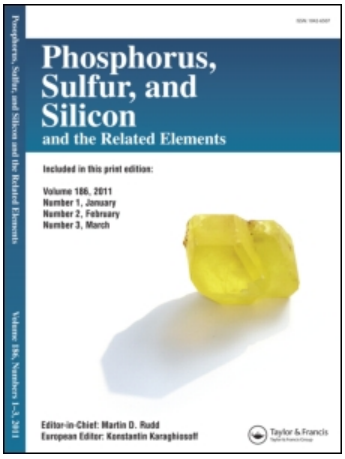

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SELECTIVE S-ALKYLATION IN PHASE TRANSFER CATALYSIS OF 2-PYRIDINE-, -PYRIMIDINE- AND BENZOXAZOLE-THIONE

Henri J. -M. Dou[a]; Parina Hassanaly[a]; Jacky Kister[a]; Jacques Metzger[a]
[a] Laboratoire de Chimie Organique A, Centre de St Jérôme, Marseille, France

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SELECTIVE S-ALKYLATION IN PHASE TRANSFER CATALYSIS OF 2-PYRIDINE-, -PYRIMIDINE- AND BENZOXAZOLE-THIONE

HENRI J.-M. DOU, PARINA HASSANALY, JACKY KISTER and JACQUES METZGER

Laboratoire de Chimie Organique A, Centre de St Jérôme, 13397 Marseille, France

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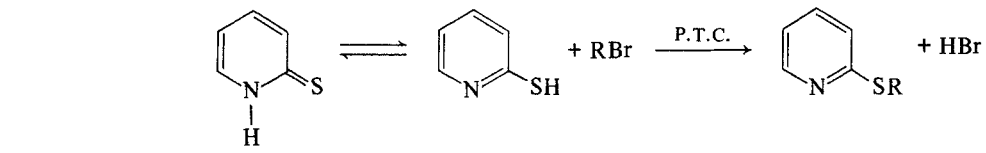
Alkylation via phase transfer catalysis of several ambident anions of the $|N-C-S|^-$ type leads exclusively to S-substitution. Yields obtained are better or equal to those given by conventional methods and experimental work-up is very much simplified compared to the latter.

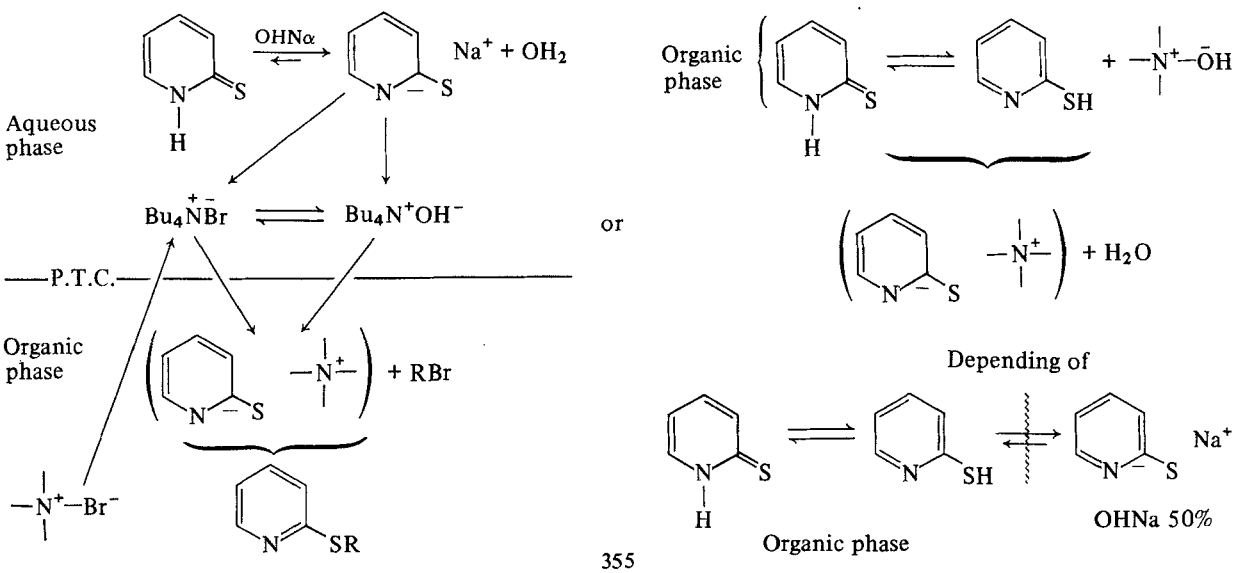
Phase transfer catalysis has been extensively used for C-alkylation reactions,[1-4] O-,[5-8] S-[9-11] and N-[12-14] alkylation. But, in the three latter cases, and especially in S-alkylation, only a few examples are available in the literature. S-alkylated heterocyclic compounds are important in the amplification phase of non-conventional photographic processes,[15] as substrates in conformational analysis[16] and for pharmaceutical and fungicidal use.[17-18]

We report in this paper the first example of S-alkylation by phase transfer catalysis of title compounds. Three main features can be emphasized:

1) only S-alkylation is detected;
2) yields are better than those obtained by conventional methods;
3) experimental work-up is very simple.

