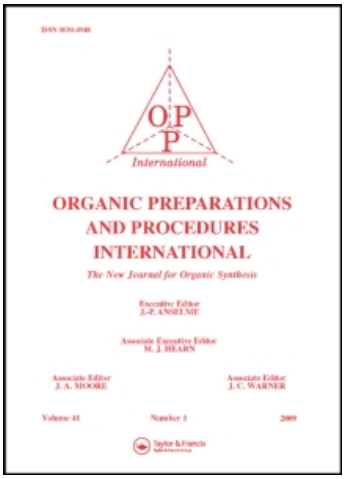

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THE CHEMISTRY OF METHANETRICARBOXYLIC ESTERS. A REVIEW

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INTRODUCTION

Methanetricarboxylic esters 1 were first reported by Conrad et al. over a century ago,[1] but were not successfully used synthetically until 1911.[2] Since that time, these triesters have found many synthetic uses as a complement to the malonic ester synthesis. Methanetricarboxylic esters have been patented for use as gasoline additives,[3] in the production of polyesters,[4,5] as a photolytic stabilizer for polypropylene,[6] and in the synthesis of pesticides.[7] It is the purpose of this review to point out the uniqueness of these triesters and to emphasize their advantages in certain synthetic procedures.

I. SYNTHESIS

1. From Malonic Esters

Methanetricarboxylic esters have generally been synthesized from malonic esters via formation of a metal salt followed by the addition of an alkyl chloroformate. Table 1 delineates the results obtained for

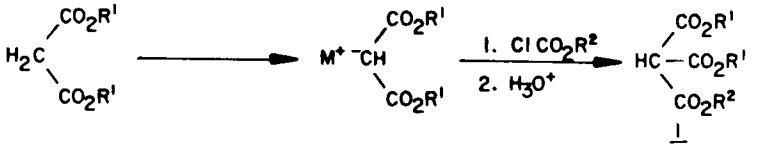

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TABLE 1. Methanetricarboxylates (1)[a]

Product	R^1	R^2	Method	Yield (%)	bp. [°C]/torr or mp. [°C]
1a	Me	Me	[A] toluene	59	46-47
1a	Me	Me	[A] xylene	39[b]	43-45
1a	Me	Me	[B]	30[c]	45-46
1b	Me	Et	[B]	--[c]	138-139/12
1c	Et	Me	[A] toluene	65[d]	140-142/12
1d	Et	Et	[C]	90[e]	135-138/12
1d	Et	Et	[C]	80	135-137/12
1e	n-Pr	n-Pr	[B]	44	160-161/10
1f	i-Pr	Me	[A] toluene	40	106.5-107/2
1g	i-Pr	i-Pr	[A] toluene	40	139-140/9-10
1h	n-Bu	n-Bu	[A] toluene	55	181-183/11
1i	i-Bu	i-Bu	[A] toluene	46	143/2
1j	s-Bu	s-Bu	[A] toluene	42	139/2.5
1k	$n\text{-}C_5H_{11}$	$n\text{-}C_5H_{11}$	[A] toluene	53	173-174/2
1l	$3\text{-}C_5H_{11}$	$3\text{-}C_5H_{11}$	[A] toluene	52	145-146/2
1m	$n\text{-}C_{10}H_{21}$	$n\text{-}C_{10}H_{21}$	[A] xylene	--	208-210/0.0015
1n	C_6H_{11}	C_6H_{11}	[A] xylene	--	163-164/0.0004
1o	Ph	Ph	[A] toluene	--	79.5-80
1o	Ph	Ph	[C]	70	79.5-80
1p	Ph	$p\text{-}CH_3C_6H_4$	[C]	61	110
1q	$p\text{-}CH_3C_6H_4$	Ph	[C]	27	109-110
1r	$p\text{-}CH_3C_6H_4$	$p\text{-}CH_3C_6H_4$	[C]	42	109-110.5

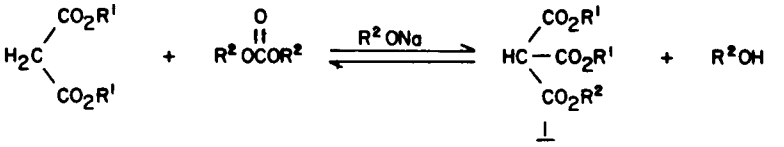
a) Ref. 8, except as otherwise noted; b) Ref. 9; c) Ref. 10; d) Ref. 11; e) Ref. 12. f) General Procedures. [A] The appropriate malonic ester (0.57 mol) was added to a stirred suspension of sodium (0.56 mol) in an aromatic hydrocarbon solvent (400 mL). After the evolution of hydrogen had subsided, the reaction was cooled to ca. 60°C and the chloroformate (0.60 mol) was slowly introduced. After refluxing (3-7 hrs), the mixture was cooled, washed several times with water, and dried. The solvent was removed in vacuo to give the crude methanetricarboxylic ester. [B] The malonic ester (0.55 mol) was slowly added to sodium (0.50 mol) in anhydrous ether (350 mL). Anhydrous benzene (350 mL) was added to form a suspension of the sodium salt; the chloroformate was added slowly and the reaction was then refluxed (3-5 hrs). Upon cooling, the mixture was washed with dilute hydrochloric or sulfuric acid, then with water, dried, and concentrated in vacuo. [C] To a mixture of magnesium turnings (1.03 mol), absolute ethanol (25 mL), and carbon tetrachloride (1 mL) a solution of the malonic ester (1.0 mol) in ethanol (80 mL) was added. The mixture was gently warmed until hydrogen evolution began; when the evolution of hydrogen was moderate, the remainder of the malonate solution was slowly added.

Footnotes to Table 1 (continued).

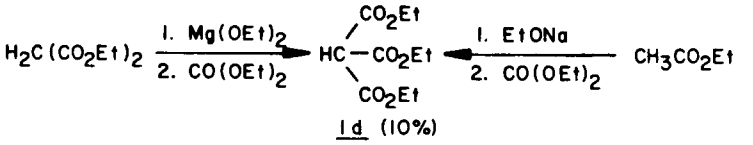
After the initial reaction subsided, the flask was cooled and ether (300 mL) was added; further heating completed the formation of the magnesium salt. The chloroformate (1.05 mol) in dry ether (100 mL) was carefully added then refluxed for 15 min. Upon cooling dilute acetic acid was added and the ethereal layer was washed with water, dried, and the solvent removed.

various malonic esters with alkyl chloroformates. Apparently the yields of 1, when ethyl or phenyl esters are involved, are dependent upon the judicious choice of the metal ion; magnesium is generally superior to sodium.[12] For example when sodium in toluene was used, only very little of 1o was obtained while 1o was generated in 80% yield with the magnesium salt.

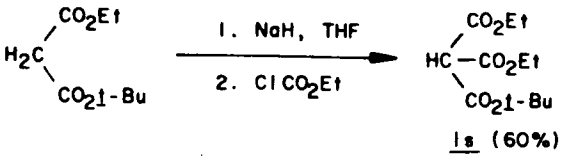
Dialkyl carbonates have been used instead of alkyl chloroformates; however, trialkyl methanetricarboxylates were obtained only when the



carbonate served as the reaction media to suppress the reverse reaction.[8,13,14] Ester 1d was isolated in 10% yield from the anion of



either diethyl malonate or ethyl acetate and diethyl carbonate. The reversibility of these reactions permitted the selective monodecarbalkoxylation of the tricarboxylic esters, which allows the use of the carbalkoxy moiety as a blocking group in a malonic ester synthesis.[15] Because of the ease of hydrolysis of t-butyl esters, Rapoport and co-workers synthesized 1s from t-butyl ethyl malonate;[15] after conversion to the sodium salt and alkylation, the t-butoxycarbonyl moiety was easily

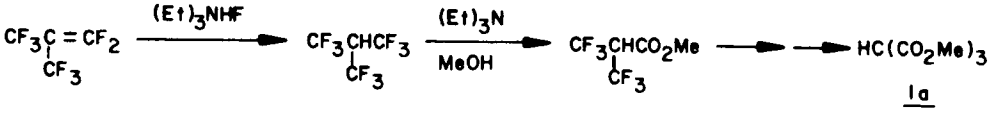


1s (60%)

removed by either 100% formic or trifluoroacetic acid. Alkylations and decarbalkoxylations will be discussed in detail in later sections.

