# Preparation of (Cyanomethylene)tributylphosphorane: A New Mitsunobu-Type Reagent

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**(Cyanomethylene)tributylphosphorane (CMBP), which promoted the alkylation of various nucleophiles (HA) with alcohols (ROH) to give RA (Mitsunobu-type reaction), was prepared in two steps starting from chloroacetonitrile.**

**Key words** Mitsunobu reaction; (cyanomethylene)tributylphosphorane (CMBP); ylide

The Mitsunobu reaction is a well-established fundamental reaction and has been applied widely in organic synthesis. In the Mitsunobu reaction, a unique dehydration occurs between alcohols and various Brønsted-Lowry acids (HA) utilizing the combination of diethyl azodicarboxylate and triphenylphosphine (Fig. 1).[1,2]

However, the reaction has a serious limitation (so-called the restriction of p$K_a$); the acidic hydrogen in HA has to have p$K_a$ of less than 11 for the reaction to proceed satisfactorily. If HA has p$K_a$ of higher than 11, the yield of RA is considerably lower, and with HA having p$K_a$ of higher than 13, the desired reaction does not occur. In order to overcome the restriction of p$K_a$ and expand the versatility of the original Mitsunobu reaction,[3—7] stabilized trialkylphosphoranes such as (cyanomethylene)tributylphosphorane (CMBP)[8] and (cyanomethylene)trimethylphosphorane (CMMP)[9,10] have been developed to replace the DEAD-TPP system.

It was noted that CMBP was the only reagent that can be effectively applied to the Mitsunobu reaction of *N*-nonsubstituted sulfonamides such as *p*-toluenesulfonamide (**1**) (Fig. 2). The sulfonamide was unfortunately converted to phosphine sulfonimide **3** without any desired *N*-alkylated product **2** when using the traditional reagent DEAD-TPP or new reagents (TMAD-PBu$_3$,[7] CMMP, *etc.*).[11]

Thus, CMBP can not only promote the reaction of nucleophiles with p$K_a$ of higher than 13, but can be also utilized for synthesis of primary amines *via* Mitsunobu alkylation of sulfonamides.

CMBP is now commercially available. However, many inquiries about the stability and handling of CMBP have been received. The reason is that we have not reported the procedure for the preparation of CMBP in detail, yet. In this paper, we would like to describe the experimental details for the preparation of this reagent and some important findings related to the handling. Furthermore, it is important to establish a facile procedure for CMBP preparation without further purification, especially when the Mitsunobu reaction is to be carried out on a large scale.

**Preparation of CMBP *via* (Cyanomethyl)tributylphosphonium Chloride (4)** CMBP could be synthesized in two steps starting from chloroacetonitrile (Fig. 3). As the first step, tributylphosphine reacted with chloroacetonitrile in nitromethane to afford phosphonium salts **4** as colorless needles in 91% yield. The process was highly exothermic, and the addition rate of chloroacetonitrile was adjusted to be maintained at below 50 °C. Since the salts **4** were hygroscopic, quick operation and storage in a desiccator were needed to prevent moisture from condensing on the product. The salts **4** were converted to CMBP by treatment with 0.95 equivalent of *n*-butyllithium in hexane at 0 °C. It is important to note that the yield of CMBP decreased dramatically, when excess base (>1.0 eq) was used. So, a fresh *n*-butyllithium solution, of which the concentration is determined by titration, should be used.

Furthermore, the Mitsunobu reaction could not unfortunately proceed effectively with in situ generated CMBP, probably because of concomitant lithium chloride, even when THF or toluene was used as a reaction solvent for the preparation of CMBP. Therefore, salt-free CMBP was obtained by Kugelrohr distillation (0.35 mmHg, 120—220 °C).

