4-Dialkylaminopyridines: Super Acylation and Alkylation Catalysts

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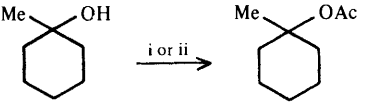
1 Introduction

Treatment of amines, alcohols, and phenols with acetic anhydride[1] (or acetyl chloride[2]) in the presence of pyridine has provided a general[3] acetylation method since the turn of the century. However, this procedure often proves to be unsatisfactory for the acetylation of deactivated substrates. It was not until the late 1960's that certain 4-dialkylaminopyridines were found, independently by two research groups,[4,5] to be much superior to pyridine as catalysts for difficult acylations.* 1-Methylcyclohexanol, a sterically hindered alcohol, gave an 86% yield of acetate (1) on reaction with acetic anhydride in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) and 1 equivalent of TEA.[5] Less than a 5% yield of (1) was obtained by the traditional method (Scheme 1).



(1)

Reagents: i, Ac_2O, pyridine, 14h, r.t. (<5% yield);
ii, Ac_2O, DMAP (4 mol %), TEA, 14h, r.t. (86% yield)

Scheme 1

The superiority of DMAP over comparable bases as a catalyst for the benzoylation of *m*-chloroaniline and benzyl alcohol is apparent from kinetic studies[6] (Table 1). Namely, catalytic activity is not directly related to pK_a, and it is reduced by the attachment of a substituent α to the pyridine nitrogen.

* Acylation is used in its generic sense, acetylation refers to XH → XAc.

[1] A. Verley and F. Bölsing, *Ber.*, 1901, **34**, 3354.

[2] A. Einhorn and F. Hollandt, *Liebigs Ann. Chem.*, 1898, **301**, 95.

[3] A. O. Fitton and J. Hill, 'Selected Derivatives of Organic Compounds', Chapman Hall, London, 1970.

[4] L. M. Litvinenko and A. I. Kirichenko, *Dokl. Akad. Nauk. SSSR, Ser. Khim.*, 1967, **176**, 97; *Chem. Abstr.*, 1968, **68**, 68325.

[5] W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 981.

[6] A. I. Kirichenko, L. M. Litvinenko, I. N. Dotsenko, N. G. Kotenko, E. Nikkel'sen, and V. D. Berestetskaya, *Dokl. Akad. Nauk. SSSR, Ser. Khim.*, 1979, **244**, 1125; *Chem. Abstr.*, 1979, **90**, 157601.

Table 1 *Effect of various bases on the relative rates of benzoylation of* m-*chloroaniline and benzyl alcohol*

Catalyst	pK_a	*Relative rate*[a] m-*Chloroaniline*[b]	*Benzyl alcohol*[c]
3-Pyridinecarbonitrile	1.39	14	12
Quinoline	4.87	138	545
Pyridine	5.23	568	9.29×10^3
Isoquinoline	5.40	2.62×10^3	3.39×10^3
2-Methylpyridine	5.96	29	435
3-Methylpyridine	5.63	1.12×10^3	2.29×10^4
4-Methylpyridine	6.02	2.96×10^3	3.98×10^4
4-Phenoxypyridine	6.25	4.80×10^3	7.98×10^4
2,6-Dimethylpyridine	6.72	8	115
DMAP	9.70	3.14×10^6	3.45×10^8
TEA	10.65	21	—

(*a*) Relative rate $= \frac{\text{rate of catalysed reaction}}{\text{rate of uncatalysed reaction}}$. (*b*) A. I. Kirichenko, L. M. Litvinenko, I. N. Dotsenko, N. G. Kotenko, E. Nikkel'sen, and V. D. Berestetskaya, *Dokl. Akad. Nauk SSSR*, 1979, **244**, 1125; *Chem. Abstr.*, 1979, **90**, 157601c. (*c*) L. I. Bondarenko, A. I. Kirichenko, L. M. Litvinenko, L. N. Dmitrenko, and V. D. Kobets, *J. Org. Chem.* (*USSR*), 1982, 2310.

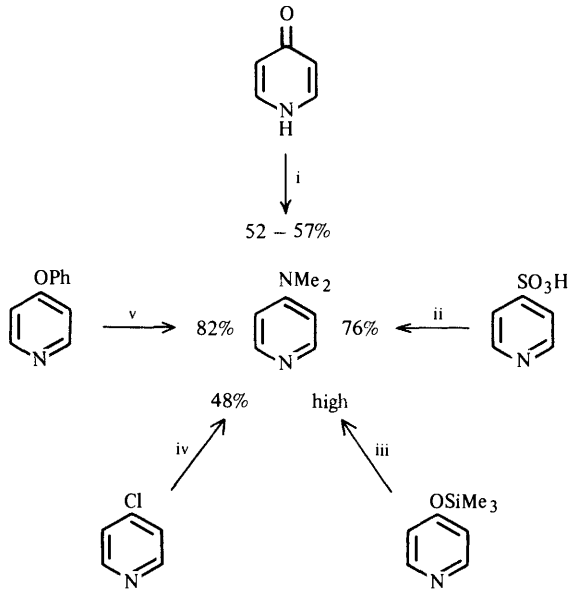
4-Dialkylaminopyridines were soon found to have general applicability for catalysis of acylations and related reactions, and the subject was reviewed[7] in 1978. That review coupled with the commercial availability of DMAP in large quantities, for the first time, stimulated great interest in its use as a catalyst in organic, polymer, analytical, and biochemistry. This review is principally concerned with the developments in the applications of DMAP that have taken place in the last five years.

2 Preparation and Physical Properties

DMAP and other 4-dialkylaminopyridines may be prepared fairly easily from suitable 4-substituted pyridines (Scheme 2). However, these methods do not provide viable commercial routes because of the relatively high cost of starting materials and the nature of the reaction conditions.

Two industrial processes have been claimed.[8,9] One, by Schering AG,[8] exploits a modification of an old reaction, that of a pyridylpyridinium salt with nucleophiles[10] (*e.g.* DMA). DMF is used in the process instead of DMA for the preparation of DMAP, which appears to avoid the formation of 4-aminopyridine

[7] G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569.
[8] H. Vorbrüggen, Schering AG, U.S.P., 4140853 (1979); Ger. Offen., 2517774 (1976); *Chem. Abstr.*, 1977, **86**, 55293.
[9] T. D. Bailey and C. K. McGill, U.S.P., 4158093 (1979); *Chem. Abstr.*, 1979, **91**, 123636.
[10] E. Koenigs and H. Greiner, *Ber.*, 1931, **64**, 1049.

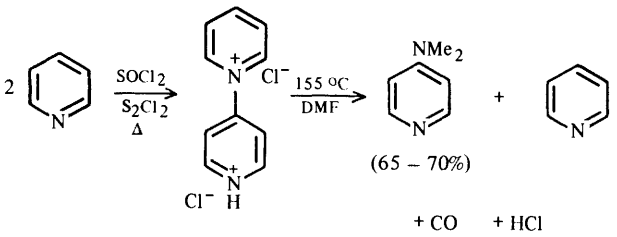


Reagents: i, HMPT, 2—4h, 220—230 °C (ref. *a*); ii, DMA, $ZnCl_2$, 2h, 150—160 °C (ref. *b*); iii, DMA, $HgCl_2$, 48h, 120 °C (ref. *c*); iv, DMA, EtOH, 2h, 100 °C; 12h, 115—130 °C (sealed tube) (ref. *d*); v, DMA.HBr, 1h, 200—210 °C (ref. *e*)

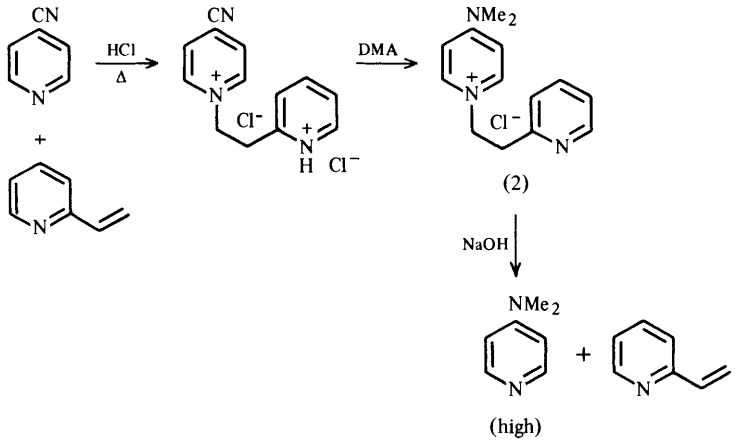
(*a*) H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 301. (*b*) Y. Suzuki, *Yakugaku Zasshi*, 1961, **81**, 1146. (*c*) H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 305. (*d*) J. W. Wibaut and F. W. Brockman, *Recl. Trav. Chim. Pays-Bas*, 1961, **80**, 309. (*e*) A. F. Vompe, N. V. Monich, N. F. Turitsyna, and L. V. Ivanova, *Dokl. Akad. Nauk SSSR*, 1957, **114**, 1235; *Chem. Abstr.*, 1958, **52**, 3803.

Scheme 2

as a by-product (Scheme 3). The other,[9] developed by Reilly Tar & Chemical Corporation, involves a novel reaction sequence (Scheme 4). In the first step, 4-cyanopyridine is quaternized with 2-vinylpyridine, which activates the 4-position towards attack by DMA to give (2). This quaternary salt is readily depyridethylated by sodium hydroxide to yield DMAP, and 2-vinylpyridine



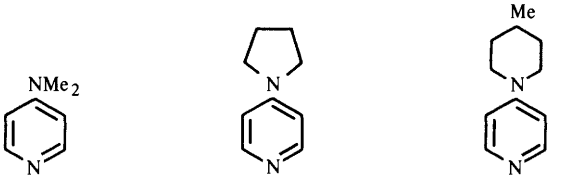
Scheme 3



Scheme 4

that is available for recycling. Recently, 2- and 4-vinylpyridines have found use as protecting groups in the alkylation of benzimidazoles.[11]

The most popular catalyst for laboratory and industrial use has proved to be DMAP (3). 4-Pyrrolidinopyridine (PPY) (4) is slightly superior to DMAP as a catalyst but this advantage is counterbalanced by its higher cost and lack of availability. A new liquid catalyst (MPP) (5) that is as effective as DMAP has been reported[12] recently. Some physical constants for (3)—(5) are given in Scheme 5.



(3)	(4)	(5)
m.p. 112 – 113 °C	m.p. 57 – 58 °C	b.p. 148°C/4 mmHg
[1122-58-3]	[2456-81-7]	[80965-30-6]

Scheme 5

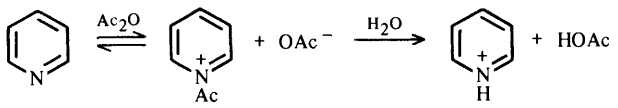
3 Mechanism of Catalysis

The study of catalysis of acylations and related reactions has a long history.[13] Indeed, Scheele reported[14] the effect of acid and alkali on esterification and

[11] M. Ichikawa, C. Yamamoto, and T. Hisano, *Chem. Pharm. Bull.*, 1981, **29**, 3042.
[12] Reilly Report 5, 'DMAP Update', Reilly Tar & Chem. Corp., Indianapolis. 1982.
[13] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.
[14] J. W. Baker and E. Rothstein, in 'Handbuch der Katalyse', ed. G. M. Schwab, Springer, Vienna, 1940, Vol. 2, p. 46.

hydrolysis in 1792. As this review is concerned mainly with applications, only a few important points about the mechanisms of catalysis will be outlined. Pyridines may act as nucleophilic or general base catalysts.