2. Miscellaneous Procedures

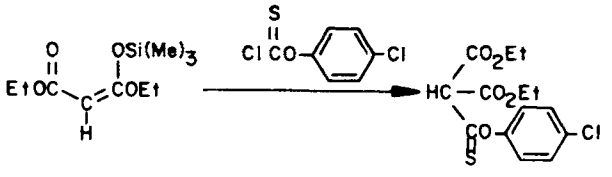
Under alkaline conditions, trifluoromethyl groups with an adjacent hydrogen were converted to carboxylic acids or esters;[16] thus repeated hydrolysis of 2-monohydroperfluoroisobutane by triethylamine and methanol gave 1a.[17] Although this reaction was not synthetically useful, it is



1a

interesting that no reaction occurred in the presence of triethylamine alone; whereas, triethylammonium fluoride and perfluoroisobutene produced the monohydroperfluoroisobutane.

Silyl enol ethers of malonic esters have also been utilized for the synthesis of methanetricarboxylic esters. This method was used to obtain thioester 2 by addition of a thiochloroformate.[18]



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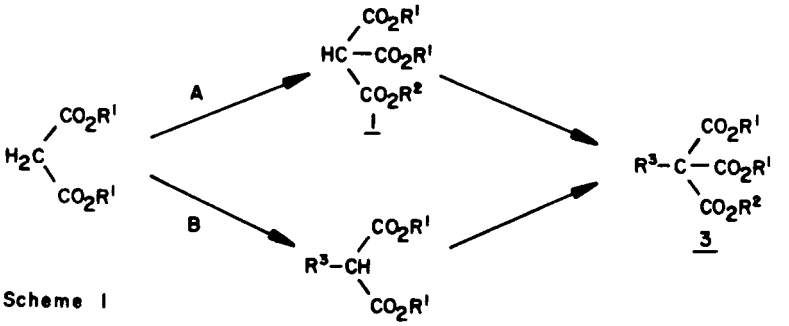
II. REACTIONS

When alkyl-1,1,1-tricarboxylic esters (3) are desired, there are two

possible synthetic routes (Scheme 1); the first involves conversion of a malonic ester to 1 (Route A) and subsequent alkylation to give 3 or alternatively alkylation of the malonic ester (Route B) followed by addition of the last alkoxycarbonyl group. In spite of the anticipated difficulties involved with alkylations of 1, Route A generally produced higher overall yields.[19,20]



Scheme I

The pK_a of methanetricarboxylic esters[21] is ~7.8, whereas the pK_a of diethyl malonate is 13.3.[21] As a result methanetricarboxylic esters (1) readily formed stable, non-hygroscopic sodium salts (4),[8,10] which are useful reagents for two carbon homologations. The reactions of methanetricarboxylic esters are primarily based upon 1 and 4; 1 condenses with amines and amine derivatives as well as adds to unsaturated carbon-carbon bonds under radical conditions, while 4 can be acylated or alkylated.

1. With Acid Derivatives

Acid chlorides react with 4 to produce the β-carbonyltricarboxylic esters 5 (Table 2). Acid chloride 5b was further functionalized as shown

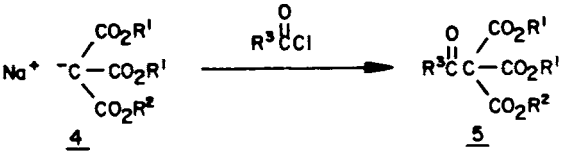
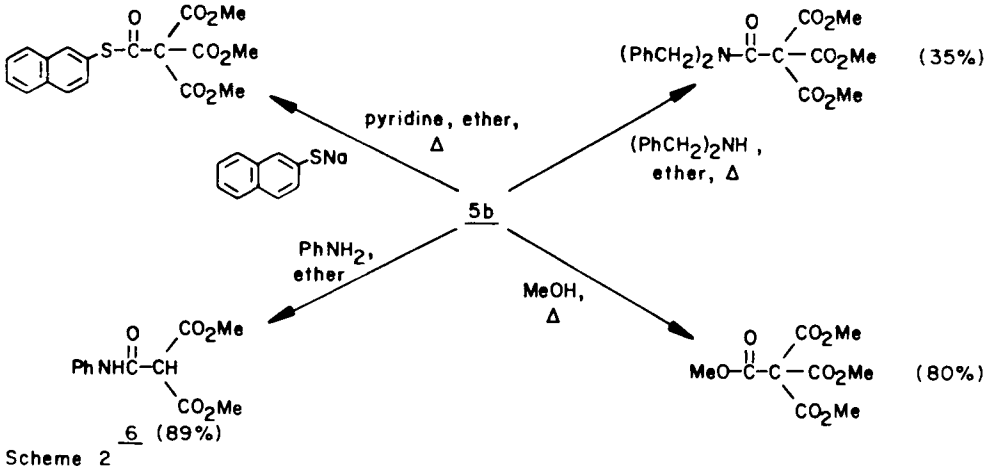


TABLE 2. Acylmethanetricarboxylates (5)[a].

Product	4	R^3	Method[d]	Yield	bp. [°C]/torr or mp.[°C]
5a	R^1=R^2= Me	Me	[A]	73[b,c]	75/0.05
5b	R^1=R^2= Me	Cl	---	66[c]	189-190
5c	R^1=R^2= Me	OMe	[A], 120°C, 3h	69	163/12; 74-75
--[e]	R^1=R^2= Me	COCl	[A]	75[c]	189-190
5d	R^1=R^2= Me	CO_2Me	[B], Δ, 1h	80	179-180/15; 91-92
5e	R^1=R^2= Me	Ph	[A], 100°C	75[b,c]	85
5f	R^1=R^2= Me	p-NO_2Ph	[A]	--[c]	121-122
5g	R^1=R^2= Et	Me	[A], Δ	--	147-148/14
5h	R^1=R^2= Et	OEt	[A], Δ, 3h	--	173.5/12
5i	R^1=R^2= Et	CO_2Et	[B], Δ, 1h	--	189-190/11
5j	R^1=R^2= Et	Ph	[A], 100°C, 3h	--	214/14
5k	R^1=R^2= i-Pr	Ph	[A], 120°	62[b]	88

a) Ref. 10; except as otherwise noted; b) Ref. 8; c) Ref. 22; d) General Procedures.[8,10,22] [A] Sodiomethanetricarboxylic ester (0.06 mol) was slowly added to an excess of the acyl chloride (0.51 mol). The reaction was complete after refluxing for 1-3 hrs. The excess acyl chloride was removed by distillation. The crude product was dissolved in benzene or ether and filtered. The solvent was removed and the product was purified by vacuum distillation. [B] The acyl chloride (0.06 mol) was added to a stirred suspension of the sodiomethanetricarboxylic ester (0.06 mol) in benzene (80 mL). The reaction was refluxed for 1 hrs, cooled, filtered, and the solvent removed in vacuo; e) $(MeO_2C)_3CCOCOC(CO_2Me)_3$.

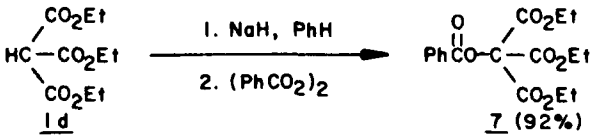
in Scheme 2.[22] Interestingly when 5b was treated with aniline, decarbalkoxylation occurred in addition to amide formation to give (89%) 6.



