Tetrahedron Letters Vol. 21, pp 3227 - 3230 0040-4039/80/0815-3227$02.00/0

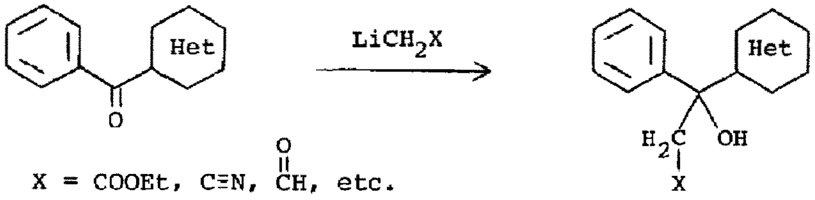
LITHIATION OF TRIMETHYLSILYL SUBSTITUTED ACETAMIDE DERIVATIVES. ADDITION TO CARBONYL COMPOUNDS.

Tina Morwick
Lilly Research Laboratories
Indianapolis, Indiana 46285

Summary: The lithio anions of N,O-bis(trimethylsilyl)acetamide and N-(trimethylsilyl)-N-methylacetamide were prepared and reacted with several carbonyl compounds to form β hydroxy acetamide and N-methylacetamide derivatives.

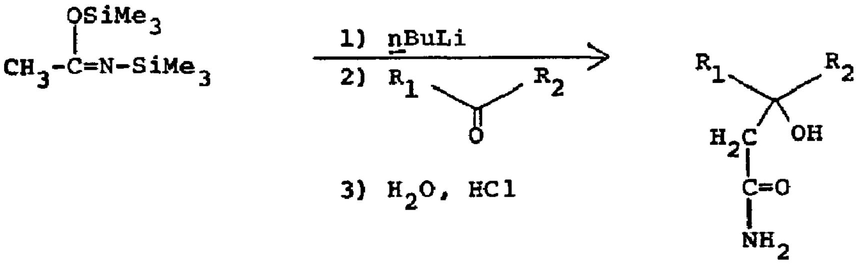
The formation of lithium anions from a variety of methyl carbonyl compounds has been well documented in the literature, and in the past few years this type of lithium chemistry has produced many valuable innovations in the area of carbon-carbon bond formation. Lithium enolates of ethyl acetate,[1] *t*-butyl acetate,[2] as well as several other esters[3] have been described. The preparation of the lithio dianion of acetic acid[4] and several other straight chain carboxylic acids has been reported by Pfeffer, Silbert and Chirinko. The utility of similar compounds, for example, the α lithio anions of "masked" acetaldehyde derivatives[5,6] and α lithio acetonitrile[7] have also been demonstrated.

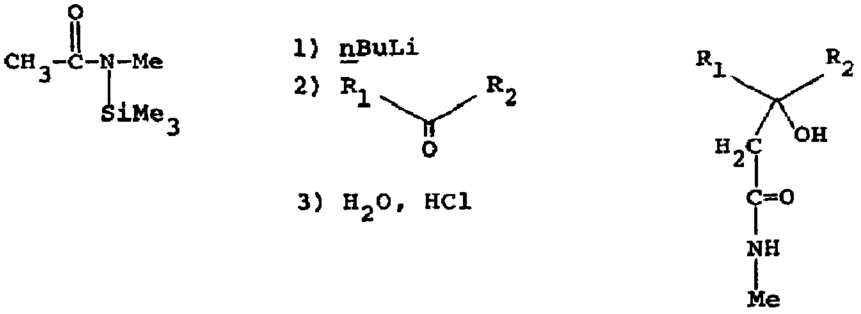
We have recently been involved in the addition of several of these lithio anions to some benzoyl heterocycles for the preparation of a series of β hydroxy esters, nitriles, aldehydes, etc.



X = COOEt, C≡N, $\overset{O}{\overset{\|}{C}}H$, etc.

Our attempts to prepare a primary amide in this series from the corresponding nitrile, acid or ester were unsuccessful due to the presence of other reactive functionalities on the heterocyclic moiety. We therefore sought a reagent to add to the ketone which would function as a protected α lithio acetamide whereby the protecting groups could be readily removed (preferably during aqueous work-up). The use of N,O-bis(trimethylsilyl)acetamide (BSA) for this purpose produced excellent results. The lithium enolate of BSA is readily generated in tetrahydrofuran at -78° using *n*-butyllithium. The addition of our substrate to this reagent at -78° in THF gave the substituted β hydroxy acetamide in excellent yield. We describe here the general utility of this reagent and a similar reagent, lithio-N-(trimethylsilyl)-N-methylacetamide for the preparation of several β hydroxy substituted carbonyl derivatives.





Subsequent to our work with these reagents, we found that lithio BSA had been used by Evans, et. al.[8] for addition to a "masked" quinone derivative for the preparation of some p quinol intermediates. In this work the reagent had been generated from lithium diisopropylamide (LDA) in THF at -78°. We found that both reagents could be successfully generated directly from n-butyllithium and added to a variety of carbonyl derivatives with moderate to excellent yields.

