Application of Phase-Transfer Catalysis in the Acridine Series; I. *S*-Alkylation and *S*-Acylation of Thioacridone and of some Halogenated Thioacridone Derivatives

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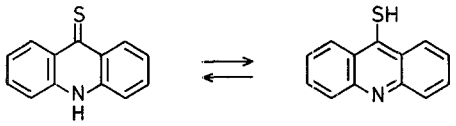
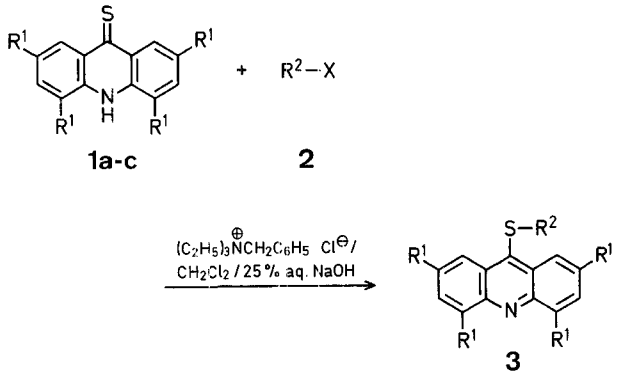
It is known that thioacridones react in alkaline medium like thiol anions, owing to the tautomerism shown below[1].



Thus, thioacridones can be *S*-alkylated and *S*-acylated under phase transfer catalysed conditions. In the present note we report on a number of such reactions according to the general scheme.



Alkylation or acylation of thioacridones is difficult, as the product acridine thioethers or thioesters undergo hydrolysis in alkaline medium. Thioethers are decomposed by hydrolysis into acridine and the corresponding mercaptan, whereas thioesters give thioacridones and the corresponding carboxylic acid[2].

Phase transfer catalysis may be a profitable means to avoid this hydrolytic decomposition, as it allows the alkylation or acylation to be carried out at low temperatures. Working at room temperature, satisfactory yields were obtained for thioacridone ethers, but only poor yields of unsubstituted thioacridone esters resulted. The yields were however practically quantitative in both cases, excepting *S*-aliphatic acyl derivatives, when the reaction was carried out at lower temperatures; between 0–5 °C the hydrolysis was completely suppressed. T.L.C. analysis of samples from the reaction mixture has shown that halogenated thioacridones react more slowly than their unsubstituted counterparts. On the other hand, halogenated thioacridone ethers are stable enough against hydrolysis to be prepared at room temperature.

Table 1. U.V. Spectra of Thioacridone and *N*-Methyl- and *S*-Methylthioacridone

Compound	λ_{max} (CH_3OH) [nm]
thioacridone	235, 282, 445, 480
N-methylthioacridone	240, 280, 455, 485
S-methylthioacridine	247, 255, 365, 389

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Table 2. Phase Transfer Alkylation or Acylation of Thioacridones

Substrate No.	R^1	R^2—X (2)	Reaction conditions (temperature/time)	Yield [%]	m.p. [°C] found	m.p. [°C] reported
1a	H	$(CH_3)_2SO_4$	0–5 °C/ 15 min	95	113–114°	113–114°[2]
1a	H	$(C_2H_5)_2SO_4$	0–5 °C/ 15 min	90	63–65°	65°[7]
1a	H	$C_6H_5CH_2Cl$	0–5 °C/ 15 min	98	106–108°	109°[2]
1a	H	CH_2=$CHCH_2Br$	0–5 °C/ 15 min	90	57–59°	—[a]
1a	H	C_6H_5COCl	0–5 °C/ 15 min	90	207–209°	209°[2]
1b	Cl	$(CH_3)_2SO_4$	20–25 °C/120 min	95	230–232°	233°[1]
1b	Cl	$(C_2H_5)_2SO_4$	20–25 °C/120 min	95	250–253°	251–252°[1]
1b	Cl	CH_2=$CHCH_2Br$	20–25 °C/120 min	90	210–212°	—[b]
1c	Br	$(CH_3)_2SO_4$	20–25 °C/120 min	90	272–274°	267°[1]
1c	Br	$(C_2H_5)_2SO_4$	20–25 °C/120 min	90	257–259°	253–254°[1]

[a] $C_{16}H_{13}NS$ (251.2) calc. C 76.49 H 5.17 N 5.57; found 76.00 5.05 5.33
I.R. (KBr): ν = 1588, 1420, 1300 cm^{-1}.

