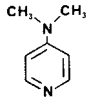
4-DMAP *(4-Dimethylaminopyridine)*

PRODUCT NO.
10,770-0

revised 4 / 96 — 4 pages

4-Dimethylaminopyridine is widely used as a hypernucleophilic acylation catalyst. This data sheet reviews its applications as an acylation catalyst and in various other chemical disciplines.



PROPERTIES:

Molecular formula	$C_7H_{10}N_2$
F.W.	122.17
Purity	99%
Physical appearance	yellow to tan crystals
m.p.	108-110°

SOLUBILITY:

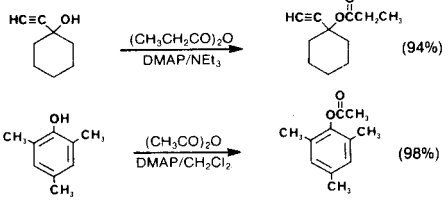
Soluble in methanol, benzene, ethyl acetate, chloroform, methylene chloride, acetone, and acetic acid. Less soluble in ether, diisopropyl ether, cyclohexane, hexane, and water.

LITERATURE REFERENCES:

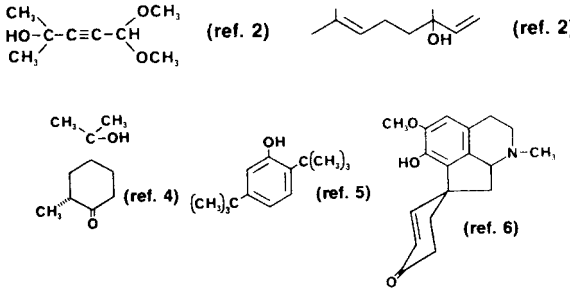
CAS No. [*1122-58-3*]
FT-IR **1**(2),766A
NMR **2**(2),645D
Beil. **22**(2), 341
RTECS# US9230000
MSD Book **1**,750B; **2**(1), 1345B
Fieser **3**,118; **9**,178; **10**,155; **12**,199

ACYLATION OF ALCOHOLS AND PHENOLS

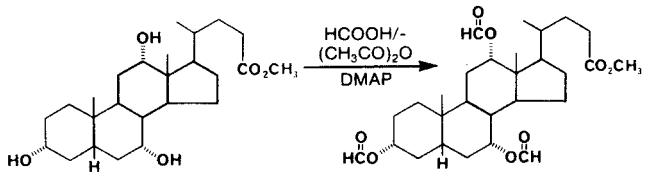
In the presence of DMAP or triethylamine containing 5-10% DMAP, sterically hindered secondary and tertiary alcohols, as well as phenols, can be acylated with carboxylic anhydrides or acyl chlorides.[1-3]



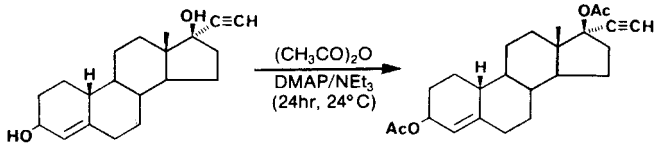
Other compounds which have been acylated successfully are shown below.



The acylation of steroids has also been accomplished with DMAP. Methyl cholate, for example, is converted to the triformate within a few hours in the presence of DMAP.[3]



The esterification of tertiary 17ß-OH groups in 17α-ethynyl steroids is of special interest since highly active progestational agents are formed.[7,8]

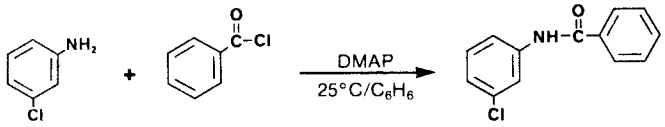


DMAP has been used in natural-product chemistry for the acetylation of a tertiary hydroxyl group of an amino sugar,[9] and for acylations of terpenes[4,10] and acetylenes[11,12] containing secondary and tertiary hydroxyl groups.

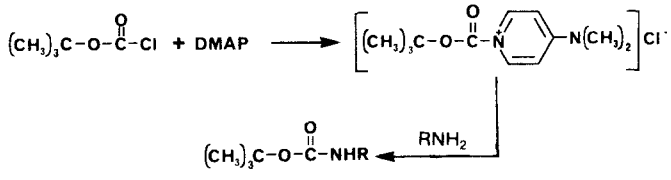
Connors and Albert recommend using acetic anhydride/-DMAP as a reagent for the quantitiative determination of hydroxyl groups in alcohols and phenols. The rate of acetylation of isopropanol at 54°C increased by a factor of 2 x 10^4 when pyridine was replaced by DMAP.[13]

ACYLATION OF AMINES

Litvinenko and Virichenko investigated the acylation of *m*-chloroaniline with benzoyl chloride to the benzanilide. In the presence of a series of tertiary organic bases, these reaction rate constants (shown in parentheses) were observed:[14] *N,N*-dimethylaniline (0.1), triethylamine (0.72), 2,6-dimethylpyridine (0.3), pyridine (1.80), 4-methylpyridine (10.0), and DMAP (10,-600).