A. Nucleophilic Catalysis.—The hydrolysis of acetic anhydride (acetylation of water) in the presence of pyridine has been shown to proceed by nucleophilic catalysis, and the unstable acetylpyridinium ion (6) was proposed as an intermediate. The mechanism (Scheme 6) was formulated on the basis of kinetic analysis.[15]



(6)

Scheme 6

Subsequently, the acetylpyridinium ion was observed[16] spectrophotometrically [λ 272 nm (ε *ca.* 4.4 × 10^3) and λ 225 nm (7 × 10^3)] in the above reaction, and in the pyridine catalysed acetylation of anilines. Pyridinolysis of 2,4-dinitrophenyl methyl carbonate,[17,18] 2,4-dinitrophenyl chloroformate[20] by a series of pyridines has been found to give curved Brønsted plots. These plots show a large dependence of rate constants on pK_a ($\beta \sim 0.8$—1.0) for most pyridines but it becomes small ($\beta \sim 0.1$—0.3) for the most basic ones. Curvature has been attributed to a change over from rate determining breakdown to formation of the tetrahedral intermediate (7).[21] This is exemplified[19] by the Brønsted plot (Figure 1) for pyridinolysis of acetic anhydride in aqueous solution by a series of pyridines of increasing basicity (Scheme 7).

The intermediate salt (8) is most readily formed in the case of the most basic pyridine in the series, DMAP. Unlike pyridine, such salts of DMAP may be isolated and are often quite stable (*see below*). Hydrolysis of intermediate salt (8) is subject to general base catalysis. The mechanism of breakdown of salts of the type (8) depends upon the nature of R[22] and the N-substituent.[23] Hydrolysis, by water of a series of 1-methoxycarbonylpyridinium ions was found[22] to be general base-catalysed and formation of the tetrahedral intermediate was rate determining (Scheme 8). A bent Brønsted plot was obtained which could not be explained by a change in the rate determining step, as (9) was

[15] A. R. Butler and V. Gold, *J. Chem. Soc.*, 1961, 4362.
[16] A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, 1970, **92**, 5432.
[17] E. A. Castro and F. J. Gil, *J. Am. Chem. Soc.*, 1977, **99**, 7611.
[18] E. A. Castro and M. Freudenberg, *J. Org. Chem.*, 1980, **45**, 906.
[19] C. Castro and E. A. Castro, *J. Org. Chem.*, 1981, **46**, 2939.
[20] P. M. Bond, E. A. Castro, and R. B. Moodie, *J. Chem. Soc., Perkin Trans. 2*, 1976, 68.
[21] M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6970.
[22] P. J. Battye, E. M. Ihsan, and R. B. Moodie, *J. Chem. Soc., Perkin Trans. 2*, 1980, 741.
[23] V. A. Savelova, I. A. Belousova, and L. M. Litvinenko, *J. Org. Chem. (USSR)*, 1982, 1333.

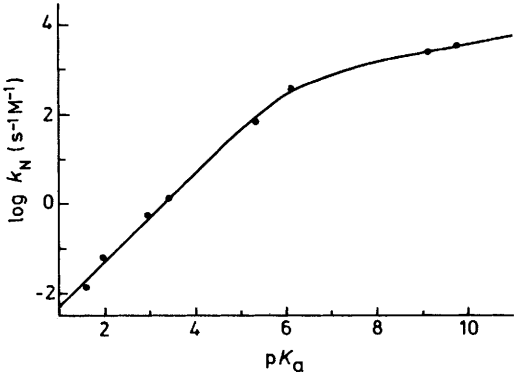
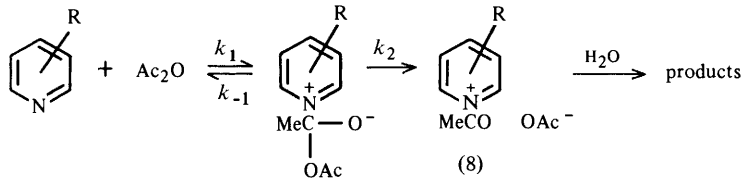


Figure 1 *Brønsted plot for the pyridinolysis of acetic anhydride by a series of pyridines in aqueous solution at 25 °C*

(Reproduced by permission from *J. Org. Chem.*, 1981, **46**, 2942)

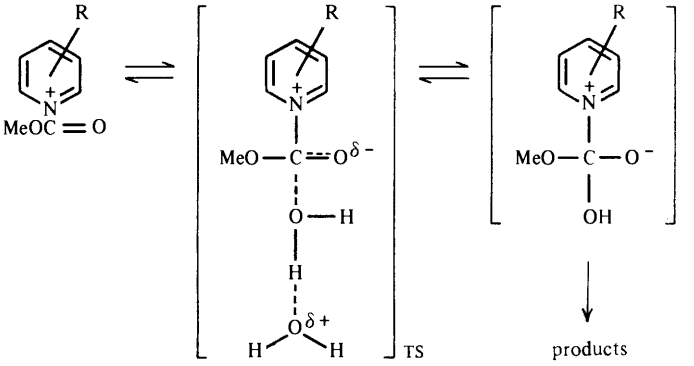


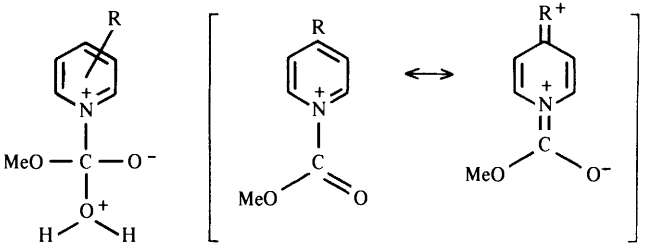
Scheme 7

ruled out as an intermediate. Curvature was tentatively ascribed to a stabilization of the ions (10) that had electron donating substituents attached at the 4-position. Such stabilization is not available to the other pyridine salts in the series. Therefore, catalysis is not truly reflected by consideration of the pK_a alone. The DMAP salt (10) (R = NMe_2) provides the prime example of this effect. General base catalysis takes place because the pyridine may take the place of the terminal water molecule in the transition state.

The effect of varying the N-substituent has been studied for the reactions of a series of *N*-arylsulphonyl-4-dimethylaminopyridinium salts with 3-nitroaniline in dichloromethane.[23] The reactivity of these salts, which exist as ion-pairs in dichloromethane, depends upon the nature of the anion, and it decreases in the order benzenesulphonate > bromide > chloride. Three independent pathways have been delineated for this reaction; *viz.* bimolecular reaction of the salt with 3-nitroaniline, trimolecular reaction involving catalysis by a second molecule of salt, and trimolecular reaction with catalysis by a second molecule of DMAP.

Some of the complexities of nucleophilic catalysis by pyridines have been outlined above. However, nucleophilic catalysis by 4-dialkylaminopyridines

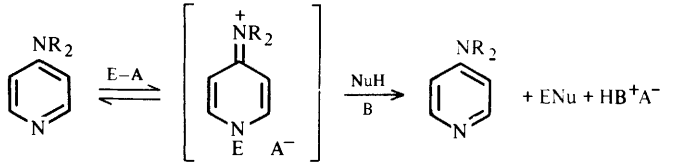




(9) (10)

Scheme 8

may be looked at from the 'opposite' point of view (Scheme 9). In this simplistic scheme, DMAP and its cogeners are considered as 'catalytic supports' for an electrophile (E) that promote reaction with a substrate (Nu—H). Examples of electrophiles that contain the elements C, Si, P, and S attached at N-1 are common (*see below*), but N-analogues do not seem to have been reported. A few points of practical importance about Scheme 9 are worthy of note. In the first step, DMAP, MPP, and PPY form *N*-acylpyridinium salts much

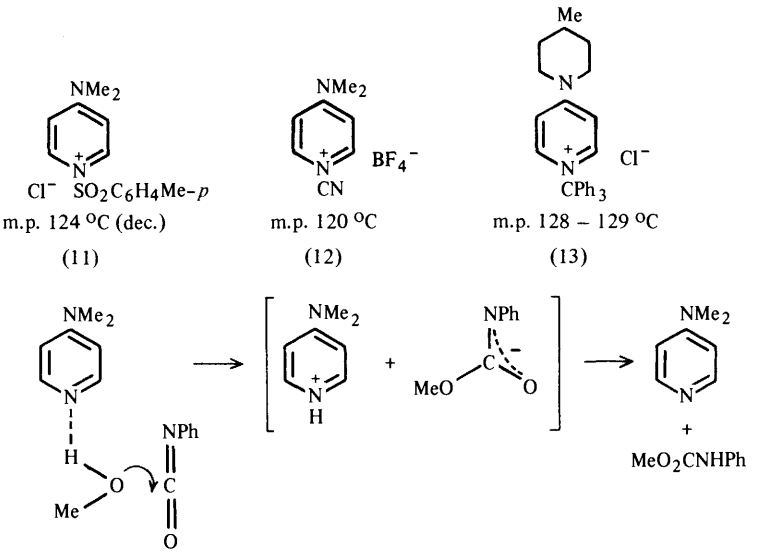


E = electrophile
A = counterion or its precursor
Nu = nucleophile
B = strong base

Scheme 9

more rapidly than other pyridines (Figure 1). Once formed these salts are stabilized by resonance (10), and in a number of cases can be isolated, *e.g.* (11),[24] (12), [25] and (13).[12] They exist as loose ion-pairs in non-polar solvents which facilites nucleophilic attack at the acyl group. The second step is subject to general base catalysis by the counter-ion. Thus acid anhydrides are better acylating agents than the corresponding acid chlorides under these conditions. In practice, a strong base such as TEA is often used to speed up the second step, and if a stoicheiometric amount is used it also has the advantage of preventing protonation of the catalytic amount of DMAP by acid formed in the reaction. As a consequence of these features, acylations in the presence of DMAP are usually carried out using acid anhydrides, a catalytic amount of DMAP (*ca.* 5—20 mole %), and a stoicheiometric quantity of an auxiliary base (*e.g.* TEA) in a nonpolar solvent (*e.g.* dichloromethane).

B. General Base Catalysis.—DMAP has been found to catalyse the formation of polyurethanes in the reaction of isocyanates with alcohols and phenols.[26] Recently, the pyridine-catalysis of a similar reaction, that of methanol with phenyl isocyanate in tetrachloromethane was studied.[27] A Brønsted plot with a slope β of 0.49 was obtained for catalysis by a series of 3- and 4-substituted pyridines.



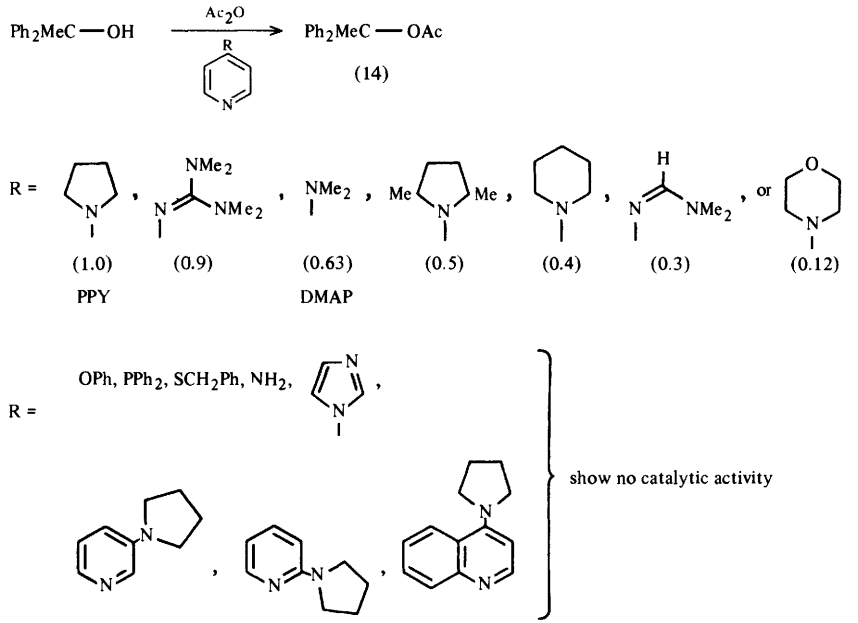
Scheme 10

[24] E. Guibé-Jampel, M. Wakselman, and D. Raulais, *J. Chem. Soc., Chem. Commun.*, 1980, 993.
[25] M. Wakselman, E. Guibé-Jampel, A. Raoult, and W. D. Busse, *J. Chem. Soc., Chem. Commun.*, 1976, 21.
[26] H. J. Twitchett, B. P., 990 637 (1965); *Chem. Abstr.*, 1965, **63**, 766.
[27] R. B. Moodie and P. J. Sanson, *J. Chem. Soc., Perkin Trans. 2*, 1981, 664.

