

# SYNLETT Spotlight 68

## 4-Dimethylamino-pyridine (DMAP)

Compiled by Christoph Grondal



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Christoph Grondal (1979) studied chemistry at the Friedrich-Wilhelms University of Bonn. Currently, he is carrying out his diploma thesis on application of functionalized cyclohexadienes in diversity oriented synthesis in the research group of Michael Müller at the Department of Bioorganic Chemistry, Institute of Biotechnology 2, Forschungszentrum Jülich GmbH.

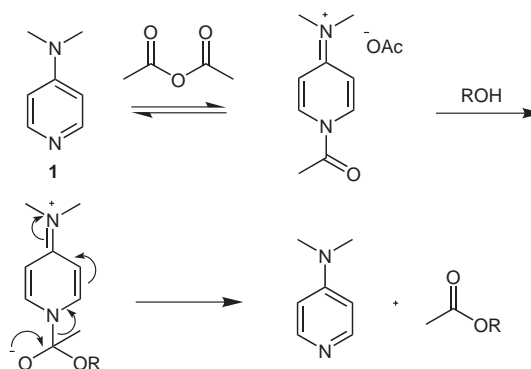
Institute of Biotechnology 2, Forschungszentrum Jülich GmbH,  
52425 Jülich, Germany  
E-mail: c.grondal@fz-juelich.de

Dedicated to Professor Steglich on the occasion of his 70th birthday.

### Introduction

In 1969 Steglich and Höfle reported 4-(dimethylamino)pyridine (DMAP) (**1**) as a very effective acylation catalyst.<sup>1</sup> Independently, the Russian group of Litvinenko and Kirichenko discovered that pyridine replaced by DMAP accelerates the reaction rate by ca.  $10^4$  for the benzylation of *m*-chloroaniline.<sup>2</sup> As a result of many investigations based on the fundamental work by Steglich et al., DMAP has been used in a large range of applications as a catalyst for acylation of alcohols, amines, phenols and enolates,<sup>3–5</sup> in particular for the acylation of sterically hindered secondary or tertiary alcohols. For example, 1-methyl-1-cyclohexanol is not acylated under basic conditions (pyridine,  $\text{Ac}_2\text{O}$ ), whereas in the presence of 4.1 mol% of DMAP a yield of 86% is achieved after 14 hours at room temperature.<sup>1</sup> It should be mentioned that DMAP shows good catalytic activity under certain conditions. Non-polar solvents like pyridine and  $\text{Ac}_2\text{O}$  (rather than acid chlorides) are suitable.

The catalytic efficiency is probably due to the stabilization of an acylpyridinium ion, which plays an important role in the catalytic cycle (Scheme 1). Steric effects, the donor ability of the amine substituent, and the good nucleophilic properties of DMAP additionally affect the reactivity of DMAP. Hassner et al. pointed out that 2-di-alkylamino-pyridines have no catalytic activity for steric reasons.<sup>6</sup>

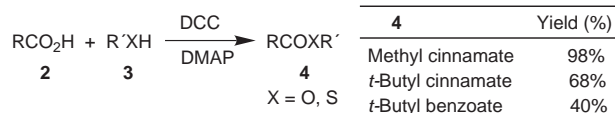


Scheme 1

It is well known that DMAP does not only serve as a catalyst for acylation reactions and (trans-) esterifications<sup>7</sup> but also for various organic transformations like the Baylis–Hillman reaction,<sup>8</sup> the Dakin–West reaction,<sup>9</sup> the protection of amines,<sup>10</sup> C-acylations,<sup>11</sup> silylations,<sup>5</sup> applications in natural products chemistry,<sup>12</sup> and many others.<sup>5</sup>

### Abstracts

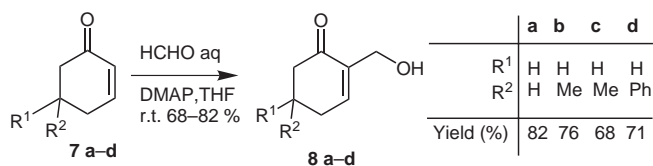
(A) Besides acylations, the most popular reaction employing DMAP as catalyst, is esterification of carboxylic acids. A simple and efficient method, introduced by Neises and Steglich,<sup>7</sup> proceeds by dicyclohexylcarbodiimide (DCC) and DMAP activation of the carboxylic acid function.



