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Synthesis and application of a novel asymmetric azo reagent: 1-(*tert*-butyl)-2-(4-chlorobenzyl) azodicarboxylate (tBCAD)

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ABSTRACT

A series of novel asymmetric azo reagents, 1-(*tert*-butyl)-2-(4-substituted benzyl) azodicarboxylate, were prepared. The synthetic process has the advantage of simpleness, easy operation, mild reaction condition and high yield. The 1-(*tert*-butyl)-2-(4-chlorobenzyl) azodicarboxylate (tBCAD) was selected for its stability and convenience to handle, and its precursor can be recycled by recrystallization with toluene. The *t*BCAD and DIAD were applied to a wide variety of Mitsunobu reactions. The experimental results showed that the performance of tBCAD in Mitsunobu reaction was comparable to that of DIAD, while the stability of tBCAD was much better than DIAD. Thus, tBCAD can be a novel, stable, effective azo-reagent for the Mitsunobu reaction.

1. Introduction

Mitsunobu reaction refers to the reaction of a primary or secondary alcohol with a nucleophile in the presence of triarylphosphine or trialkylphosphine and an azo reagent.[1,2] Since its first discovery in 1967 by the Japanese chemist Oyo Mitsunobu,[3,4] the Mitsunobu reaction has found a wide range of applications due to its stereoselectivity, versatility, effectiveness and mild reaction condition, especially in the field of pharmaceutical industry.[5–8] The application of Mitsunobu reaction, initially used for synthesizing esters, was gradually extended to the domain of ammonias, azides, ethers, thioesters and thioethers, etc.[9] Azo reagents, as an inevitable component of Mitsunobu reaction have aroused great attention. Traditionally, diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) is the appropriate and universal alternative, though other reagents have been developed and reported with excellent results (Fig. 1).[10–15] Despite the widespread usage of DEAD and DIAD, conventional azo-reagents can still be problematic: they (a) are unstable in the absence of solvent, light, heat or even collision, (b) are difficult to separate hydrazine by-products, (c) are not usually amenable to recycle and (d) exist explosion hazards.[16–19] Research aimed at solving these drawbacks and discovering better, stable and non-hazard azo reagents has been a hit since then.

After carefully studying the related literature on newly developed azo reagents and phosphine reagents,[20–25] we found, however, that asymmetrical azo reagents were rarely reported. Only Sivaraman Dandapani and Dennis P. Curran reported F-DEAD-2, and Daniel P. Furkert's group synthesized ACCs.[14,15] Both F-DEAD-2 and ACCs displayed unique properties compared to the symmetric ones with similar structure. Therefore, we designed a new synthetic route to produce a series of modified novel asymmetric azo reagents to testify our hypothesis. Among those, the best one is 1-(*tert*-butyl)-2-(4-chlorobenzyl) azodicarboxylate (tBCAD), which has similar reactivity to DIAD, while possessing unique advantages, including easy handling, as a pure stable solid, facile separation and preeminent recycling capability. Herein we present a detailed report on the synthesis of tBCAD.

2. Results and discussion

2.1. The synthesis methodology and properties of azo reagents

The traditional azo reagents (DEAD, DIAD) are synthesized by

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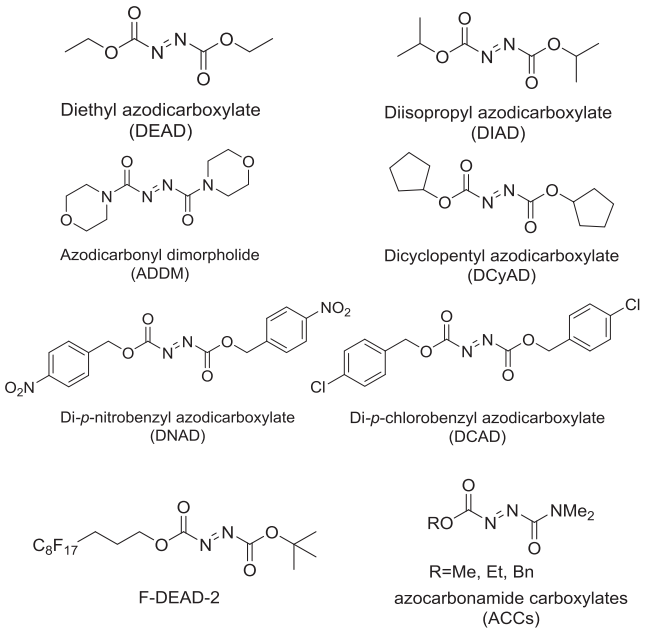
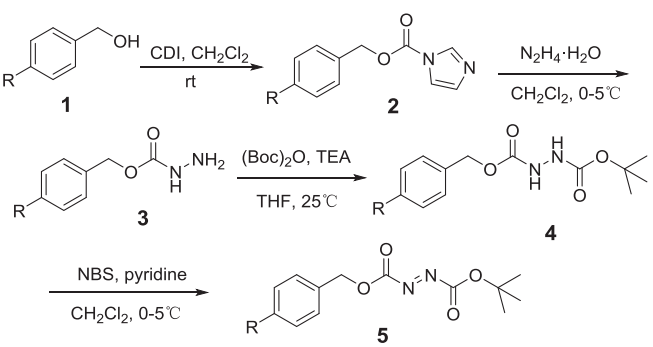


Fig. 1. Mitsunobu reagents.

first intermixing alkyl chloroformate with hydrazine. Alkyl chloroformates are prepared by mixing the alkyl alcohols with phosgene. However, considering the toxicity of phosgene and alkyl chloroformate, we selected *N, N′*-carbonyldiimidazole (CDI) as a substitute for phosgene.

