CHEMICALS NOTE

Recently Modified Mitsunobu Reactions

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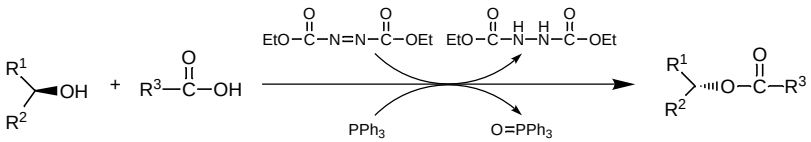
In 1967 O. Mitsunobu reported the generation of the esters in high yield from the reaction of alcohols and carboxylic acids in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) [1]. This reaction represents an epoch-making reaction which involves the activation of the alcoholic hydroxyl group and the subsequent carbon-oxygen bond cleavage caused by the attacking carboxylate anions to give an ester with complete Walden-inversion of the alcohol component. Furthermore, not only the carboxylic acids as the nucleophilic component but the imide or thiol can also be utilized and the reactions proceed under mild conditions. The above reaction constitutes one of the most important organic reactions and is called “Mitsunobu Reaction” as a token of respect for its developer [2].



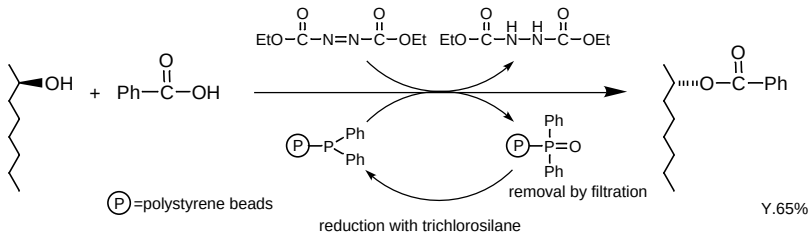
The Mitsunobu reaction has found widespread use in many fields because of its high reliability and extensive applicability. For example, when Chem.abstr. is traced by the keyword "Mitsunobu" from 1967 up to today, one encounters about 1,000 related reports, indicating the high utilization of this reaction.

However, the generation of phosphine oxide and hydrazinedicarboxylate as by-products often prevents the desired product from being isolated. Furthermore, the p*K*a of the usable acid component must be below 13, preferably below 11. Because the Mitsunobu reaction has demonstrated a very excellent reactive ability, efforts have been made toward widening the utilization scope.

1. Removal of By-products

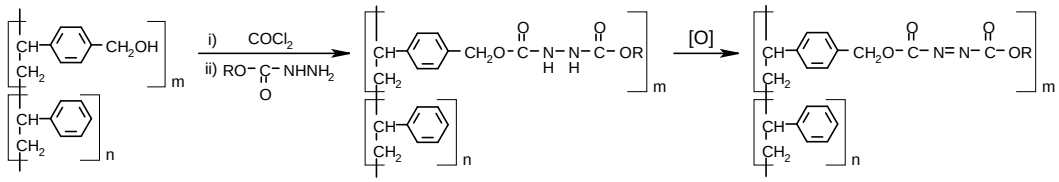
The Mitsunobe reaction is a condensation-dehydration reaction with loss of a water molecule from alcohols and carboxylic acids. This is a result of the strong affinity for oxygen by TPP and for hydrogen by DEAD. This constitutes a simultaneous redox reaction in which TPP is oxidized to an oxide and with DEAD being reduced to hydrazinedicarboxylate. Accordingly, one cannot avoid by-products, phosphine oxide and hydrazinecarboxylate, which are generated. Moreover, these by-products often prevent the desired products from being further isolated.

R.A. Amos and co-workers [3] employed polystyryldiphenylphosphine which constitutes TPP anchored to polystyrene resin in the Mitunobe reaction. In this system, TPP, in excess, and the resulting oxide are anchored to the polystyrene resin, and they can be easily removed by means of filtration. The resulting oxide can be reduced by trichlorosilane to TPP and reused again. The chiral alcohol, 2-octanol, reacts with benzoic acid with complete Walden-inversion to give the corresponding ester, thus, demonstrating that the characteristics of the Mitsunobu reaction are preserved.

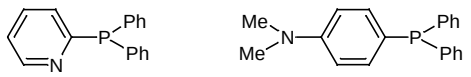


This methodology can also be applied to combinatorial chemistry. For example, A.R. Tunoori and co-workers[4] have configured a library of the aryl alkyl ethers from phenols and alcohols by means of liquid phase synthesis using polystyryldiphenylphosphine.

Similarly, an attempt to anchor dialkyl azodicarboxylate to a resin was also conducted. L.D. Arnold and co-workers [5] reacted hydroxymethylpolystyrene first with phosgene, and second with a carbazilic ester, followed by oxidation to synthesize azodicarboxylate. This resin affords good results in combination with TPP.

