Di-2-methoxyethyl Azodicarboxylate (DMEAD): An Inexpensive and Separation-friendly Alternative Reagent for the Mitsunobu Reaction

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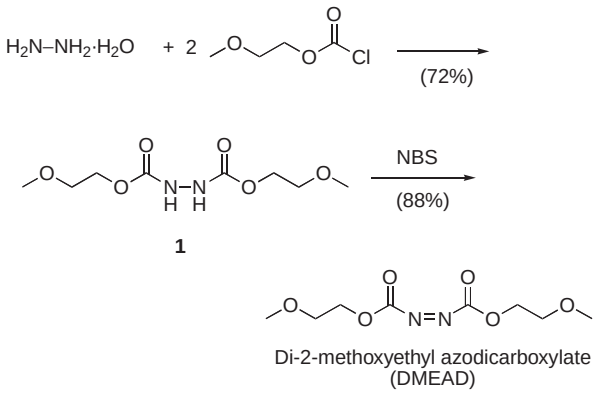
Di-2-methoxyethyl azodicarboxylate (DMEAD) was prepared as an alternative of DEAD or DIAD for the Mitsunobu reaction. Removal of the hydrazinedicarboxylate generated from DMEAD becomes much easier owing to the polar and water-soluble property.

The Mitsunobu reaction is popular in organic synthesis to introduce an acidic nucleophile (carboxylic acid, phenol, imide, etc.) to an alcoholic function under mild conditions.[2] The notable property of this reaction is complete inversion of stereochemistry at the alcoholic function. The original procedure consists of mixing an alcohol and a nucleophile with diethyl azodicarboxylate (DEAD) and triphenylphosphane at ambient temperature.[3] This oxidant–reductant combination to cause dehydration in the Mitsunobu reaction is still widely used although diisopropyl azodicarboxylate (DIAD) is also conveniently employed as a more stable analogue of DEAD. A major drawback of this process is formation of two co-products, hydrazinedicarboxylate and phosphane oxide, which must be removed from the reaction mixture to isolate a target compound. Many efforts have been undertaken to solve this issue: e.g., one of the reagents is supported by polymer or solid to perform the separation by filtration, or is attached to an acidic, basic, or fluorous function to allow the separation by extraction into a basic or acidic aqueous layer or into fluorous solvent. These modifications of the original oxidant or reductant are considered to intend a separation-free or separation-friendly process.[4,5]

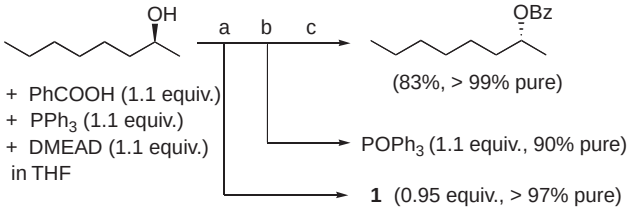
Formation of triphenylphosphane oxide is practically insignificant matter in the separation process due to its facile crystallization in non-polar solvents. In contrast, separation of the other co-product, diethyl or diisopropyl hydrazinedicarboxylate requires highly capable column chromatography to isolate a target compound. One also often faces a problem that several side products of the hydrazinedicarboxylate cannot be removed completely from the product. In situ recycling of DEAD that makes it a catalyst is one of the solutions.[6] Total removal of the hydrazinedicarboxylate and the side-products can be performed by polymerization of norbornene units incorporated in the reagent as to be called impurity annihilation.[7] Very recently, di-4-chlorobenzyl analogue was reported,[8] where the hydrazinedicarboxylate can be removed by the crystallization. We have made another approach to this issue by molecular design to enable the separation of a hydrazinedicarboxylate by extraction with neutral water. The preparation cost and handling were also considered to compete with DEAD and DIAD in the commercial source. Di-2-methoxyethyl azodicarboxylate (DMEAD) is a new reagent, which will be detailed in this report.



Scheme 1. Synthesis of DMEAD.

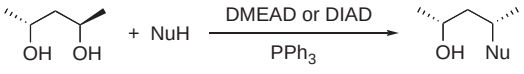
Di-2-dimethoxyethyl hydrazinedicarboxylate (**1**) was prepared by mixing hydrazine hydrate and 2-methoxyethyl chloroformate in ethanol in the presence of sodium carbonate (72% yield after recrystallization, Scheme 1).[9,10] Solubility of **1** is good in chloroform (0.25 g/mL) and ethyl acetate (0.1), but very poor (<0.01) in less polar ether and toluene. In contrast, **1** is well soluble in water (0.55 g/mL). The solubility is better than those of the methyl analogue (0.15) and the ethyl or isopropyl analogue (<0.01). Since **1** is not only a precursor of DMEAD but also a co-product in the Mitsunobu reaction, the observed solubility supports our molecular design intended to separate **1** after the Mitsunobu reaction by extraction with neutral water.

After several trials of oxidation of **1** under different conditions,[9] NBS in toluene[11] was found to result in the best results to give DMEAD. Extraction and single recrystallization (toluene/hexane) of the reaction mixture gave essentially pure DMEAD in 88% yield.[12,13] It should be noted that distillation required for preparation of DEAD and DIAD can be omitted in the case of DMEAD.



Scheme 2. A procedure for the Mitsunobu reaction: (a) Extraction with toluene and water, and aqueous layer was concentrated; (b) Toluene layer was dried, concentrated, suspended in hexane, and filtered; (c) Filtrate was purified by a silica-gel column.

