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Dicyclopentyl azodicarboxylate (DCpAD): A new alternative azo-reagent for the Mitsunobu reaction

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Abstract

Dicyclopentyl azodicarboxylate is introduced as a new azo-reagent which can be conveniently prepared in two steps and be used in the Mitsunobu reaction. Though there are no distinct difference of reactivity between DCpAD and DEAD, the former is a more preferable azo-reagent for its stability.

Keywords: Dicyclopentyl azodicarboxylate; Mitsunobu reaction; Azo-reagent

The Mitsunobu reaction, initiated by Mitsunobu in the late 1960s, has become one of the most widely used reactions in organic chemistry [1–3]. The Mitsunobu reaction, due to its scope, stereoselectivity, and mild reaction conditions, has wide applications in total synthesis, heterocyclic, and medicinal chemistry [4–8] and becomes the standard method for the inversion of configuration in secondary alcohols or the synthesis of aryl ether.

The condensation of an acidic pronucleophile with an alcohol promoted by using the redox couple of a trialkyl or triaryl phosphine and a dialkyl azodicarboxylate (azo-reagent) is known as the Mitsunobu reaction which has been extensively reviewed [9–11]. Traditional dialkyl azodicarboxylates are commercially available and they are usually prepared with hydrazine hydrate [12–14]. Among them DEAD is the commonest one, but it is not stable enough in the absence of solvent and is sensitive to light and heat. Moreover, it is susceptible to explosion upon strong heating or impact. Hence, it is preferred to be handled in solution.

We developed a new and efficient azo-reagent which was first used in the Mitsunobu reaction and we found that it was stable and could be stored indefinitely at room temperature.

1. Results and discussion

Dicyclopentyl hydrazinedicarboxylate **2** was readily prepared in good yields by adding a solution of cyclopentyl chloroformate in toluene to an aqueous solution of $NaHCO_3$ and 80% hydrazine hydrate in water at room temperature. Oxidation was performed by addition of Br_2 and pyridine to DCM slurry of hydrazine **2** at room temperature, which transforms the white mixture to orange in color (Scheme 1). Finally the reagent **1** was obtained. The structures of **1** and

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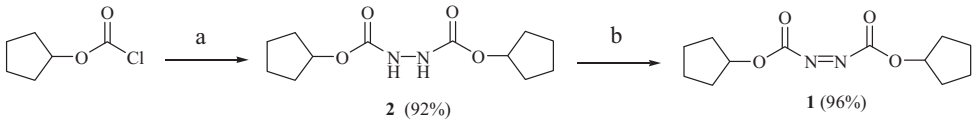


Scheme 1. Synthesis of dicyclopentyl azodicarboxylate: (a) $N_2H_4{\cdot}H_2O$, toluene/H_2O, rt.; (b) Br_2, pyridine, toluene, rt.

Table 1
The influence of illumination on the stability of compound **1** with time at room temperature.

Exposure time (days)	The purity of compound **1** kept under different preservation condition (%)		
	Kept in dark place	Kept under natural daylight	Kept under fluorescent light
0	99.37	99.37	99.37
2	99.31	99.25	99.33
4	99.35	99.30	99.29
6	99.41	99.28	99.37
8	99.28	99.31	99.32
10	99.32	99.33	99.25

Table 2
The purity of compound **1** kept under different temperature with time in dark place.

Temperature (°C)	Purity (%)										
	0 h	24 h	48 h	72 h	96 h	120 h	144 h	168 h	192 h	216 h	240 h
25	99.37	99.31	99.39	99.40	99.29	99.33	99.28	99.35	99.33	99.28	99.36
40	99.37	99.30	99.39	99.38	99.28	99.33	99.37	99.33	99.35	99.32	99.31
55	99.37	99.36	99.31	99.35	99.28	99.34	99.39	99.31	99.27	99.33	99.35
70	99.37	99.27	99.38	99.25	99.31	99.34	99.27	99.24	99.30	99.31	99.30
85	99.37	99.35	99.27	99.31	99.24	99.32	99.29	99.34	99.26	99.30	99.28

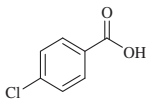
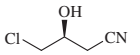
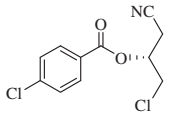
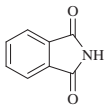
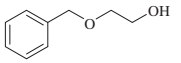
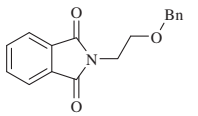
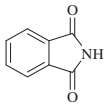
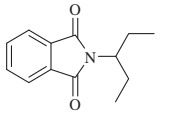
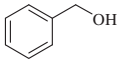
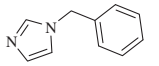
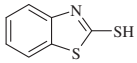
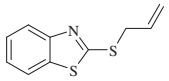
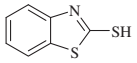
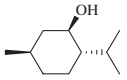
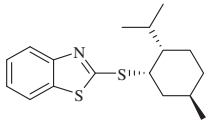
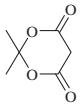
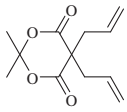
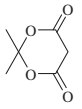
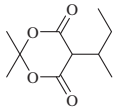
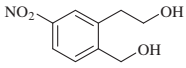
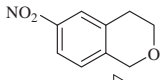
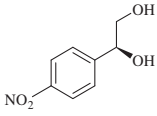
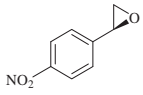
2 were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis [15]. The thermal stability of **1** was evaluated by the decomposition temperature. By thermal gravimetric analysis (TGA) and differencial scanning calorimetry (DSC), DCpAD was found to decompose at 306 °C, while DEAD was found to decompose at 210 °C. The higher decomposition temperature indicates more stability at high temperatures.

