolated the same as above (Scheme 1 and Table 1).

1-Methoxy-6-methylxanthone (**6**).

Compound **6** was prepared by following the general procedure **A** with methanol or sodium methoxide, within 5 hours, in 95% yield from **4**; white needles (acetone/petroleum ether); mp 116-121 °C; R_f = 0.32 (CCl_4/MeOH-95:5); IR(KBr): 2850(w, alkyl), 1660 (s, C=O, γ-pyrone), 1610, 1600(s,Ar), 1480(s), 1300(m), 1280(m), 1260(m), 1180(w), 1100(s), 950(m), 900(w), 800 cm^{-1} (s); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.40 (s, 3H, Me), 3.89 (s,3H, O-CH_3), 6.94 (d, 1H, J = 7.9 Hz, H-2 or H-4), 7.6(d, 1H, J = 8.1 Hz, H-4 or H-2), 7.18(d, 1H, J = 7.8 Hz, H-7), 7.28(s, 1H, H-5), 7.68(t, 1H, J = 8.0 Hz, H-3), 7.93(d, 1H, J = 7.8 Hz, H-8); ^{13}C NMR (DMSO-d_6, 62.89 MHz): δ 21.6, 56.5, 106.6, 109. 9, 111.9, 117.3, 120.6, 125.7, 126.1, 135.6, 145.9, 154.7, 157.6, 160.5, 174.8; UV(MeOH) λ 234 (ε_{max}=10000), 280(ε=5000), 345 nm(ε=3000); MS:m/z (EI) =241(M^++1, 12), 240(M^+,60), 211(48), 194(35), 181(20), 149(17), 135(10), 121(12), 111(20), 97(31), 81(100, base peak), 73(4%).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found C, 74.7; H, 5.2.

1-Ethoxy-6-methylxanthone (**7**).

Compound **7** was prepared by following the general procedures **A** with ethanol or sodium ethoxide, within 5 or 8 hours, in 95% yield from **4**; white needles (acetone/petroleum ether); mp 116-118 °C; R_f = 0.4 (CCl_4/MeOH-95:5); IR(KBr): 2840(w, alkyl), 1670(s,C=O, γ-pyrone), 1610, 1600(s,Ar), 1480(m), 1460(m), 1420(w), 1280(m), 1090(s), 800 cm^{-1} (s); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.42 (t, 3H, J = 6.6 Hz, CH_2-CH_3), 2.43 (s, 3H, Ar-CH_3), 4.14 (q, 2H, J = 6.7 Hz, -OCH_2-), 6.93 (d, 1H, J = 7.9 Hz, H-2 or H-4), 7.07 (d, 1H, J = 8.1 Hz, H-4 or H-2), 7.21 (d, 1H, J = 7.7 Hz, H-7), 7.31 (s, 1H, H-5), 7.66 (t, 1H, J = 8.0 Hz, H-3), 7.95 (d, 1H, = 7.9 Hz, H-8); ^{13}C NMR (DMSO-d_6, 62.89 MHz): δ 14.9, 21.6, 64.8, 107.5, 109.7, 112.1, 117.4, 120.5, 125.7, 126.1, 135.6, 145.9, 154.7, 157.7, 159.8, 174.7; UV(MeOH) λ 234(ε_{max}=11000), 280(ε=5700), 345 nm(ε=3500); MS:m/z (EI) =255(M^++1, 10), 254(M^+, 51), 239(100, base peak), 235(20), 226(50), 211(35), 210(47), 198(18), 197(19), 181(30), 169(18), 141(20), 115(40), 91(18), 75(22%).

Anal Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.5. Found C, 75.45; H, 5.6.

1-Propoxy-6-methylxanthone (**8**).

Compound **8** was prepared by following the general procedure **A** with propanol or sodium propoxide, within 8 or 10 hours, in 85% yield from **4**; white needles (acetone/petroleum ether); mp 112-115 °C; R_f = 0.5 (CCl_4/MeOH-95:5); IR(KBr): 2830(w, alkyl), 1670(s, C=O, γ-pyrone), 1610, 1600(s,Ar), 1470(s), 1420(w), 1290(m), 1270(m), 1110(w), 1090(s), 900(w), 800 cm^{-1}(s); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.08 (t, 3H, J = 7.20 Hz, -CH_2CH_3), 1.79 (q, 2H, J = 6.38 Hz, -CH_2-CH_3), 2.42 (s, 3H, Ar-CH_3), 4.03 (t, 2H, J = 5.76 Hz, -O-CH_2-), 6.92 (d, J = 8.04 Hz, 1H, H-2 or H-4), 7.07 (d, 1H, J = 8.24 Hz, H-4 or H-2), 7.20 (d, 1H, J = 7.73 Hz, H-7), 7.66(t, 1H, J = 8.26 Hz, H-3), 7.96 (d, 1H, J = 7.95 Hz, H-8); ^{13}C NMR (DMSO-d_6): δ 21.6, 22.4, 70.4, 107.3, 109.7, 112.1, 117.4. 120.6, 125.7, 126.1, 135.6, 145.9, 154.8, 157.7, 160.0, 174.8; UV(MeOH) λ 234 (ε_{max}=9500), 281(ε=4500), 344 nm(ε=3500); MS:m/z (EI)=268 (M^+,14), 240(20), 239(100, base peak), 225(50), 210(40), 197(29), 181(10), 169(25), 141(10), 115(33), 91(12), 75(10%).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.1; H, 5.97. Found C, 75.9; H, 5.56.

