

A Convenient Preparation of Di-*p*-chlorobenzyl Azodicarboxylate (DCAD) for Mitsunobu Couplings

Benjamin R. Taft, Elizabeth C. Swift, Bruce H. Lipshutz*

Department of Chemistry & Biochemistry, University of California, Santa Barbara, Santa Barbara, CA 93106, USA

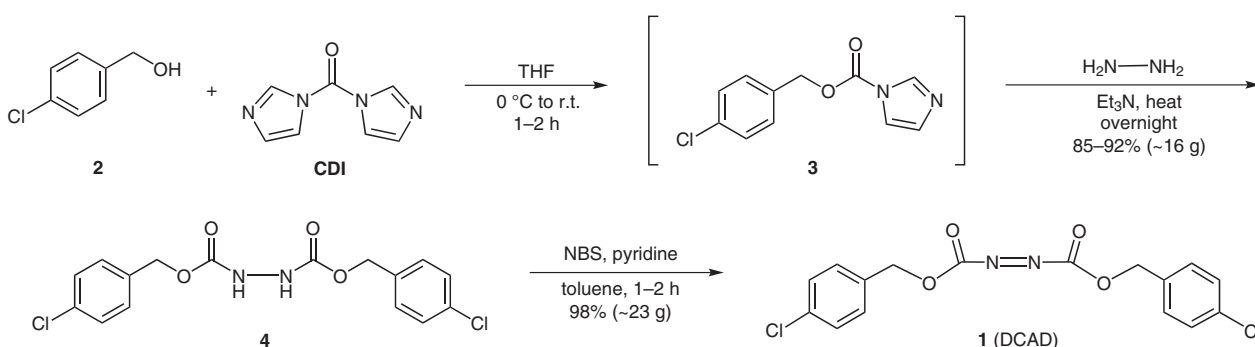
Fax +1(805)8938265; E-mail: Lipshutz@chem.ucsb.edu

Received 27 August 2008



Abstract: Gram-scale synthesis of pure, bench-stable solid di-*p*-chlorobenzyl azodicarboxylate (DCAD) is performed in two steps *without* resorting to chromatography. This novel reagent effects Mitsunobu couplings with yields comparable to DEAD or DIAD, while addressing several of the drawbacks frequently associated with these common reagents.

Keywords: Mitsunobu reaction, azo compounds, alcohols, esters, DCAD



Scheme 1 Two-pot procedure for the synthesis of DCAD (**1**)

Introduction

Since its discovery in 1967, the Mitsunobu reaction has found many synthetic applications due to its versatility and effectiveness.¹ Despite widespread use, traditional azo-reagents can be problematic: they (a) are unstable in the absence of solvent, (b) oftentimes lead to difficult-to-separate hydrazine by-products, and (c) are not usually amenable to recycle. Research aimed at solving some of these drawbacks continues.² Diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) are typically the reagents of choice, although others have also been developed.² One alternative recently introduced from our laboratory is di-*p*-chlorobenzyl azodicarboxylate (DCAD, **1**),³ which has similar reactivity to DEAD and DIAD in numerous Mitsunobu reactions. Reagent **1** has several advantages, including easy handling as a pure, bench-stable solid, facile separation of its reduced form generated from use, and recycling capability. Herein we present a detailed report on the synthesis of DCAD (**1**) involving a two-step process that has been scaled to >15 gram batches.

Scope and Limitations

DCAD (**1**) is readily prepared by initial treatment of a slurry of 1,1'-carbonyldiimidazole (CDI) in anhydrous THF with one equivalent of *p*-chlorobenzyl alcohol (CBA, **2**) at 0 °C followed by 1–2 hours of mixing (Scheme 1). The CDI slurry should be off-white in color; when in solution it becomes transparent and slightly yellow following the addition of CBA.⁴ The resulting in situ-derived carbamate **3** is then exposed to hydrazine and heated to reflux for several hours to afford the corresponding dicarboxylate derivative **4**. Purification is achieved simply by removing the solvent (in vacuo) and washing the crude solid in a fritted funnel with cold water. The water washing step ensures removal of the imidazole by-product, along with any remaining CDI. Following a *rapid* wash with 4:1 hexanes–Et₂O to remove final traces of CBA, the hydrazine dicarboxylate **4** is isolated as a pure, white, amorphous powder in high yield (91–92%), mp 178–179 °C.⁵ Purified product **4** shows a single spot by TLC, *R*_f = 0.45, (1:1 EtOAc–hexanes).³ With proper washings (500–750 mL of cold H₂O per 50 mmol product), the imidazole impurity can be thoroughly removed.