The influence of illumination and the effect of temperature on the stability of compound **1** were studied and the results were shown in Tables 1 and 2, respectively. We kept the compound **1** under different conditions within ten days. Finally we found that the purities of these samples have no obvious difference. So the stability of DCpAD may be insensitive to these preservation conditions.

The performance of DCpAD in the Mitsunobu reaction was tested for different combinations of alcohols with some common nucleophiles, in comparison with that of DEAD, and the results were given in Table 3 The pronucleophile used in the Mitsunobu reaction is normally a relative acid compound containing an O–H, S–H, or an N–H group with pKa $\leq$ 15. Some common nucleophiles are carboxylic acids, phenols, imides, purines, thiocarboxylic acids, and thiols. Thus, this reaction permits C–O, C–S, C–N, or C–C bonds formed by the condensation of an acidic component with a primary or a secondary alcohol under Mitsunobu reaction conditions.

When a chiral secondary alcohol is used, configurational inversion of alcohol occurs under mild and neutral conditions. For the two strong electron withdrawing groups at β-position, (*S*)-4-chloro-3-hydroxybutanenitrile is an active optically alcohol which converted to the completely inverted ester with 4-chlorobenzoic acid in good yields (entry 1). Phthalimide reacted smoothly with a primary or a secondary aliphatic alcohol and gave the corresponding *N*-substituted imide (entry 2 and 3). When imidazole which is less active in a Mitsunobu-type alkylation reacted with benzyl alcohol under the usual Mitsunobu conditions, the *N*-alkylimidazole was obtained in poor yields and the reaction did not proceed completely over 24 h (entry 4). A thiol here also tried to couple with a primary alcohol or a less reactive secondary alcohol and its corresponding thioether was obtained in good yields (entry **5** and **6**). The reaction of Meldrum's acid with a primary alcohol such as allyl alcohol was investigated. Rewardingly, the

Table 3
Different combinations of the pronucleophile and alcohol.

Entry	Nu–H	Alcohol	Product	Yield (%)[a]	
				DCpAD	DEAD
1				89[b,d]	85[b,d]
2				87[b]	89[b]
3				88[b]	86[b]
4				30[b]	25[b]
5				92[b]	90[b]
6				86[b]	85[b]
7				93[c]	90[c]
8				85[b]	86[b]
9	–			68	65
10	–			87[d]	85[d]

[a] Isolated, chromatographically pure material.
[b] These reactions were conducted with alcohol (1.0 equiv), 1.1 equiv of acidic pronucleophile, 1.1 equiv of Ph_3P, and 1.1 equiv of azodicarboxylate reagent at room temperature in CH_2Cl_2 and the isolated yields based on alcohols.
[c] These reactions were conducted with Meldrum' acid (1.0 equiv), 2.5 equiv of alcohol, 2.5 equiv of Ph_3P, and 2.5 equiv of azodicarboxylate reagent at room temperature in CH_2Cl_2 and the isolated yields based on Meldrum's acid.
[d] Determined by HPLC analysis with a chiral AD-H column.

dehydrative alkylations proceeded smoothly and dialkylated Meldrum's acid was isolateded in good yields. When Meldrum's acid reacted with secondary butyl alcohol only the monoalkylated Meldrum's acid was obtained due to steric hindrance (entry 7 and 8). Cyclic ether and chiral epoxides were also easily formed under the standard Mitsunobu conditions (entry 9 and 10). All these common nucleophiles tested in this paper could not react with tertiary alcohol such as *tert*-butanol owing to steric hindrance at the tertiary carbon.

In summary, we have developed a novel azo-reagent which can be conveniently prepared in good-to-excellent yield and purified without resorting to chromatography. It was conveniently used for various Mitsunobu couplings. Though the results showed that they had no obvious difference of reactivity between DCpAD and DEAD in the Mitsunobu

reaction, the former is more stable than DEAD and can be stored at ambient temperatures. In addition, the raw materials for preparation of DCpAD are commercially available and cheap. All of these advantages make DCpAD an attractive alternative to azo-reagents in the Mitsunobu reactions.

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[15] Analytical data for compounds 1, 2. Compound **1**: mp 54.3–55.9 °C; IR (NaCl, neat): 2968, 2876, 1770, 1437, 1243 cm^{-1}; ^{1}H NMR (500 MHz, $CDC1_3$): δ 5.41–5.45 (m, 2H), 1.93–2.00 (m, 8H), 1.64–1.80 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.85, 80.57, 35.52, 25.32; MS (ESI): *m/z* 277.1 ($M+Na^+$); Anal. Calcd. for $C_{12}H_{18}N_2O_4$ (254.13): C56.68, H7.13, N11.02. Found: C56.58, H7.06, N11.08. Compound **2**: mp 101.9–103.2 °C; IR (NaCl, neat): 3256, 2965, 2876, 1737, 1687, 1524, 1255 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (s, 2H), 5.15 (m, 2H), 1.59–1.88 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.60, 81.68, 33.70, 25.65; MS (ESI): *m/z* 257.1 ($M+H^+$), 279.1 ($M+Na^+$), 512.9 ($2M+H^+$), 535.1 ($2M+Na^+$); Anal. Calcd. for $C_{12}H_{20}N_2O_4$ (256.14): C56.23, H7.87, N10.93. Found: C56.18, H7.75, N10.83.