A general base catalysis mechanism (Scheme 10) was proposed for this reaction from the β-value, the steric effect of 2,4,6-trimethylpyridine deuterium isotope, and solvent effects. This reaction provides one of the few that has been shown to involve general base catalysis by DMAP. Almost all the important synthetic applications of DMAP to be discussed probably occur by nucleophilic catalysis, but not all individual examples have been examined closely.

4 Applications in Synthetic Organic Chemistry

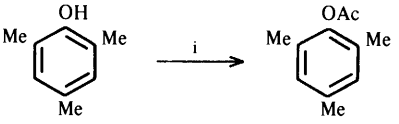
A. Types of Reaction Catalysed.—(i) *Acylation.* DMAP is now commonly used to facilitate the acylations of sterically hindered and other deactivated alcohols. Several studies have employed this reaction to compare the catalytic ability of a number of 4-dialkylaminopyridines and related compounds. The acetylation of 1,1-diphenylethanol to (14) with 2 molar equivalents of acetic anhydride and TEA in the presence of 0.1 molar equivalents of catalyst was stopped before completion, and the progress of the acetylation was determined by n.m.r. or g.c.[28] The relative effects of the catalysts compared to the best one, PPY, are given (Scheme 11). This order follows the order of reactivity of the



Scheme 11

[28] A. Hassner, L. R. Krepski, and V. Alexanian, *Tetrahedron*, 1978, 34, 2069.

enamines of the respective amines towards electrophiles.[29] A recent study of the acetylation of t-butyl alcohol, carried out in a similar way, also indicates that PPY (1.0) is the best catalyst.[30] However, DMAP (0.9) and MPP (0.75), the new liquid catalyst, are almost as good; but *N*-methylimidazole (0.1) is much inferior. The acetylation of mesitol is easier than those described above, and in this reaction DMAP and MPP are again about equally as effective[12] (Scheme 12).

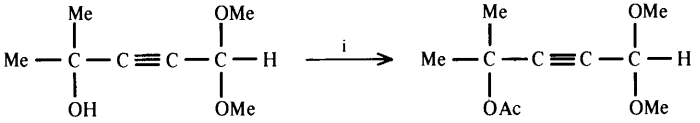


(0.1 mol)

Reagents: i, Ac_2O (0.16 mol), 2h, r.t., CH_2Cl_2, alone (0%)
+ DMAP (94%)
+ MPP (91%)

Scheme 12

Acetylation of the t-alkynol (15) is sufficiently easy in the presence of DMAP that the acid labile acetal function survives (Scheme 13).[31] DMAP has found use in the preparation of (propargyl acetate)dicobalt hexacarbonyl complexes which dimerize readily in the presence of trimethylaluminium.[32]



(15) (18 mmol) (93%)

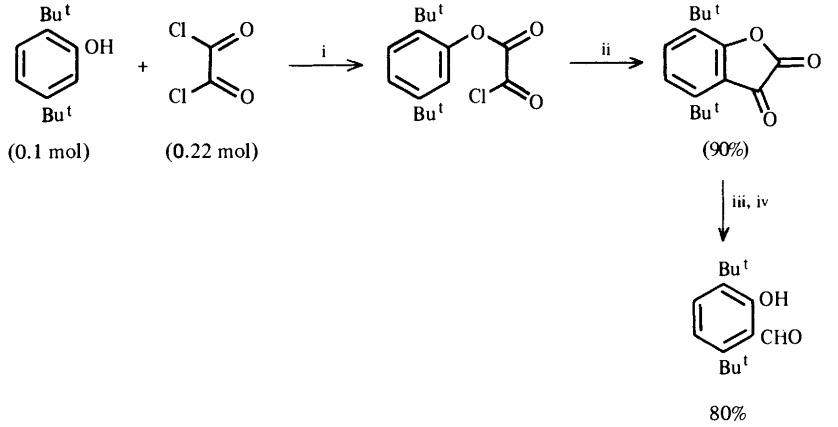
Reagents: i, Ac_2O (25 mmol), DMAP (30 mmol), CH_2Cl_2, 20 min, r.t.

Scheme 13

Sterically hindered phenols are very difficult to formylate by the conventional Reimer-Tiemann, Gattermann, and Duff procedures. The sequence (Scheme 14), which depends upon DMAP catalysis in the first step, provides a high yield route to sterically hindered *o*-hydroxybenzaldehydes.[33]

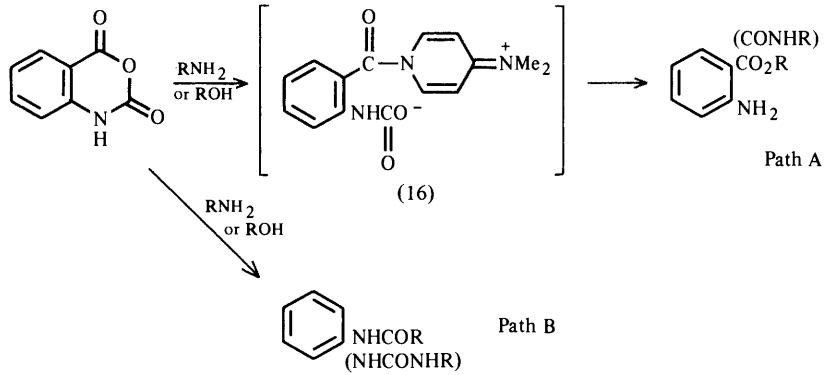
The value of isatoic anhydrides as an *o*-aminobenzoylating agent for primary amines and alcohols is enhanced when it is used with DMAP, as the competing reaction (Path B) is suppressed (Scheme 15).[34] A DMAP salt (16) was suggested as an intermediate.

[29] S. F. Dyke, in 'Chemistry of the Enamines', Cambridge University Press, London, 1973.
[30] G. L. Goe, L. M. Huckstep, and E. F. V. Scriven, *Chem. Ind. (London)*, 1982, 722.
[31] G. Höfle and W. Steglich, *Synthesis*, 1972, 619.
[32] S. Padmanabhan and K. M. Nicholas, *J. Organomet. Chem.*, 1981, **212**, 115.
[33] D. J. Zwanenburg and W. A. P. Reynen, *Synthesis*, 1976, 624.
[34] M. C. Venuti, *Synthesis*, 1982, 266.



Reagents: i, DMAP (4.1 mmol), $CHCl_3$, 10h, reflux;
ii, $AlCl_3$; iii, LAH; iv KIO_4.

Scheme 14



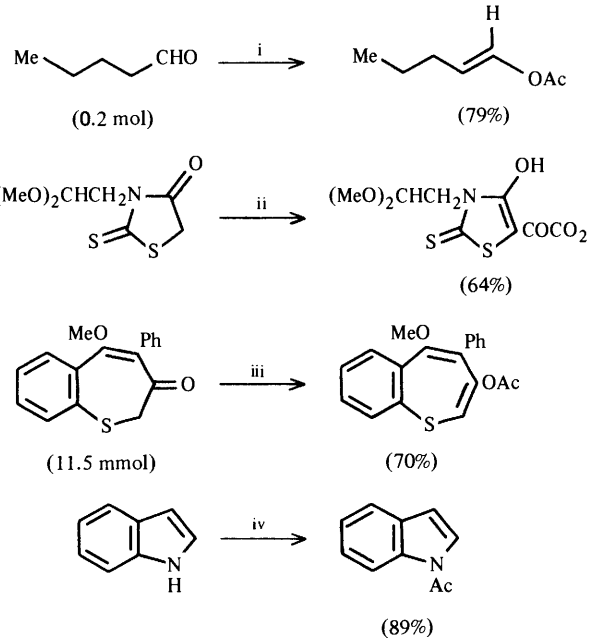
Yields: NHR; R = Bu^n (93%), $PhCH_2$ (97%), Bu^t (73%)
OR; R = Ph (98%), $PhCH_2$ (90%), Ph_2CH (81%)

Scheme 15

C- and *O*-acylation of enolates are known (equations 1—3).[35-37] The presence of just a catalytic amount of DMAP proves useful for the *N*-acetylation of indoles and related heterocycles (equation 4).[38]

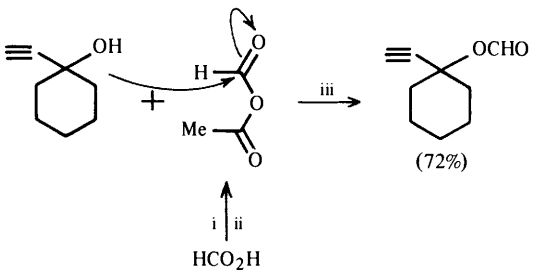
Acylation and esterification using preformed mixed anhydrides constitutes a well established method, but preparation of such compounds is not always

[35] T. J. Cousineau, S. L. Cook, and J. A. Secrist, III, *Synth. Commun.*, 1979, **9**, 157.
[36] D. H. R. Barton, E. Buschmann, J. Haüsler, C. W. Holzapfel, T. Sheradsky, and D. A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1107.
[37] H. Hofmann, H.-J. Haberstroh, B. Appler, B. Meyer, and H. Herterich, *Chem. Ber.*, 1975, **108**, 3596.
[38] K. Nickisch, W. Klose, and F. Bohlmann, *Chem. Ber.*, 1980, **113**, 2036.



Reagents: i, DMAP (0.02 mol), TEA (0.4 mol), Ac_2O (1.0 mol), 12—14h, 50 °C;
ii, $ClCOCO_2Et$, DMAP, pyridine, CH_2Cl_2, 3h, reflux;
iii, Ac_2O, DMAP, TEA, MeCN, −10 °C, 4 days; iv, Ac_2O (1.2 mmol), DMAP (1 mmol), TEA (1.2 mmol), CH_2Cl_2, 24h, r.t.

easy.[39] Use of DMAP allows the high-yield generation of mixed anhydrides *in situ* (Scheme 16). This may be achieved by the slow addition of acetic anhydride to formic acid at low temperature.[5] The reaction mixture is then warmed slowly to room temperature to ensure that the alcohol reacts

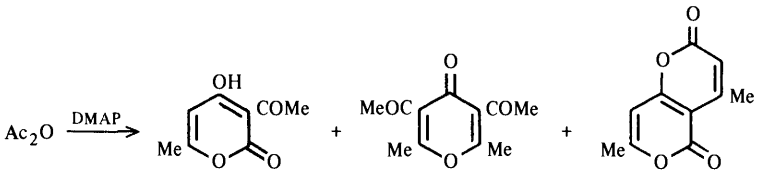


Reagents: i, DMAP, TEA, CH_2Cl_2, −40 °C; ii, Ac_2O added over 30 min, −35 °C; iii, warmed to r.t. over 1h

Scheme 16

[39] E. Haslam, *Tetrahedron*, 1980, 2409.

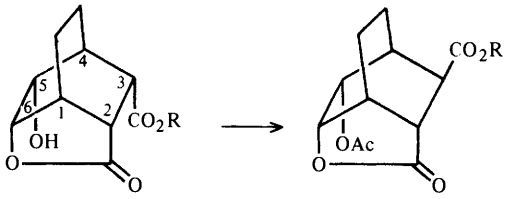
selectively at the formyl group of the anhydride. Maintenance of strict temperature control, and the mode of addition are particularly important in the first step to avoid self condensation of the acetic anhydride (Scheme 17). The mixed anhydride approach also avoids the use of halides, which tend to give poorer yields than anhydrides.



