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THE IN SITU PROTECTION OF ALDEHYDES VIA α-AMINO ALKOXIDES

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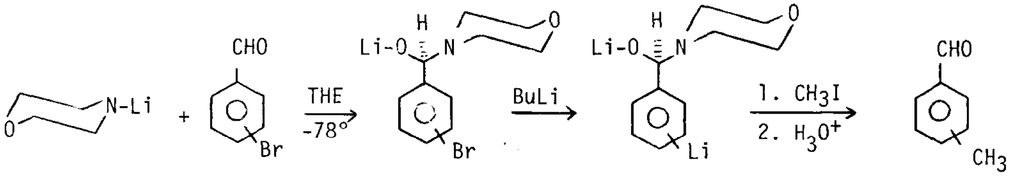
Summary: Aromatic and aliphatic aldehydes can be protected in situ via the formation of α-amino alkoxides and their O-trimethylsilyl derivatives.

The addition of an organolithium reagent to a N,N-disubstituted amide forms an intermediate α-amino alkoxide which is stable to further reaction with organometallics (e.g. n-BuLi, THF, RT, 16 h).[1] These adducts undergo elimination on hydrolysis to provide ketones, and thus can be considered as carbonyl protecting groups. This concept has been ingeniously utilized by Gronowitz,[2] and subsequently by others,[3] to prepare ortho-substituted aromatic ketones via one-pot syntheses.

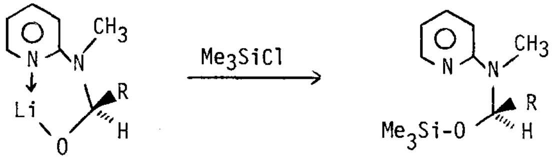
The potential of α-amino alkoxides as carbonyl protecting groups, combined with our own interest in the chemistry of α-(N-methyl-N-(2-pyridyl)) amino alkoxides,[4] prompted us to investigate other routes to these intermediates. We have found that α-amino alkoxides are readily formed by the addition of an aldehyde to the lithium amide of certain secondary amines. This allows for the in situ protection of aromatic and aliphatic aldehydes in high yield as indicated in the table.

The initial studies were performed using lithium morpholide[5] and monobromobenzaldehydes. The adduct (1) was formed in THF at -78° (15 min) and subsequently treated with n-BuLi to provide an intermediate dianion 2 via lithium-halogen exchange. Addition of methyl iodide followed by aqueous workup provided high yields of the tolualdehydes 3 (entries 1-3).



1 2 3

Lithium morpholide is limited as a reagent for aldehyde protection due to its strong basic and nucleophilic properties. This limitation was circumvented by the use of lithium 2-(N-methyl-N-(2-pyridyl))-amide (LMPA) as the lithium amide component. LMPA is a relatively weak base, as compared to lithium morpholide, and does not metalate or attack aliphatic esters (entries 4-5). However, LMPA does react with aromatic and aliphatic aldehydes very readily even at low temperatures (THF, -78°) to form the addition adducts 4.



4 5

Adducts 4 are susceptible to nucleophilic attack with certain organometallic reagents (RLi and LAH),[4] however, they are relatively stable to Grignard reagents at 0° and can be utilized as an aldehyde protecting group for Grignard reactions (entry 4). The intermediate 4 can be converted to protected derivative 5, which is stable to organolithium reagents and LAH, by the addition of chlorotrimethylsilane (1.1-1.5 equiv Me$_3$SiCl, RT, 1 h; see entries 5-11). This methodology allows for the one-pot *in situ* protection[6] of an aldehyde for organometallic reactions. The protecting groups 4 and 5 are removed quantitatively on aqueous workup (dilute HCl, <5 min).

This method of protection is limited to aldehyde carbonyls, as ketones (e.g. acetophenone, benzylacetone, and 4-tert-butylcyclohexanone) are converted to their enolate anions with LMPA.

