CONVENIENT SYNTHESIS OF ESTERS OF 2-PYRROLECARBOXYLIC ACID AND OF PYRIDINECARBOXYLIC ACIDS BY SOLID-LIQUID PHASE TRANSFER CATALYSIS WITHOUT ADDED SOLVENT

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Abstract - By reaction of aromatic K-carboxylates having nucleophilic N-atom in solid-liquid phase transfer catalysis (PTC) conditions without added solvent (catalyst : tetraalkylammonium halide) with alkylating reagents, the corresponding esters are prepared. By a judicious choice of experimental conditions, the amounts of N-alkylated products can be lowered. From 2-pyrrolecarboxylic acid, the three isomers of pyridine-carboxylic acid and o-aminobenzoic acid, corresponding esters of ethyl, benzyl, n-octyl and n-cetyl, generally are obtained with good yields.

We have recently published synthesis of esters of acetic[1] and various aromatic acids[2] in very easy and mild conditions by reaction of aromatic K-carboxylates with stoichiometric amounts of alkylating compounds in solid-liquid PTC conditions using tetrabutylammonium bromide (TBAB) or Aliquat 336 = tricaprylylmethylammonium chloride (TMAC). We now report that the same procedure can be used for different aromatic carboxylate salts bearing nucleophilic N-atom for which N-alkylation would be possible. We can quote that the synthesis of these esters was not described in any PTC conditions.

$$ArCO_2K + RX \xrightarrow[\text{no solvent}]{\text{PTC condition}} KX + ArCO_2R$$

1. Synthese of esters from potassium 2-pyrrolecarboxylate (Table I)

To our knowledge, only ethyl 2-pyrrolecarboxylate is described in the literature by reaction of the silver carboxylate with ethylating reagent[3]. We have prepared ethyl, benzyl and n-octyl esters in > 90% yields without N-alkylated products.

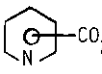
Table I : Synthesis of alkyl 2-pyrrole carboxylates by PTC condition with TCMAC-catalysis, 24h at T° C.

experimental conditions		ester yields (%)	
alkylating reagent	T (°C)	a)	b)
$(C_2H_5O)_2SO_2$	rt (c)	92	87
$C_6H_5CH_2Br$	rt (c)	93	87
$nC_8H_{17}Br$	85	100	93

a) by GLC with internal standard
b) isolated by column chromatography on silica gel
c) rt = room temperature

2. Esters from the three isomers of potassium pyridinecarboxylate (Table II)

Classical syntheses of these esters by reaction of the acids[4] or its acid chlorides[5-8] with the corresponding alcohols give poor or moderate yields. Good yields can be obtained only by the reaction of silver carboxylates with alkyl iodides[4] or by a sophisticated esterification method[9,10]

Table II : Ester yields for 
and 
by PTC condition

experimental conditions				ester yields (%)					
alkylating reagent	catalyst	t (h)	T (°C)	2-CO_2R a)	2-CO_2R b)	3-CO_2R a)	3-CO_2R b)	4-CO_2R a)	4-CO_2R b)
$(C_2H_5O)_2SO_2$	TBAB	24	rt	51	49	24		29	
C_2H_5Br	TBAB	43	rt	32		80	82	93	87
$C_6H_5CH_2Br$	TBAB	24	rt	23		6		7	
$C_6H_5CH_2Cl$	TBAB	24	rt	66	62	82	80	70	65
$nC_8H_{17}Br$	TCMAC	24	85	100	92	81		79	
$nC_8H_{17}Br$	TCMAC	24	60			93	89	93	90
$nC_{16}H_{33}Br$	TCMAC	40	85	96	90	75		77	
$nC_{16}H_{33}Br$	TCMAC	72	60			90	90	96	96
$Br(CH_2)_3Br$	TBAB	48	60				54		
$Br(CH_2)_4Br$	TCMAC	30	60		50				

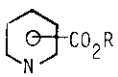
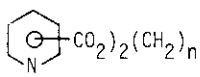
a) by GLC with internal standard

b) isolated

(Table III). Under the solid-liquid PTC condition , N-alkylation is a troublesome side reaction ; nevertheless the work-up procedure easily allows the removal of quaternized products (see experimental part).