(16%) (3%) (0.3%)

Scheme 17

Treatment of the mixed anhydride lactone (17) with acetic anhydride and DMAP in pyridine results in acetylation with epimerization at C-3 (Scheme 18).[40] Presumably, epimerization occurs first with relief of steric crowding at C-5 and this permits acetylation. The methyl ester (18), that has a less acidic proton attached to C-3, does not undergo reaction. DMAP has been employed to catalyse many other types of acylation, including phosphorylations,[7] sulphonylations,[41] and sulphinylations.[42]



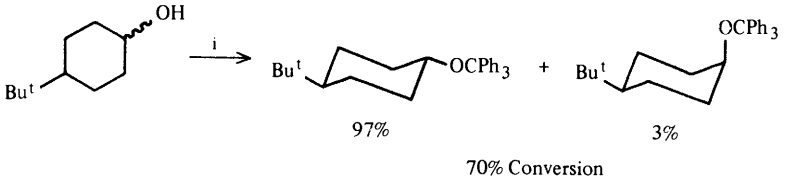
(17) R = Ac
(18) R = Me

R = Ac

Scheme 18

(ii) *Tritylation.* A *cis–trans* mixture of 4-t-butylcyclohexanol gives almost exclusively the *trans* (equatorial) ether on reaction with trityl chloride and DMAP (Scheme 19).[43] This result was attributed to a kinetic factor originating from the large steric requirement of the alkylating agent, the *N*-trityl-4-dimethylaminopyridinium salt (19). Selective tritylation of a primary alcohol

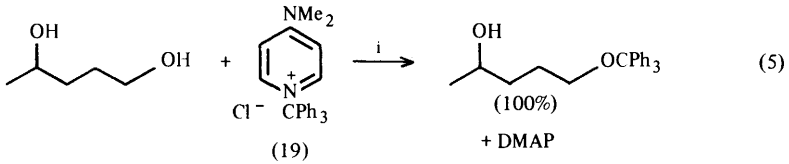
[40] R. M. Carman and S. S. Smith, *Aust. J. Chem.*, 1981, **34**, 1285.
[41] E. Guibé-Jampel, M. Wakselman, and D. Raulais, *J. Chem. Soc., Chem. Commun.*, 1980, 993.
[42] P. W. Henniger and J. K. Van Der Drift, Ger. Offen., 2235390 (1973); *Chem. Abstr.*, 1973, **78**, 124608.
[43] S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 95.



Reagents: i, Ph_3CCl, DMAP, CH_2Cl_2, 40—45 °C, 18—24h

Scheme 19

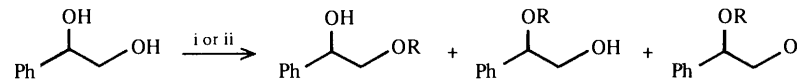
in the presence of a secondary one may be achieved with this salt (equation 5).[44] MPP is as effective as DMAP in catalysing the tritylation of benzyl alcohol.[12]



(5)

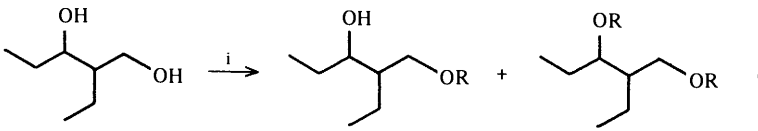
Reagents: i, CH_2Cl_2, 25 °C, 16h

(iii) *Silylation.* DMAP is very much superior to imidazole for promoting the selective silylation of primary alcohols to TBDMS ethers (equations 6 and 7).[45] Furthermore, only a catalytic amount of DMAP is required (*cf.* imidazole, equation 6), and use of DMF as a solvent can be avoided. Diols



Reagents: i, TBDMCS, DMAP (4 mol%), CH_2Cl_2, TEA, 8h, r.t.; ii, TBDMCS, imidazole (220 mol%) DMF, 8h, r.t.

95%	0	5%	(6)
59%	11%	30%	

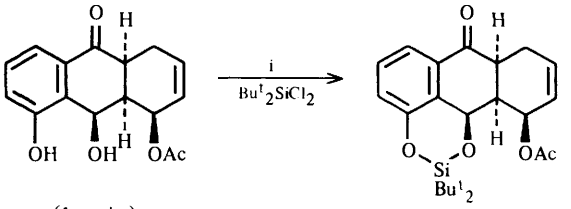


(98%) (trace) (7)

Reagents: i, TBDMCS, DMA (4 mol%), CH_2Cl_2, TEA, 8h, r.t.; TBDMCS = t-butyldimethylchlorosilane, R = t-butyldimethylsilyl

[44] O. Hernandez, S. K. Chaudhary, R. H. Cox, and J. Porter, *Tetrahedron Lett.*, 1981, 1491.
[45] S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99.

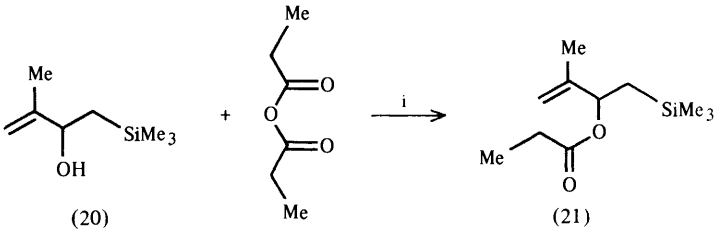
may be derivatized readily with di-t-butyldichlorosilane and DMAP in acetonitrile (equation 8). Di-t-butylsilylene derivatives are more stable towards Lewis acids than the corresponding isopropylidene and diphenylsilylene derivatives. They have the added advantage of readily undergoing cleavage by pyridine hydrofluoride.[46]



(1 equiv.) (65%) (8)

Reagents: i, iv, DMAP (2 equiv.), TEA (4 equiv.), 1h, 70 °C

(iv) *Esterification and Lactonization.* Esterification carried out by treating an alcohol with an anhydride is merely an example of acylation [see section 4.A(i)]. Nevertheless, one example where the use of DMAP is invaluable is worth mentioning. The acid sensitive alcohol (20) affords the ester (21) (also acid sensitive) in virtually quantitative yield when it reacts with propionic anhydride, TEA, and DMAP (Scheme 20).[47]

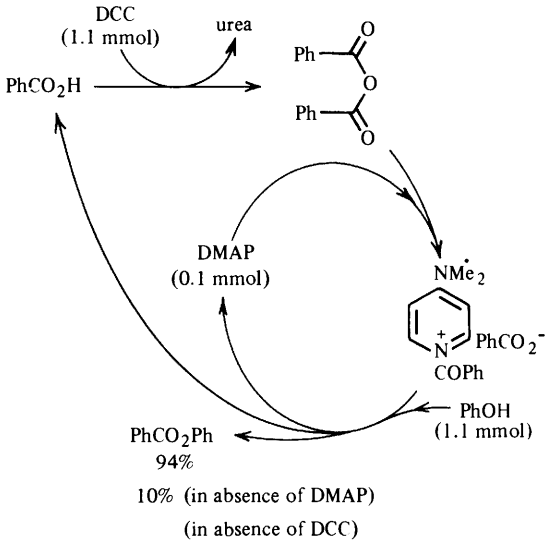


Reagents: i, TEA, DMAP, 25 °C

Scheme 20

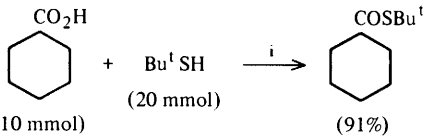
Extension of the above method to the esterification of carboxylic acids is less successful, as only half of the starting acid is esterified even under ideal conditions. Furthermore, one equivalent of base (TEA) is required and it is often necessary to preform the anhydride. These difficulties were overcome by three groups of workers at about the same time (Scheme 21).[48–50] The beauty of this method lies in the fact that use of 1.1 equivalents of DCC allows

[46] B. M. Trost and C. G. Caldwell, *Tetrahedron Lett.*, 1981, 4999.
[47] S. R. Wilson and M. F. Price, *J. Am. Chem. Soc.*, 1982, **104**, 1124.
[48] B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
[49] A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 1978, 4475.
[50] F. E. Ziegler and G. D. Berger, *Synth. Commun.*, 1979, 539.



Scheme 21

almost complete conversion of acid into ester, and the other disadvantages are removed. The method is well-suited to esterification of highly hindered alcohols and *N*-protected amino-acids; and it may be used for the introduction of bulky protecting groups (*e.g.* benzyl and t-butyl). Thiol esters may be prepared by this approach (equation 9).[50] It also provides an excellent cyclization method. The example chosen illustrates two cyclizations,[51] which both yield a potentially important new orally active antihypotensive agent (22) (Scheme 22).[52] The diastereomer (23) exhibits no such activity.

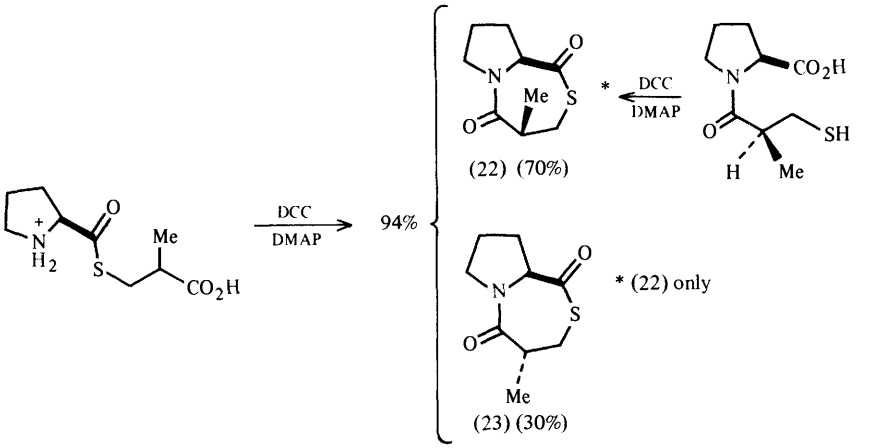


(9)

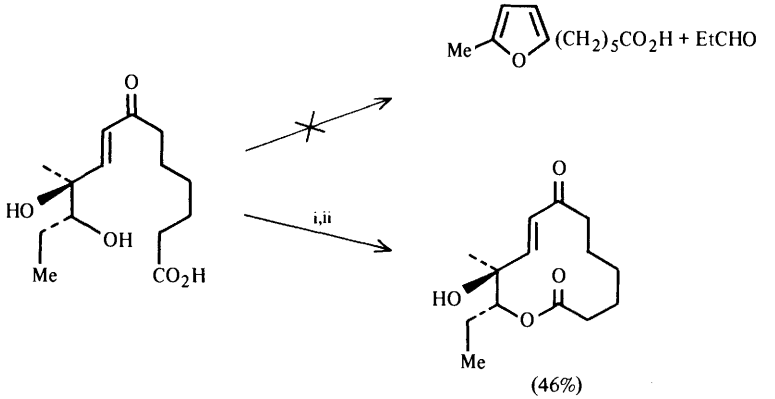
Reagents: i, DMAP (5 mol%), CH_2Cl_2, then DCC at 0 °C for 5 min, then 3h at 30 °C

The mixed anhydride approach incorporating DMAP catalysis provides an excellent method for the preparation of sterically hindered esters,[53] macrocyclic lactones (Scheme 23),[53] and thiol esters.[54] The employment of 2,4,6-trichlorobenzoyl chloride to form the mixed anhydride has a double advantage. Closure

[51] D. H. Kim, *J. Heterocycl. Chem.*, 1980, **17**, 1647.
[52] M. A. Ondetti, U.S.P., 1980, 4 192 945.
[53] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.
[54] Y. Kawanami, Y. Dainobu, J. Inanaga, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 943.



