

Simplification of the Mitsunobu Reaction. Di-*p*-chlorobenzyl Azodicarboxylate: A New Azodicarboxylate

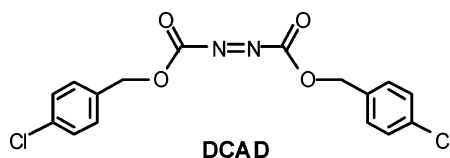
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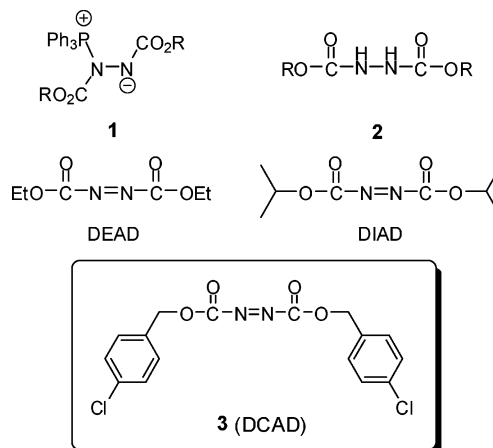
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ABSTRACT



Di-*p*-chlorobenzyl azodicarboxylate (DCAD) is introduced as a novel, stable, solid alternative to DEAD and DIAD for a variety of Mitsunobu couplings. DCAD/ Ph_3P -mediated reactions in CH_2Cl_2 generate a readily separable hydrazine byproduct.

The Mitsunobu coupling is among an elite group within a vast array of name reactions.¹ It is used so frequently that oftentimes literature reviews,² as well as its origins,³ are excluded from among the citations. These reactions rely on an initial adduct **1** formed between Ph_3P and an azodicarboxylate, with the diethyl derivative (i.e., DEAD; Figure 1) credited with the majority of reported examples.² The diisopropyl ester (DIAD) is also very commonly utilized.² Notwithstanding its popularity, research continues to address various aspects of Mitsunobu chemistry as usage evolves with time. Perhaps chief among these lies the issue of product separation from triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$) and the attendant hydrazines **2**, with new technologies having been recently reviewed.^{4,5} Additional alternatives, such as Charette's



stable orange crystalline solid (mp 108–110 °C)

Figure 1. Reaction intermediates and azodicarboxylate reagents used in Mitsunobu couplings.

(1) (a) *Name Reactions*, 2nd ed.; Li, J., Ed.; Springer-Verlag: Berlin, Germany, 2003; p 265. (b) *Strategic Applications of Named Reactions in Organic Synthesis*; Kurti, L., Czako, B., Eds.; Elsevier: Burlington, MA, 2005; pp 294–295.

(2) (a) Mitsunobu, O. *Synthesis* **1981**, 1, 1–28. (b) Hughes, D. L. *Organic Reactions*; Wiley: New York, 1992; Vol. 42, pp 335–656.

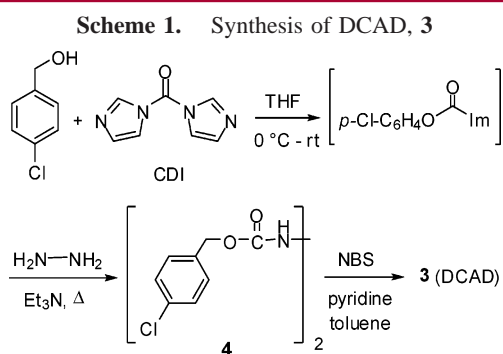
(3) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, 40, 2380–2382. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, 44, 3427–3430. (c) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, 94, 679–680.

(4) (a) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 13, 2763–2772. (b) Dandapani, S.; Curran, D. P. *Chem.–Eur. J.* **2004**, 10, 3130–3138.

recent report on a phosphonium salt analogue of DEAD, continue to appear.⁶ Our goal was to develop a new solution-based reagent that offers the important feature of straight-

forward separation and recovery of the hydrazine byproduct. Such a reagent not only would facilitate purification of the desired product but also might encourage recycling of what would otherwise be regarded as chemical waste. In this Letter we describe, along with full experimental details, the preparation of di-*p*-chlorobenzyl azodicarboxylate (DCAD) **3**, a typical procedure for its selected use in Mitsunobu reactions, direct comparison data for reactions also run with DEAD, and the successful reisolation of the byproduct hydrazine dicarboxylate.