[b] $C_{16}H_9Cl_4NS$ (389.0) calc. C 49.40 H 2.31 N 3.60; found 49.22 2.15 3.19
I.R. (KBr): ν = 1590, 1419, 1300 cm^{-1}.

According to literature data, the alkylation of ambident anions of the type N—C—O under phase transfer catalytic conditions leads to a mixture of *N*- and *O*-alkylated products with the *N*-alkyl derivative predominating[3,4], whereas alkylation of ambident anions of the N—C—S type yields exclusively *S*-substituted products[5].

In the reactions investigated in the present work, alkylation also took place only at the S-atom, as demonstrated by the following data:

- T.L.C. of the crude reaction product shows the absence of *N*-substituted derivatives;
- the U.V. spectra of the reaction products support their acridine structure, and are markedly different from those of compounds with acridone-type structures (Table 1);
- there is a large difference between the melting points of *S*-substituted derivatives and those of *N*-substituted compounds, a fact that can be used in assigning the structural type of a given substance: *S*-methylthioacridine m.p. 113–114 °C, *N*-methylthioacridone m.p. 263 °C; *S*-ethylthioacridine m.p. 65 °C, *N*-ethylthioacridone m.p. 218 °C[6].

In contrast to the products obtained by acylation with aromatic acid chlorides, the corresponding aliphatic derivatives are very unstable. Thus, when the reaction was carried out at low temperatures with acetyl chloride as an acylating agent, T.L.C. analysis showed the conversion of thioacridone into the *S*-acetyl derivative, but we were not able to isolate this reaction product. However, the stability of *S*-aliphatic acyl derivatives was improved when reagents containing longer alkyl chains were employed; it was thus possible to isolate by preparative T.L.C. (working in a dark room) the *S*-propanoylthioacridine. This compounds undergoes rapid conversion into thioacridone in solution, in solid or adsorbed state. A better stability is displayed by *S*-hexanoylthioacridine, prepared in the same way; it can be kept for some time in solution but still decomposes rather rapidly in the adsorbed state. It is interesting to note that the aliphatic acyl derivatives are so unstable that even the basicity of the phase transfer catalyst can exert a negative influence on their formation; thus, when a larger amount of catalyst was used, a total lack of acylated product was observed, instead of the expected acceleration of the reaction.

The microanalyses for the isolated products were in satisfactory agreement with the calculated values and the U.V. spectra also supported the thioacridine structures.

Any attempt to prepare this type of compounds by classical methods was so far unsuccessful. The results of the alkylations carried out in this work are summarised in Table 2.

Alkylation or Acylation of Thioacridone (1a); General Procedure:
The alkylating or acylating agent **2** (1.5 mmol) is added to a mixture of dichloromethane (10 ml), 25% aqueous sodium hydroxide (10 ml), thioacridone (**1a**; 1.0 mmol), and triethylbenzylammonium chloride (23 mg, 0.1 mmol). This reaction mixture is stirred at the temperature given in Table 2, until no more thioacridone (**1a**) can be detected by T.L.C. analysis. The mixture is then diluted with water (10 ml), the organic layer separated, washed successively with dilute hydrochloric acid and water, then dried with anhydrous magnesium sulphate. The solvent and excess **2** are removed in vacuo, and the residue is purified by recrystallization from ethanol/water, acetone/water, or dioxan/water mixtures (charcoal added).

Alkylation of Halothioacridinones 1b, c; General Procedure:
The reaction is carried out as described above; part of the product is, however, obtained as a precipitate. This solid is filtered off and recrystallized together with the rest of the product obtained via concentration of the organic phase. T.L.C. analyses are run on plates covered with silica gel, eluting with 9:1, benzene/ethanol.

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