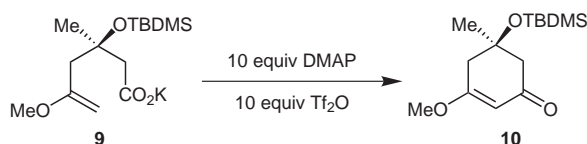
(B) A new efficient and simple route for the functionalization of nitrogen atoms using DMAP (i.e. introduction of protecting groups onto -amine, -amide, -pyrrole, -indole) has been developed recently. The twofold protection of an aminofunction **5** is possible by DMAP catalysis as well.<sup>10</sup>



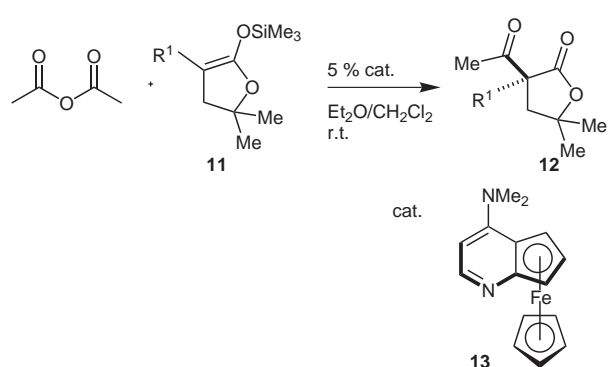
(C) Traditionally, the Baylis–Hillman reaction is catalyzed by DABCO. The hydromethylation of cyclohexenones with aqueous formaldehyde by the Baylis–Hillman reaction is catalyzed by DMAP or 4-(pyrrolidino)pyridine, whereas DABCO is not suitable in this case for steric reasons.<sup>8</sup>



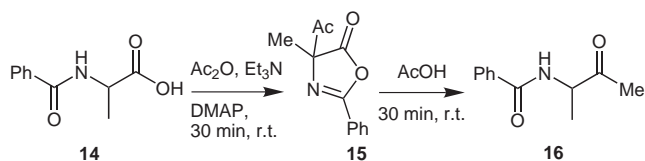
(D) Treatment of **9** with *N*-triflyl-4-(dimethylamino)pyridinium triflate enables a new approach to substituted cyclohexenones **10**. This reagent is easily formed from DMAP and triflic anhydride, and is used in a 10-fold excess.<sup>12</sup>



(E) Axial<sup>13</sup>- and planar-chiral<sup>11</sup> derivatives of DMAP for example **13** can also serve as enantioselective nucleophilic catalysts<sup>14</sup> e.g. the asymmetric intermolecular C-acylation processes of silyl ketene acetals. This method accommodates a wide range of aromatic substituents (R<sup>1</sup>) and also heteroaromatic groups are tolerated. The reaction describes an alternative route to Claisen-like reactions introducing a new quaternary stereocenter in good ee.<sup>11,15</sup>



(F) The transformation of an  $\alpha$ -amino acid into the corresponding  $\alpha$ -acetylaminomethylketone is known as the Dakin–West reaction. Traces of DMAP catalyze the reaction, which can be carried out under mild condition, and several sensitive protecting groups are tolerated.<sup>9</sup>



## References

- (1) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
- (2) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk* **1967**, *176*, 97.
- (3) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
- (4) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.
- (5) Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21.
- (6) Hassner, A.; Krepski, L. R. *Tetrahedron* **1978**, *34*, 2069.
- (7) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
- (8) Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965.
- (9) Buchanan, G. L. *Chem. Soc. Rev.* **1988**, *17*, 91.
- (10) Regnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494.
- (11) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050.
- (12) Müller, M.; Lamotke, K.; Löw, E.; Mayer-Veenstra, E.; Steglich, W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2483.
- (13) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.
- (14) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844.
- (15) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 234.