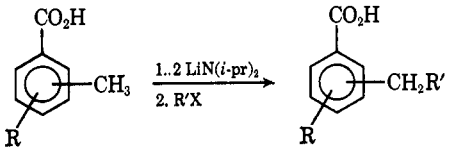
Table I. Alkylation of Methylbenzoic Acids[a]



R = H, CH_3

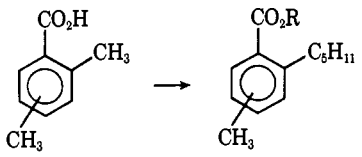
Acid	Alkylating agent	Yield, %	Methyl ester, bp	Carboxylic acid
o-Toluic	1-Bromobutane	69–73	102–105° (2.0 mm)	Bp 116–118° (0.20 mm)
m-Toluic	1-Bromobutane	26	117–119° (2.0 mm)	Mp 58–59°
p-Toluic	1-Bromobutane	54–58	119–121° (2.0 mm)	Mp 86–88° (126–127°)[b]
	1-Bromo-4-methylpentane	51–65	110–112° (0.25 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.

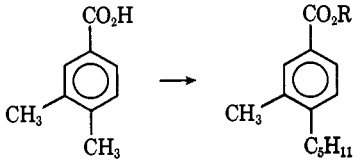
Equation 4 illustrates the results obtained with 2,4- and 2,5-dimethylbenzoic acids. Glpc and nmr analysis



(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

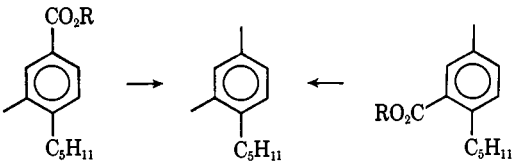


(5)

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).

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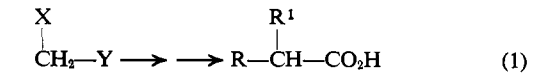
Metalated Carboxylic Acids. III. Monoalkylation of Alkylacetic Acids. A Possible Alternative to the Malonic Ester Synthesis for the Preparation of Dialkylacetic Acids

Sir:

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

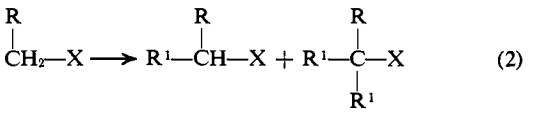
group.[1] The process requires appropriate selection of the activating substituents, stepwise introduction of the desired alkyl groups, and ultimate removal of one of the activating groups. This succession of distinct operations accomplishes the overall transformation indicated in eq 1. The choice of reaction conditions, nature of



(1)

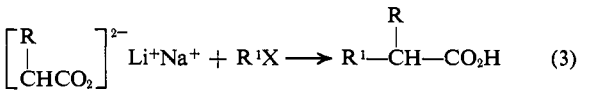
the alkylating agent, and the order of introduction of the alkyl groups all influence the degree of success in these procedures.[1]

Dialkylation is a significant side reaction in many carbanion alkylations and a variety of procedural modifications have been devised to minimize overreaction.[1] Dialkylation is particularly serious in the alkylation of alkylacetonitriles,[1,2] malononitriles,[1] and alkylacetamides[3] (eq 2, X = CN, $CONR_2$), and, although it is minimal in the alkylation of esters[1] (eq 2, X = CO_2R),



(2)

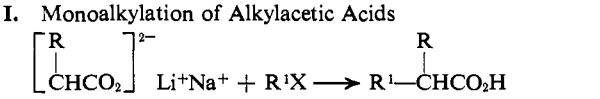
overall yields are frequently modest.[1,4] However, excellent results have been reported[5] when suitable choices of base, ester, and reaction conditions are made. This report describes the preparation of dialkylacetic acids by the monoalkylation of metalated alkylacetic acids (eq 3) in which dialkylation is minimal.