Scheme 2

No decarbalkoxylation was observed with dibenzylamine or sodium thionaphthalate under similar conditions; this may be due to steric restrictions. Decarbalkoxylation by nucleophiles is a common and often undesired side reaction with methanetricarboxylic esters.

Tartronates, which are precursors to barbituric acids, have been prepared by Lawesson, et al. via the reaction of peroxides with the anion of active methylene compounds.[23] Thus, the tartronate 7 was obtained (92%) from the sodium salt of 1d and benzoyl peroxide.[23]

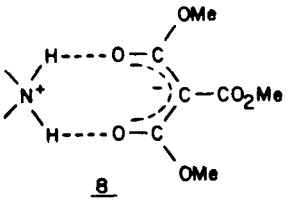


2. With Amines and Amine Derivatives

Methanetricarboxylic esters 1, their sodium salts 4, and substituted methanetricarboxylic esters 3 reacted with substituted amines, hydrazines, and ureas to give a variety of derivatives. Simple amines gave either ammonium salts or tris-amides depending upon the reaction conditions; hydrazines and ureas formed heterocycles and barbiturates, respectively. The ammonium salts of 1a, listed in Table 3, were formed upon standing from a mixture of the amine and 1a,[24] and were assigned structure 8 based upon their infrared spectra.

TABLE 3. Ammonium Salts of 1a.

				IR data [cm^{-1}]		
Salt	Amine	Yield	m.p.[°C]	νNH_2^+	νCO	$\nu C{=}C$
7a	$(n\text{-}Bu)_2NH$	79	94-96	2550-2730, 1580	1739, 1681	1613
7b	pyrrole	46	81-83	2760, 1585	1740, 1690	1632
7c	piperidine	84	96-98	2630-2750, 1585	1745, 1695	1625
7d	morpholine	58	63-65	2630, 1580	1755, 1690	1625
7e	$C_6H_{11}NH_2$	66	97-98	2500-2790, 1585	1745, 1695	1631



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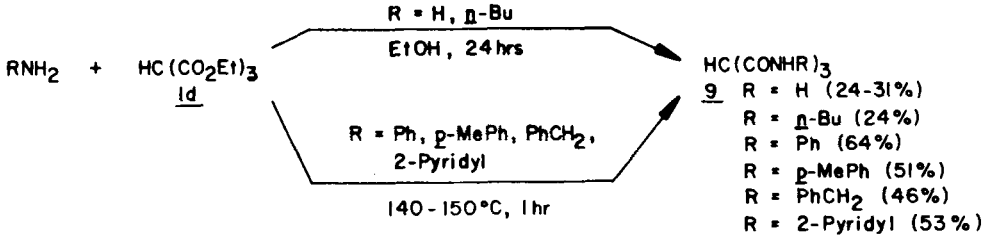
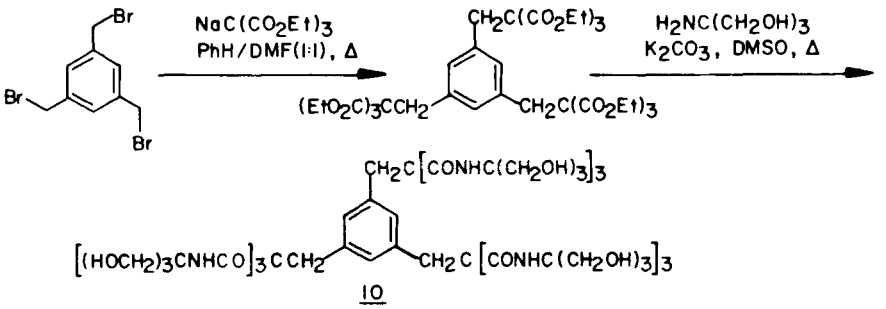
The tris-amides 9 have been prepared via the reaction of the triester 1d with several amines.[25] The infrared spectra of 9 were compared



to their malonamide and acetamide analogs.[25] Tris-amide formation was utilized by Newkome et al. for the introduction of polar groups of the arborols 10 and 11.[26,27]



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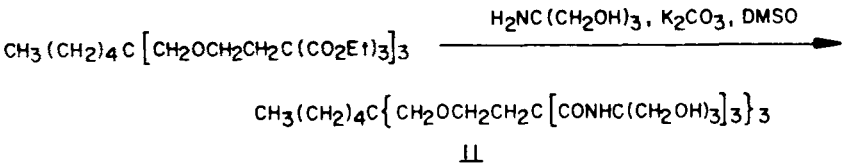
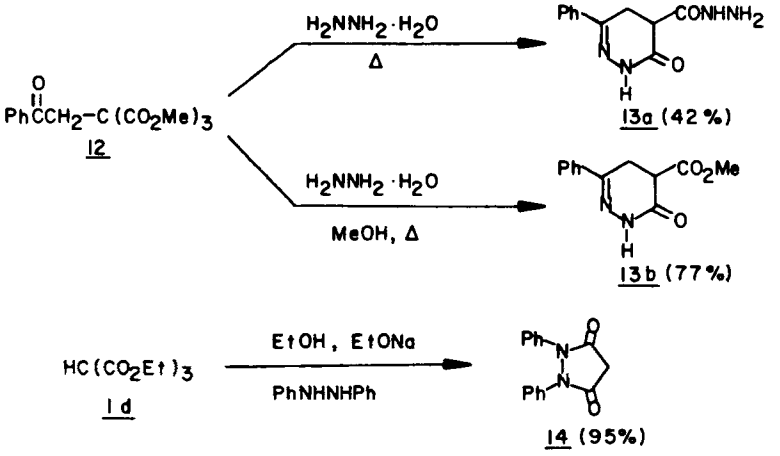
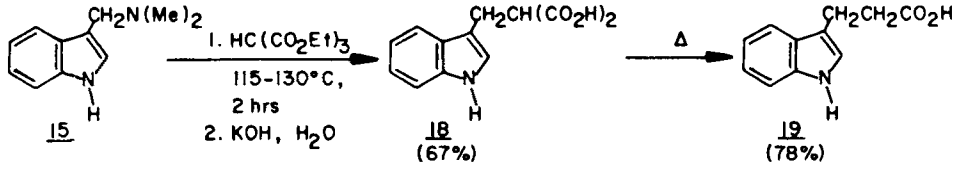


11

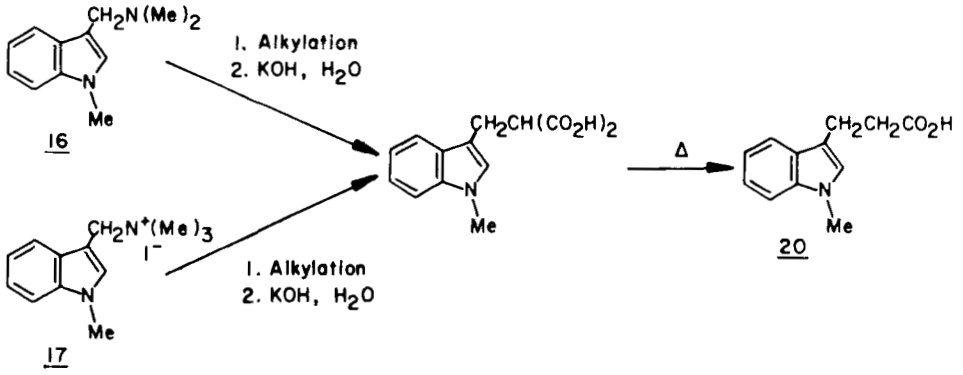
The ketotriester 12 and hydrazine hydrate were heated to give (42%) the diazaheterocycle 13a while in refluxing methanol 13b was obtained in 77% yield.[22] The 5-membered heterocycle 14 resulted from the reaction of 1d and N,N-diphenylhydrazine with sodium ethoxide in ethanol.[28]



