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REGIO-SELECTIVE BROMINATION REACTION OF HYDROXY ACETOPHENONES USING NBS AS BROMINATING REAGENT

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ABSTRACT
Freshly crystallized NBS has been used to brominate hydroxy acetophenone at low temperature in aqueous acetone as solvents. From experimental results it has been observed that NBS is excellent region-specific brominating reagent for ortho hydroxy acetophenones provided ortho position of hydroxy acetophenones must be unsubstituted. The bromination took place at adjourning position of hydroxy group of the hydroxy acetophenones and would provide quantitative yield when 1.2 equivalent NBS used as reagent. The temperature of reaction mixture has been maintained at 0 ^{0}C and reaction mixture has been stirred over a period of 12-48 h with the help of a stirrer. Twenty-five different kinds of hydroxy acetophenones have been used to study the reactions and to optimize the reaction condition.

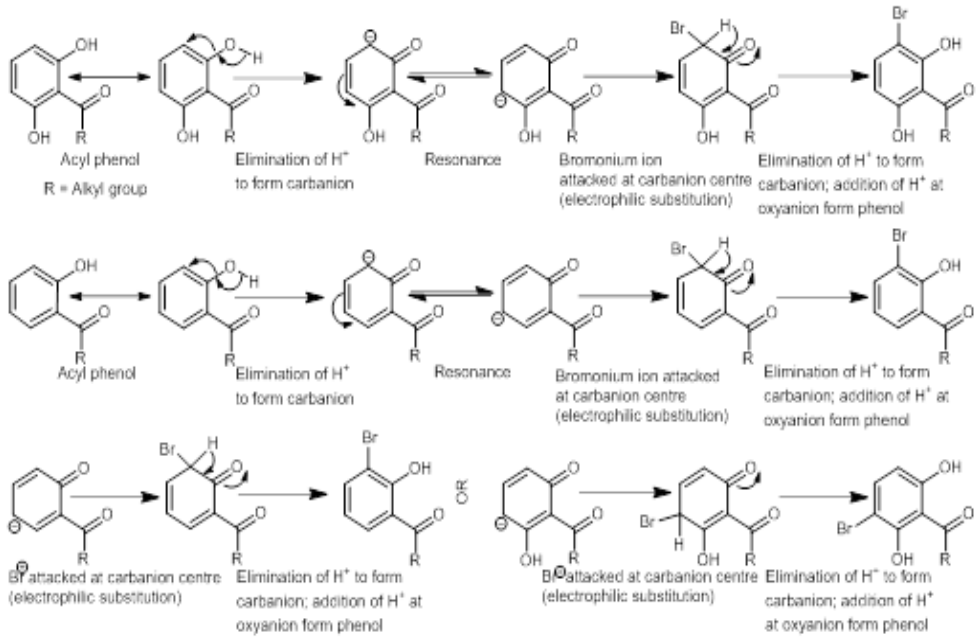
KEYWORDS: Hydroxy acetophenone; bromination; N-bromo succinimide; low temperature; aqueous acetone as solvent; *regio*-specific bromination.

INTRODUCTION

A variety of brominating reagent has been used to brominate in aromatic nucleus. Amongst, N-bromo succinimide is an excellent.[1,2] NBS has been used to brominate hydroxy acetophenone at low temperature in aqueous acetone as solvents. It has been noticed that NBS is act as region-specific brominating reagent for ortho hydroxy acetophenones provided ortho position of hydroxy acetophenone should be without any substituent. The bromination must be occurred at adjourning position of hydroxy group of the hydroxy acetophenones and would provide quantitative yield when 1.2 equivalent NBS used as reagent.[2, 3] The temperature of reaction mixture should be maintained at 0^{0}C and reaction mixture has been stirred over a period of 12 h with the help of a stirrer. A variety of hydroxy acetophenones have been used as substrates to performed the reactions and to optimize the reaction condition.

RESULTS AND DISCUSSION

In general, N-Bromo succinimide is used as brominating reagent in different kinds of organic compounds to insert bromine atom either in aromatic nucleus or in unsaturated part of the organic compounds. But when hydroxy acetophenones were used as substrates for bromination reaction, the bromine atom has been inserted at the adjacent position of phenolic hydroxy group of acetophenones when 1.2 equivalent NBS used as reagent in aqueous acetone as solvents with continuous stirring with a span of 12 h.[3] The reaction was quenched and usual work up to yield respect bromo hydroxy acetophenones. The yield of the reaction product is almost quantitative. It is an efficient and single spot method for bromination of different types of hydroxy acetophenones under certain condition. The condition is that the adjourning position of hydroxy group of hydroxy acetophenone must be unsubstituted. In a specific case, if 2, 6-dihydroxy acetophenone is used as substrate for bromination reaction and 1.2 equivalent N-Bromo succinimide added to yield monobromide hydroxy acetophenone whereas dibromo hydroxy acetophenone formed in presence of 2.4 equivalent NBS as reagent.[3]



A series of experiments have been performed for bromination using NBS as reagent by changing substrates with higher analogues. The substrates which are used to optimize and confirmed the aforesaid reaction are listed in table given below.