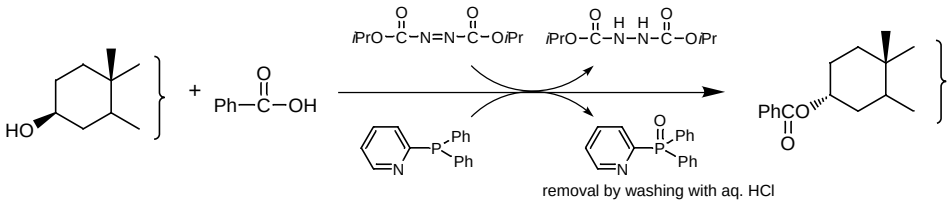


A method to remove the unreacted phosphine and the by-product, phosphine oxide, has also been considered. A basic functional group was introduced into TPP and upon completion of the reaction, it was washed by acid. Diphenyl(2-pyridyl)phosphine **1** and (4-dimethylaminophenyl)diphenylphosphine **2** were developed to contain a basic amine functional group attached to the phosphine group.



1 **2**

D.Camp and co-workers [6] have reported that in the Mitsunobu reaction using diphenyl(2-pyridyl)phosphine **1**, cholestane 3α-ester can be obtained in 80% yield from cholestane-3β-ol and benzoic acid. In this instance, they have removed the by-product, phosphine oxide by washing the organic layer with 2M hydrochloric acid upon completion of the reaction. Furthermore, the reaction has been followed by ^{31}P n.m.r. which showed that the basic component has no effect on the reaction rate nor reaction mechanism.



M.von Itzstein and co-workers [7] have employed (4-dimethylaminophenyl)diphenylphosphine **2** as a replacement for TPP. This phosphine has a basic dimethylamino group. For this reason, the accompanying oxide by-product can be removed by washing with dilute hydrochloric acid. They have also observed the reaction via ^{31}P.n.m.r. and reported the results of their investigation.

2. Application toward Weak Acids

The mechanism of the Mitsunobu reaction is considered as shown in Figure 1. A betaine **3** is formed from TPP and DEAD. This betaine reacts with an alcohol to yield an anion **4** and a phosphonium **5**. An anion **7** is generated by proton abstraction by the anion **4** from acid **6**. This anion **7** attacks the phosphonium **5** to give the desired Walden invertion product **8**. If the acidity of the acid **6** is low and the p*K*a value is over **11**, the proton abstraction by the anion **4** from the acid **6** is inhibited and the anion **4** attacks the phosphonium **5** to yield an undesired product **9**.

T. Tsunoda and co-workers [8] have carried out an additional investigation of DEAD and TPP in order to apply the Mitsunobu reaction to weak acids with high pKa value. This investigation constitutes a new system by converting the ethoxy terminal of DEAD to the amino group in order to increase the basicity of anion **4**. Sterically bulky groups

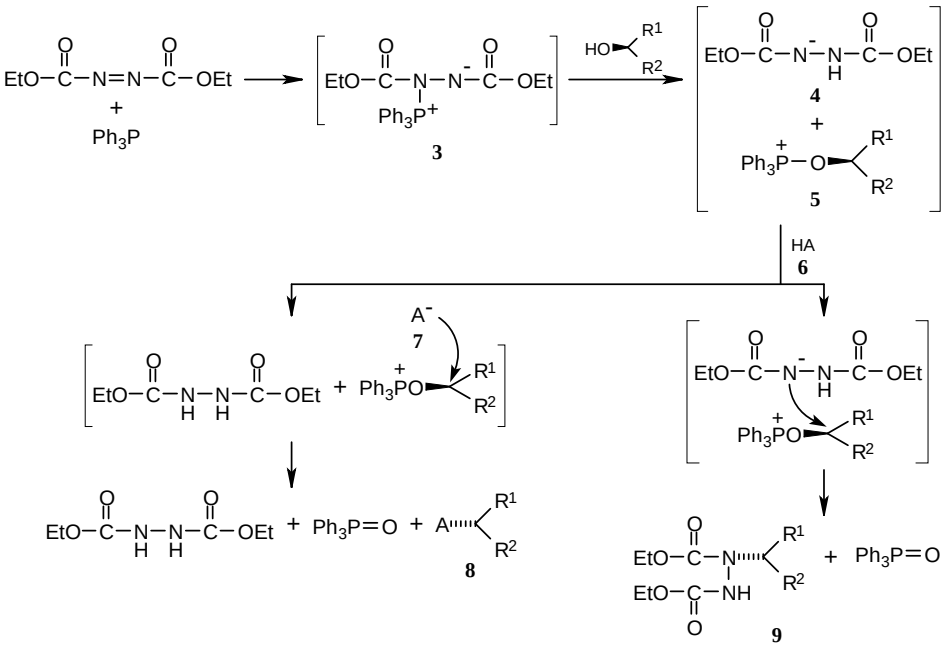
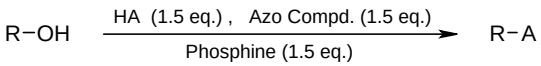


Fig. 1 Mechanism of Mitsunobu reaction

were introduced on the amino group in order to inhibit the increased nucleophilic substitution activity as a result of the increased basicity. This system is able to easily abstract the proton from **6**. To achieve this, they utilized azo compounds such as 1,1′-(azodicarbonyl)dipiperidine **10** and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide **11** in combination with tri-*n*-butylphosphine (TBP).