Nicotinate and isonicotinate are the most susceptible to be concerned for N-alkylation reaction, especially with more reactive reagents (C_2H_5X or $C_6H_5CH_2X$). For those compounds, better results are obtained by the reaction with less reactive alkylating reagents (ethyl bromide or benzyl chloride rather than diethyl sulfate or benzyl bromide) ; at room temperature for example benzyl nicotinate or isonicotinate was obtained with < 10% yields using benzyl bromide while in > 70% yield from benzyl chloride. The case of ethyl picolinate is an exception ; diethyl sulfate gave 50% yield while ethyl bromide gave lower yield.

With less reactive alkylating reagents ($nC_8H_{17}X$ and $nC_{16}H_{33}X$) warming is necessary. Alkyl bromides, the most reactive halides in these solid-liquid conditions (see[1]) are the best and can be raised up to > 90% ester yields, provided that for nicotinate and isonicotinate isomers, the reaction temperature is 60°C (at 85°C, N-alkylation increases). Finally, we have tested our method with α, ω-dibromoalkanes : moderate ester yields are observed in contrast to very low yields by acid chloride-alcohol method[7,8].

Table III : Ester yields of  and 

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Comparison between PTC condition and literature results

Ester	2-CO_2R					3-CO_2R			4-CO_2R	
	A	B	C	D	E	A	C	E	A	E
1 R = C_2H_5	51	49[4]		100[4]		80			93	
1 R = $C_6H_5CH_2$	66				87[9]	82	67[5]	96[9]	70	94[9] 95[10]
1 R = nC_8H_{17}	100	20[4]				93	66[6]		93	
1 R = $nC_{16}H_{33}$	96	39[4]		88[4]		90	- [6]		96	
2 n = 3						54	14[8]			
2 n = 4	50		6[7]							

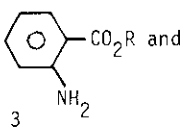
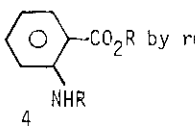
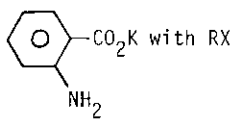
A solid-liquid PTC condition
B $ArCO_2H$ + ROH (acid catalyst)
C ArCOCl + ROH
D $ArCO_2H$ + RI + Ag_2O (xylene - reflux)
E[9] $ArCO_2H$ + ROH + 2-chloro 1-methyl pyridinium iodide + $(C_2H_5)_3N$
E[10] $ArCO_2H$ + ROH + 2-chloro 1-methyl pyridinium iodide + pyrimidone derivate

3. Esters from the three isomers of potassium aminobenzoate

Only the ortho isomer gives significant amounts of esters, according to the fact that reactivity of ortho-substituted benzoates is more pronounced than that of the other two isomers in solid-liquid PTC condition [2]. Unfortunately from anthranilate salt, although quaternized N-products can be removed in the final work-up, a mixture of amino ester and N-alkylated amino ester is always obtained. Ratio of O-alkylated/ O + N alkylated compounds fluctuates with temperature, nature of the catalyst (TBAB better than TCMAC), nature of the alkylating reagent (ethyl bromide or benzyl chloride gave a higher value of the ratio than diethyl sulfate or benzyl bromide), stoichiometry of the two reactants (excess of potassium carboxylate increases the ratio mono-/di-alkylated products). The results are indicated in Table IV.

Practical applications

Ester synthesis by reaction with carboxylate K-salts in solid-liquid PTC condition is an efficient method for many points of view : good yields, mild conditions and an easy work-up. Success of this experimental procedure occurs with nucleophilic N-substituted carboxylates : 2-pyrrole or isomers of pyridine compounds. Only with tested examples, failure or small interest occurs with aminobenzoate salts for which the catalysed BF_3 esterification described by Kadaba appears to be more convenient[11].

Table IV : Yields of  and  by reaction of 

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in PTC condition with TBAB-catalysis

RX	reaction conditions t(h)	T(°C)	ratio $ArCO_2K/RX$	% conversion rapported to RX (a) 3	4
$(C_2H_5O)_2SO_2$	24	rt	1	50	36
	-	-	2	50	16
	2	60	1	46	44
	-	-	2	63	24
C_2H_5Br	8	60	1	45	20
	-	-	2	74	10
$C_6H_5CH_2Br$	24	rt	1 (b)	4	26
$C_6H_5CH_2Cl$	24	rt	1 (b)	10	44
	2,5	85	1 (b)	15	28
	-	-	2	65	24
$nC_8H_{17}Br$	1	85	1	67	16
	-	-	2	86	14

