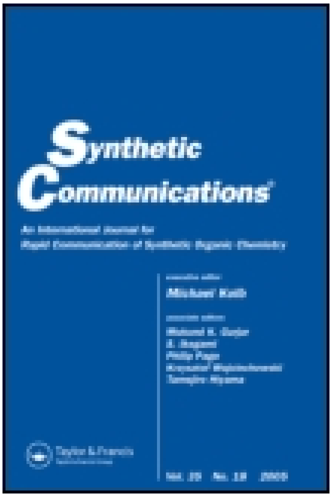

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: B. China Raju , Parvathi Neelakantan & U. T. Bhalerao (2004) A Facile and Convenient Method for the Synthesis of Nitro Phenols and Chloropyridinols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:16, 2903-2909, DOI: 10.1081/SCC-200026626

To link to this article: http://dx.doi.org/10.1081/SCC-200026626

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 16, pp. 2903–2909, 2004

A Facile and Convenient Method for the Synthesis of Nitro Phenols and Chloropyridinols

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ABSTRACT

An efficient, simple, and practical method of preparation of nitro phenols and chloropyridinols has been reported by the active chlorine displacement of chloro nitro benzenes and poly chloro pyridines in the presence of alkali metal hydroxide in low polarity solvent with very good yields.

Key Words: Nitro phenols; Chloropyridinols; Alkali metal hydroxide; Tertiary butanol.

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DOI: 10.1081/SCC-200026626
0039-7911 (Print); 1532-2432 (Online)

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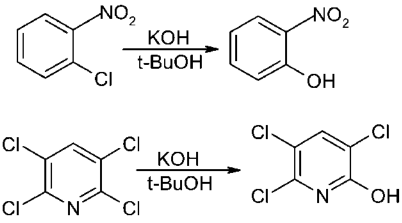
INTRODUCTION

Nitro phenols and chloropyridinols are important intermediates in organic synthesis for the preparation of various heterocyclic compounds with applicational importance in pharmaceuticals and agrochemicals. Nitro phenols are valuable intermediates in drugs,[1] adhesion inhibitors,[2] adhesives,[3] and antineoplastic agents.[5] Dinitro phenols and chloro nitro phenols are also valuable compounds as binding materials for glass fiber reinforced plastics[6] and as sea lamprey larvicides.[6] Chloropyridinols are most important intermediates for the synthesis of insecticides and herbicides.[7] The general method for the preparation of nitro phenols are nitration of phenols,[8] cleavage of phenolethers,[9] direct hydroxylation,[10] and nucleophilic displacement.[11] Among these methods, the widely used method is nucleophilic halogen displacement of chloro nitro benzenes and chloropyridines. A few reagents are reported for the preparation of nitro phenols and chloropyridinols by the nucleophilic displacement of chloro nitro benzenes and chloro pyridines using aqueous metal hydroxides with phase-transfer catalysts[11] and pressure reactions.[12] Our continuing interest in the preparation of pesticides[13] and pesticide intermediates,[14] have led us to report an efficient, simple, and practical method for the preparation of nitro phenols (**1b**–**3b**), chloropyridinols (**4b** and **5b**) from chloro nitro benzenes (**1a**–**3a**) and chloropyridines (**4a** and **5a**) in presence of potassium hydroxide in tertiary butanol (Sch. 1). The common method reported for the preparation of nitro aryl ethers are the nucleophilic aromatic substitution of chloro nitro benzenes with alkoxides.[15] Basani et al.[16] reported the reaction of 4-chloro nitro benzene with various alkoxides in the parent alcohols, a substantial yield of substitution product obtained only with ethoxide, where as dichloro azoxybenzene, dichloro azobenzene, and chloro anilines are the main products in 2-propanol and tertiory butanol. Paradisi et al.[17] achieved the substitution products and inhibited the formation of reduced products by using the phase-transfer catalysts. Under similar conditions, no substitution products was reported in tertiary butyl alcohol.



Scheme 1.

The attempted reaction of 2-chloro nitro benzene in the presence of alkali metal hydroxides in parent alcohols under reflux conditions gave substitution product 2-nitro anisole (74%) with methanol. Where as 2-ethoxy nitro benzene (30.6%), dichloro azobenzene (0.63%), and chloro aniline (8%) are the main products with ethanol. Dichloro azobenzene (10%) and chloro aniline (38%) are the only products with 2-propanol. Interestingly, under similar conditions, tertiary butanol gave only nitro phenol (74%) in good yield. This interesting reaction with potassium hydroxide in presence of tertiary butanol (Bottle grade) prompted us to study and explore the feasibility of this method to prepare industrially important intermediates such as 2-nitro phenol (**1b**), 2,4-dinitro phenol (**2b**), 5-chloro-2-nitro phenol (**3b**), 3,5,6-trichloro-2-pyridinol (**4b**), 3,4,5,6-tetrachloro-2-pyridinol, and 2,3,5,6-tetrachloro-4-pyridinol (**5b**).