For the preparation of CMBP on a large scale, a more vacuum-tight distillation apparatus was needed to prevent the decomposition of CMBP to tributylphosphine oxide during the distillation. So, a method for the preparation of CMBP without distillation was developed. After the treatment of the salts **4** with *n*-butyllithium, the transferred clear and pale yellow supernatant layer of the reaction mixture was concentrated under vacuum (1 mmHg) as quickly as possible to give

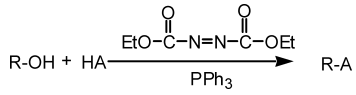


Fig. 1

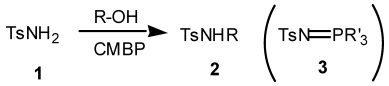


Fig. 2

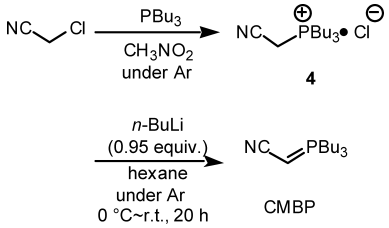


Fig. 3

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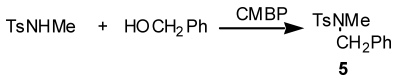


Fig. 4

crude CMBP as a yellow-brown oil. Since most of lithium chloride was removed by this operation, the residue was diluted with toluene (or other solvents) to afford a solution of partially purified CMBP, which could be employed for the Mitsunobu reaction without additional operations. A reliable estimate of the concentration of the CMBP toluene solution was given by the reaction of benzyl alcohol with *N*-methyl-*p*-toluenesulfonamide (Fig. 4).

**Handling and Storage of CMBP** Since CMBP was very sensitive to air and moisture, all procedures for the purification of the product should be carried out under a dry argon atmosphere, even for NMR, IR, and Mass spectra. The distilled neat CMBP could be stored in a brown sealed ampule for months at 10 °C under an argon atmosphere without decomposition. CMBP could also be stored as a solution in dry toluene or THF in a brown sealed ampule for months.

## Experimental

**General** Hexane, benzene and toluene were distilled from calcium hydride under an argon atmosphere before use. $^{31}$P-NMR spectra were recorded on a Varian Unity-600 (121.5 MHz) with 85% $H_3PO_4$ as an external standard[12] in $CDCl_3$.

**(Cyanomethyl)tributylphosphonium Chloride (4)** A 3-l, two-necked, round-bottomed flask was equipped with a magnetic stirring bar, a rubber septum, and a reflux condenser connected to an argon-filled balloon. The system was flame-dried, flushed with argon, and charged with tributylphosphine (332 ml, 1.32 mol) and nitromethane (1.5 l) using syringes through the rubber septum. To the stirred mixture was added dropwise neat chloroacetonitrile (84 ml, 1.33 mol) over a 1 h period *via* a syringe changing to a yellow homogeneous solution. The process was highly exothermic, and the addition rate of chloroacetonitrile was adjusted to maintain the mixture at below 50 °C. The resulting mixture was stirred for 16 h at room temperature, then concentrated on a rotary evaporator. The residual yellow oil solidified when a small amount of AcOEt was added. The solid was recrystallized by dissolution in boiling AcOEt–$CHCl_3$ (2500 ml—30 ml) and cooling to room temperature to afford 315.9 g (86%) of **4** as colorless needles. The mother liquor was then concentrated and recrystallized again to afford an additional 19.0 g (5%) of the material.

The physical properties were as follows: mp 98—100 °C. IR (KBr) cm$^{-1}$: 2251 (CN). $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.00 (t, 9H, $J$=7.5 Hz), 1.47—1.77 (m, 12H), 2.58—2.74 (m, 6H), 5.27 (d, 2H, $J$=15.9 Hz). $^{13}$C-NMR (150 MHz, $CDCl_3$) $\delta$: 11.35 (d, $J$=49.5 Hz), 13.25 (s), 19.12 (d, $J$=45.0 Hz), 23.43 (d, $J$=4.5 Hz), 23.83 (d, $J$=16.4 Hz), 112.29 (d, $J$=8.9 Hz). $^{31}$P-NMR (121.5 MHz, $CDCl_3$) $\delta$: 36.17 (s). CI-MS, *m*/*z* (rel intensity) 242 (100%, $M^+-Cl^-$). High resolution mass spectrum, Calcd for $C_{14}H_{29}NP$, 242.2038. Found 242.2033.

