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Pentaalkylguanidines as etherification and esterification catalysts.

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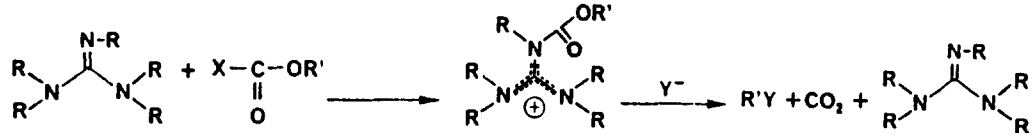
Abstract : Several pentaalkylguanidines have been prepared and found to be superior catalysts for the preparation of aryl and aralkyl ethers from carbonates and for the methylation of phenols with dimethylcarbonate. They also act as effective catalysts for esterification of acids with alkyl chloroformates but not for the acetylation of tertiary alcohols with acetic anhydride.
Résumé : Diverses pentaalkylguanidines ont été préparées et utilisées comme catalyseurs pour la décarboxylation des carbonates d'aryl et d'alkyl et pour la méthylation des phénols par le diméthylcarbonate. L'estérification à l'aide des chloroformiates d'alkyl a été étudiée.

The use of carbonic acid diesters or carbonochlorhydric acid esters as alkylating agents has been thoroughly studied in an attempt to substitute for the hazardous dialkyl sulfates or alkyl iodides. Dimethylcarbonate appears to be the reagent of choice for the methylation of thiols[1], phenols[2], acids[3] and amines[4], whereas alkyl chloroformates have been used for the esterification of acids[5]. Although most of these reactions are catalyzed by DMAP, there has been a constant search for alternative catalysts and processes to obtain mild reaction conditions. These include the use of Lewis acids[6], potassium carbonate under gas-liquid phase transfer conditions[7] and quaternary ammoniums salts[8]. As we were studying the synthetic potential of dialkylcarbonates, we thought that pentaalkylguanidines should be good catalysts for this kind of reaction.

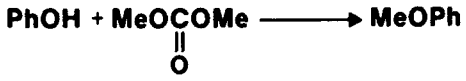
Strong guanidine bases have long been known[9] and used in catalytic reactions[10]. Sterically hindered pentaalkylguanidines have also proved to be of considerable synthetic interest[11] and have been used successfully in base catalyzed alkylations and eliminations[12]. The free bases and their salts have also been used in industrial processes[13]. As strong bases, we thought that they can easily generate the required phenoxide anion and are nucleophilic enough to attack the carbonyl of the intermediate mixed aryl alkyl carbonate (Scheme 1). Also, nucleophilicity of the guanidine can be carefully controlled so that alkylation of the catalyst itself does not

occur. Owing to the fact that alkylation rates of hindered guanidines have been found to be very slow[14], this could be easily accomplished through a proper choice of the substituents. On the other hand, guanidinium salts have been reported to be good phase transfer catalysts[15] and to enhance the nucleophilicity of their counter anion[16]. Delocalization of charge over the three nitrogens in the assumed intermediate guanidinium ion may favor nucleophilic catalysis in a way similar to that observed with acyl pyridinium salts. Pentasubstituted guanidines have also been shown to catalyze the reaction between phenyl isocyanate and an alcohol[12]. Finally, it should also be pointed out that 1,1,3,3-tetramethyl-4-(4-pyridyl)guanidine is one of the best aminopyridine catalysts already described[17].



