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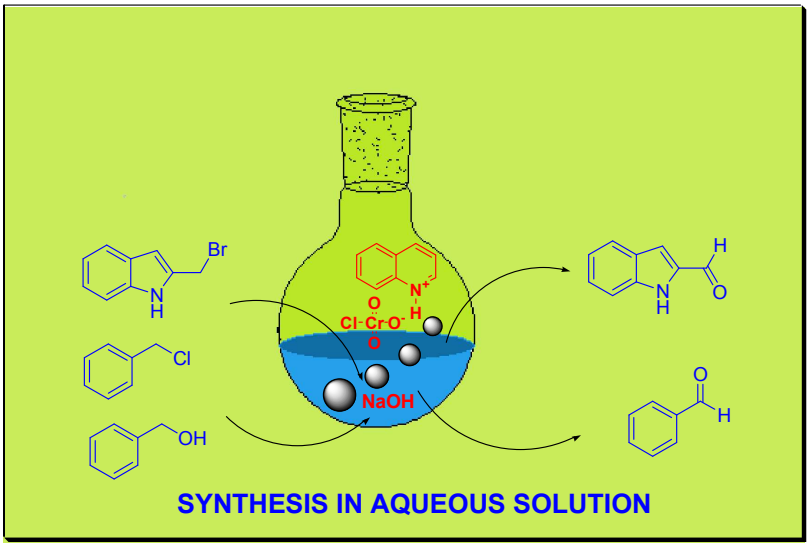

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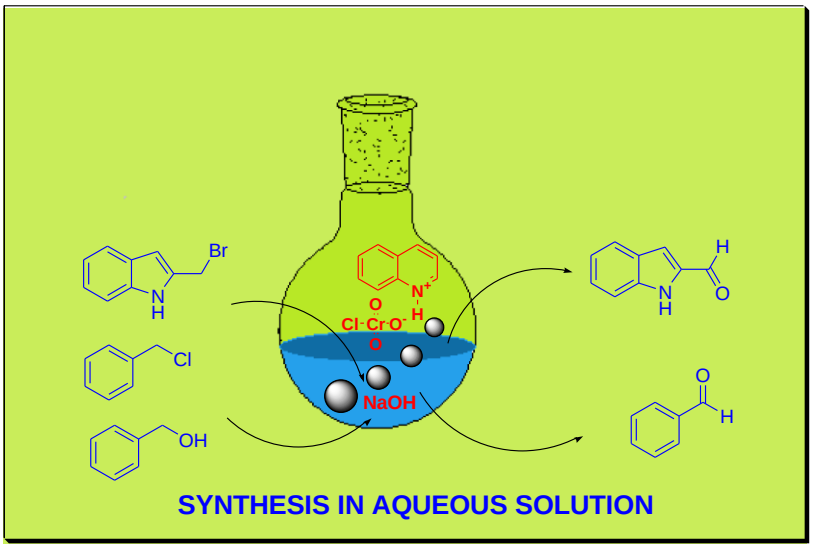

Using water as the only solvent for oxidation of alcohols and organic halides, a complete solventless process for the preparation of water immiscible aldehydes.

Oxidative transformation of alcohols and organic halides in aqueous solution

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Abstract: An efficient and new methodology for one pot conversion of organic halides and alcohols to their corresponding aldehydes or ketones has been developed using quinolinium chlorochromate in aqueous medium without adding any cosolvent. The same protocol has been applied further for the oxidative conversion of 2-(bromomethyl)-5,7-dinitro-1H-indole to its corresponding aldehyde in presence of sodium hydroxide.

Keywords: Aqueous media, quinolinium chlorochromate, oxidation, halides, aldehydes, Fischer indole synthesis, indoles.

Introduction

New and alternative ways for chemical synthesis[1] are in great demand for properly harnessing the benefits of chemistry and few such alternatives available are the use of new class of solvents such as ionic liquids, catalytic and atom economic reactions together with efficient energy techniques such as microwaves and ultrasonic irradiations. Adding to this context, organic transformations in aqueous media[2] have gained much attention in the last two decades. Water being a readily available, economical and harmless solvent, is the focus of synthetic chemists in recent times; and lot of chemical reactions previously considered impossible in water are feasible today. Few among these to list are benzoin condensation,[3] allylation reactions,[4-5] Suzuki Coupling,[6] Barbier type alkylation,[7] Friedel-Crafts[8] and Mannich reactions.[9]

