

Rapid, High Yield Condensations of Esters and Nitriles *via* Kation¹

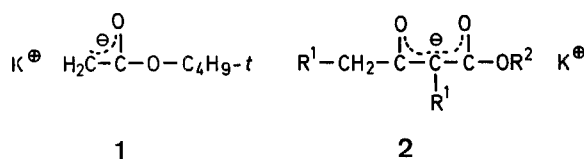
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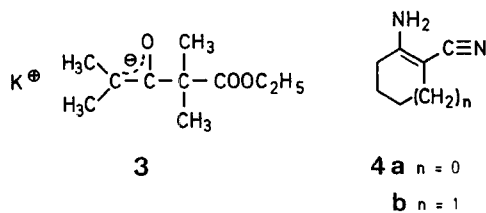
Potassium hydride reacts rapidly with esters and nitriles in tetrahydrofuran at room temperature producing high to quantitative yields of the condensation dimers.

A wide variety of base systems have been utilized to accomplish condensations involving esters²⁻⁹. Of these, sodium hydride has been described as possessing several attractions: essential irreversibility, low nucleophilicity, and ease of handling. It is, however, a heterogeneous agent and is relatively sluggish, often requiring prolonged reactions, elevated temperatures, and/or "activation" by addition of alcohol.

Potassium hydride is considerably more reactive than lighter saline hydrides toward C—H, N—H, and O—H¹⁰ bonds. Addition of an ester such as ethyl propanoate to 1.2 mol-equiv. of potassium hydride suspended in tetrahydrofuran at 20–25° resulted in a vigorous exothermic reaction accompanied by rapid evolution of hydrogen. Controlled addition over 10–15 minutes allowed a moderated reaction with hydrogen evolution paralleling ester addition. Mild acidic hydrolysis afforded the β -ketoester in essentially quantitative yield. Reaction of *t*-butyl acetate with potassium hydride proceeded smoothly; no evidence for a significant concentration of the α -metalated ester (**1**)¹¹ was found upon quenching.




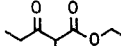

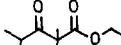

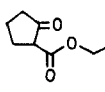




Formation of anions such as **2** is considered to contribute to forcing ester condensation. With α -substituted esters in which such anion formation is precluded – e.g. ethyl 2-methylpropanoate – successful condensations have been reported only with soluble strong base, in low to moderate yield¹². Potassium hydride reacted smoothly with ethyl 2-methylpropanoate at room temperature to produce the β -ketoester quantitatively. The formation of the ketone enolate (**3**) appears necessary for complete condensation: 1.0 mol of potassium hydride per mol of ester function is required for quantitative reaction, with evolution of 1.0 mol of hydrogen; 0.5 mol-equiv. of potassium hydride yields approximately 50% conversion, with starting material recovered.



Thorpe-Ziegler cyclization¹³ of dinitriles similarly proceeds smoothly with potassium hydride in tetrahydrofuran at room temperature to give the enamionitriles (**4**) in high yield.

Condensations are summarized in the Table. From these preliminary results it is clear that potassium hydride represents a reactive convenient reagent for condensations.

Table. Representative Condensations via Kallation

Substrate (mmol)	Reaction time ^a	Hydrolysis of reaction mixture ^b	Product ^c	b.p. or m.p.	Yield (%) ^d
 (50)	20 min	HOAc/0° + H ₂ O/0°		91°/15 torr	> 95 (82) ^e
 (50)	120 min	HOAc/-78° + H ₂ O/0°		— ^f	> 95
 (25)	20 min	HOAc/0° + H ₂ O/0°		108–110°/14 torr	> 95 (86) ^e
 (50)	75–120 min	H ₂ O/0°		m.p. 147–148°	79–88 (63) ^g
 (50)	90 min	H ₂ O/0°		m.p. 94–95°	83 (67) ^g

^a Time from beginning of addition.

^b Rapid addition of 1.2 equiv. of acetic acid or 5.0 equiv. of water with vigorous stirring, followed by sufficient water to give a clear two-phase system.

^c Products had physical and spectral properties consistent with published values and with structure. All products were homogeneous by G.L.P.C.

^d Unless otherwise stated, yield by G.L.P.C. against added internal standard; conditions: phenyl silicone stationary phase.

^e Yield of product isolated by distillation.

^f Isolated by preparative G.L.P.C.; conditions: phenyl silicone stationary phase, temperature 125°.

^g Yield after two recrystallizations. Two crops obtained in each recrystallization had identical m.p.

General Procedure for Condensations with Potassium Hydride:

In a 250 ml round-bottomed flask (fitted with a polytetrafluoroethylene covered magnetic stirring bar, injection port closed with a rubber septum, and a condenser attached to a bubbler or gas meter) was placed potassium hydride as a 40% w/w dispersion in mineral oil^{1,4} (5.5 g, 55 mol of potassium hydride). Under an atmosphere of dry nitrogen or argon, the oil was replaced with tetrahydrofuran (80 ml, dried over 4A molecular sieve). The mixture was cooled in a 20° water bath and the substrate was added with stirring either over 15 min (esters) or in one portion (nitriles). Gas evolution generally commenced within 10 to 60 sec. When the gas evolution was complete, the reaction mixture was cooled and hydrolyzed (foaming, hydrogen evolution). Details for representative compounds are summarized in the Table.

Received: February 2, 1975

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For recent reports employing NaH/DMSO (probably Na[⊖]CH₂SOCH₃ is the active base) and Na[⊖]N[Si(CH₃)₃]₂ see: J. J. Bloomfield, P. V. Fennessey, *Tetrahedron Lett.* **1964**, 2276. C. Krüger, *J. Organometal. Chem.* **9**, 125 (1967).

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