Ammonium Hydrotribromide Salts as Convenient and Selective Brominating Agents of Aryl Methyl Ketones

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Summary: A simple and improved protocol for the α-monobromination of acetophenone and acetyl carbazole derivatives using different ammonium hydrotribromide salts under mild reaction condition was described.

Key words: α-Monobromination, Aryl methyl ketones, Ammonium hydrotribromide salts, Acetyl carbazole.

Introduction

Bromo ketones are useful intermediates in the synthesis of a variety of biologically active compounds [1-3]. So the α-bromination of carbonyl compounds is an important transformation in synthetic organic chemistry. A number of methods have been described for the bromination of ketones, employing compounds such as cupric bromide [4], ammonium bromide [5], dioxane dibromide [6], H_2O_2-HBr [7] and Br_2/AcOH [8]. Many of these methods, despite of good yields, suffer from one or more disadvantages such as harsh reaction conditions, long reaction time and etc. From the green chemistry point of view, the use of molecular bromine has several drawbacks such as: the reagent itself is harmful and there are difficulties in handling and maintaining the stoichiometric ratio during the reaction. In addition, some reactions require high temperature, strong basic conditions, dry and harsh reaction conditions or suitable catalysts for the reaction to proceed.

In recent years the main emphasis is being placed towards the use of environmentally benign synthetic systems. Solid organic ammonium tribromides (OATB), such as pyridinium hydrobromide (Py. HBr_3) [9], tetramethyl ammonium tribromide (TMATB) [10], terabutyl ammonium tribromide (TBATB) [11], cetyl trimethyl ammonium tribromide (CetTMATB) [12], pyrrolidone-bromine complex, (pyrrolidone),.HBr, (PHT) [13] and *N*-methyl pyrrolidine-2-one hydro tribromide (MPHT) [14], due to their ease of handling and ability to maintain the desired stoichiometry, are finding increasing applications as the alternative substrate of toxic and hazardous molecular bromine in various organic reactions.

In continuation of our interest in organohalogen chemistry [15], herein we report α-monobromination of aryl methyl ketones without any catalyst at room temperature using some ammonium hydrotribromide salts as brominating agents under mild reaction conditions.

Experimental

All solvents were purified before use by standard purification methods. The organic extracts were dried with anhydrous sodium sulfate. All the tertiary amines were purchased from Fluka or Merck. Melting points were recorded on a Philips Harris C4954718 apparatus and are not corrected. Infrared spectra were measured with a Bruker FT-IR spectrometer using KBr disks.^{1}H-NMR spectra were recorded on a Bruker spectrometer (300 MHz). ^{13}C-NMR spectra were recorded on a 75 MHz spectrometer from Bruker. All measurements were made in duterated chloroform and dimethyl sulfoxide. Analytical thin layer chromatography (TLC) was carried out on precoated aluminum sheet with silica gel 60 F_{254} obtained from Merck and detection was made with the help of a UV lamp (λ 254 nm). Elemental analyses were performed on a Leco Analyzer 932.

General procedure for the synthesis of ammonium hydrotribromide salts.

To MeOH (4mL) in an ice bath was added successively HBr (30% in acetic acid) (5mL) while maintaining the internal temperature between 10-15°C. Elemental bromine (1.2 mL) was added and

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the solution was stirred for 10min, then the tertiary amines (0.051mmol) were added slowly. The mixture was stirred at 10°C until the reaction was completed, which was determined by solid formation or TLC using $CHCl_3$/MeOH/EtOAc (10:1:2) as eluent.

- Pyridinium hydrotribromide salt (I). Orange crystal, 95% yield, m.p. 129-130°C.
- Triethyl ammonium tribromide salt (II). Brown viscose, 75% yield.
- N,N-Dimethyl anilinium tribromide salt (III). Brown viscose, 78% yield.
- N-Methyl morpholinium tribromide salt (IV). Light brown viscose, 80% yield.
- 2-Amino-3-carboxylic acid pyridinium tribromide salt (V). Light orange solid, 58% yield, m.p. 129-130°C.

