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ORIGINAL PAPER

Ethylenebis(*N*-methylimidazolium) ditribromide (EBMIDTB): an efficient reagent for the monobromination of 1,3-diketones and *β*-ketoesters

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Abstract Ethylenebis(*N*-methylimidazolium) ditribromide, a stable crystalline solid, is easily prepared by reaction of the corresponding dibromide salt with bromine in *n*-hexane. 1,3-Diketones and *β*-ketoesters can be brominated chemoselectively to the corresponding α-monobrominated products by using this reagent at 0–5 °C. Under the same reaction conditions, diethyl malonate, ethyl cyanoacetate, and malonitrile were monobrominated at moderate yield.

Keywords α-Bromination · *β*-Dicarbonyl compounds · Monobrominated product · Ethylenebis(*N*-methylimidazolium) ditribromide

Introduction

The chemoselective α-bromination of *β*-dicarbonyl compounds is an important organic transformation [1–3], because the resulting α-brominated products are valuable building blocks in organic synthesis [4]. The monobromination of these compounds at the α-position (if the position contains no substituent) is delicate, as disubstituted products are also formed [5, 6].

The reagents reported for this transformation include molecular bromine [7], Br_2/NaH [8], NBS/Et_3N [9, 10], NBS/NaH [11], $CuBr_2$ with [hydroxy(tosyloxy) iodo]benzene [12], NBS/$Mg(ClO_4)_2$ [13], NBS/silica-supported $NaHSO_4$ [14], NBS/Amberlyst-15 [15], NBS/ionic liquids [16], NBS/sulfonic acid functionalised silica [17], NBS under solvent free conditions [18], H_2O_2–HBr [19], bromodimethylsulfonium bromide [20], and V_2O_5–H_2O_2 catalysed oxidation of ammonium bromide [21]. Although most of these methods provide good yields, many of them suffer from one or more disadvantages. From the green chemistry point of view [22], the use of molecular bromine has several drawbacks: the reagent itself is harmful and hazardous and there are difficulties in handling and maintaining the stoichiometric ratio during the reaction. In addition, some reactions involve strong basic conditions. Moreover, NBS also has some limitations, such as the requirement for dry [12] and harsh reaction conditions [14].

On the other hand, the use of tribromide reagents in organic synthesis has gained considerable interest. Tribromides are more suitable than liquid bromine because of their crystalline nature, which facilitates their storage, transport and maintenance of desired stoichiometry. These reagents are used for the bromination of aromatic and carbonyl compounds [23]. Organic ammonium tribromides such as tetrabutyl [24, 25], tetramethyl [26], cetyl [27], benzyltrimethyl [27–30], pentylpyridinium [31, 32], pyridinium [33–36], and *DBU* [37] are used for bromination of aromatic compounds. Selective bromination of C–H α to a ketonic carbonyl function can be effected by pyridinium hydrobromide perbromide [38], phenyl trimethylammonium perbromide [39, 40], 2-pyrrolidone hydrotribromide [41], and 2-carboxyethyltriphenylphosphonium tribromide [42].

In this paper we report a new reagent for the α-monobromination of 1,3-dicarbonyl compounds that offers several advantages in comparison with previously reported

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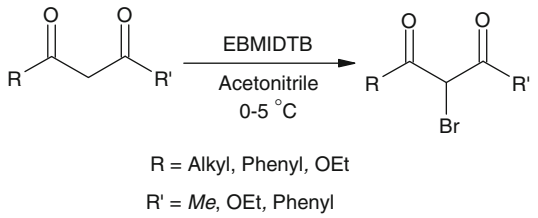


Scheme 1

reagents. The reagent, ethylenebis(*N*-methylimidazolium) ditribromide (EBMIDTB) is readily accessible, can be considered a convenient storage strategy for molecular bromine, is less hazardous, easy to handle, and facilitates maintenance of the stoichiometric ratio while carrying out the reactions (Scheme 1).

To the best of our knowledge, this is the first report of the α-monobromination of 1,3-dicarbonyl compounds using ditribromide reagents.

