SYNLET1 Spotlight 171

Benzophenone Imine
Compiled by Abel Crespo

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Introduction

Benzophenone imine or (diphenylmethylene)amine (DPMA-H, 1) is a valuable reagent in organic synthesis. It is a commercially available liquid which is easily prepared by addition of phenylmagnesium bromide to benzonitrile followed by hydrolysis with methanol or by reaction of benzophenone with ammonia.

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \\
& \quad \text{Ph}
\end{align*}
\]

Synthetic applications of 1 have been historically related to peptide chemistry, specifically as protecting group of primary amines during the preparation of optically active \(\alpha\)-amino acids. Used in conjunction with other anion-stabilising groups, 1 provides activation for proton abstraction. More recently, the development of highly efficient tin-free palladium-catalysed amination methodologies by the groups of Buchwald and Hartwig increased its synthetic utility as convenient ammonia surrogate in catalysed coupling reactions.

Abstracts

(A) A. de Meijere et al. have published the base-catalysed reaction of benzophenone imine (1) with methyl-2-chloro-2-cyclopropylideneacetate (2) to give 1,4-adduct 4, which is a valuable intermediate in the synthesis of cyclopropyl-\(\beta\)-amino acids. The formal [2+4] cycloaddition of 1 and 2 affords substituted quinolines.

\[
\begin{align*}
1 + \text{Cl} & \xrightarrow{\text{MeCN, EtOH, DMSO, CsOH·H}_2\text{O}} \text{Cl} \quad \text{COOMe} \\
& \quad \text{NH} \\
& \quad \text{Ph}
\end{align*}
\]

(B) DPMA-H (1) serves as amino-protecting group in the enantioselective synthesis of functionalized \(\alpha\)-amino acids and small peptides using a chiral quaternary ammonium salt as catalyst.

\[
\begin{align*}
\text{Ph} & \text{N} \quad \text{Ph} \quad \text{N} \\
& \quad \text{Ph} \quad \text{Ph}
\end{align*}
\]
(C) Benzophenone imine of glycine Wang resin (12) [prepared from F-moc of glycine Wang resin (11) by treatment with piperidine–DMF and then DPMA-H in NMP and glacial acetic acid] can be alkylated with α,ω-dihaloalkanes affording the valuable reactive intermediate 13. Synthetic manipulation at the living group (X), cleavage of protecting fragments and resin yield the side-chain-reactive unnatural amino acids 17–19.25

(D) DPMA-H (1) is employed in the Buchwald–Hartwig reaction as a convenient ammonia surrogate in the palladium- and nickel-catalysed amination of organic electrophiles 20. The benzophenone imine adducts 21 can be isolated in pure form or cleaved directly to the corresponding primary anilines 22 under mild conditions by catalytic hydrogenation, treatment with hydroxylamine hydrochloride or a catalytic amount of HCl in wet THF.11 A new series of improved catalysts for this transformation was recently documented.12

(E) Benzophenone imine (1) has been used in the preparation of the trifluoromethylated homoallylamine 26, a useful starting material to achieve the synthesis of α-trifluoromethylated nitrogen heterocyclic compound 27 through an alkylation–ring-closure-metathesis (RCM)13 sequence.

References