1-[2-(2-Hydroxyethoxy) ethoxy]-6-methylxanthone (**9**).

To a stirring solution of sodium (0.1 g, 4 mmol) in diethylene glycol (2 ml) was added xanthone **4** (95 mmol) in DMF (10 ml), and the reaction mixture was heated at 120 °C for 2 hours. Then water (200 ml) and HCl (1 ml, 0.5 *M*) was added and the product was extracted with ethyl acetate (3 × 100 ml). The organic layer was washed with water (2 × 50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated to give compound **9** in 92% yield. Viscous oil; R_f = 0.27(CCl4/MeOH-90:10); IR(KBr): 2850(w,alkyl), 1650(s, C=O, γ-pyrone), 1610(s,Ar), 1490(m), 1460(s), 1360(w), 1320(s), 1270(m), 1220(9s), 1150(s), 1030(s), 870(s), 780(m), 760 cm^{-1}(s); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.50 (s,3H,Me), 3.22 (br s,1H, OH), 3.82 (t, J = 7.5 Hz, 4H, -CH_2-O-CH_2-), 4.06 (t,J = 7.5

Hz, 2H, -CH_2-OH), 4.24 (t, J = 7.5 Hz, 2H, ArO-CH2-), 6.78 (s,1H), 7.03 (d,J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H); UV(MeOH) λ 233 (ε_{max}=10000), 278(ε=4500), 343 nm(ε=3000); MS:m/z (EI)=315(M^++H^+, 100, base peak), 314(M+, 28), 299(31), 268(5), 252(25), 239(23), 226(54), 198(20), 181(18), 168(16), 153(23), 115(37), 107(40), 91(42), 76(60%).

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.79; H, 5.7. Found C, 69.1; H, 5.36.

1-[(2-Aminoethyl)amino]-6-methylxanthone (**10**).

A stirring mixture of fluoroxanthone **4** (5 mmol), and ethylenediamine (0.05 mol) in DMF (10 ml) was refluxed for 3 hours. Then water (200 ml) was added and the precipitate was filtered off to give compound **10** in 88% yield; recrystallized from acetone/*n*-hexane as shiny yellow needles; mp 155-156 °C (dec.); R_f = 0.32 (CH_2Cl_2/MeOH-80:20); IR(KBr): 3600 (s, NH), 3320(d,NH_2), 2910, 2870(w,alkyl), 1630(s,H-bonded C=O, γ-pyrone), 1595(s,Ar), 1550(s), 1470(w), 1280(s), 1230(s), 1170(s), 1120(m), 1080(s), 940(s), 870(s), 790(s), 760 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.49 (br t ,2H, exchange NH_2), 2.49 (s, 3H, Me), 3.05 (t, J = 7.5 Hz, 2H, -CH_2-NH_2), 3.36 (dt, J_1 = 7.5 Hz, J_2 = 5 Hz, 2H, NH-CH_2-), 6.40 (d, J = 7.5 Hz, 1H, H-2 or H-4), 6.65 (d, J = 7.5 Hz, 1H, H-4 or H-2), 7.21 (d, J = 7.5 Hz, 1H, H-7), 7.39 (t, J = 7.5 Hz, 1H, H-3), 7.7 (s, 1H, H-5), 8.3 (d, J = 7.5 Hz, 1H, H-8), 9.67 (br s, 1H, exchange NH Ar); ^{13}C NMR (DMSO-d_6, 62.89 MHz): δ 21.7, 45.7, 101.9, 104.4, 106.1, 117.3, 119.5, 125.6, 125.7, 136.6, 146.1, 151.8, 155.1, 157.7, 178.8; UV(MeOH) λ 233(ε_{max}=112200), 268(ε=6000), 305(ε=2000), 404 nm (ε=3000); MS: m/z (EI)=268(M^+, 10), 251(10), 239(24), 238(100, base peak), 225(5), 210(25), 181(11), 123(5), 91(5), 76(5%).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97. Found C, 71.8; H, 5.63.

1-[2-(2-Aminoethyl)aminoethylamino]-6-methylxanthone (**11**).

