SYNLETT
Spotlight 68

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

4-Dimethylamino-pyridine (DMAP)

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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. 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. 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, 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, Ac$_2$O), whereas in the presence of 4.1 mol% of DMAP a yield of 86% is achieved after 14 hours at room temperature. It should be mentioned that DMAP shows good catalytic activity under certain conditions. Non-polar solvents like pyridine and Ac$_2$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.

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, proceeds by dicyclohexylcarbodiimide (DCC) and DMAP activation of the carboxylic acid function.

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\begin{align*}
\text{RCO}_2\text{H} + R\text{'X}H & \rightarrow \text{RCOX'} \\
\text{DCC} & \rightarrow \text{DMAP} \\
\text{4} & \text{Yield (\%)}
\end{align*}
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| Methyl cinnamate | 98% |
| t-Butyl cinnamate | 68% |
| t-Butyl benzoate | 40% |

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(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 6 is possible by DMAP catalysis as well.10

(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.8

(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.12

(E) Axial13- and planar-chiral11 derivatives of DMAP for example 13 can also serve as enantioselective nucleophilic catalysts14 e.g. the asymmetric intermolecular C-acylation processes of silyl ketene acetics. This method accommodates a wide range of aromatic substituents (R1) and also heteroaromatic groups are tolerated. The reaction describes an alternative route to Claisen-like reactions introducing a new quaternary stereocenter in good ee11,15

(F) The transformation of an α-amino acid into the corresponding α-acetylaminoalkylmethylketone 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.9

References