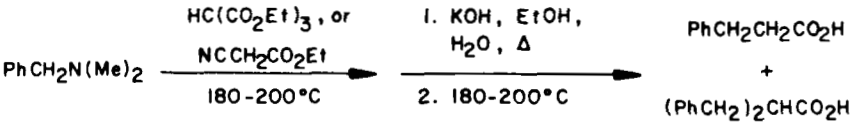
Active methylene compounds have been alkylated by treatment with tertiary amines,[29,30] quaternary ammonium salts,[30] and N,N-dimethylformamide diethylacetal.[31] Snyder et al.[30] studied the alkylation of several active methylene compounds by gramine (15), 1-methylgramine (16), and 1-methylgramine methiodide (17). Triethyl methanetricarboxylate (1d) and gramine (15) were heated for 2 hrs. at 115-130°C, then saponified with



KOH to give (67%) 18; decarboxylation afforded (78%) indole-3(β)-propionic acid (19).[30] Alkylation of diethyl malonate, ethyl cyanomalonate, ethyl cyanoacetate or 1d by the methiodide of 1-methylgramine, followed by hydrolysis and decarboxylation gave N-methylindole-3(β)-propionic acid (20).[30] Of the active methylene compounds mentioned, 1d gave the

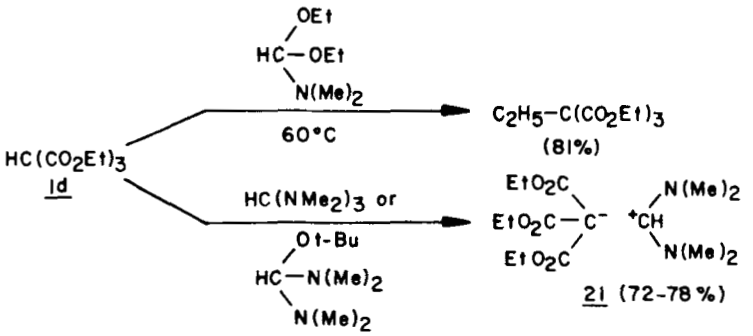


highest overall yield (56%). Analogous reactions with 1-methylgramine also gave 20 but in consistently lower yields. The alkylations of 1d and ethyl cyanoacetate with benzyldimethylamine to give a mixture of hydro-



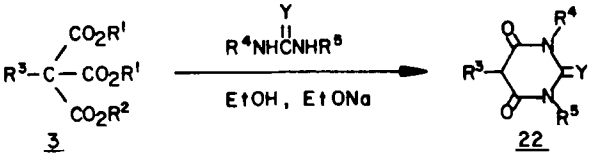
cinnamic acid and dibenzylacetic acid were found to evolve dimethylethylamine and trimethylamine, respectively.[29] The mechanism proposed involves initial formation of a quaternary ammonium carboxylate upon heating the tertiary amine and the ester; the quaternary ammonium cation is the alkylating species.[29]

Diethyl malonate, ethyl cyanomalonate, and malononitrile were alkylated by treatment with N,N-dimethylformamide diethylacetal in only ca. 50% yield while triethyl methanetricarboxylate (1d) was alkylated in 81%.[31]



Use of t-butylaminal or tris-(dimethylamino)methane in place of N,N-dimethylformamide diethylacetal produced the tetramethylformamidium salt 21.[31]

A series of 5-alkylbarbituric acids 22 was easily synthesized by condensation of alkyl-1,1,1-tricarboxylic esters (3) with urea derivatives



3 22

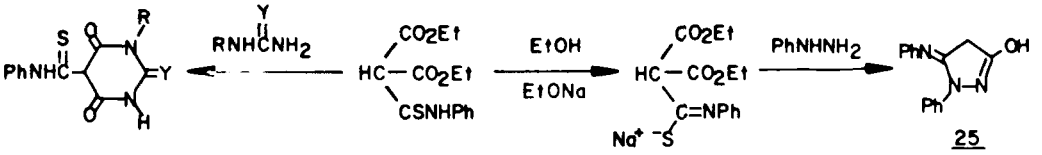
with concomitant decarbalkoxyation;[32] the results are summarized in Table 4. This procedure involved simplified isolation of the barbituric acids and gave generally higher yields than syntheses from malonic esters.[32] Further, diethyl phenylthiocarbamoyl malonate (23) was synthesized and condensed with urea derivatives to give (Scheme 3) 24[33], where the thioamide moiety remained intact. However, when

TABLE 4. Barbituric acids (22)[a] prepared from alkyl-1,1,1-tricarboxylates (3).

3 (R^1=R^2=Et)	Amine Derivative	Product		Yield[b]	mp. [°C]
R^3= H	H_2NCONH_2	12a	R^4=R^5=H; Y=O	71	245
R^3= H	$H_2NCONHPh$	12b	R^4=H; R^5=Ph; Y=O	80	262
R^3= H	$H_2NCONHNHPh$	12c	R^4=H; R^5=NHPh; Y=O	62	260
R^3= Me	H_2NCONH_2	12d	R^4=R^5=H; Y=O	81	202-203
R^3= Et	H_2NCONH_2	12e	R^4=R^5=H; Y=O	81	194
R^3= $CH_2CH{=}CH_2$	H_2NCONH_2	12f	R^4=R^5=H; Y=O	79	167
R^3= $CH_2CH{=}CH_2$	$H_2NCONHPh$	12g	R^4=Ph; R^5=H; Y=O	70	152
R^3= CH_2Ph	H_2NCONH_2	12h	R^4=R^5=H; Y=O	81	206-208
R^3= CH_2Ph	MeNHCONHMe	12i	R^4=R^5=Me_3; Y=O	50	116-117
R^3= CH_2Ph	H_2NCSNH_2	12j	R^4=R^5=H, Y=S	70	218-220

a) Ref. 32; b) General Procedure. Triethyl alkyl-1,1,1-tricarboxylate (42.0 mmol) and the urea derivative (42.0 mmol) were added to a stirred solution of sodium (87.0 mmol) in absolute ethanol (50 ml) and then refluxed for 6hrs. Neutralization afforded the desired barbituric acid, as a white solid.

the sodium salt of 23 was condensed with phenylhydrazine, the thioamide participated in the reaction to give 25.



24 a R = H, Y = O
b R = Me, Y = O
c R = Ph, Y = O
d R = H, Y = NH

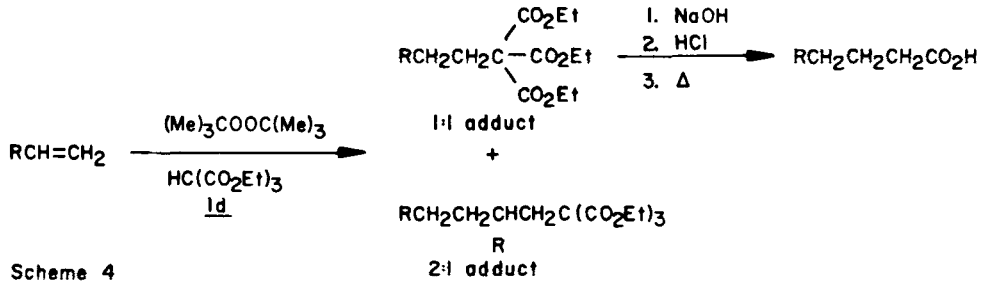
23

25

Scheme 3

3. Radical Reactions

In the presence of a radical initiator, triethyl methanetricarboxylate (1d), adds to terminal alkenes (Scheme 4) to form predominately the 1:1 adduct (50-75%) along with traces of the 2:1 adduct. Saponification of the 1:1 adduct followed by decarboxylation provided a convenient route to

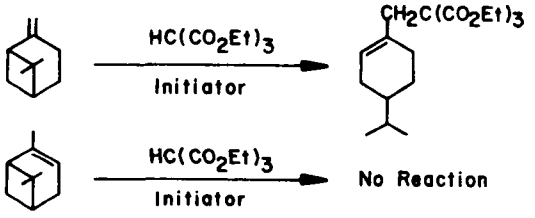


Scheme 4

n-alkylcarboxylic acids and represents a two-carbon homologation of the starting olefin. Unlike radical additions of malonic or acetic esters to olefins, the radical additions of methanetricarboxylic esters are regiospecific and limited exclusively to α-olefins.[34] A thorough discussion of the radical reactions of methanetricarboxylic esters has been given in a review of radical additions of carboxylic acids and their derivatives,[34] thus only several of the salient features will be presented here.

