Tetrahedron 67 (2011) 1456–1462

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Di-*p*-nitrobenzyl azodicarboxylate (DNAD): an alternative azo-reagent for the Mitsunobu reaction

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ARTICLE INFO

Article history:
Received 29 September 2010
Received in revised form 8 December 2010
Accepted 14 December 2010
Available online 17 December 2010

Keywords:
DNAD
Mitsunobu reaction
Azo-reagent
Separation-friendly

ABSTRACT

Di-*p*-nitrobenzyl azodicarboxylate is prepared in 83.6% yield in two steps as a bright yellow solid, which can be used as an azo-reagent in the Mitsunobu reaction. When a chiral secondary alcohol was used, sufficient configurational inversion of alcohol occurred under Mitsunobu conditions. That the hydrazine produced from DNAD is semisoluble in some solvents such as THF and CH_2Cl_2 makes it separated easily from the reaction mixture just via filtration. Then the recovered hydrazine compound can be re-exposed to oxidant to produce DNAD. Because DNAD is more stable than DIAD at ambient temperatures and allows easy separation, it is a good alternative azo-reagent for the Mitsunobu reaction.

1. Introduction

The Mitsunobu reaction, discovered by Mitsunobu in the late 1960s, has been extensively reviewed[1–3] and has become one of the most widely used reactions in organic chemistry.[4–6] It is the standard method for the inversion of configuration in secondary alcohols and has wide applications in total synthesis, heterocyclic and medicinal chemistry due to its scope, stereoselectivity, and mild reaction conditions.[7–10] Though it is a powerful process in organic synthesis, a major drawback of this redox-condensation is the requirement of two reagents, a phosphine and a dialkyl azodicarboxylate, which both produce stoichiometric amounts of byproducts.

Traditional azo-reagents such as diethyl azodicarboxylate (DEAD) and diisopropyl azodicarboxylate (DIAD) are commercially available and can be used interchangeably in most cases, but they are sensitive to light, heat and moisture and often be stored below 4 °C in dark and dry area. In addition, diethyl and diisopropyl hydrazinedicarboxylates arising from DEAD and DIAD are problematic during the separation of the product and they are difficult to be recycled. Fine chromatography is usually required to isolate the pure target product from the unreacted reagents and byproducts. This situation limits the direct application of the Mitsunobu reaction in combinatorial library syntheses.

In order to solve some of these problems, many researches are focusing on the development of new alternative reagents (Fig. 1) and modern strategy level separations to simplify the removal of byproducts.[11–21] Even with the development of such dialkyl azodicarboxylate ester analogues, DEAD and DIAD are still the major azo-reagents used in Mitsunobu reactions due to the availability of them.

Our goal was to find an effective alternative azo-reagent that should offer the important feature of straightforward separation and recovery of the hydrazinedicarboxylate arising from the Mitsunobu reaction. Fortunately, a lot of experimental results in our laboratory show that di-*p*-nitrobenzyl azodicarboxylate (DNAD) is such an ideal reagent that not only facilitates purification of the desired product but also encourages recycling the hydrazine byproduct. The triphenylphosphane oxide produced from the triphenylphosphane can be removed by filtration with a proper solvent due to its low solubility in some solvents such as cyclohexane. So one-step removal of the two byproducts via filtration was feasible when triphenylphosphane and DNAD were employed. A survey of the literature shows that there is no report on the application research of it in the Mitsunobu reaction until now. So this paper describes the preparation of DNAD by a commercially available process and its advantages as an azo-reagent in the Mitsunobu reaction.

2. Results and discussion

2.1. Preparation and physical properties of DNAD

Di-*p*-nitrobenzyl hydrazinedicarboxylate (**2**) was readily prepared as white solid powder in 88% yield (Scheme 1). Since **2** is not only a precursor of DNAD but also a co-product in the Mitsunobu reaction, its properties are of importance for the separation and

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doi:10.1016/j.tet.2010.12.036