The oxidative transformation of halides and alcohols to their corresponding carbonyl compounds is of great importance during the synthesis of fine or special chemicals such as medicinally or biologically active compounds, perfumes and agrochemicals.[10] Traditionally, the oxidation of alcohols was carried out by the use of metal based oxidizing reagents[11] such as those of chromium[12] [Cr(VI)] and manganese[13] [Mn (VII)]. In addition to these, recently other reagents such as tertiary butyl hydroperoxide[14] (TBHP), hydrogen peroxide[15] and sodium hypochlorite[16] are also utilized for these reactions, particularly in association with a catalyst.[17] On the contrary, oxidation of organic halides to the corresponding aldehydes and ketones is relatively difficult.[18] The classical methods for this transformation are the Hass-Bender[19] and

Sommelet reaction.[20] The obvious choice for these oxidative transformations were the Cr based oxidants such as Jones, Sarrett and Collins reagents.[21] Most of them are non-selective, undergo rapid deactivation and produce carboxylic acids as an end product. Controlled oxidation of alcohols or alkyl halides to aldehyde is a difficult task; and in order to overcome these limitations organic derivatives of Cr (VI) have been prepared and are being extensively used in non aqueous solvents[21] for different synthetic endeavors.

Chlorochromate, fluorochromate and dichromate derivatives of pyridine[22] and quinoline[23] are some of the noticeable organic derivatives of Cr (VI). These derivatives were found to be better in their reactivity and selectivity compared to the traditional Cr oxidants and offers a benefit of solubility in organic solvents. Recently, guanidinium chlorochromate [GCC] has been employed in presence of phase-transfer catalyst[24] for the oxidation of different benzylic and aliphatic alcohols in water. Pyridinium chlorochromate [PCC] has been used to oxidize 5,6-dihydropyrans[25] to corresponding anhydromevalonolactone in dichloromethane providing good to excellent yields. Quinolinium fluorochromate [QFC] was used for the oxidation of alcohols and phenanthrene[26] in dichloromethane. It was also used for the oxidative conversion of oximes, tosylhydrazones and N,N-dimethylhydrazones[27] to corresponding carbonyl compounds in good to excellent yields. Another analogue quinolinium chlorochromate [QCC] finds application in the mild and selective oxidation of alcohols,[28] aromatic anils,[29] lactic and glycolic acids[30] and Methionine,[31]all in non-aqueous organic solvents.

QCC is a yellow to brown solid, not much sensitive to moisture and stable[32] in aqueous solutions for considerable period. Quinolinium ion in QCC provides selectivity[28] and stability to the reagent in comparison to pyridinium and isoquinolinium analogues such as PCC and isoquinolinium chlorochromate [IQCC]. Quinolinium ion, in fact, is better in providing the selective oxidation of secondary alcohols in presence of primary and can be used for the oxidation of wide variety of substrates. This selectivity, probably, is a result of different charge densities on chromium center in various chlorochromate analogues. Quonlinium ion, being bigger in size in comparison to pyridinium ion, has lesser positive charge per unit area and hence stabilizes the negative charge in chromium center to lesser extent. The reagent is even more selective than IQCC, which is a result of different orientation of nitrogen atom[28] in the respective cations.

Kinetic study, during the oxidation of different substituted bezaldehydes under pseudo-first-order conditions using QCC, has revealed that both electron-releasing and electron-

withdrawing substituent can increase the rate of reaction. This indicates that reaction operates through two different mechanisms and the reagent is effective in performing the oxidation of electron rich and electron deficient substrates with equal ease. Certain oxidation reactions such as oxidation of 3-methyl-2,6-diphenyl-piperidin-4-ones[33] are accelerated by the presence of electron releasing substituents, which may be attributed due to increase of electron density in the reaction center. QCC is also employed for the oxidation of bezaldehyde[34] in the presence of cetyl trimethylammonium bromide in acidic aqueous solutions. Kinetic studies have revealed that the reaction rate is increased by the presence of surfactant due to the formation of micelles. Also, organic acids such as acetic acid decreases the rate of reaction in aqueous solutions.[35]

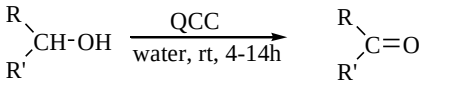
Most of the oxidations processes are either performed in organic solvents or in aquo-organic mixtures. Furthermore, methodologies describing oxidation in aquo-organic mixtures are mainly focused on kinetic studies and does not provide synthetic details. Simultaneously, no work addresses the problem of waste generation at the end of reaction. The work described in this paper has the potential to develop solventless synthetic procedure using QCC in aqueous solution, is equally effective for natural product synthesis and generates clean waste at the end of reaction. Due to the wide demand for developing new synthetic methodologies in aqueous media, and our continuing endeavors to use new and alternative media for organic synthesis[36-37] we are reporting to the best of our knowledge, the first use of QCC for the oxidation of different alcohols and halides in aqueous medium, without using any co-solvent.