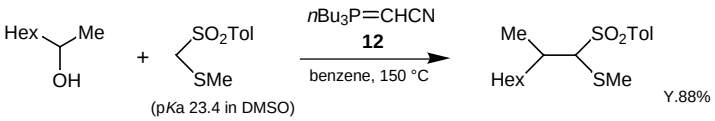
In the systems of 1,1′-(azodicarbonyl)dipiperidine **10** and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide **11**, and TBP as shown in Table **1**, the Mitsunobu reaction proceeds in high yields in spite of the amide having p*K*a value higher than **11**. Accordingly, the method developed by Tsunoda and co-workers attracts a great deal of attention as a method to moderate the limitation of p*K*a and extend the scope in the application of the Mitsunobu reaction.



HA	R−OH	DEAD−TPP	**10**−TBP	**11**−TBP
$CF_3CONHCH_2Ph$ (p*K*a 13.6)	$PhCH_2OH$	3	53	86
		—	56	78
$TsNHMe$ (p*K*a 11.7)	$PhCH_2OH$	65	86	99
		51	99	96

Table 1. Mitsunobu alkylation with some azo compounds (% Yield of RA)

They have further investigated the use of cyanomethylenetri-*n*-butylphosphorane **12** in the Mitsunobu reaction[10]. With cyanomethylenetri-*n*-butylphosphorane **12**, acid components having high p*K*a values can be utilized and the cyanomethylenetri-*n*-butylphosphorane **12** alone can achieve the functions of both DEAD and TPP.



The isolation of the desired product can be readily performed by employing a combination of DEAD anchored to the resin and phosphine **1**,**2** having basic functional group, or that of TPP anchored to a resin and DEAD. The methods developed by Tsunoda and co-workers to use 1,1′-(azodicarbonyl)dipiperidine **10**-TBP, *N*,*N*,*N*′,*N*′-Tetramethylazodicarboxamide **11**-TBP or cyanomethylenetri-*n*-butylphosphorane moderate the limitation of p*K*a and extend the scope of the Mitsunobu reaction beyond the conventional DEAD-TPP system, thus further enhancing the usefulness of the Mitsunobu reaction. Because of its excellent reactivity, cyanomethylenetri-*n*-butylphosphorane **12** especially is expected to be useful in applications for the synthesis of physiologically active compounds.

References

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NEW MITSUNOBU REAGENT / TSUNODA REAGENT

C1500	Cyanomethylenetri-*n*-butylphosphorane		1g JPYen 12,500

PHOSPHINES

D2411	Dicyclohexylphenylphosphine		5g JPYen 12,300
D1019	Diethylphenylphosphine		5ml JPYen 21,400
D2478	(4-Dimethylaminophenyl)diphenylphosphine	5g JPYen 17,400	1g JPYen 5,950
D2471	Diphenyl-2-pyridylphosphine		1g JPYen 9,300
T0361	Tri-*n*-butylphosphine	500ml JPYen 27,700	25ml JPYen 2,000
T1165	Tricyclohexylphosphine (15% in Toluene)	500ml JPYen 50,000	25ml JPYen 5,950
T1005	Tri-*n*-hexylphosphine	500ml JPYen 45,600	25ml JPYen 4,800
T0503	Tri-*n*-octylphosphine	500ml JPYen 50,000	25ml JPYen 4,300
T0519	Triphenylphosphine	500g JPYen 7,650	25g JPYen 1,200

AZODICARBOXYLIC ESTERS / AMIDES

A0776	Dibenzyl Azodiformate (40% in Dichloromethane)		25g JPYen 8,400
A0705	Diethyl Azodiformate (40% in Toluene)	250g JPYen 25,500	25g JPYen 5,000
A1246	Diisopropyl Azodiformate (40% in Toluene)	250g JPYen 13,800	25g JPYen 2,950
A0882	Dimethyl Azodiformate (40% in Toluene)		25g JPYen 9,300
A1051	1,1′-(Azodicarbonyl)dipiperidine		5g JPYen 7,950
A1458	*N*,*N*,*N*′,*N*′-Tetramethylazodicarboxamide		1g JPYen 7,650

Azodicarboxylic esters are susceptible to explosion when subjected to heat, impact and friction. In order to alleviate the risk, azodicarboxylic esters are available as a 40% solution in organic solvents. We recommend to use them in the solution as received. Under compelling circumstances requiring heating operations such as compression, distillation or drying, please carry out experiments in the required minimum amount only and in addition, to use fully-equipped safety measures such as a safety shield.

Org. Synth., **72**, 273 (1995); *ibid.*, Coll. Vol. 3, 375 (1955); *ibid.*, Coll. Vol. 4, 411 (1963).