Scheme 1

The required guanidines were easily and inexpensively prepared from a urea and a primary amine through a known procedure[11]. The appropriate urea or thiourea is treated with phosgene in toluene or acetonitrile to give the corresponding chloroamidinium salt in good yield which reacts with an excess of amine to yield the expected guanidine . These guanidines were then tested and compared with DMAP in the alkylation of phenol with dimethyl carbonate. We found that the conversion of phenol to anisole was complete at lower temperature than described for DMAP[7]. In order to obtain a fair comparison with DMAP, we set the temperature such that only a medium conversion of phenol was obtained. Under these conditions, the guanidine's catalytic activity is at least comparable with that of DMAP, with an observed maximum in the case of 1,1,3,3-tetrabutyl-4-methyl-guanidine (Table 1). This guanidine was extensively used in model reactions (see below) together with 1,1,3,3,4-pentamethylguanidine. Although the latter is slightly less efficient, it is sometimes preferred to 1,1,3,3-tetrabutyl-4-methylguanidine because of its increased water solubility which considerably facilitates the work-up procedure. 1,1,3,3-Tetrabutyl-4-methylguanidine was used to catalyze the methylation of various phenols and was found to give the corresponding methyl ethers in almost quantitative yields even in the case of highly hindered phenols (Table 2). Attempts to lower the temperature of the reaction near the boiling point of dimethyl carbonate and thus avoid the use of pressure equipment resulted in dramatically slower rates, e.g. total conversion in about fifteen days.



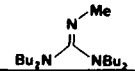
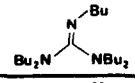
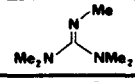
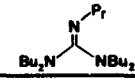
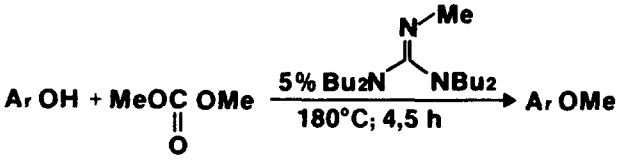
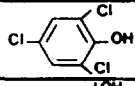
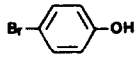
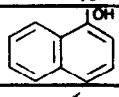
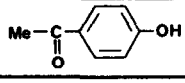
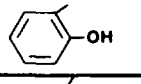
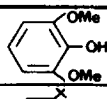
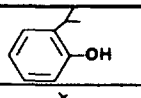
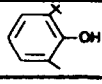
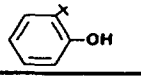
Catalyst	Time h	Temperature °C	Yield %
	4,5	160	100
	4,5	140	38
DMAP	4,5	140	27
	4,5	140	18
	4,5	140	9,5
	4,5	140	12

Table 1



Phenol	Yield* %	Phenol	Yield* %
	54		100
	95		94
	91		90
	82		88
	96		93

*g.c. yield

Table 2

We examined also the decarboxylation of mixed aryl alkyl carbonates which we assumed to be the easy step of the alkylation process (Scheme 1). Since these carbonates are readily available from phenols and alkyl chloroformates, this could provide an easy access to aryl ethers thus avoiding the need for pressure equipment. As expected, decarboxylation occurs at lower temperatures than in the reaction with dimethyl carbonate. We again compared DMAP with variously substituted guanidines (Table 3). In this case, anisole was obtained in slightly higher yields than when we used the new catalysts. Steric hindrance on the 4-nitrogen of the guanidine does not seem to be favorable probably because of the lower nucleophilicity of the corresponding guanidines. Also, substitution of the 4-nitrogen by a phenyl or a heteroatom reduces catalytic activity. Although the decarboxylation reaction accepts a variety of substituents on the aromatic ring, this procedure is not well suited for hindered phenols because of the difficulty to prepare the starting aromatic carbonate (Table 4).

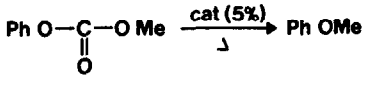
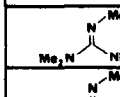
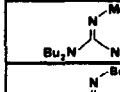
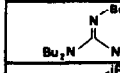
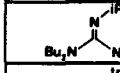
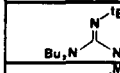
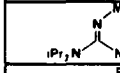
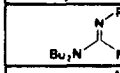
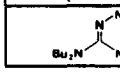