Results and discussion

Organic reactions in aqueous media have attracted great attention in recent years because of the several benefits water offers as a solvent such as cost effectiveness, non-toxicity and simplified work up. Also, the miscibility of different organic salts such as ionic liquids[38] and chromium salts can be controlled by varying the cationic or anionic part. Prompted by this thought, we have utilized a mild and selective reagent QCC for developing a new methodology for oxidative transformations in water. Herein, we are reporting oxidation of different alcohols (**Scheme 1**) and halides without using any co-solvent in water at ambient temperature using QCC.

Initially, we prepared QCC by the reported method[23] and tested its effectiveness in water for the oxidation of 1 mol equivalent of benzyl alcohol at ambient temperature for 3 hrs and observed that its conversion to bezaldehyde was 50% as determined by ^{1}H NMR analysis. We were excited to see that the reagent is working effectively in pure water, and now our focus was

to increase the in solution yield further without adding any co-solvent. In this regard, we further increased the reaction temperature to 45-50°C, but no appreciable change was observed. Also, increasing the reaction time to 12 hrs did not bring any change in the yield. Finally, we were able to get the increased yield of benzaldehyde by taking 1.5 mol equivalents of QCC at ambient temperature (**Figure I**). We were able to oxidize variety of alcohols (1 mmol) with QCC (1.5 mmol) in water by stirring the contents at 25-30°C for 4-14 hrs and various results obtained are compiled in **Table 1**. The progress of the reaction was monitored by TLC and the isolated products were characterized by IR and ^{1}H NMR spectroscopy. Water immiscible liquid products, such as benzaldehyde, forms a distinct layer on water at the end of reaction and were recovered by distillation without using any organic solvent for extraction.



R= alkyl , aryl
R'= H, alkyl

Scheme 1: Oxidation of alcohols with QCC.

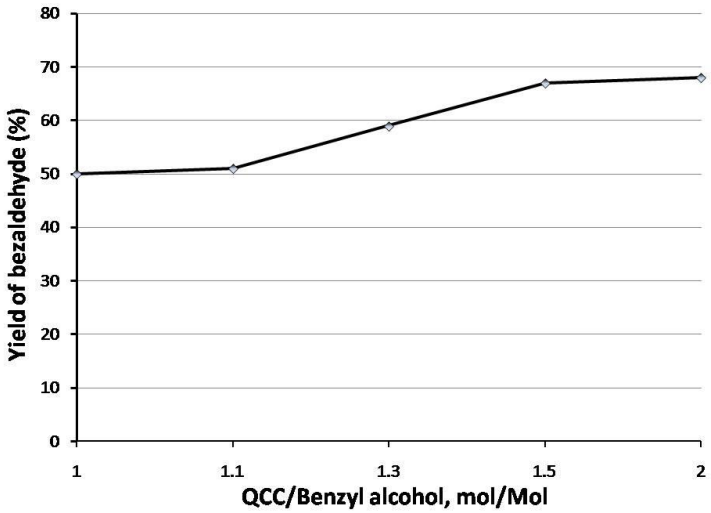


Figure I: Oxidation of 1 mmol of benzyl alcohol with different quantities of QCC.

Oxidation process in water is facilitated by the polar nature and stoichiometric use of QCC. It has the tendency to go into water and hence making the medium suitable for the organic reaction by increasing the solubility. Mechanistically, Oxygen atom in alcohol coordinates to the Cr (VI) atom forming the chromate ester by displacing chlorine, which then acts as a base, abstracting proton and finally results in the oxidation of alcohol to the respective carbonyl

compound. Non bonded electron pairs in organic halides may show similar interaction with Cr centre (**Figure II**), as shown by oxygen atom in alcohols, resulting in the formation of intermediate analogous to chromate esters. This can prove beneficial for the one pot conversion of halides directly to their corresponding carbonyl compounds (aldehyde or ketone), therefore we next attempted the conversion of benzyl chloride to benzaldehyde in water using QCC by keeping all the parameters constant. Contrary to our predictions no conversion to benzaldehyde was reported in this case. We also performed the reaction at elevated temperatures up to refluxing and by adding a co-solvent THF, but no conversion to aldehyde was reported.

