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ONE POT CONVERSION OF ALKYL HALIDES INTO THIOLS UNDER MILD CONDITIONS

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Summary: Alkyl halides are converted into the corresponding thiols in good yields at room temperature under neutral conditions by reaction with 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione.

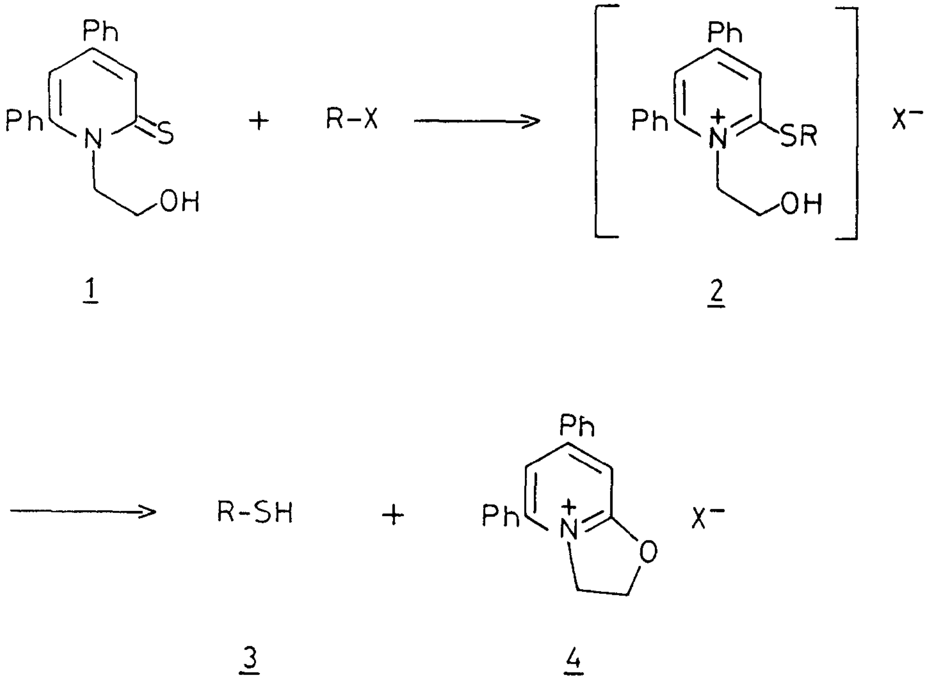
Thiol preparation from halides generally involves the formation of a C-S bond by nucleophilic displacement followed by the transformation of the resulting intermediate into a thiol. Widely used laboratory methods for the preparation of thiols include the reaction of alkyl halides with thiourea,[1] 1-methylpyridine-2-thione,[2] or 1,2-benzisothiazole-3(2H)-thione 1,1-dioxide sodium salt,[3] followed in each case by hydrolysis.

These methods often involve the isolation of the intermediate and its treatment under strongly acidic or basic conditions to induce hydrolysis. The mildest method currently available appears to be by the decomposition of alkyl halide-dimethylthioformamide adducts in neutral non-aqueous solvents.[4]

We now report that the use of 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione as reagent allows the one-pot conversion of n-alkyl chlorides, bromides and iodides into the corresponding thiols in good yield at 20°C and in neutral solution.

The reagent 1 is readily available. It is prepared from 4,6-diphenyl-2-pyrone[5] by reaction with P_4S_{10} which gives 4,6 diphenylpyran-2-thione,[6] converted by ethanolamine into 1.[7] The overall yield is 67% from 4,6-diphenyl-2-pyrone, and batches of 15g of 1 can readily be prepared.

Pyridine-2-thione 1 reacts with n-alkyl iodides or arylmethyl bromides in dry benzene at 20°C to give directly the corresponding thiols 3 together with the 2,3-dihydro-5,7-diphenyloxazolo[3,2-a]pyridinium salt 4 (Method A)[8] (see Table).



n-Alkyl chlorides or bromides do not react with 1 at a significant rate at 20°C in benzene. However, when benzene was replaced by acetonitrile as solvent, and tetraethylammonium iodide was used as a halide-exchange agent, the corresponding thiols were then obtained in 61-66% yields at 20 °C (Method B).[9] The results are summarised in the Table.

