

Application of *n*-Butyl Lithium in the Synthesis of Some Methoxy-Substituted Aromatic Carboxylic Acids

By IAN W. MATHISON, RICHARD C. GUELDNER, and DIANNA M. CARROLL

The application of *n*-butyl lithium for the rapid synthesis of methoxy-substituted aromatic carboxylic acids is reported. New compounds associated with this study are described.

SYNTHETIC STUDIES by the authors on isoquinolines as potential cardiovascular agents (1-4) were patterned on the D and E rings of reserpine particularly incorporating the 3,4,5-trimethoxybenzoyl radical. The marked antiarrhythmic activity observed with decahydroisoquinoline compounds possessing this moiety (4), as well as the documented importance of the 3,4,5-trimethoxybenzoyl radical for neurosedative and analgesic activity (5), led the authors to investigate the synthesis of other methoxy-substituted aromatic carboxylic acids in order to ascertain the biological effects induced by various methoxy substitutions in the above series of compounds. The authors report improved, rapid syntheses for some methoxy benzoic acids and a new direct synthesis for tetramethoxyterephthalic acid, using *n*-butyl lithium as the key reactant.

Many studies have been carried out on the applications and anomalies of lithiation of aromatic systems (6). In general, metalation with *n*-butyl lithium occurs *ortho* to ether functions, *i.e.*, $-\text{OCH}_3$. The authors have demonstrated that treatment of 1,2,4,5-tetramethoxybenzene with 2 moles *n*-butyl lithium for 40 min. in tetrahydrofuran, under standard metalation conditions, followed by carbonation of the resulting lithium derivative with solid CO_2 , yielded the corresponding tetramethoxyterephthalic acid (I). The reported melting point for a compound presumed to be tetramethoxyterephthalic acid (7), obtained from oxidative degradation of a natural product, halfordin, is considerably higher (20°) than that for the authors' sample. Although analytical data were reported, no spectral data were reported by these workers. The authors' spectral and analytical data were consistent with the proposed structure for their compound. To further substantiate the structure of the above terephthalic acid and thus the entry of two lithium atoms during the above metalation, methylation of the dilithiated product was carried out using dimethyl sulfate. The resulting tetramethoxy-*p*-xylene had the required spectral and analytical data. Oxidation of this *p*-xylene derivative using potassium permanganate yielded the identical tetramethoxyterephthalic acid (I) prepared from the carbonation of the dilithiated 1,2,4,5-tetramethoxybenzene. Additionally the authors examined the product obtained from treatment of 1,2,4,5-tetramethoxybenzene with 1 mole of *n*-butyl lithium. As expected, only the monocarboxylic acid, 2,3,5,6-tetramethoxybenzoic acid, was produced as a result of the introduction of

one lithium atom into the aromatic ring followed by carbonation. Purification of the product yielded a compound not previously reported, although Bargellini *et al* (11) reported an unspecified tetramethoxybenzoic acid produced during the action of cyanogen bromide on 1,2,3,5-tetramethoxybenzene. The melting point of their acid compares with the authors' product and its formation from 1,2,3,5-tetramethoxybenzene is explainable by methoxyl migration considering the reaction conditions reported by these investigators. Treatment of 1,2,3,5-tetramethoxybenzene with 1 mole of *n*-butyl lithium yielded the expected 2,3,4,6-tetramethoxybenzoic acid. NMR data verified the structure of this compound although Nierenstein (8) had previously reported a compound of higher melting point. Attempts to introduce two lithium atoms into this molecule to form tetramethoxyisophthalic acid were not successful.

Treatment of 3,5-dimethoxytoluene with 1 mole of *n*-butyl lithium, followed by carbonation of the resulting metalated intermediate, yielded 2,6-dimethoxy-4-methylbenzoic acid; as anticipated the lithium atom was introduced adjacent to the two methoxyl groupings. It was shown that extended reaction times (105 min.) were necessary to obtain good yields in this reaction.

The above studies indicate that metalation of appropriately substituted methoxy benzenes with *n*-butyl lithium, followed by carbonation with solid carbon dioxide is a rapid, direct method for the synthesis of methoxy-substituted aromatic carboxylic acids and is superior to previously reported procedures.