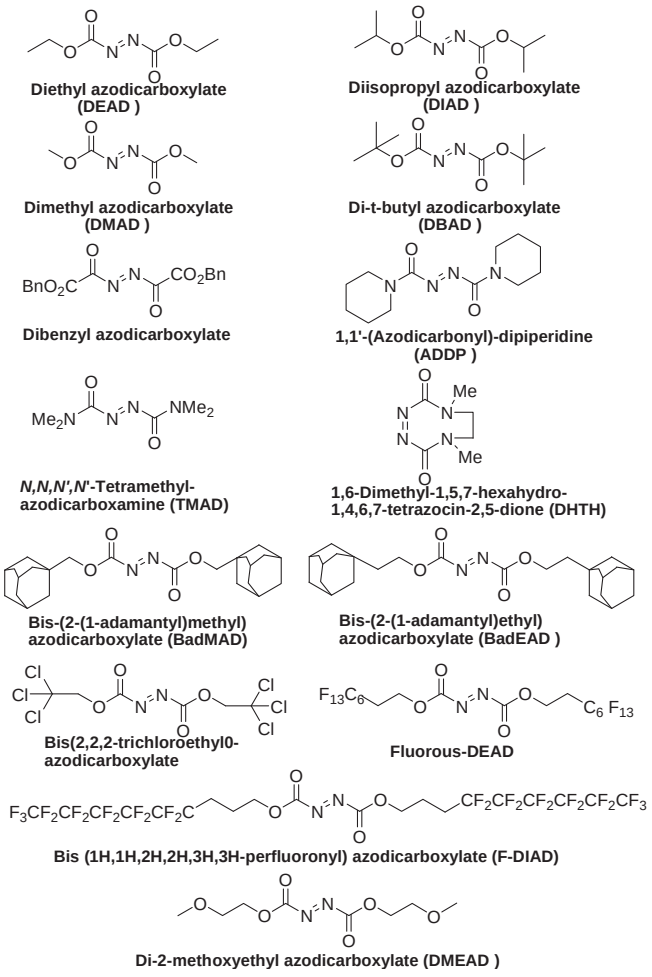
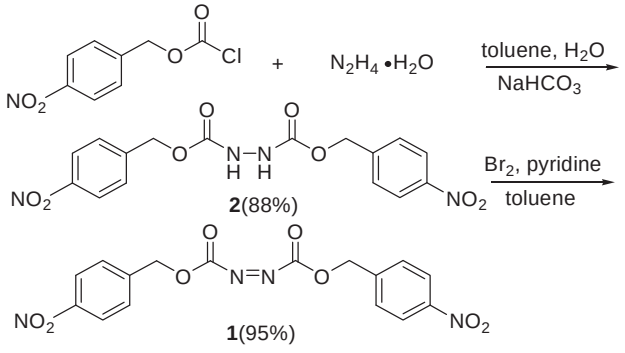


Fig. 1. Mitsunobu coupling reagents.



Scheme 1. Synthesis of di-*p*-nitrobenzyl azodicarboxylate.

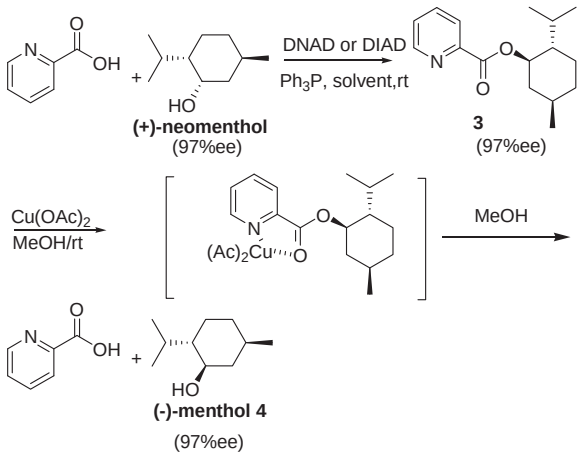
recycling process. The poor solubilities of **2** (<0.005 g/mL, 25 °C) in CH_2Cl_2 and (<0.01 g/mL, 25 °C) in THF make it easy to be separated from the product and recovered just via filtration after the completion of the Mitsunobu reaction. For compound **2** is not very stable at room temperature when it's exposed to air, it should be stored under 5 °C or directly used to the next step.

Oxidation was performed by addition of Br_2 and pyridine to a toluene slurry of hydrazine **2** at room temperature, which transformed the white mixture to orange in color. Finally the pale yellow solid reagent **1** was obtained after workup. Unlike DIAD, the former is stable and can be stored indefinitely at room temperature. As a matter of fact, DNAD exposed to air for more than six months at room temperature still works well. Common chromatographic purification was not needed in either step of this procedure; the washings reported herein were sufficient to yield clean compounds.

2.2. Esterification with inversion

As mentioned in Introduction, the feature that the configuration of the stereogenic center in a chiral secondary alcohol can be inverted under Mitsunobu conditions is valuable. The stereospecificity of the reaction was studied using common organic solvents and the optical (+)-neomenthol, which is a less reactive optically alcohol for steric hindrance effect but could be converted to the diastereomerically pure (−)-menthol ester with picolinic acid (Table 1).

Table 1
Stereospecificity in the reaction of an optically active alcohol with DNAD (or DIAD) and PPh_3



Entry	Solvent	Time/h	Yield/%[a]		ee/%[b]
			DNAD	DIAD	
1	Toluene	3.5(5.0)[c]	83	81	97
2	THF	2.0(4.5)[c]	92	85	97
3	CH_2Cl_2	1.8(3.0)[c]	94	86	97
4	CH_3CN	3.0(5.0)[c]	85	83	97

[a] Reactions were carried out with 1.0 equiv of alcohol and 1.2 equiv of all other reagents.
[b] Determined by HPLC analysis with a chiral AD-H column.
[c] The Mitsunobu reaction time with DIAD.

