Synthesis and Application of γ-Picolinium Bromochromate as a New, Mild and Regioselective Reagent for Bromination of Active Aromatic Compounds

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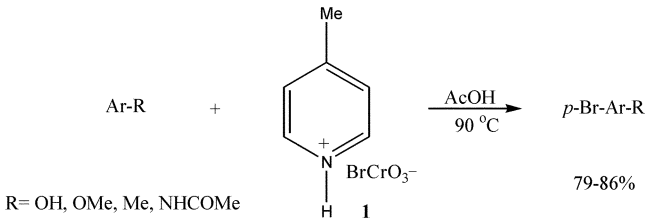
Brominated aromatic compounds are valuable intermediates in organic synthesis and they have been used widely in industrially important products and biologically active substrates as antitumor, antifungal, antibacterial, antineoplastic and antviral compounds.[1,2] The need for isomerically pure bromoaromatics has led to investigations into more selective brominating agents and several methods have been reported in the literatures. Reactions making use of organic ammonium tribromides (OATB) like tetrabutylammonium tribromide (TBATB),[3,4] 1,8-diazabicyclo[5.4.0]-tetrabutylammoniumtribromide,[5] pyridine hydrobromide perbromide,[6] methods employing anodic brominations in organic solvents,[7] and bromine trifluoride[8] have been fully investigated. Various methods of oxidative nuclear bromination of aromatic molecules have been developed including KBr-H_2O_2 using metal-oxo catalysts,[9] KBr-$NaBO_3 \cdot 4H_2O$,[10] ^{t}BuOBr-zeolite,[11] LiBr-$(NH_4)_2Ce(NO_3)_6$,[1] and Oxone-NaBr.[12] Quite recently, Firouzabadi and the coworkers have reported heteropoly acid cesium salt/cetyltrimethylammonium bromide as a catalytic heterogeneous system which highly controls regioselective bromination of aromatic compounds with bromine.[13] Some of these protocols suffer from harsh reaction conditions or cumbersome extraction procedures. Therefore milder and environmentally less toxic methods are desirable.

Following our continued interest in the development of mild and regioselective halogenating reagents,[14] herein we report synthesis and application of γ-picolinium bromochromate (γ-PBC) as a mild, efficient and highly regioselective oxidative mono-brominating reagent for the bromination of aromatic compounds. The reagent was conveniently prepared by the reaction of equimolar quantities of chromium trioxide, 47% aqueous hydrobromic acid and γ-picoline in 88% yield (m.p. 285 °C, decomposed)). γ-PBC is a dark brown solid, non-hygroscopic, air-stable and moderately light sensitive, which should be protected from the light during preparation and storage. The reagent is insoluble in THF, Et_2O, benzene, toluene, nitrobenzene, ethyl acetate and acetone, sparingly soluble in $CHCl_3$ and H_2O, soluble in DMF, DMSO. The pH value for 0.01 M water solution of γ-PBC is 3.37, and this value is higher than pyridinium chlorochromate (1.75),[15] pyridinium bromochromate (3.35 for 0.03 M aq. solution)[16] and lower than quinolinium bromchromate (QBC) (3.87).[16] The structure of the reagent (**1**) was confirmed by elemental analysis, ^{1}H NMR and IR (KBr) which clearly showed Cr=O stretching vibrations at 1040, 955 and 760 which is comparable with the related bands in QBC.[16]



Scheme 1

The brominating potential of this reagent in regioselective bromination of aromatic compounds in glacial acetic acid at 90 °C was investigated (Table 1). Our results indicate that γ-PBC monobrominate the active aromatic compounds in an oxidative bromination reacton conveniently. In this study the regent is *para*-selective and no trace of other regioisomers and dibromo products could be detected. However, acetophenone as aromatic substrate with electron withdrawing group gave a mixture of regio-isomers (*meta/para* ratio 3 : 1 by ^{1}H NMR) and highly deactivated aromatic compounds such as nitrobenzene entirely resist the bromination reaction.

