Tetrahedron Letters No. 40, pp 4063 - 4066, 1972. Pergamon Press. Printed in Great Britain.

ESTERIFICATION OF HINDERED CARBOXYLIC ACIDS.
ALKYLATION OF CARBOXYLATE SALTS.

P. E. Pfeffer, T. A. Foglia, P. A. Barr, I. Schmeltz and L. S. Silbert

Eastern Regional Research Laboratory*
Philadelphia, Pennsylvania 19118

(Received in USA 10 July 1972; received in UK for publication 1 September 1972)

Recent reports[1] on the esterification of sterically hindered acids prompt us to present our results of a similar study in which we utilized a new mild procedure particularly applicable to the esterification of hindered carboxylic acids.

Dialkyl and trialkyl acetic acids (1, 4 and mixtures of 1 and 2), obtained as products of carboxylations of olefins[2], and alkylations of α-anions[3], were in the present instance easily methylated for analytical purposes (i. e. for glc) by diazomethane. The disadvantages associated with the use of this reagent, however, including its inapplicability to methylation on a preparative scale as well as its limitation to methyl ester preparation only, led us to turn to other methods of esterification.

Classical acid catalyzed esterifications with various alcohols and protonic acids proved to be of limited use for 1 and mixtures of 1 and 2, although the Fisher modification[4] was successfully applied to 1. An alternative reagent, BF_3-etherate plus alcohol, also gave varying results with the different acids (Table I), quantitatively converting 1 to ester after 60 minutes, while on the other hand failing to give quantitative yields of ester from 4 and 5 and mixtures of 1 and 2 even after prolonged reaction times. Similarly, the use of dimethyl sulfate resulted in incomplete methylations and like diazomethane, had the disadvantage of affording only the methyl ester.

In the present study, we have found that esterification of the hindered acids (1, 4, 5 and mixtures of 1 and 2) could be satisfactorily effected with alkyl halides using hexamethylphosphoramide (HMPA) as cosolvent under alkaline conditions (Table). With this system, esterification was found to be generally rapid and quantitative, and allowed the preparation of esters other than the methyl variety. Acids of type 1 were quantitatively esterified in 5 min (98% conversion) while those of type 4 and mixtures of 1 and 2 were quantitatively esterified in 30 minutes.

Utilizing this procedure, mesitoic acid (5) was methylated in 96% yield after 20 minutes. This result parallels those reported by Grundy et al[1] for the esterification of related hindered acids. Interestingly, the present method

---

*Eastern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

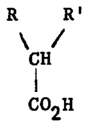
appears to be most satisfactory for hindered acids, since slower reaction rates were observed with pelargonic acid (3)(Table). In the latter instance, the BF_3-etherate reagent was notably more effective. In competitive experiments, acids 3 and 4 were reacted with limited quantities of alkyl halides. In these instances it was found that the rate of esterification for branched acid 4 is approximately five times that of its non-branched analog 3. These observed rate differences may be due to the insolubility of the anion of 3 in the reaction medium. The results however would seem to indicate that the present esterification procedure, in contrast to previous methods, has the potentiality of effectively separating branched acids from their linear counterparts.

Unlike most other esterifications, the one introduced herein is performed in alkaline medium utilizing KOH. Although K-O-t-C_4H_9 and LiOH have also been successfully employed, it appears that sodium carboxylates tend to react more slowly (Table). Furthermore, omission of HMPA as co-solvent resulted in significantly lower conversions within the same reaction times. Moreover, different alkyl halides may be used in which both the alkyl and halide moieties may be varied (Table). The use of HMPA as solvent for basic esterifications has been noted in the current literature by other workers[5,6] although their methods differ somewhat from our own and have been limited to the preparation of unbranched esters.

More importantly it should be emphasized that the utility of the present method lies in its effectiveness for the preparation of highly hindered esters; a typical procedure of which is described below:

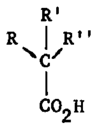
To a solution of acid 4 (5 mmole) in 50% EtOH:HMPA (10 ml) was added powdered KOH (5.3 mmole). The mixture was heated at 50°C until complete solution occurred, and then the alkyl halide (10 mmole) was added in one portion. The mixture was stirred at 50° for 30 min. and poured into H_2O, acidified with dil. HCl and extracted with hexane. The ester was isolated by removal of solvent *in vacuo*.

ACID STRUCTURES



1

$R + R' = C_{16}H_{32}$

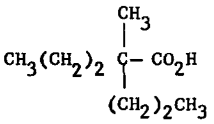


2

$R + R' + R'' = C_{16}H_{32}$

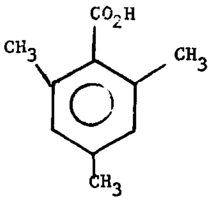
$CH_3(CH_2)_7CO_2H$

3



$CH_3(CH_2)_2C(CH_3)((CH_2)_2CH_3)-CO_2H$

4



5

COMPARISON OF ESTERIFICATION METHODS

		METHOD (PERCENT CONVERSION[a])		
Acid	Time (min.)	$BF_3 \cdot Et_2O + CH_3OH$	$(CH_3)_2SO_4$, CH_3OH	KOH, HMPA, EtOH, CH_3I
1	5	50	--	98$^+$
	15	65	55	--
	30	--	--	80[b], 90[c]
	60	98$^+$	85	50[d], 95[e]
1 + 2	30	15	10 (80)[f]	98$^+$
	60	20	20	--
	240	35	30	--
	18 hr	85	85	--
3	5	100	--	--
	30	--	--	49
	60	--	--	59
	120	--	--	94
4	5	--	--	69
	30	0	5 (99)[f]	99$^+$(77)[b]
	60	0	11	
5	20	0	95[g]	96$^+$
	60	0	--	55[h]
	120	--	--	80[h]

a) Percent conversion for 1 + 2 determined by I.R. while 3, 4 and 5 by GLC.

b) Used NAOH as base; c) LiOH as base; d) omitted HMPA as cosolvent; e) butyl ester derived from reaction with butyl bromide; f) used procedure of Grundy et al; g) conversion reported by Grundy, et al.; h) 2-octyl ester derived from reaction with 2-iodooctane at 75°C.

REFERENCES

1. J. Grundy, B. G. James and G. Pattenden, Tetrahedron Letters, 757 (1972); D. J. Raber and P. Gariano, Tetrahedron Letters, 4741, (1971).
2. T. A. Foglia, I. Schmeltz and G. Maerker, J. Org. Chem., Manuscript submitted for publication.
3. P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, Jr., J. Org. Chem., 37, 451, (1972) and references listed therein.
4. M. Coopersmith, A. J. Rutkowski and S. J. Fusco, Ind. Eng. Chem. Prod. Res. Develop., 5 46 (1966).
5. H. Normant and T. Cuvigny, Bull. Soc. Chim. Fr., 1867 (1965). L. C. Mitchell, J. Am. Oil Chem. Soc., 49, 281 (1972).
6. W. J. Le Noble and H. Frank Morris, J. Org. Chem., 34, 1969 (1969); A. L. Kurts, I. P. Beletskaya, A. Masias, S. S. Yufit and O. A. Reutov, Zh. Org. Khimii, 4, 1377 (1968), Eng. Trans. 4, 1327 (1968).