(3)

The procedure affords useful yields of dialkylacetic acids (Table I) and it avoids some of the limitations of the malonic ester synthesis or related procedures. For example, special procedures designed to overcome problems in introducing,[1] blocking,[1,6] and removing[1,6,7] a second activating group are obviously avoided since none is present. The order of introduction of alkyl groups appears not to be a significant limitation (Table I) in the success of the alkylation, only in the ease of separation of the final mixture. The alkylation is relatively insensitive to the steric bulk of the substituent initially present, a result which is possibly related to the structure of the metalated species.[8] Finally, the alkylacetic acids which serve as the point of departure in the present method are readily available.

Table I. Monoalkylation of Alkylacetic Acids



Alkyl halide	Metalated carboxylic acid	Yield,[a] %
n-C_4H_9Br	$CH_3CH_2CO_2H$	54
n-C_4H_9Br	$CH_3(CH_2)_2CO_2H$	55
n-C_4H_9Br	$CH_3(CH_2)_3CO_2H$	84
n-C_4H_9Br	$(CH_3)_2CHCH_2CO_2H$	83
n-C_4H_9Br	$CH_3(CH_2)_4CO_2H$	87
n-$C_6H_{13}Br$	$CH_3(CH_2)_4CO_2H$	86
n-$C_6H_{17}Br$	$CH_3(CH_2)_4CO_2H$	88
n-C_4H_9Br	$(CH_3)_3CCH_2CO_2H$	81
n-C_4H_9Br	$CH_3(CH_2)_8CO_2H$	86
n-C_4H_9Br	*C*-$C_6H_{11}CH_2CO_2H$	84
n-C_4H_9Br	*C*-$C_5H_9CH_2CO_2H$	87
n-C_4H_9Br	$C_6H_5OCH_2CO_2H$	70[b]

[a] Satisfactory combustion analyses and consistent spectral data have been obtained for all products reported. [b] Isolated as the methyl ester.

The principal limitation of the present method is the result of poor solubility of salts of lower carboxylic acids. Poorly soluble salts are incompletely metalated in the solvent system most commonly employed (THF–heptane) and mixtures of metalated and unmetalated alkylcarboxylates result. Reduced yields of monoalkylated products and the appearance of measurable dialkylation are then observed. For example, the lower yield for the alkylation of propionic acid (Table I) can be accounted for in part by the isolation of 14% of dialkylated product, 2-butyl-2-methylhexanoic acid. Generally, salts of carboxylic acids higher than propionic acid are completely metalated and dialkylation, where detectable, accounts for less than 5% of the product. The following procedure is typical.

To a slurry consisting of a suspension of sodium hydride in mineral oil and diisopropylamine (300 mmol) in 300 ml of tetrahydrofuran (1 ml/mmol) was added 1 equiv (300 mmol) of caproic acid. After heating to reflux briefly, the suspension of sodium caproate was cooled and 1 equiv (300 mmol) of *n*-butyllithium was injected at $t < 10°$. The mixture was warmed to 30° briefly to complete the metalation, then it was cooled and 1 equiv (300 mmol) of 1-bromohexane was added. After stirring for several hours at 30°, water was added and the product, 2-butyloctanoic acid, was isolated after acidification of the aqueous layer. Glpc analysis of the crude product (58.5 g) showed two components in relative amounts 6.5:93.5, corresponding to caproic acid and 2-butyloctanoic acid. Distillation gave 86% of 2-butyloctanoic acid, bp 110–113° (0.50 mm); glpc, 100%. Glpc examination of the still pot residue revealed *possible* dialkylated product which amounted to not more than 0.4%.

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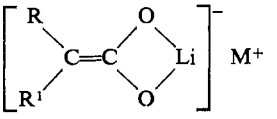
(8) Incomplete results offer tentative support for a delocalized "ate" structure as a gross representation of metalated aliphatic (alicyclic) carboxylic acids.



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