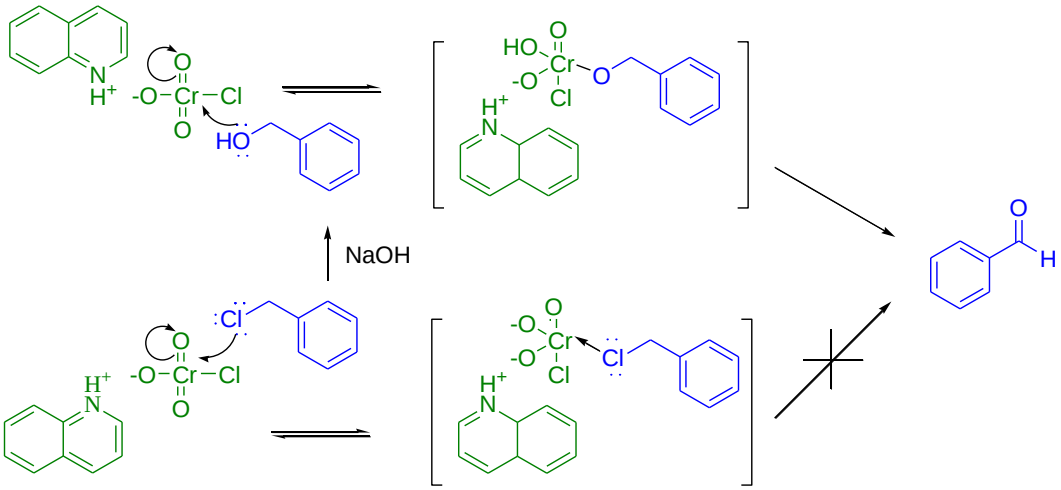


Figure II: Plausible complex formation by the interaction of alcohols and halides with QCC.

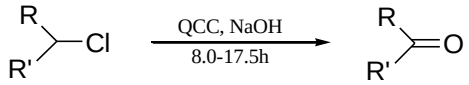
Table 1: Comparative yields during oxidation of alcohols with QCC.

S. No.	R	R'	Time (h)	Yield (%)
1.	C_6H_5	H	4	62
2.	4-$(CH_3O)C_6H_4$	H	4	81
3.	4-$(Cl)C_6H_4$	H	4	76
4.	4-$(NO_2)C_6H_4$	H	4	65
5.	Cyclohexyl (including C in general formula)	-	14	64
6.	C_2H_5	CH_3	14	77*
7.	C_5H_{11}	H	14	52

***Product was not isolated and only percentage conversion from ^{1}H NMR is reported.**

Addition of equimolar quantity of a hydroxide base may result in nucleophilic substitution of halide to corresponding alcohol that may be used *in situ* for the generation of bezaldehyde. Therefore, we next performed the reaction in basic medium by using one mole equivalent of NaOH at a temperature between 45-50°C, followed by the addition of QCC at room temperature resulting in very less conversion (<10%) of halide to aldehyde. We next doubled the molar equivalents of base with respect to halide and increase in product yield up to 38% was observed. Further optimization revealed that aromatic halides are converted into corresponding carbonyls in 7-8 hrs, whereas no conversion for aliphatic chlorides such as chlorohexane and 2-chlorobutane was observed under similar conditions. Thinking that solubility might hinder the oxidation process, we also attempted it in a mixture of water/THF (8:2), but no change was reported in this case.

Thus we were able to convert respective halide (1mmol) into aldehydes by stirring it with NaOH (2 mmol) in water (3 mL) at a temperature 45-50°C for 2.0-2.5 hrs followed by the addition of QCC (1.5 mmol) at room temperature (**Scheme 2**) and the results obtained are compiled in **Table 2.** The progress of the reactions was monitored *via* TLC and the isolated products were characterized with the help of IR and ^{1}H NMR spectroscopy. The reaction, plausibly, involves the nucleophilic displacement of halide with hydroxyl group (generated from NaOH) to form alcohol, which was *in situ* used for the oxidation.



R= alkyl , aryl
R'= H, alkyl

Scheme 2: Oxidation of halides with QCC.

