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NOTE

THE SELECTIVE METALATION OF 1-METHOXYNAPHTHALENE IN EITHER THE 2- OR 8-POSITION

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In an earlier paper from this laboratory[1] it was reported that 1-methoxynaphthalene underwent concurrent attack by n-butyllithium in ether at the 2- and 8-positions with product composition of 83% of 2-lithio-1-methoxynaphthalene and 17% 8-lithio-1-methoxynaphthalene as represented by the methyl esters of the carboxylic acids obtained by carbonation. In the earlier work it was noted that product composition changed to 65% 2-isomer and 35% 8-isomer if n-butyllithium prepared in ether replaced the "salt-free" n-butyllithium prepared commercially in hexane.

High levels of 8-metalation have been reported in the metalation of 1-[(dimethylamino)methyl]naphthalene[2] and 1-aminonaphthalene[3] with n-butyllithium.

In this paper we should like to report the results of further investigations of 1-methoxynaphthalene which indicate that attack at *either* the 2- or 8-position can be made highly selective by proper choice of reaction solvent and alkyllithium reagent.

We first repeated the metalation of 1-methoxynaphthalene with n-butyllithium in ether/hexane solvent as reported earlier[1] with product composition indicating 73% 2-metalation and 27% 8-metalation. Replacement of ether solvent by cyclohexane in a second run caused no significant change (72% 2- and 28% 8-metalation) in product composition nor in total yield (*ca.* 28%) of mixed carboxylic acid product (excluding valeric acid). The same reaction conditions except that one equivalent of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was present allowed a shift in product composition to >99.3% 2-metalation and <0.3% 8-metalation. The yield of 1-methoxy-2-naphthalenecarboxylic acid was 60%. Essentially the same results were obtained in the presence of *N,N,N',N'*-tetraethylethylenediamine (TEEDA). Replacement of n-butyllithium with tert-butyllithium in the system containing TMEDA caused a slight shift in product composition to 99% 2-metalation and 1% 8-metalation and yield of carboxylic acid back to about 20%.

On the other hand metalation of 1-methoxynaphthalene with tert-butyllithium in pentane/cyclohexane solvent gave a product representing 97% of 8-metalation and 3% 2-metalation, although again the yield of acid was only 20%. A second run gave < 1% 2-metalation and >99% 8-metalation.

Thus it is possible to change sharply the relative rates of metalation of the 2- and 8-positions in 1-methoxynaphthalene by shifts between n-BuLi and tert-BuLi and between pure hydrocarbon solvent and hydrocarbon/amine solvent mixtures.

The 8-metalation of 1-methoxynaphthalene with high selectivity constitutes a useful synthetic technique for obtaining 1,8-disubstituted naphthalene derivatives.

EXPERIMENTAL SECTION

Metalation with n-butyllithium in presence of TMEDA

A solution of 7.9 g (0.05 mol) of 1-methoxynaphthalene in 20 ml of cyclohexane was added under a nitrogen atmosphere to a mixture of 31 ml (0.05 mol) of 1.6 *M* n-butyllithium in hexane (Foote Mineral Co. product), 5.8 g (0.05 mol) TMEDA and 10 ml of cyclohexane. The mixture was stirred at room temperature for 2 h after which it was carbonated by pouring into a slurry of anhydrous ether and powdered solid carbon dioxide. Excess dilute aqueous hydrochloric acid was added, the organic layer separated and extracted with saturated aqueous sodium bicarbonate solution. The extracts were acidified (HCl) and the crude acid mixture filtered off and thoroughly dried for removal of most of any remaining valeric acid. The product weighed 6.0 g, 59% yield assuming 1-methoxynaphthalenecarboxylic acid. The mixture melted at 123–125°. The melting point of 1-methoxy-2-naphthalenecarboxylic acid is 126–127°[4].

Metalation with tert-butyllithium

Eleven g (0.07 mol) of 1-methoxynaphthalene in 50 ml of cyclohexane was added to a solution of 50 ml of 1.59 *M* tert-butyllithium (0.08 mol) in pentane (Lithium Corp. of America product). Reaction time was 13 h at room temperature and work-up was as indicated in the prior metalation. The yield was 2.9 g (20%) of product melting at 154–157°.

A second run at 26 h reaction time gave a 35% yield of product, melting at 157–159°.

Analysis of reaction products

The procedure for conversion to mixed methyl esters for vapor phase chromatographic analysis was carried out as described earlier[1,5]. A Wilkins–Anderson "Autoprep" Model A-700 was used with a $30' \times \frac{3}{8}''$ column with SE-30 silicone. The instrument was operated at a column temperature of 180° and a helium flow rate of 200 ml/min. The retention time for methyl 1-methoxy-2-naphthoate was 24.2 min and for methyl 1-methoxy-8-naphthoate was 26.8 min. The peaks were identified by addition of authentic samples. Conversion of peak areas to mole ratios was made by use of known composition of the two esters approximating the composition of the reaction product esters.

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