Tetrahedron Letters No. 38, pp 3463 - 3466, 1974. Pergamon Press. Printed in Great Britain.

# THE SELECTIVE ORTHO-FORMYLATION OF PHENOLS

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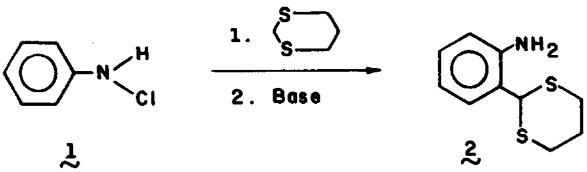
(Received in USA 9 July 1974; received in UK for publication 15 August 1974)

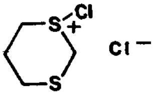
Recently, we described a process for the selective ortho-formylation of anilines.[3] This procedure involved the reaction of N-chloroanilines (1) with dithiane and base to produce the "protected" o-aminobenzaldehyde derivative 2. We now wish to report a major modification of this synthetic approach which permits the selective ortho-formylation of phenols.



1 2

Of the multitude of methods available for the introduction of the formyl moiety onto the aromatic nucleus, essentially all have limitations. In general, they either occur in poor yield, lack specificity, or are restricted to electron-rich aromatic compounds. One or more of these limitations can be associated with each of the most widely used reactions (Gattermann,[4] Gattermann-Koch,[5] Reimer-Tiemann,[6] Vilsmaier-Haack,[7] Duff[8,9]) for formylating aromatic compounds. Our selective formylation of anilines suggested to us that a related procedure, which would not be subject to the limitations described above, might be able to be developed for phenols.

Utilizing concepts developed for the alkylation of phenols,[10] we reasoned that the extension of our aniline formylation process to phenols would require use of either the chlorosulfonium chloride, 3, or of the salt, 4, formed through the reaction of N-chlorosuccinimide and



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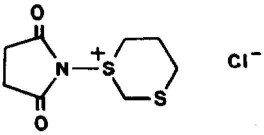

4

dithiane. In practice, 4 proved to be the reagent of choice. In a typical procedure, 1.7 equivalents of a phenol, 5, was allowed to react with 1.0 equivalent[11] of 4[12] for 15 min. at -70°. One equivalent of triethylamine was then added and the reaction mixture was allowed to warm to 25°. The reaction mixture was washed with water, and the organic phase was separated, dried, and concentrated. Chromatography of the crude residue gave the "protected" formylated phenol 6. The exclusive ortho-substitution pattern, and the ample mechanistic precedence provided by our previous work, suggested that this reaction was best viewed in terms of the initial formation of the oxosulfonium salt 7. Treatment of this salt with base should produce the ylid 9, which would be expected to spontaneously rearrange to give the dienone 10. Hydrogen transfer and concurrent rearomatization of the ring produced 6. The yields of 6 are listed in Table 1. Also shown in Table 1 are the yields obtained in the hydrolysis of the thioacetals to the

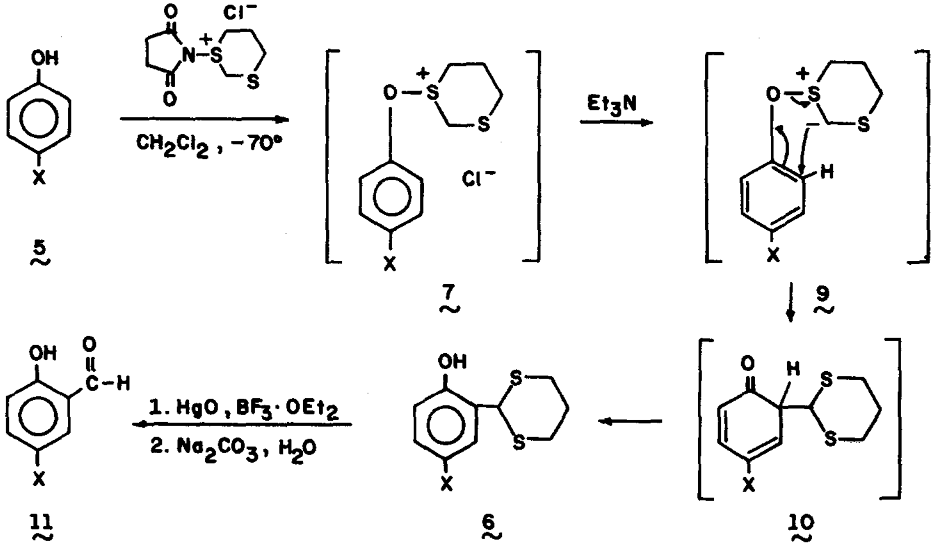

Table 1. Yields Obtained in the Formylation of Phenols.

