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Working with Hazardous Chemicals

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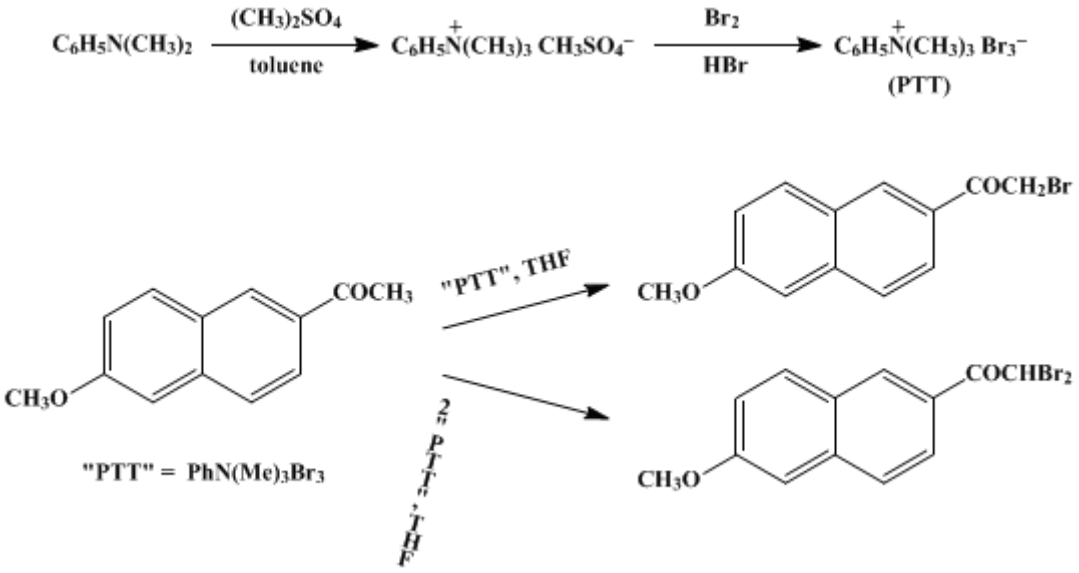
SELECTIVE α-BROMINATION OF AN ARALKYL KETONE WITH PHENYLTRIMETHYLAMMONIUM TRIBROMIDE: 2-BROMOACETYL-6-METHOXYNAPHTHALENE AND 2,2-DIBROMOACETYL-6-METHOXYNAPHTHALENE

[Ethanone, 2-bromo-1-(6-methoxy-2-naphthalenyl)- and Ethanone, 2,2-dibromo-1-(6-methoxy-2-naphthalenyl)-]



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Checked by David Walba and Robert E. Ireland.

1. Procedure

Caution! All operations should be carried out in a well-ventilated hood because dimethyl sulfate is highly toxic and the bromoketones are lachrymators and skin irritants.

A. *Phenyltrimethylammonium sulfomethylate*. A solution of 24.8 g. (25.9 ml., 0.205 mole) of freshly distilled *N,N*-dimethylaniline (Note 1) in 100 ml. of toluene (Note 2) is prepared in a 250-ml. Erlenmeyer flask equipped with a thermometer and a magnetic stirrer. The solution is stirred and heated to about 40°. Heating is stopped and 25 g. (19 ml., 0.20 mole) of distilled dimethyl sulfate (Note 3) is added with an addition funnel over 20 minutes. Within minutes, the colorless sulfomethylate starts to crystallize. The temperature which varies very little during the previous addition, rises slowly for one hour thereafter and approaches 50°. The reaction is allowed to proceed at ambient temperature for 1.5 hours after the addition is complete before it is heated on a steam bath for one hour. After cooling, the phenyltrimethylammonium sulfomethylate is filtered, washed with 20 ml. of dry toluene, and dried under vacuum, yielding 44–46.5 g. (89–94%) (Note 4).

B. *Phenyltrimethylammonium tribromide*. A solution of 10 g. (0.040 mole) of phenyltrimethylammonium sulfomethylate in 10 ml. of 48% hydrobromic acid diluted with 10 ml. of water is prepared in a 125-ml. Erlenmeyer flask equipped with a magnetic stirrer. Bromine (7.8 g., 2.5 ml., 0.049 mole) (Note 5) is added to the stirred solution from a dropping funnel over 20 minutes. An orange-yellow precipitate forms immediately, and the slurry is stirred at room temperature for 5–6 hours. The product, phenyltrimethylammonium tribromide (PTT), is filtered, washed with about 10 ml. of water, and air-dried under an efficient hood. The crude PTT, *ca.* 15 g., is recrystallized from 25 ml.

of acetic acid, giving, after filtration and air-drying, 12.9–14.0 g. (86–93%) (Note 6) of orange crystals, m.p. 113–115°.