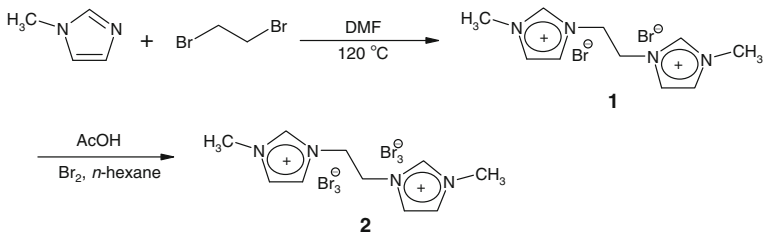
Results and discussion

EBMIDTB (**2**) is prepared easily from the inexpensive starting materials *N*-methylimidazole, 1,2-dibromoethane, and bromine (Scheme 2). When an equivalent amount of 1,2-dibromoethane and *N*-methylimidazole are mixed in *DMF*, ethylenebis(*N*-methylimidazolium) dibromide (EBMIDB) forms as a white solid [43]. Treatment of EBMIDB (**1**) with bromine afforded the corresponding ditribromide **2** as an orange solid in high yield. Compound **2** was characterized by ^{1}H NMR, ^{13}C NMR, and CHN analysis. Iodometric titration measurement of Br_3^- was in accordance with the proposed structure of ditribromide **2**. The iodometric equivalent weight was determined by the reaction of **2** with iodide in a water-acetonitrile solution followed by titration with thiosulfate solution [44]. This measurement showed two moles of Br_3^- in one molecule of ditribromide **2**. ^{1}H NMR and ^{13}C NMR spectra agreed well with the proposed structure of **2**. The CHN analysis also confirmed the structure of this reagent. It is soluble in acetonitrile, dimethylsulfoxide and insoluble in dichloromethane and acetic acid. This compound is stable for several months without loss of activity.

In our first experiments, dibenzoyl methane was chosen as a model substrate to identify optimal reaction conditions. This compound was treated with 0.5 mmol **2** at 0–5 °C in acetonitrile, resulting in complete conversion within 20 min to give the corresponding α-monobrominated product in 90% yield. When the reaction solvent was changed to CH_2Cl_2, $CHCl_3$, or H_2O, the reaction required a much longer time and a lower yield of monobrominated product was obtained.

A wide range of active methylene compounds were transformed into the corresponding α-monobrominated products by treatment with **2** in acetonitrile at 0–5 °C (Table 1). Various unsubstituted 1,3-diketones were exclusively α-monobrominated in good yields (Table 1; entries 1–6). Monoalkyl substituted 1,3-diketone was also brominated chemoselectively at the α-position (Table 1; entry 7). Under the same reaction conditions, *β*-ketoesters were smoothly converted to the corresponding α-monobrominated product in good yields (Table 1; entries 8–9). Reaction of diethyl malonate, ethyl cyanoacetate, and malonitrile with this reagent gave a lower yield of the corresponding α-monobrominated product while requiring longer reaction times (Table 1; entries 10–12). No significant amount of dibrominated products was found in these reactions. However, if we changed the mole ratio of **2** and 1,3-dicarbonyl compound to 1:1, the α,α-dibrominated product can be obtained in moderate yields. A good feature of this reagent is that it can be regenerated. To regenerate the reagent from the aqueous layer obtained after the α-monobromination of 1,3-dicarbonyl compounds, the aqueous layer was concentrated and treated with bromine in *n*-hexane. The recovered reagent is identical in all respects with the parent EBMIDTB reagent.

In conclusion, we have developed a general method for the mild α-monobromination of *β*-ketoesters and 1,3-diketones using **2**. Additionally, **2** is air-stable, easy to handle, and can be stored for long periods without decomposition. This method is also effective for the bromination of aromatic dicarbonyl compounds without



Scheme 2

Table 1 Selective α-monobromination of active methylene compounds using ethylenebis(*N*-methylimidazolium)ditribromide (EBMIDTB)

Entry	Substrate	Product[a]	Time/min	Yield/%[b]	M.p/°C[a]
1	*Ph*$COCH_2CO$*Ph*	*Ph*COCHBrCO*Ph*	20	90	91–93 [18, 45]
2	$CH_3COCH_2COCH_3$	$CH_3COCHBrCOCH_3$	20	85	–
3	*Ph*$COCH_2COCH_3$	*Ph*$COCHBrCOCH_3$	20	80	32–33 [18]
4	Cyclohexane-1,3-dione	2-Br-cyclohexane-1,3-dione	20	90	168–170 [46]
5	5,5-*Me*$_2$-cyclohexane-1,3-dione	2-Br-5,5-*Me*$_2$-cyclohexane-1,3-dione	20	95	174–176 [47]
6	Indane-1,3-dione	2-Br-indane-1,3-dione	40	85	115–118 [48]
7	2-*Me*-cyclopentane-1,3-dione	2-Br-2-*Me*-cyclohexane-1,3-dione	30	90	Oil [49]
8	CH_3COCH_2COOEt	$CH_3COCHBrCOOEt$	40	85	Oil [50]
9	*Ph*$COCH_2COOEt$	*Ph*COCHBrCOO*Et*	40	85	Oil [51]
10	*Et*$OCOCH_2COOEt$	*Et*OCOCHBrCOO*Et*	90	50	Oil [52]
11	$NCCH_2COOEt$	NCCHBrCOO*Et*	90	50	Oil [53]
12	$NCCH_2CN$	NCCHBrCN	90	50	64–65 [54]