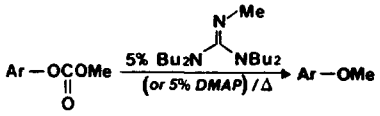
Table 3

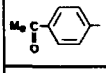
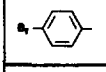
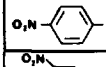
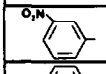
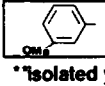
Catalyst	Temperature	Time h	Yield* %
DMAP	110°C	1	54
	130°C	2	95
	110°C	1,25	45
	110°C	1	93
	110°C	1	84
	110°C	1	79
	110°C	15	49
	140°C	1	13
	140°C	2	17
	140°C	2	5

*g.c. yield

DMAP and the guanidines were also effective in the decarboxylation of substituted diaryl carbonates at temperature lower than those described with conventional base catalysis[18] (Scheme 2). However, decarboxylation of unsymetrical diaryl carbonates did not lead to the expected corresponding aryl ethers as exemplified for phenyl 4-nitrophenylcarbonate. Instead, we ob-

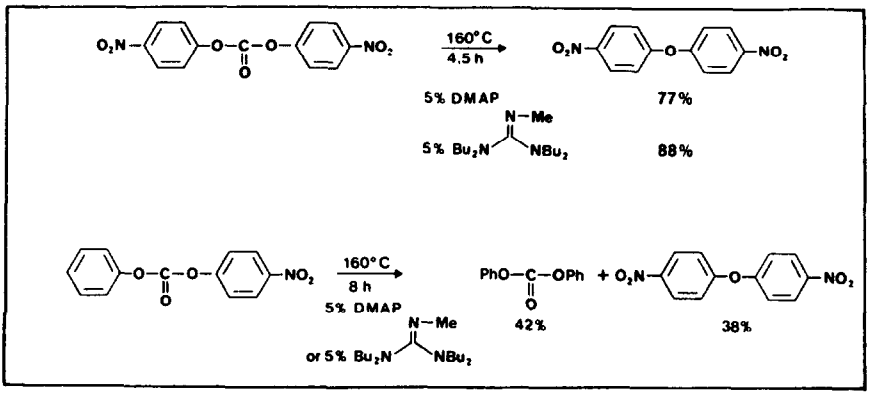
tained an approximately one to one mixture of diphenyl carbonate and dinitrophenylether which corresponds to the competition between substitution on the carbonyl and aromatic nucleophilic substitution. Also, the synthesis of unsymetrical diaryl ethers through the decarboxylation of equimolecular mixtures of symetrical carbonates was unsuccessful as previously described[19] (Scheme 2).



Ar	Temp.	Time h	Yield* %	Ar	Temp.	Time	Yield*
	110°C *(130° C)*	1 h *(2 h)*	93 *(95)***		110°C 140°C -	1 h 4 h *(2 h)*	29 100 *(86)*
	130°C 140°C *(140° C)*	1 h 4 h *(1,5 h)*	28 87 *(81)*		130°C 140°C *(140° C)*	1 h 4 h *(2 h)*	13 60 *(69)*
	110°C 130°C *(140° C)*	1 h 1 h *(0,75 h)*	72 92 *(69)*		130°C *(140° C)*	2 h *(2 h)*	27 *(84)*
	110°C 130°C *(140° C)*	1 h 1 h *(0,3 h)*	51 80 *(80)*		110°C *(110° C)*	1 h *(4 h)*	84 *(92)*
	110°C *(140° C)*	1 h *(0,25 h)*	84 *(81)*		140°C *(140° C)*	1 h *(1 h)*	77 *(89)*
	110°C *(140° C)*	1 h *(0,5 h)*	93 *(85)*		140°C	1 h	74**
	140°C *(140° C)*	4 h *(3 h)*	46 *(70)*				

**isolated yield *g.c. yield

Table 4



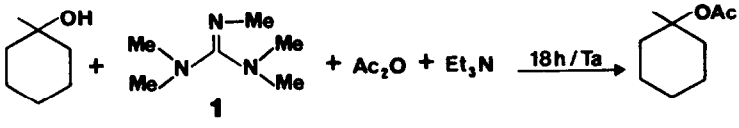
Scheme 2

We have also examined the replacement of DMAP by pentaalkylguanidines in the known[10] esterification of carboxylic acids with alkyl chloroformates. The results were comparable with those obtained previously[10] (Table 5). However, our attempts to extend DMAP's mimic to the acetylation of tertiary alcohols were unsuccessful (Scheme 3). The catalytic activity of pentamethylguanidine was found to be very low as compared to that of DMAP under the same conditions. This is probably due to the high basicity of the guanidines, wherein the catalyst is inactivated by protonation from the acetic acid by-product. This is confirmed by the medium yield obtained when we used equimolecular amounts of pentaalkylguanidine.