Table. The *In Situ* Protection of Aldehydes

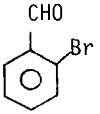
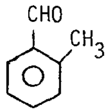
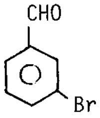
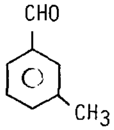
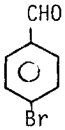
Entry	Reactant(s)	Reaction Conditions[c]	Product(s)[a]	% Yield[b]
1		1. Lithium morpholide THF, -78° 2. *n*-BuLi, -78° 3. CH$_3$I		85
2		"		90
3		"		86

Table. (continued)

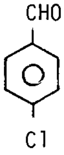
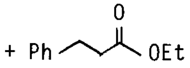
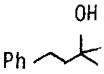
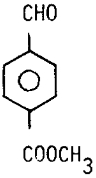
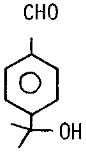
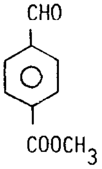
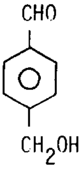
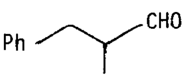
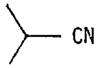
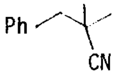
Entry	Reactant(s)	Reaction Conditions[c]	Product(s)[a]	% Yield[b]
4	 A +  B	1. 1.1 LMPA, -23° 2. 3 equiv CH_3MgCl, 0°	A +  C	87; 90
5	A + B	1. 1.1 LMPA, -23° 2. 1.1 Me_3SiCl, RT, 1 h 3. xs CH_3Li	A + C	89; 82
6		1. 1.1 LMPA, -23° 2. 1.1 Me_3SiCl 3. xs CH_3MgCl		76
7		1. 1.1 LMPA, -23° 2. 1.1 Me_3SiCl 3. xs LAH		89
8	 D	1. 1.5 LMPA, -78° 2. 1.5 Me_3SiCl, RT, 1 h 3. 1.0 n-BuLi 4. CH_3I		86
9	 E	1. 1.5 LMAP, -78° 2. 1.5 Me_3SiCl 3. CH_3Li, -78°, 1 h 4. EtOAc; H_3O^+	E	87

Table. (continued)

Entry	Reactant(s)	Reaction Conditions[c]	Product(s)[a]	% Yield[b]
10	E	1. 1.5 LMAP, -78° 2. 1.5 Me_3SiCl 3. LAH, -78°, 1 h 4. EtOAc; H_3O^+	E	92
11	 +  F	1. 1.5 LMAP, -78° 2. 1.5 Me_3SiCl 3. 1.1 LDA 4. Benzyl chloride	F + 	80; 71[d]

[a] All known products had identical spectral and physical properties with authentic samples. The product from entry 6 is a new compound and its structure is consistant with all spectral and elemental analyses.

[b] Reactions were performed on a 3 mmole scale and all yields are for isolated, pure, material obtained from preparative layer chromatography (silica gel, acetone-hexane).

[c] The workup consisted of pouring the reaction mixture into cold 10% aqueous HCl followed by extraction with ether.

[d] The yield was determined by ^1H nmr analysis of the mixture isolated from preparative layer chromatography.

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References and notes

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5. Lithium N-methylanilide and lithium piperidide were also used; however, the solubility of these lithium amides, or their aldehyde adducts, was too low for convenient use in THF at low temperatures.
6. Ketones have been protected toward hydride reduction via the in situ formation of enolate anions. D. H. R. Barton, R. H. Hesse, C. Wilshire, and M. M. Pechet, J. Chem. Soc., Perkin Trans. 1, 1075 (1977); G. R. Kieczykowski, and R. H. Schlessinger, J. Am. Chem. Soc., 100, 1938 (1978); D. J. Goldsmith, A. J. Lewis, and W. C. Still, Tetrahedron Lett., 4807 (1973); G. A. Kraus and K. Frazier, J. Org. Chem., 45, 4262 (1980).

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