DMAP also reacts with *tert*-butoxycarbonyl chloride to form the *tert*-butoxycarbonyl derivative, and effective reagent for preparing *t*-BOC amino acids in aqueous solution.[15,16]



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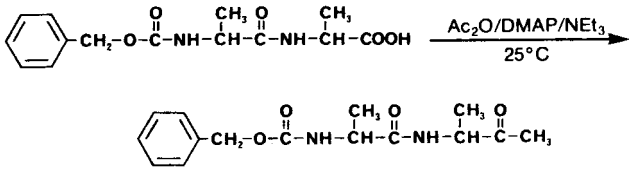
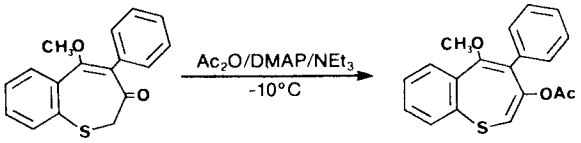
Acylation of Enolates

The conversion of even sensitive amino acids such as tryptophan into α-acyl amino ketones is carried out with good yields in the presence of DMAP or DMAP/triethylamine.[1,17] The mild conditions allow the exchange of a carboxyl group for an acyl group in N-protected peptides. This method can be used for the determination of C-terminal amino acids in peptides.[18]



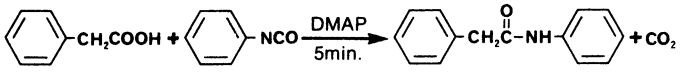
O-Acylation of Enolates

In some instances the reaction of enolates with acetic anhydride/DMAP may result in O-acylation. Hofmann *et al.* transformed the bicyclic ketone shown below into the l-benzothiepin derivative using DMAP.[19]

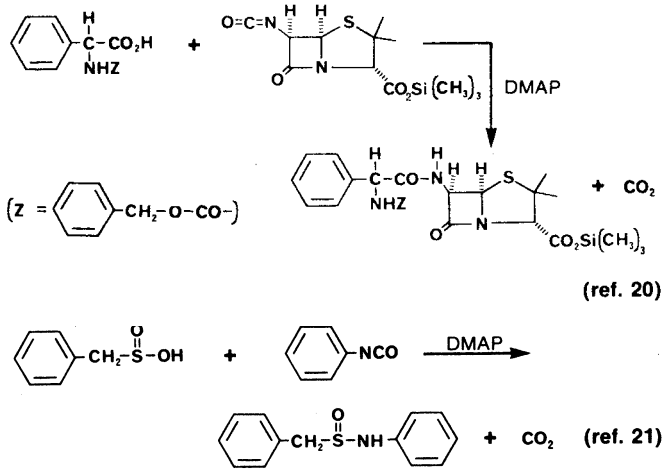


Reactions of Isocyanates

DMAP strongly accelerated reactions of isocyanates with carboxylic acids to form amides, compared with pyriding-catalyzed reactions.[20]

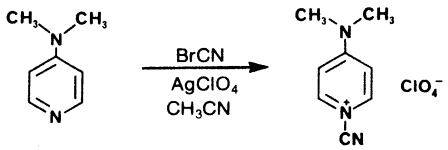


DMAP was used in similar reactions yielding anampicillin derivative[20] and sulfinamides.[21]

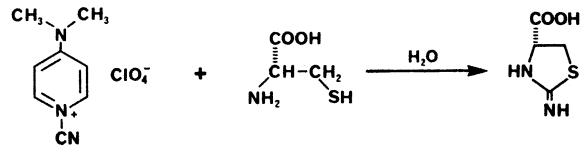


Cyanylation of SH Groups

Reaction of SMAP with cyanogen bromide gives the stable l-cyano-40dimethylaminopyridinium perchlorate salt. This salt is especially suited for reacting with SH groups in proteins.[22]

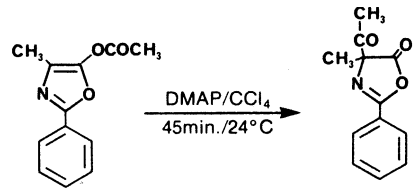


In the example below, the pyridinium perchlorate salt adds to the SH group of cysteine in water to yield 2-imino-4-carboxy-thiazolidine.[22]

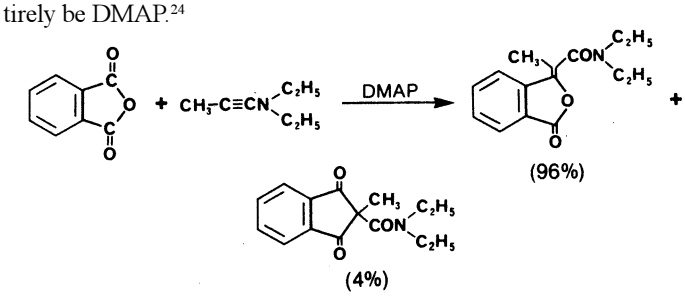


Nucleophilic Rearrangements with DMAP

According to Steglich and Höfle, acyloxyoxazoles rearrange to oxazolinones with DMAP at about 10^4 times as fast as with pyridine.[23]



In another observation by Höfle and Steglich, the course of the reaction between phthalic anhydride and an ynamine is changed entirely be DMAP.[24]



Without DMAP catalysis, only the minor product is formed!

