Alkali Metal Alkoxides for Organic Synthesis

Alkali metal alkoxides are moderately strong, base reagents that are used in drug and chemical synthesis applications, such as alkylation, arylation, acylation, solvolysis of esters, condensation, elimination, isomerization, rearrangements, transfer hydrogenation, Wittig reactions, and redox reactions. The reactivity can be fine-tuned to the desired reaction by correct choice of alcoholate and counterion. The wide range of properties and solubilities of the bases available from Callery, LLC allows for process optimization and high yields.

The base strength can be varied with the structure of the alcohol and choice of solvent. As alkyl groups are added to the alcohol, the alkoxide anion becomes a stronger base compared to primary alkoxides and hydroxide. Furthermore, the higher base strength and steric bulk of the tertiary alkoxides influence the speed, selectivity, and specificity. Larger steric bulk of the alkoxide reduces the nucleophilicity of the anion, decreasing the amount of undesired reactions. Greater substitution on the alcohol increases solubility in non-polar solvents, as will be discussed later.

Potassium bases deprotonate substrates faster due to the softer nature of the ion pair and the corresponding higher reactivity anion.[1] All alkali metal alkoxides reside in tetramer, hexamer and other aggregate forms but lithium cations are more tightly associated with the anion.[2] Thus, lithium alkoxides react slower, kinetically, than potassium alkoxides. Sodium alkoxides are intermediate in reactivity. Contact and solvent-separated ion pairs also influence reactivity. For example, in DMSO, the cations are solvated thus increasing the basicity of the alkoxide.

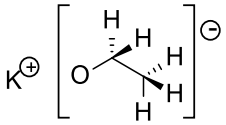
Primary alkoxides are in general only soluble in the alcohol from which they are derived, typically 15-20 wt% at ambient temperature. One notable exception is sodium isopropoxide which has very low solubility in isopropanol. Fortunately, it is highly soluble in tetrahydrofuran. Secondary and tertiary alkoxides are soluble in ethers, and when the tertiary alcohol is branched high solubility in hydrocarbons is achieved, see tables and plots at the end of this document. Alkali metal alkoxides are reactive towards carbon dioxide and moisture in the air. Reaction with water vapor releases the alcohol which will coordinate with the alkali metal alkoxide forming an alcoholate complex (usually insoluble).

Due to their higher solubility, branched tertiary alkoxides, such as sodium mentholate, potassium *t*-amylate or 3,7-dimethyl-3-octylate, can be used in combination with an alkyl lithium to generate a “Superbase”. In this process the potassium and lithium exchange to give a highly reactive alkyl potassium species. Superbases are used in polymerization to control the microstructure of the polymer and functionalization of polymers by deprotonation on the backbone or pendant groups.[3] For example, polystyrene can be derivatized by metalation with 2-ethylhexyllithium/potassium *t*-amylate and subsequent reaction with an electrophile or a monomer to graft a co-polymer.

Alkali metal alkoxides can also be used as anionic initiators in ring-opening polymerization (ROP). For example, potassium t-butoxide (KTB) polymerizes styrene oxide via a ring-opening in the beta-position, however potassium isopropoxide (KIP) ring opens the oxirane in beta- or alpha positions leading to polymers with differing properties.[4] KTB was used as a catalyst to form a copolymer of lactide-gylcine.[5] KTB was used to polymerize *trans*-hexahydro-benzofuranone.[6]

Potassium Ethoxide

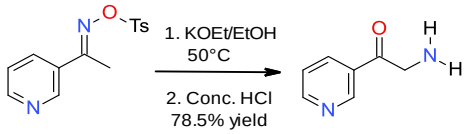
CAS Reg. # [917-58-8]



Potassium ethoxide (also called potassium ethylate) is commercially available as a 24 wt% solution in denatured ethanol.

