Preparation of (Cyanomethylene)trimethylphosphorane as a New Mitsunobu-Type Reagent

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(Cyanomethylene)trimethylphosphorane (CMMP) mediates Mitsunobu-type reactions, which are a versatile method for the alkylation of various nucleophiles (HA) with alcohols (ROH) to give RA. CMMP is quite effective for the reaction of carbon nucleophiles whose pK_a value are higher than 13. CMMP, which is very sensitive to air and moisture, was synthesized in two steps starting from chloroacetonitrile.

Key words Mitsunobu reaction; (cyanomethylene)trimethylphosphorane (CMMP); ylide; azo compound

The Mitsunobu reaction is a very versatile method for the alkylation of various nucleophiles (HA) with alcohols (ROH) to give RA, utilizing the redox system of diethyl azodicarboxylate (DEAD)–triphenylphosphine (TPP) (Fig. 1).[1,2]

Without any prerequisite activation of the alcohol, it is a unique alkylation reaction and widely applied to various phases of organic synthesis. However, the reaction has a serious limitation; the acidic hydrogen in HA has to have pK_a lower than 11 for the reaction to proceed satisfactorily. If HA has a pK_a higher than 11, the yield of RA is considerably lower, and with HA having a pK_a higher than 13, the desired reaction does not occur. In order to overcome these drawbacks and expand the versatility of the original Mitsunobu reaction, stabilized trialkylphosphoranes such as (cyanomethylene)tributylphosphorane (CMBP)[3] and (cyano-methylene)trimethylphosphorane (CMMP)[4] have been developed to replace the DEAD–TPP system.

These new reagents were designed based on the structural similarity between the ylide **2** and the betaine **1** generated as an important intermediate in the Mitsunobu reaction (Fig. 2). The ylide **2**, which is another resonance form of trialkylphosphorane, was expected to behave similarly with **1** towards a mixture of ROH and HA to yield RA along with the by-products, trialkylphosphine oxide and acetonitrile (Fig. 3).

In fact, the trialkylphosphoranes, especially CMMP, mediate the Mitsunobu-type reactions of various kind of nucleophiles (Fig. 4) with pK_a of 11—23, such as *N*-methyltosylamide (**3**, pK_a 11.7),[5,6] (cyanomethyl)phenylsulfone (**4**, pK_a 12.0 in DMSO[7]),[5,6] (methylthiomethyl)tolylsulfone (**5**, pK_a 23.4 in DMSO[8]),[5,6] benzyl phenyl sulfone (**6a**, pK_a 23.4 in DMSO[9]),[10] 3-[(phenylsulfonyl)methyl]pyridine (**6b**, pK_a 16.7 in DMSO[9])[10] and geranyl phenyl sulfone (**7**, pK_a 22.5 in DMSO[9]).[11]

The useful attributes of the new Mitsunobu reaction are as follows. 1) These reactions with secondary alcohols proceed with the complete Walden inversion of the stereochemistry at the carbinyl carbon. 2) The reaction of the DEAD–TPP redox system (the traditional Mitsunobu reaction) is not normally effective at higher temperature, whereas the reaction of CMBP and CMMP even at higher temperature can be carried out satisfactorily, because they are quite thermally stable although very sensitive to air and moisture. Furthermore, 3) in the traditional Mitsunobu reaction, one problem is the laborious purification of the product from dihydro-DEAD and triphenylphosphine oxide, whereas the use of the phosphoranes leads to an easy workup. Acetonitrile produced in place of dihydro-DEAD can be easily evaporated, and the removal of tributyl- or trimethylphosphine oxide can be attained by SiO_2 column chromatography because of its high polarity. As an alternative workup for the reaction with CMMP, aqueous treatment of the reaction mixture is also quite effective because of the good aqueous solubility of trimethylphosphine oxide.

Thus, the very high reactivity observed for the bond formation of C–N, C–C, and others[12,13] renders these reagents and these procedures highly valuable and competitive from a synthetic point of view. Furthermore, it is a new substantial finding that the reagents can behave not only as a Wittig reagent[14] but also as a Mitsunobu-type reagent.[4]