To ascertain the efficacy of the process for organic synthesis and promote its use in process chemistry, we further applied the methodology for the oxidation of indole derivative namely 2-(bromomethyl)-5,7-dinitro-1H-indole (**3**), which was synthesized by Fischer indole synthesis.[39,40] Simultaneously this oxidation will open a route for the synthesis of 2-substituted indole aldehydes from corresponding halide in aqueous media that can further be used for the generation of chiral centre. In the first stage we prepared 1-bromopropane-2-one by the reported method[41] by adding bromine to acetone in presence of $CaCO_3$ at 0-5°C and then stirring the contents at room temperature for 3 hrs to afford crude product, which was purified by vacuum distillation.

We next synthesized the corresponding hydrazone 1-(1-bromopropan-2-yl)-2-(2,4-dinitrophenyl) hydrazine (**2**) by reacting equimolar amount of 2,4-dinitrophenyl hydrazine (**1**) with 1-bromopropane-2-one in ethanol in the presence of catalytic amount of acetic acid which was recrystallized in ethanol to afford pure product. Finally the corresponding halide **3** was obtained by cyclisation of the **2** at elevated temperature (115-125°C) with polyphosphoric acid (PPA) and was also purified by re-crystallisation in ethanol.

After the synthesis of the 2-(bromomethyl)-5,7-dinitro-1H-indole (**3**) we moved our attention towards its oxidation with QCC in aqueous medium under the optimized conditions (**Scheme 3**). We were successful in obtaining the corresponding carbonyl derivative **4** by reacting **3** with QCC in alkaline medium. Product formation at different stages was also ascertained by UV-visible absorption spectroscopy where the formation of indole nucleus in **3** was marked with a shift towards higher wavelength (**Figure III**). This shift is observed due to extending conjugation as we move from compound **2** to **3**. Also, the mass spectrum of **3** is very peculiar of the organic bromides where two peaks of equal intensity are observed at *m/z* 298 and 300.

Table 2: Comparative yields during oxidation of halides with QCC.

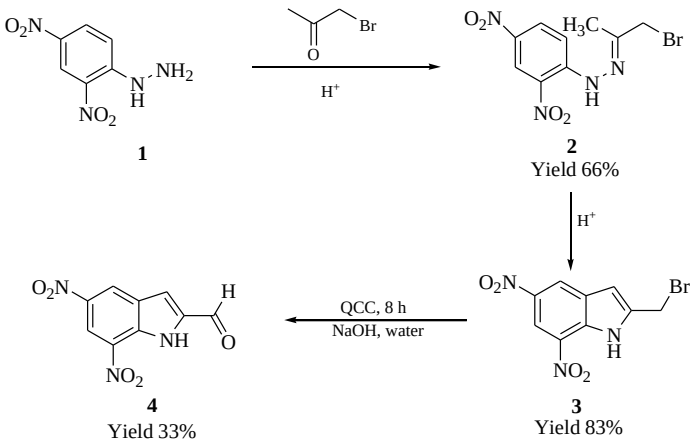
S. No.	R	R'	Time (h)	Yield (%)
1.	C_6H_5	H	8	38
2.	4-(Cl)C_6H_4	H	8	35
3.	Cyclohexyl (including C in general formula)	-	18	37
4.	C_2H_5	CH_3	18	-
5.	C_5H_{11}	H	18	-

In order to increase the scope of the developed methodology, we were interested in removing the chromium ions completely from the aqueous waste. Cr^{+6} has been considered as a toxic form whereas the Cr^{3+} has been considered an essential nutrient component for metabolizing[42-43] fats, sugars and proteins. In literature several methods are available for the removal of chromium such as ion exchange,[44] reverse osmosis,[45] adsorption[46] and the most common method for the removal of Cr^{+6} is its reduction to Cr^{3+} followed by its coagulation and

filtration. Various reducing agents including metal salts and metals themselves can be used for this purpose such as ferrous sulfate,[47] iron[48] etc.

The aqueous waste obtained in the reaction was first reduced to Cr^{3+} species which was subsequently removed from water. Initially, we determined the amount of Cr^{+6} leached into water[49] by dissolving a definite amount of QCC into water. We found that 60% of QCC remain suspended in water and 40% gets dissolved in it. The heterogeneous mixture was filtered to remove undissolved QCC. Filtrate, thus obtained, was reduced with $FeSO_4$ and coagulated by adding $Ca(OH)_2$. The precipitates were removed by filtration to remove solid waste and aqueous solution was checked for the traces of chromium ions that were found to be absent.