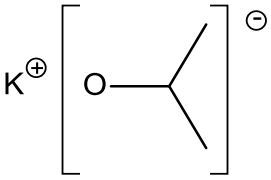
Hepatitus C drug intermediates were prepared by Gilead using potassium ethoxide to place the ethoxy group via chloride exchange.[7] 3-Chloroisoquinoline was dissolved in KOEt 24 wt% in ethanol and heated under pressure to 150°C for 24 h for a 48% isolated yield of 3-ethoxyisoquinoline.

In the synthesis of telithromycin, Chengdu Wins Chem used potassium ethoxide in a Neber rearrangement of a tosylhydrozone to form an intermediate *alpha*-amino ketone.[8]



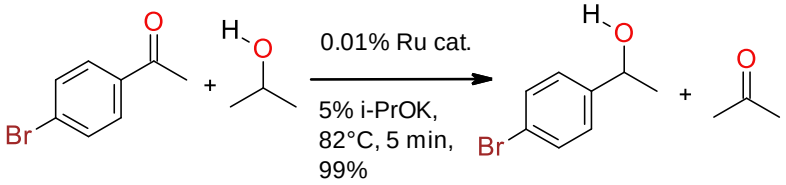
Potassium *i*-Propoxide (KIP)

CAS Reg. # [6831-82-9]



Potassium isopropoxide (KIP, also called potassium isopropylate) is available at 20 wt% in isopropanol.

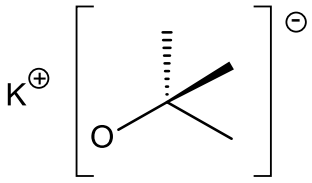
Transfer hydrogenation reactions using KIP and a ruthenium complex as catalysts is an effective method for rapid high yield ketone reductions.[9]



KIP was used in the synthesis of a norborenyltriene intermediate to make chromophores for dye-sensitized solar cells.[10] Iron isoproxide, used in the synthesis of magnetite nanoparticles, was prepared from KIP and iron chloride.[11]

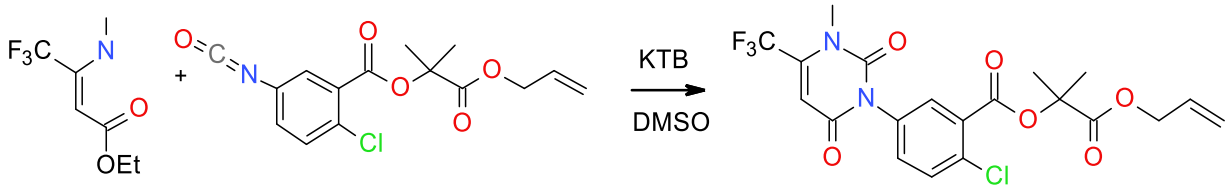
Potassium *tert*-Butoxide (KTB)

CAS Reg. # [865-47-4]

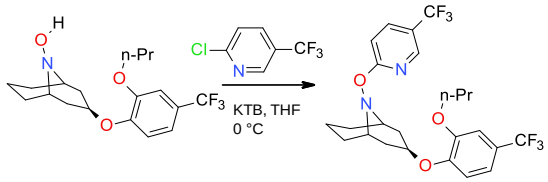


Potassium *tert*-butoxide (also known as potassium *tert*-butylate, KTB) is quite soluble in ethers and amines but is only slightly soluble in hydrocarbon solvents. The rate of deprotonation with KTB is 5 to 6 orders of magnitude faster than with potassium methoxide. Selective deprotonation can be achieved with KTB due to the steric hindrance provided by the tertiary butyl group.