Scheme 22



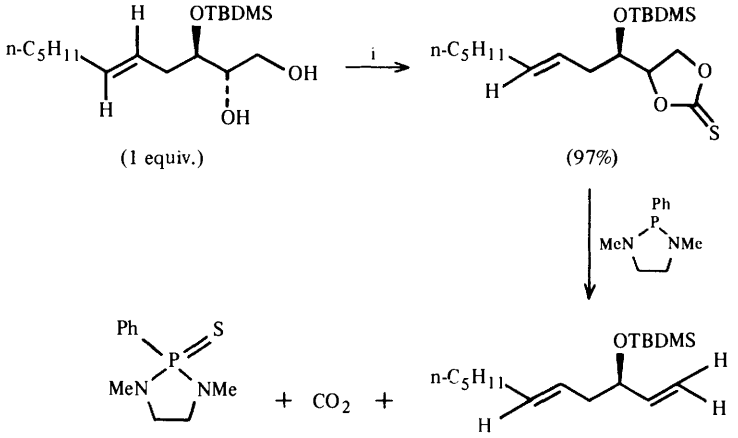
Reagents: i, TEA, THF, r.t., then 2,4,6-trichlorobenzoyl chloride, 2h, r.t.;
ii, DMAP, PhH, reflux, 40h

Scheme 23

takes place exclusively at the less hindered carbonyl group of the mixed anhydride, and trichlorobenzoate is an excellent leaving group. Similar advantages apply to the use of FTNB with DMAP for similar reactions.[55–57]

(v) *Conversion of 1,2-Diols into Alkenes.* An improved mild procedure appeared recently that utilizes DMAP and thiophosgene for the stereospecific synthesis of alkenes from 1,2-diols (Scheme 24).[58] The advantage of this process is

[55] S. Kim and S. Yang, *Chem. Lett.*, 1981, 133.
[56] S. Kim and S. Yang, *Synth. Commun.*, 1981, **11**, 121.
[57] S. Kim, K. H. Ahn, and S. Yang, *Bull. Korean Chem. Soc.*, 1982, **3**, 70.
[58] E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, 1982, 1979.

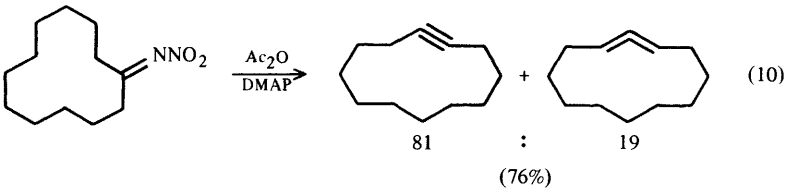


Reagents: i, DMAP (2.4 equiv.), Cl_2CS (1.2 equiv.), CH_2Cl_2, 0 °C, 1h

Scheme 24

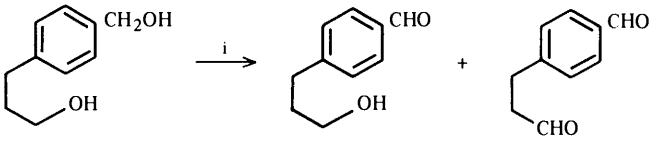
that the intermediate thionocarbonate can be formed at 0 °C in one hour, whereas use of thiocarbonylimidazole requires heating at reflux in toluene or xylene.

(vi) *Conversion of Nitrimines into Alkynes and Alkenes.* Nitrimines, which may be prepared from ketoximes and nitrous acid, undergo fragmentation to alkynes and/or allenes on acetylation with acetic anhydride and DMAP (equation 10).[59]

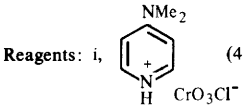


(vii) *Oxidation.* 4-(Dimethylamino)pyridinium chlorochromate (24) is a mild selective oxidizing agent suitable for the conversion of allylic and benzylic alcohols into the corresponding carbonyl compounds.[60] The selectivity of the reagent was demonstrated in the oxidation of the diol (25) (equation 11), pyridinium chlorochromate gives roughly an equal amount of both products. 4-(Dimethylamino)pyridine 1-oxide has been found to convert active halides into aldehydes and ketones *via* DMAP salts which were then treated with the super base DBU (Scheme 25).[61]

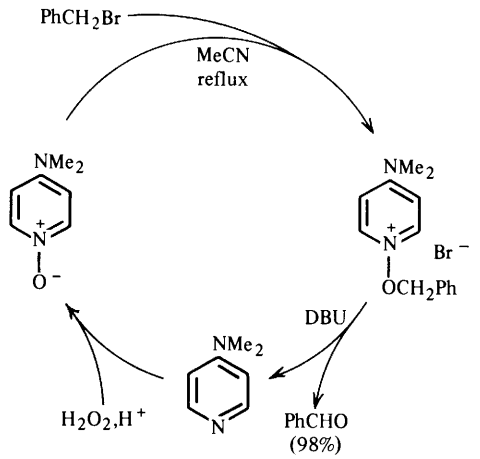
[59] G. Büchi and H. Wüest, *J. Org. Chem.*, 1979, **44**, 4116.
[60] F. S. Guziec, jun., and F. A. Luzzio, *J. Org. Chem.*, 1982, **47**, 1787.
[61] S. Mukaiyama, J. Inanaga, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 2221.



(25) (62%) (<2%) (11)



(24)



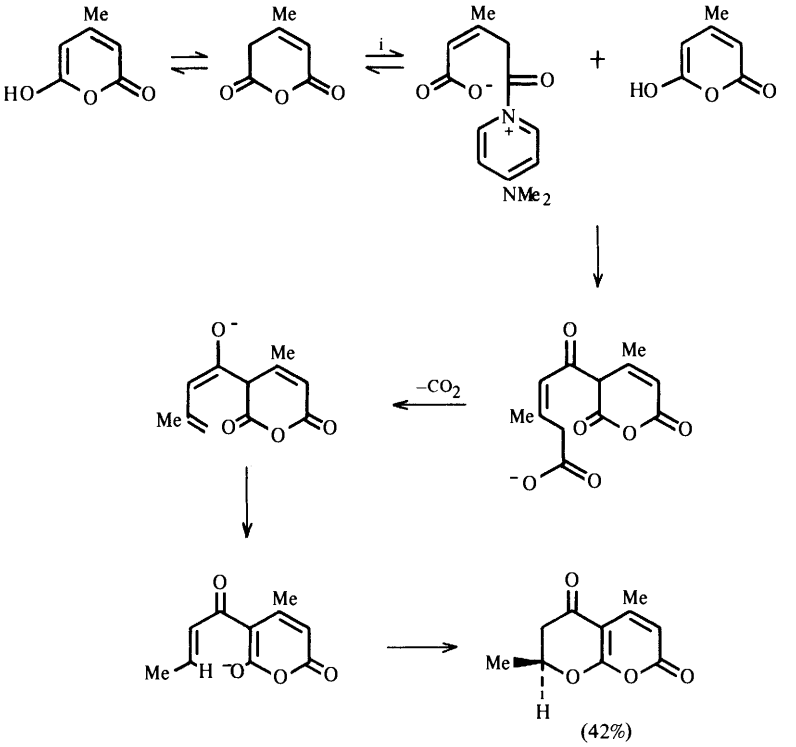
Scheme 25

(viii) *Formation of Heterocycles.* 4-Methyl-6-hydroxy-2-pyrone (a cyclic anhydride) dimerizes when heated with a catalytic amount of DMAP in xylene. This reaction does not occur in the absence of DMAP. The so-formed dimer subsequently undergoes decarboxylation to afford a coumarochromanone (Scheme 26).[62]

Condensations of β-enaminoesters with formaldehyde are catalysed by DMAP (Hantzch Synthesis) (Scheme 27).[63]

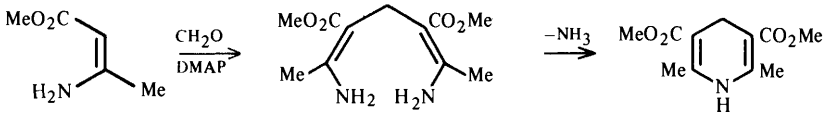
Aryl isocyanates trimerize to triazinones on heatng with DMAP in ethyl acetate.[7] Annelation of carbonyl sulphide to cyclic *o*-aminonitriles is much easier in the presence of DMAP (equation 12).[64]

[62] S. D. Burke, J. O. Saunders, and C. W. Murtiashaw, *J. Org. Chem.*, 1981, **46**, 2425.
[63] H. Wamhoff, G. Hendrikx, and M. Ertas, *Liebigs Ann. Chem.*, 1982, 489.
[64] M. A. Hernandez, F.-L. Chung, R. A. Earl, and L. B. Townsend, *J. Org. Chem.*, 1981, **46**, 3941.

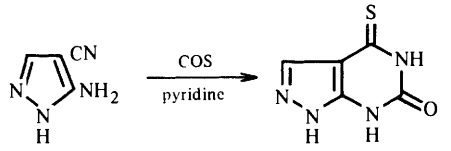


Reagents: i, DMAP, xylene, reflux

Scheme 26



Scheme 27

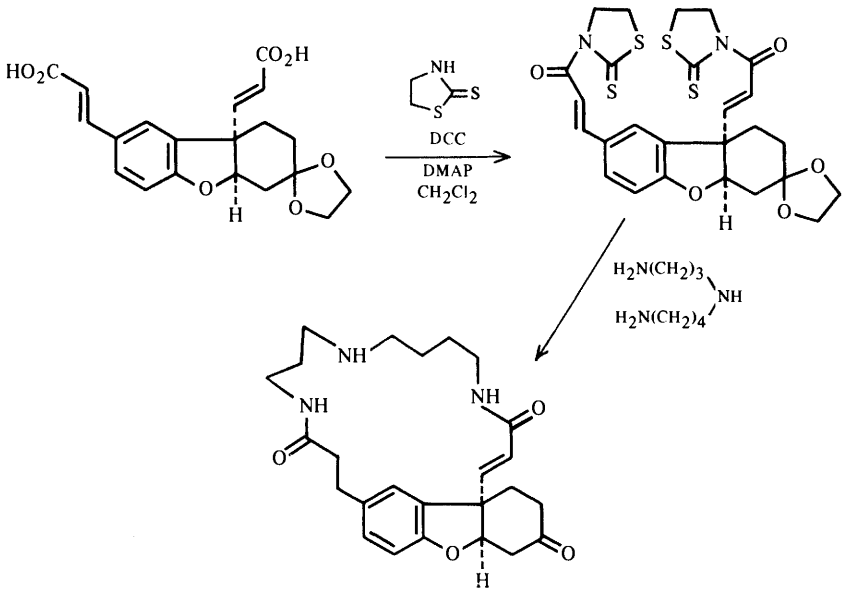


(12)

95 °C, 62h (74%)
+ DMAP, 95 °C, 37h (100%)

B. Applications in Natural Products Chemistry.—4-Dialkylaminopyridines are now used so commonly in natural products chemistry that only a selective account can be given here. Other examples may be found in the two reviews quoted.[7,12]

Use of DMAP–DCC facilitates the penultimate step in a new synthesis of some macrocyclic spermidine alkaloids, *e.g.* lunarine (26) (Scheme 28).[65]

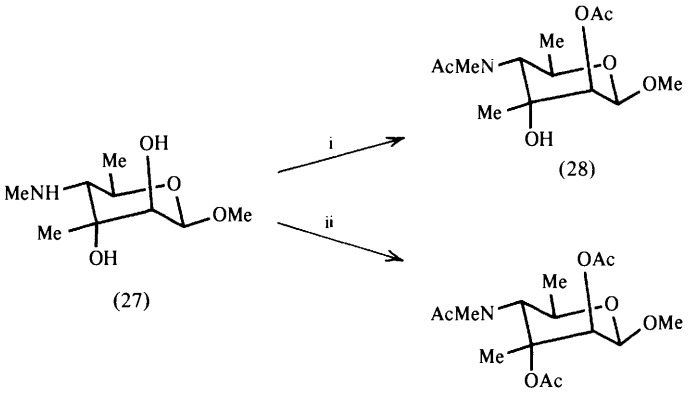


(26)

Scheme 28

DMAP has also found application in the synthesis of racemic tenellin,[66] apovincamine,[67] and spermidines;[68] the resolution of a 9-oxaergoline;[69] and the acylation of 11,12-dihydroglaziovine.[70] Treatment of (27) with acetic anhydride in pyridine results in mono-*O*-acetylation to give (28), acetic anhydride–DMAP–TEA is required for di-*O*-acetylation (Scheme 29).[71]

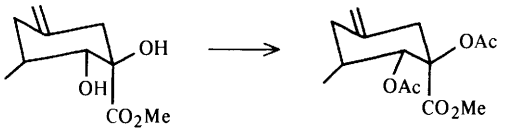
[65] E. Fujita, *Pure Appl. Chem.*, 1981, **53**, 1141.
[66] D. R. Williams and S.-Y. Sit, *J. Org. Chem.*, 1982, **47**, 2846.
[67] B. Danieli, G. Lesma, and G. Palmisano, *Gazz. Chim. Ital.*, 1981, **111**, 257.
[68] H. Yamamoto and K. Maruoka, *J. Am. Chem. Soc.*, 1981, **103**, 6133.
[69] P. S. Anderson, J. J. Baldwin, D. E. McClure, G. F. Lundell, and J. H. Jones, *J. Org. Chem.*, 1982, **47**, 2184.
[70] J. S. Bindra and A. Grodski, *J. Org. Chem.*, 1977, **42**, 910.
[71] A. S. Mesentsev and V. V. Kuljaeva, *Tetrahedron Lett.*, 1973, 2225.