The present method which takes place under mild and neutral reaction conditions and requires only a simple work-up to afford the desired thiol, is thus a useful addition to the existing ones due its simplicity, convenience, and good yields.

Reagent 1 was designed to lead to the formation of the N-substituted 4,6-diphenyl-2-alkylthiopyridinium cation 2 as an intermediate susceptible to a facile intramolecular nucleophilic displacement to yield the corresponding thiol 3 and 2,3-dihydro-5,7-diphenyloxazolo[3,2-a]pyridinium cation 4.[10]

Earlier work in our groups has been concerned with the pyrylium mediated conversions of amines[11] and also with the analogous use of 4,6-diphenylpyran-2-thione via the corresponding N-substituted 4,6-diphenyl-1,2-dihydropyridine-2-thiones and their S-alkylated pyridinium salts.[12] One of our groups has also reported the reaction of 4,6-diphenyl-2-methylthiopyrylium cation with oxygen-containing nucleophiles leading to the displacement of methanethiolate ion to give O-substituted pyrylium salts.[13]

Table. Thiols from Halides and 1-Hydroxyethylpyridine-2-thione 1

Halide R	X	Reaction time (h)	Method	Thiol[a] Yield (%)
4-$ClC_6H_4CH_2$	I	3	A	89
4-$H_3CC_6H_4CH_2$	Br	10	A	76
$C_6H_5CH_2$	Br	20	A	80
4-$BrC_6H_4CH_2$	Br	20	A	74
4-$O_2NC_6H_4CH_2$	Br	20	A	67
n-C_6H_{13}	I	24	A	69
4-$BrC_6H_4COCH_2$	Br	10	A	72[b]
4-$ClC_6H_4CH_2$	Cl	24	B	72
n-C_4H_9	Cl	28	B	65
n-C_5H_{11}	Cl	26	B	61
n-C_6H_{13}	Br	24	B	66
n-C_7H_{15}	Br	26	B	65

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[a] Thiols were identified by IR and ^{1}H-NMR spectral comparison with authentic specimens. [b] Isolated as disulfide.

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7 Experimental for the preparation of 1: Ethanolamine (3.66 g, 60 mmol) was added to 4,6-diphenyl-2H-pyran-2-thione (13.2 g, 50 (mmol) in boiling methanol (250 ml) and the resulting mixture was heated at reflux for 5 h. After cooling volatiles were removed under reduced pressure and the residual material was thoroughly washed with water, dried under vacuum and the crude pyridine-2-thione 1 (12.75 g, 83%) thus obtained was used without further purification in the next step.

8. Preparation of thiols (Method A): The pyridine-2-thione 1 (1 mmol) was dissolved in dry benzene (40 ml), the appropriate alkyl halide (1 mmol) added, and the resultant solution stirred at 20 °C until 1 had completely disappeared from the reaction mixture (checked by t.l.c. analysis). The yellow 2,3-dihydro-5,7-diphenyloxazolo(3,2-a)pyridinium halide 4 precipitated, and was filtered off and washed with more benzene. The combined filtrate gave after solvent removal at 50°C, the nearly pure thiol 3 which was then distilled under reduced pressure. The halide salt 4 could, if desired, be purified by recrystallisation from methanol/diethyl ether.

9. (Method B): A mixture of 1 (1.3 mmol), tetraethylammonium iodide (1 mmol), acetonitrile (25 ml), and the appropriate alkyl halide (1 mmol) was stirred at room temperature (for reaction times see Table). Work-up was as in the Method A and the iodide salt 4 was filtered off. Solvent was removed from the filtrate and the residue was extracted with n-hexane (3x30 ml). After evaporation of the n-hexane, distillation gave the thiol of purity higher than 85% as checked by g.l.c. analysis.

10. Salt 4 X = I, pale yellow prisms (from methanol/diethyl ether) m.p. 213-5 °C. IR (Nujol): 3060, 1630, 1570, 1470, 1220, 970, 870, 770, 710, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$-TFA): = 8.0-7.4 (m, 12H); 5.20 (m, A_2B_2, 4H). $C_{19}H_{16}INO$ (401.25): Calcd. C, 56.87; H, 4.02; N, 3.49. Found C, 56.66; H, 3.95; N, 3.32%.

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