Hydration of nitriles can be accomplished with KTB without the assistance or transition metal catalysts.[12] Aryl- or heteroaryl uracils, useful as herbicides, were prepared with substantially increased yields over previous methods by cycloaddition of isocyanates in the presence of 0.1 to 0.3 equivalents of KTB in DMF or DMSO solvents.[13]

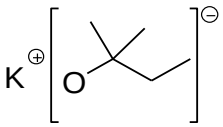


Nippon Soda used KTB for deprotonation of a hydroxylamine in a route to make an intermediate during the synthesis of insecticide, Acynonapyr.[14]



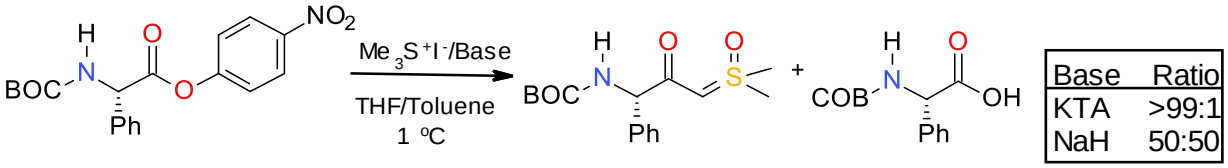
Potassium *tert*-Amylate (KTA)

CAS Reg. # [41233-93-6]



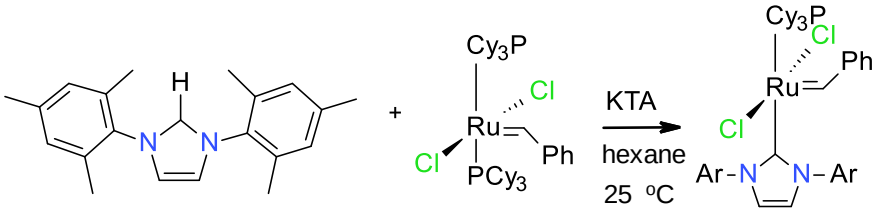
Potassium tertiary amylate (KTA) is also known as potassium *t*-pentoxide or potassium *t*-amyloxide. The high hydrocarbon solubility of potassium *tert*-amylate gives it an advantage over sodium and potassium alkoxides derived from *tert*-butanol or primary alcohols. In the synthesis

of α-chloroketones from amino acid phenyl esters, a sulfur ylide was formed by deprotonation with KTA.[15] The amount of desired product was dramatically increased with KTA versus NaH.



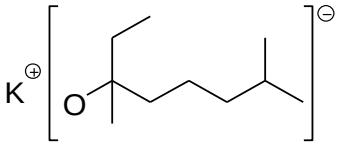
Base	Ratio
KTA	>99:1
NaH	50:50

The high solubility of KTA aided in the development of mild reaction conditions to convert imidazolium salts to free carbenes in the synthesis of ruthenium olefin metathesis catalysts.[16]

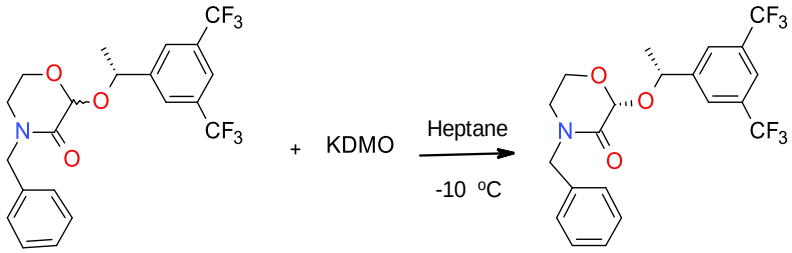


Potassium 3,7-Dimethyl-3-Octylate (KDMO)

CAS Reg. # [263148-42-1]

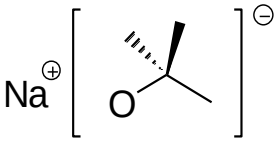


KDMO is highly soluble in alkanes and is liquid when neat, providing advantages in reactor utilization. An epimerization driven crystallization using KDMO as the base gave a high yield and diastereomer ratio of an intermediate in the synthesis of aprepitant.[17]



Sodium *tert*-Butylate (STB)

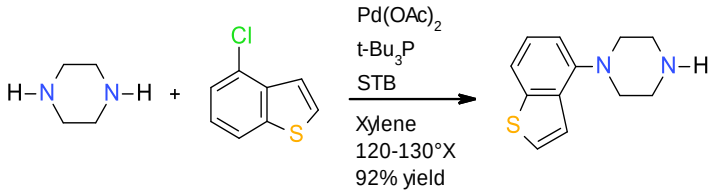
CAS Reg. # [865-48-5]



Sodium *tert*-butylate (STB) is more soluble than potassium tert-butoxide in hydrocarbon solvents but is minimally soluble in tertiary butanol, <5 wt%. For higher solubility in hydrocarbon solvents, both sodium and potassium *tert*-amylate are excellent choices, see the table at the end of this document.