In the conventional Mitsunobu reaction, the nucleophiles are believed to undergo an S_N2 mechanism.[22–24] Therefore, a complete inversion of stereochemistry at the alcoholic function could be expected and the results were consistent with the mechanism. Compared to the esterification reaction under the Mitsunobu conditions with DIAD/PPh_3, that with DNAD/PPh_3 gave higher yields and took less time for completion. Compound **2** precipitated constantly during the reaction leading to the low concentration of it in the reaction mixture. As far as chemical reaction kinetics is concerned, this situation may accelerate the reaction rate. The influence of different solvents on the reaction was also investigated. The reactions with THF and CH_2Cl_2 as solvent gave excellent yields of the product in comparison of those using toluene or CH_3CN as solvent (Table 1, entries 2 and 3). With the success of the reaction in hand, we then examined the methanolysis of picolinate ester **3** promoted by copper acetate.[25] The methanolysis of picolinate ester **3** with copper acetate in methanol proceeded smoothly and afforded the inverted (−)-menthol under essentially neutral conditions.

2.3. Further study on applicability of DNAD

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 $pK_a \leq 15$. Some common nucleophiles are carboxylic acids, phenols, imides, purines, thiocarboxylic acids, and thiols. The performance of DNAD in the reaction was tested for different combinations of alcohols with some common nucleophiles, in comparison with that of DIAD, and the results were given in Table 2. 2-Amino-6-chloro-purine has poor solubility in some common organic solvents such as THF and is not a great nucleophile for activated alcohols leading to a poor yield of the desired coupling product.[26] Herein, the purine coupled with 2-chloroethanol or benzyl alcohol under the optimized Mitsunobu conditions[27] and gave the N-9 selective nonsugar nucleoside in good-to-excellent yield (entries 3 and 4), but it was still difficult to couple it with other common alcohols. All the other pronucleophiles except imidazole, which is less active in a Mitsunobu-type alkylation for its low of pK_a, could couple with a common primary or secondary alcohol smoothly and all these reactions employing DNAD/PPh_3 gave better results than those employing DIAD/PPh_3. However, all these nucleophiles tested in this paper couldn't react with tertiary alcohol

Table 2
Different combinations of the pronucleophile and alcohol

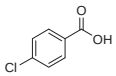
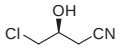
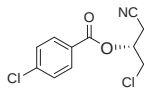
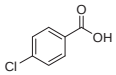
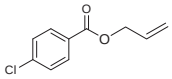
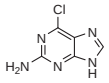
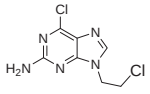
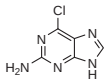
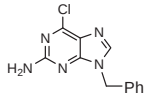
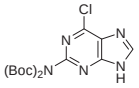
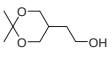
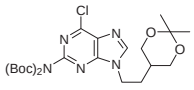
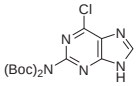
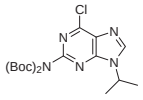
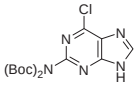
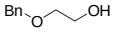
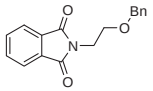
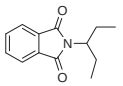
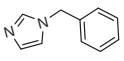
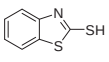
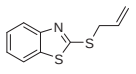
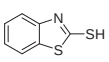
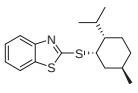
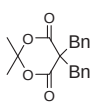
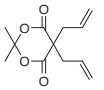
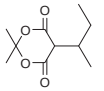
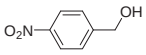
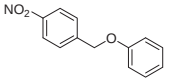
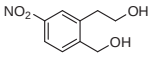
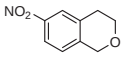
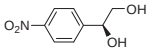
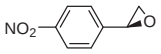
Entry	Nu–H	Alcohol	Product	DNAD(DIAD)	
				Time/h	Yield/%[a]
1				1.8(2.5)	92(85)[b,e]
2				0.5(1.2)	95(88)[b]
3				8.5(14)	85(76)[c]
4				11(18)	83(72)[c]
5				0.3(1.5)	93(88)[b]
6				1.0(2.4)	90(83)[b]
7			—	—	0(0)[b]
8				2.5(4.5)	92(89)[b]
9				3.8(5.6)	87(83)[b]
10				14(24)	55(25)[d]
11				0.3(0.4)	93(86)[b]
12				2.2(3.8)	88(85)[b,e]
13				4.0(6.5)	85(79)[d]

Table 2 (*continued*)

Entry	Nu–H	Alcohol	Product	DNAD(DIAD)	
				Time/h	Yield/%[a]
14				2.5(4.5)	94(90)[d]
15				3.0(5.6)	88(85)[b]
16				1.2(2.0)	90(86)[b]
17	—			2.5(4.0)	72(65)
18	—			1.0(2.2)	92(85)[e]

