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9-(4-METHOXYPHENYL)XANTHEN-9-THIOL: A USEFUL REAGENT FOR THE PREPARATION OF THIOLS

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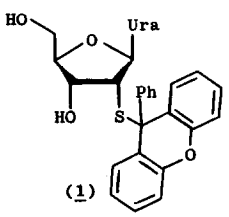
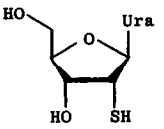
Summary: Treatment of 5'-chloro-5'-deoxynucleosides (5) with the conjugate base of 9-(4-methoxyphenyl)xanthen-9-thiol (3b), followed by acid-promoted removal of the 5'-*S*-[9-(4-methoxyphenyl)xanthen-9-yl] group in the presence of pyrrole gives the corresponding 5'-deoxy-5'-mercaptonucleosides (7) in good yields.

Thiols are of considerable importance both in chemistry and biology. It is not therefore surprising that, despite the variety of procedures already described in the literature for their preparation[1], new methods are still being investigated[2,3]. In this article, we describe what we believe to be a general method for the conversion of alcohols (*via* sulphonate esters[4] or alkyl halides) into the corresponding thiols. The present method is based on our previous observation[5] that treatment of *S*-(9-phenylxanthen-9-yl) derivatives of 2'-deoxy-2'-mercapto-nucleosides [e.g. (1)] with an excess of pyrrole in acetic acid solution at 70°C leads to the corresponding thiols [e.g. (2)] in good yields. It would appear from studies involving nucleoside derivatives[6] that it may be advantageous to generate the thiol function under acidic conditions as spontaneous aerial oxidation of thiols to the corresponding disulphides sometimes occurs readily in basic media.



(1)

Ura = uracil-1-yl



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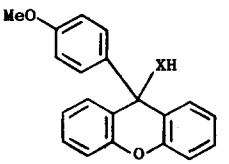
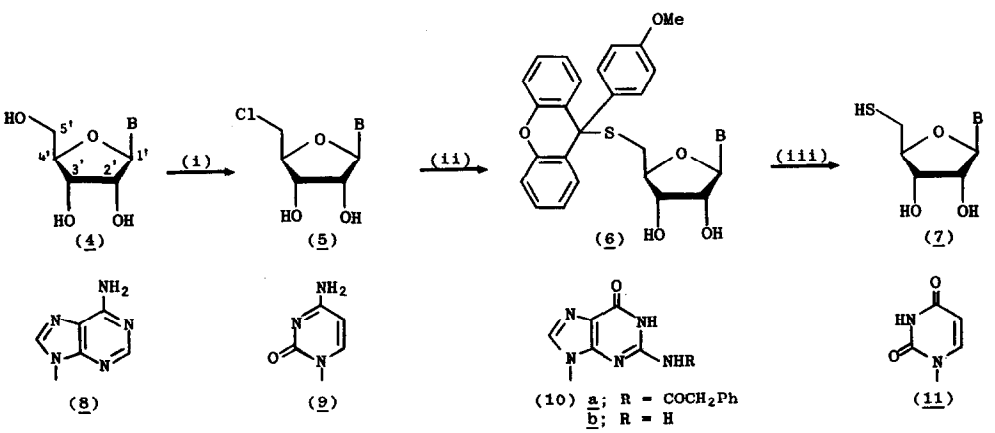


(3) a; X = O
b; X = S

The key reagent in the present study, 9-(4-methoxyphenyl)xanthen-9-thiol [AXT, (3b)] was obtained as a pure crystalline solid, in 89% isolated yield by treating 9-(4-methoxyphenyl)xanthen-9-ol[7] (3a) with hydrogen sulphide and dichloroacetic acid in dichloromethane solution at 0°C. The use of AXT (3b) in the transformation of alcohols into thiols is illustrated (see Scheme) in the conversion of common ribonucleosides (4) into the corresponding 5'-deoxy-5'-mercapto-derivatives (7). Adenosine (4; B = 8),