Oxidation is performed by addition of NBS and pyridine to a toluene slurry of hydrazine dicarboxylate **4** at room temperature, which transforms the white mixture to orange in color (Scheme 1). This event is nearly quantitative.

Table 1 Mitsunobu Couplings Mediated by DEAD/Ph₃P and DCAD/Ph₃P^a

Entry	Acid	Alcohol	Product	Time (h)	DEAD Yield (%) ^b	DCAD Yield (%) ^b
1	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H			18	98 ^c	88 ^c
2	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H			0.75	97	98
3				1	76 ^d	80 ^d
4				1.5	quant	quant

^a All reactions were conducted with 0.3 M alcohol (1.0 equiv), 1.1 equiv of acid, 1.1 equiv of Ph₃P, and 1.1–1.2 equiv of azodicarboxylate.

^b Isolated, chromatographically pure material.

^c Optical rotations measured in CHCl₃ for reaction with DEAD: [α]_D²⁰ –19.4 (*c* = 10.7 mg/mL) and DCAD: [α]_D²⁰ –19.4 (*c* = 10.0 mg/mL).

^d Optical rotations measured in CHCl₃ for reaction with DEAD: [α]_D²⁰ –15.9 (*c* = 9.0 mg/mL) and DCAD: [α]_D²⁰ –15.9 (*c* = 16.2 mg/mL).

tive, reaching completion within 1–2 hours. Impurities are removed via standard aqueous workup and careful extractions with aqueous Na₂S₂O₃, HCl (1%), and aqueous NaHCO₃. Of note is that Na₂SO₃ cannot be substituted for Na₂S₂O₃ during washing; that is, an aqueous solution of Na₂SO₃ can reduce DCAD (**1**) back to its precursor hydrazine dicarboxylate **4**. No chromatographic purification is needed in either step of this procedure; the washings reported herein are sufficient to yield clean material. The slightly light sensitive title compound **1** is isolated as bright-orange crystalline flakes that, unlike DEAD and DIAD, can be stored indefinitely at room temperature on the shelf (Figure 1).

**Figure 1** DCAD (**1**), an orange, bench-stable solid

DCAD (**1**) can be used in the same fashion as DEAD or DIAD for all reactions screened to date. Ester formation is smoothly effected in CH₂Cl₂ at room temperature and yields are comparable to those using DEAD (Table 1, entries 1, 2). Inversion of absolute stereochemistry of the secondary alcohol in optically pure (*S*)-(+)-methyl lactate

occurs as expected. Phthalimide can be used to arrive at an optically active protected amine, and lastly, a thiol can be converted to its propargylic derivative in quantitative yield (Table 1, entries 3, 4). Reactions performed in CH₂Cl₂ precipitate the DCAD hydrazine precursor **4**, which can be easily separated from the product and recovered via filtration. This material can then be recycled by re-exposure to NBS.

In conclusion, bench-stable reagent DCAD (**1**) can be conveniently prepared on a multi-gram scale in purified form *without* resorting to chromatography. This bright orange solid can be used for various Mitsunobu couplings with a variety of reaction partners, with yields comparable to those typically seen using DEAD or DIAD. Furthermore, the simplicity of handling this bench-stable solid, along with the facile separation of spent material and the capability of recycling, makes DCAD a very attractive alternative to azo-reagents traditionally used in Mitsunobu reactions.

