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Chemo-and Regioselective Bromination of Aromatic Compounds in the Presence of γ -picolinium Bromochromate (γ -PBC) /CH₃CN

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ABSTRACT

Regioselective oxidative bromination of activated aromatic compounds has been studied using γ -Picolinium bromochromate in either CH₃COOH or CH₃CN is reported. The results obtained revealed excellent yields of monobromo compounds at *para*- position under thermal condition especially in methyl cyanide.

Key words: regioselective, oxidative, bromination, γ -picolinium bromochromate (γ -PBC), thermal condition.

INTRODUCTION

Brominated aromatic compounds are valuable intermediates in organic synthesis and they have been used widely in industrially important products and biologically active substrates as antitumor, antifungal, antibacterial, antiviral compounds,^{1,2} and also found in pharmaceutically and biologically important compounds.³ Until now various methods have been developed for the bromination of aromatic compounds using a variety of brominating agents under various conditions.⁴ Development of modern coupling reactions such as the Still-Kumada, Heck and Sonogashira reactions has greatly increased the demand for brominated aromatic compounds.⁵

Direct treatment of aromatic compounds with molecular bromine normally results in a mixture of mono-, di-, and polysubstituted products.⁶ In addition direct bromination of activated aromatic compounds by bromine generates hydrogen bromide, which is corrosive, toxic and pollutes the environment.⁷⁻⁹

To overcome these difficulties, numerous methods have been proposed to increase the selectivity and also the yields of the desired *para*-products.¹⁰⁻¹²

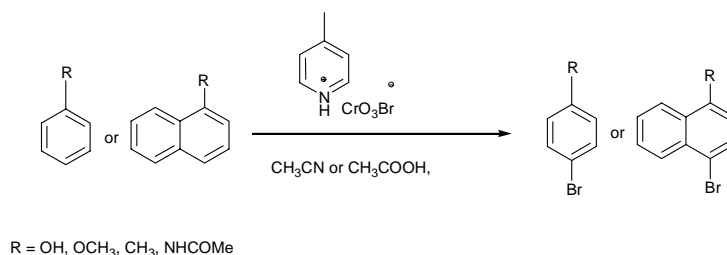
RESULTS AND DISCUSSION

There are many different methods available to brominating of aromatic compounds.

Some of them have regioselective with good yields.¹³⁻¹⁴

In order to this type of regioselective bromination of aromatic compounds, here we report

the use of γ -picolinium bromochromate as the source of bromine and oxidizing agent in either CH_3COOH or CH_3CN as solvents for the bromination of a number of activated aromatic compounds. (Scheme 1)



Scheme 1

The reagent was conveniently prepared by the reaction of equimolar quantities of chromium trioxide, 47% aqueous hydrobromic acid and γ -picoline (γ -PBC) in 88% yield.

γ -PBC is a dark brown solid, non-hygroscopic, air-stable and moderately light sensitive, which during preparation and storage should be protected from the light.

The chemo- and regioselective brominating ability of this reagent in the suitable polar solvents and under thermal condition for several aromatic compounds was investigated. The results are shown in Table 1.

However, in the other efforts when we utilized a CH_3CN instead of CH_3COOH surprisingly the yield of all reactions improved up to ~ 30-33% and the reaction times was also considerably reduced. The reactions were performed under reflux condition at 90 °C. As shown in Table 1, the methoxy benzenes were successfully reacted to afford the desired monobrominated products (Table 1, entries 1-5). *N,N*-dimethylaniline and *N,N*-diethylaniline gave mainly the *para* isomer as the major product (Table 1, entries 6 and 7). 1-Naphthol was also brominated in good yield (Table 1, entry 8). Acetanilide and 7-hydroxycoumarin gave the brominated compounds in good yields (Table 1, entries 9 and 10). Some other aromatic compounds such as phenol, 8-hydroxyquinoline, salicylanilide, 2,6-DMP, *m*-cresol, resorcinol, 3,5-xyleneol and 3-hydroxy-5-

methylphenol were quantitatively converted to the *para*-brominated products with respect to the hydroxyl groups (Table 1, entries 11-18). 2-Bromoethoxybenzene was quantitatively reacted to give the corresponding *para*-brominated product (Table 1, entry 19). When the amine substituent is available in the *para*-position of the aromatic ring and the substituents are huge, no reaction was observed and the starting material was recovered unreacted after 10h refluxing in either CH_3COOH and /or CH_3CN (Table 1, entries 20 and 21).