[a] All of the products were identified by comparing melting point and ^{1}H NMR with those of authentic samples reported in literature

[b] Yields refer to isolated products

causing ring brominations. We believe that **2** provides an excellent complement to other reagents for this transformation such as *NBS*.

Experimental

Melting points were measured on Electro Thermal 9100. NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C with BRUKER DRX500. Elemental analysis was done with PERKIN ELMER 2-2400 and the obtained results agreed favourably with the calculated values.

*Ethylenebis(N-methylimidazolium) ditribromide (**2**, $C_{10}H_{16}Br_6N_4$)*

A mixture of 4.85 g *N*-methylimidazole (58.5 mmol) and 2.3 cm^3 1,2-dibromoethane (26.6 mmol) was stirred in 40 cm^3 *DMF* at 120 °C for 2 h. After cooling the mixture, a white solid formed, which was filtered off, washed with diethyl ether (2 × 20 cm^3), and dried under vacuum. This solid was dissolved in 40 cm^3 acetic acid. To this mixture was added dropwise a solution of 2.3 cm^3 Br_2 (43.75 mmol) in 20 cm^3 *n*-hexane The resulting orange solid was collected by filtration, washed with diethyl ether, and dried under vacuum to give 10.4 g **2**. Mp 103–105 °C; ^{1}H NMR (500 MHz, *DMSO*-d_6): δ = 3.80 (s, 2CH_3), 4.62 (s, 2CH_2), 7.36 (pseudo t, 2H-imi), 7.65 (pseudo t, 2H-imi), 8.94 (s, 2H, NCHN) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): δ = 37.0 (CH_3), 49.4 (CH_2), 123.2 (imi-C), 124.9 (imi-C), 138.0 (NCHN) ppm.

*General procedure for α-monobromination of a β-dicarbonyl compound with **2***

To a stirred solution of 1 mmol β-dicarbonyl compound in 10 cm^3 acetonitrile was added 0.5 mmol **2** at 0–5 °C. After completion of the reaction as monitored by TLC, 15 cm^3 water were added to the reaction mixture, which was then extracted with dichloromethane (2 × 25 cm^3). The combined organic layer was dried (Na_2SO_4). After filtration, the solvent was evaporated, and the residue was purified by filtration through a short silica gel column (eluent: *n*-hexane and ethyl acetate). The spectroscopic data for the known products compared well with the reported data.

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References

1. Larock RC (1999) In: Comprehensive organic transformations, 2nd edn. VCH, New York, p 717
2. Erian AM, Sherif SM, Gaber HM (2003) Molecules 8:793
3. Benjamin WA, House HO (1972) Modern synthetic reactions, 2nd edn. Benjamin, New York, p 459
4. Misra AP, Raj K, Bhaduri AP (1999) Synth Commun 29:3227
5. Hoffman RV, Weiner WS, Maslouh N (2001) J Org Chem 66:5790
6. Honda Y, Katayama S, Kojima M, Suzuki T, Isawa K (2002) Org Lett 4:447
7. Hakam K, Thielmann M, Thielmann T, Winterfeldt E (1987) Tetrahedron 43:2035
8. Stotter PL, Hill KA (1972) Tetrahedron Lett 40:4067
9. Karimi S, Grohmann KG (1995) J Org Chem 60:554
10. Bateson JH, Quinn AM, Southgate R (1986) J Chem Soc Chem Commun 1151
11. Curran DP, Bosch E, Kaplan J, Newcomb M (1989) J Org Chem 54:1826
12. Coats SJ, Wasserman HH (1995) Tetrahedron Lett 36:7735
13. Yang D, Yan Y, Lui B (2002) J Org Chem 67:7429
14. Das B, Venkateswarlu K, Mahender G, Mahender I (2005) Tetrahedron Lett 46:3041
15. Meshram HM, Reddy PN, Sadashiv K, Yadav JS (2005) Tetrahedron Lett 46:623
16. Meshram HM, Reddy PN, Vishnu K, Sadashiv K, Yadav JS (2006) Tetrahedron Lett 47:991

