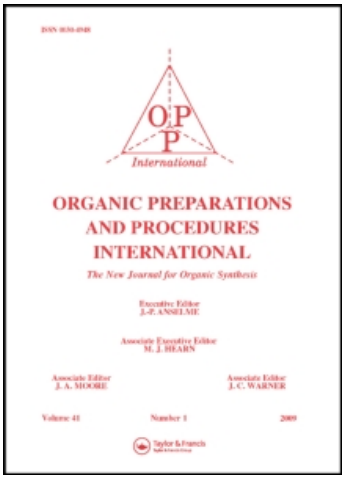

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SYNTHESIS OF SOME SUBSTITUTED BROMOANISOLES[1]

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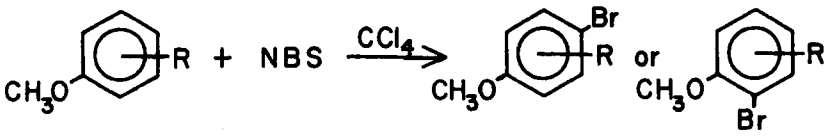
It has been reported[3] that the purity of *N*-bromosuccinimide is critical in the preparation of bromomethylarenes. When volatile impurities were not removed by keeping the *N*-bromosuccinimide at 0.5 mm over phosphorus pentoxide for 8 hr immediately before use, nuclear bromination predominated in the case of 2-methylnaphthalene to produce 1-bromo-2-methylnaphthalene.[3] However, when the *N*-bromosuccinimide had been purified by the above mentioned method, better than 90% yield of 2-naphthylmethyl bromide was obtained.

We have found that in the case of certain activated methoxy-substituted



1 2 3

a R = o-CH_3 ; b R = m-CH_3 ; c R = p-CH_3

d R = o-OCH_3 ; e R = m-OCH_3

benzenes, *N*-bromosuccinimide, purified by recrystallization from H_2O, followed by drying at 0.5 mm over phosphorus pentoxide for 15 hr and then used immediately gave only bromoarene derivatives *rather than bromoalkyl compounds*. No bromination was observed with anisole, but good yields were

obtained when either *ortho*-(1a), *meta*-(1b), or *para*-methoxytoluene (1c), or 1,2-(1d), or 1,3-dimethoxybenzene (1e) was used. Runs without benzoyl peroxide catalyst gave returns somewhat lower than when the catalyst was included (example, 75% with benzoyl peroxide and 81.5% with benzoyl peroxide in the synthesis of 4-bromo-3-methylanisole).

4-Bromo-1,2-dimethoxybenzene has been prepared by a similar procedure without the purification process described for *N*-bromosuccinimide[4] but on a scale five times larger than we have employed. Thus, we have developed a general bromination procedure applicable on a 0.1 mole scale and for five substituted methoxy benzenes reported herein. The interesting aspect is that bromination does not occur on the ring substituents, *even after* purification of the *N*-bromosuccinimide.

4-Bromo-1,2-dimethoxybenzene (2d), 1-bromo-2,4-dimethoxybenzene (1e), and 4-bromo-3-methylanisole (2b) have been prepared in good yields with thallium (III) induced bromination.[5,6] However, because of the cost and toxicity of thallium (III) compounds, our route offers a simple, inexpensive and rapid method of obtaining the three above compounds as well as 4-bromo-2-methylanisole (2a) and 2-bromo-4-methylanisole (3c). The structures of the products were confirmed by infrared, proton magnetic resonance and mass spectrometry. In addition, a Grignard reagent derived from 4-bromo-3-methylanisole (2b) gave, with CO_2, 2-methyl-4-methoxybenzoic acid (4), the physical properties of which agreed with those in the literature.[7]

2-Bromo-4-methylanisole (3c) has been used recently in the preparation of 1-methyl-4-methoxy-7-isopropylnaphthalene;[8] 4-bromo-2-methylanisole (2a) has been useful in the synthesis of compounds in the diterpene series.[9,10]

EXPERIMENTAL

General Procedure. - The following general procedure for bromination of *m*-methylanisole is applicable for all five compounds prepared. However, the yields and the physical properties are provided under the name for each product.

4-Bromo-3-methylanisole (2b). - *m*-Methylanisole (0.1 mole, 12.2 g) (1b) was stirred at reflux for 12 hr with 0.1 mole (17.8 g) of *N*-bromosuccinimide [which had been recrystallized from water and kept under vacuum (0.5 mm) with phosphorus pentoxide for 15 hr prior to use], 75 ml of carbon tetrachloride and a catalytic amount of benzoyl peroxide (0.02 mole %). After the 12 hr heating period, the mixture was cooled and the succinimide was filtered. The solvent was removed and the product 2b was distilled under vacuum; bp 59-60°/0.1 mm, lit.[11] bp 81-3°/4 mm (16.4 g, 81.5% yield); ir(film) μ: 3.30 (AR-H) 3.45 (C-H), 8.05 (Ar-O-CH_3); pmr ($DCCl_3$), δ 2.27 (s, 3, ArCH_3), 3.62 (s, 3, OCH_3), 6.58 (q, 1, J_{meta} = 3 Hz, J_{ortho} = 8.5 Hz, Ar*H*), 6.68 (d, 1, J_{meta} = 3 Hz, Ar*H*), 7.28 (d, 1, J_{ortho} = 8.5 Hz, Ar*H*); mass spectra, m/e [70 eV] (relative intensity): 79 (81.8), 200 (molecular ion, ^{79}Br, 100), 202 (molecular ion ^{81}Br, 96.7)