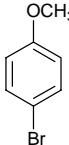


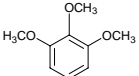
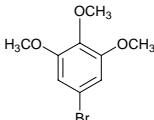
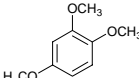
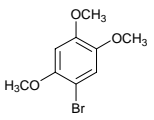
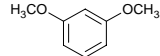
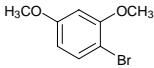

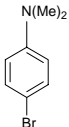

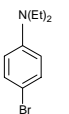

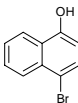
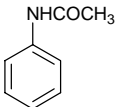
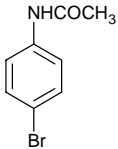
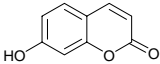
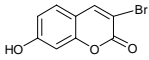
EXPERIMENTAL

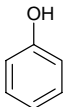
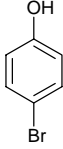
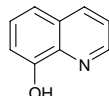
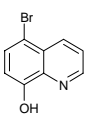
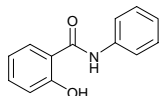
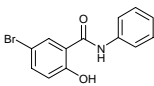


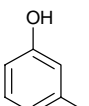
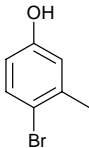
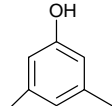
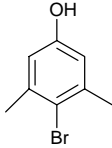
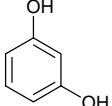
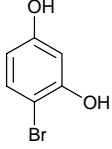
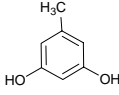
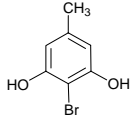
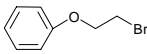
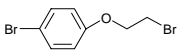
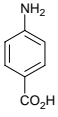
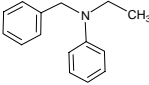
All products were identified by comparison of their spectral and physical data with those of the known samples.¹⁵ Melting points were measured on a Mettler Fp5 apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu IR-470 spectrophotometer. The ¹H NMR spectra were recorded on a Bruker 500 MHz instrument using solvent as internal standard (CDCl_3 at 7.31 ppm). Solvents were purchased from the Merck chemical company.

General procedure for the preparation of γ -picolinium bromochromate

To a cold (0°C) stirred solution of chromium trioxide (6.0 g, 60.0 mmol) in water (7.5 ml), 47% aqueous hydrobromic acid (6.9 g, 60.0 mmol) was slowly added. To this solution γ -picoline (5.7 g, 60.0 mmol) was added dropwise in 15min, and stirring was continued at 0°C for 3 hours. The reaction

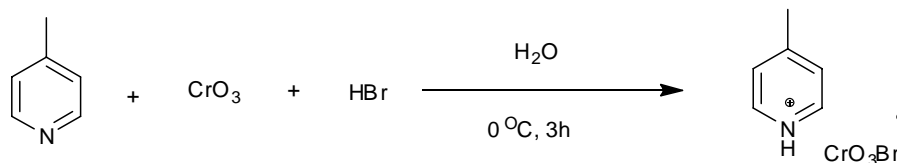
Table 1: Bromination of aromatic compounds with γ -PBC in CH_3COOH and CH_3CN under thermal condition

| Entry | Substrate | Product | CH_3COOH | | CH_3CN | |
|-------|---|---|--------------------------|-----------|------------------------|-----------|
| | | | Time (min) | Yield (%) | Time (min) | Yield (%) |
| 1 |  |  | 180 | 86 | 35 | 92 |
| 2 |  |  | 360 | 74 | 85 | 86 |
| 3 |  |  | 210 | 65 | 55 | 84 |
| 4 |  |  | 150 | 81 | 25 | 90 |
| 5 |  |  | 270 | 78 | 55 | 89 |
| 6 |  |  | 330 | 69 | 55 | 78 |
| 7 |  |  | 170 | 72 | 40 | 83 |
| 8 |  |  | 270 | 79 | 80 | 88 |
| 9 |  |  | 240 | 80 | 70 | 86 |
| 10 |  |  | 310 | 71 | 100 | 83 |

| | | | | | | |
|----|---|---|-----|----|-----|----|
| 11 |  |  | 150 | 81 | 65 | 87 |
| 12 |  |  | 260 | 63 | 110 | 76 |
| 13 |  |  | 420 | 67 | 50 | 86 |
| 14 |  |  | 140 | 75 | 75 | 87 |
| 15 |  |  | 250 | 74 | 50 | 83 |
| 16 |  |  | 190 | 78 | 75 | 86 |
| 17 |  |  | 120 | 84 | 35 | 89 |
| 18 |  |  | 110 | 84 | 55 | 87 |
| 19 |  |  | 240 | 73 | 50 | 84 |
| 20 |  | No Reaction | - | - | - | - |
| 21 |  | No Reaction | - | - | - | - |

mixture was evaporated at 60 °C under vacuum to produce a dark brown solid which was washed by

diethyl ether and dried by vacuum pump to give γ -picolinium bromochromate (14.5 g, 52 mmol) in 88% yield. (Scheme 2)



Scheme 2

Dark brown solid, Yield = 88%, m.p. 285 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 2.76 (s, 3H), 7.95 (d, 360. 2H, $J = 6.12$ Hz), 8.67 (d, 2H, $J = 6.12$ Hz); IR (KBr, v/cm^{-1}): 3400, 3050, 2900, 1605, 1495, 1040, 955, 760.