Bromination of acetanilide was also conducted by γ-PBC in glacial acetic acid under microwave (MW) irradiation which provided *para*-bromoacetanlide in 85% yield. The reaction under MW was also *para*-selective and showed a considerable rate enhancement (Table 1) in comparison to thermal condition. Full investigation of application of this methodology to the bromination of aromatic substrates is in progress.

In conclusion, we have found γ-picolinium bromochromate as an easily accessible, mild, efficient and regioselective brominating reagent, which afforded the corresponding bromoorganics in good yields.

Experimental Section

General. Melting points were measured with Electro Thermal and are uncorrected. IR spectra were determined on Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Brucker AC, FT-NMR (500 MHz) in $CDCl_3$

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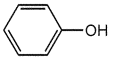
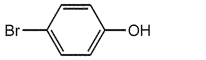
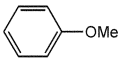
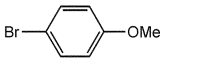
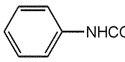
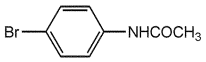
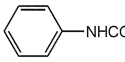
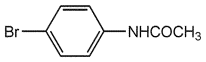
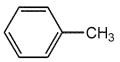
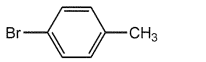
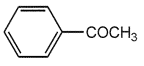
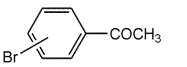
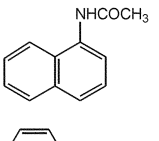
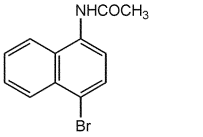
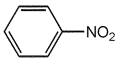
Table 1. Bromination of Aromatic Compounds by the γ-PBC Reagent (**1**)

Substrate	Product	Solvent	Time/h	Yield (%)[a,b]
		HOAc	2.5	81
		HOAc	3	86
		HOAc	4	80
		HOAc	0.13	85[c]
		HOAc	3.5	79
		HOAc	5.5	70[d]
		HOAc	4	82
	–	HOAc	6	–

[a]All products were analysed by comparison of spectroscopic data (IR, ^{1}H NMR) with authentic samples. [b]Isolated yield. [c]Bromination of acetanilide (10 mmol) in glacial AcOH (25 mL) by γ-PBC (20 mmol) under MW iradiation was completed in 8 min. producing *para*-bromoacetanilide in 85% yield. [d]Isolated as a mixture of *meta/para* (ratio 3 : 1) isomers.

with Me_4Si as internal standard. TLC was carried out on Merck Kieselgel 60H, F_{254}. All solvents used were dried and distilled according to standard procedures.

Preparation of γ-Picolinium Bromochromate (1). 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 drop wise in 15 min. and stirring was continued at 0 °C for 3 h. The 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, m.p. 285 °C (d); IR (KBr), 3400, 3050, 2900, 1605, 1495, 1040, 955, 760, 360 cm^{-1}; ^{1}H NMR (D_2O) δ ppm, 8.67 (d, J = 6.12 Hz, 2H), 7.95 (d, J = 6.12 Hz, 2H), 2.76 (s, 3H). Anal. calcd for $C_6H_8BrCrNO_3$: C, 26.28; H, 2.91; N, 5.11; Cr, 18.98. Found, C, 26.21; H, 2.73; N, 5.30; Cr, 18.67.

General Procedure for the Bromination by γ-Picolinium Bromochromate (1). To a magnetically stirred suspension of γ-picolinium bromochromate (20.0 mmol) in glacial acetic acid (25 mL) aromatic substrate (10.0 mmol) (Table 1) was added 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/ethyl acetate: 2/1). After completion of the reaction which was evidenced from the change in colour of the content to green, the reaction mixture was poured into water (100 mL) and extracted by ether (3 × 20 mL). The combined ethereal extract was washed with aqueous $NaHCO_3$, water and dried ($MgSO_4$). The organic phase was evaporated in vacuo and purified by column chromatography (petroleum ether/ethyl acetate: 4/1) to produce the brominated product (Table 1).

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