Improved Synthesis of Tertiary Alkylacetic Acids and Esters

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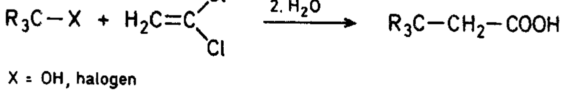
Tertiary alkylacetic acids (R_3CCH_2COOH) are prepared by reaction of 1,1-dichloroethene with a reagent capable of forming readily a tertiary alkyl carbenium ion with sulfuric acid in the absence of boron trifluoride. With tertiary butyl reagents, the yields are good and the method is convenient at laboratory and larger scales. The yields of carboxylic acids fall sharply with increasing steric effects. The esters are obtained directly, by adding alcohols, in a one-pot synthesis; with C_1–C_3 alcohols the reaction is selective.

Tertiary alkyl carboxylic acids (Koch acids) $R_3C—COOH$ are important synthetic intermediates[1]. The chemical properties and the thermal stability of their derivatives are largely determined by the steric hindrance of the tertiary alkyl groups[2]. On the other hand, quantitative studies of steric effects show that the neopentyl substituent is more bulky than the *t*-butyl substituent in the aliphatic series[3,4,5]. Therefore, we describe an improved method of synthesis of tertiary alkylacetic acids (and esters) $R_3C—CH_2—COOH$ (COOR') which are bulkier homologs of Koch acids.

A direct method has been described for the preparation of tertiary alkylacetic acids by reacting 1,1-dichloroethene with a reagent (olefin, alcohol, or alkyl halide), which readily forms a carbenium[6] ion in concentrated sulfuric acid in the presence of boron trifluoride as catalyst, and subsequent treatment with water[7] (Scheme A).

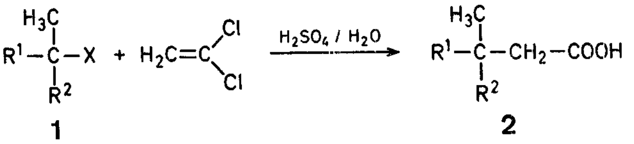


Scheme A

Recently, this method was modified by replacing gaseous boron trifluoride by boron trifluoride dihydrate, which is more easily handled and less expensive[8]. We now report that tertiary alkylacetic acids and their esters can be obtained readily by using only 95 to 100 % sulfuric acid without a Lewis acid; the results obtained are superior or equivalent to those previously described when using boron trifluoride.

The results of the preparation of the acids are reported in Table 1. The precursors of the carbenium ions required are mainly tertiary alcohols. We have also synthesized *t*-

Table 1. Tertiary Alkylacetic Acids **2** prepared



Run	Substrate No.	R^1	R^2	X	Ratio[a] $H_2C=CCl_2$/**1**	Conc. of H_2SO_4 [% by wt]	Reaction Times[b] A	Reaction Times[b] B	Reaction Temperatures[b] A	Reaction Temperatures[b] B	Product	Yield [%]	b.p. [°C]/torr found	b.p. [°C]/torr reported	Molecular Formula[d]
1	**1a**	CH_3	CH_3	OH	1.42[g]	99	1.75 h	0.75 h	2 °C	2 °C	**2a**	90[e]	64°/10	190°/ atmos.	$C_6H_{12}O_2$ (116.2)
2	**1b**	CH_3	CH_3	Cl	1.5	99	2 h	2 h	6 °C	6 °C	**2a**	77			
3	**1c**	CH_3	CH_3	OCH_3	1.8	99	2 h	0.5 h	5 °C	5 °C	**2a**	55			
4	**1d**	CH_3	C_2H_5	OH	1.5	99	1.5 h	1.5 h	6 °C	6 °C	**2b**	53	206–208°/ atmos.	209–210°/ atmos.	$C_7H_{14}O_2$ (130.2)
5	**1d**	CH_3	C_2H_5	OH	1.53	96–98	2 h	1 h	4 °C	11 °C	**2b**	72[e]			
6	**1d**	CH_3	C_2H_5	OH	1.56	96–98	3 h	1.5 h	2 °C	11 °C	**2b**	75[f]			
7	**1e**	C_2H_5	C_2H_5	OH	1.5	99	1.5 h	2 h	4 °C	4 °C	**2c**	13[h]	52°/0.6	–	$C_8H_{16}O_2$ (144.2)
8	**1c**	C_2H_5	C_2H_5	OH	0.83	96–98	2 h	3 h	4 °C	17 °C	**2c**	30[e,h]			

[a] Molar ratio of reagents; the values 1.42 or 1.53 are obtained after statistical optimisation.

