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Mechanically Induced Solid-State Generation of Phosphorus Ylides and the Solvent-Free Wittig Reaction

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Mechanical alloying via high-energy ball-milling is a scalable experimental technique, which is broadly used for the preparation and modification of metals, hydrides, and other inorganic solids.[1] In contrast, mechanochemistry is seldom attempted in organic synthesis, and when it is, mechanical processing of organic reactants is followed by additional treatment (usually heating), or it is carried out in the presence of a solvent.[2] Consequently, little is known about chemical reactions taking place during mechanical milling of organic solids. Furthermore, only indirect evidence confirming just a few chemical transformations of solid organic compounds as a result of milling has been presented to date.[2e,f]

We show that three major types of phosphorus ylides, that is, stabilized, semistabilized and nonstabilized phosphoranes, can be generated mechanochemically in a solid state. Stabilized ylides were isolated in a pure form, while semistabilized and nonstabilized phosphoranes were trapped by a solid organic carbonyl compound and transformed into ethenes and triphenylphosphine oxide in a solvent-free mechanochemical Wittig-type reaction. Conventionally, phosphorus ylides are produced in a solution,[3] and the solid-state preparation of phosphoranes was not reported before.

Solid phosphonium salts, **1a−d**, and an excess of anhydrous K_2CO_3 were ball-milled in a hardened-steel vial with steel balls under helium for various periods of time (Scheme 1 and Table 1). Forced air-cooling of the vial was employed to prevent its heating during ball-milling experiments. The obtained powders were analyzed using solid-state ^{31}P nuclear magnetic resonance (NMR) spectroscopy, X-ray powder diffraction (XRD), and differential thermal analysis (DTA) prior to any further treatment.

Two stable phosphorus ylides, (benzoylmethylene)triphenylphosphorane (**2a**) and (carbethoxymethylene)triphenylphosphorane (**2b**), were prepared in nearly quantitative yields (Scheme 1, Table 1). To prepare ylide **2a**, (phenacyl)triphenylphosphonium bromide (**1a**) and anhydrous K_2CO_3, taken in a 1:1.2 molar ratio, were ball-milled in a Spex 8000 mill for 1 and 3 h. The solid-state ^{31}P magic angle spinning (MAS) NMR spectrum of the powder sample after ball-milling for 1 h consists of two peaks at $\delta^{31}P = 23$ and 17 ppm (Figure 1b). The peak at $\delta^{31}P = 23$ ppm corresponds to the unreacted **1a** (Figure 1a) remaining in the reaction mixture. The location of the second peak at $\delta^{31}P = 17$ ppm is consistent with pure **2a** (Figure 1d). After ball-milling for 3 h, the spectrum of the reaction mixture (Figure 1c) contains only one signal at $\delta^{31}P = 17$ ppm, indicating a complete transformation of **1a** into **2a**. The sample ball-milled for 1 h was reexamined 6 months after the completion of the mechanical treatment. No continuing changes, that is, no thermal solid-state reactions were detected. Similarly, **2b** was prepared mechanochemically from (carbethoxymethyl)triphenylphosphonium bromide (**1b**) and anhydrous K_2CO_3, see Table 1.

Scheme 1. Mechanochemical Generation of Phosphoranes

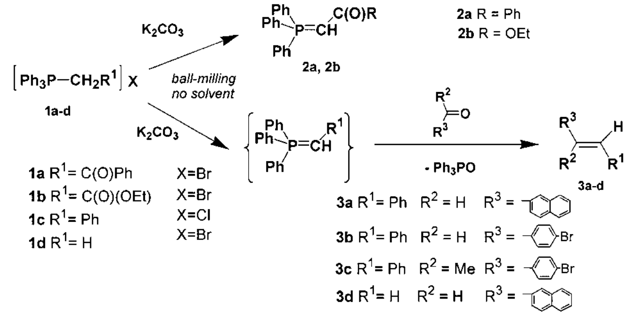

Table 1. Mechanochemically Prepared Compounds

compound	milling time, h	yield, %	*E*:*Z* ratio[a]	reference[b]
2a	3	99	−	*c*
2b	4	96	−	3b, 8
3a	7	85[d]	1.6:1[e]	7
3b	8	92[d]	2:1	9
3c	14	70[d]	3.4:1	10
3d	20	73[d]	−	11
4	4	99	−	6
5	8	93[d]	3.5:1	7

[a] *E*:*Z*-isomer ratio as determined by the liquid-state ($CDCl_3$) ^1H NMR spectroscopy. [b] References used for identification of the compounds. [c] Identified by comparison with the commercial phosphorane. [d] Triphenylphosphine oxide was isolated as a coproduct in the yields matching that of ethene. [e] Estimated ratio based on the amount of the isolated *E*-isomer.

Semistabilized and nonstabilized phosphoranes were generated from (benzyl)triphenylphosphonium bromide (**1c**) or (methyl)-triphenylphosphonium bromide (**1d**) by mechanical processing with an excess of K_2CO_3 in the presence of stoichiometric amounts of solid organic carbonyl compounds. The latter served as traps for highly reactive phosphoranes. Thus, we successfully carried out several solvent-free Wittig-type reactions and prepared a series of aromatic ethenes **3a−d** (Scheme 1, Table 1) in high yields. Again, the solid-state ^{31}P MAS NMR confirmed the completion of all performed reactions during ball-milling (e.g., Figure 1e−g).