R	R'	Yield[a](%)			
		10% DMAP[b]	5% Bu4 Me gua	5% Mes gua	catalyst
Ph_2CH-	Me	98	93	88	
Ph_2CH-	Et	93	91	86	
Ph_2Ch-	iPr	95	-	83	
$PhCH_2OC(O)NH$-$CH(CH_3)$	Me	96	91	-	
$^tBuOC(O)NH$-CH-CH_2Ph	Bzl	93	-	69	
Ph	CH_2-CCl_3	55	60	-	

a) isolated yield b) from J. Org. Chem. **50**, 560, 1985

Table 5



Catalyst	Yield %
5% 1	15
100% 1	59
5% DMAP	93

Scheme 3

In conclusion, although their activity seems to be limited to the field of carbonic acid chemistry, pentaalkylguanidines have been shown to be valuable catalysts for the synthesis of ethers and esters in a way similar to that of DMAP. This and other interesting properties[4] demonstrates the high potential value of these inexpensive and readily available compounds.

Experimental section

Capillary melting points are reported uncorrected. ^{1}NMR spectra were recorded on a Varian EM 360A spectrometer using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. IR spectra were recorded on a Beckmann Acculab 4 spectrometer. Optical rotations were measured with a Perkin Elmer 241 MC polarimeter. Elemental analysis were performed by ICSN, Gif-sur-Yvette.

N,N,N',N'-Tetrabutylchloroamidinium chloride-(Hood! Review phosgene safety precautions before repeating!)

N,N,N',N'-Tetrabutylurea (142 g, 0.5mol) is stirred neat at 80°C while phosgene gas (75 g, 0.75 mol) is bubbled in over 2 hours. The reaction mixture is then stirred at 80°C until no more carbonyl absorption at 1640cm^{-1} could be detected (usually 5 hours). Excess phosgene is then evaporated under vacuo and ethyl ether is added to the crystalline residue. After 2 hours standing at 0-5°C, the crude product (140 g, 83%) is filtered under dry nitrogen. This product is used as such in the following steps. IR : 1610 cm^{-1}. Anal. Calcd. for $C_{17}H_{36}Cl_2N_2$: Cl, 20.9. Found : Cl, 21.5.

2-Methyl-1,1,3,3-tetrabutylguanidine

Excess methylamine (20 g, 0.65 mol) is bubbled at 0°C into a stirred solution of N,N,N',N'-tetrabutylchloroamidinium chloride (66.7 g, 0.2 mol) in dry acetonitrile (200 mL). The solution is then stirred at room temperature for 1 hour and refluxed for one more hour. The solvents are evaporated off and the residue cautiously treated with 30% aqueous sodium hydroxide (150 mL) and extracted twice with ether (100 mL). The extracts are dried concentrated under vacuo and distilled under reduced pressure to give the guanidine (48.2 g, 82%), b.p.$_{0.1}$ 140-145°C. Anal. Calcd for $C_{18}H_{39}N_3$: C, 72.66 ; H, 13.21 ; N, 14.12. Found : C, 72.77 ; H, 13.06 ; N, 14.39.

The following guanidines are similarly prepared :

1,1,2,3,3-Pentabutylguanidine

Yield : 74% . b.p.$_1$ 43°C. IR : 1610 cm^{-1}. Anal. Calcd. for $C_{21}H_{45}N_3$: C, 74.27 ; H, 13.36 ; N, 12.37. Found : C, 73.73 ; H, 13.13 ; N, 12.95.