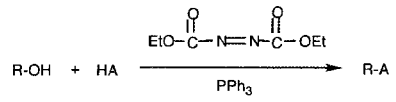

Fig. 1. Mitsunobu Reaction

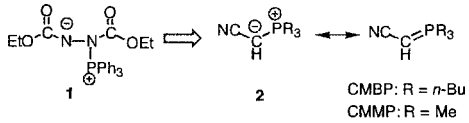

Fig. 2. New Reagents

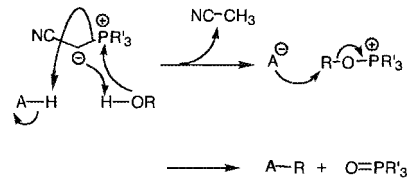

Fig. 3. Reaction Mechanism

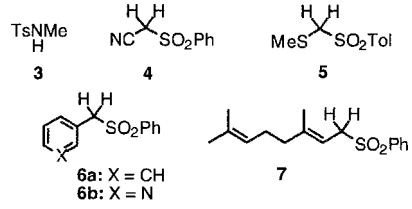

Fig. 4. Nitrogen and Carbon Nucleophiles

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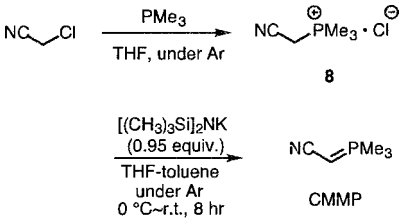

Fig. 5. Preparation of CMMP

Now, CMBP is commercially available, whereas CMMP is not, although the latter is more reactive than the former. Furthermore, many inquiries about the stability and handling of CMMP have been received. The reason is that we did not report the procedure for the preparation of CMMP in detail, yet. In this paper, we would like to describe the experimental details for the preparation of this reagent and some important findings for the handling.

Preparation of CMMP *via* (Cyanomethyl)trimethylphosphonium Chloride (8) CMMP could be synthesized in two steps starting from chloroacetonitrile (Fig. 5). As the first step, trimethylphosphine reacted with chloroacetonitrile below 40 °C in tetrahydrofuran (THF) to afford phosphonium salts **8** as colorless needles in 81% yield. Since the salts **8** were hygroscopic, quick operations and storage in a desiccator were needed to prevent moisture from condensing on the product.

The salts **8** were converted to CMMP by the treatment with 0.95 equivalent of potassium hexamethyldisilylamide in a mixture of THF and toluene. It is important to note that the yield of CMMP decreased dramatically, when excess base (>1.0 eq) was used. Furthermore, use of the salts **8**, which were crumbled well by stirring with the magnetic stirring bar, gave better results for the reaction with the base.

Handling and Storage of CMMP Since CMMP 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. CMMP could be stored in a screw-top vial with a rubber septum for months at 10 °C under an argon atmosphere without decomposition. The vial was wrapped with aluminum foil to protect from light by way of caution. Reweighing the product should be avoided even in a glove bag maintained under an argon atmosphere, because of its sensitivity to air and moisture. Thus, CMMP stored in a vial should be used in one portion for the Mitsunobu-type reaction. CMMP could also be stored as a solution in dry THF (about 1 M, 4 ml) in a brown sealed ampule for months at 10 °C under an argon atmosphere without decomposition. Since CMMP precipitated at low temperature, the ampule was warmed slightly to completely dissolve the precipitate prior to use for Mitsunobu-type reaction. A portion of the solution in one ampule could be used three times (after storage of 3, 6 d, and 3 months) after the first use for the Mitsunobu-type reactions with no decrease in yield.

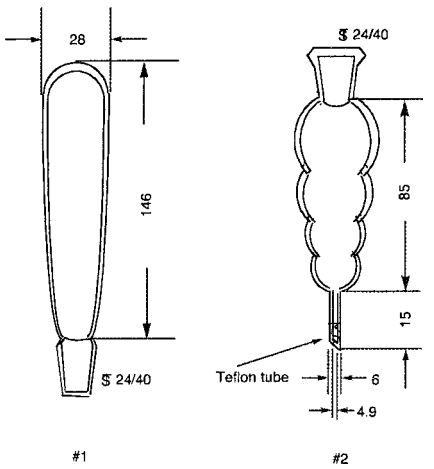

Fig. 6. Glassware

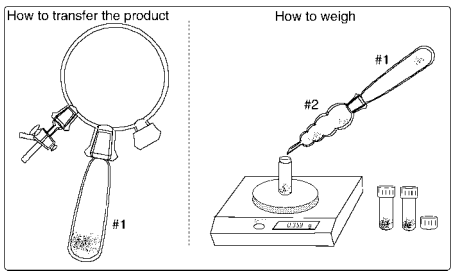

Fig. 7. Operation in an Argon Glove Bag

Experimental

General A THF solution of trimethylphosphine (1.0 M) was purchased from Aldrich Chemical Company, Inc. Benzene was distilled from calcium hydride under an argon atmosphere before use. THF was distilled from benzophenone ketyl under an argon atmosphere prior to use.