cytidine (4; B = 9), 2-*N*-phenylacetylguanosine (4; B = 10a) and uridine (4; B = 11) were converted by a modification [Scheme, step (i)] of Kikugawa and Ichino's procedure[8] into the corresponding 5'-chloro-5'-deoxynucleosides (5; B = 8, 9, 10a and 11, respectively) in satisfactory yields[9]. The latter compounds (5) were then allowed to react with a two- to three-fold excess of AXT (3b) and a smaller excess of N^1,N^1,N^3,N^3-tetramethylguanidine in an atmosphere of nitrogen, in dimethyl sulphoxide at room temperature for 3 hr. The nucleoside products were then treated (see below for an explanation) with triphenylphosphine [*ca.* 0.5 mol. equiv. with respect to starting material (5)] in glacial acetic acid at 50°C for 2 hr. After work-up and chromatography, the pure 5'-*S*-[9-(4-methoxyphenyl)xanthen-9-yl] derivatives[11] (6) of the corresponding 5'-deoxy-5'-mercaptoribonucleosides (7) were obtained in good [see Table] isolated yields. When the protected thiol derivatives [(6; B = 8), (6; B = 10b) and (6; B = 11)] were heated with an excess (*ca.* 8 mol. equiv.) of pyrrole in the presence of triphenylphosphine (*ca.* 0.2 mol. equiv.) in acetic acid-water (98:2 v/v) solution at 70°C for 3 hr, the pure 5'-deoxy-5'-mercaptoribonucleosides [(7; B = 8), (7; B = 10b) and (7; B = 11), respectively], free from the corresponding dimeric disulphides[12], were obtained and isolated in good yields [see Table][14]. Finally, 5'-deoxy-5'-mercaptocytidine (7; B = 9) was obtained and isolated as its pure hydrochloride salt [Table, entry no. 6], in 80% yield after (6; B = 9) had been allowed to react with a small excess of concentrated hydrochloric acid in 2-mercaptoethanol solution[5] at room temperature overnight.

Scheme



Reagents: (i) (a) $SOCl_2$, $(Me_2N)_3PO$, (b) NH_3 or aq. Et_3N; (ii) (a) $(Me_2N)_2C{=}NH$, AXT (3b), Me_2SO, N_2, RT, 3 hr, (b) Ph_3P, AcOH, N_2, 50°C, 2 hr; (iii) [for (6; B = 8), (6; B = 10b), and (6; B = 11)] pyrrole, Ph_3P, AcOH, N_2, 70°C, 3 hr.

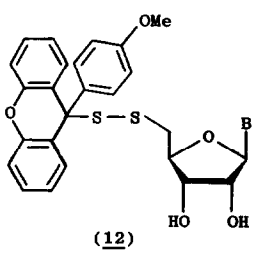
When the reaction between an activated nucleoside derivative [e.g. (5)] and the conjugate base of AXT (3b) proceeds slowly or if oxygen is not excluded from the reaction mixture, it is likely that the resulting *S*-[9-(4-methoxyphenyl)xanthen-9-yl] derivative

[e.g. (6)] will be contaminated with the corresponding disulphide[15] [e.g. (12)]. If the crude nucleoside products are then allowed to react with triphenylphosphine in acetic acid at 50°C [see above and Scheme, step (ii)(b)], sulphur is extruded from the disulphide to give triphenylphosphine sulphide and the pure *S*-[9-(4-methoxyphenyl)xanthen-9-yl] derivative[16] [e.g. (6)]. As triphenylphosphine is normally included in the reaction medium during 5'-unblocking [Scheme, step (iii)], it should not also be necessary to treat the products of the displacement reaction [step (ii)] with triphenylphosphine in acetic acid unless it is proposed to isolate the protected thiol [e.g. (6)] in a pure state.

TABLE. Yields and Physical Properties of Synthetic Products

Entry No.	Product	Yield (%)[a]	m.p. (°C)[b]	N.m.r. Spectroscopic Data[c] H-5'	-SH	C-5'
1	(6; B = 8)	88	183-184 dec.(MeCN)	2.42 (7.3, 12.6), 2.61 (6.5, 12.6)	-	33.24
2	(6; B = 9)	80	-	2.32 (7.7, 12.5), 2.50 (4.5, 12.5)	-	33.27
3	(6; B = 10b)	70	187-189 dec.(MeOH)	2.35 (7.2, 12.9), 2.55 (6.2, 12.9)	-	33.29
4	(6; B = 11)	82	127-129 (EtOH)	2.34 (7.3, 12.9), 2.53 (5.6, 12.9)	-	33.08
5	(7; B = 8)	82	75-77 (H_2O)	2.79 (6.3, 13.8), 2.88 (5.8, 13.8)	2.53	26.46
6	(7; B = 9)[d]	80	163-165 (EtOH)	2.78 (6.1, 13.9), 2.86 (4.9, 13.9)	2.55	26.10
7	(7; B = 10b)	85	>210 dec. (H_2O)	2.74 (6.3, 13.8), 2.83 (6.1, 13.8)	2.42	26.41
8	(7; B = 11)	85	173 (EtOH)	2.73 (6.1, 13.9), 2.81 (5.6, 13.9)	2.46	26.16

