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<u>Abstract</u>

Tetrabutylammonium dichlorobromide: An efficient and mild reagent for *geminal* bromochlorination of α - diazo carbonyl compounds

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An efficient and mild one-pot procedure for *geminal* bromochlorination of α -diazo carbonyl compounds has been developed for the first time using tetrabutylammonium dichlorobromide (TBADCB) *via* metal carbenoids. This protocol was found to be highly selective and does not result in dichlorination or dibromination products. The reagent, TBADCB, is commercially available, easy to prepare and handle.

Tetrabutylammonium dichlorobromide: An efficient and mild reagent for *geminal* bromochlorination of α-diazo carbonyl compounds

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^b School of Basic Sciences, Vel Tech University, Avadi, Chennai, 600062 Key words: Geminal bromochlorination, Diazo compounds, Dichlorobromide.

Introduction of halogens on aliphatic chain or aromatic nucleus had always been of great interest due to their important biological activities.¹ Several natural products such as halomon, chloramphenical, nucleocidin, rogioloxepanes etc. have been found to possess halogens in aliphatic chain while several drugs and pesticides are found to have halogens in the aromatic nucleus.² Further, halides are highly versatile intermediates in organic synthesis due to its ability to act as leaving group.³ Even though, several methods and reagents are available for *vicinal* dihalogenation, ⁴ *geminal* heterodihalogenation is rarely studied.

Geminal heterodihalogenation is generally achieved by a two-step process comprising bromination followed by chlorination or vice versa.⁵ The major problems associated with this route are dihalogenation which reduces the yield considerably and difficulties in separation. Displacement of nitrogen from diazo compounds with halogens has also been understood as the simplest alternate method to access *gem* dihalogenation.⁶This reaction was further extended to interhalogen compounds such as ICl, IBr etc. to introduce two different halogen atoms to the same carbon atom. This reaction was used to synthesize several β -lactam derivatives such as penicillinates 1 and 2 (Fig. 1).⁷ Even though such reactions are known with ICl and IBr, stable and commercially available mixed halides, no attempt has been made to introduce Br and Cl since BrCl is a gas at room temperature and is not readily available.



Fig. 1

In this communication, we wish to report, for the first time, the use of tetrabutylammonium dichlorobromide, n-Bu₄N⁺BrCl₂⁻ (TBADCB) as a selective and efficient reagent to achieve *geminal* bromochlorination of diazo carbonyls and imines in good yields at mild condition. In continuation of our research on diazo compounds,⁸ we found that diazo compound **3a**, prepared from ethyl acetoacetate *via* diazo transfer reaction, reacts with TBADCB in the presence of Cu(OTf)₂ (5 mol%) at 40 °C in CH₂Cl₂ to give *gem* bromochlorinated compound **4a** in good yield (**Scheme 1**).⁹



Scheme 1: Geminal bromochlorination

In order to standardize the reaction condition we screened several catalysts such as Pd(PPh₃)₄, Rh₂(OAc)₄, Cu(hfacac)₂, CuI, Pd(dppf)Cl₂, Pd(OAc)₂, etc.¹⁰ that are known to form carbenoids with diazo compounds and the results are tabulated (**Table 1**). A control experiment was also carried out without catalyst and the reaction failed. It is noteworthy to observe that this *gem* bromochlorination required catalyst while Br₂, ICl, etc. reacts with diazo compounds in the absence of catalyst. Cu(hfacac)₂ and Cu(OTf)₂ gave comparable yields while CuI even at 20 mol% catalyst loading gave poor yield. Palladium catalysts were found to be not as effective as copper catalysts. To our surprise, Cu and Pd promote this reaction at different degree of oxidation. We presume that TBADCB might have oxidized Cu(I) and Pd(0) to result in Cu(II) and Pd(II) which promotes *geminal* bromochlorination. Rh₂(OAc)₄ was found to be highly reactive at higher temperature and gave several spots but proceeded smoothly to complete bromochlorination at 10 °C to furnish **4** in excellent yield (91%). Among the solvents, CH₂Cl₂ and CHCl₃ gave better yields while ethers gave moderate yields. When the reaction was carried out in toluene, a mixture of **4a** and 4-bromo toluene (36%) was obtained along with **4** (25%).