2-Propyl-1,1,3,3-tetrabutylguanidine

Yield : 84% . b.p.$_{0.6}$ 139-140°C. IR : 1610 cm^{-1}. Anal. Calcd. for $C_{20}H_{43}N_3$: C,73.78 ; H, 13.31 ; N, 12.91. Found : C, 73.60 ; H, 13.07 ; N, 13.31

2-tert-butyl-1,1,3,3-tetrabutylguanidine

Yield : 82% . b.p.$_{0.05}$ 116-117°C. IR : 1610 cm^{-1}. Anal. Calcd. for $C_{21}H_{45}N_3$: C, 74.27 ; H, 13.36 ; N, 12.37. Found : C, 74.21 ; H, 13.21 ; N, 12.79.

2-Phenyl-1,1,3,3-tetrabutylguanidine

Yield : 84% . b.p.$_{0.03}$ 151-152°C. IR : 1610 cm^{-1}. Anal. for $C_{23}H_{41}N_3$: C, 76.82 ; H, 11.49 ; N, 11.69. Found : C, 76.39 ; H, 11.54 ; N, 12.55.

2-Methyl-1,1,3,3-tetraisopropylguanidine

Phosgene (10 g, 0.1 mol) is added to a solution of N,N,N',N'-tetra-isopropylurea[4](3.3 g, 13 mmol) in ether (60 mL). After 2 hours stirring at room temperature, evaporation of solvents and excess phosgene leaves a white solid which is dissolved in dry acetonitrile (13 mL). Excess methylamine is passed through this solution at 0°C. The solvent is evaporated, the residue treated with aqueous 30% sodium hydroxide (10 mL) and extracted twice with ether (10 mL). The organic phase is dried, filtered, evaporated and distilled under reduced pressure to yield 2.45 g (75%) of the guanidine b.p.$_{0.02}$ 60°C. IR 1610 cm^{-1}. NMR ($CDCl_3$, TMS) 1.15 (12H, d, 6Hz, 2xMe2) 1.25 (12H, d, 6Hz, 2xMe2) 2.9 (3H, s, N-Me) 3.4 (2H, septet, 2xCH) 3.8 (2H, septet, 2xCH). Anal. Calcd. for $C_{14}H_{31}N_3$, 0.25 H_2O : C,68.37 ; H, 12.91 ; N, 17.08. Found : C, 68.58 ; H, 12.79 ; N, 17.14.

General procedure for the synthesis of arylmethyl carbonates

The required phenol (0.1 mol) is dissolved in dry THF (100 mL) and converted to its sodium salt with sodium hydride (0.1 mol). Methyl chloroformate (0.1 mol) is added slowly to this solution and reacted at room temperature for approximately 3 hours. The reaction mixture is washed twice with saturated aqueous potassium carbonate, twice with brine, dried and filtered. The solvent is evaporated and the residue distilled under reduced pressure to give the expected carbonate with satisfactory spectral and physical data.

General procedure for the decarboxylation of aryl methyl carbonates

The required carbonate is mixed with the proper amount of catalyst (generally 5 mol%) and heated neat until the evolution of carbon dioxide has completely ceased.The reaction mixture is then analyzed by quantitative gas chromatography (internal standard on a 3m 10% OV17 on Chromsorb W column) or the product isolated by conventional techniques (distillation or column chromatography)(Table 4). Purities are checked either by thin layer or gas chromatogaphy. Spectral data of products are consistent with the expected anisole structure.

Comparative procedures for the preparation of anisole

a)15.2 g (0.1 mol) of phenyl methyl carbonate and 0.366 g (3 mmol) of DMAP are mixed and heated 2 hours at 130°C. The crude mixture is then distilled to yield 8.9 g (82%) anisole (b.p.$_{18}$ 50°C)

b)15.2 g (0.1 mol) of phenyl methyl carbonate and 1.5 g (5 mmol) of 1,1,3,3-tetrabutyl-4-methyl-guanidine are mixed and heated 1 hour at 110°C. The crude mixture is then distilled to yield 8.9 g (82%) anisole (b.p.$_{18}$ 50°C)

General procedure for methylation with dimethylcarbonate

The required phenol (10 mmol), dimethyl carbonate (30 mmol) and the catalyst (1.5 mmol) are placed in a sealed tube and heated in an oil bath (Caution : evolution of carbon dioxyde may cause overpressure in the tube). After cooling down the tube is opened and the residue analyzed by quantitative gas chromatography (internal standard on a 3m 10% OV17 on Chromsorb W column).