C. *2-Bromoacetyl-6-methoxynaphthalene*. To a solution of 1 g. (0.005 mole) of 2-acetyl-6-methoxynaphthalene [*Org. Synth.*, **Coll. Vol. 6**, 34 (1988)] in 10 ml. of anhydrous tetrahydrofuran (Note 7) contained in a 125-ml. Erlenmeyer flask is added 1.88 g. (0.00500 mole) of PTT in small portions over a 10 minute period. A white precipitate forms immediately and the solution becomes pale yellow. After 20 minutes, 50 ml. of cold water is added, and the crystalline precipitate (Note 8) is filtered and washed with 10 ml. of water. The crude, white 2-bromoacetyl-6-methoxynaphthalene (*ca.* 1.3 g., m.p. 100–105°) is recrystallized from 32 ml. of cyclohexane, yielding 1.1 g. (79%) of crystalline product, m.p. 107–109° (lit. 107–108°)[2] (Note 9) and (Note 10).

D. 2,2-*Dibromoacetyl*-6-*methoxynaphthalene*. To a solution of 1 g. (0.005 mole) of 2-acetyl-6-methoxynaphthalene [*Org. Synth.*, **Coll. Vol. 6**, 34 (1988)] in 10 ml. of anhydrous tetrahydrofuran (Note 7) contained in a 125-ml. Erlenmeyer flask is added 3.76 g. (0.0100 mole) of PTT in small portions over 10 minutes. A white precipitate forms and the solution becomes yellow over one hour. Cold water (50 ml.) is added, and the crystalline product (Note 8) is filtered and washed with 10 ml. of water. The crude 2,2-dibromoacetyl-6-methoxynaphthalene (*ca.* 1.7 g., m.p. 110–117°) is recrystallized from 15 ml. of ethanol, filtered, and washed with 2 ml. of ethanol, yielding 1.40–1.55 g. (78–87%) of slightly yellow product, m.p. 116.5–118° (lit. 118–119°)[3] (Note 9) and (Note 11).

2. Notes

1. Commercial *N,N*-dimethylaniline was redistilled, b.p. 78° (13 mm.).
2. Benzene can also be used, but toluene is preferable because of its lower toxicity.
3. Commercial dimethyl sulfate was distilled, b.p. 70° (13 mm.). A slight deficiency of dimethyl sulfate ensures the complete utilization of this toxic product.
4. This product is slightly hygroscopic, but no special precautions are required for handling.
5. Bromine (B & A, ACS Reagent Grade) was used without further purification.
6. The "active bromine" can be titrated according to the following procedure: about 300 mg. of PTT is dissolved in 50 ml. of acetic acid, 10 ml. of a 5% solution of potassium iodide in ethanol is added, and the liberated iodine is titrated with a 0.1 *N* solution of sodium thiosulfate. Percent "active bromine": calculated 42.5%; found 42.1–42.5%. The molecular weight of PTT is 375.96.
7. Tetrahydrofuran was purified and dried as previously described [*Org. Synth.*, **Coll. Vol. 5**, 976 (1973)]. PTT is remarkably soluble in tetrahydrofuran (630 g. per 1. at 20°). Under the same conditions, the solubility of the resulting phenyltrimethylammonium bromide is only 0.09 g. per 1.
8. If the product precipitates as an oil, mere standing at room temperature may cause it to crystallize. If not, the addition of *ca.* 3 ml. of tetrahydrofuran, followed by swirling will usually induce crystallization.
9. *This product, like other bromoketones, can be very irritating to exposed skin.*
10. ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H, OCH_3), 4.54 (s, 2H, COCH_2Br), 7.20 (m, 4H, Ar*H*), 7.90 (m, 1H, Ar*H*), 8.21 (m, 1H, Ar*H*).
11. ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H, OCH_3), 6.86 (s, 1H, COC*H*Br_2), 7.20 (m, 4H Ar*H*), 7.90 (m, 1H, Ar*H*), 8.50 (m, 1H, Ar*H*).

3. Discussion

Quaternary ammonium perhalogenides, being solid compounds, constitute convenient halogen sources. Of the different compounds studied and reported,[2] pyridine hydrobromide perbromide[4] is the most popular. Phenyltrimethylammonium tribromide (PTT), the utility of which was recognized by Marquet and Jacques,[5] has the advantage of high stability and ease of preparation. The procedure described herein is a modification of that of Vorländer and Siebert.[6]

When dissolved in tetrahydrofuran, PTT (like pyridine hydrobromide perbromide) is a source of Br_3^- ions, the properties of which are different from those of molecular bromine. In particular, it is much less electrophilic and less reactive toward aromatic rings and double bonds,[7] and is thus a selective brominating reagent for ketones[3] or ketals[3,8] when the molecule has double bonds or activated aromatic nuclei which would be attacked by bromine. The two examples of use of this reagent clearly

differentiate between its reactivity from that of bromine. Reaction of bromine with 2-acetyl-6-methoxynaphthalene (in diethyl ether solution) gives a mixture of products, the main constituent of which results from ring bromination (2-acetyl-5-bromo-6-methoxynaphthalene).[9]