1,3-Dimethyl imidazolidine-2-one hydrotribromide salt (VI). Pale yellow crystal, 91% yield, m.p.98-100°C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.96 (s, 6H, $3CH_3$), 3.65 (s, 4H, $2CH_2$), 10.70 (bs, 1H, OH). ^{13}C-NMR ($CDCl_3$) δ (ppm) 32.06, 46.21, 161.60. FT-IR ν_{max} (KBr disk): 3421, 2936, 1635, 1502, 1246 cm^{-1}.

General Procedure for α-monobromination of Aryl Methyl Ketones with Ammonium Hydrotribromide Salts

A solution of aryl methyl ketone (1mmol) in solvent (5mL) was stirred at room temperature and then ammonium hydrotribromide salt (1mmol) was added. The mixture was then stirred for 30 additional minutes at this temperature. After completion the reaction, the mixture poured in cold water and the solid product was collected and recrystallized in EtOH.

2-Bromo-1-phenylethanone (2a). White crystal, m.p. 49-50 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.99 (1H, d, J = 7.4 Hz, Ar), 7.62 (1H, t, J = 7.4 Hz, Ar), 7.50 (2H, t, J = 7.4 Hz, Ar), 4.46 (2H, s, CH_2). FT-IR ν_{max} (KBr disk): 3001, 2951, 1691, 1446, 1389, 1196, 991, 748, 685, 621, 550 cm^{-1}.

2-Bromo-1-(4-methoxyphenyl) ethanone (2b). White crystal, m.p. 69 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.95 (2H, d, J = 7.4 Hz, Ar), 6.95 (2H, d, J = 7.4 Hz, Ar), 4.40 (2H, s, CH_2), 3.90 (3H, s, CH_3). FT-IR ν_{max} (KBr disk): 2951, 1691, 1591, 1389, 1262, 1196, 991, 748, 685, 621, 550 cm^{-1}.

2-Bromo-1-(4-nitrophenyl) ethanone (2c). Yellow solid, m.p. 101 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.21 (2H, d, J = 7.2 Hz, Ar), 8.61 (2H, d, J = 7.2 Hz, Ar), 4.41 (2H, s, CH_2). FT-IR ν_{max} (KBr disk): 3058, 3001, 1659, 1601, 1491, 1389, 1196, 991, 852, 748, 685, 565 cm^{-1}.

2-Bromo-1-(4-bromophenyl) ethanone (2d). White crystal, m.p. 108 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.90 (2H, d, J = 7.6 Hz, Ar), 7.64 (2H, d, J = 7.2 Hz, Ar), 4.48 (2H, s, CH_2). FT-IR ν_{max} (KBr disk): 2951, 1691, 1389, 1280, 1196, 991, 748, 685, 621, 558 cm^{-1}.

2-Bromo-1-(3-methoxyphenyl) ethanone (2e). White crystal, m.p. 61 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (1H, d, J = 7.5 Hz, Ar), 7.53 (1H, s, Ar), 7.24 (1H, t, J = 7.8 Hz, Ar), 7.17 (1H, J_1 = 7.8 Hz, J_2 = 2.4 Hz, Ar), 4.47 (2H, s, CH_2), 3.89 (3H, s, CH_3). FT-IR ν_{max} (KBr disk): 2944, 1697, 1575, 1480, 1430, 1294, 1244, 1186, 1004, 779, 682, 615, 564 cm^{-1}.

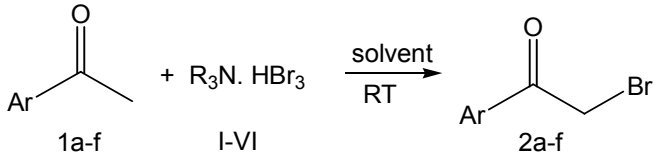
3,6-Bis(2-bromoacetyl)-N-ethyl carbazole (2f). Yellow solid, m.p. 172-174 °C. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.50 (t, J = 7.2 Hz, 3H, CH_3), 4.42 (q, J = 7.2 Hz, 2H, CH_2), 4.60 (s, 4H, $2\times CH_2$), 7.46-8.80 (m, 6H, Ar). ^{13}C-NMR ($CDCl_3$) δ (ppm): 19.74, 29.37, 40.08, 124.78, 130.51, 130.98, 132.19, 136.41, 144.82, 191.92. FT-IR ν_{max} (KBr disk): 3091, 1597, 1460, 1262, 753 cm^{-1}.