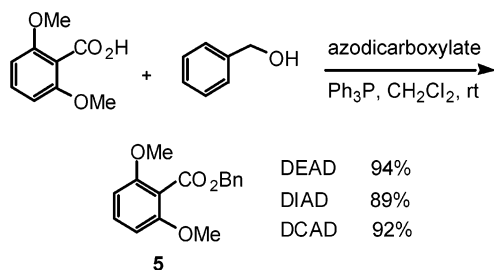
DCAD is readily prepared in two steps by the initial treatment of *p*-chlorobenzyl alcohol with an equivalent of 1,1'-carbonyldiimidazole (CDI) in THF (Scheme 1). The in



situ-derived carbamate is subsequently exposed to hydrazine, leading to the corresponding dicarboxylate derivative **4** (84%). Oxidation with NBS affords the solid reagent **3** (98%), which, unlike liquids DEAD or DIAD, can be stored at room temperature.

To evaluate DCAD, initially, esterification of 2,6-dimethoxybenzoic acid with benzyl alcohol was selected for comparison with both DEAD and DIAD (Scheme 2). Under

Scheme 2. Comparison of Azodicarboxylate Reagents in a Mitsunobu Coupling^a



^a Reactions were carried out with 1.0 equiv of benzyl alcohol and 1.1 equiv of all other reagents.

identical conditions, benzyl ester **5** was formed in each case in essentially the same isolated yields, suggesting that the rates and efficiency of DCAD are comparable to the industry standards.⁷

Several types of additional Mitsunobu couplings mediated

by DCAD/Ph₃P are highlighted in Table 1, together with results for the analogous reactions using DEAD/Ph₃P. Two related cases of ester formations include coupling of *p*-nitrobenzoic acid with (*S*)-(+)-methyl lactate to afford the (*R*)-diester product of inversion **6** (entry 1) and with glycidol to give epoxide **7** (entry 2). Etherifications, of both an intermolecular (entry 3) and intramolecular (entry 4) nature were carried out. The former involved nonracemic 2-octanol and led to product **8**, indicative of the expected inversion. Nucleophilic components based on nitrogen, also well-known partners in Mitsunobu reactions,² showed similar behavior in the presence of either DCAD or DEAD. Phthalimide could be smoothly converted to the optically active protected amine derivative **9** (entry 5), and very sensitive retinol led to low yields of isolated polyene **10** as a mixture of two regioisomers (entry 6; S_N2 and presumably the product of S_N2' displacement). Much better results were forthcoming using succinimide together with geraniol (entry 7). Intramolecular

(5) (a) DBAD: Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999**, *40*, 4497–4500. (b) PS-DEAD: Arnold, L. D.; Assil, H. I.; Vederas, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3973–3976. (c) Chromatography-free Mitsunobu: Proctor, A. J.; Beautement, K.; Clough, J. M.; Knight, D. W.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 5151–5154. (d) Phosphine oxide complex: Anderson, N. G.; Lust, D. A.; Colapret, K. A.; Simpson, J. H.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1996**, *61*, 7955–7958.

(6) Poupon, J.-C.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1415–1420.