The reaction course is demonstrated by the following Scheme:





RESULTS

They are summarized in Table 1.

In the case of 2-alkylthio-pyrimidine, the products were purified by distillation or recrystallization to show the validity of the method. For the 2-alkylthio-pyridine, melting points of the picrates of the crude products agree with literature data. For the 2-alkylthiobenzoxazoles only spectroscopic data could be used for identification since the pk values of the bases did not allow the formation of the picrates. In this case, also, it was necessary to determine the threshold hydrolysis since the substrate is very sensitive to basic media. When 2 N sodium hydroxide is used, hydrolysis is achieved in 2 hours, but with 50% concentration (18 M) the hydrolysis is very slow.

The selective S-alkylation is not surprising, since for 2-pyridine-thione,[19] only thio-alkylation is obtained. But the experimental method is very useful, since the unreacted substrate remained in the sodium hydroxide. The only impurity (which can be removed by water washing of the organic phase) is the quaternary salt catalyst. The unreacted alkyl halide may be evaporated with the solvent if it has a low boiling point, or it is separated by distillation. This latter operation may even be avoided if the crude product is extracted from the reaction medium by hydrochloric acid.

EXPERIMENTAL

2-Pyridine, 2-benzoxazole-thione: 0.01 mole of substrate are dissolved in 100 cc of benzene and 0.01 mole of alkyl halide are added together with 0.0006 mole of tetrabutylammonium bromide (T.B.A.B.) and 50 cc of aqueous sodium hydroxide (18 M). The mixture is then stirred for x hours (see x in Table I). After reaction, the organic layer is separated, washed twice with water, dried over sodium sulfate and evaporated to yield the crude product.

TABLE I

S-Alkylation of 2-pyridine, -pyrimidine-, benzoxazole-thione

Alkyl halide[a]	Reaction time and temperature	2-Alkylthio-pyridine[d]		2-Alkylthio-pyrimidine[e]		2-Alkylthio-benzoxazole[d]	
Methyl iodide	24 h; 30°	*A*	78%				
	2 h; 40°			*B*	95%		
	24 h; 30°					*C*	80%
	4 h; 35°						81%
Ethyl bromide	24 h; 30°	*D*	78%				
	16 h; 30°			*E*	82%		
	5 h; 30°				78%		
i-Propyl bromide	10 h; 55°			*F*	72%		
Allyl bromide	18 h; 60°			*G*	85%		
	5 h; 60°				83%		
n-Butyl bromide	24 h; 50°					*H*	82%
	2 h; 60°						78%
	2 h; 60°			*I*	80%		
	30'; 30°[b]				60%		
	2 h; 62°	*J*	81%				
i-Butyl bromide	48 h; 60°	*K*	70%				
	48 h; 50°					*L*	57%
Benzyl bromide	24 h; 60°	*M*	69%				
	3 h; 60°		70%				
	1 h; 60°			*N*	75%[c]		

[a] *n*-Butyl and benzyl chlorides gave identical results, whereas iodides are catalyst poisons.
[b] To allow comparison with Ref. 9. Two-fold excess of *n*-butylbromide are used.
[c] Recrystallization in ethanol.
[d] Yields of crude products.
[e] Yields after distillation.

TABLE II

Melting point and boiling points of the 2-alkylthio-title compounds

Boiling points	Lit.	Melting points	Lit.
A:	100°/33 mmHg[20]	Picrate 148–50°	
B:	108–11°/28 mmHg[21]	Picrate 90°	91°[22]
C: 50–2°/0.02			
D:		Picrate 111°	113°[19]
E: 62°/0,1	115°/20 mmHg[23]		
G: 84°/0.2			
H: 130°/4	122°/3 mmHg[24]		
I: 120°/2			
J:		Picrate 111–2°	113°[19]
M:		Picrate 154°	155°[19]
N:		m.p. 56°	