Results and Discussion

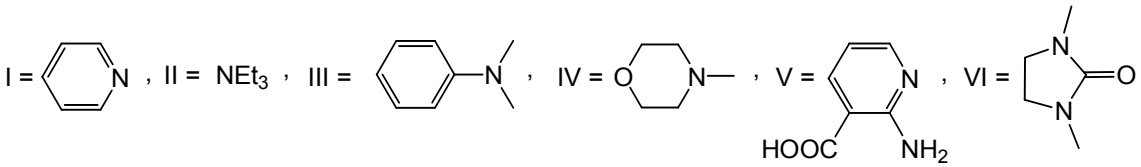
Acetophenone was used as a target molecule in evaluation of various halogenating agents with respect to mono and disubstitution in several studies. Five acetophenone derivatives (1a-e) beside 3,6-diacetyl-9-ethyl carbazole (1f) were brominated by different ammonium hydrotribromide (I-VI) and bromo derivatives (2a-f) were obtained in good yields (Scheme 1).

The reagents are prepared from the inexpensive starting materials.

The method has been applied to a series of aromatic ketones. The present method furnished only the mono brominated products. This method is associated with only the methyl group of ketones, without bromination of aromatic ring. The results of these studies are summarized in tables 1-6.



Ar = C_6H_5, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 3-$MeOC_6H_4$, 3-(6-acetyl-9-ethylcarbazole)



Scheme-1: Bromination of compounds **(1a-f)** by different ammonium hydrotribromide **(I-VI).**

Table-1: α-monobromination of acetophenone and acetyl carbazole derivatives by pyridinium hydrotribromide salt in THF

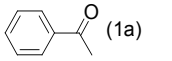
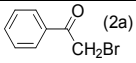
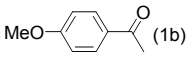
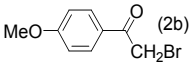
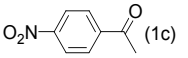
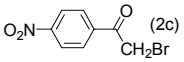
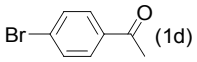
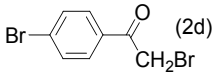
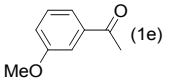
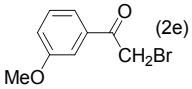
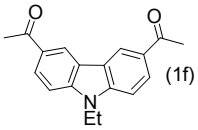
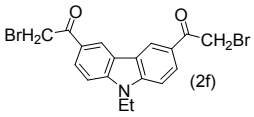
Entry	Substrate	Product	Molar ratio Subs./reagent	Time (min)	Yield (%)
1	 (1a)	 (2a)	1:1	30	90
2	 (1b)	 (2b)	1:1	20	86
3	 (1c)	 (2c)	1:1	5	98
4	 (1d)	 (2d)	1:1	200	85
5	 (1e)	 (2e)	1:1	210	70
6	 (1f)	 (2f)	1:2	35	84

Table-2: α -monobromination of acetophenone and acetyl carbazole derivatives by triethyl ammonium hydrotribromide salt in THF

Entry	Substrate	Product	Molar ratio Subs./reagent	Time (min)	Yield (%)
1	(1a)	(2a)	1:1	30	92
2	(1b)	(2b)	1:1	20	85
3	(1c)	(2c)	1:1	18	98
4	(1d)	(2d)	1:1	15	87
5	(1e)	(2e)	1:1	20	85
6	(1f)	(2f)	1:2	25	81

Table-3: α-monobromination of acetophenone and acetyl carbazole derivatives by N,N-dimethyl anilinium hydrotribromide salt in THF

Entry	Substrate	Product	Molar ratio Subs./reagent	Time (min)	Yield (%)
1	(1a)	(2a)	1:1	40	83
2	(1b)	(2b)	1:1	25	85
3	(1c)	(2c)	1:1	45	95
4	(1d)	(2d)	1:1	30	80
5	(1e)	(2e)	1:1	25	68
6	(1f)	(2f)	1:2	25	91

Table-4: α-monobromination of acetophenone and acetyl carbazole derivatives by N-methyl morpholinium tribromide salt in THF.

