

Preparation of Deuterium Labelled Organophosphonium Salts (Wittig Salts) under Hydrothermal Condition Catalyzed by Molecular Sieves

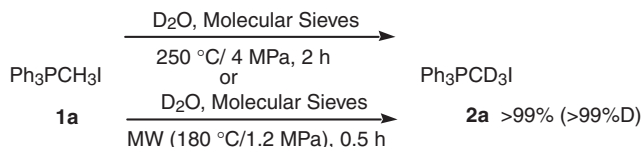
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Organophosphonium salt was converted into deuterium labelled ones under hydrothermal condition in the presence of molecular sieves. The hydrothermal condition can be obtained by either heating D₂O in an autoclave or irradiating with microwave to D₂O in a sealed vial.


Although various methods to prepare deuterium labelled compounds have been reported, efficiency and selectivity of H–D exchange of organic compounds are still challenging.¹ In these methods, deuterium oxide is favourable as a deuterium source, from the economical point of view.² Recently, we reported the complete H–D exchange reaction of hydrocarbons in the presence of transition metal catalyst under hydrothermal condition (200–250 °C/4–5 MPa) of deuterium oxide.³ Thus, the use of hydrothermal condition will give us a novel and efficient method. In this communication, we wish to report the regioselective H–D exchange reaction of α -position of organophosphonium salt under hydrothermal condition. The salt will be good precursor for an alkene carrying D atom on sp² carbon. Previously, Schlosser had already reported that basic condition of deuterium oxide exchanges protons at α -position of organophosphonium salt efficiently in mild condition.⁴ The method was really well investigated and gives us practical methods. However, only one drawback is work-up procedure. A use of base in deuterium oxide arises a necessity for neutralization, which requires also a deuterated acid such as DCl in D₂O. To avoid the use of protic base, we planned to use hydrothermal water, which is obtained by heating the water in closed pot over boiling point, in a presence of insoluble additive. The condition can be realized also by heating with microwave apparatus.⁵ As shown in Scheme 1, we found that treatment of methyltriphenylphosphonium iodide (**1a**) in hydrothermal condition (250 °C/4 MPa) or microwave irradiation (180 °C/1.2 MPa) in the presence of molecular sieves gave (methyl-d₃)triphenylphosphonium iodide (**2a**) quantitatively.



Scheme 1. H–D exchange of methyltriphenylphosphonium iodide.

The detailed procedures of the reaction were as follows. A mixture of phosphonium salt (**1**, 2.0 mmol) and molecular sieves (4A or 3A, 5–6 cylindrical pellets (ϕ ca. 3.2 mm, ca. 5-mm length)) was treated with deuterium oxide (15 mL) at 250 °C in autoclave (30 mL).^{3,6} After 2 h, the mixture was filtered and con-

Table 1. Deuteration of Wittig salts on α -carbon

| $\text{RCH}_2\text{PPh}_3\text{X}$ 1 | Additive D ₂ O | $\text{RCD}_2\text{PPh}_3\text{X}$ 2 | |
|---|------------------------------|--|----------------------------------|
| Phosphonium salt | Condition ^a | Additive ^b | D % of 2 ^{c,d,e} |
| (Ph ₃ PCH ₂ CH ₂ CH ₃)I 1b | HT(250 °C) / 2 h | – | 39 |
| | 110 °C / 3 h | MS | >99 |
| | HT(250 °C) / 2 h | Pd black | 82 |
| | | Pd/C (5 wt%) Activated Carbon | >99 74 |
| (Ph ₃ PCH ₂ (CH ₂) ₄ CH ₃)I 1c | MW / 0.5 h | – | <1 |
| | | MS | >99 |
| (Ph ₃ PCH ₂ (CH ₂) ₄ CH ₃)I 1c | HT(250 °C) / 2 h | MS | >99 |
| | MW / 0.5 h | MS | >99 |
| (Ph ₃ PCH ₂ CH ₂ CH=CH ₂)Br 1d | HT(250 °C) / 2 h | MS | >99 |
| | MW / 0.5 h | MS | >99 |
| (Ph ₃ PCH ₂ CH ₂ Ph)Br 1e | HT(250 °C) / 2 h | MS | 63 |
| | MW / 0.5 h | MS | >99 |
| (Ph ₃ PCH ₂ OCH ₃)Cl 1f | HT(180 °C) / 2 h | MS | >99 |
| | MW / 0.5 h | MS | Decompose |
| (Ph ₃ PCH ₂ CH ₂ CH ₂ )Cl 1g | HT(180 °C) / 2 h | MS | >99 |
| | MW / 0.5 h | MS | Decompose |
| (Ph ₃ PCH ₂ CH ₂ CH ₂ PPh ₃)I ₂ 1h | HT(250 °C) / 2 h | MS | >99 |
| | MW / 0.5 h | MS | >99 |
| (Ph ₃ PCH ₂ CH ₂ PPh ₃)I ₂ 1i | HT(250 °C) / 2 h | MS | >99 |
| | MW / 0.5 h | MS | >99 |
| (Ph ₃ PCH ₂ CH=C(CH ₃) ₂)Br 1j | HT(250 °C) / 2 h | MS | >99 |
| | MW / 0.5 h | MS | Decompose |