17. Das B, Venkateswarlu K, Holla H, Krishnaiah M (2006) J Mol Catal 253:107
18. Pravst I, Zupan M, Stavber S (2006) Green Chem 8:1001
19. Podgorsek A, Stavber S, Zupan M, Iskra J (2007) Green Chem 9:1212
20. Khan AT, Ali MA, Goswami P, Choudhury LH (2006) J Org Chem 71:8961
21. Khan AT, Goswami P, Choudhury LH (2006) Tetrahedron Lett 47:2751
22. Clark JH (1995) Chemistry of waste minimisation. Chapman & Hall, London
23. Kavala V, Naik S, Patel BK (2005) J Org Chem 70:4267
24. Bora U, Bose G, Chaudhuri MK, Dhar SS, Gopinath R, Khan AT, Patel BK (2000) Org Lett 2:247
25. Chaudhuri MK, Khan AT, Patel BK, Dey D, Kharmawophlang W, Lakshmiprabha TR, Mandal GC (1998) Tetrahedron Lett 39:8163
26. Avramoff M, Weiss J, Schachter O (1963) J Org Chem 23:3256
27. Chaudhuri MK, Bora U, Dehury SK, Dey D, Dhar SS, Khan AT, Patel BK, Dey D, Kharmawophlang W, Choudary BM, Mennepalli LK Patent No. US 2004126308
28. Kajigaeshi S, Kakinami T, Tokiyama H, Hirakawa T, Okamoto T (1987) Chem Lett 1987:627
29. Jordan AD, Luo C, Reitz AB (2003) J Org Chem 68:8693
30. Kajigaeshi S, Kakinami T, Tokiyama H, Yamasaki H, Hirakawa T, Okamoto T (1987) Bull Chem Soc Jpn 60:2667
31. Salazar J, Dorta R (2004) Synlett 7:1318
32. Tanaka K, Shiraishi R, Toda F (1999) J Chem Soc Perkin Trans 1:3069
33. Markovic R, Baranac M, Dzambaski Z (2004) Heterocycles 63:851
34. Fischer LF, Fiecher M (1967) Reagents for organic synthesis. Wiley, New York, p 967
35. Reeves WP, Lu CV, Schulmeier B, Jonas L, Hatlevik O (1998) Synth Commun 28:499
36. Paquet LA (ed) (1995) Encyclopedia of reagents for organic synthesis, vol 6. Wiley, New York, pp 4738, 4370
37. Muathen HA (1992) J Org Chem 57:2740
38. Djerassi C, Scholz CR (1948) J Am Chem Soc 70:417
39. Marquet A, Jacques J (1962) Bull Soc Chim Fr 1962:90
40. Johnson WS, Bass JD, Williamson KL (1963) Tetrahedron 19:861
41. Awang DV, Wolfe S (1969) Can J Chem 47:706
42. Armstrong VW, Chishti NH, Ramage R (1975) Tetrahedron Lett 6:373
43. Hosseinzadeh R, Tajbakhsh M, Khaledi H, Ghodrati K (2007) Monatsh Chem 138:871
44. Skoog DA, West DM, Holler FJ (1988) Fundamental of analytical chemistry, 5th edn. Saunders, New York, pp 342–344
45. Garg HG (1961) J Org Chem 26:948
46. Hutmacher HM, Kruger H, Musso H (1977) Chem Ber 110:3118
47. Blout ER, Eager VW, Silverman DC (1946) J Am Chem Soc 68:566
48. Arcus CL, Barrett GC (1960) J Chem Soc 1960:2098
49. Ramberg L, Wideavist S (1937) Ark Kemi Mineral Geol 12A:12
50. Kondrat'eva GV, Kogan GA, Fadeeva TM, Zav'yalov SI (1964) Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya 1964:1648
51. Veber M, Duong KNV, Gaudemer A (1981) J Organomet Chem 209:393
52. Howk BW, McElvain SM (1932) J Am Chem Soc 54:282
53. Shahak I, Bergmann ED (1960) J Chem Soc 1960:3225
54. Pearson RG, Dillon RL (1953) J Am Chem Soc 75:2439