SYNLETT
Spotlight 397

Di-*tert*-butyl Azodicarboxylate

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

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Introduction

Di-*tert*-butyl azodicarboxylate (DBAD, **1**, Figure 1), also represented as BocN=NBoc, is a yellow crystalline reagent, insoluble in water. It is a light-sensitive compound with a melting point in the range of 90–92 °C.[1]

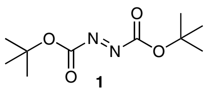
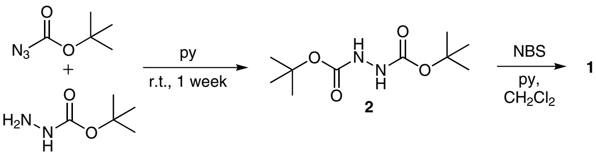


Figure 1 Di-*tert*-butyl azodicarboxylate (DBAD)

DBAD (**1**) has been widely used for several important reactions and for the synthesis of natural and biological active compounds. Recently, several examples have been published showing the relevance of this reagent in key organic reactions, especially in the α-amination of carbonylic compounds.[2]

Preparation

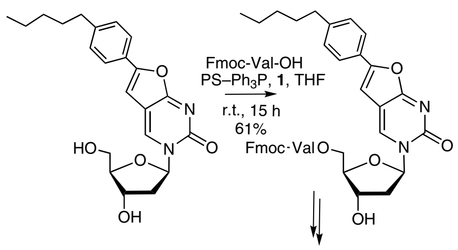
DBAD (**1**) is commercially available, but it can be prepared through several methods.[1,3,4] Originally, **1** was synthesized via a two-step reaction involving the preparation of di-*tert*-butyl hydrazodiformate **2**, followed by NBS oxidation of **2** (Scheme 1).[1,3] Recently **1** has been prepared from **2** with pyridine and bromine in dichloromethane.[4]



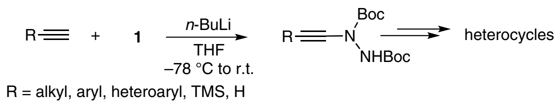
Scheme 1 DBAD preparation

Abstract

(A) DBAD (**1**) is useful in Mitsunobu reactions; generally alcohols are converted into a variety of functional groups in the presence of **1** and Ph_3P. A recent example is the combined use of polymer-supported triphenylphosphine (PS–Ph_3P) and **1** to the regioselective coupling of amino acids on the 5′-position of a nucleoside affording the prodrug precursors.[5]



(B) Recently a general route to synthesize ynehydrazides was reported to establish C_{sp}–N bonds via addition of in situ generated lithium acetylides to DBAD (**1**). This method is useful for the selective synthesis of heterocyclic structures by exploiting both alkyne and hydrazide functional groups in ring-forming reactions.[6]



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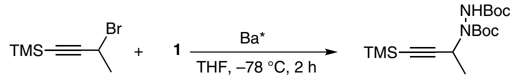
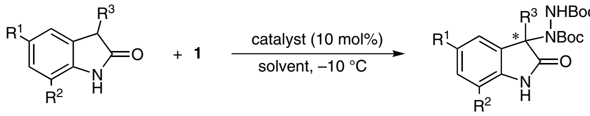
(C) A Barbier-type propargylation of DBAD (**1**) with γ-trialkylsilylated propargylic halides, promoted by reactive barium, is a synthetically useful method regarding the regioselectivity affording various propargylic hydrazides in moderate to high yields.[7]

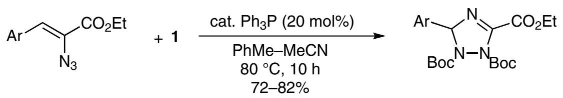


(D) Direct amination of unprotected 3-aryl and aliphatic substituted oxindoles with DBAD (**1**) in the presence of bifunctional quinine-derived thiourea catalyst is achieved in good to excellent yield and enantioselectivity, establishing a tetrasubstituted stereogenic carbon center at the C3 position of oxindoles.[8]

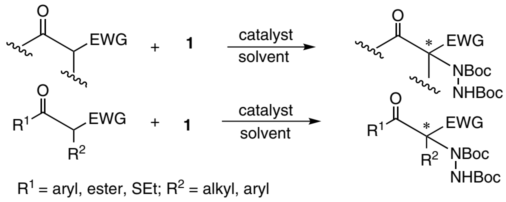


R^1 = H, Me, MeO, X; R^2 = H, Me; R^3 = Ar, H, Me, X

(E) Synthesis of 1,2,4-triazolines by triphenylphosphine-triggered reaction of **1** with 2-azidoacrylates proceeds efficiently.[9] The 1,2,4-triazole is an important scaffold present in compounds with antiviral, anticancer, anti-inflammatory, and anticonvulsant properties.

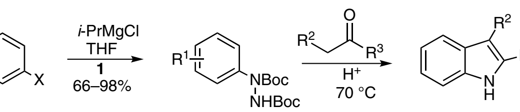


(F) DBAD (**1**) is an asymetric α-hydrazination reagent for α-amination of carbonylic compounds possessing an electron-withdrawing group (EWG). Several cyclic β-keto esters, 1,3-diketone, malonates, and α-cyano ketone can be aminated by reaction with **1**, catalyzed by squaramide.[10] α-Substituted α-cyano acetates[11] and α-cyano thioacetates[12] in the presence of a catalyst lead to products in high yields and enantioselectivities. Additionally, catalytic asymmetric direct amination of α-monosubstituted nitroacetates with **1** and Hatakeyama's catalyst β-ICD affords α-aliphatic substituted nitroacetates with high enantioselectivity.[13]



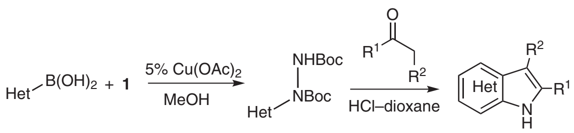
R^1 = aryl, ester, SEt; R^2 = alkyl, aryl

(G) An improved method for the Fischer indole synthesis consists first on the halogen–magnesium exchange of haloarenes and quenching with **1**, followed by reaction with ketones under acidic conditions.[14]



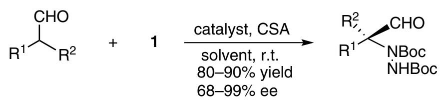
R^2 = alkyl, aryl; R^3 = alkyl, aryl, ester

(H) DBAD (**1**) is used to prepare azaindoles and pyrrolo-fused heterocycles from boronic acids and enolizable aldehydes and ketones. A one-pot reaction involving a copper-catalyzed boronic acid coupling to **1** and a Fischer indolization allows the synthesis of a variety of biologically interesting heterocycles.[15]



R^1 = H, alkyl, aryl; R^2 = alkyl, aryl

(I) The direct asymmetric amination of α-branched aldehydes is achieved by reaction with **1** in the presence of an ion pair catalyst containing a chiral counteranion derived from simple mixing a cinchona alkaloid derived diamine and chiral camphorsulfonic acid (CSA). This reaction allows synthesis of biologically important α-methyl phenylglycine.[16]



R^1 = Ar, Pr; R^2 = Me, Et, *i*-Pr

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