In a typical procedure which involves the condensation of chloro nitro benzenes/chloropyridines with potassium hydroxide in the presence of tertiary butanol gave nitro phenols/chloropyridinols. The pentachloro pyridine (**5a**) yielded two isomeric products 3,4,5,6-tetrachloro-2-pyridinol and 2,3,5,6-tetrachloro-4-pyridinol (**5b**) was confirmed by its ^{13}C NMR, which agrees very well with that of reported values.[12a] These isomers were methylated with methyl iodide and the obtained products were confirmed by ^1H NMR. Two methoxyl groups appeared as separate singlets in the region of 3.80 and 4.04 in the ratio of 60 : 40.[18] Under similar conditions 2-chloro-5-methylpyridine[14d] (**6a**) and 2-chloropyridine (**7a**) failed to react. The important factor to be considering here is the presence of water in tertiary butanol (catalytic quantity). The rate of reaction has a direct effect on the water content in the medium. The presence of water more than the required amount decreases the yield of the alcohol formed. The results summarized in Table 1 clearly indicating the nucleophilic displacement of halogens with hydroxy group under reflux conditions. All the products were well characterized by its ^1H NMR, IR, and mass and compared with authentic samples.

In conclusion, potassium hydroxide in tertiary butanol was found to be mild and highly efficient for the synthesis of nitro phenols and chloropyridinols through the nucleophilic displacement reaction of chloro nitro benzenes and chloropyridines in good yields. The present method offers several advantages such as mild reaction conditions, cleaner reactions, and simple experimental procedures make this an attractive alternative to currently available methods.

EXPERIMENTAL

The ^1H NMR spectra were recorded on Gemini 200 MHz spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. IR spectra were recorded

Table 1. A facile and convenient method for the preparation of nitro phenols and chloropyridinols.

S. no.	Substrate	Product	M.p.°C Found (lit.)	Yield (%)	Reference
1	2-Chloro nitro benzene	Nitro phenol	43.8 (43–45)	70	[8]
2	2,4-Dichloro nitro benzene	2-Nitro-5-chlorophenol	41.5 (42–-43)	77	[10a]
3	2-Chloro-5-nitro benzene	2,4-Dinitro phenol	107.3 (106–108)	42	[10a]
4	2,3,5,6-Tetrachloro pyridine	3,5,6-Trichloro-pyridine	169–171 (106–108)	88	[11d]
5	Pentachloro pyridine	3,4,5,6-Tetrachloro pyridine	223–224	90	[7c]
		2,3,5,6-Tetrachloro pyridine	233–234 (220–221)		
6	2-Chloro-5-methylpyridine	—	—	—	
7	2-Chloropyridine	—	—	—	

Note: All the products were well characterized by IR, ^{1}H NMR, and MS and compared with authentic samples.

on a Nicolet 740 FT IR spectrometer and Mass spectra obtained on VG Micro mass 7070H. Melting points were obtained on a Toshniwal melting point apparatus and are uncorrected.

Typical Experimental Procedure

2,4-Dichloro nitro benzene (6.06 g, 0.032 mol) and potassium hydroxide (4.4 g, 0.078 mol) were refluxed in tertiary butanol (25 mL) for 10 hr. The reaction mixture was cooled, solvent removed under reduced pressure. The residue was dissolved in water (20 mL) and extracted with dichloromethane to remove the unreacted product. The aqueous layer was acidified with conc. hydrochloric acid and extracted with dichloromethane. The organic layer dried over sodium sulfate, concentrated and on flash chromatography afforded the 2-nitro-5-chloro phenol (**3b**, 4.23 g, 77%), m.p. 41.5°C, lit. 42–43°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.94 (d, 1H, aromatic), 7.18 (s, 1H, aromatic), 8.02 (d, 1H, aromatic), 10.62 (s, 1H, OH, D_2O exchangeable). IR (KBr): 3200, 1610, 1580, 1320, 1240 and 1180 cm^{-1} MS: m/e 173, 175 M+.

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Received in India April 12, 2004