Optimum yields of addition products were obtained when the ratio of tricarboxylate to olefin is 5:1, the temperature is 140-170°C, and di-t-butylperoxide is the initiator.[34] Addition products are obtained with

terminal alkenes and alkynes, but not with cyclic or internal alkenes. For example, triethyl methanetricarboxylate added to the exocyclic methylene of β-pinene with rearrangement to the p-menthene system in 52% yield,[35] while



under similar conditions α-pinene resulted in recovery (>90%) of starting materials and no isolated adducts.[34] The absence of adducts with cyclic and internal alkenes probably arose from the steric requirements of the methanetricarboxylic ester. Further examples are given in Table 5. The radical additions of 1d to olefins have also been initiated by ^{60}Co γ-radiation; however, the yields are considerably lower (5-50%)[39] than those of peroxide initiated reactions.

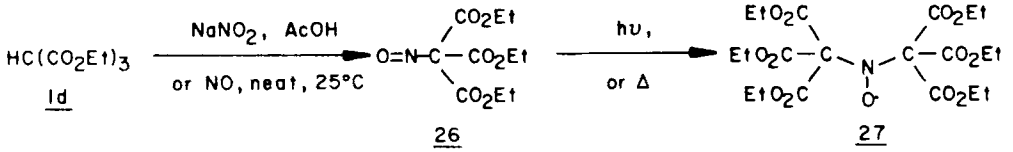
TABLE 5. Radical Additions of Triethyl Methanetricarboxylate (1d) to Alkenes (Alkynes)[b].

Alkene, or Alkyne	Ratio of 1d: Alkene (alkyne)	Yield (%)	1:1 adduct b.p.[°C]/torr
n-$C_3H_7CH{=}CH_2$	5	52	104-108/0.4-0.5
n-$C_3H_7C{\equiv}CH$	5	30[b]	111-112/0.1
n-$C_4H_9CH{=}CH_2$	5	51	108/0.05
n-$C_4H_9C{\equiv}CH$	5	27[b]	127-127.5/0.3
n-$C_3H_7C(Me){=}CH_2$	--	<5	128-132/0.6
n-$C_5H_{11}CH{=}CH_2$	5	75	115.5-124/0.1-0.2
n-$C_6H_{13}CH{=}CH_2$	5 10	73[c] 50-55[d]	128-133/0.2-0.3
cyclooctene	--	trace	137-140/0.1
n-$C_6H_{13}C{\equiv}CH$	5	26[b]	123/0.1
n-$C_3H_7C{\equiv}C$-n-C_3H_7	5	--[b]	none isolated
n-$C_7H_{15}C{\equiv}CH$	5	38[b]	--

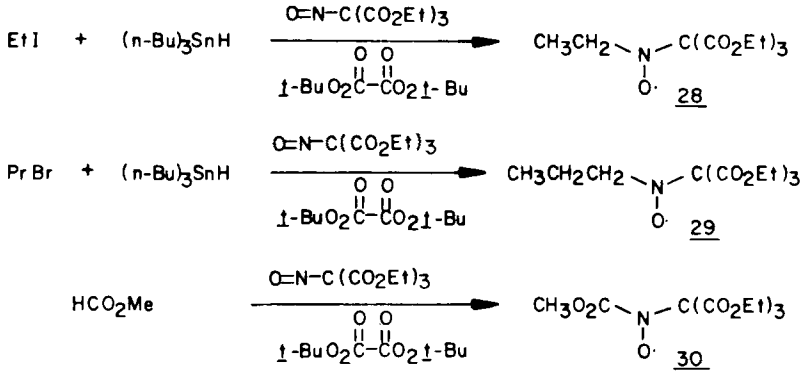
n-$C_8H_{17}C{\equiv}CH$	5	33[b]	145-146/0.1
n-$C_9H_{19}CH{=}CH_2$	5	72	144/0.08
$MeO_2CC_8H_{16}CH{=}CH_2$	5	51[c]	--
n-$C_{10}H_{21}CH{=}CH_2$	5	70[c]	157-158/0.15
$PhC{\equiv}CH$	5	--[b]	none isolated

a) Ref. 34, except as otherwise noted; b) Ref. 36; c) Ref. 37; d) Ref. 38.

Flesia et al.[40] have prepared the nitroso triester 26; treatment of 1d with sodium nitrite in acetic acid gave predominately the stable blue radical species 27 in addition to 26 while the neat reaction of



nitrous oxide with 1d gave essentially pure 26. It was determined that 27 was a thermal and/or photochemical decomposition product of 26, thus complete purification of 26 was impossible. However, 26 was conveniently generated in situ by the latter procedure; the radical adducts 28, 29, and 30 were characterized.[40] The advantages of 26 over 2-methyl-2-nitrosopropane and perdeuterio-2-methyl-2-nitrosopropane as radical trapping agents[41,42] include simplicity of preparation, higher yields, and improved resolution of signals.[40]



4. Alkylations

Alkali metal salts of 1, i.e. 4, have been alkylated, generally by alkyl halides; however, the reaction has several limitations. The salts of 1 are practically insoluble in most organic solvents except polar aprotic solvents, such as acetone, dioxane, and N,N-dimethylformamide. Alkylations with primary or secondary halides tend to be slow except when N,N-dimethylformamide is the solvent. Selection of the alkyl groups of the triester is also important; the trimethyl ester 4a generally gave poorer yields than the corresponding reactions of the triethyl ester 4d. The synthetic details for a variety of alkylations are given in Table 6.

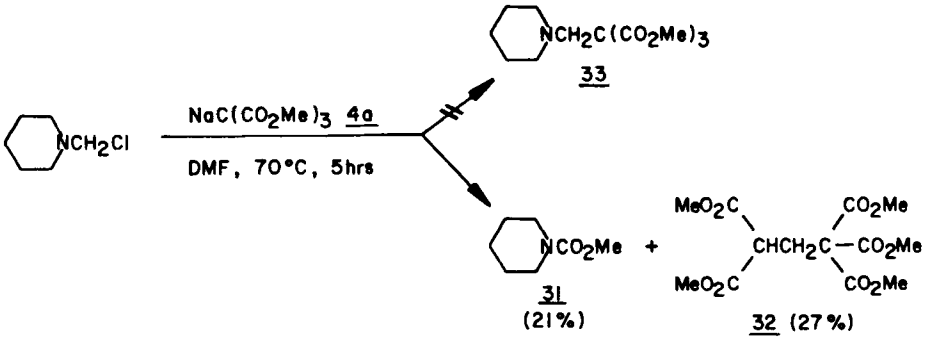
TABLE 6. Alkylations of Sodiomethanetricarboxylic Esters[a].