EXPERIMENTAL

Apparatus—All melting points were determined using a Swissco melting point apparatus and are corrected. Elemental analyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England. IR spectra were recorded on a Perkin-Elmer model 137B Infracord spectrophotometer. NMR spectra were recorded on a Varian A60 spectrometer using tetramethylsilane as internal standard.

Tetramethoxyterephthalic Acid (I)—To 1,2,4,5-tetramethoxybenzene (1.1 g.) in tetrahydrofuran (100 ml.) (freshly distilled from lithium aluminum hydride) was added, in small portions, a solution of 15% *n*-butyl lithium in hexane (4.5 ml.) under nitrogen. In approximately 45 sec. a white precipitate formed. The mixture was stirred for an additional 30 min. At this time excess solid carbon dioxide was added and the resulting mixture evaporated on a rotary evaporator. The solid residue was dissolved in distilled water and acidified. Gentle warming of this solution on a steam bath caused the remaining traces of tetrahydrofuran to be removed. The mixture was allowed to cool

Received May 16, 1968, from the Department of Medicinal Chemistry, University of Tennessee College of Pharmacy, Memphis, TN 38103.

Accepted for publication July 10, 1968.

The authors would like to acknowledge the generous financial support provided by Marion Laboratories, Inc., Kansas City, Mo., during the course of this continuing research program.

and stand overnight. The precipitated solid was filtered (13 g.) and recrystallized from acetone-ethyl acetate as colorless prisms (11.6 g.), m.p. 249.5–251.5°.

Anal.—Calcd. for $C_{12}H_{14}O_8$: C, 50.35; H, 4.93. Found: C, 50.42; H, 5.04.

The NMR spectrum (deuterated dimethyl sulfide) showed two groups of protons in a ratio 1:6, consistent with the $-COOH$ and $-OCH_3$ protons. The carboxyl protons 6.1–7.5 p.p.m. were considerably upfield from the expected peak position indicating considerable shielding or solvent effects. Addition of D_2O removed this peak position confirming the assignment of a carboxyl proton to this peak. The IR spectrum (KBr) was consistent with the proposed structure (1720 cm^{-1} , $-COOH$).

Tetramethoxy-p-xylene (II)—To 1,2,4,5-tetramethoxybenzene (2.00 g.) in tetrahydrofuran (100 ml.) was added a solution of 15% *n*-butyl lithium in hexane (8.6 ml.) in a similar manner to that described for Compound I. The reaction was allowed to proceed for 1.5 hr. At this time the mixture was cooled to 0° and dimethyl sulfate (2.7 g.) added to the precipitated mixture. The precipitate immediately dissolved and the resulting solution stirred for an additional 1.5 hr. The solution was then concentrated using a rotary evaporator. Water and 5 *N* sodium hydroxide were added and further concentration was carried out to yield a low melting solid (1.95 g.). This material was crystallized from ethanol-water (10:1) to yield colorless prisms, m.p. 82–83°.

Anal.—Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.74; H, 7.93.

The NMR (carbon tetrachloride) showed peaks at 3.7 p.p.m. $-OCH_3$ and 2.05 p.p.m. $-CH_3$ (2:1) consistent with the proposed structure.

Compound II (0.46 g.), obtained from above, was added to a solution of potassium permanganate (1.4 g.) in water (100 ml.). The mixture was heated to reflux; after 45 min. the solution had decolorized. The solution was cooled and the precipitated manganese dioxide filtered. The filtrate was evaporated to near dryness, made acidic, and the precipitate filtered. The recrystallized precipitate (from water) had a m.p. 251.0–252.0°. Mixture melting point data with Compound I showed no depression of the melting point and thus confirmed this oxidation product to be Compound I.

2,3,5,6-Tetramethoxybenzoic Acid (III)—1,2,4,5-Tetramethoxybenzene (1.1 g.) was treated with 15% *n*-butyl lithium in hexane (2.1 ml.) in tetrahydrofuran (100 ml.) in an identical manner to that previously described for I. Treatment of the lithiated benzene derivative with carbon dioxide followed by an identical workup procedure outlined for I, yielded 1.0 g. solid which was recrystallized from water to yield colorless needles, m.p. 150.5–151.5°.