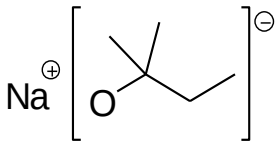
STB was used to prepare pegylated derivatives of Dolutegravir sodium in a process that conserved solvent.[18]

STB is one of the preferred bases for the palladium catalyzed Buchwald-Hartwig amination of arylbromides and chlorides.[19] For example, during the synthesis of an intermediate for Brexpiprazole, a recently approved antipsychotic drug, 4-chlorobenzothiophene was aminated with piperazine.[20]

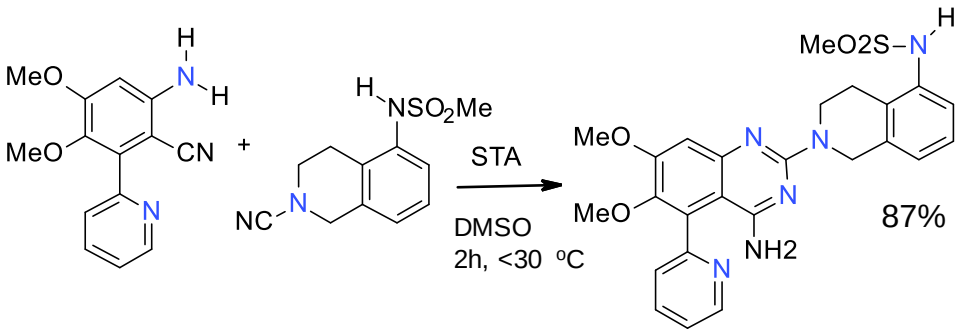


Sodium *tert*-Amylate (STA)

CAS Reg. # [14593-46-5]

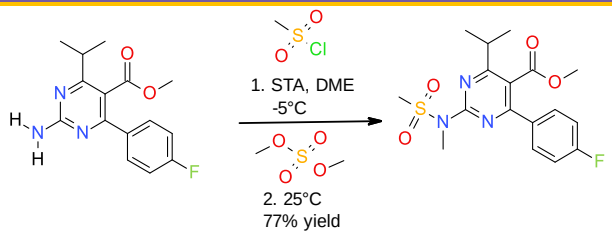


Sodium *tert*-amylate (STA) is a strong, hydrocarbon-soluble base used for deprotonation, elimination, and isomerization reactions. See table below for solubility data; STA is also highly soluble in THF (45 wt%) and 2-MeTHF (53 wt%) at ambient temperature.



In a convergent synthesis of quinazolines, shown above, STA was used to condense a benzonitrile with the cyanotetrahydroisoquinoline.[21]

One AstraZeneca route to Rosuvastatin Calcium uses STA for deprotonation to form a sulfonamide and methylate the nitrogen in a two-step sequence, see reaction scheme on the next page.[22]



In summary, alkoxide bases are a key part of the organic chemist's toolbox as well as reagents for synthesis of catalysts and inorganic materials. In addition, Callery's alkoxide bases contain very low hydroxide content to help maximize yield and minimize by-products. A wide range of nucleophilic and non-nucleophilic bases are available for your applications.