TABLE III

n.m.r., m.s. and u.v. datas of the synthesized compounds

Compounds	n.m.r., m.s., u.v.
2-Pyridine-thione	n.m.r. ($CO(CD_3)_2$): 7.62–7.80 (m) 1H; 6.64–6.86 (m) 2H; 7.30–7.44 (m) 1H.
2-Methylthio-pyridine	*A*: n.m.r. ($CO(CD_3)_2$): 8.44 (d) 1H; 6.95–7.70 (m) 3H; 2.55 (s) 3H. m.s.: 39, 51, 52, 78, 79, 80, 92, 124, *125*.
2-Ethylthio-pyridine	*D*: n.m.r. ($CO(CD_3)_2$): 8.55 (d) 1H; 6.95–7.85 (m) 3H; 3.15 (q) 2H; 1.30 (t) 3H. m.s.: 39, 51, 52, 67, 78, 79, *106*, 111, 124, 138, 139.
2-*i*-Butylthio-pyridine	*K*: n.m.r. ($CO(CD_3)_2$): 8.44 (d) 1H; 6.95–7.30 (m) 3H; 3.92 (m) 1H; 1.40 (d) 3H; 1.52–1.80 (m) 2H; 1.0 (t) 3H. m.s.: 39, 41, 51, 52, 67, 78, 79, 80, 83, 93, 104, 106, *111*, 112, 124, 133, 138, 152, 167.
2-*n*-Butylthio-pyridine	*J*: n.m.r. ($CDCl_3$): 8.55 (d) 1H; 6.80–7.00 (m) 2H; 6.40–6.60 (m) 1H; 3.22 (t) 2H; 1.20–1.80 (m) 4H; 0.88 (t) 3H.
2-Benzylthio-pyridine	*M*: n.m.r. ($CO(CD_3)_2$): 4.45 (s) 2H; 8.38–8.44 (d) 1H; 6.86–7.60 (m) 8H. s.m.: 39, 41, 45, 50, 51, 52, 63, 65, 79, 80, 91, 110, 124, 164, *168*, 169, 186, 201.
2-Methylthio-pyrimidine	*B*: n.m.r. (C_6D_6): 8.14 (d) 2H; 6.30 (t) 1H; 2.38 (s) 3H. u.v. ethanol: 251, 287 (10,455, 1273).
2-ethylthio-pyrimidine	*E*: n.m.r. ($CDCl_3$): 8.50 (d) 2H; 6.95 (t) 1H; 3.18 (q) 2H; 1.41 (t) 3H. u.v. ethanol: 252, 282.5 (15,287, 1890).
2-*i*-propylthio-pyrimidine	*F*: n.m.r. ($CDCl_3$): 8.50 (d) 2H; 6.92 (t) 1H; 3.95 (sept.) 1H; 1.48 (d) 6H. u.v. ethanol: 253, 285 (19,678, 1876).
2-Allylthio-pyrimidine	*G*: n.m.r. ($CDCl_3$) 8.53 (d) 2H; 6.92 (t) 1H; 5.07–5.41 (m) 2H; 5.77–6.20 (m) 1H; 3.82 (d) 2H. u.v. ethanol: 251, 283.5 (16,117, 2068).
2-*n*-butylthio-pyrimidine	*I*: n.m.r. ($CDCl_3$) 8.51 (d) 2H; 6.95 (t) 1H; 1.31–1.95 (m) 4H; 0.97 (t) 3H. u.v. ethanol: 252.5, 283.5 (15,206, 1738).
2-Benzylthio-pyrimidine	*N*: n.m.r. ($CDCl_3$): 8.50 (d) 2H; 6.89 (t) 1H; 4.42 (s) 2H; 7.12–7.60 (m) 5H. u.v. ethanol: 253, 283 (17,025, 2597).
2-Benzoxazole-thione	n.m.r. ($CO(CD_3)_2$): 7.15–7.54 (m) 4H.
2-Methylthio-benzoxazole	*C*: n.m.r. ($CDCl_3$): 7.50–7.69 (m) 2H; 7.22–7.50 (m) 2H; 2.80 (s) 3H. m.s.: 63, 64, 79, 119, 120, 122, 132, 150, *165*.
2-*n*-Butylthio-benzoxazole	*H*: n.m.r. ($CO(CD_3)_2$): 7.48–7.70 (m) 2H; 7.20–7.48 (m) 2H; 3.36 (t) 2H; 1.30–2.10 (m) 4H; 0.96 (t) 3H. m.s.: 39, 41, 57, 64, 91, 122, 123, *151*, 152, 160, 165, 207.
2-*i*-butylthio-benzoxazole	*L*: n.m.r. ($CO(CD_3)_2$): 7.70–7.48 (m) 2H; 7.48–7.21 (m) 2H; 3.90 (m) 1H; 1.54 (d) 3H; 1.80 (m) 2H. m.s.: 39, 41, 57, 91, 122, *151*, 152, 153, 207, 208.

2-pyrimidine thione: 0.04 mole of substrate, 150 cc of benzene, 0.04 mole of alkyl halide, and 0.0024 mole of T.B.A.B. and 15 cc of aqueous sodium hydroxide (18 M) were work-up as above.

ANALYTICAL

The structures of the various products were determined by n.m.r. (XL 100, TMS as internal standard) and mass spectrometry (Varian Mat 111). For the 2-alkylthio-pyrimidines, u.v. data have been established, S-alkylation is demonstrated by n.m.r. since ^1H chemical shifts of protons adjacent to the sulfur atom showed the expected values, and mass spectrometry, where the usual pattern of the S–R structure is obtained. N-alkylation would afford a NCH_2-R' rupture.

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