A stirring mixture of fluoroxanthone **4** (5 mmole), and diethylenetriamine (0.05 mole) in DMF (10 ml) was refluxed for 2 hours. Then water (200 ml) was added and the precipitate was isolated by filtration to give compound **11** in ~95% yield; recrystallized from acetone/*n*-hexane as yellow needles; mp 110-111 °C (dec.); R_f = 0.3 (CH_2Cl_2/MeOH-80:20); IR(KBr): 3500-3400 (b, NH_2, NH), 2830(w, alkyl), 1630(s, H-bonded C=O, γ-pyrone), 1600, 1585(s, Ar), 1520(w), 1450(m), 1420(m), 1290(m), 1230(m), 1180(m), 1030(w), 950(m), 800 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.57 (br s, 3H, exchane NH_2, NH), 2.54 (s, 3H, Me), 2.83 (dt, J_1 = 7.5 Hz, J_2 = 5 Hz, 4H, -CH_2-NH+CH_2-NH_2), 6.57 (d, J = 7.5 Hz, 1H, H-2 or H-4), 7.16 (d, J = 7.5 Hz, 1H, H-4 or H-2), 7.37 (d, J = 7.5 Hz, 1H, H-7), 7.48 (t, J = 7.5 Hz, 1H, H-3), 7.74 (s, 1H, H-5), 8.24 (d, J = 7.5 Hz, 1H, H-8), 9.68 (br, s, 1H, exchange Ar-NH); ^{13}C NMR(DMSO-d_6, 62.89 MHz): δ 21.6, 45.8, 101.9, 104.4, 106.2, 117.2, 119.1, 125.4, 138.6, 146.1, 151.2, 155.04, 157.0, 178.2; UV(MeOH) λ 233(ε_{max}=10000), 278(ε=4500), 343 nm (ε=3000); MS:m/z (EI)=312 (M^++1, 1). 311(M^+, 1.7), 281(6), 252(11), 251(30), 239(73), 238(100, base peak), 225(6), 210(18), 181(9), 153(6), 115(37), 85(5), 73(36%).

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.45; H, 6.75. Found C, 69.15; H, 6.59.

Compound **11** was also obtained from chloroxanthone **5** under above mentioned conditions in 65% yield, but refluxing of 0.005 mole of compound **5**, K_2CO_3(0.005 mole) and diethylenetriamine (0.05 mole) in DMF or DMSO (10 ml) within 2-3 hours produced xanthone **11** in quantitative yield which isolated as the same above.

Di(6-methylxanthono) Sulfide (**12**).

To a stirring solution of haloxanthone **4** (1 mmol) in DMF (10 ml) was added sodium thioxanthate (5 mmol, 0.67 g) and heated under reflux for 5 hours. Then water (100 ml) was added and the precipitate was isolated by filtration to give compound **12** in 60% yield; pale yellow plates; mp 220-222 °C (dec.); R_f = 0.75(CCl_4/MeOH-90:10); IR(KBr): 1660(s, C=O, γ-pyrone), 1615, 1585(s,Ar), 1450(s), 1350(m), 1320(m), 1290(m), 1160(w), 1120(w), 950(s), 870(s), 780 cm^{-1}(s); ^{1}H NMR($CDCl_3$, 250 MHz): δ 2.5 (s, 6H, 2 x Me), 7.10 (d, J = 7.5 Hz, 2H, 2 × H-4), 7.28 (d, J = 7.5 Hz, 2H, 2 × H-7), 7.4 (s,2H, 2 × H-5), 7.54 (d, J = 7.5 Hz, 2H, 2 × H-2), 7.65 (t, J = 7 Hz, 2H, 2 × H-3), 8.01 (d, J = 7.5 Hz, 1H, 2 × H-8); ^{13}C NMR(DMSO-d_6 , 62.89 MHz): δ 21.7, 117.4, 117.6, 119.7, 120.0, 126.2, 127.8, 134.9, 146.9, 155.0, 157.6, 174.8; UV(MeOH) λ 210(ε_{max}=8500), 335 nm(ε=2000); MS: m/z (EI)=452(M^++2,12), 451(M^++ 1,35), 450(M^+, 100, base peak), 435(20), 433(8), 418(20), 316(13), 300(5), 242(40), 241(95), 226(10), 225(20), 210(18), 209(17), 181(11), 152(20), 115(8), 97(15), 83(25), 77(11), 73(11%).

Anal. Calcd. for $C_{28}H_{18}O_4S$: C, 74.66; H, 4. Found C, 74.21; H, 3.86.

Similarly, reaction of holoxanthone **4** or **5** (0.001 mol) with Na_2S (0.1 g) in DMF (10 ml) within 5 or 8 hours produced sulfide **12** in 45 and 30% yields respectively, which was isolated as the same above work up.

Acknowledgement.

Partial support of this work by Shiraz University Research Council and Professor N. Iranpoor for his helpful comments is gratefully acknowledged.

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