[b] During (A) and after (B) addition of reagent.

[c] Yield of pure product isolated by distillation.

[d] Satisfactory microanalyses obtained: C ±0.16, H ±0.14; exception: **2c**, C −0.89.

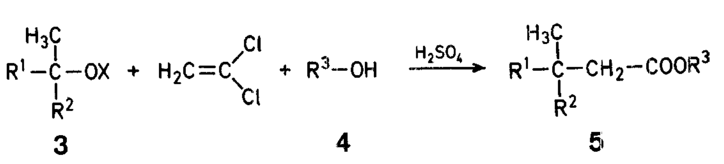
[e] After optimisation by a simplex design.

[f] Reaction in a 1 gallon reactor.

[g] For similar conditions, see Refs.[17,18].

[h] Yield by G.L.C. using internal standard.

Table 2. Tertiary Alkylacetates **5** prepared



Run	Substrate No.	R^1	R^2	X	Alcohol **4** R^3	Reaction[a] Temperature	Product	Yield [%][b]	b.p. [°C]/torr found	b.p. [°C]/torr reported	Molecular Formula[c]
9	**3a**	CH_3	CH_3	H	CH_3	40 °C	**5a**	63	121–122°/ atmos.	125–126°/ atmos.	$C_7H_{14}O_2$ (130.2)
10	**3a**	CH_3	CH_3	H	CH_3	75 °C	**5a**	76			
11	**3b**	CH_3	CH_3	CH_3	CH_3	40 °C	**5a**	68			
12	**3a**	CH_3	CH_3	H	C_2H_5	40 °C	**5b**	50	35°/8	144°/atmos.	$C_8H_{16}O_2$ (144.2)
13	**3a**	CH_3	CH_3	H	*n*-C_3H_7	40 °C	**5c**	52	25°/1.6	92°/65	$C_9H_{18}O_2$ (158.2)
14	**3a**	CH_3	CH_3	H	*i*-C_3H_7	40 °C	**5d**	34	49.5°/5	–	$C_9H_{18}O_2$ (158.2)
15	**3a**	CH_3	CH_3	H	*n*-C_4H_9	40 °C	**5e**	46	91°/30	–	$C_{10}H_{20}O_2$ (172.3)
16	**3a**	CH_3	CH_3	H	*i*-C_4H_9	40 °C	**5f**	43	47.6°/4	–	$C_{10}H_{20}O_2$ (172.3)
17	**3a**	CH_3	CH_3	H	*n*-C_5H_{11}	40 °C	**5g**	42	47°/1	–	$C_{11}H_{22}O_2$ (186.3)
18	**3c**	C_2H_5	CH_3	H	CH_3	75EC	**5h**	49	31°/4	–	$C_8H_{16}O_2$ (144.2)
19	**3d**	C_2H_5	C_2H_5	H	CH_3	75 °C	**5i**	13[d]	58°/2	–	$C_9H_{18}O_2$ (158.2)

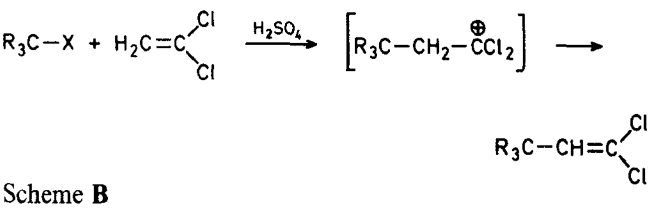
[a] Temperature during addition of alcohol **4**; other reaction times and temperatures: 1. addition of reagent, 1.5 h, 5 °C; 2. after addition of reagent, 1 h, 5 °C; 3. during addition of alcohol, 2 h, temperature as given.

[b] Yield of pure, distilled product.

[c] Satisfactory microanalyses obtained: C ±0.18, H ±0.12; exceptions: **5g**, C ±0.89 and **5h**, C −0.90.

[d] Yield by G.L.C. using an internal standard.

butylacetic acid, the simplest tertiary alkylacetic acid, from *t*-butyl chloride in a slightly lower yield than from *t*-butyl alcohol, and also from methyl *t*-butyl ether, an oxygenated compound of increasing importance[9] because of its use as octane booster[10]. With *t*-butyl alcohol or chloride, the reaction is very selective and the only minor product detected is the olefin derivative formed by elimination from the addition intermediate (Scheme **B**).