a) by GLC analysis with internal standard

b) important N-quaternized products

EXPERIMENTAL PROCEDURE

In the first step, the potassium salt of carboxylic acid is obtained by dissolution of the acid in aqueous KOH solution (stoichiometric amounts) ; water is then evaporated (10 torr followed by 0.1 torr vacuum 2h 60°C)and finally the salt is mechanically grounded into a fine powder. Potassium carboxylate (10mmoles), alkylating reagent (generally in stoichiometric amounts, unless other indications in the tables) and tetraalkylammonium halide (TBAB or TCMAC 1mmole) are added in a 25ml flask. The mixture is shaken 15min at rt, then left for appropriate time and temperature ; finally it is diluted twice with 20ml ether (warm ethyl acetate for n-cetyl esters), catalyst, potassium salts or quaternized products are filtered through a short column of Florisil (5g). The crude products are analysed by GLC with internal standard and finally purified by column chromatography on silica gel. IR. NMR, melting points and elementary analyses are in agreement with the assigned structure or with the authentic sample.

Melting points and ^1H NMR spectra (90MHz, i.s. = TMS) for new compounds :

Benzyl 2-pyrrolecarboxylate : mp 54-55°C ; (CCl_4) 10.4 ppm (m) NH ; 7.35 ppm (m) C_6H_5 ; 6.95 ppm (m) H-3, H-5 ; 6.15 ppm (m) H-4 ; 5.3 ppm (s) CH_2.

N-Octyl 2-pyrrolecarboxylate : oil ; (CCl_4) 10.4 ppm (m) NH ; 6.9-6.7 ppm (m) H-3, H-5 ; 6.2-6.05 ppm (m) H-4 ; 4.25 ppm (t) CH_2O ; 1.65 ppm (m) $\underline{CH_2}CH_2O$; 1.3 ppm (m) $(CH_2)_5$; 0.9 ppm (m) CH_3.

N-Octyl isonicotinate : oil ; (CCl_4) 8.75 ppm (dd) 2(H-2) ; 7.75 ppm (dd) 2(H-3) ; 4.3 ppm (t) CH_2O ; 1.65 ppm (m) $\underline{CH_2}CH_2O$; 1.3 ppm (m) $(CH_2)_5$; 0.9 ppm (m) CH_3.

N-Cetyl isonicotinate ; mp 49.5-50°C ; (CCl_4) 8.75 ppm (dd) 2(H-2) ; 7.75 ppm (dd) 2(H-3) ; 4.3 ppm (t) CH_2O ; 1.6 ppm (m) $\underline{CH_2}CH_2O$; 1.3 ppm(m) $(CH_2)_{13}$; 0.9 ppm (m) CH_3.

Benzyl anthranilate : oil ; ($CDCl_3$) 7.95 ppm (dd) H-3 ; 7.5-7.1 ppm (several m) H-6, C_6H_5 ; 6.7 ppm (m) H-4, H-5 ; 5.65 ppm (m) NH_2 ; 5.3 ppm (s) CH_2.

Benzyl N-benzylanthranilate : oil ; ($CDCl_3$) 8.2 ppm (m) NH ; 8 ppm (dd) H-3 ; 7.5-7.1 ppm (several m) H-6, $2C_6H_5$; 6.7-6.5 ppm (m) H-4, H-5 ; 5.3 ppm (s) CH_2O ; 4,4 ppm (d) NH-$\underline{CH_2}$.

N-Octyl anthranilate : oil ; (CCl_4) 7.8 ppm (dd) H-3 ; 7.15 ppm (m) H-6 ; 6.65-6.4 ppm (m) H-4, H-5 ; 5.65 ppm (m) NH_2 ; 4.2 ppm (t) CH_2O ; 1.65 ppm (m) $\underline{CH_2}CH_2O$; 1.3 ppm (m) $(CH_2)_5$; 0.9 ppm (m) CH_3.

N-Octyl N-n-octylanthranilate : oil ; (CCl_4) 7.85 ppm (dd) H-3 ; 7.75 ppm (m) NH ; 7.4-7 ppm (m) H-6 ; 6.65-6.4 ppm (m) H-4, H-5 ; 4.25 ppm (t) CH_2O ; 3.2 ppm (m) $NHC\underline{H_2}$; 1.9-1.2 ppm (several m) $2(CH_2)_6$; 0.95 ppm (m) $2CH_3$.

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