Reagents: i, Ac_2O, pyridine; ii, Ac_2O, DMAP, TEA

Scheme 29

The diol (29) (an intermediate in the total synthesis of leucogenenol) is resistant to acetylation by acetic anhydride–pyridine, but it gives a 95% yield of (30) when DMAP is added (equation 13).[72]

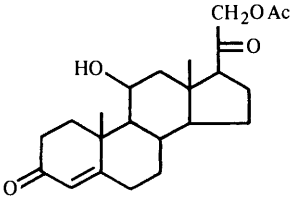


(29) (30) (95%) (13)

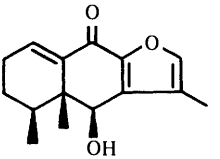
The hydroxy-groups indicated in the steroids listed may be acylated under DMAP or PPY catalysis; hydroxycholesterol (1α),[73] methyl cholate (3α, 7α, 12α),[74] (31) (11β),[75] testosterone (17β).[76] Dialkylaminopyridine catalysts have been applied widely[7] to assist in the acylation of terpene and related alcohols, *e.g.* (32),[77] (33),[78] (34),[79] (35).[80]

β-Lactam ring formation has been achieved using the DCC–DMAP method, but the yield is poor and epimerization takes place (equation 14).[81]

[72] R. G. Salomon, M. F. Salomon, M. G. Zagorski, J. M. Reuter, D. J. Coughlin, *J. Am. Chem. Soc.*, 1982, **104**, 1008.
[73] D. H. R. Barton, R. H. Hesse, M. M. Pechet, and E. Rizzardo, *J. Am. Chem. Soc.*, 1973, **95**, 2748.
[74] G. Höfle and W. Steglich, *Synthesis*, 1972, 619.
[75] W. Steglich and G. Höfle, Ger. Offen., 1969, 1 958 954; *Chem. Abstr.*, 1971, **75**, 34 673.
[76] J. Müller and J. E. Herz, *Steroids*, 1979, 793.
[77] L. P. J. Burton and J. D. White, *J. Am. Chem. Soc.*, 1981, **103**, 3226.
[78] K. Yamakawa and T. Satoh, *Chem. Pharm. Bull.*, 1981, **29**, 3474.
[79] J. P. Genet and F. Piau, *J. Org. Chem.*, 1981, **46**, 2414.
[80] P. A. Grieco, P. A. Tuthill, and H. L. Sham, *J. Org. Chem.*, 1981, **46**, 5005.
[81] T. Kametani, T. Nagahara, Y. Suzuki, S. Yokohama, S.-P. Huang, and M. Ihara, *Tetrahedron*, 1981, **37**, 715.

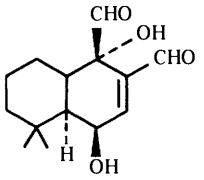


(31)



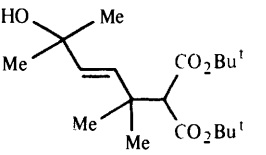
(33) (85%)

(Ac_2O, pyridine, DMAP)



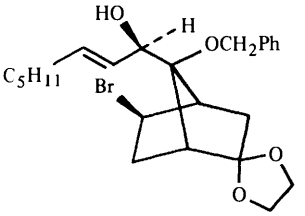
(32) (81%)

(Ac_2O, pyridine, DMAP)



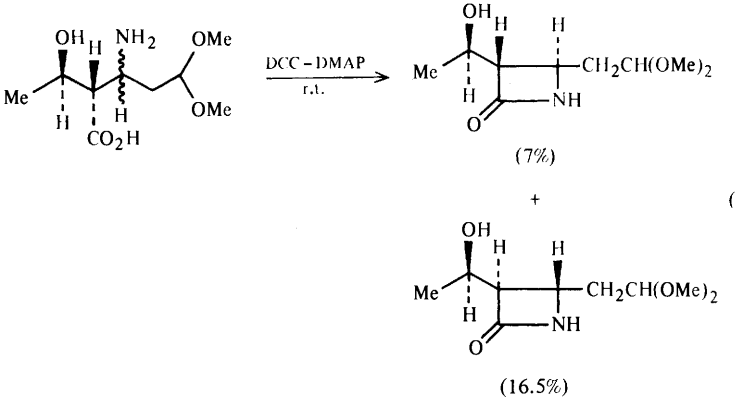
(34) (65%)

(Ac_2O, TEA, CH_2Cl_2, DMAP)



(35) (82%)

(Ac_2O, pyridine, CH_2Cl_2, DMAP)



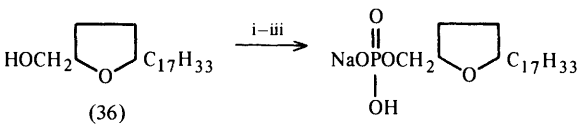
(7%)

+

(16.5%)

(14)

DMAP catalysis has proved helpful in the phosphorylation of the oleyltetrahydrofuran (36) (a Darmstoff analogue) (equation 15).[82]



(36) (15)

Reagents: i, $POCl_3$, DMAP, pyridine, CH_2Cl_2, r.t., 6h; ii, H_2O; iii, Dowex-50 (Na^+)

5 Uses in Analytical Chemistry and Biochemistry

These two fields are combined under one heading as many of the analytical methods described have biochemical applications.

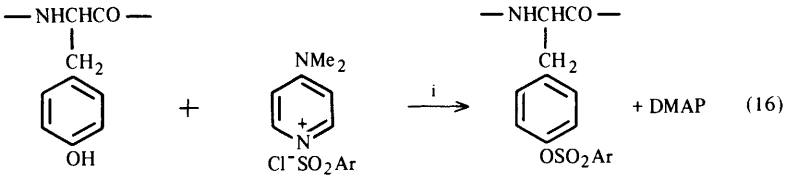
A. Determination of Hydroxy-groups.—The determination of hydroxy-groups in alcohols, phenols, glycols, and sugars is an old analytical problem. This was traditionally carried out by heating the alcohol under reflux in an acetic anhydride–pyridine mixture for 1 hour, or more. The mixture was then titrated,[83] or analysed by gas chromatography.[84] Addition of DMAP to the acetylation mixture permits total conversion into the ester in 5—10 minutes at 54 °C for typical primary and secondary alcohols.[83] This method has been applied to the analysis of clindamycin palmitate hydrochloride.[84]

(i) *Urinary Monohydric and Dihydric Phenols.* A procedure for the extraction of mono- and di-hydric phenols from urine has been described.[85] This involves treating a dilute solution of phenols (*viz.* *p*-cresol, 4-methylcatechol, resorcinol, and catechol) with acetic anhydride in the presence of DMAP. The acetate derivatives were then analysed by gas chromatography (OV-7 column). This method is particularly suited for the quantitative estimation of dihydric phenols, which is sometimes difficult. Concurrent azlactone formation, from norleucine and glycine, was noted in the above procedure (*see below*).

(ii) *Glycolipids and Diglycerides.* Glycosphingolipids react rapidly with benzoic anhydride and DMAP in pyridine to give benzoyl derivatives that can be analysed by h.p.l.c.[86] Rapid benzoylation with benzoic anhydride avoids unwanted formation of *N*-benzoyl derivatives, which occurs when benzoyl chloride is used. DMAP has been used to assist in the attachment of a *p*-nitrobenzoate chromophore to diglycerides in order to increase the ease of detection of such compounds by h.p.l.c.[87]

(iii) *Phenolic Groups in Tyrosine Residues.* The 1-tosyl and 1-dansyl salts of DMAP react specifically with Tyr residues of proteins in aqueous media to give *O*-arylsulphonates (equation 16).[88] The tosyl reagent is specific for

[82] R. A. Wiley, W. Harris, C. Brungardt, and M. Marx, *J. Med. Chem.*, 1982, **25**, 121.
[83] K. A. Connors and K. S. Albert, *J. Pharm. Sci.*, 1973, **62**, 845; S.-F. Lin and K. A. Connors, *J. Pharm. Sci.*, 1981, **70**, 235.
[84] E. L. Rowe and S. M. Machkovech, *J. Pharm. Sci.*, 1977, **66**, 273.
[85] V. Fell and C. R. Lee, *J. Chromatogr.*, 1976, **121**, 41.
[86] S. K. Gross and R. H. McCluer, *Anal. Biochem.*, 1980, **102**, 429.
[87] M. Batley, N. H. Packer, and J. W. Redmond, *J. Chromatogr.*, 1980, **198**, 520.
[88] E. Guibé-Jampel, M. Wakselman, and D. Raulais, *J. Chem. Soc., Chem. Commun.*, 1980, 993.



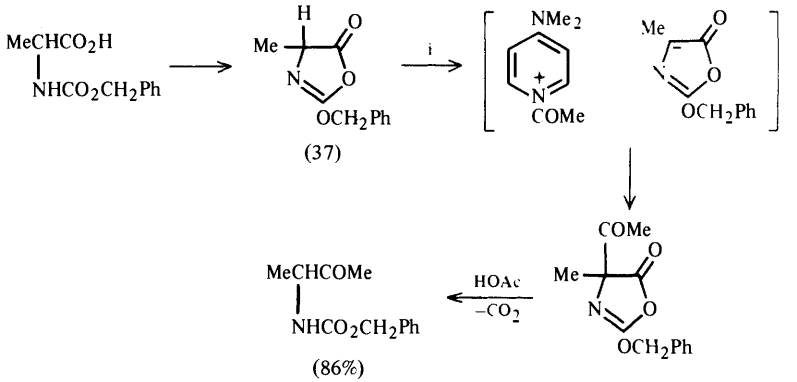
(11) (Ar = *p*-MeC_6H_4)

Reagents: i, pH 10—11.5, Li_2CO_3, then (11) in three portions, 20 min, 5 °C

Tyr^{A19} of oxidized bovine insulin, and it has proved superior to the corresponding derivative of *N*-methylimidazole for this purpose. It has also been found effective for the determination of Tyr in calcitonins. The dansyl reagent has been used for the modification of two Tyr residues in prolactin, and four Tyr residues in bovine serum albumin.

B. Amino-acid and Protein Chemistry.—DMAP and some of its salts have found many uses in amino-acid and protein chemistry, apart from those mentioned in Section 5.A(iii).

(i) *Dakin–West Reaction.* Reaction of an α-amino-acid with acetic anhydride in pyridine to form α-acetylamino-ketones is known as the Dakin–West reaction.[89] The original authors suggested[90] that the transformation involves an intermediate oxazolone (37), and this was confirmed subsequently by kinetic and mechanistic studies.[91] One of the first reports about 4-dialkylaminopyridine catalysis showed that the Dakin–West reaction, which usually requires vigorous conditions (*e.g.* 100—130 °C, 15h), may be carried out at room temperature, and in better yield, when DMAP is added (Scheme 30). DMAP catalyses both the 4-acetylation of oxazolone (37), and the decarboxylative ring fission.