Procedures

All reactions were conducted in oven-dried, argon purged glassware using Teflon[®] coated magnetic stir bars and rubber septum stoppers. THF and pyridine were freshly distilled from Na/benzophenone ketyl and CaH₂, respectively, prior to use. CBA and CDI were purchased from Alfa Aesar and used as received. Hydrazine (anhyd) was purchased from Aldrich and used as received. NBS was purchased from ACROS and used as received. TLC analyses were performed on commercial Kieselgel 60 F₂₅₄ silica gel plates. NMR spectra were obtained on a Varian Inova system using DMSO-*d*₆ or CDCl₃ as solvent, with proton and carbon resonances at 400 and 100

MHz, respectively. Mass spectral data were acquired on a VF Autospec or an analytical VG-70-250-HF instrument.

Bis(4-chlorobenzyl) Hydrazine-1,2-dicarboxylate (**4**)

A clear solution of 4-chlorobenzyl alcohol (**2**; 14.258 g, 100.0 mmol) in anhyd THF (40 mL) was added dropwise via cannula at 0 °C to an off-white slurry of 1,1'-carbonyldiimidazole (16.215 g, 100.0 mmol) in anhyd THF (50 mL). The resulting clear, pale yellow solution was stirred and warmed to r.t. over 2 h. Hydrazine (1.55 mL, 49.5 mmol) and freshly distilled Et₃N (14.02 mL, 101.0 mmol) were sequentially added and the solution was refluxed in an 80 °C oil bath for 12 h. After cooling, the solution was concentrated in vacuo leading to an amorphous white solid that was transferred to a fritted Büchner funnel and washed (vacuum filtration) with cold H₂O (5 × 150 mL) and 1:4 Et₂O–hexanes (2 × 100 mL). The colorless solid was then collected and dried in vacuo to afford the title compound; yield: 16.598 g (91%); *R_f* = 0.45 (1:1 EtOAc–hexanes, KMnO₄ stain); mp 177–179 °C.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.35, 8.98 (NH rotamers, 2 H), 7.45–7.28 (m, 8 H), 5.08 (s, 4 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 156.5, 135.7, 132.8, 129.8, 128.9, 65.3.

HRMS-ESI: *m/z* calcd for C₁₆H₁₄Cl₂N₂O₄ + Na [M + Na]⁺: 391.0222; found: 391.0227.

Di-*p*-chlorobenzyl Azodicarboxylate (DCAD, **1**)

Freshly distilled pyridine (5.21 mL, 64.67 mmol) and NBS (11.51 g, 64.67 mmol) were sequentially added to a slurry of **4** in toluene (250 mL). After stirring the resulting orange cloudy mixture for 2 h, the mixture was diluted with toluene (375 mL, to completely dissolve all solids) and washed with H₂O (300 mL), sat. aq Na₂S₂O₃

(300 mL), 1% aq HCl (225 mL), sat. aq NaHCO₃ (300 mL), H₂O (3 × 225 mL), and brine (300 mL). The organics were then dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the title compound as orange crystalline flakes; yield: 23.020 g (99%); mp 107–108 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.38 (s, 8 H), 5.40 (s, 4 H).

¹³C NMR (100 MHz, CDCl₃): δ = 160.1, 135.4, 132.1, 130.4, 129.2, 70.1.

HRMS-ESI: *m/z* calcd for C₁₆H₁₂Cl₂N₂O₄ + Na [M + Na]⁺: 389.0066, found: 389.0083.

Acknowledgment

Financial support provided by the NSF is warmly acknowledged.

References

- (1) Toy, P. H.; But, T. Y. S. *Chem. Asian J.* **2007**, 2, 1340.
- (2) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763.
- (3) (a) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, 8, 5069. (b) Our originally reported *R_f* for the hydrazine dicarboxylate **4** is misleading, as the material was impure due to the presence of residual imidazole.
- (4) Optimum results were achieved using CDI and CBA obtained from Alfa Aesar.
- (5) Imidazole is water soluble while **4** is not. Use of 1:1 hexanes–Et₂O leads to substantial loss of product **4**. Exposure time of the product to solvent can be minimized by using vacuum filtration.