A typical procedure is as follows. A solution of BSA (4.95 ml, 20 mm) in 50 ml of tetrahydrofuran was cooled to -78°. A solution of n-butyllithium (1.6N in hexane) (12.5 ml, 20 mm) was added dropwise maintaining the temperature at less than -70°. The mixture was stirred at -78° for 15 minutes. A solution of benzophenone (3.64 g, 20 mm) in 50 ml of tetrahydrofuran was added dropwise again maintaining temperature at less than -70°. The mixture was stirred at -78° for ninety minutes. The mixture was then allowed to warm to room temperature while water (100 ml) and 1N HCl (25 ml) were added. Tetrahydrofuran was evaporated with vacuum. The product was isolated by filtration as a white, fluffy solid (4.65 g, 96.5% yield; m.p. 214-216°).[9]

The following tables summarize our use of these reagents with a variety of substrates.

Table I: Reaction with Lithio-N,O-bis(trimethylsilyl)acetamide

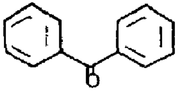
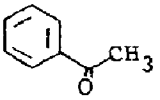
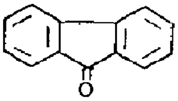
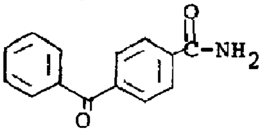
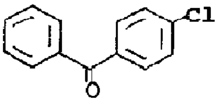
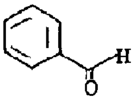
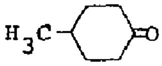
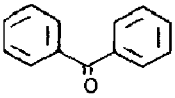
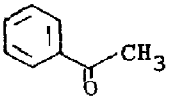
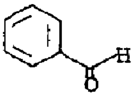
Substrate	Yield	M.P. °C	EIMS, M^+	Anal.[a]	NMR (DMSO-δ)
	96.5%	214-16	241	C,H,N	3.18 (s, 2H, CH_2) 7.2-7.7 (m, 10H, ArH)
	88.0%	72-3	179	C,H,N	1.53 (s, 3H, CH_3) 2.65 (d, 2H, CH_2) 7.20-7.73 (m, 5H, ArH)
	88.9%	150-2	239	C,H,N	2.70 (s, 2H, CH_2) 7.1-8.0 (m, 8H, ArH)
 [b]	73.9%	189-90	284	C,H,N	3.15 (s, 2H, CH_2) 7.1-8.0 (m, 9, ArH)
	58.0%	164-5	275	C,H,N	3.10 (s, 2H, CH_2) 7.1-7.6 (m, 9H, ArH)
	42.4%	116-17	165	C,H,N	2.45 (d, 2H, CH_2) 5.00 (t, 1H, CH) 7.2-7.6 (m, 5H, ArH)
	57.0%	132-3	171	C,H,N	0.7-1.8 (m, 12H, CH, $4CH_2$, CH_3) 2.15, 2.25 (s,s,2H,CH_2

Table II: Reaction with Lithio-N-(trimethylsilyl)-N-methylacetamide

	88.6%	136-8	255	C,H,N	2.70 (d, 3H, CH_3) 3.20 (s, 2H, CH_2) 7.2-8.0 (m, 10H, ArH)
	88.9%	54-7	-	C,H,N	1.5 (s, 3H, CH_3) 2.50 (s, 2H, CH_2) 2.63 (d, 3H, CH_3) 7.1-7.7 (m, 5H, ArH)
	38.0%	105-6	179	C,H,N	2.48 (d, 2H, CH_2) 2.63 (d, 3H, CH_3) 5.1 (t, 1H, CH) 7.2-7.6 (m, 5, ArH)

---

[a] Analytical results obtained for these elements were within ±0.4% of the theoretical.

[b] 2 equivalents of BSA and n BuLi were used.

Attempted preparation of the lithium derivatives of the corresponding unprotected acetamide and N-methylacetamide with one, two or three equivalents of *n*-butyllithium and reaction with typical substrates under similar conditions was unsuccessful, and none of the desired addition products were detected.

Notes and References

1. M. W. Rathke, J. Am. Chem. Soc., 92, 3222 (1970).
2. M. W. Rathke and D. F. Sullivan, ibid., 95, 3050 (1973).
3. M. W. Rathke and A. Lindart, ibid., 93, 2318 (1971).
4. P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, J. Org. Chem., 37, 451 (1972).
5. G. Wittig and H. Reiff, Angew. Chem. Internat. Edit., 7, 7 (1968).
6. A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, J. Org. Chem., 38, 36 (1973).
7. E. M. Kaiser and C. R. Hauser, ibid., 33, 3402 (1968).
8. D. A. Evans and R. Y. Wong, ibid., 42, 350 (1977).
9. IR (KBr disc) 1650 (νC=O), 3360-3190 (νNH), 1405 (νC-O), and 3480 cm^{-1} (νOH); NMR (d_6-DMSO) δ3.18 (2H, CH_2), 7.2-7.65 (10H ArH), 6.65-6.85 (broad NH); M$^+$, m/e 241; Anal. Calcd. for CHN: C, 74.67; H, 6.27; N, 5.81. Found: C, 75.00; H, 6.50; N, 6.08.

(Received in USA 15 February 1980)