| Phenol | X | % Yield of 6[a] | % Yield of 11 from 6 | Overall % Yield of 11 from 5 |
|---|---|---|---|---|
| 5a | p-Cl | 42 | 79 | 33 |
| 5b | H | 30 | 67 | 20 |
| 5c | p-$CH_3$ | 46 | 76 | 35 |
| 5d | p-$OCH_3$ | 39 | 78 | 30 |

a) % Yield of 6 was based on unrecovered phenol. The % conversion ranged from 64-74%.

corresponding aldehydes. The procedure used to accomplish this hydrolysis involved treatment of the thioacetal with mercuric oxide and boron trifluoride etherate followed by neutralization with aqueous sodium carbonate.[13] As can be noted from Table 1, the overall yields of 11 from 5 ranged from 20 to 35%.

In an alternate approach to the preparation of 11, we explored the oxidative conversions of 12. Previously, we had demonstrated that phenols could be ortho-methylthiomethylated (5 → 12) in good yield.[10] If the methylthiomethyl moiety of 12 could be specifically oxidized, a suitable "protected" aldehyde function should be generated. Prior to any oxidation, it was deemed necessary to protect the hydroxyl function. This was accomplished by acetylation of 12 to give 13. Oxidation of 13 was readily accomplished with N-chlorosuccinimide. Instead of attempting to isolate and purify the intermediate formed via the oxidative procedure, the crude product was hydrolyzed directly to the aldehyde in aqueous tetrahydrofuran at 100°. Table 2 gives the yields of 12, 13, and 11 obtained by this process. As can be noted from Table 2, the

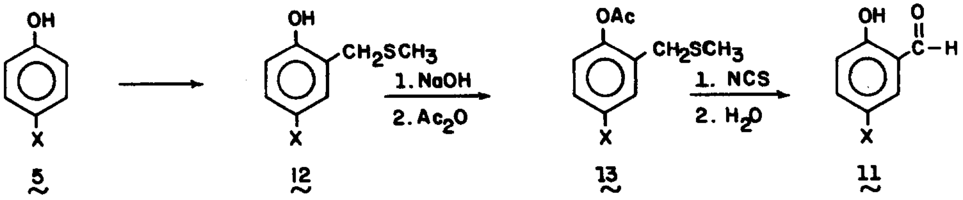

Table 2. Yields Obtained in the Formylation of Phenols.

| Phenol | % Yield of 12 from 5 | % Yield of 13 from 12 | % Yield of 11 from 13 | % Yield of 11 from 5 |
|---|---|---|---|---|
| 5a | 70 | 92 | 65 | 42 |
| 5b | 62 | 90 | 54 | 30 |
| 5c | 69 | 86 | 52 | 31 |
| 5d | 58 | 93 | 62 | 34 |
| 5e[a] | 72 | 90 | 48 | 31 |

a) o-nitrophenol

yields obtained through this procedure are relatively insensitive to substituent groups. Functionality varying from strongly electron-donating (methoxyl) to strongly electron-withdrawing (nitro) can be tolerated.

In summary, we have developed two new methods for the selective ortho-formylation of phenols. Based on our previous observations, we would expect these procedures to be applicable to a variety of hydroxylated aromatic compounds.

**Acknowledgement.** We are indebted to the National Cancer Institute and to the Institute of General Medical Sciences of the Public Health Service for partial support of this study.

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11. In a series of experiments, variation of the ratio of reagents indicated that the best yields were obtained using this ratio of phenol to sulfonium salt.
12. The preparation of **4** was readily accomplished by the mixing of N-chlorosuccinimide and dithiane in methylene chloride at -70°. The reagent was used *in situ*.
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