Polymerization with DMAP

Literature references city DMAP as catalyzing the formation of polyurethanes[25,26] including *p*-tolylene diisocyanate and glycols, polyepoxides,[27] and polyamides.[28]

Toxicity and Handling

4-DMAP is readily absorbed through the skin and is highly toxic by skin absorption. It also causes skin and eye burns. All skin and eye contact and inhalation should be avoided. Appropriate OSHA/MSHA-approved respirator, chemical-resistant gloves and impervious or disposable protective clothing should be worn. Work should be carried out in a chemical fume hood. More detailed health and safety information is available in the Aldrich Material Safety Data Sheet.

Storage

Store in a cool, dry, and well ventilated area.
Keep container closed.

References:

1• Steglich, W.; Höfle, G. *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
2• Höfle, G.; Steglich, W. *Synthesis* **1972**, 619.
3• Steglich, W.; Höfle,G., DOX 1,958,954 (1969); *Chem. Abstr.* **1971**, *75*, 34673k.
4• McMurry, J.E.; Musser, J.H.; Ahmad, M.S.; Blaszczak, L.C. *J. Org. Chem.* **1975**, *40*, 1829.
5• Zwanenburg, D.J.; Reynen, W.A.P. *Synthesis* **1976**, 624.
6• Bindra, J.S.; Grodski, A. *J. Org. Chem.* **1977**, *42*, 910.
7• Dryden, Jr., H.L., DOS 2,137,856 (U.S. Patent 3,678,082) (1970); *Chem. Abstr.* **1972**, *76*, 127269u.
8• Herz, J.E.; Cruz, M.S.; Torres, J.V.; Murillo, A. *Synth. Commun.* **1977**, *7*, 383.
9• Mesentsev, A.S.; Kuljaeva, V.V. *Tetrahedron Lett.* **1973**, 2225.
10• Bohlmann, F.; Franke, H. *Chem. Ber.* **1971**, *104*, 3229.
11• Bohlmann, F.; Vogel, D. *Chem. Ber.* **1974**, *107*, 654.
12• Bohlmann, F.; Zdero, C. *Chem. Ber.* **1976**, *109*, 901.
13• Connors, K.A.; Albert, K.S. *J. Pharm. Sci*, **1973**, *62*, 845.
14• Litvinenko, L.M.; Kirichenko, A.I. *Dokl. Akad. Nauk. SSSR* **1967**, *176*, 97; *Chem. Abstr.* **1968**, *68*, 68325.
15• Guibé-Jampelo, E.; Wakselman, M. *Chem. Commun.* **1971**, 267.
16• Guibé-Jampelo, E.; Wakselman, M., Fr. Demande 2,115,552; *Chem. Abstr.* **1973**, *84*, 84814g.
17• Lepschy, J.; Höfle, G.; Wilschowitz, L.; Steglich, W. *Justus Liebigs Ann. Chem.* **1974**, 1753.
18• Bodanszky, M.; Izdebski, J.; Muramatsu, I. *J. Am. Chem. Soc.* **1969**, *91*, 2351.
19• Hofmann, H.; Haberstroh, H.-J.; Appler, B.; Meyer, B.; Herterich, H. *Chem. Ber.* **1975**, *108*, 3596.
20• Koninklijke Nederlandsche Gist-en Spiritusfabriek N.V., DOS 2,155,152 (1972); *Chem. Abstr.* **1972**, *77*, 88491j.
21• Henniger, P.W.; Van der Drift, J.K., DOS 2,235,390 (1973), Koninklijke Nederlandsche Gist-en Spiritusfabried N.V.; *Chem Abstr.* **1973**, *78*, 124608j.
22• Wakselman, M.; Guibé-Jampel, E.; Raoult, A.; Busse, W.D. *Chem. Commun.* **1976**, 21.
23• Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1970**, 4727.
24• Höfle, G.; Steglich, W. *Chem. Ber.* **1972**, *105*, 1368.
25• ICI, Brit. Patent 990,635; *Chem. Abstr.* **1965**, *63*, 4482h.
26• ICI, Brit. Patent 990,633; *Chem. Abstr.* **1965**, *63*, 5861e.
27• Ciba-Geigy, Brit. Patent 1,201,756.
28• ICI, Brit. Patent 1,207,673 (1970); *Chem. Abstr.* 1971, *74*, 32529y.

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