Nickel chloride catalyzed arylation of 3-mercaptopropionic acid: a facile one step route to 3-aryl mercaptopropionic acids from unactivated aryl halides and arenes

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Nickel chloride catalyzed arylation of 3-mercaptopropionic acid by (i) unactivated aryl halides (path a) and (ii) diphenyliodonium bromide (path b) gave 3-aryl mercaptopropionic acid (3) in good yield.

3- Aryl mercaptopropionic acids (3) are the key intermediates in the synthesis of thiochroman-4-ones (4). A variety of thiochroman-4-ones have been shown to exhibit antitumour, antifertility, anticonvulsant, antidepressant, antihypertensive, antiamebic, antimicrobial and anti-inflammatory properties. Our continuing interest in the synthesis of thiochroman-4-one derivatives, required a facile synthesis of 3. Nucleophilic displacement of halogen of activated aryl halides by 3-mercaptopropionic acid has been frequently used for the preparation of 3, however, this method suffers from a serious drawback as undesirable substituents remain associated to the aryl ring in the final product. Recently, a few techniques have been developed which do not require the presence of activating groups for the nucleophilic displacement of halogens from aryl halides. The use of arene tricarbonylchromium complex of aryl halide is one such technique which facilitates the nucleophilic displacement of halogen from arene substrates. But as hexacarbonylchromium complex is an expensive reagent, this process has not been economically viable for the large scale halide displacements. While looking for other possible facile and more practical procedures, we noticed that cuprous mercaptides have been used to effect the nucleophilic displacement of halides from unactivated aryl halides in pyridine : quinoline mixture to give the corresponding sulphides. In a quest to develop a procedure which avoided the preparation of cuprous mercaptides and generated 3 in one step directly from unactivated aryl halides and mercaptopropionic acid, we discovered in the present work that NiCl\textsubscript{2}.6H\textsubscript{2}O was a better catalyst (path a) to effect this reaction (Scheme 1).

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The procedure consisted of heating an equimolecular mixture of arylbromide/iodide (0.01 mol), 3-mercaptopropionic acid (0.01 mol) and catalytic amount of NiCl\textsubscript{2}.6H\textsubscript{2}O (0.001 mol) in pyridine : quinoline mixture (1:3, v/v, 10 ml) for 2 h. Addition of conc. HCl (10 ml) precipitated pure 3 from the reaction mixture in high yield. The procedure described opens the possibility of using an unactivated aryl halides for the preparation of 3. The process worked well on aryl halides containing electron releasing substituents. (Table 1a).

Arylation of mercaptans by diaryliodonium salts has been known. Phenylation of thioglycollic acid with diphenyliodonium chloride has been reported to give phenyl mercaptaeic acid. Use of copper oxide has been shown to catalyze the process. This result prompted us to use diphenyliodonium bromide for the phenylation of 3-mercaptopropionic acid through path-b with NiCl\textsubscript{2}.6H\textsubscript{2}O as a catalyst (Scheme 1). The procedure consisted of heating an equimolecular mixture of diphenyliodonium bromide (0.01 mol), 3-mercaptopropionic acid (0.01 mol)
and catalytic amount of NiCl$_2$.6H$_2$O (0.001 mol) in pyridine: quinoline mixture (1 : 3 v/v, 10 ml) for 2.5 h. Addition of conc. HCl (10 ml) precipitated pure 3a from the reaction mixture in a moderate yield (Table 1b).

Six coordinated nickel complexes of general formula NiL$_2$.6H$_2$O and Ni X$_2$L$_2$ have been reported with deprotonated ligands of mercaptaoacetic acids and mercapto succinic acids. We believe that a weak complex of Ni$^{II}$ species is formed from 3-mercaptopropionic acid, the active mercaptide centre of which enters into the nucleophilic displacement of X$^-$. As diaryliodonium salts are not readily available commercially and its preparation is cumbersome, we found path-a, a more practical and viable route for the preparation of 3.

Characterization of the products 3a-d was made by spectroscopic means as well as by direct comparison with authentic samples prepared through known routes.

**Experimental**

All the melting points are uncorrected. IR spectra were recorded on Pye Unicam Model SP3-300 infracord in nujol and on KBr pellets. $^1$H NMR spectra were recorded on Varian EM 360 L using CDCl$_3$ as solvent and TMS as internal reference.

**3-Phenyl mercaptopropionic acid (3a-d). General procedure**: 

Path-a: Aryl halide (1a-d; 0.01 mol), mercaptopropionic acid (1.06 g, 0.01 mol) and NiCl$_2$.6H$_2$O (0.23 g, 0.001 mol) were heated in pyridine: quinoline mixture (1 : 3 v/v) mixture (10 ml) for 2 h. Cooled mixture was acidified with conc. HCl (10 ml). The precipitated acid was filtered, dried and recrystallized from diethyl ether-petroleum ether mixture to give 3a-d in 85-73% yield.

| Compd. | R    | X     | Time (h) | Product | Yield% |
|--------|------|-------|----------|---------|--------|
| 1a     | H    | 1     | 2        | 3a      | 85     |
| b      | CH$_3$ | 1     | 2.5      | b       | 78     |
| c      | OCH$_3$ | 1     | 2.5      | c       | 76     |
| d      | NHCOCH$_3$ | Br | 3        | d       | 73     |

(b) 3-Phenyl mercapropionic acid (3a) from diphenyliodonium bromide (path-b)

2 – – 2.5 3a 42

#Products were duly characterized by elemental analysis, IR and $^1$H NMR spectral data and were compared with the authentic samples.

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