ORGANIC LETTERS

2006
Vol. 8, No. 22
5069−5072

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

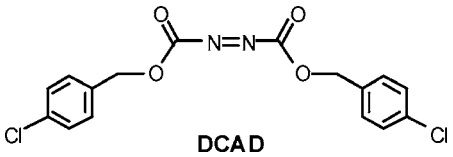
Bruce H. Lipshutz,* David W. Chung, Brian Rich, and Ricardo Corral

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106

lipshutz@chem.ucsb.edu

Received July 28, 2006

ABSTRACT



DCAD

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 ($Ph_3P{=}O$) and the attendant hydrazines **2**, with new technologies having been recently reviewed.[4,5] Additional alternatives, such as Charette's 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-

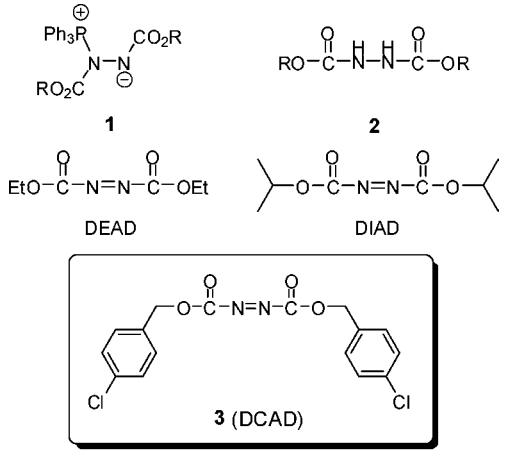


Figure 1. Reaction intermediates and azodicarboxylate reagents used in Mitsunobu couplings.

(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.

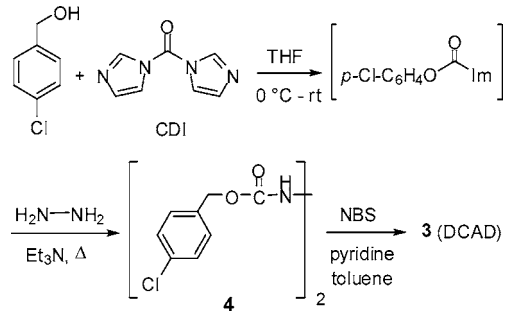
(4) (a) Dembinski, R. *Eur. J. Org. Chem.* **2004**, *13*, 2763−2772. (b) Dandapani, S.; Curran, D. P. *Chem.−Eur. J.* **2004**, *10*, 3130−3138.

10.1021/ol0618757 CCC: $33.50
Published on Web 09/29/2006

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

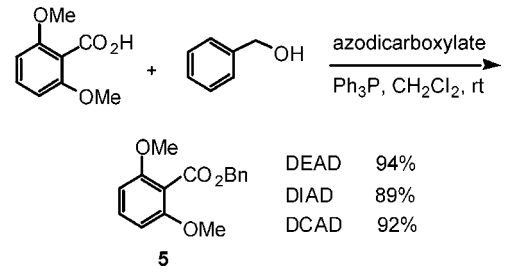
Scheme 1. Synthesis of DCAD, **3**



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/Ph_3P are highlighted in Table 1, together with results for the analogous reactions using DEAD/Ph_3P. 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.

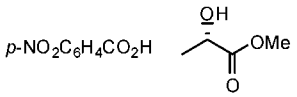
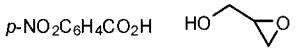
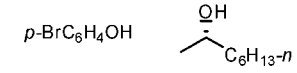
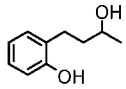
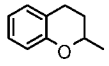
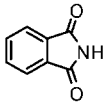
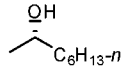
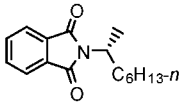
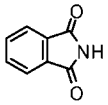
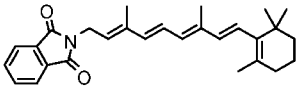
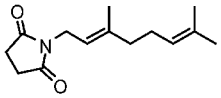
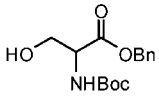
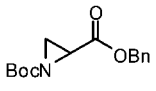
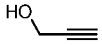
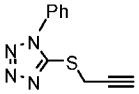
(7) The unsubstituted dibenzyl azodicarboxylate is also commercially available and gave a roughly comparable yield in this reaction. However, the hydrazine byproduct does not show the same solubility profile in CH_2Cl_2 as DCAD and, therefore, was not pursued further.

(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 $Na_2S_2O_3$ (15 mL), 1 wt % aqueous HCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL), water (3 × 15 mL), and brine (15 mL). The organics were then dried over anhydrous Na_2SO_4 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 ($CDC1_3$) δ 7.38 (s, 8H), 5.40 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 160.10, 135.54, 132.10, 130.46, 129.28, 70.14; HRMS(ESI+) *m/z* calcd for $C_{16}H_{12}N_2O_4Cl_2Na$ 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 Et_2O/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 ($KMnO_4$ 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); ^{13}C NMR (DMSO-d_6) δ 156.38, 135.64, 132.65, 129.77, 128.46, 65.16; HRMS(ESI+) *m/z* calcd for $C_{16}H_{14}N_2O_4Cl_2$ 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 CH_2Cl_2 (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 CH_2Cl_2 (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.; Thebtaranonth, C.; Thebtaranonth, Y. *Phytochemistry* **1984**, *23*, 199−200.

Table 1. Comparison of Mitsunobu Couplings Mediated by DEAD/Ph_3P and DCAD/Ph_3P[a]

entry	acid	alcohol	product	time (h)	DEAD yield (%)[b]	DCAD yield (%)[b]
1				18	98[c]	88[c]
			6			
2				0.75	97	98
			7			
3				19.5	83[d]	77[d]
			8			
4	-----			0.5	86	90
5				1	76[e]	80[e]
			9			
6		all-*trans*-retinol		1.5	16[f]	33[f]
			10			
7		geraniol		1	79	74
8	-----			1	92	88
9				1.5	quant	quant
	11		**12**			

[a] All reactions were conducted with 0.3 M alcohol (1.0 equiv), 1.1 equiv of acid, 1.1 equiv of Ph_3P, 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 Ph_3P at −78 °C. [b] Isolated, chromatographically pure material. [c] Optical rotations measured in $CHCl_3$ for reaction with DEAD: $[\alpha]_D^{20} = -19.4°$ ($c = 10.7$ mg/mL). DCAD: $[\alpha]_D^{20} = -19.4°$ ($c = 10.0$ mg/mL). [d] Optical rotations measured in $CHCl_3$ for reaction with DEAD: $[\alpha]_D^{20} = -8.4°$ ($c = 10.1$ mg/mL). DCAD: $[\alpha]_D^{20} = -8.2°$ ($c = 10.7$ mg/mL). [e] Optical rotations measured in $CHCl_3$ for reaction with DEAD: $[\alpha]_D^{20} = -15.9°$ ($c = 9.0$ mg/mL). DCAD: $[\alpha]_D^{20} = -15.9°$ ($c = 16.2$ 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 CH_2Cl_2, 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 CH_2Cl_2 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.

Acknowledgment. We are pleased to warmly acknowledge financial support of this work by the NSF (CHE 05-50232) and fellowships to R.C. (NIH) and B.R. (College of Creative Studies at UCSB). Technical assistance by Mr. Shawn Jia (UCSB) is greatly appreciated. Vitamin A (acetate) was generously supplied by Dr. Keith Drouet (Cambridge Major Labs).

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.

OL0618757