Product	Sodium Salt	Alkylating Agent	Procedure[f]	Yield	b.p. [°C]/torr or m.p. [°C]
$CH_3C(CO_2Me)_3$	4a	CH_3I	[B], Δ, 12hrs	78[b]	116-117/10
$CH_3C(CO_2Et)_3$	4d	CH_3I	[A], 140°C, 2hrs	--[c]	130/11
	4d	CH_3I	[A], Δ, 1.5hrs	80	125-127/7
	4d	$(CH_3)_2SO_4$	[B], 25°C, 10 min	89	130-132/10
$C_2H_5C(CO_2Et)_3$	4d	C_2H_5Br	[B], Δ, 4hrs	77	139/7
	4d	C_2H_5I	[A], 140°C, 2hrs	--[c]	146/17
	4d	$(C_2H_5)_2SO_4$	[B], 25°C, 10 min	86	142/10
	4d	C_2H_5-$OSO_2C_6H_5$	[B], Δ, 9hrs	77	142/11
$BrCH_2CH_2C(CO_2Et)_3$	4d	$BrCH_2CH_2Br$	[D], 90°C, 10hrs	91[d]	--
$BrCH_2CH_2CH_2CH_2C(CO_2Et)_3$	4d	$BrCH_2(CH_2)_3Br$	[D], 85°C, 20hrs	70[d]	120-125/0.05
$CH_3CH_2CH_2CH_2C(CO_2Et)_3$	4d	$CH_3(CH_2)_3Br$	[D], 85°C, 20hrs	85[d]	125-130/1
	4d	$CH_3(CH_2)_3OTos$	[B], Δ, 10hrs	80	165-167/10
$CH_3CH_2CH_2CH_2C(CO_2Et)_2CO_2t\text{-}Bu$	4a	$CH_3(CH_2)_3Br$	[D], 75°C, 16hrs	86[d]	100-110/0.1
$CH_2{=}CHCH_2C(CO_2Me)_3$	4a	$CH_2{=}CHCH_2Br$	[B], Δ, 12hrs	26[b]	108-110/15

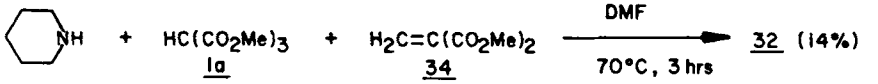
$CH_2=CHCH_2C(CO_2Et)_3$	4d	$CH_2=CHCH_2Br$	[C], Δ, 1h	72	142/11
$CH_2=CHCH_2C(CO_2Et)_3$	4d	$CH_2=CHCH_2Br$	[B], Δ, 2hrs	97	142/11
$HC\equiv CCH_2C(CO_2Me)_3$	4a	$HC\equiv CCH_2Br$	[B], Δ, 12hrs	22[b]	98/0.2
$C_6H_5CH_2C(CO_2Et)_3$	4d	$C_6H_5CH_2Cl$	[C], Δ, 2hrs	59	195-197/12
$CH_3OCH_2C(CO_2Me)_3$	4a	CH_3OCH_2Cl	[B], Δ	81[b]	80/0.01; 39-40
$C_6H_5CH_2OCH_2C(CO_2Me)_3$	4a	$C_6H_5CH_2OCH_2Cl$	[B], Δ	87[b]	115-117/0.01
$CH_3COCH_2C(CO_2Me)_3$	4a	CH_3COCH_2Cl	[B], Δ	12[b]	80-82/0.01; 92
$CH_3COCH_2C(CO_2Et)_3$	4d	CH_3COCH_2Cl	[B], Δ, 7hrs	72	165/8
$PhCOCH_2C(CO_2Me)_3$	4a	$PhCOCH_2Br$	[B], Δ	60[b]	95-96
$PhCOCH_2C(CO_2Et)_3$	4d	$PhCOCH_2Br$	[B], Δ, 2hrs	--	226/7
$EtO_2CCH_2C(CO_2Et)_3$	4d	EtO_2CCH_2Cl	[B], Δ, 2½hrs	72	179-180/14
$EtO_2CCH(CH_3)C(CO_2Et)_3$	4d	$EtO_2CCH(CH_3)Br$	[B], Δ, 3hrs	--	190/8
$PhSCH_2C(CO_2Me)_3$	4a	$PhSCH_2Cl$	[B], Δ	68[b]	105-110/0.01
$PhCH_2CH_2SCH_2C(CO_2Me)_3$	4a	$PhCH_2CH_2SCH_2Cl$	[B], Δ	74[b]	110-115/0.01
$(Et)_2NCH_2CH_2C(CO_2Me)_3$	4a	$(Et)_2NCH_2CH_2Cl$	[B], Δ	54[b]	75/0.01
$C_5H_{10}NCH_2CH_2C(CO_2Me)_3$	4a	$C_5H_{10}NCH_2CH_2Cl$	[B], Δ	60[b]	80/0.01
$C_6H_5CONHCH_2C(CO_2Me)_3$	4a	$PhCONHCH_2Cl$	[B], 25°C	72[e]	84
$Cl_3CCONHCH_2C(CO_2Me)_3$	4a	$Cl_3CCONHCH_2Cl$	[B], 25°C	60[e]	100-102/0.01; 54

a) Ref. 10, 20; except as otherwise noted; b) Ref. 22; c) Ref. 10; d) Ref. 15; e) Ref. 43. f) [A][10] The sodiomethanetricarboxylic ester (28 mmol) was added to an excess of the alkyl halide (180 mmol) and heated at 130-170°C for several hours. Upon cooling, anhydrous ether was carefully added and the mixture was filtered. Removal of the ether and fractional distillation in vacuo gave the desired alkylated product. [B][14,22] The alkylating agent (42 mmol) was added to a stirred suspension of the sodiomethanetricarboxylic ester (38 mmol) in dry dioxane (80 mL) under the conditions given. The mixture was filtered and the dioxane removed in vacuo. [C][14] The sodiomethanetricarboxylic ester (0.10 mol) and the alkyl halide (0.10mol) were dissolved in acetone (60 mL) and refluxed (1-4 hrs). The reaction was cooled, filtered, and the acetone was evaporated. [D][17] Sodiomethanetricarboxylic ester (33.0 mmol) dissolved in benzene/N,N-dimethylformamide (1:1; 40 mL) was added to the alkyl halide (66.0 mmol) and heated at 75°-90°C for 10-20 hrs. After cooling, benzene (100 mL) was added, and the solution was washed with water (3 X 80 mL), dried, and evaporated to give the crude product.

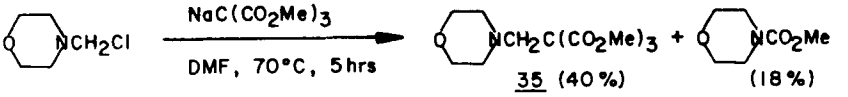
A common side-reaction arises from the presence of a nucleophilic group within the alkylating species, which can effect decarbalkoxylation and subsequent decomposition of the desired product. Thus, the reaction of N-chloromethylpiperidine with 4a gave a mixture of 31 and 32 instead of the anticipated 33;[43] the pentamethyl ester 32 probably originated from the methylene malonate 34, which was a decomposition product of initially



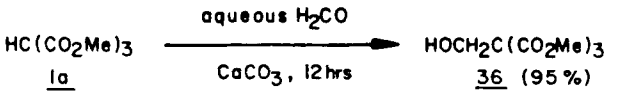
formed 33. This was verified by the subsequent synthesis of 32 from 34.[43]



An analogous reaction occurred with N-chloromethylmorpholine; however, in this case some of the expected 35 was isolated.