(Cyanomethyl)trimethylphosphonium Chloride (8) A 200-ml, 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 a THF solution of trimethylphosphine (1.0 M, 100 ml) using a syringe through the rubber septum. To the stirred solution was added dropwise neat chloroacetonitrile (7.6 ml, 0.12 mol) over a 7 min period *via* a syringe resulting in the formation of **8** as a white precipitate. During the addition the reaction temperature was maintained at *ca.* 40 °C by cooling (ice and water) the exothermic reaction. The resulting mixture was stirred for 12 h at room temperature, then filtered by suction through a sintered glass funnel. The cake was washed with dry benzene (50 ml×2), then dried under reduced pressure over phosphorus pentoxide (P_2O_5) (20 °C, <5 mm) for 3 h. The solid was recrystallized by dissolution in boiling 2-propanol (400 ml) and cooling to room temperature to afford 12.4 g (81%) of **8** as colorless needles. The mother liquor was then concentrated and recrystallized from 2-propanol (230 ml) to afford an additional 1.12 g (7%) of the material. The physical properties were as follows: mp 208—253 °C (decomp.); IR (KBr) cm^{-1}: 2251 (CN); ^{1}H-NMR (300 MHz, DMSO-d_6, 10 mg/ml)[15]: δ: 2.14 (d, 9H, J=15.3 Hz), 4.48 (d, 2H, J=16.8 Hz); ^{1}H-NMR (300 MHz, DMSO-d_6, 20 mg/ml): δ: 2.08 (d, 9H, J=15.3 Hz), 4.23 (d, 2H, J=16.8 Hz); ^{13}C-NMR (75.5 MHz, DMSO-d_6, 52 mg/ml): δ: 7.57 (d, J=53.5 Hz), 14.1 (d, J=53.0 Hz), 113.1 (d, J=9.2 Hz); ^{31}P-NMR (121.5 MHz, DMSO-d_6, 52 mg/ml): δ: 174.7 (s); CI-MS, m/z (rel intensity) 116 (100%, M^+-Cl^-). High resolution mass spectrum, Calcd for $C_5H_{11}NP$, 116.0629. Found 116.0638.

CMMP A 500-ml, three-necked, pear-shaped, flat-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)trimethylphosphonium chloride (10.2 g, 67.5 mmol) in dry THF (330 ml). To the cooled (0 °C) and stirred suspension was added dropwise potassium hexamethyldisilylamide (128 ml, 64.0 mmol, 0.5 M in toluene) over a 25 min period *via* a syringe through one of rubber septa. With the addition, the undissolved phosphonium salt dissolved and a white precipitate of potassium chloride was formed. After the addition the resulting mixture was allowed to warm to room temperature and was stirred for 1.5 h, then the mixture was kept at room temperature without stirring for 6 h to solidify the potassium chloride cake on the bottom of the flask. The clear and yellow-orange 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 rubber septa. The solvent and hexamethyldisilylamine in the transferred supernatant were removed under vacuum (1 mmHg) as quickly as possible to give crude CMMP as a light yellow-pink crystalline solid. To the flask 26 ml of dry benzene was added to dissolve the crude product at 42 °C. The solution was cooled to room temperature and then aged for 3 h at that temperature to afford crystals of the product. The supernatant layer was removed by decantation *via* a stainless steel cannula under positive argon pressure through the rubber septum. A small amount of solvent in the crystalline residue was removed under vacuum (1 mmHg) through the three-way stopcock. The flask containing the crystalline CMMP which was crumbled well by the stirring of the magnetic stirring bar was put into an argon glove bag in which there were a balance, screw-top vials with rubber septa, and glassware equipment like #1 and #2 (Fig. 6). One of two septa was replaced with glassware #1, and then the flask was turned to transfer the product into the glassware #1. The glassware #2 was connected to #1, and then the product was weighed in the screw-top vial (Fig. 7). With these operations, 6.48 g (83%) of pure CMMP was obtained as light yellow-pink fine granules. The physical properties were as follows: mp 57—62 °C (in a sealed capillary). IR ($CHCl_3$ under Argon) cm^{-1}: 2135 (CN); ^{1}H-NMR (200 MHz, $CDCl_3$ under Argon): δ: 1.03 (s, 1H), 1.64 (d, 9H, J=12.8 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$ under Argon): δ: −0.86 (d, J=127 Hz), 14.6 (d, J=61.6 Hz), 127.6 (d, J=7.47 Hz); ^{31}P-NMR (121.5 MHz, $CDCl_3$ under Argon): δ: 154.7 (s); CI-MS (inlet; GC), *m*/*z* (rel. intensity) 116 (100%, M^++1). High resolution mass spectrum, Calcd for $C_5H_{11}NP$, 116.0629. Found 116.0632.

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15) The chemical shift of the protons is some what concentration dependent.