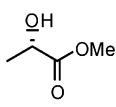
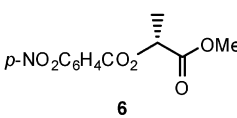
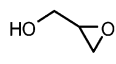
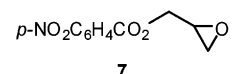
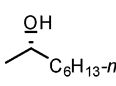
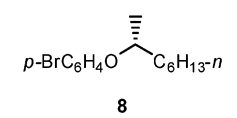
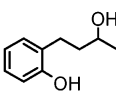
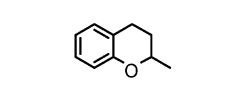
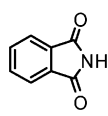
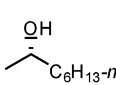
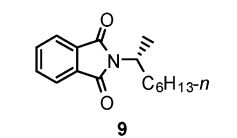
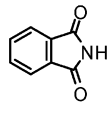
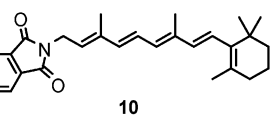
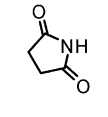
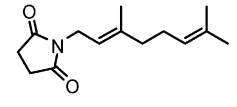
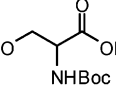
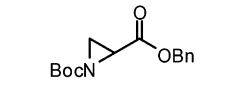
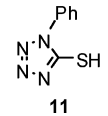
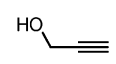
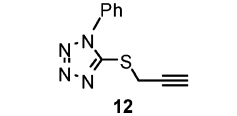
(7) The unsubstituted dibenzyl azodicarboxylate is also commercially available and gave a roughly comparable yield in this reaction. However, the hydrazine byproduct does not show the same solubility profile in CH₂-Cl₂ as DCAD and, therefore, was not pursued further.

(8) (a) **Di-(*p*-chlorobenzyl) azodicarboxylate (DCAD) [3]**. Pyridine (0.610 mL, 7.54 mmol) and NBS (1.34 g, 7.54 mmol) were sequentially added to a suspension of **4** (2.73 g, 7.39 mmol) in toluene (28.0 mL). After stirring the resulting orange cloudy mixture at rt for 17 min, the mixture was diluted with 25–30 mL of toluene and washed with water (15 mL), saturated aqueous Na₂S₂O₃ (15 mL), 1 wt % aqueous HCl (15 mL), saturated aqueous NaHCO₃ (15 mL), water (3 × 15 mL), and brine (15 mL). The organics were then dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford the title compound as orange crystalline flakes (2.66 g, 98%): mp 108–110 °C; IR (NaCl, neat) 2360, 2342, 1764 cm⁻¹; ¹H NMR (CDCl₃) δ 7.38 (s, 8H), 5.40 (s, 4H); ¹³C NMR (CDCl₃) δ 160.10, 135.54, 132.10, 130.46, 129.28, 70.14; HRMS(ESI+) *m/z* calcd for C₁₆H₁₂N₂O₄Cl₂Na 389.0066 (M + Na)⁺, found 389.0083. (b) **Di-(*p*-chlorobenzyl) hydrazodicarboxylate [4]**. A solution of 4-chlorobenzyl alcohol (2.75 g, 19.30 mmol) in THF (11.0 mL) was slowly added at 0 °C to a solution of 1,1'-carbonyldiimidazole (3.13 g, 19.30 mmol) in THF (9.0 mL), and the resulting solution was stirred at 0 °C to rt for 1 h. Hydrazine (0.300 mL, 9.56 mmol) and triethylamine (2.70 mL, 19.37 mmol) were sequentially added, and the solution was refluxed for 7.5 h after taking 30 min to achieve reflux temperature. The solution was concentrated in vacuo to a peach-colored slurry that was transferred into a fritted buchner funnel and washed with water (5×) and 1:1 Et₂O/hexanes (3×) to afford the title compound as a light-pink powder (2.96 g, 84%): *R*_f = 0.05 major rotamer, 0.43 minor rotamer (KMnO₄ stain); 1:1 EtOAc/hexanes; mp 171–173 °C; IR (NaCl, neat) 3239, 2360, 1750, 1695 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 9.34, 8.97 (mix of rotamers, 2H total), 8.94 (d, 1H), 7.46–7.30 (m, 8H), 5.08 (s, 4H); ¹³C NMR (DMSO-*d*₆) δ 156.38, 135.64, 132.65, 129.77, 128.46, 65.16; HRMS(ESI+) *m/z* calcd for C₁₆H₁₄N₂O₄Cl₂ 391.0222 (M + Na)⁺, found 391.0227.