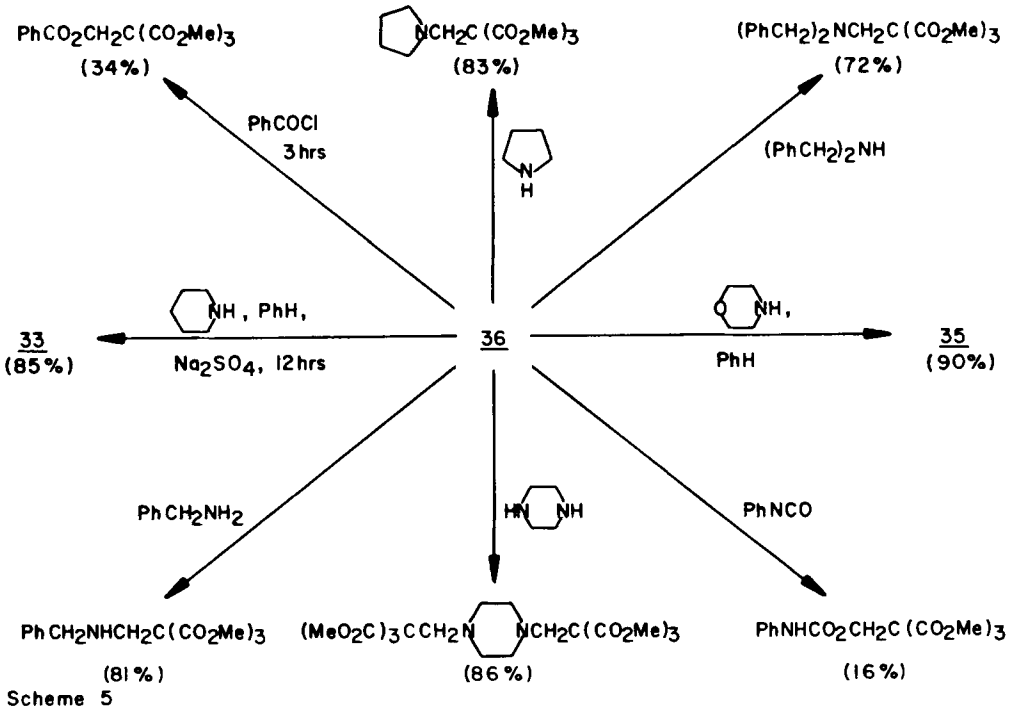


In order to circumvent these side-reactions, an alternate synthesis from 2,2,2-tricarbomethoxyethanol (36) was devised;[43] 36 was prepared by the addition of 1a to aqueous formaldehyde in the presence of base.



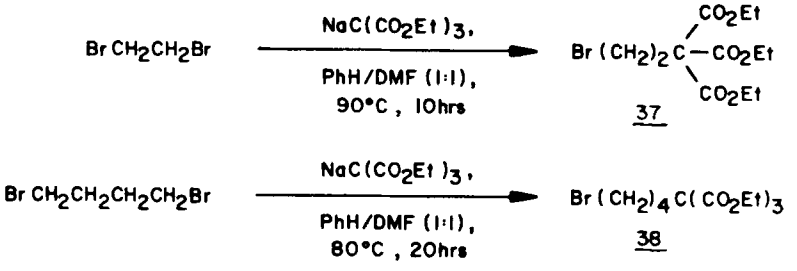
This very reactive alcohol was easily condensed with secondary amines to afford N,N-disubstituted-2-amino-1,1,1-tricarbomethoxyethanes (Scheme 5),[43] and thus 33 and 35 were obtained in excellent yields.

The malonic ester synthesis is among the oldest and most utilized classical organic reactions;[44] however, for some substrates it does have disadvantages: dialkylation often takes place with reactive halides, eliminations can occur, alkyl halides containing relatively acidic

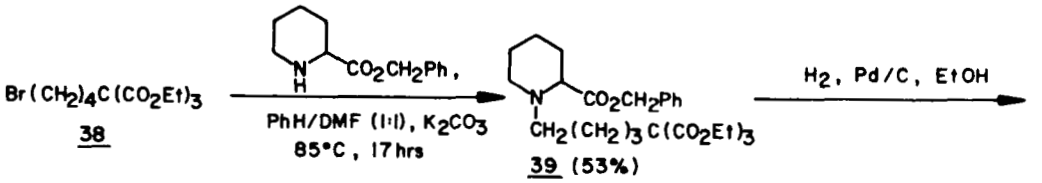


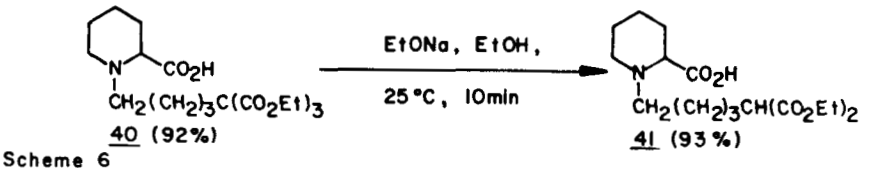
Scheme 5

hydrogens can seldom be used, and the synthesis of haloalkylmalonic esters from dihalo alkanes is essentially impossible since inter- or intramolecular dialkylations usually occur. Intramolecular cyclization predominates when cyclopropane or cyclopentane rings are formed.[45] To bypass these difficulties Rapoport and co-workers utilized the carbethoxy moiety as a blocking group;[15] thus, triethyl 3-bromopropane-1,1,1-tricarboxylate (37) and 5-bromopentane-1,1,1-tricarboxylate (38) were prepared in good yields (>70%).[15] A synthetic application of this concept is shown in Scheme 6;



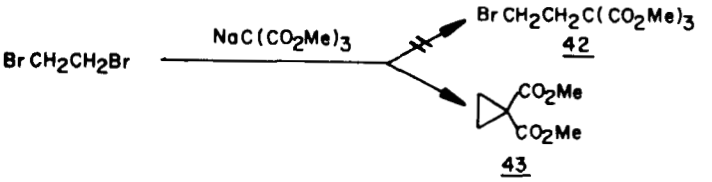
triethyl 5-bromopentane-1,1,1-tricarboxylate (38) was treated with benzyl pipecolate to form the N-alkylated pipecolate ester 39. Hydrogenolysis of 39 to the acid 40 followed by removal of the blocking group gave N-[5,5-bis-(ethoxycarbonyl)-n-pentyl]pipecolic acid 41.[15]



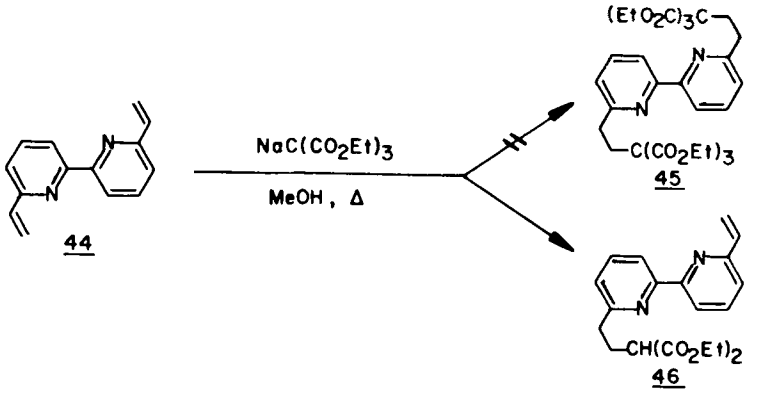


Scheme 6

Analogous attempts to prepare trimethyl 3-bromopropane-1,1,1,-tricarboxylate (42) have proven unsuccessful;[46] dimethyl cyclopropane-1,1-dicarboxylate (43) was obtained when the reaction was performed in benzene/N,N-dimethylformamide (1:1) at 90°C, while in refluxing dioxane starting materials were recovered (>90%).