Table 1: A series of experiments have been performed for bromination using NBS as reagent.

Serial no.	Entry number	Scale (mM)	NBS used (equivalent)	Duration (hr)	Solvent used	% yield
1	2, 6-dihydroxy acetophenone	1.0	1.2	12	10% aq. acetone	90
2	4, 5-dichloro-2, 6-dihydroxy acetophenone	1.0	1.2	12	10% aq. acetone	95
3	2, 4-dihydroxy acetophenone	1.0	1.2	12	10% aq. acetone	95
4	1(2,6-dihydroxy phenyl) tetra-dodecan-1-one	1.0	1.2	12	10% aq. acetone	95
5	4-methoxy-2, 6-dihydroxy benzophenone	1.0	1.2	12	10% aq. acetone	95
6	2, 6-dihydroxy-4-octyl phenol	1.0	1.2	12	10% aq. acetone	95
7	2, 6-dihydroxy-octyl benzene 1, 2 diols	1.0	1.2	12	10% aq. acetone	85
8	2, 6-dihydroxy-octyl benzene [d] [1, 3] dioxole	1.0	1.2	12	10% aq. acetone	95
9	2-hydroxy aceto-naphthoquinone	1.0	1.2	12	10% aq. acetone	95
10	2-hydroxy flavone (salvigenin)	1.0	1.2	12	10% aq. acetone	30*
11	2-hydroxy-4-methoxy flavone (methoxy salvigenin)	1.0	1.2	12	10% aq. acetone	30*
12	2-hydroxy-4-hydroxy flavone	1.0	1.2	12	10% aq. acetone	30*
13	2-hydroxy-3-hydroxy-4-hydroxy flavone	1.0	1.2	12	10% aq. acetone	30*
14	2-hydroxy-6 methoxy acetophenone	1.0	1.2	12	10% aq. acetone	95
15	2-hydroxy-5-methoxy acetophenone	1.0	1.2	12	10% aq. acetone	95
16	2, 4-dihydroxy acetophenone	1.0	1.2	12	10% aq. acetone	90
17	2-hydroxy acetophenone	1.0	1.2	12	10% aq. acetone	90
18	2, 5-dihydroxy acetophenone	1.0	1.2	12	10% aq. acetone	90
19	2-hydroxy-4-methoxy acetophenone	0.7	1.2	12	10% aq. acetone	90
20	2-hydroxy benzophenone	1.0	1.2	12	10% aq. acetone	90
21	2, 6-dihydroxy octyl benzene	1.0	2.2	12	10% aq. acetone	90
22	1(2,6-dihydroxy phenyl) tetra-dodecan-1-one	1.0	2.2	12	10% aq. acetone	95
23	2, 6-dihydroxy-4-octyl phenol	1.0	2.2	12	10% aq. acetone	90
24	2, 6-dihydroxy-octyl benzene 1, 2 diols	1.0	2.2	12	10% aq. acetone	90
25	2, 6-dihydroxy-octyl benzene [d] [1, 3] dioxole	1.0	2.2	12	10% aq. acetone	95

CONCLUSION

Bromination of 2-hydroxy acetophenones or its derivatives with 1.2 equivalent N-bromo succinimide at 0 ^{0}C over a span of 12 h with continuous stirring, bromination reaction took place at the adjacent position of hydroxy group of acetophenones (*viz*. *regio*-selective

bromination of hydroxy acetophenones or their derivatives) provided respective positions is unsubstituted. If 2, 6-dihydroxy acetophenones (hydroxy groups attached both the ortho positions of acetoxy group in acetophenones) or their derivatives are used as substrates for bromination reaction using 2.2 equivalent N-bromo succinimide or excess, *regio*-selective dibromination occurred at the adjacent positions of hydroxy groups.

Experimental section

The compounds used in the bromination studies were either isolated from natural resources or commercially procured.

General procedure for bromination of hydroxy acetophenones using NBS: Hydroxy acetophenones and 10-15 mL aqueous acetone were charged in a 25 mL three necked round bottom flask fitted with a magnetic stirrer. The reactant mixture was cooled at 0 ^{o}C using acetone dry ice. Gradually added NBS in a portion to the reaction mixture and temperature of reaction mixture was maintained at 0 ^{o}C for 30 min. The reaction mixture was quenched with ice cold water and extracted with ether or ethyl acetate followed by usual worked up and dried over $NaSO_4$.The solvent was removed using rota vapour under reduced pressure to obtain desired product. This procedure was used for bromination of all these substrates under similar reaction condition.

General experimental procedure

N-bromo succinimide was purchased from commercial source. It was crystallized thrice times from hot water to yield colourless crystalline substance. This crystalline NBS was used for bromination of different hydroxy acetophenones. Melting points were incorrected, IR spectra recorded neat on a Thermal Scientific Nicolet 670 spectrophotometer with Omnic software. Preparative TLC was performed on 0.50 mm thick silica gel 60 F254 layer with fluorescent indicator coated on 20 cm x 20 cm glass sheets.[5, 6] TLC plate visualization was accomplished with UV light (254 nm) UV spectra were measured on a Shimadzu UV160 A double beam spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian AR 500 NMR machine.

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Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this article.

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