Table 1. Product yields[a] and purities in the reaction of (*R*,*R*)-2,4-pentanediol with varied nucleophiles



Nucleophile (pK_a)	DMEAD		DIAD	
	Yield /%	Purity /%	Yield /%	Purity /%[b]
Benzoic acid (4.20)	74	100	74	72
4-Nitrobenzoic acid (3.44)	79	100	83	64
Phenol (9.95)	84	100	80	100
4-Methoxyphenol (10.20)	82	100	83	77
4-Methoxycarbonylphenol (8.74)	83	100	91	66

[a]The yields are based on the amounts of the nucleophiles. Diastereomeric purities were confirmed to be >98% by NMR. [b]The most impurity was diisopropyl hydrazinedicarboxylate.

Easy isolation of the Mitsunobu product was demonstrated with recovery of both of the co-products by using DMEAD. (*S*)-2-Octanol (2 g) was converted to its benzoate ester with 1.1 equiv. of reagents, benzoic acid, triphenylphosphane, and DMEAD, in THF at room temperature (Scheme 2). After concentration, the mixture was dissolved in toluene and washed with water. The water layer was re-extracted with toluene once more. The aqueous layer contained only **1**, and the purity determined by the ^{1}H NMR after concentration was >98%. The yield of **1** based on the employed amount (1.1 equiv.) of DMEAD was 86%, which is 95% of the theoretical value. The organic layer was dried, concentrated, and suspended in hexane. Triphenylphosphane remained in part was consumed during the process and almost all the phosphane oxide was recovered as crystalline by the filtration. Some side products produced from DMEAD were included in the crystalline part. The filtrate was concentrated and purified by a silica-gel column to give the (*R*)-benzoate product in 83% yield. Required amount of silica gel for the separation was less than a half of that in the usual process with DEAD or DIAD. Inversion of the stereochemistry was confirmed by the optical rotation.

The reactivity of DMEAD in the Mitsunobu reaction was further demonstrated with (*R*,*R*)-2,4-pentanediol, where excess use of the reagents is not allowed to obtain a singly modified product. Table 1 summarizes isolated yields of the product with different nucleophiles by using DMEAD in addition to the same reactions with DIAD as reference.[14] The isolated yields were very similar between DMEAD and DIAD to conclude that they have no difference in the reactivity in the Mitsunobu reaction. The product purity was not always high owing to the difficulty in the chromatographic separation of the hydrazine analogue when DIAD was employed. In contrast, complete separation to give the pure products was achieved in the reactions with DMEAD owing to the high polarity of **1** and its analogues as side products.[15]

In the present study, we have shown that **1** formed as a co-product in the Mitsunobu reaction with DMEAD could easily be removed by simple extraction with neutral water, and that DMEAD can be a separation-friendly alternative of DEAD in the Mitsunobu reaction. The production cost of DMEAD is clearly less than the other alternatives so far reported to solve the separation problem, and the preparation is even easier than that of DEAD or DIAD.

References and Notes

1 Graduate student from Toyo Kasei Kogyo, Co. Ltd.
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10 A solution of hydrazine hydrate (15 g, 300 mmol) in 99.5% ethanol (75 mL) was cooled to 5 °C with an ice–water bath. 2-Methoxyethyl chloroformate (41.52 g, 300 mmol) was added dropwise in keeping the temperature below 20 °C. After 5 min, 2-methoxyethyl chloroformate (41.52 g, 300 mmol) was added simultaneously with a solution of sodium carbonate (31.76 g, 300 mmol) in water (120 mL) below 20 °C. After 1 h, the mixture was concentrated under vacuum, and then treated with acetone (100 mL) to precipitate inorganic salts. Filtration, concentration, and purification by recrystallization with a mixture of acetone (75 mL) and toluene (120 mL) gave 50.91 g of a colorless solid (**1**, 71.9% yield). mp 71.3–76.5 °C; Anal. Calcd for $C_8H_{16}N_2O_6$: C, 40.68; H, 6.83; N, 11.96%. Found: C, 40.88; H, 7.49; N, 12.07%. IR (KBr) 1755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (brs, 2H), 4.27–4.25 (m, 4H), 3.58–3.56 (m, 4H), 3.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.59, 70.40, 64.68, 58.69.
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12 To a solution of **1** (45 g, 190.5 mmol) and pyridine (15.09 g, 1.0 equiv.) in toluene (450 mL) was added *N*-bromosuccinimide (37.31 g, 1.1 equiv.) slowly at room temperature. After vigorous stirring for 2 h, the reaction mixture was washed with water (180 mL × 2), dried over magnesium sulfate, concentrated under vacuum, and then purified by recrystallization with a mixture of toluene (67.5 mL) and hexane (337.5 mL) to give 39.26 g of DMEAD as yellow prisms (88.0% yield). mp 39.9–40.4 °C; Anal. Calcd for $C_8H_{14}N_2O_6$: C, 41.03; H, 6.03; N, 11.96%. Found: C, 41.09; H, 6.65; N, 11.98%. IR (KBr) 1782 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51–4.49 (m, 4H), 3.66–3.63 (m, 4H), 3.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.04, 69.45, 67.85, 58.84.
13 Decomposition temperature observed by DSC for DMEAD was 210 °C, which is somewhat lower than that of DEAD (227 °C by our measurement).
14 A ratio of (*R*,*R*)-2,4-pentanediol, nucleophile, triphenylphosphane, and DMEAD (DIAD) is fixed to be 1/0.85/1/1. All the reactions were carried out at room temperature by addition of one of the azodicarboxylates to a mixture of the other three, except for the case with 4-nitorobenzoic acid that was added at last. The product was isolated by extraction and silica-gel column chromatography.
15 The efficiency of the product isolation depends on the polarity of the hydrazine analogues. The *R f* value on TLC (SiO_2, elution with a mixture of hexane and ethyl acetate = 1/1) was 0.65 for diisopropyl analogue (0.44 for diethyl), while very small 0.08 for **1**.

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