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REACTION OF LITHIO N,N-DIMETHYL-TRIMETHYLSILYLACETAMIDE WITH ACYLATING REAGENTS. A SYNTHESIS OF β-ENAMINO AMIDES

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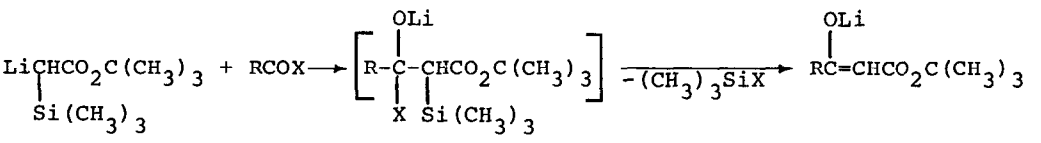
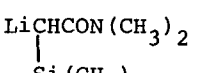
Lithio tert-butyl trimethylsilylacetate, 1, reacts with acyl imidazoles (X = ) to give good yields of β-keto esters, presumably by elimination of trimethylsilylimidazole from intermediate 2.[2] However, attempts to react 1



1 2

with other, less reactive, acylating reagents (X = OR, NR_2) were unsuccessful because of the instability of 1 at higher temperatures.

We found that the lithium enolate, 3, of N,N-dimethyltrimethylsilylacetamide has much greater stability.[3] For example, THF solutions of 3 are stable for at



3

least a week at 25°C and for several hours at reflux. Accordingly, we have examined the reaction of 3 with a variety of acylating reagents.

Reaction of 3 with acetyl chloride gives a mixture of products, containing minor amounts of the β-keto amide, 4, together with recovered amide and N,N-diisopylacetamide.

$$3 + CH_3COCl \xrightarrow[THF]{-78^\circ} \xrightarrow{H_3O^+} \underset{4\ (11\%)}{CH_3COCH_2CON(CH_3)_2} + \underset{(50\%)}{(CH_3)_3SiCH_2CON(CH_3)_2} + \underset{(10\%)}{CH_3CON[CH(CH_3)_2]_2}$$

Reaction of 3 with ethyl acetate likewise gives a mixture of products. Interestingly, the vinyl ether 6 is formed, presumably by elimination of trimethylsilyloxide from intermediate 5. Reaction of 3 with other esters gave

$$3 + CH_3CO_2C_2H_5 \xrightarrow[2\ hr]{25^\circ} \underset{5}{\left[CH_3C(OLi)(OC_2H_5)CHSi(CH_3)_2CON(CH_3)_2\right]} + 4 + \underset{6\ (11\%)}{CH_3C(OC_2H_5)=CHCON(CH_3)_2}$$

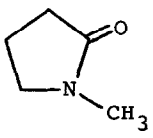
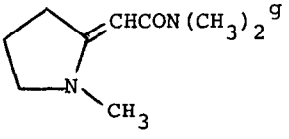
similar results, but attempts to increase the yield of vinyl ether were unsuccessful

Addition of 3 to N,N-dimethylacetamide results in a slow reaction, complete in 2 hours at reflux temperature. The product is the enamino amide, 8, formed in 78% yield (GLC).

$$3 + CH_3CON(CH_3)_2 \xrightarrow[68^\circ]{2\ hr} \underset{7}{\left[CH_3C(OLi)(N(CH_3)_2)CHSi(CH_3)_3CON(CH_3)_2\right]} \xrightarrow{-LiOSi(CH_3)_3} \underset{8\ (78\%)}{CH_3C(N(CH_3)_2)=CHCON(CH_3)_2}$$

Results obtained with other amides are shown in the table.

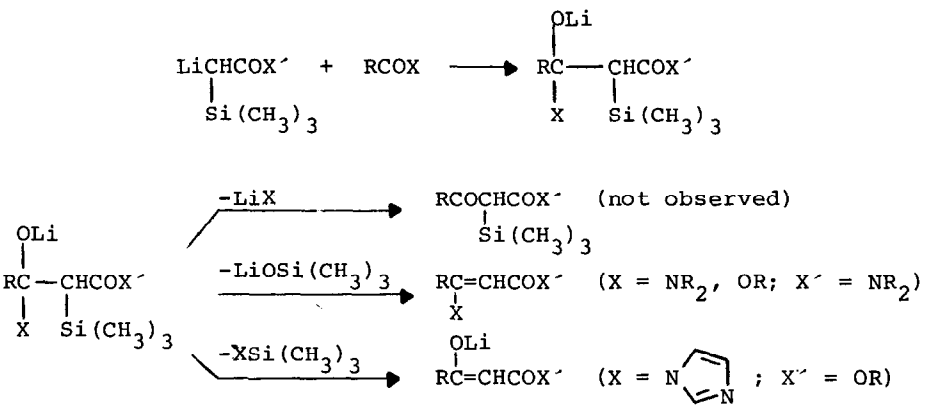
TABLE. Reaction of Amides with Lithio N,N-Dimethyltrimethylsilylacetamide