4-Bromo-2-methylanisole (2a). - Identical conditions as used with 2b were applied to 2a for 24 hrs. After evaporation of the solvent, the solid was recrystallized from 4:1 benzene:hexane to give 2a; mp 66.5-67°, lit.[10] mp 68° (18.2 g, 90.5% yield); ir (KBr) μ: 3.30 (Ar-H) 3.54 (C-H), 8.02 (Ar-O-CH_3); pmr ($DCCl_3$), δ 2.17 (s, 3, CH_3), 3.77 (s, 3, OCH_3), 6.65 (d, 1, J_{ortho} = 9.0 Hz, Ar*H*), 7.27 (m, 2, Ar*H*); mass spectra m/e [70 eV] (relative intensity): 79 (100), 200 (molecular ion, ^{79}Br, 46.2), 202 (molecular ion, ^{81}Br, 42.5).

2-Bromo-4-methylanisole (3c). - The same procedure was used with 1c as with 2a. The work-up was the same as in the general procedure to give pure 3c;

bp 77-80°/1 mm, lit.[8] bp 90°/4 mm (11.4 gm, 56.7% yield); ir(film) μ: 3.30 (Ar-H) 3.42 (C-H), 7.97 (Ar-O-CH_3); pmr ($DCCl_3$), δ 2.17 (s, 3, CH_3), 3.72 (s, 3, OCH_3), 6.92 (m, 3, Ar*H*); mass spectra, m/e [70 eV] (relative intensity): 79 (100), 200 (molecular ion, ^{79}Br, 29.0), 202 (molecular ion ^{81}Br, 28.3).

4-Bromo-1,2-dimethoxybenzene (2d). - Ether 1d was treated as above for 17.5 hr. Following work-up, the product 2d was vacuum distilled; bp 83-85°/0.02 mm, lit.[4] bp 116.5-117.5°/4.5-5 mm (15.9 g, 73% yield); ir(film) μ: 3.30 (Ar-H) 3.42 (C-H), 8.13 (Ar-O-CH_3); pmr ($DCCl_3$), δ 3.75 (s, 6, OCH_3), 6.63 (m, 1, Ar*H*), 6.94 (m, 2, Ar*H*); mass spectra, m/e [70 eV] (relative intensity): 79 (100), 216 (molecular ion ^{79}Br, 66.3), 218 (molecular ion ^{81}Br, 59.2). With unpurified NBS, the yield of 2c was 61.5%.

1-Bromo-2,4-dimethoxybenzene (2e). - Ether 1e was treated as above for 15 hr. Following work-up, the product 2e was distilled; bp 93-95°/0.03-0.04 mm, lit.[12] bp 135°/18 mm (16.5 gm, 76% yield); ir(film) μ: 3.30 (Ar-H) 3.38 (C-H), 8.20 (Ar-O-CH_3); pmr ($DCCl_3$), δ 3.66 (s, 3, OCH_3), 3.72 (s, 3, OCH_3), 6.31 (m, 2, Ar*H*), 7.29 (d, 1, J_{ortho} = 8.5 Hz, Ar*H*); mass spectra, m/e [70 eV] (relative intensity: 79 (100), 216 (molecular ion ^{79}Br, 15.2), 218 (molecular ion ^{81}Br, 12.2).

2-Methyl-4-methoxybenzoic acid (4). - A Grignard reagent was made in the usual manner from 2b and ether. Carbonation and work-up in the common fashion gave 4 (32.5%); mp 177-177.5°, lit.[7] mp 177°; ir (KBr) μ: 3.02 (-OH), 3.50 (C-H), 6.08 (C=O), 8.10 (Ar-O-CH_3).

REFERENCES

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2. Research Assistant, Biomedical Grant RRO 7077-07, Fall, 1972. Merck, Sharp, Dohme Fellow, Spring, 1973. Dow Fellow, Summer, 1974. Predoctoral candidate, 1972-present.

3. N. B. Chapman and J. F. A. Williams, J. Chem. Soc., 5044 (1952).

4. R. A. B. Bannard and G. Latremouille, Can. J. Chem., 31, 469 (1953).

5. A. McKillop, D. Bromley, and E. C. Taylor, J. Org. Chem., 37, 88 (1972).

6. K. L. Erickson and H. W. Barowsky, J. Chem. Soc. (D), 1596 (1971).

7. D. Peltier, Bull. Soc. Sci. Bretagne, 31, 7 (1956).

8. K. Adachi, Yuki Gosei Kagaku Kyokai Shi, 29, 515 (1951), Chem. Abstr., 75, 140999 (1971).

9. J. Detobelle and M. Fetizon, Bull. Soc. Chim. France, 1900 (1961).

10. D. Nasipuri and D. N. Roy, J. Indian Chem. Soc., 40, 327 (1963).

11. M. S. Carpenter, W. M. Easter, and T. F. Wood, J. Org. Chem., 16, 586 (1951).

12. G. P. Rice, J. Amer. Chem. Soc., 48, 3125 (1926).

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