Preparation of veratrole

Catechol (11.0 g, 0.1 mol), dimethyl carbonate (25 mL) and 1,1,3,3-tetrabu-

tyl-4-methyl-guanidine (1.49 g, 5 mmol) are placed into a stainless steel autoclave and heated at 180°C during 3 hours. After cooling down and releasing the pressure, the resulting liquid is dissolved in dichloromethane, washed with 2N chlorhydric acid and distilled to yield 9.6 g (70%) of veratrole (b.p. 204-207°C)

Decarboxylation of phenyl 4-nitrophenyl carbonate

Phenyl 4-nitrophenyl carbonate (2.6 g, 10 mmol) is heated neat with DMAP (0.5 mmol) at 160°C for 8 hours. After cooling to room temperature, the reaction mixture is chromatographed on silica gel (eluant : hexanes-ethyl acetate 9-1) to give diphenyl carbonate (0.9 g ; 42%) m.p. 80°C and bis(4-nitrophenyl)ether (1.0 g ; 38%) m.p. 135-136°C (lit.[19] 142-143°C).

Esterification of diphenylacetic acid

Diphenylacetic acid (1.06 g, 5 mmol) and triethylamine (0.75 mL) are dissolved in dichloromethane (10 mL) and cooled to 0°C. Methyl chloroformate (0.386 mL, 5 mmol)is added and the mixture kept at 0°C for 5 min. Pentamethylguanidine (64.6 mg, 0.5 mmol) is then added, the reaction mixture stirred at room temperature for 1 hour and washed successively with dilute aqueous chlorhydric acid, aqueous sodium bicarbonate and water. The organic phase is dried and the solvent evaporated to leave 1.0 g (88%) of diphenylacetic acid methyl ester m.p. 58-59°C (lit.[10] 59-60°C).

Similarly prepared are the ethyl ester, 86%, m.p. 56-57°C (lit.[10] 57-59°C) and isopropyl ester, 83%, m.p. 41-42°C (lit.[10] 40-41°C).

N-(tert-Butyloxycarbonyl)-L-phenylalanine benzylester

N-(tert-Butyloxycarbonyl)-L-phenylalanine (2.65 g, 10 mmol) and triethylamine (1.06 g 10.5 mmol) are dissolved in dichloromethane (20mL) and cooled to 0°C. Benzyl chloroformate (1.7 g, 10 mmol) is slowly added. The mixture is stirred 10 min at 0°C and pentamethylguanidine (129 mg, 1 mmol) dissolved in dichloromethane (10 mL) is added. After stirring 1 hour at room temperature, the reaction mixture is washed successively with 0.1 N chlorhydric acid, saturated aqueous potassium carbonate and water. The organic phase is dried, filtered, evaporated and the residue is filtered over silica (elution with chloroform) to leave 2.45 g (69%) of the methyl ester m.p. 61-63°C (lit.[10]64-65°C), [α]D -11.6 (c 2 MeOH) (lit.[10] -11.8).

Acetylation of 1-methylcyclohexanol

To a stirred mixture of 1-methylcyclohexanol (1.14 g, 10 mmol), triethylamine (2.0 g, 20 mmol) and acetic anhydride (2.0 g, 20 mmol) was added 1.0 mmol of the acylation catalyst. The reaction was monitored by gc (a 25 m wide-bore 0.53 mm CP-Sil 5 CB column at 110°C was used). The retention times for the alcohol and the acetate were 2.2 and 5.4 min respectively.

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