Communications to the Editor

Metalated Carboxylic Acids. II. Monoalkylation of Metalated Toluic Acids and Dimethylbenzoic Acids

Sir:

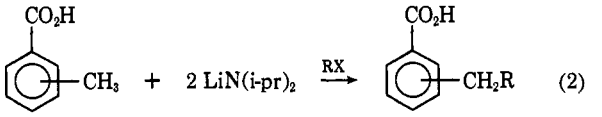
Isobutyric acid has been alkylated without preliminary alteration of the carboxyl function[1] (eq 1). The procedure, which was claimed to be general for aliphatic

$$[C(CH_3)_2CO_2]^{2-}Li^+_2 \xrightarrow{R^1X} R'C(CH_3)_2CO_2H \quad (1)$$

carboxylic acids, was illustrated by several examples which implied a useful synthetic alternative to the Haller–Bauer sequence[2] for the preparation of trisubstituted acetic acids. Of several hundred examples studied, the results obtained with crotonic acid[3] among other considerations prompted attempts to metalate carboxylic acids with more extensive conjugated systems. The present report describes some reactions of metalated toluic acids with selected electrophilic reagents alluded to in the earlier report[1] and extends these results to dimethylbenzoic acids which undergo monoalkylation at a single, selective site.

The addition of a tetrahydrofuran (THF) solution of *o*-toluic acid to 2 equiv of lithium diisopropylamide in THF–heptane at 0° produced a deep red, homogeneous solution. Isolation of the *o*-toluic acid after injection of deuterium oxide revealed the absence of deuterium incorporation as determined by spectral analysis. Removal of the mixed solvents from another solution on a vacuum line left a deep red gum whose nmr spectrum in THF displayed integrated signals for diisopropylamine in the ratio of 1 molecule of diisopropylamine per molecule of *o*-toluic acid. Additionally, treatment of the deep red solution with 1-bromobutane gave *o*-pentylbenzoic acid (Table I). These results suggest (1) lithium diisopropylamide in THF–heptane is a sufficiently strong base to abstract a proton from the methyl group of lithium *o*-toluate,[4] (2) the carbanionic intermediate is at least weakly associated with diisopropylamine, and (3) proton transfer on acidification (deuterium oxide addition) is a complicated process in which the diisopropylamine proton is transferred exclusively to the carbanionic site by a noncompetitive process.[5] The latter result affords additional evidence for the formation of a molecular complex between the carbanionic species and diisopropylamine.

The addition of 1-bromobutane to a solution containing toluene and 1 equiv of lithium diisopropylamide in THF–heptane under identical conditions produced pentylbenzene in low yield (5%). Thus metalation of the aromatic methyl group of the toluic acids implies an activating influence exerted by the carboxylate substituent which is consistent with a positive Hammett σ value recorded for an aromatic carboxylate group.[7] Table I summarizes alkylations of all three toluic acids

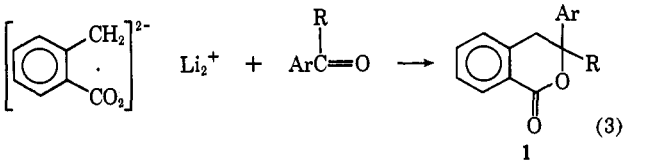


(2)

(eq 2). The yields reported were determined after distillation of the methyl esters prepared by Fischer esterification of the crude reaction products. Glpc analysis of the crude esters indicated minimal dialkylation (1–5%). Methyl *o*-(1-butylpentyl)benzoate (9%) was isolated from one of the repetitions using *o*-toluic acid in which the amount of dialkylated product was unusually large. The corresponding acids were obtained by hydrolysis of the esters. Most interesting of these results is the metalation and alkylation of *m*-toluic acid.[9] Likewise, 3,5-dimethylbenzoic acid gave 5-pentyl-*m*-toluic acid [Me ester; 31%; bp 127–129° (2.0 mm)] and 3-methyl-*o*-anisic acid gave 3-pentyl-*o*-anisic acid [Me ester; 35%; bp 102–104° (0.50 mm)]. Synthetically, this alkylation procedure provides a useful method for elaborating aromatic carboxylic acids bearing a methyl substituent *regardless* of its orientation.

The carbanionic intermediate can be generated by several procedural variations. For example, treatment of the lithium toluates prepared from the acids and excess lithium hydride with 1 equiv of lithium diisopropylamide generated exogenously and finally with 1 equiv of 1-bromobutane gave yields of pentylbenzoic acids comparable to those reported in Table I. More conveniently, *n*-butyllithium can be injected into a mixture of the lithium toluate (from lithium hydride and the toluic acid) and diisopropylamine in THF with similar final results. The lithium toluate fails to compete successfully with diisopropylamine for available *n*-butyllithium. Once formed, lithium diisopropylamide reacts with the lithium toluate by proton abstraction to produce the desired carbanionic species.

Metalated carboxylic acids react by addition to carbonyl groups (eq 3). The model selected to illustrate



(3)

1

the reaction, *o*-toluic acid, does not produce optimal results. The products, **1** (Ar = R = C_6H_5, 28%; Ar = 4-$CH_3OC_6H_4$; R = H, 24%) can be more success-

(1) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967). For other examples illustrating reactions with epoxides, see P. L. Creger, U. S. Patent No. 3,413,288 (1968); British Patent No. 1,089,788 (1967); British Patent No. 1,079,840 (1967).

(2) K. E. Hamlin and A. W. Weston, *Org. Reactions*, **9**, 1 (1957).

(3) Unpublished results.