Once, we were sure that the method is capable to remove Cr^{6+} ions from water after reduction with $FeSO_4$, we next treated the waste generated at the end of the reaction. Reaction mass was first filtered to remove undissolved solid and the filtrate was then reduced with inexpensive $FeSO_4$. The solid precipitates obtained after coagulation with $Ca(OH)_2$ were removed by filtration and mother liquor obtained was found to be acidic (*pH*= 3.97). It was made neutral by adding 0.1N $Ca(OH)_2$ and finally discarded.



Scheme 3: Oxidation of 2-(bromomethyl)-5,7-dinitro-1H-indole with QCC.

Conclusions

We have developed a new protocol for the oxidative transformation of alcohols and organic halides to aldehydes using QCC in aqueous solution. The method is efficiently used under solventless conditions for the oxidation process and generates clean waste after its reduction with $FeSO_4$. The work demonstrates efficient use of QCC in natural product synthesis

and opens an insight into those reactions that need chromium species exclusively for their transformations such as 5-hydroxymethyl preparation[50] (5-HMF) from biomass resources.

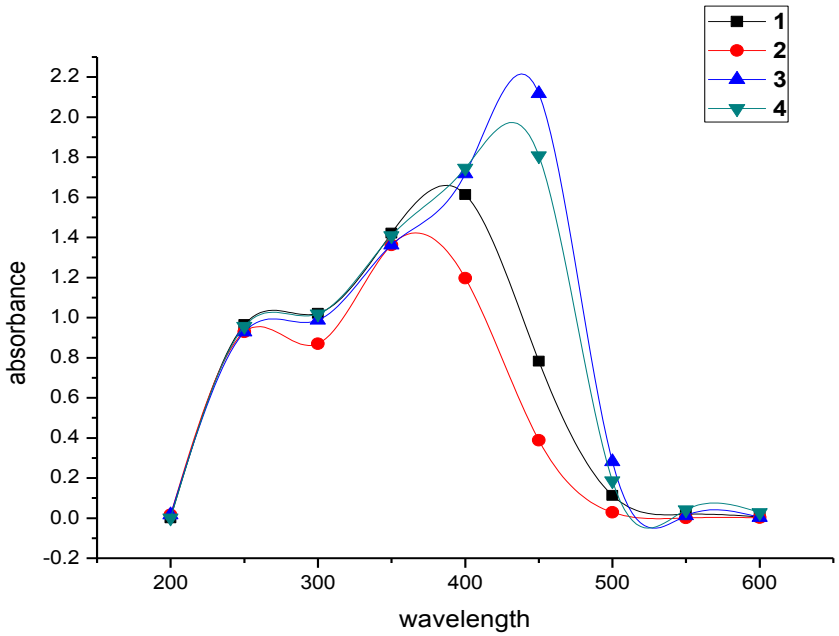


Figure III: Comparative UV-Visible absorption spectrum of 1, 2, 3 and 4.

Experimental

a) General procedure of oxidation of alcohols:

Alcohol (5 mmol) was added to water (15 mL) at room temperature followed by the addition of QCC (7.5 mmol, 2.02 g) and the mixture is stirred for the specified time (**Table 1**). After the completion of reaction as indicated by TLC, the crude product was extracted using diethyl ether (3×5mL) and the combined organic layer was washed with dil. HCl solution (5 mL), distilled water (2×5mL); and finally dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure followed by the chromatographic separation afforded the pure product.

b) Solventless procedure of oxidation of benzyl alcohol:

QCC (15 mmol, 4.04 g) was added to a mixture of distilled water (12 mL) and benzyl alcohol (10 mmol, 1.0 mL) and stirred at room temperature for 4 h. After the completion of reaction as monitored by TLC, upper organic layer of the product was separated from the aqueous layer and further washed with dil. HCl solution (5 mL) and distilled water (2×5 mL). Crude product thus obtained was further distilled to get pure benzaldehyde (0.53g, 52%).

c) General procedure of oxidation of halides:

Sodium hydroxide (10 mmol, 0.40 g) was added to a suspension of distilled water (15 mL) and halide (5 mmol) at a temperature between 45-50°C and stirred for 2.5 h, followed by the addition of QCC (7.5 mmol, 2.02g) at room temperature. The reaction contents were further stirred for the specified time (**Table 2**) and the progress of the reaction was monitored by TLC. Finally, the crude product was extracted using diethyl ether (3×5mL) and combined organic layer was washed with dil. HCl solution (5 mL), distilled water (2×5 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure afforded crude product which was purified by chromatographic separation.

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Notes and references

†for the spectroscopic data of indole derivatives and methodology used for the removal of chromium see supplementary information available at DOI: 10.1039/b000000x/

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