[a] Isolated yield.
[b] These reactions were conducted with alcohol (1.0 equiv), 1.1 equiv of acidic pronucleophile, Ph_3P, and azodicarboxylate reagent at rt in CH_2Cl_2 and isolated yields based on alcohols.
[c] The reactions were conducted with 2-amino-6-chloro-purine (1.0 equiv), 2.0 equiv alcohol, 2.1 equiv of Ph_3P, and azodicarboxylate reagent at 70 °C in THF and isolated yields based on 2-amino-6-chloro-purine.
[d] These reactions were conducted with Meldrum's acid (1.0 equiv), 2.5 equiv of alcohol, Ph_3P, and azodicarboxylate reagent at rt in CH_2Cl_2 and isolated yields based on Meldrum's acid.
[e] Determined by HPLC analysis with a chiral AD-H column.

such as *tert*-butanol owing to steric hindrance at the tertiary carbon.

3. Conclusions

In summary, the di-*p*-nitrobenzylic azodicarboxylate is very stable at ambient temperatures and can be conveniently prepared in good yields. When DNAD and DIAD were used for various Mitsunobu couplings, these reactions employing DNAD/PPh_3 usually gave higher isolated yields of products and took less time for completion than those with DIAD/PPh_3. Furthermore, its hydrazine precursor **2** can be easily separated directly from the reaction mixture via filtration and then recycled by re-exposure to NBS or Br_2. In addition, the commercially available and cheap raw materials of preparing DNAD reduce the cost. All of the advantages make DNAD a very attractive alternative to azo-reagents traditionally used in the Mitsunobu reactions.

4. Experimental section

4.1. General

Chemicals were reagent-grade, purchased from commercial suppliers, and used without further purification. Absolute THF, CH_2Cl_2, CH_3CN, and toluene used in reactions were prepared by distillation over a drying agent (THF: Na/benzophenone; CH_2Cl_2: CaH_2; CH_3CN: P_2O_5; toluene: Na). TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), All anhydrous reactions were performed under nitrogen in flame-dried glassware using anhydrous solvents. ^1H NMR and ^{13}C NMR spectra were recorded on BRUKER AVANCE DX500. Chemical shifts are given in parts per million relative to tetramethylsilane (TMS) and the coupling constants *J* are given in hertz. The spectra were recorded in $CDCl_3$ or DMSO-d_6 as solvent at room temperature. Melting points were obtained on a Melting Point WRR. Optical rotations were measured on a WZZ-2S automatic digital polarimeter. Enantiomeric purities were determined by HPLC analysis using a chiral AD-H column. Elementary analysis was recorded on Flash EA1110 (ThermoFinnigan). Mass spectra were recorded on a Finnigan LCQ DECA XP^{plus}.

4.2. Preparation of hydrazinedicarboxylate (2)

A solution of *p*-nitrobenzyl chloroformate (10.78 g, 50 mmol) in toluene (50 mL) was added to an aqueous solution (water 50 mL) of $NaHCO_3$ (5 g, 60 mmol) and 80% hydrazine hydrate (1 g, 20 mmol) at room temperature. The mixture was stirred at room temperature for 6 h and then precipitated crystals were cropped by filtration, washed with toulene, and dried in vacuo at 25 °C to give **2** (6.87 g, 88%) as white solid powder. Mp 172–173 °C; IR (NaCl, neat) 3248, 2365, 1755, 1698 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 5.25 (s, 4H), 7.62 (d, J=8.2 Hz 4H), 8.25 (d, J=8.2 Hz, 4H), 9.48 (mix of rotamers, 2H total); ^{13}C NMR (500 MHz, DMSO-d_6) δ 156.81, 148.09, 128.80, 120.99, 65.60; MS (ESI): m/z=391.3 ($M+H^+$), 413.4 ($M+Na^+$). Anal. Calcd for $C_{16}H_{14}N_4O_8$ (390.08): C, 49.24; H, 3.62; N, 14.35. Found: C, 49.18; H, 3.57; N, 14.43.

4.3. Preparation of di-*p*-nitrobenzyl azodicarboxylate (1)

Bromine (6.0 mmol) in 10 mL dichloromethane was added dropwise to a dichloromethane (50 mL) solution of hydrazine **2** (5.0 mmol) and pyridine (10 mmol) cooled to 0 °C under nitrogen. The reaction mixture turned from colorless to yellow upon addition and ran at rt. After completion, the mixture was diluted to 100 mL with dichloromethane, washed with 5% aqueous HCl (2×50 mL), saturated aqueous $NaHCO_3$ (50 mL), water (3×50 mL), and saturated NaCl (50 mL). The organic phase was then dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the title compound as pale yellow solid (18.4 g, 95%). Mp 146–147.5 °C; IR (NaCl, neat) 2365, 2338, 1761 cm^{-1}; ^1H NMR (500 MHz, $CDC1_3$) δ 5.39 (s, 4H), 7.37

(d, J=8.5 Hz, 4H), 8.21 (d, J=8.5 Hz, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.10, 147.84, 128.15, 120.46, 69.14; MS (ESI): m/z=389.3 (M+H$^+$), 411.3 (M+Na$^+$). Anal. Calcd for $C_{16}H_{12}N_4O_8$ (388.07): C, 49.49; H, 3.12; N, 14.43. Found: C, 49.58; H, 3.06; N, 14.38.