(37)

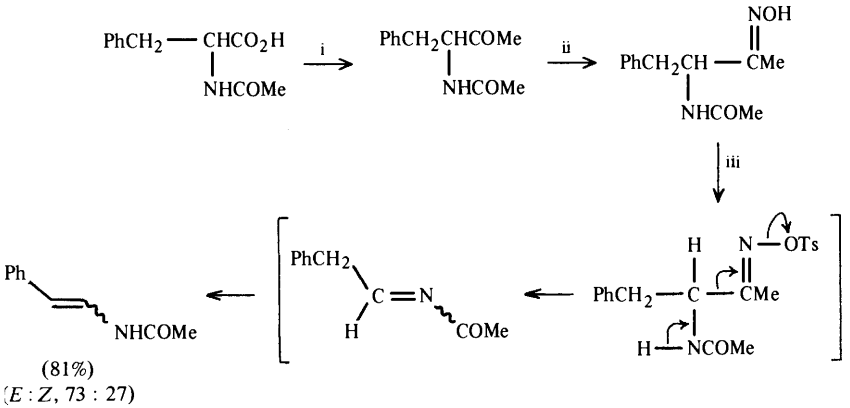
(86%)

Reagents: i, Ac_2O, DMAP, TEA, 25 °C

Scheme 30

[89] H. D. Dakin and R. West, *J. Biol. Chem.*, 1928, **78**, 91.
[90] H. D. Dakin and R. West, *J. Biol. Chem.*, 1928, **78**, 745.
[91] N. L. Allinger, G. L. Wang, and B. B. Dewhurst, *J. Org. Chem.*, 1974, **39**, 1730.

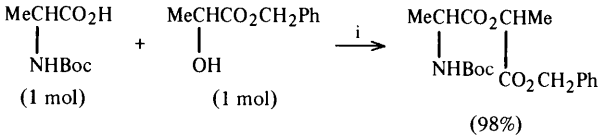
There are many examples of the application of the modified Dakin–West procedure, and several of these (*e.g.* determination of *C*-terminal amino-acids in peptides, formation of trifluoroalanine, and conversion of glutamic acid into a pyrrolidone) have been discussed previously.[7] More recently, it has been employed for the conversion of *N*-acetylamino-acids into enamides (Scheme 31),[92] and in the preparation[93] of a series of novel acylamino-α-keto-esters which are valuable precursors for the synthesis of imidazo-triazinones.



Reagents: i, Ac_2O, DMAP, TEA, 20—40 °C; ii, NH_2OH, NaOAc, H_2O, 2h, 60—80 °C; iii, TsCl, TEA, MeCN, 3h, −10 to 20 °C

Scheme 31

(ii) *Depsipeptide Synthesis.* The DCC–DMAP method is effective for the coupling of *N*-t-butoxycarbonylamino-acids and carboxy-protected hydroxy-acids (equation 17).[94]



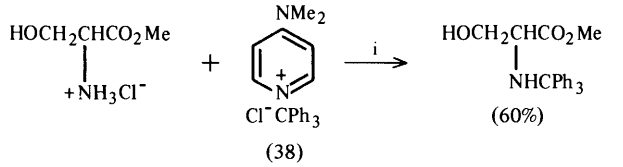
(17)

Reagents: i, DMAP (1 mol), DCC (1.1 mol), CH_2Cl_2, 25 °C

(iii) *Selective* N-*Protection.* *N*-Trityl-4-dimethylaminopyridinium chloride (38) has been used for the selective *N*-tritylation of serine methyl ester (equation 18).[44]

(iv) *Reagents for Sulphydro-groups in Cysteine Residues.* 1-Cyano-4-dimethylaminopyridinium perchlorate (12) reacts readily with thiols in neutral

[92] U. Redeker, N. Engel, and W. Steglich, *Tetrahedron Lett.*, 1981, 4263.
[93] I. Charles, D. W. S. Latham, D. Hartley, A. W. Oxford, and D. I. C. Scopes, *J. Chem. Soc., Perkin 1*, 1980, 1139.
[94] C. Gilon, Y. Klausner, and A. Hassner, *Tetrahedron Lett.*, 1979, 3811.



(38) (18)

Reagents: i, Pr^i_2 EtN, DMF, 24h, 25 °C

or acidic media. It has the advantage of being a water soluble reagent, thus avoiding the need for organic solvents that can denature proteins. The Cys residues numbers 7 and 19 of the reduced B-chain of bovine insulin are quantitatively cyanylated at pH 3.5 by this reagent.[25]

(v) *Solid Phase Peptide Synthesis.* Addition of DMAP improves the efficiency of the DCC mediated reaction for the anchoring of the first amino-acid residue onto hydroxymethylpolystyrene supports used for solid phase peptide synthesis.[95-97] The coupling efficiencies of DCC, DCC–HOBT (1-hydroxybenzotriazole), and DCC–DMAP were compared for automated solid phase synthesis on a hydroxymethyl resin (styrene–1% DVB copolymer).[98] The protected heptapeptide-resin samples so-formed were analysed for their amino-acid content (Table 2). The DCC–DMAP method was found to be clearly

Table 2 *Amino-acid composition of Boc-Ala-Cle-Ile-Val-Pro-Arg(Tos)-Gly-OCH$_2$-resin prepared by the methods indicated*

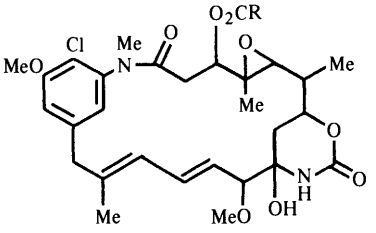
Amino-acid	*DCC*[a]	*DCC–HOBT*[a]	*DCC–DMAP*[a]
Gly	1.00	1.00	1.00
Arg	0.81	0.94	0.96
Pro	1.02	0.92	1.34
Val	0.88	0.74	1.01
Ile[b]	0.83	0.73	0.99
Cle[c]	0.65	0.65	0.84
Ala	0.89	0.64	1.01

(*a*) Hydrolysis was carried out in 12N-propionic acid (1:1), 130 °C, 6h. (*b*) Includes D-alloisoleucine produced during acid hydrolysis. (*c*) Cycloleucine.

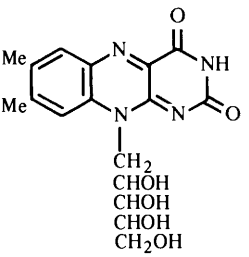
[95] B. W. Erickson and R. B. Merrifield, in 'The Proteins', ed. H. Neurath and R. L. Hill, 3rd Edn., Academic, N.Y., 1976, Vol. 2, p. 255.
[96] S. S. Wang, C. C. Yang, I. D. Kulesha, M. Sonenberg, and R. B. Merrifield, *Int. J. Peptide Protein Res.*, 1974, **6**, 103.
[97] G. Barany and R. B. Merrifield, in 'The Peptides: Analysis, Synthesis, Biology', Academic, N.Y., 1980, Vol. 2.
[98] S. S. Wang, J. P. Tam, B. S. H. Wang, and R. B. Merrifield, *Int. J. Peptide Protein Res.*, 1981, **18**, 459.

the best, especially for the coupling of sterically hindered amino-acids in the Cle-Ile-Val region. Furthermore, h.p.l.c. analysis of the crude protected hepta-peptide amide Boc-Ala-Cle-Ile-Val-Pro-Arg(Tos)-Gly-NH_2 prepared by the DCC–DMAP method showed it to be purer than those prepared by the other methods. Racemization has been observed during DCC–DMAP catalysed coupling of Boc-PheOH with HGlu(OBzl)OCH_2-resin.[98] Other instances of racemization have been reported also in depsipeptide and solid phase peptide synthesis.[99–100] In the latter case, racemization of urethane-protected amino-acids was attributed to 2-alkoxyoxazole formation [Section 5.B(i)].[100] This difficulty with the DCC–DMAP method may be overcome[101] in the above example by using 2-nitrophenylsulphenyl (Nps) as the protecting group. Thus, Nps-Phe-OH can be converted into Nps-Phe-OMe in 94% yield on treatment with MeOH–DCC–DMAP (5 min at 0 °C, and 3h at 25 °C).

C. Nucleotides and Nucleosides.—Phosphonylation is a most important reaction in nucleic acid chemistry as it provides the main method for formation of internucleotide bonds in oligonucleotide synthesis. A major problem is side reactions of the moiety with a condensing agent at the O-6 oxo-group. A new method has appeared that involves protecting O-6 by reaction with di-n-butylthioxophosphoranyl bromide and DMAP which is virtually quantitative, and regiospecific (Scheme 32).[102] The condensing agent may then be attached to the 3′-hydroxy-group in 94% yield, compared with 15% when guanosine is unprotected at O-6. Dialkyl and diaryl phosphoryl halides, phosphinothioyl halides, arenesulphonyl chlorides, and trialkylsilyl chlorides have been introduced successfully at O-6 with DMAP catalysis.[103] The 5′-hydroxy-group of thymidine may be phosphorylated easily in DMAP–pyridine.[104] DMAP has found use recently to assist in the attachment of a tri-isopropylbenzene sulphonyl group

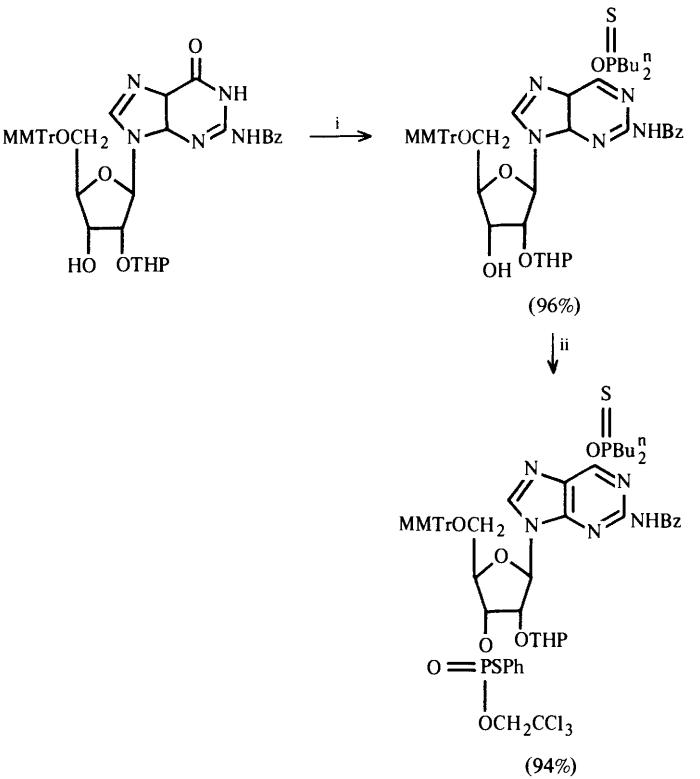


(39) R = H or C_{1-15}



(40)

[99] N. L. Benoiton and F. M. F. Chen, *J. Chem. Soc., Chem. Commun.*, 1981, 1225.
[100] E. Atherton, N. L. Benoiton, E. Brown, R. C. Sheppard, and B. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1981, 336.
[101] B. Neises, T. Andries, and W. Steglich, *J. Chem. Soc., Chem. Commun.*, 1982, 1132.
[102] M. Sekine, J-i. Matsuzaki, M. Satoh, and T. Hata, *J. Org. Chem.*, 1982, **47**, 571.
[103] H. P. Daskalov, M. Sekine, and T. Hata, *Tetrahedron Lett.*, 1980, 3899.
[104] H. A. Kellner, R. G. K. Schneiderwind, H. Eckert, and I. K. Ugi, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 577.

