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Potassium hydride in paraffin: a useful base for Williamson ether synthesis

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ABSTRACT

A procedure for the preparation of potassium hydride in paraffin from potassium metal has been developed. The KH (P) so produced proved to be an efficient base for the Williamson ether synthesis.

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Although C. A. Brown[1] first reported that potassium hydride (KH) was more reactive than sodium hydride (NaH), KH has not been as widely used in synthesis as might be expected.[2] Largely, this is because KH comes commercially as a slurry in mineral oil, so it is operationally difficult to dispense precisely. We earlier reported the preparation of KH in a more convenient form, as an air stable 50% by weight homogenate in paraffin, termed KH (P).[3] We now describe a convenient preparation of KH (P) directly from K metal, and report that KH (P) is a superior base for the Williamson ether synthesis.[4]

We prepared KH (P) by exposing K metal in an equal weight of melted paraffin to ~1000 psi H_2 at 120 °C overnight.[5] The product after cooling was homogeneous by titration and appeared to be identical in every way to the KH (P) we had previously prepared[3] by washing the mineral oil off of commercial KH.

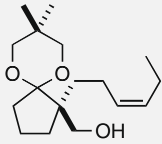
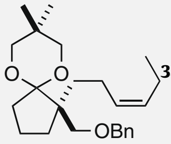
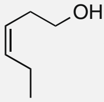
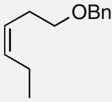
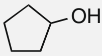
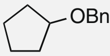
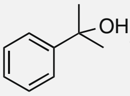
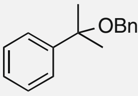
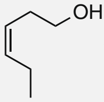
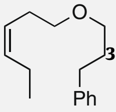
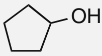
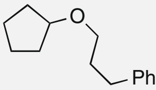
With inexpensive KH now readily available, we have been exploring additional applications in organic synthesis. Alkyl ethers such as benzyl ethers are the most common and important protecting groups in organic synthesis. Alkyl ethers are generally formed by the treatment of the parent alcohols with the corresponding alkyl halides, the Williamson ether synthesis. We examined the efficacy of KH (P) in the conversion of a range of alcohols into the corresponding ethers (Table 1). The yields in Table 1 refer to reactions employing 1.0 mmol of alcohol, 2.0 mmol of KH (P), and 2.0 mmol of benzyl bromide. We were pleased to observe that KH (P) worked very well as the base in the synthesis of benzyl ethers.[6,7] Even the sensitive tertiary benzyl alcohol delivered the benzyl ether **3d** (entry 4) in excellent yield.[8] This has become the method of choice for benzyl ether preparation in our laboratory.

We also tested the KH (P) in more challenging cases, entries 5 and 6, in which elimination competed with ether formation. By way of comparison, the conditions of entry 6, but using NaH in place of KH, gave **3f** in 51% yield.

In conclusion, Williamson ether synthesis using KH (P) as the base is rapid and reliable. We believe that KH (P), a stable and easily handled solid, will find many applications in organic synthesis.[2]

Potassium hydride in paraffin: Paraffin wax (for canning, MP = 48–50 °C, 50 g) was warmed to melting in a 300-mL glass jar. To the melted wax was added freshly cut potassium metal

Table 1
Williamson ether synthesis using KH (P)

Entry	Alcohol	Ether[a]	Yield[b] (%)
1	 **1a**	 **3a**	91
2	 **1b**	 **3b**[c]	96
3	 **1c**	 **3c**[d]	96
4	 **1d**	 **3d**[e]	99
5	 **1b**	 **3e**	91
6	 **1c**	 **3f**	82

[a] Ethers were prepared from the alcohol, 2 equiv of KH (P), and 2 equiv of the appropriate bromide.
[b] Isolated yield of purified product after chromatography.
[c] Ref. 6.
[d] Ref. 10.
[e] Ref. 7.

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(48.75 g) in about 10 g pieces. The jar was then placed in a Parr reactor equipped with a mechanical stirrer and heating mantle. After being purged with H_2 (g), the temperature was increased to 120 °C. At that temperature, the reactor was charged to 1000 psi H_2 (g) and stirred at 450 rpm. The reactor was periodically recharged to 1000 psi as H_2 (g) was consumed. Once the pressure was maintained above 900 psi, the mixture was stirred for a further 12 h at 120 °C. After cooling to 60 °C, the jar was removed from the Parr reactor and manually homogenized (using the mechanical stirrer from the Parr reactor) as it solidified. Once cooled to room temperature, the KH (P) was titrated.[3] An average of two titrations was within ±1% of the expected titer.[3]

Ether **3a**: Alcohol **1a** (280 mg, 0.99 mmol), bromide **2a** (342 mg, 2.0 mmol), and KH (P) (160 mg, 2.0 mmol) were stirred in dry THF (3 mL) at room temperature under N_2. The reaction was monitored by TLC. After about 1 h, the reaction mixture was partitioned between petroleum ether and 10% aqueous NaCl. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ether **3a** (338 mg, 91% yield) as a colorless oil, TLC $R_f = 0.44$, (5% MTBE/petroleum ether); ^{1}H NMR δ 0.70 (s, 3H), 0.93 (t, $J = 7.5$ Hz, 3H), 1.18 (s, 3H), 1.44–2.30 (m, 12H), 3.33–3.60 (m, 6H), 4.48 (d, $J = 12.4$ Hz, 1H), 4.57 (d, $J = 12.4$ Hz, 1H), 5.25–5.44 (m, 2H), 7.23–7.34 (m, 5H); ^{13}C NMR δ d[9] 14.5, 22.3, 23.2, 127.2, 127.4, 128.2, 130.5, 130.8; u 18.8, 20.5, 22.7, 27.5, 30.2, 31.0, 31.4, 51.9, 71.1, 71.4, 72.0, 73.3, 109.2, 139.2; IR (film) 2955, 2864, 1459, 1112 cm^{-1}; HRMS (CI) calcd for $C_{24}H_{37}O_3$ (MH$^+$) 373.2743, found 373.2734.

Acknowledgments

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4. 50% by weight KH in paraffin, prepared by the protocol outlined here, is available from Sigma–Aldrich, Product #708860. Note that the paraffin runs at the solvent front when products are purified by silica gel chromatography. It can also be washed off the KH under inert atmosphere if desired.
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