4.4. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexylpicolinate (3)

A 100 mL round bottom flask was charged with picolinic acid (616 mg, 5.0 mmol), (+)-neomenthol (390 mg, 2.5 mmol), and triphenylphosphine (1311 mg, 2.5 mmol). The flask was flushed with nitrogen, and THF (30 mL, freshly distilled from Na) was added, and the solution cooled to −20 °C for 10–15 min. A solution of DNAD (5.0 mmol) in dichloromethane was then added dropwise to the solution for 10 min. The temperature of the bath was maintained at −20 °C for 5 h, and the cold bath was allowed to slowly warm to ambient temperature and to stir overnight. Filtration of the reaction mixture afforded the reduced azodicarboxylate **2** as a white powder. The reaction mixture was then concentrated in vacuo, and the products were purified by flash chromatography (eluted with 1:6 EtOAc/hexane) to afford the title compound as a colorless oil (575 mg, 88%). $[\alpha]_D^{20}$ −70.5 (c 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J=4.0 Hz, 1H), 7.27 (d, J=4.0 Hz, 1H), 7.19 (d, J=7.6 Hz, 1H), 6.88 (d, J=7.6 Hz, 1H), 4.37 (q, J=7.1 Hz, 1H), 2.37 (q, J=4.4 Hz, 1H), 2.02–2.05 (m, 1H), 1.57–1.67 (m, 3H), 0.80–1.14 (m, 13H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.48, 151.52, 151.13, 141.25, 131.54, 125.55, 71.74, 50.36, 45.29, 34.79, 31.88, 26.04, 24.02, 21.84, 21.23, 16.32. Anal. Calcd for $C_{16}H_{23}NO_2$ (261.17): C, 73.53; H, 8.87; N, 5.36. Found: C, 73.62; H, 8.76; N, 5.48.

4.5. Preparation of (−)-menthol (4)

A 50 mL round bottom flask was charged with $CHCl_3$ (10 mL), picolinate ester **3** (653 mg, 2.5 mmol), methanol (890 μL, 20.8 mmol), and $Cu(OAc)_2$ (230 mg, 12.6 mmol). The reaction mixture was allowed to stir for 6 h at which point it was judged complete by TLC. The reaction mixture was diluted with hexane (10 mL) and washed with disodium EDTA (l0 mL of a 0.1 M solution). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to an oil. Flash chromatography (eluted with hexane then 6:1 hexane/EtOAc) provided the corresponding (−)-menthol (355 mg, 2.28 mmol, 91%) as colorless needles. Mp 42–43 °C; $[\alpha]_D^{20}$ −48.5 (c 2, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38–3.43 (td, J_1=10.4 Hz, J_2=4.2 Hz, 1H), 2.16–2.18 (m, 1H), 1.95–1.98 (m, 1H), 1.59–1.67 (m, 2H), 1.45 (m, 2H), 0.80–1.11 (m, 13H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 71.74, 50.36, 45.29, 34.79, 31.88, 26.04, 23.38, 22.43, 21.23, 16.32. Anal. Calcd for $C_{10}H_{20}O$ (156.15): C, 76.86; H, 12.90. Found: C, 76.69; H, 12.79.

4.6. General procedure for the Mitsunobu reactions

An alcohol (1.0 equiv) was added to a solution of acidic pronucleophile (1.1 equiv) and phosphine reagent (1.1 equiv) in anhydrous CH_2Cl_2 or THF under a N_2 atmosphere at 0 °C. The resulting suspension/solution was treated with azo-reagent (1.1 equiv) and the reaction mixture was continued stirring at room temperature up to completion of the reaction, indicated by TLC monitoring (The reaction mixture was filtered to recover the reduced azodicarboxylate **2** if DNAD was used as the azo-reagent.). The solvent was evaporated and the residue dissolved in cyclohexane. The triphenylphosphane oxide precipitated and was filtered off and then the filtrate evaporated under reduced pressure. The product was purified by column chromatography on silica gel to afford the pure products.