[a]The percentages indicated relate to isolated yields of (6; B = 8, 9, 10b and 11), based on (5; B = 8, 9, 10a and 11), respectively, and of (7; B = 8, 9, 10b and 11), based on (6; B = 8, 9, 10b and 11), respectively. [b]Crystallization solvents are indicated in parentheses; compound (6; B = 9), which was crystallized from propan-2-ol, sintered at ca. 130°C and then melted in the range 135-150°C. [c]N.m.r. spectra were measured in DMSO-d_6 solution with a Bruker AM 360 spectrometer. Coupling constants (in Hz, measured after the addition of D_2O) are given in parentheses. The 5'-deoxy-5'-mercaptoribonucleoside SH proton resonance signals are too close to the resonance signal of contaminating DMSO-d_5 to allow their multiplicities and coupling constants to be determined. [d]The data under entry no. 6 relate to the hydrochloride salt of (7; B = 9).



(12)

Although 5'-deoxy-5'-mercaptoribonucleosides (7) have previously been described[17,18] in the literature, it is not clear that any of this group of compounds have been fully characterized. In conclusion, we believe that the present method, involving the use of AXT (3b), is likely to prove to be of general application in the synthesis of thiols.

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9 The isolated yields of (5; B = 8), (5; B = 9), (5; B = 10a) and (5; B = 11) obtained by this procedure[8] were 76, 70, 90 and 55%, respectively; (5; B = 11) may be prepared in much higher yield by an alternative method[10].

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11 In the cases of (6; B = 8), (6; B = 9) and (6; B = 11), the products were treated with ammonia/methanol-dioxane after step (ii)(b) [see Scheme]; in the case of the guanosine derivative, the product (6; B = 10a) obtained was treated with methylamine, and crystalline (6; B = 10b) [Table, entry no. 3] was isolated.

12 Disulphides may be reduced to the corresponding thiols by treatment[13] with triphenylphosphine in protic solvents. A small quantity of triphenylphosphine has been added as a precaution against oxidative dimerization occurring during the course of these 5'-unblocking reactions. It appeared from t.l.c. evidence and from their ^{13}C n.m.r. spectra that the 5'-deoxy-5'-mercaptoribonucleosides (7) obtained [Table, entries nos. 5-8] were free from the corresponding dimeric disulphides which display characteristic C-5' resonance signals in the region of 40.7 - 41.0 p.p.m. [J.H. Marriott and C.B. Reese, unpublished observations].

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14 Satisfactory microanalytical data were obtained for all new compounds described.

15 When 5'-chloro-5'-deoxycytidine (5; B = 9) was stirred with AXT [(3b), 4.0 mol. equiv.] and triethylamine in dry dimethyl sulphoxide solution at room temperature with no particular care being taken to exclude atmospheric oxygen, a slow reaction ensued. Isolation of the nucleoside products gave a *ca.* 1:1 mixture of (6; B = 9) and what is believed to be (12; B = 9) in *ca.* 73% combined isolated yields. The H-5' and C-5' resonance signals [at δ 1.93 and 39.96 p.p.m., respectively] are believed to be characteristic of such 5'-disulphides (12). Under normal reaction conditions, with N^1,N^1,N^3,N^3-tetramethylguanidine as base [Scheme, step (ii)(a)], only *ca.* 5-10% of disulphide (12) is formed. It seems possible that the latter disulphides (12) may result from the formation of the conjugate base of (3, X = S_2) in the reaction medium before all the chloro-compound (5) has been consumed; (3, X = S_2) would be obtained if AXT (3b) underwent oxidative dimerization followed by the loss of one 9-(4-methoxyphenyl)xanthen-9-yl group.

16 Thus a mixture[15] of (6; B = 9) and (12; B = 9) was converted into pure (6; B = 9).

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