Finally, we found that the mechanochemical preparation of stabilized phosphorus ylides and the solvent-free Wittig reaction can be successfully carried out as a "one-pot" process starting with triphenylphosphine, an organic halogenide, and an organic carbonyl compound in the presence of K_2CO_3 (Scheme 2, Table 1). In this way, we synthesized the ylides **2a** and **4,** and the bromostilbene **5**. It is worth noting that **4** is usually prepared in a solution in a multiple-step process,[6] while in our approach the reactants were simply ball-milled together for 4 h. In all cases, the completion of

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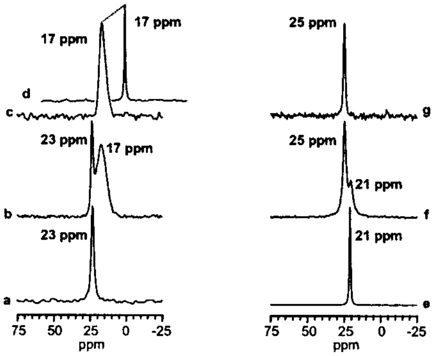
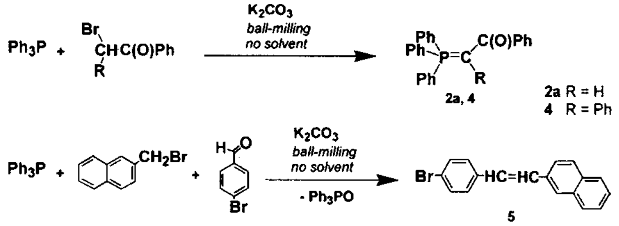


Figure 1. Solid-state ^{31}P MAS NMR spectra of: (a) crystalline **1a** (Lancaster synthesis); reaction mixtures after ball-milling of **1a** with K$_2$CO$_3$ for (b) 1 h and (c) 3 h; (d) crystalline **2a** (Alfa Aesar); (e) crystalline **1d** (Aldrich); (f) reaction mixture after ball-milling of **1d** with K$_2$CO$_3$ in the presence of 2-naphthaldehyde for 10 h (the reaction is essentially complete after 20 h); (g) crystalline triphenylphosphine oxide. Spectra were obtained at 161.9 MHz under single-pulse excitation, 20 kHz MAS and continuous wave ^{1}H decoupling. The more efficient method of cross-polarization from ^{1}H nuclei yielded similar results.

Scheme 2. "One-Pot" Mechanochemical Synthesis



mechanochemical transformations was confirmed by the solid-state ^{31}P MAS NMR spectroscopy.

Two distinct dissimilarities between the conventional and the mechanochemically induced Wittig reactions of semistabilized and nonstabilized phosphorus ylides are worth noting. First, both (benzylene)- and (methylene)triphenylphosphoranes can be generated mechanochemically using K$_2$CO$_3$, while their preparation in a solution requires much stronger bases.[3] As far as we are aware, deprotonation of a (methyl)triphenylphosphonium salt with an alkali metal carbonate was never reported in the literature. Second, while the Wittig reaction between (benzylene)- or (2-naphthylene)triphenylphosphoranes and aromatic carbonyl compounds in a solution produces preferably *Z*-stilbenes or mixtures with nearly equal content of *Z*- and *E*-isomers,[3,7] the mechanochemical technique discriminates between *Z*- and *E*-substituted products in favor of more thermodynamically stable *E*-stilbenes.

To obtain preliminary insights into the processes resulting in the mechanochemical generation of phosphorus ylides, the powder obtained after ball-milling of the phosphonium salt **1a** with K$_2$CO$_3$ for 1 h was studied using DTA and XRD. The major objective was to explore the possibility of local melting of the reactants and, hence, hidden liquid-state reactions during mechanical processing. The data on the local temperature rise in different types of mills during milling of inorganic solids[1,4] and our results on mechanical treatment of LiAlH$_4$-based composites[5] showed that the materials' temperature during milling in a Spex 8000 mill do not exceed 110 °C. Since melting points of **1a** and anhydrous K$_2$CO$_3$ are 265 and 891 °C, respectively, their melting during mechanical processing is unlikely. On the other hand, the likelihood of the formation of low-melting eutectics from these compounds during ball-milling required further investigation.

Our experiments produced no evidence for melting of the studied material below 180 °C, which is the melting point of the ylide **2a** formed during mechanical processing. Furthermore, DTA, XRD, and NMR data (compare Figure 1, c and d) revealed the presence of an amorphous phase in the ball-milled sample. Partial loss of crystallinity was also observed during mechanical treatment of the pure **1a** and **2a** for 1 h. According to DTA and in situ high-temperature XRD, crystallization of the amorphous components in the investigated powders occurs between 70 and 105 °C, also indicating that the temperature of the reaction mixtures during processing remained below ∼70 °C.

The acquired data confirm the solid-state character of the events leading to the mechanochemical generation of phosphorus ylides. They also allow us to explain the latter as a sequence of solid-state processes, which include: (i) breaking the crystal lattice of a phosphonium compound and the formation of an amorphous phase and (ii) a deprotonation of an amorphous phosphonium salt by microcrystalline K$_2$CO$_3$ in a heterogeneous solid-state reaction.

In conclusion, mechanically induced solid-state generation of phosphorus ylides and the solvent-free Wittig reaction have been observed for the first time. The completion of the reactions during ball-milling has been directly confirmed by solid-state ^{31}P MAS NMR spectroscopy. High-energy mechanical processing is responsible for both the amorphization of the reactants and mass transfer in a solid state, thus playing a critical role in the discovered chemical transformations.

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Supporting Information Available: Experimental details, DTA and XRD data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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