4.6.1. (R)-3-Chloro-1-cyanopropan-2-yl 4-chlorobenzoate (entry 1). Following the general procedure: Flash chromatography eluted with hexane to 1:12 EtOAc/hexane afforded the title compound as a colorless oil (92%). $[\alpha]_D^{20}$ +28.5 (c 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–8.01 (m, 2H), 7.40–7.42 (m, 2H), 4.21 (d, J=3.5 Hz, 1H), 3.65 (d, J=5.2 Hz, 2H), 2.68–2.78 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.78, 140.21, 131.30, 127.61, 126.30, 118.04, 69.35, 47.83, 21.96. Anal. Calcd for $C_{11}H_9Cl_2NO_2$ (257.00): C, 51.19; H, 3.51; N, 5.43. Found: C, 51.12; H, 3.46; N, 5.35.

4.6.2. Allyl 4-chlorobenzoate (entry 2). Following the general procedure: Flash chromatography eluted with hexane to 1:10 EtOAc/hexane afforded the title compound as a colorless oil (95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, J_1=6.7 Hz, J_2=1.8 Hz, 2H), 7.42 (dd, J_1=6.7 Hz, J_2=1.8 Hz, 2H), 6.03 (m, 1H), 5.39–5.43 (dd, J_1=17.2 Hz, J_2=1.5 Hz, 1H), 5.29–5.31 (dd, J_1=10.5 Hz, J_2=1.25 Hz, 1H), 4.82 (dt, J_1=5.7 Hz, J_2=1.4 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.04, 139.62, 134.28, 131.15, 129.23, 128.47, 114.19, 68.62. Anal. Calcd for $C_{10}H_9ClO_2$ (196.03): C, 61.08; H, 4.61. Found: C, 61.16; H, 4.46.

4.6.3. 2-Amino-6-chloro-9-(2-bromoethyl)purine (entry 3). White solid (85%). Mp 182–183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 5.08 (s, 2H), 4.27 (t, J=5.7 Hz, 2H), 3.89 (t, J=5.7 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.04, 155.57, 150.30, 142.72, 122.20, 52.21, 40.18. Anal. Calcd for $C_7H_7Cl_2N_5$ (231.01): C, 36.23; H, 3.04; N, 30.18. Found: C, 36.19; H, 3.09; N, 30.21.

4.6.4. 2-Amino-6-chloro-9-benzylpurine (entry 4). Colorless needles (83%). Mp 212.4–213.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.27–7.36 (m, 5H), 5.32 (s, 2H), 5.04 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.11, 154.98, 151.49, 146.56, 135.98, 130.13, 128.70, 128.04, 120.35, 49.68. Anal. Calcd for $C_{12}H_{10}ClN_5$ (259.06): C, 55.50; H, 3.88; N, 26.97. Found: C, 55.41; H, 3.77; N, 27.11.

4.6.5. 2-[Bis(tert-butoxycarbonyl)amino]-6-chloro-9-[2-(2,2-dimethyl-1,3-dioxan-5-yl)ethyl]purine (entry 5). white solid (93%). Mp>280 °C (dec); IR (KBr) 3117, 2936, 1753, 1694, 1644, 1603, 1567, 1536, 1474, 1426 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H), 4.02 (t, J=7.23 Hz, 2H), 3.79 (dd, $H_{eq.}$ J_1=11.57 Hz, J_2=4.46 Hz, 2H), 3.56 (dd, $H_{ax.}$ J_1=11.57 Hz, J_2=8.77 Hz, 2H), 1.67 (q, J=7.22 Hz, 2H), 1.53–1.61 (m, 1H), 1.47 (s, 18H), 1.39 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 154.34, 151.74, 151.49, 151.09, 146.56, 128.04, 104.79, 81.68, 71.52, 50.76, 33.70, 28.58, 26.20, 25.65; MS (ESI): m/z=512.2 (M+H$^+$), 534.2 (M+Na$^+$), 1045.6 (2M+Na$^+$). Anal. Calcd for $C_{23}H_{34}ClN_5O_6$ (511.22): C, 53.95; H, 6.69; N, 13.68. Found: C, 53.85; H, 6.57; N, 13.73.

4.6.6. 2-[Bis(tert-butoxycarbonyl)amino]-6-chloro-9-isopropylpurine (entry 6). White solid (90%). Mp 229.5–231.8 °C; IR (KBr) 3121, 2955, 1771, 1720, 1648, 1598, 1561, 1536, 1495, 1478,1456 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 4.12–4.27 (m, 1H), 1.71 (d, J=6.2 Hz, 6H), 1.47 (s, 18H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 153.65, 151.92, 151.59, 151.29, 145.61, 128.53, 82.69, 52.73, 28.52, 24.55; MS (ESI): m/z=412.2 (M+H$^+$), 435.2 (M+Na$^+$), 845.5 (2M+Na$^+$). Anal. Calcd for $C_{18}H_{26}ClN_5O_4$ (411.17): C, 52.49; H, 6.36; N, 17.00. Found: C, 52.55; H, 6.27; N, 17.13.

