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Di-tert-butyl Azodicarboxylate
Marina J. Dias Pires

Marina J. Dias Pires was born in 1987 in Coimbra, Portugal. She received her Industrial Chemistry degree from the University of Coimbra in 2009 and her M.Sc. in Chemical and Industrial Processes from the same university in 2011. Presently, she is doing research under the supervision of Prof. M. Manuel B. Marques at the Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa. Her research is focused on the synthesis of biologically active glycopeptides.

REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal
E-mail: marinapires4@gmail.com

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 Ph3P. A recent example is the combined use of polymer-supported triphenylphosphine (PS–Ph3P) 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=C–N bonds via addition of in situ generated lithium acetylide 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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A Barbier-type propargylation of DBAD (I) with γ-trialkylsilylated propargylic halides, promoted by reactive barium, is a synthetically useful method regarding the regioselectivity afforded various propargylic hydrazides in moderate to high yields.1

Direct amination of unprotected 3-aryl and aliphatic substituted oxindoles with DBAD (I) 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.2

Synthesis of 1,2,4-triazolines by triphenylphosphine-triggered reaction of I with 2-azidoacrylates proceeds efficiently.9 The 1,2,4-triazole α-substituted nitroacetates with high α-methyl phenylglycine, inflammatory, and anticonvulsant properties.

DBAD (I) is used to prepare azaindolines and pyrrolo-fused heterocycles from boronic acids and enolizable aldehydes and ketones. A one-pot reaction involving a copper-catalyzed boronic acid coupling to azaindoles with DBAD (I) is an asymmetric 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 I, catalyzed by squaramide.10 α-Substituted α-cyano acetates11 and α-cyano thioacetates12 in the presence of a catalyst lead to products in high yields and enantioselectivities. Additionally, catalytic asymmetric direct amination of α-monosubstituted nitroacetates with I and Hatakeyama’s catalyst β-ICD affords α-aliphatic substituted nitroacetates with high enantioselectivity.13

An improved method for the Fischer indole synthesis consists first on the halogen–magnesium exchange of haloarenes and quenching with cat. Ph3P (20 mol%) one-pot reaction involving a copper-catalyzed boronic acid coupling to azaindoles with DBAD (I) is an asymmetric 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 I, catalyzed by squaramide.10 α-Substituted α-cyano acetates11 and α-cyano thioacetates12 in the presence of a catalyst lead to products in high yields and enantioselectivities. Additionally, catalytic asymmetric direct amination of α-monosubstituted nitroacetates with I and Hatakeyama’s catalyst β-ICD affords α-aliphatic substituted nitroacetates with high enantioselectivity.13

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