Table 1: Geminal Bromochlorination of Diazo compounds

^aDiazo compound (2 mmol), TBADCB (2.4 mmol), catalyst (5 mol%), solvent (6 ml), 40 °C, 2 h. ^bAll the solvents were properly dried and used. ^cYield refers to isolated yield. ^d20mol% CuI was used. ^eReaction was carried out at 10 °C with 2 mol% catalyst. ^f36% Bromo toluene was also obtained. ^gyield of bromo toluene was calculated based on TBADCB.

Encouraged with this result, to study the scope of this *gem* bromochlorination reaction, we screened several diazocompounds and the yields are presented in **table 2**. Both diazo carbonyls and diazo imines underwent bromochlorination smoothly under the reaction condition to give the products in good to excellent yields. Diazo compounds derived from 1,3 -diketones, β -ketoesters and 1,3-diesters all gave the *gem*-bromochlorination. Meldrum's acid derived diazo compound was found to be unstable under the reaction condition and failed to give the desired product. The bromochlorinated product from ethyl diazoacetate was purified using pentane and CH₂Cl₂. All the products were characterized properly by spectroscopic techniques such as ¹H, ¹³C NMR, IR and Mass spectra.

Since tetrabutylammonium dichlorobromide is well known to brominate anisole,¹¹ a reactivity study was carried out under the same condition. Accordingly, when TBADCB was

treated with diazo compound **3a** and anisole, 1 equivalent each, in the presence of catalyst $Cu(OTf)_2$ at 40 °C 4-bromoanisole was obtained as the major product (67%) while bromochlorination was obtained in 27% yield (Scheme 2).

A similar experiment was carried out with styrene and obtained the *vicinal* bromochlorination of styrene exclusively.¹² *Geminal* bromochlorination and cyclopropenation was not at all observed (**Scheme 3**), which clearly shows that the *vicinal* bromochlorination is extremely faster than *geminal* bromochlorination.



 Table 2:
 Geminal Bromochlorination of diazo compounds: Substrate Scope



Mechanistically, the reaction is expected to proceed through metal carbenoids **A** formed by the reaction of $Cu(OTf)_2$ with diazo compounds. Since the bromine atom in $BrCl_2^-$ is eletrophilic, proven by aromatic electrophilic substitution reactions of TBADCB, chlorine atom is expected to be nucleophilic and attack the carbenoid to form anionic intermediate **B** which adds to the electrophilic bromine atom to give the product **4** (Fig. **2**). Alternatively, it may also be expected to go through halogen insertion. Since halogen insertion takes place without catalyst and the present protocol for *geminal* bromochlorination failed in the absence of catalyst, we believe that this reaction proceeds through nucleophilic attack on carbenoids.



Fig. 2: Proposed Mechanism for gem bromochlorination

In conclusion we have developed a novel protocol for the *geminal* bromochlorination of diazo carbonyl compounds using a cheap, readily available and less toxic reagent tetrabutylammonium dichlorobromide. The reaction condition was mild and the product was formed with greater selectivity. Further, this methodology could be extended for *gem* iodobromination, *gem* iodochlorination, etc. by employing suitable ammonium mixed halides. The synthetic applications of gem α , α '-bromochlorinated carbonyl compounds are under investigation.

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- ⁹ To a solution of diazo compound and tetrabutylammonium dichlorobromide in CH₂Cl₂ at 40 °C was added copper (II) trifluoromethanesulfonate and the reaction mixture was stirred for 2 h. After completion of the reaction, the reaction was quenched, diluted with CH₂Cl₂ washed with water, brine, dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel) using pet. ether: ethyl acetate (95:5) to get pure compound.

Ethyl 2-bromo-2 chloro-3 oxo-butonate (4a): pale yellow liquid, Yield: 89%, **IR** (KBr) 2928, 1761, 1039, 754, 705 cm⁻¹. ¹**H NMR** (500 MHz, CDCl₃) δ 4.4 - 4.3 (q, 2H, *J* = 8.0 Hz), 2.55 (s, 3H), 1.37 (t, 3H, *J* = 6.8 Hz); ¹³**C NMR** (125 MHz, CDCl₃) δ 191.3, 163.3, 81.8, 64.6, 23.4, 13.7; MS (ESI): m/z calcd. for C₆H₈O₃BrCl 241, found 242 (M+1), 243 (M+2).

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