(9) **General procedure for Mitsunobu couplings. Benzyl 2,6-dimethoxybenzoate [5]**. A solution of **3** (820 mg, 2.23 mmol) in CH₂Cl₂ (6.0 mL) was slowly added at rt via cannula to a solution of triphenylphosphine (586 mg, 2.23 mmol), 2,6-dimethoxybenzoic acid (409 mg, 2.24 mmol), and benzyl alcohol (210 μL, 2.03 mmol) in CH₂Cl₂ (2.0 mL), and the resulting cloudy mixture was stirred at rt for 33 min. Filtration of the mixture afforded the reduced azodicarboxylate **4** as a white powder (675 mg, 82 mol % recovery). The filtrate was concentrated in vacuo. Flash chromatography of the crude product (hexanes to 1:9 EtOAc/hexanes) afforded the title compound as a colorless oil that gradually crystallized upon standing at rt (508 mg, 92%). The spectral data matched those provided in the literature.¹⁰

(10) Kodpinid, M.; Sadavongvivad, C.; Thebthanonth, C.; Thebthanonth, Y. *Phytochemistry* **1984**, *23*, 199–200.

Table 1. Comparison of 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		 6	18	98 ^c	88 ^c
2	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H		 7	0.75	97	98
3	<i>p</i> -BrC ₆ H ₄ OH		 8	19.5	83 ^d	77 ^d
4	---			0.5	86	90
5			 9	1	76 ^e	80 ^e
6		all- <i>trans</i> -retinol	 10	1.5	16 ^f	33 ^f
7		geraniol		1	79	74
8	---		 BocN	1	92	88
9	 11		 12	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 reagent, except for entry 4, which was run at 0 °C, and entry 6, which was run with 1.05 equiv of phthalimide and 1.05 equiv of Ph₃P at –78 °C. ^b Isolated, chromatographically pure material. ^c Optical rotations measured in CHCl₃ for reaction with DEAD: [α]_D²⁰ = –19.4° (*c* = 10.7 mg/mL). DCAD: [α]_D²⁰ = –19.4° (*c* = 10.0 mg/mL). ^d Optical rotations measured in CHCl₃ for reaction with DEAD: [α]_D²⁰ = –8.4° (*c* = 10.1 mg/mL). DCAD: [α]_D²⁰ = –8.2° (*c* = 10.7 mg/mL). ^e Optical rotations measured in CHCl₃ for reaction with DEAD: [α]_D²⁰ = –15.9° (*c* = 9.0 mg/mL). DCAD: [α]_D²⁰ = –15.9° (*c* = 16.2 mg/mL). ^f Mixture of two regioisomers.

attack by nitrogen in Boc-protected benzyl serine cleanly led to aziridination (entry 8). Last, thiol **11** was quantitatively converted to the corresponding propargylic derivative **12** by both azodicarboxylates. All reactions studied with DCAD were performed in CH₂Cl₂, which was chosen to reflect the very limited solubility of hydrazine byproduct **4** in this solvent.

To quantify the level at which **4** could be recovered, Mitsunobu reactions for all but product **10** were carefully processed upon completion. Dilution of each reaction mixture with additional CH₂Cl₂ followed by filtration led to isolated hydrazine in 66–82% yield. Moreover, the residual material

has very different polarities by TLC (e.g., *R*_f in 1:1 EtOAc/hexanes = 0.05, major rotamer) relative to reduced DEAD (*R*_f = 0.37) and DIAD (*R*_f = 0.39) and has some (albeit far less than expected) UV activity on silica gel plates.

In summary, an alternative reagent to DEAD and DIAD, the *p*-Cl-benzylic analogue (DCAD, **3**),⁸ useful in Mitsunobu reactions, has been developed.⁹ It is easily prepared in only two pots and leads to yields of desired coupling products and reaction rates that are comparable to those of the commonly used reagents. By contrast, DCAD offers the following advantages: (1) it is a stable solid at ambient temperatures; (2) the polarity of its reduced byproduct on

silica gel is distinctly different from those of DEAD/DIAD; and (3) in particular, its hydrazine byproduct is removed, in large measure, by precipitation with CH_2Cl_2 directly from the reaction mixture, simplifying and potentially expanding the use of the Mitsunobu reaction.

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Supporting Information Available: Procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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