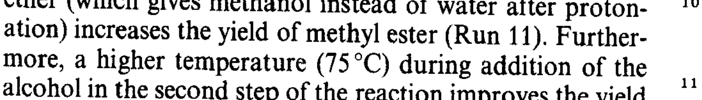
$$R_3C{-}X + H_2C{=}CCl_2 \xrightarrow{H_2SO_4} \left[R_3C{-}CH_2{-}\overset{\oplus}{C}Cl_2\right] \longrightarrow R_3C{-}CH{=}CCl_2$$

Scheme **B**

The moderate yield from methyl *t*-butyl ether can be improved by hydrolyzing the by-product methyl ester. For the higher acids prepared from reagents where the methyl groups of the tertiary butyl are replaced by the ethyl group, the yields are much lower due to steric effects already reported[7], and to the formation as by-products of other tertiary alkylacetic acids from rearrangement and fragmentation of the initial carbocation[11,12]. The lower yields have been improved by applying statistical optimisation methods[13,14] (Runs 5, 8). It appears particularly that the temperature, which must be low during the addition of the reagents, has to be raised thereafter.

A pilot experiment was carried out (Run 6) to test the synthesis at a larger scale. The reproduction of the laboratory results was satisfactory.

The results of the synthesis of esters are reported in Table 2. The preparation of these esters from the corresponding acids according to the usual methods is limited by steric effects owing to their branched structure[15,16]. By a modification of the method of preparation of the acids, we have been able to prepare the esters directly in a one-pot synthesis (Scheme **C**).



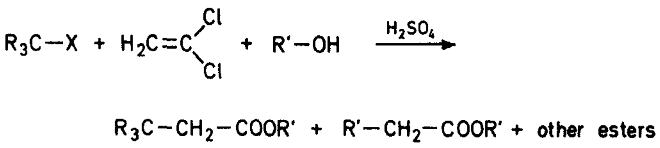
$$R_3C{-}X + H_2C{=}CCl_2 + R'{-}OH \xrightarrow{H_2SO_4} R_3C{-}CH_2{-}COOR'$$

$X = OH, OCH_3$

Scheme **C**

The sulfuric acid must be concentrated enough (99–100% by weight) to decrease the formation of carboxylic acids as by-products. An additional possibility is to replace the tertiary alcohols by tertiary alkyl ethers; e.g. methyl *t*-butyl ether (which gives methanol instead of water after protonation) increases the yield of methyl ester (Run 11). Furthermore, a higher temperature (75 °C) during addition of the alcohol in the second step of the reaction improves the yield of ester.

When the number of carbon atoms of the alcohol for esterification increases, the yield of ester drops gradually. Moreover for C_4 and higher alcohols, the by-product esters are more and more important [especially for the isoalkyl alcohols (Runs 14, 16)]. This is probably due to the ionisation of these alcohols, producing additional carboxylic esters directly or after rearrangement and fragmentation of the carbenium intermediates formed (Scheme **D**). Therefore, the method is selective for the preparation of methyl, ethyl, and propyl (isopropyl) esters of the acids previously described.



$$R_3C{-}X + H_2C{=}CCl_2 + R'{-}OH \xrightarrow{H_2SO_4} R_3C{-}CH_2{-}COOR' + R'{-}CH_2{-}COOR' + \text{other esters}$$

Scheme **D**

Tertiary Alkylacetic Acids 2 (Table 1); General Procedure:
In a reactor fitted with a condenser, a thermometer, a separatory funnel, and a mechanical stirrer, is placed concentrated sulfuric acid (60 ml; pilot scale: 1.6 l). A mixture of the precursor of the carbocation **1** (0.125 mol; pilot scale: 7.68 mol) and 1,1-dichloroethene is added dropwise at the temperature and for the period reported in Table 1, with vigorous stirring. Stirring is continued for a further period and at the temperature reported. The mixture is poured on crushed ice, and the aqueous solution is extracted three times with hexane. The organic layer is washed with a solution of 2 normal aqueous potassium hydroxide until basic. The carboxylic acid is liberated with concentrated hydrochloric acid, and extracted with benzene. The benzene is removed and the product distilled under reduced pressure, affording the carboxylic acid **2** with satisfactory ^{1}H-N.M.R. spectra and microanalyses.

Esters 5 of Tertiary Alkylacetic Acids (Table 2); General Procedure:
The general procedure is identical with the above, but, before pouring the mixture on ice, the alcohol for esterification **4** is added dropwise and the mixture is stirred gently at the temperature and for the period reported in Table 2. The esters are contained in the organic layer after addition of dilute potassium hydroxide. Hexane is removed and the product distilled under reduced pressure affording the esters **5** of tertiary alkylacetic acids with satisfactory ^{1}H-N.M.R. spectra and microanalyses.

Received: October 2, 1984

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