General procedure for the bromination with γ -PBC in $\text{CH}_3\text{CN}/\text{CH}_3\text{COOH}$ under thermal condition

To a magnetically stirred suspension of γ -PBC (20.0 mmol) in $\text{CH}_3\text{CN}/\text{CH}_3\text{COOH}$ (25 ml) was added aromatic substrates (10.0 mmol) (Table 1) in portions during 5 min. The reaction mixture was heated at 90 °C for the desired reaction time (Table 1), and the progress of the reaction was monitored by TLC (petroleum ether / EtOAc: 2/1). After completion of the reaction which was evidenced from the change in color of the mixture to green, the reaction mixture was poured into water (100 ml) and extracted by $(\text{Et})_2\text{O}$ (3 \times 20 ml). The combined ethereal extract was dried over MgSO_4 . The organic phase was evaporated by vacuum pump and purified by column chromatography (petroleum ether / EtOAc: 4/1) to produce the brominated products (Table 1).

Spectral Data of the Selected Products

4-Bromoanisole (Entry 1, Table 1)

Liquid. b.p. 215 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 3.77 (s, 3H), 6.78 (d, 2H, $J = 8.9$ Hz), 7.37 (d, 2H, $J = 8.9$ Hz); IR (KBr, v/cm^{-1}): 3300, 2860, 1590, 1487, 1289, 1239, 1070, 1033.

4-Bromo-methoxynaphthalene (Entry 2, Table 1)

Liquid. b.p. 146-147 °C, IR (KBr, v/cm^{-1}): 3350, 2930, 1590, 1475, 1120, 1040.

1-Bromo-2,3,4-trimethoxybenzene (Entry 3, Table 1)

Viscous oil. m.p. 75-75 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 3.84 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 6.58 (d, 1H, $J = 9.0$ Hz), 7.20 (d, 1H, $J = 9.0$ Hz); IR (KBr, v/cm^{-1}): 3020, 2870, 1580, 1220, 1070.

1-Bromo-2,4,5-trimethoxybenzene (Entry 4, Table 1)

Liquid. b.p. 263 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 3.81 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.54 (s, 1H), 7.01 (s, 1H).

3-Methoxy-4-bromoanisole (Entry 5, Table 1)

Liquid. b.p. 246 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 3.82 (s, 3H), 3.89 (s, 3H), 6.42 (d, 1H, $J = 2.2$ Hz), 6.45 (d, 1H, $J = 2.2$ Hz), 7.65 (d, 1H, $J = 8.8$ Hz).

***N,N*-Dimethyl-4-bromoaniline (Entry 6, Table 1)**

Viscous oil. m.p. 54-55 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 2.98 (s, 6H), 6.66 (d, 2H, $J = 8.9$ Hz), 7.37 (d, 2H, $J = 8.9$ Hz); IR (KBr, v/cm^{-1}): 3030, 2960, 1590, 1450, 1340, 1075.

***N,N*-Diethyl-4-bromoaniline (Entry 7, Table 1)**

Viscous oil. m.p. 67-68 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 1.14 (t, 6H, $J = 7.1$ Hz), 3.31 (q, 4H, $J = 7.1$ Hz), 6.54 (d, 2H, $J = 8.8$ Hz), 7.65 (d, 2H, $J = 8.9$ Hz); IR (KBr, v/cm^{-1}): 3100, 2930, 1589, 1489, 1360, 1070.

4-Bromo-acetanilide (Entry 9, Table 1)

Solid. M.p. 165-167 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 2.04 (s, 3H), 7.47 (d, 2H, $J =$

8.9 Hz), 7.56 (d, 2H, $J = 8.9$ Hz), 10.07 (s, 1H); IR (KBr, ν/cm^{-1}): 3300, 2900, 1640, 1590, 1483, 1070.

4-Bromophenol (Entry 11, Table 1)

Solid. M.P. 61-63 °C, $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 5.45 (s, 1H), 6.77 (d, 2H, $J = 8.9$ Hz), 7.38 (d, 2H, $J = 8.9$ Hz); IR (KBr, ν/cm^{-1}): 3350, 2960, 1530, 1490, 1250, 1070.

4-Bromoresorcinol (Entry 17, Table 1)

Solid. M.p 100-101 °C. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 6.36 (d, 1H, $J = 2.7$ Hz), 6.56 (d, 1H, $J = 2.7$ Hz), 7.25 (d, 1H, $J = 8.2$ Hz).

CONCLUSION

In brief, we have developed a simple reagent system, $\tilde{\alpha}$ -PBC as an efficient brominating agent for activated aromatic compounds at thermal condition. A notable advantages of this system lies in its ability to chemoselectively brominates of *para* vs. *ortho* positions, simple workup, good chemo-, and regioselectivity and the products readily available under CH_3CN as a solvent in short time and with high to excellent yields that make this method as a useful method.

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