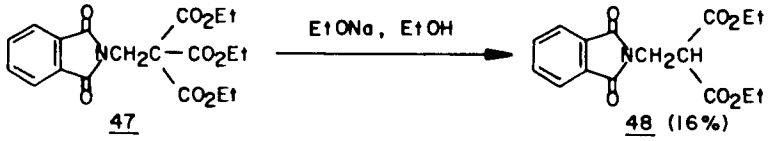
Nucleophiles are known to undergo Michael-type reactions with 2-(or 4-)vinylpyridines.[47] Thus, 6,6'-divinyl-2,2'-dipyridine (44) was treated with 2 equivalents of 4d in refluxing methanol in hopes of obtaining the bis-addition product 45; however, only the decarbalkoxylated mono-addition product 46 was obtained.[48]



44 45 46

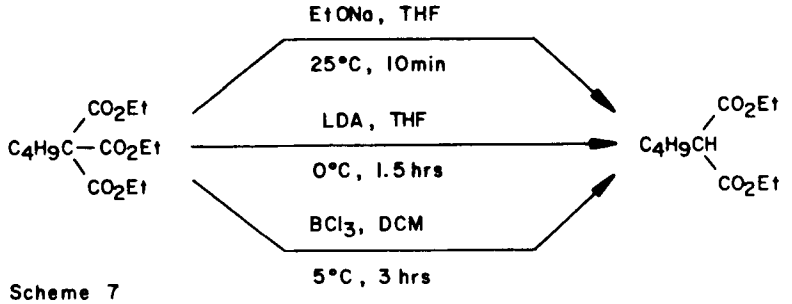
5. Decarbalkoxylations

Several decarbalkoxylations have already been discussed; however a few, more convenient procedures have been developed in recent years. Older methods consisted of heating the triester with sodium in alcohol;[8,10,11,43] thus 48 was obtained from 47 in 16% yield.[43]



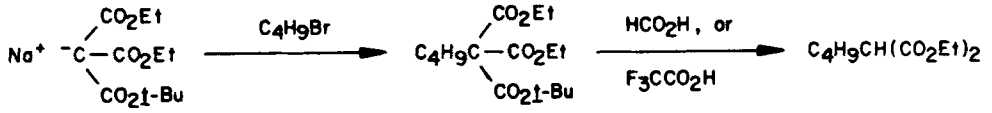
47 48 (16%)

In order for the carbalkoxy moiety to serve as a useful blocking group in the malonic ester synthesis, improved decarbalkoxylation methods were developed; the three best procedures are shown in Scheme 7.[15] All three methods were quantitative by GC analysis and isolated yields were >90%.



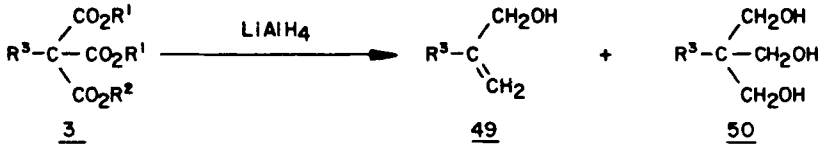
Scheme 7

An alternative method was based on the ease of hydrolysis of t-butyl esters; diethyl t-butyl pentane-1,1,1-tricarboxylate was prepared and easily decarbalkoxyated by treatment with either 100% formic or trifluoroacetic acid.[15]



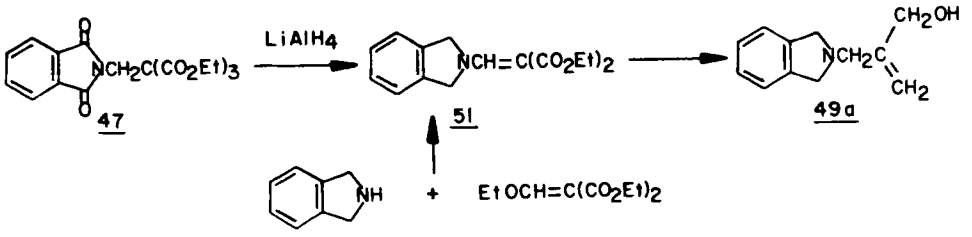
6. Reductions

Reduction of alkyl-1,1,1-tricarboxylic esters (3) with lithium aluminium hydride gaves a predominance of allylic alcohol 49 as well as a



3 49 50

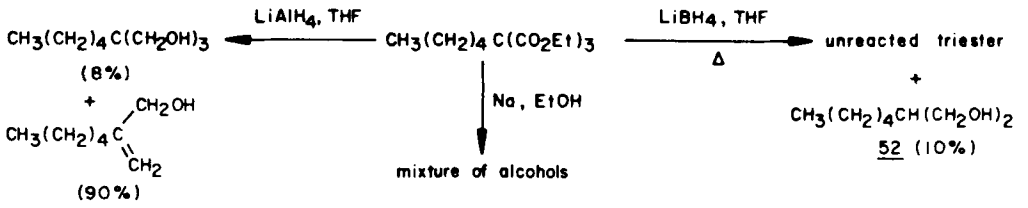
small amount of the anticipated 50.[43,49] For example, 49a was the only isolated product from the reduction of 47.[43] In addition, the decarbalk-



47 51 49a

oxylated intermediate was substantiated by the separate synthesis and subsequent reduction of 51.[43]

Several attempts to reduce triethyl hexane-1,1,1-tricarboxylate failed.[26,49] Lithium aluminum hydride gave 90% of the allyl alcohol and only 8% of the desired triol. Bouveault-Blanc[50] conditions gave a mixture of alcohols, and lithium borohydride in refluxing tetrahydrofuran[51] gave (10%) the diol 39 as well as recovered starting material (>80%).

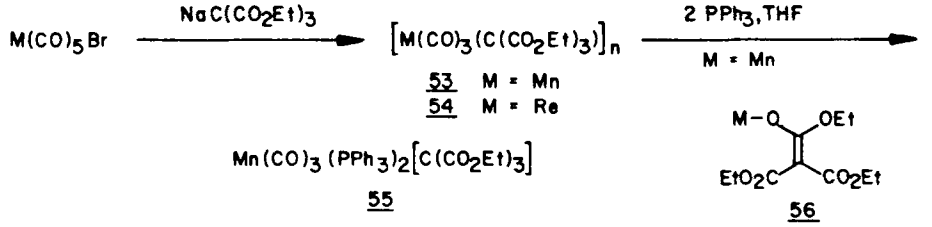


Sodium borohydride,[52-54] diborane-dimethylsulfide,[55] and triethoxysilyl-hydride[56] reductions all gave recovered starting material (>85%).

7. Miscellaneous

Oxidation of 1d with lead tetraacetate gave recovered 1d (86%), an unidentified oil, and hexaethyl ethane-1,1,1,2,2,2-hexacarboxylate (3%).[57]

Carbonyl complexes of manganese and rhenium have been treated with 4d to give 53 and 54, respectively.[58] Complex 53 was converted



to the monomeric complex 55 with triphenylphosphine. Based upon the infrared spectra of 53-55, the general structure 56 was assigned.[58]

Substituent effects on the stability of enolates and related carbanions including tricarbonylmethanes[59] have been studied by ^{13}C NMR. ^{13}C NMR has also been applied to the study of protonated esters in FSO_3H-SbF_5 solution.[60]

III. CONCLUSIONS

Methanetricarboxylic esters form a class of easily prepared compounds which have diverse, yet untapped, potential applications, some of which are described herein. Radical additions of methanetricarboxylic esters to

terminal olefins and alkylation of sodiomethanetricarboxylic esters provide convenient routes to alkyl-1,1,1-tricarboxylic esters. Further reactions allow the synthesis of various heterocycles, while selective monodecarbalkoxylation gave the corresponding malonic ester derivative; saponification and decarboxylation is a two carbon homologation to the acid. This is a useful sequence which bypasses many of the disadvantages of the malonic ester synthesis. The methods outlined here may well provide synthetic routes to molecules which are not readily accessible by other means.

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