**(Cyanomethylene)tributylphosphorane (CMBP)** A 300-ml, three-necked, round-bottomed flask was equipped with a magnetic stirring bar, a three-way stopcock as a gas inlet connected to a vacuum/argon line, and a rubber septum for each of the remaining inlets. The system was flame-dried, flushed with argon, and charged with a suspension of (cyanomethyl)tributylphosphonium chloride (**4**) (10.0 g, 36.2 mmol) in dry hexane (100 ml). To the cooled (0 °C) and stirred suspension was added dropwise *n*-butyllithium (23 ml, 34.5 mmol, 1.5 M in hexane) over a 10 min period *via* a syringe through one of the rubber septa. After the addition was completed, the resulting mixture was allowed to warm to room temperature and was stirred for 20 h. During the stirring, an insoluble pale yellow viscous oil and a precipitate of lithium chloride was formed. To the resulting mixture was added 50 ml of dry benzene to dissolve the viscous oil, which was crude CMBP. After sonication (30 min) followed by stirring (1 h), the mixture was kept at room temperature without stirring for 3 h to solidify the lithium chloride cake on the bottom of the flask. The clear and pale yellow supernatant layer was transferred to another three-necked flask (equipped with a magnetic stirring bar, a three-way stopcock as a gas inlet connected to a vacuum/argon line, and a rubber septum for each of the remaining inlets) by decantation *via* a stainless steel cannula under positive argon pressure through one of the rubber septa. The solvent in the transferred supernatant was removed under vacuum (1 mmHg) as quickly as possible to give crude CMBP as a yellowish-brown oil. The residue was purified by bulb-to-bulb distillation (0.35 mmHg, 120—220 °C) to give 8.37 g of pure CMBP as a light yellowish-brown oil in 95% yield.

The physical properties were as follows: IR (neat under argon) cm$^{-1}$: 2137 (CN). $^1$H-NMR (300 MHz, $CDCl_3$ under argon) $\delta$: 0.79 (br d, 1H, $J$=5.1 Hz), 0.96 (t, 9H, $J$=7.2 Hz), 1.36—1.60 (m, 12H), 1.69—1.81 (m, 6H). $^{13}$C-NMR (150 MHz, $CDCl_3$ under argon) $\delta$: −7.21 (d, $J$=123.0 Hz), 13.36 (s), 23.64 (d, $J$=4.4 Hz), 23.82 (d, $J$=56.1 Hz), 23.82 (d, $J$=14.3 Hz), 128.55 (d, $J$=7.8 Hz). $^{31}$P-NMR (121.5 MHz, $CDCl_3$ under argon) $\delta$: 26.50 (s). CI-MS, *m*/*z* (rel intensity) 242 (100%, $M^+$+1). High resolution mass spectrum, Calcd for $C_{14}H_{29}NP$, 242.2038. Found 242.2047.

**Toluene Solution of CMBP for Large Scale Reaction** The salts **4** (30.0 g, 108 mmol) were treated with *n*-butyllithium following the procedure described above. The clear and pale yellow supernatant layer was transferred to another three-necked flask and the solvent was removed. Then, the residue was dissolved with toluene (100 ml) to afford a solution of CMBP. The concentration of CMBP in the solution was estimated as follows. To a solution of benzyl alcohol (1.5 mmol) and *N*-methyl-*p*-toluenesulfonamide (1.5 mmol) in dry toluene (4 ml) was added 1 ml of the CMBP solution under an argon atmosphere at room temperature. The resulting mixture was stirred at 100 °C for 24 h, and evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt, 10/1—5/1, v/v) to yield *N*-benzyl-*N*-methyl-*p*-toluenesulfonamide (**5**) as a colorless solid (209 mg, 0.76 mmol). The reaction gave 0.93 mmol of **5**, when using distilled neat CMBP (1.0 mmol) or a solution of distilled CMBP (1.0 M in toluene, 1.0 ml). Thus, a solution of CMBP without further purification gave lower yield, probably because of a small amount of lithium chloride, which could not be removed. However, this result suggested that the concentration of the solution was at least up to 0.76 M.

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12) $^{31}$P-NMR spectra Data of CMMP salt and CMMP reported in ref. 10 should be corrected as follows: $^{31}$P-NMR of CMMP salt (121.5 MHz, DMSO-$d_6$) $\delta$: 33.52 (s), $^{31}$P-NMR of CMMP (121.5 MHz, $CDCl_3$ under argon) $\delta$: 13.16 (s).