The synthetic route used in this article (Scheme 1) is safe and environmentally friendly, while simple to operate with high-yield. The first step adopted *N, N′*-carbonyldiimidazole (CDI), which was solid with low toxicity. The reaction condition was not rigorous. Room temperature would make it happen. The second step was ice water bathing, which operated with no difficulty.[26–28] The total yield of the two steps was 89.1% (R = Cl). The workup was simply by washing the reaction solution with pure water. The yield of the third step was 86.6% (R = Cl), which was comparable to that of other reported symmetric azo regents.[11,12] Similarly, more asymmetric azo reagents can be conveniently synthesized by introducing different substituents on the side of **3**. Finally, the last step yield was almost quantitative. The detailed results were given in Table 1.

The five azo reagents were exposed to the air at room temperature. Their decomposition was monitored by TLC and ^{1}H NMR



Scheme 1. The Synthetic route of asymmetric azo reagents.

Table 1
The products, reaction time and corresponding yields of each synthetic step.

N	R	Product	Time/h	Yield/%
1	Cl	**2a**	1	–
2		**3a**	1.5	89.1[a]
3		**4a**	5	86.6
4		**5a**	2	96.0
5	NO_2	**2b**	1	–
6		**3b**	1.5	85.7[a]
7		**4b**	5	80.4
8		**5b**	2	96.8
9	SO_2CH_3	**2c**	1	–
10		**3c**	1.5	85.1[a]
11		**4c**	5	86.9
12		**5c**	2	91.8
13	H	**2d**	1	–
14		**3d**	1.5	86.9[a]
15		**4d**	5	84.8
16		**5d**	2	98.5
17	OCH_3	**2e**	1	–
18		**3e**	1.5	94.4[a]
19		**4e**	5	84.0
20		**5e**	2	98.6

[a] The total yield of the first two steps.

spectroscopy. Except tBCAD **5a**, the other four azo reagents decomposed to various degrees in 9 days while tBCAD did not disintegrate in 1 month. We also determined the decomposition temperature of tBCAD, which was 154 °C by DSC-TGA. Thus, tBCAD was selected as our desired novel asymmetric azo reagent, which was stable at room temperature. Since tBCAD was selected according to the stability, we afterwards, studied the properties of its precursor **4a**. It turned out that the precursor **4a** was a very stable white solid that was simple and convenient for storage and usage. More importantly, the solubility of **4a** in toluene was very low (<0.008 g/mL). Therefore, after tBCAD's employment in the Mitsunobu reaction, **4a** can be recovered by recrystallization with toluene, and the corresponding azo reagent tBCAD was obtained by one more step of oxidation. Finally, we studied the effect of tBCAD in Mitsunobu reaction.

2.2. Effect of 1-tert-butyl-2- (4-chlorobenzyl) azodicarboxylate (tBCAD) in Mitsunobu reaction

The compounds served as nucleophilic precursors in the Mitsunobu reaction are generally acidic compounds containing O–H, S–H, or N–H group. These nucleophilic precursors react with primary alcohols or secondary alcohols forming new C–O C–S or C–N bond in the reaction.[9] 1-(*tert*-butyl)-2- (4-chlorobenzyl) azodicarboxylate (tBCAD) was adopted as an azo reagent in the Mitsunobu reaction mixed with triphenylphosphine. The results were compared with those of DIAD/PPh_3. After the reaction yields were calculated, the results were given in Table 2.

One of the salient features of the Mitsunobu reaction is that when the secondary carbon attached to the alcoholic hydroxyl group having a chiral center, the chirality is completely reversed via an S_N2 mechanism.[29–31] That has been widely used in pharmaceutical industry and becomes a standard method of chiral flip.[5–7] In this paper, Mitsunobu reaction was carried out using chiral secondary alcohols (*S*) - (−) - 1-phenylethyl alcohol with acetic acid (Table 2, Entry 1) and benzoic acid (Table 2, Entry 3) to obtain chiral completely inverted products. With tBCAD as the azo reagent, the reaction yielded a yield of 69.5% (90% ee, Entry 1) for 10 h, and the yield of the reaction with DIAD as azo reagent was only 70% (91% ee, Entry 1).[32] Because of steric hindrance, the reactivity of the secondary alcohol was worse than that of the primary alcohol (Table 2, Entry 1–4). The performance of 1-octanol was better than that of