4.6.7. 2-(2-(Benzyloxy)ethyl)isoindoline-1,3-dione (entry 8). Following the general procedure: Flash chromatography eluted with hexane to 1:6 EtOAc/hexane afforded the title compound as a beige solid (92%). Mp 72–73 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36–8.41 (m, 2H), 8.18–8.23 (m, 2H), 7.28–7.43 (m, 5H), 4.53 (s, 2H), 3.70 (t, J=4.5 Hz, 2H), 3.54 (t, J=4.5 Hz, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 166.41, 137.56, 131.56, 130.71, 129.08, 128.80, 127.53, 120.99, 72.92, 71.38, 61.29. Anal. Calcd for $C_{17}H_{15}NO_3$ (281.11): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.44; H, 5.32; N, 4.94.

4.6.8. 2-(Pentan-3-yl)isoindoline-1,3-dione (entry 9). Following the general procedure: Flash chromatography eluted with hexane to 1:9 EtOAc/hexane afforded the title compound as a white solid

(87%). Mp 132.3–134.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.92 (m, 2H), 7.64–7.66 (m, 2H), 3.95–4.02 (m, 1H), 1.88–2.01 (m, 4H), 0.94 (t, J=7.55 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.09, 132.73, 131.36, 123.98, 50.91, 26.48, 11.93. Anal. Calcd for $C_{13}H_{15}NO_2$ (217.11): C, 71.87; H, 6.96; N, 6.45. Found: C, 71.71; H, 6.83; N, 6.41.

4.6.9. 1-Benzyl-1H-imidazole (entry 10). Following the general procedure: Flash chromatography eluted with hexane to 1:6 EtOAc/hexane afforded the title compound as a yellow solid (55%). Mp 72–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.22–7.31 (m, 3H), 7.14 (d, J=6.5 Hz, 2H), 7.06 (s, 1H), 6.94 (s, 1H), 5.02 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 137.32, 136.43, 130.91, 130.45, 129.98, 125.82, 120.18, 51.64. Anal. Calcd for $C_{10}H_{10}N_2$ (158.08): C, 75.92; H, 6.37; N, 17.71. Found: C, 75.84; H, 6.32; N, 17.94.

4.6.10. 2-(Allylthio)benzo[d]thiazole (entry 11). Following the general procedure: Flash chromatography eluted with 1:5 EtOAc/hexane afforded the title compound as a colorless oil (93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (d, J=7.8 Hz, 1H), 7.33–7.36 (m, 1H), 7.28 (d, J=7.8 Hz, 1H), 7.21–7.24 (m, 1H), 6.03 (d, J=6.7 Hz, 1H), 5.41 (q, J=6.7 Hz, 1H), 5.29–5.31 (m, 1H), 4.81–4.83 (m, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 190.27, 141.71, 129.83, 128.30, 127.50, 124.60, 122.09, 117.29, 112.86, 47.05. Anal. Calcd for $C_{10}H_9NS_2$ (207.02): C, 57.93; H, 4.38; N, 6.76. Found: C, 57.89; H, 4.34; N, 6.79.

4.6.11. 2-((1S,2S,5R)-2-Isopropyl-5-methylcyclohexylthio)benzo[d]thiazole (entry 12). Following the general procedure: Flash chromatography eluted with 1:8 EtOAc/hexane afforded the title compound as a colorless oil (88%). $[\alpha]_D^{35}$ +91.5 (c 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J=8.25 Hz, 1H), 7.56 (d, J=7.49 Hz, 1H), 7.23–7.43 (m, 2H), 3.51–3.58 (m, 1H), 2.15–2.17 (m, 1H), 1.95–1.98 (m, 1H), 1.59–1.67 (m, 2H), 1.45 (m, 1H), 1.09–1.11 (m, 1H), 0.86–0.99 (m, 8H), 0.80–0.85 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.09, 154.57, 136.09, 128.04, 123.91, 120.76, 120.04, 50.76, 47.83, 41.30, 35.44, 31.74, 27.22, 26.95, 23.48, 20.70, 20.43. Anal. Calcd for $C_{17}H_{23}NS_2$ (305.13): C, 66.84; H, 7.59; N, 4.58. Found: C, 66.71; H, 7.77; N, 4.49.

4.6.12. 5,5-Dibenzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (entry 13). Flash chromatography eluted with 1:10 EtOAc/hexane afforded the title compound as a white solid (85%). Mp 233–234 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.38 (m, 10H), 3.56 (s, 4H), 1.12 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.13, 137.71, 129.46, 127.60, 125.22, 101.97, 63.92, 47.28, 24.46. Anal. Calcd for $C_{20}H_{20}O_4$ (324.14): C, 74.06; H, 6.21. Found: C, 73.93; H, 6.15.