Entry	Substrate	Product	Molar ratio Subs./reagent	Time (min)	Yield (%)
1	(1a)	(2a)	1:1	35	84
2	(1b)	(2b)	1:1	35	87
3	(1c)	(2c)	1:1	25	96
4	(1d)	(2d)	1:1	40	70
5	(1e)	(2e)	1:1	30	90
6	(1f)	(2f)	1:2	40	87

Table-5: α-monobromination of acetophenone and acetyl carbazole derivatives by 2-amino-3-carboxylic acid pyridinium hydrotribromide salt in THF

Entry	Substrate	Product	Molar ratio Subs./reagent	Time (min)	Yield (%)
1	(1a)	(2a)	1:1	30	90
2	(1b)	(2b)	1:1	20	85
3	(1c)	(2c)	1:1	55	85
4	(1d)	(2d)	1:1	45	85
5	(1e)	(2e)	1:1	30	86
6	(1f)	(2f)	1:2	35	78

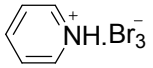
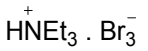
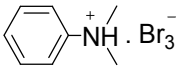
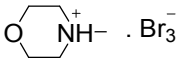
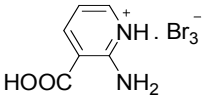
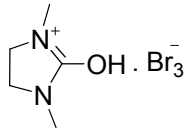
Table-6: α-monobromination of acetophenone and acetyl carbazole derivatives by 1,3-dimethyl imidazolidine-2-one hydrotribromide salt in THF

Entry	Substrate	Product	Molar ratio Subs./reagent	Time (min)	Yield (%)
1	(1a)	(2a)	1:1	30	94
2	(1b)	(2b)	1:1	20	90
3	(1c)	(2c)	1:1	15	95
4	(1d)	(2d)	1:1	15	85
5	(1e)	(2e)	1:1	20	90
6	(1f)	(2f)	1:2	60	91

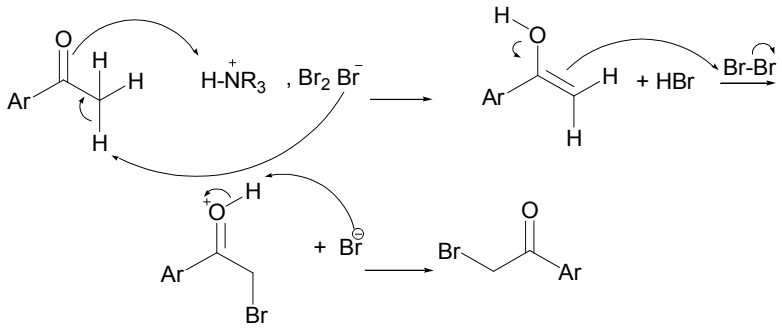
According to these results bromination selectivity occurred at α-carbon of the ketone favorable to enolization. All these reagents are readily accessible, easily storable in comparison with molecular bromine, less hazardous, easy to handle and facilitate maintenance of the stoichiometric ratio while carrying out the reaction.

The effect of various solvents on α-monobromination of **(1a-f)** compounds was also studied in different organic solvents under similar reaction condition, and the results are summarized in Table 7. Among the different solvents used for the α-monobromination of aryl methyl ketones THF was found to be the most promising reaction medium for this transformation.

Table-7: Solvent effect on α-monobromination of acetophenone by ammonium hydrotribromide salts.

Entry	ammonium hydro tribromide salt	MeOH	EtOH	AcOH	THF	CH_3CN	DMF
		Time (min)/Yield (%)	Time (min)/Yield (%)	Time (min)/Yield (%)	Time (min)/Yield (%)	Time (min)/Yield (%)	Time (min)/Yield (%)
1		50 / 87	65 / 83	120 / 90	30 / 90	160 / 87	220 / 70
2		90 / 87	65 / 74	200 / 85	30 / 92	180 / 65	220 / 85
3		95 / 80	65 / 80	210 / 77	40 / 83	250 / 55	300 / 65
4		180 / 68	80 / 75	210 / 87	35 / 84	20 / 86	310 / 70
5		30 / 90	55 / 98	200 / 85	30 / 90	20 / 86	210 / 70
6		60 / 80	70 / 85	180 / 83	30 / 90	25 / 90	280 / 85

The possible mechanism for this bromination is shown in Scheme 2.