(4) F. H. Rash, S. Boatman, and C. R. Hauser, *J. Org. Chem.*, **32**, 372 (1967), report *p*-toluic acid failed to alkylate in a sodium amide–ammonia system.

(5) If exchange occurred between deuterium oxide and diisopropylamine prior to neutralization of the carbanion, at least some deuterium incorporation could be expected.[6] None was detected.

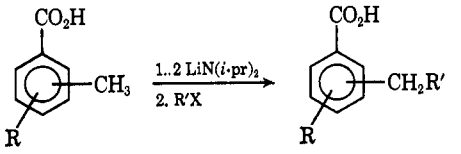
(6) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 44.

(7) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953). Less favorable values have also been recorded.[8]

(8) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

(9) J. G. Atkinson, J. J. Csakvary, G. T. Herbert, and R. S. Stuart, *J. Amer. Chem. Soc.*, **90**, 498 (1968), have reported deuterium exchange in *m*-toluic acid.

Table I. Alkylation of Methylbenzoic Acids[a]



R = H, CH_3

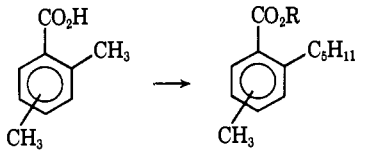
Acid	Alkylating agent	Yield, %	Methyl ester, bp	Carboxylic acid
o-Toluic	1-Bromobutane	69–73	102–105° (2.0 mm)	Bp 116–118° (0.20 mm)
m-Toluic	1-Bromobutane	26	117–119° (2.0 mm)	Mp 58–59°
p-Toluic	1-Bromobutane	54–58	119–121° (2.0 mm)	Mp 86–88° (126–127°)[b]
	1-Bromo-4-methylpentane	51–65	110–112° (0.25 mm)	Mp 132–133°
2,4-Dimethylbenzoic	1-Bromobutane	57	116–119° (2.0 mm)	Mp 51–52°
2,5-Dimethylbenzoic	1-Bromobutane	67	118–121° (2.0 mm)	Mp 57–59°
3,4-Dimethylbenzoic	1-Bromobutane	82–89	130–134° (2.0 mm)	Mp 77–79°

[a] Satisfactory combustion analyses and consistent spectral data have been obtained for all products reported. [b] *p*-Pentylbenzoic acid[c] melts (mp 86–88°) to form a liquid crystalline (mesomorphic) state which shows a very sharp transition to an isotropic liquid at 126–127°. [c] G. H. Brown and W. G. Shaw, *Chem. Rev.*, **57**, 1049 (1957).

fully obtained by use of metalated N-methyl-*o*-toluamide.[10]

Empirical observations suggested considerable differences in the ease of metalation of the various toluic acids. If these apparent differences were real and if they were a reflection of substantially different pK_a values associated with the methyl groups depending on their orientations relative to the carboxyl group, then selective metalation and, hence, selective alkylation might be possible in aromatic carboxylic acids which contain more than one methyl substituent. When several appropriately chosen dimethylbenzoic acids were employed as models, selective monoalkylation was observed (Table I). The series $o > p > m$ describes the order of preferential reactivity of one methyl group in the presence of a second methyl substituent with a different orientation.

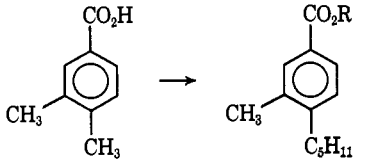
Equation 4 illustrates the results obtained with 2,4- and 2,5-dimethylbenzoic acids. Glpc and nmr analysis



(4)

R = H, CH_3

conclusively established the *ortho*-methyl group as the preferred reaction site ($o > m, p$). The alkylation of 3,4-dimethylbenzoic acid produced a single product, **2**, as determined by glpc analysis (eq 5). The structure of

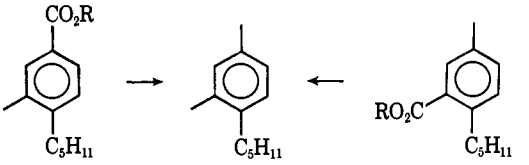


(5)

2

R = H, CH_3

the product could not be established by nmr analysis since both methyl groups in the starting dimethylbenzoic acid displayed the same chemical shift. Accordingly, the following sequence was employed to establish **2** as the correct structure.



2 **3** **4**

R = CH_3

The pentylxylene [bp 103–104° (5.0 mm)], **3**, obtained by a two-stage reduction[11] of ester **2** proved to be identical with that obtained from the alkylation product of 2,5-dimethylbenzoic, **4**, and proved to be different from the pentylxylene obtained from the alkylation product of 2,4-dimethylbenzoic acid by ir, nmr, and glpc analysis.

With **2** established as the structure of the single alkylation product of 3,4-dimethylbenzoic acid, the series for the preferred reaction site in dimethylbenzoic acids becomes $o > p > m$. Thus, the reaction sequence—metalation, alkylation—affords a technique for selectively elaborating dimethylbenzoic acids in synthetically useful yields.

(10) R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, 29, 3514 (1964).

(11) A. Streitwieser and W. C. Langworthy, *J. Amer. Chem. Soc.*, **85**, 1758 (1963).

P. L. Creger
Chemistry Department, Medical and Scientific Affairs Division
Parke, Davis and Company
Ann Arbor, Michigan 48106
Received December 9, 1969

Metalated Carboxylic Acids. III. Monoalkylation of Alkylacetic Acids. A Possible Alternative to the Malonic Ester Synthesis for the Preparation of Dialkylacetic Acids

Sir:

The preparation of dialkylacetic acids is often accomplished by the stepwise alkylation of malonic ester or related derivatives containing an active methylene