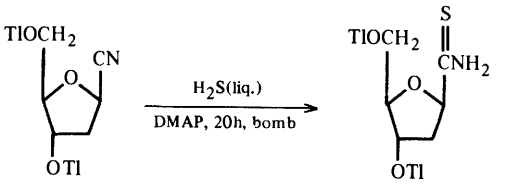


Reagents: i, $Bu^n_2P(S)Br$, TEA, DMAP, CH_2Cl_2, 4h, r.t.;
ii, $PhSP(O)OCH_2CCl_3$/TPS, pyridine, 7h;
$O^-C_6H_{11}\overset{+}{N}H_3$
MMTrCl = monomethoxytrityl chloride

Scheme 32

at O-6[105] a benzoyl group at 2′-hydroxy, [106] and to facilitate 'transient protection',[107] and semi-automated oligonucleotide synthesis.[108] Glycosylthiocarboxamides are versatile intermediates for the synthesis of *C*-nucleosides and they can be prepared in high yield from a ribofuranosyl cyanide on reaction with hydrogen sulphide and DMAP in a pressure vessel (equation 19).[109]

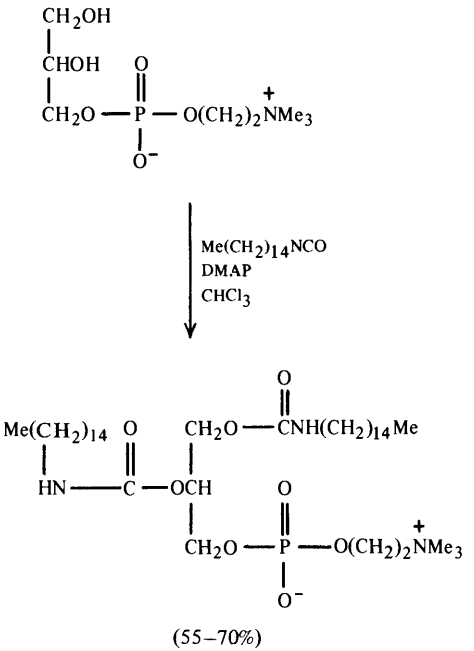
[105] B. L. Gaffney and R. A. Jones, *Tetrahedron Lett.*, 1982, 2257.
[106] E. Ohtsuka, H. Morisawa, and M. Ikehara, *Chem. Pharm. Bull.*, 1982, **30**, 874.
[107] G. S. Ti, B. L. Gaffney, and R. A. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 1316.
[108] E. Ohtsuka, H. Takashima, and M. Ikehara, *Tetrahedron Lett.*, 1982, 3081.
[109] M. V. Pickering, P. C. Srivastava, J. T. Witkowski, and R. K. Robins, *Nucleic Acid Chem.*, 1978, 145.



(85%) (19)

The cyano-sugar is recovered unchanged when this procedure is carried out in the absence of DMAP.

D. Lipids.—DMAP is a valuable catalyst for the derivatization of glycosphinogolipids[110] (per-*o*-benzoyl) and diglycerides[111] (*p*-nitrobenzoates) prior to analysis by h.p.l.c. Some carbamoyl analogues of phosphatidylcholines, which do not undergo degradation with phospholipase A_2, have been prepared by a DMAP catalysed reaction (equation 20).[112]



(55–70%) (20)

[110] S. K. Gross and R. H. McCluer, *Anal. Biochem.*, 1980, **102**, 429.
[111] M. Batley, N. H. Packer, and J. W. Redmond, *J. Chromatogr.*, 1980, **198**, 520.
[112] C. M. Gupta and A. Bali, *Biochim. Biophys. Acta*, 1981, **663**, 506.

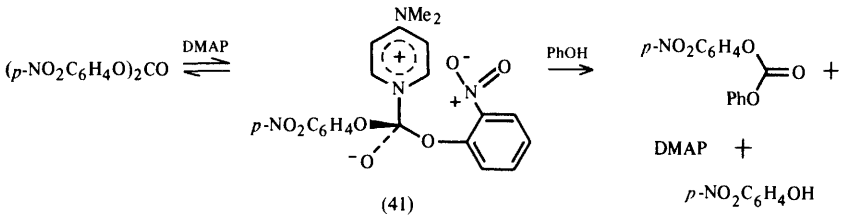
6 Industrial Applications

A. Organic Chemistry.—Many patent claims have appeared in recent years that exploit the catalytic rôle of DMAP. These applications are based on principles discussed already, therefore they will be outlined briefly. Maytansinoids of the type (39), which have antimitotic, antitumor, antifungal and protozoacidal activity, may be prepared by the DMAP–DCC method.[113] Riboflavin forms a tetranicotinate (40) with nicotinic anhydride in DMAP–HMPT.[114] DMAP has been employed to catalyse the formation of arylacetamido-[115] and sulphamido-[116] derivatives of penicillanic acids, and phosphorothioates and phenyl phosphonothioates[117] of pyrimidones that have insecticidal and acaricidal activity.

B. Polymer Chemistry.—DMAP catalyses the formation of polyurethanes,[118] polyurethane coatings and foams,[119] and isocyanate oligomers having intramolecular uretidinedione rings.[120] All of these reactions probably involve general base catalysis by DMAP (see 3.B). DMAP has been used for the incorporation of an aqueous dispersion of titanium dioxide and bis-tertiary amines into poly(hexamethyleneadipamide) for use as delustering agents.[121] Other uses include catalysis of the reaction of poly(ethyleneterephthalate) with an epoxy-compound, *e.g.* *N*-(2,3-epoxypropyl)benzamide to give a heat-resistant polymer that is suitable for the manufacture of tyre cords.[122] Processes for the preparation of polyhydric alcohols[123] and polycarbonates[124] have been reported. 1-Sulphonyl-4-dimethylaminopyridinium salts function as quick-acting hardeners for protein-containing layers.[125] DMAP has been found effective as an accelerator for the curing of composite restorative resins in dental practice.[126] Low molecular weight polystyrene has been grafted onto cellulose acetate in a

[113] N. Hashimoto and T. Kishi, Ger. Offen., 2911248 (1979), (to Takeda Ind. Ltd.); *Chem. Abstr.*, 1980, **92**, 94449.
[114] Y. Kuroyanagi, M. Ban, and K. Suzuki, Japan Kokai, **77**, 62297 (to Sanwa Chem. Lab.); *Chem. Abstr.*, 1977, **87**, 184898.
[115] Koninklijke Nederlandsche Gisten Spiritusfabriek N.V., Ger. Offen., 2155152; *Chem. Abstr.*, 1972, **77**, 88491.
[116] P. W. Henniger and J. K. van der Drift, Ger. Offen., 2235390; *Chem. Abstr.*, 1973, **78**, 124608.
[117] H. H. Freedman, S. D. McGregor, M. Yoshimine, and L. M. Kroposki, Belg. P., 832047 (to Dow Chem. Co.); *Chem. Abstr.*, 1977, **86**, 43811.
[118] H. J. Twitchett, B.P., 990637 (1965); *Chem. Abstr.*, 1965, **63**, 766; J. H. Wild and F. E. G. Tate, U.S.P., 3144452 (1964); *Chem. Abstr.*, 1964, **61**, 16068.
[119] H. J. Twitchett, B.P., 990635 (1965), *Chem. Abstr.*, 1965, **63**, 4483.
[120] A. Nishikawa, H. Yokono, and J. Mukai, Japan Kokai, 76262 (1976); *Chem. Abstr.*, 1977, **87**, 135294.
[121] V. Mathews, B.P., 1208691 (1970); *Chem. Abstr.*, 1971, **74**, 14116.
[122] S. D. Lazarus and K. Chakravarti, U.S.P., 4130541 (1978); *Chem. Abstr.*, 1979, **90**, 138985.
[123] L. Kaplan, Ger. Offen., 2643913; *Chem. Abstr.*, 1978, **89**, 214898.
[124] D. B. G. Jaquiss, V. Mark, and L. C. Mitchell, U.S.P., 4286085.
[125] P. Bergthaller, W. Himmelmann, and L. Rosenhahn, Ger. Offen., 2547589 (1977); *Chem. Abstr.*, 1977, **87**, 76374.
[126] G. M. Brauer, D. M. Dulik, J. M. Antonucci, D. J. Termini, and H. Argentar, *J. Dent. Res.*, 1979, **58**, 1994.

homogeneous solution with the aid of DMAP.[127] Grafting yields of 83% have been obtained using DMAP which compares with 63% (pyridine as catalyst) and 1% (no catalyst). DMAP is a better acetylation catalyst than *N*-methylimidazole for the determination of the hydroxyl number of polyether alcohols, particularly for those containing secondary hydroxy-groups.[128] Transesterifications of aromatic carbonates, that are of significance in polymer chemistry, are catalysed by DMAP. The effect is most spectacular in the case of the reaction of phenol with *o*-nitrophenyl carbonate which gives a quantitative yield of products with added auxiliary base (Scheme 33).[129] A specially



(41)

Scheme 33

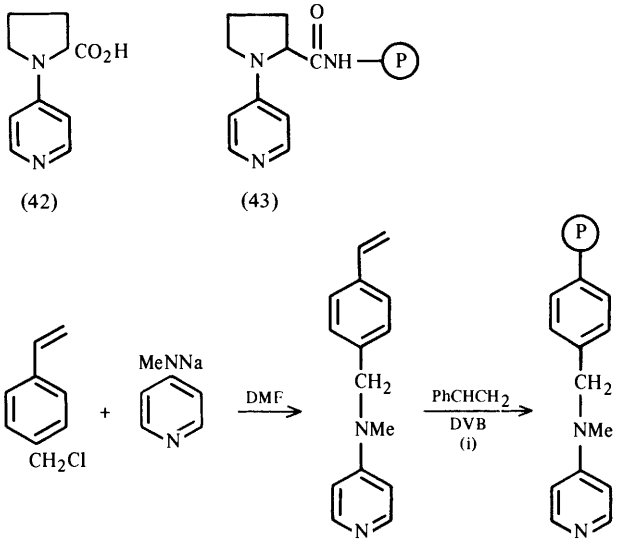
stabilized intermediate (41) was proposed to explain this effect, as the *p*-nitrophenyl isomer does not react as easily under similar conditions.

7 Other Dialkylaminopyridine Catalysts

A. Polymeric Catalysts.—4-Dialkylaminopyridine carboxylic acids of the type (42) have been attached to poly(ethyleneimines) to form modified polymers (43) that catalyse the hydrolysis of nitrophenyl esters.[130–131]

A new polymer-supported acylation catalyst has been reported recently.[132] Polymer bound 4-(*N*-benzyl-*N*-methylamino)pyridine can be prepared by polymerization (Scheme 34). This polymer has been used sucessfully to catalyse the acetylation of linalool. It may be recovered by filtration and regenerated by washing with sodium hydroxide, acetone, and vacuum drying.

[127] P. Månsson and L. Westfelt, *J. Polym. Sci., Polym. Chem. Ed.*, 1981, **19**, 1509.
[128] R. Gnauck and R. Algeier, *Plaste Kautsch.*, 1982, **29**, 274; *Chem. Abstr.*, 1982, **97**, 128 182.
[129] D. J. Brunelle, *Tetrahedron Lett.*, 1982, 1739.
[130] M. A. Hierl, E. P. Gamson, and I. M. Klotz, *J. Am. Chem. Soc.*, 1979, **101**, 6020.
[131] E. J. Delaney, L. E. Wood, and I. M. Klotz, *J. Am. Chem. Soc.*, 1982, **104**, 799.
[132] M. Tomoi, Y. Akada, and H. Kakiuchi, *Makromol. Chem., Rapid Commun.*, 1982, **3**, 537.

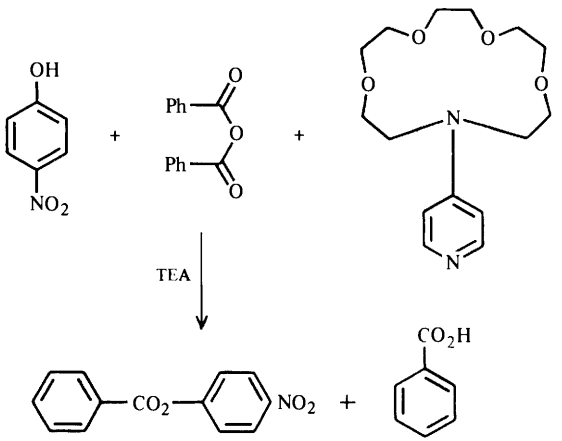


(42) (43)

i, Suspension copolymerization

Scheme 34

B. Crown-ether Catalysts.—Analogues of DMAP [*e.g.* (44)] have been prepared with crown ethers incorporated at the 4-position.[133] Complexes of these with various metals (*e.g.* sodium, potassium, lithium, and rubidium) are better catalysts than the ligand alone for transacylation (Scheme 35).



Scheme 35

[133] J. P. Dix, A. Wittenbrink-Dix, and F. Vögtle, *Naturwissenschaften*, 1980, **67**, 91.