Scheme-2: The possible mechanism for bromination by ammonium hydrotribromide salts.

Conclusion

Formation of monobrominated products in excellent yields within short times, easy synthesis of reagents, simple experimental procedure, catalyst-free conversion and easy work up, make this an improved and facile synthetic tool for monobromination of acetophenone and acetyl carbazole derivatives.

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References

1. A. M. Erian, S. M. Sherif and H. M. Gaber, The Chemistry of α-Halo Ketones and their Utility in Heterocyclic Synthesis, *Molecules.*, **8**, 793 (2003).
2. B. S. Holla, R. Gonsalves, B. K. Sarojini and S. Shenoy, Synthesis of Some New Biologically Active Triazino-Thiadiazinones, *Indian. J. Chem.*, **408**, 475 (2001).
3. R. Martinez, 2-Aryl-7,7-dimethyl-5,6,7,8-tetrahydrothieno[3,2-c]azepin-4-ones from 5,5-dimethyl-1,3-Cyclohexanedione, *J. Heterocycl. Chem*., **36**, 687 (1999).
4. L. C. King and G. K. Ostrum, Selective Bromination with Copper (II) Bromide1, *J. Org. Chem*., **29**, 3459 (1964).
5. A. T. Khan, P. Goswami and L. H. Choudhury, A Mild and Environmentally Acceptable Synthetic Protocol for Chemoselective α-Bromination of *β*-Keto Esters and 1,3-Diketones, *Tetrahedron Lett*., **47**, 2751 (2006).
6. S. J. Pasaribu and L. R. Williams, Selective Bromination of Substituted Acetophenones with Dioxan Dibromide, *Aust. J. Chem*., **26**, 1327 (1973).
7. A. Podgorserk, S. Stavber, M. Zupan and J. Iskara, Bromination of Ketones with H_2O_2–HBr "on water", *Green Chem.*, **9**, 1212 (2007).
8. H. Greenberg, T. Van Es and O. G. Backeberg, The Action of Bromine in Acetic Acid on 4,5-diphenyl-2-imidazolone, *J. Org. Chem.,* **30**, 3937 (1965).
9. C. Djerassi and C. R. Scholz, Brominations with Pyridine Hydrobromide Perbromide*, J. Am. Chem. Soc*., **70**, 417 (1948).
10. F. D. Chattaway and G. Hoyle, Perhalides of Quaternary Ammonium Salts, *J. Chem. Soc*., 654 (1923).
11. M. K. Chaudhuri, A. T. Khan and B. K. Patel, An Environmentally Eenign Synthesis of Organic Ammonium Tribromides (OATB) and Bromination of Selected Organic Substrates by Tetrabutylammonium Tribromide (TBATB), *Tetrahedron Letters*, **39**, 8163 (1998).
12. G. Kar, A. K. Saikia, V. Bora, S. K. Dehury and M. K. Chaudhuri, Synthesis of Cetyltrimethylammonium Tribromide (CTMATB) and its Application in the Selective Oxidation of Sulfides to Sulfoxides, *Tetrahedron Lett*., **44**, 4503 (2003).
13. D. V. C. Awang and S. Wolfe, Pyrrolidone Hydrotribrornide: a Brominating Agent with Selectivity for Ketones, *Can. J. Chem.* **47**, 706 (1969).
14. S. Singhal, S. L. Jain and B. Sain, A Simple and Improved Regioselective Bromination of Aromatic Compounds Using *N*-methylpyrolidin-2-one hydrotribromide and Aqueous Hydrogen Peroxide Under Mild Reaction Conditions, *Molecular Catal* A*: Chemical.*, **258**, 198 (2006).
15. S. Jasouri, J. Khalafy, M. Badali and M. Piltan, Selective Bromination of 4-chloro-1-indanone and Synthesis of (4-chloro-2,3-dihydro-1*H*-indene-2-yl) methanamine, *S. Afr. J. Chem*., **63**, 83 (2010).