Many other examples have been described that illustrate the selectivity of PTT, not possible with bromine. Steroid and terpene α-bromoketones have been selectively obtained in molecules containing double bonds[3] or cyclopropane rings;[10,11,12] anisyl cyclohexyl ketone gives the α-bromoketone in very good yield with the aromatic ring remaining unattacked;[3] 5,7-dimethoxyflavanone can be brominated in good yield at the position alpha to the keto group, although the aromatic ring is activated by two methoxy groups.[13] A similar selectivity has been observed in the analogous case of 2-methyl-2-(2-benzyloxy-5-methoxyphenyl)cyclopentanone.[14] PTT has also been used for the selective bromination of 4-oxo-4,5,6,7-tetrahydrobenzofuran.[15]

Anhydrous tetrahydrofuran contributes to the selectivity of the reagent because of the stability of Br_3^- in this solvent. Moreover, tetrahydrofuran acts as a buffer by reaction with the liberated hydrobromic acid, which is why PTT in tetrahydrofuran can also be very useful if the substrate bears acid-sensitive functions. Acid-catalyzed epimerization can also be avoided: 2-bromobenzo[6.7]bicyclo [3.2.1]oct-6-en-3-one gives the diaxial 2,4-dibromoketone[16] and 3,4-dihydro-1-(*p*-tolylsulfonyl)benz [*c,d*]indol-5(1*H*)-one leads to the expected bromoketone, in spite of the tendency of this type of molecule to isomerize into the naphthalenoid system.[17] The importance of the solvent appears in the bromination of 1,5-cycloöctanedione: in tetrahydrofuran, the pure *cis-trans-cis* isomer is isolated,[18] whereas in dichloromethane, a mixture of two tetrabromo ketones is obtained.[19] It must be emphasized that anhydrous tetrahydrofuran must be used because small amounts of water can greatly retard the rate of bromination of ketones, with resulting decreased selectivity.

Other uses of this reagent have also been described. Tosylhydrazones undergo oxidation to tosylazoalkenes, using PTT followed by treatment with base; this reaction fails with molecular bromine, dioxane dibromide, or *N*-bromosuccinimide in a range of solvents.[20] PTT has also been recommended for the aromatization of 2-substituted-6-benzoyl-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]-benzothiazoles.[21]

Recently, other bromination reagents containing Br_3^- have been described: pyrrolidone hydrotribromide,[22] 2-carboxyethyltriphenylphosphonium perbromide,[23] and Amberlyst A 26-Br_3^- .[24]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,4-dihydro-1-(p-tolylsulfonyl)benz[c,d]indol-5(1H)-one

phenyltrimethylammonium tribromide (PTT)

PTT

pyridine hydrobromide perbromide

2-carboxyethyltriphenylphosphonium perbromide

Amberlyst A 26

Br_3^-

ethanol (64-17-5)

acetic acid (64-19-7)

Benzene (71-43-2)

diethyl ether (60-29-7)

HYDROBROMIC ACID (10035-10-6)

bromine (7726-95-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

dimethyl sulfate (77-78-1)

cyclohexane (110-82-7)

iodine (7553-56-2)

toluene (108-88-3)

N,N-dimethylaniline (121-69-7)

dichloromethane (75-09-2)

Tetrahydrofuran (109-99-9)

N-bromosuccinimide (128-08-5)

2-Acetyl-6-methoxynaphthalene (3900-45-6)

PHENYLTRIMETHYLAMMONIUM TRIBROMIDE (4207-56-1)

2-Bromoacetyl-6-methoxynaphthalene

2,2-Dibromoacetyl-6-methoxynaphthalene

Ethanone, 2-bromo-1-(6-methoxy-2-naphthalenyl)- (10262-65-4)

Phenyltrimethylammonium sulfomethylate

phenyltrimethylammonium bromide (16056-11-4)

2-acetyl-5-bromo-6-methoxynaphthalene

anisyl cyclohexyl ketone

5,7-dimethoxyflavanone (1036-72-2)

2-methyl-2-(2-benzyloxy-5-methoxyphenyl)cyclopentanone

4-oxo-4,5,6,7-tetrahydrobenzofuran (16806-93-2)

2-bromobenzo[6.7]bicyclo[3.2.1]oct-6-en-3-one

pyrrolidone hydrotribromide

Dioxane dibromide

Ethanone, 2,2-dibromo-1-(6-methoxy-2-naphthalenyl)- (52997-56-5)

1,5-cyclooctanedione