^a HT: Hydrothermal condition. A mixture of 2.0 mmol of **1** and 15 mL of deuterium oxide in 30-mL Teflon lined autoclave (see Ref. 3). MW: Microwave condition. A mixture of 1.0 mmol of **1** and 3 mL of deuterium oxide in 10-mL glass vial (see Ref. 8).

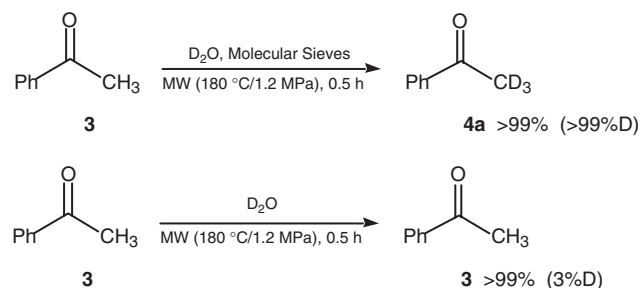
^b MS: molecular sieves 4A, 2–6 cylindrical pellets (ϕ ca. 3.2 mm, ca. 5-mm length), Wako pure chemical. Active Carbon: Granular 4–14 mesh, Aldrich. ^c Determined by ¹H NMR and ²H NMR. ^d Deuteration was observed at α -carbon only (see Ref. 3). ^e The counter anion of obtained labelled Wittig salts was the original halide.

centrated in vacuo. The obtained residue was deuterated phosphonium salt **2**. The reaction was also examined under microwave irradiation. The microwave system is considered to be a potential substitution for the autoclave of hydrothermal reaction. As microwave system, we used Discover system from CEM corporation.^{7,8} In a pressure 10-mL vial which can be sealed by a septum, a mixture of phosphonium salt (2.0 mmol) and molecular sieves (4A or 3A, 2–3 pellets in deuterium oxide (3.0 mL) was placed. The mixture was irradiated with microwave (100 W) maintaining 180 °C and 1.2 MPa for 15 min. After being cooled, the mixture was filtered and concentrated in vacuo. The obtained residue was deuterated phosphonium salt.

The other examples are shown in Table 1. Except the decomposition cases, the phosphonium salts were recovered quantitatively after deuteration. Various additives besides molecular sieves were examined in reactions using **1b** as a substrate. Both molecular sieves and palladium on activated carbon showed prominent effect for the acceleration for H–D exchange. From the economical and practical point of view, we chose molecular sieves as an additive. The phosphonium salts carrying ethereal functional groups were decomposed under microwave irradiation. As the irradiation heated an ionic salt directly and drastically faster than the surrounding deuterium oxide, the salts decomposed thermally. On the contrary, traditional heating in autoclave did not spoil the salts in these cases and performed H–D exchange reaction. The procedure would not heat the salts beyond the established reaction temperature.

The role of the molecular sieves is not perfectly clear. Molecular sieves, however, can be considered to be a weak solid base. Simple heating of water beyond the boiling point in a closed pot causes a decrease of pK_w .⁹ This means that the hydrothermal water is acidic. An addition of molecular sieves may change the condition into neutral or weakly basic one. When the allylic phosphonium salt **1j** was treated even with moderate base like sodium carbonate, it will isomerize into the alkenyl phosphonium compound.⁴ In the present method, molecular sieves did not undergo such isomerization reaction during the exchange reaction.

As shown in Scheme 2, a ketone was treated with molecular



Scheme 2. H–D exchange reaction of acetophenone catalyzed by molecular sieves.

sieves and hot water under microwave irradiation. The acidic protons were exchanged with D atom of deuterium oxide. Without molecular sieves, the same condition did not show sufficient exchange reactions.

As described above, the role of molecular sieves may be considered to be a solid base. The combination with either hydrothermal or normal water will offer a new reaction condition and site for organic compounds.

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