4.6.13. 5,5-Diallyl-2,2-dimethyl-1,3-dioxane-4,6-dione (entry 14). Flash chromatography eluted with hexane to 1:12 EtOAc/hexane afforded the title compound as colorless oil (94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87–5.97 (m, 2H), 4.92–5.06 (m, 4H), 2.78 (d, J=7.1 Hz, 4H), 1.52 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.01, 140.87, 122.56, 104.13, 64.98, 47.32, 32.07. Anal. Calcd for $C_{12}H_{16}O_4$ (224.10): C, 64.27; H, 7.19. Found: C, 64.19; H, 7.08.

4.6.14. 5-sec-Butyl-2,2-dimethyl-1,3-dioxane-4,6-dione (entry 15). Following the general procedure: Flash chromatography eluted with 1:9 EtOAc/hexane afforded the title compound as white solid (88%). Mp 79.3–81.2 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.38 (d, J=4.1 Hz, 1H), 2.86–2.95 (m, 1H), 1.71 (s, 6H), 1.28–1.36 (m, 2H), 1.02 (d, 3H), 0.82 (t, J=7.45 Hz, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) δ 169.02, 106.37, 56.11, 37.17, 27.52, 24.38, 17.51, 10.90. Anal. Calcd for $C_{10}H_{16}O_4$ (200.10): C, 59.98; H, 8.05. Found: C, 60.09; H, 7.97.

4.6.15. p-Nitrobenzyl phenyl ether (entry 16). Following the general procedure: Flash chromatography eluted with hexane to 1:5 EtOAc/hexane afforded the title compound as a bright yellow solid (90%). Mp 90.2–91.3 °C; ^{1}H NMR (500 MHz, $CDC1_3$) δ 8.00 (d, J=9.1 Hz, 2H), 7.53 (d, J=9.1 Hz, 2H), 7.28 (m, 2H), 7.28 (m, 2H), 6.87–6.96 (m, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.35, 148.48, 147.99, 129.81, 127.70, 124.04, 121.73, 114.71, 71.22. Anal. Calcd for $C_{13}H_{11}NO_3$ (229.07): C, 68.11; H, 4.84; N, 6.11. Found: C, 68.19; H, 4.99; N, 6.02.

4.6.16. 6-Nitro-3,4-dihydro-1H-isochromene (entry 17). Following the general procedure: Flash chromatography eluted with 1:6 EtOAc/hexane afforded the title compound as a white solid (72%). Mp: 84.5–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J=9.1 Hz, 1H), 7.97 (s, 1H), 7.25 (d, J=9.1 Hz, 1H), 4.88 (s, 2H); 4.12 (t, J=6.0 Hz, 2H); 3.08 (t, J=6.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.19, 144.46, 137.88, 127.60, 124.37, 117.68, 71.38, 61.29. Anal. Calcd for $C_9H_9NO_3$ (179.06): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.25; H, 5.13; N, 7.71.

4.6.17. (S)-2-(4-Nitrophenyl)oxirane (entry 18). Following the general procedure: Flash chromatography eluted with hexane to 1:8 EtOAc/hexane afforded the title compound as a light yellow solid (92%). Mp 73.5–75.3 °C; 98% ee; $[\alpha]_D^{25}$ +37.9 (c 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J=8.2 Hz, 2H), 7.38 (d, J=8.2 Hz, 2H), 3.97 (dd, J_1=4.0 Hz, J_2=2.5 Hz, 1H), 3.25 (dd, J_1=5.5 Hz, J_2=3.9 Hz, 1H), 2.69 (dd, J_1=5.5 Hz, J_2=2.5 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 149.18, 144.73, 128.18, 123.43, 61.29, 49.74. Anal. Calcd for $C_8H_7NO_3$ (165.04): C, 58.18; H, 4.27; N, 8.48. Found: C, 58.25; H, 4.35; N, 8.57.

Acknowledgements

We express our appreciation to Sanhe Pharmachem Co, Ltd for offering financial support to us.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.12.036. These data include MOL files and InChIKeys of the most important compounds described in this article.

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26. When 2-amino-6-chloro-purin and 2-chloroethanol were reacted at room temperature under diluted conditions, the coupling product was obtained in less than 35% isolated yield even after running the reaction for 30 h.
27. The 2-amino-6-chloro-purine (1.0 equiv) was added to a solution of alcohol (1.0 equiv) and PPh_3 (1.05 equiv) in anhydrous THF under a N_2 atmosphere. The resulting suspension/solution was treated with azo-reagent (1.05 equiv) and the reaction mixture was then stirred at 70 °C for about 6 h. Then the second portions of alcohol (1.0 equiv), PPh_3 (1.05 equiv), and azo-reagent (1.05 equiv) were added to the reaction mixture sequentially. The mixture was stirred for about another 6 h at the same temperature. The mixture was cooled and the hydrazine precursor was separated directly from the reaction mixture via filtration. Then the mixture was treated with saturated sodium chloride, and extracted with dichloromethane. The combined organic layer was then washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. Flash silica gel chromatography gave the pure product.