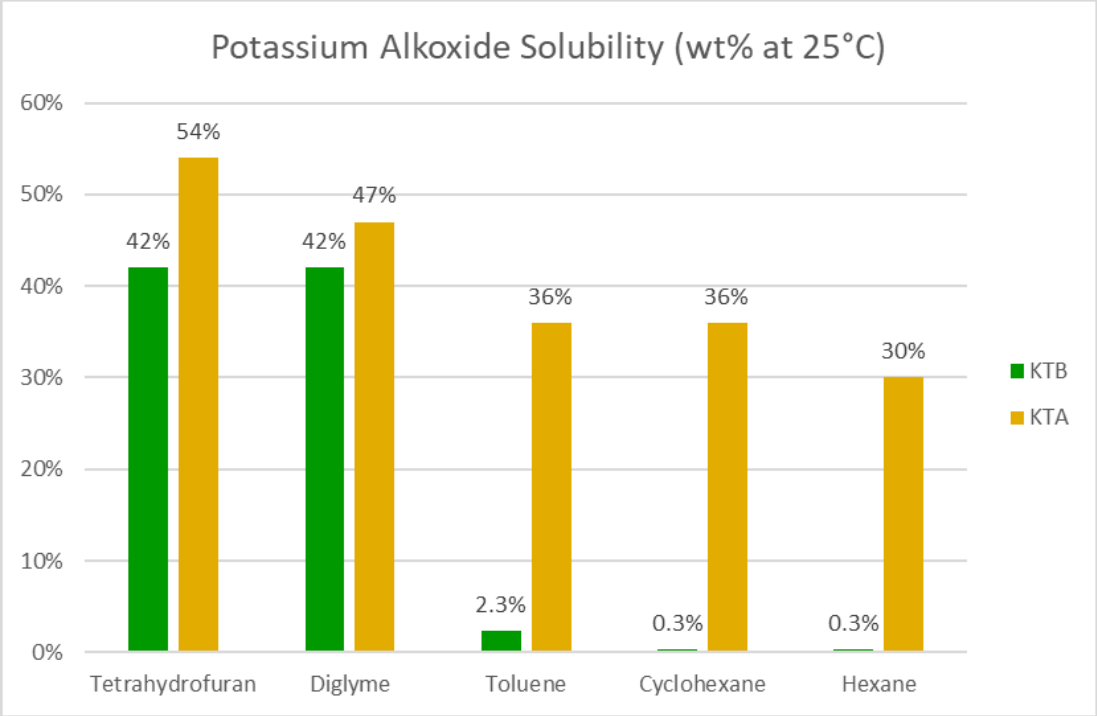
Custom Alkoxides

Product Name	Alternate Name	Acronym	CAS Reg. #
Potassium Methoxide	Potassium Methylate	KOMe	[765-33-8]
Potassium *n*-Propoxide	Potassium *n*-Propylate	KNP	[16872-93-8]
Potassium *n*-Butoxide	Potassium *n*-Butylate	KNB	[2372-45-4]
Potassium *i*-Butoxide	Potassium *i*-Butylate	KIB	[14764-60-4]
Sodium *n*-Propoxide	Sodium *n*-Propylate	SNP	[6819-41-6]
Sodium *n*-Hexylate		SNH	[19779-06-7]
Sodium *i*-Propoxide	Sodium *i*-Propylate	SIP	[683-60-3]
Sodium Mentholate		NaM	[1321-38-1]
Sodium 3,7-Dimethyl-3-Octylate		NaDMO	[263148-59-0]

The custom alkoxide products listed above are manufactured upon receipt of customer orders. Alkali metal alkoxide and metal amide products are available in a variety of solvents. Please contact Callery, LLC (ph. 724-538-1200) to discuss your desired alkoxide or product in a custom solvent or at a specific concentration.

Solubility of Selected Alkoxides (weight % at 25 ºC)

Solvent	KTB	KTA	STB	STA
Hexane	**<1**	**30**	**11**	**60**
Cyclohexane	**<1**	**36**	**14**	**>50**
Toluene	**2.3**	**36**	**6**	**41**
Tetrahydrofuran	**40**	**>50**	**38**	**45**
Diglyme	**42**	**47**	**28**	**47**
t-Butanol	**18**	**-**	**<5**	**-**
t-Amyl alcohol	**-**	**>20**	**-**	**10**



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