Anal.—Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.39; H, 5.80.

The IR spectrum was consistent with the proposed structure: major peaks (KBr) at 3400 cm^{-1} (OH), 1750 cm^{-1} (COOH), and 1060 cm^{-1} (OCH_3).

2,3,4,6-Tetramethoxybenzoic Acid (IV)—1,2,3,5-Tetramethoxybenzene (1.54 g.) was treated with 15% *n*-butyl lithium (3.23 ml.) in tetrahydrofuran in the usual manner. The reaction was allowed to

proceed for 20 min. and then carbonated by the addition of solid carbon dioxide. The usual workup yielded a solid (1.14 g.) which was recrystallized from ethanol-benzene as colorless prisms, m.p. 152–152.5° (with decomposition) [lit. value 184–186° (8)].

Anal.—Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.79; H, 5.82.

The NMR spectrum (deuterated acetone) showed peaks at 3.8 p.p.m. ($-OCH_3$), 5.7 p.p.m. ($-COOH$), and 6.5 p.p.m. ($-CH$), consistent with the proposed structure.

2,6-Dimethoxy-4-methylbenzoic Acid (V)—3,5-Dimethoxytoluene (3.28 g.) was treated with 15% *n*-butyl lithium (9.0 ml.) under the standard conditions, with cooling, outlined in I. The reaction was allowed to proceed for 105 min. and then terminated by addition of solid carbon dioxide. The tetrahydrofuran was removed *in vacuo* and the resulting solid suspended in water and extracted with chloroform (to remove any unreacted 3,5-dimethoxytoluene). The aqueous layer was acidified and filtered. The filtered solid (2.35 g.) was recrystallized from water as colorless prisms, m.p. 189–190° [lit. value 180–182° (9)].

2,3,4-Trimethoxybenzoic Acid (VI)—1,2,3-Trimethoxybenzene (1.39 g.) was treated in tetrahydrofuran (100 ml.) with 15% *n*-butyl lithium in hexane (3.5 ml.) under the previously described conditions for a period of 45 min. Solid carbon dioxide was added at this time. The tetrahydrofuran was evaporated and the residue suspended in water. The insoluble starting material was filtered and the filtrate acidified. No precipitate appeared. The solution was extracted with chloroform. The chloroform extract was evaporated to yield a viscous mass which was recrystallized from water to yield 0.7 g. colorless prisms, m.p. 98–100° [lit. value 97° (10)]. Further amounts of product were obtained from the aqueous layer by concentration followed by chloroform extraction.

REFERENCES

- (1) Mathison, I. W., *J. Org. Chem.*, **30**, 3558(1965).
- (2) Mathison, I. W., *J. Med. Chem.*, **11**, 181(1968).
- (3) Mathison, I. W., and Guedner, R. C., *J. Org. Chem.*, **33**, 2510(1968).
- (4) Mathison, I. W., Guedner, R. C., Lawson, J. W., Fowler, S. J., and Peters, E. R., *J. Med. Chem.*, 1968, in press.
- (5) Kasztreiner, E., Borsy J., and Vargha, L., *Biochem. Pharmacol.*, **11**, 651(1952).
- (6) Adams, R., "Organic Reactions," Vol. VIII, Wiley, New York, N. Y., 1954, p. 276.
- (7) Hegarty, M. R., and Lahey, F. N., *Australian J. Chem.*, **9**, 120(1956).
- (8) Nierenstein, M., *J. Chem. Soc.*, **111**, 4(1917).
- (9) Robertson, A., and Robinson, R., *J. Chem. Soc.*, **1927**, 2196.
- (10) Karrer, P., Rebmann, A., and Zeller, E., *Helv. Chim. Acta*, **3**, 261(1920).
- (11) Bargellini, G., and Madasani, F., *Gazz. Chim. Ital.*, **61**, 684(1931); through *Chem. Abstr.*, **26**, 1264(1932).



Keyphrases

Carboxylic acids, methoxy substituted—syntheses

n-Butyl lithium—methoxy-substituted carboxylic acids syntheses

IR spectrophotometry—structure

NMR spectroscopy—structure