Amide	Product[a]	Yield, %[b]
$HCON(CH_3)_2$	$(CH_3)_2NCH{=}CHCON(CH_3)_2$[c]	75 (65)
$CH_3CON(CH_3)_2$	$(CH_3)_2N(CH_3)C{=}CHCON(CH_3)_2$[d]	70 (65)
$CH_3CH_2CON(CH_3)_2$	$(CH_3)_2N(CH_3CH_2)C{=}CHCON(CH_3)_2$[e]	70 (65)
$CH_3CH_2CH_2CON(CH_3)_2$	$(CH_3)_2N(CH_3CH_2CH_2)C{=}CHCON(CH_3)_2$[f]	50 (46)
	 [g]	-(40)

[a]All products gave satisfactory results for C, H analysis. [b]GLC yields, isolated yields in parentheses. [c]mp 63-64°C, ^{1}H NMR (CCl_4): δ7.1 (d, 1H), δ4.6 (d, 1H), δ 2.9 (s, 6H), δ2.8 (s, 3H), δ2.8 (s, 3H). [d]bp (5 torr) 108-110°C, ^{1}H NMR (CCl_4) δ4.5 (s, 1H), δ2.9 (s, 6H), δ2.8 (s, 3H), δ2.8 (s, 3H), δ2.2 (s, 3H). [e] ^{1}H NMR (CCl_4): δ4.5 (s, 1H), δ3.0 (s, 6H), δ3.0 (s, 3H), δ2.94 (s, 3H), δ2.9 (m, 2H), δ1.2 (t, 3H). [f] ^{1}H NMR (CCl_4): δ4.6 (s, 1H), δ3.0 (s, 6H), δ2.94 (s, 3H), δ2.91 (s, 3H), δ2.87 (m, 2H), δ1.54 (m, 2H), δ1.07 (t, 3H). [g]bp (0.5 torr) 126-128°C, ^{1}H NMR (CCl_4): δ4.6 (s, 1H), δ3.2 (m, 4H), δ2.8 (s, 6H), δ2.7 (s, 3H), δ1.9 (m, 2H).

β-Enamino amides are presumably available by aminolysis of β-keto amides, in a reaction which works well with the corresponding β-keto esters.[4] The reaction of 3 with amides provides a unique synthesis of β-enamino amides (and, by hydrolysis, the corresponding β-keto amides[5]), incorporating a carbon-carbon bond forming step not achievable by other, presently available, methods. In addition, the results extend the increasing synthetic versatility of the

enolates of α-silyl carbonyl compounds.[6] For the reaction with acylating reagents, two of the three possible paths have now been observed:



The following procedure for the reaction of 3 with N,N-dimethylacetamide is representative. A 100 mL flask equipped with magnetic stirring, reflux condenser, septum inlet and mercury bubbler was flushed with nitrogen and immersed in an ice-water bath. The flask was charged with 25 mL of a 1M solution of lithium diisopropylamide in THF and 4.35 mL (25 mmol) of N,N-dimethyltrimethylsilylacetamide[3] was then added dropwise. The solution was allowed to stir 15 min to give a colorless solution of 3. N,N-dimethylacetamide (2.3 mL, 25 mmol) was added and the solution was heated to reflux for two hours. The cooled reaction mixture was extracted with 5 mL of water and the separated organic layer dried over anhydrous K_2CO_3. Vacuum distillation gave 2.7 g, 68%, of N,N-dimethyl-3-dimethylamino-2-butenoamide.

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REFERENCES

1. Alfred P. Sloan Foundation Fellow, 1976-1977.
2. S.L. Hartzell and M.W. Rathke, Tetrahedron Lett., 2757 (1976).
3. R.P. Woodbury and M.W. Rathke, J. Org. Chem., 000,000 (1977).
4. c.f. G.E. Wilson, G.R. Harvey and G.A. Berchtold, J. Org. Chem., 30, 2642 (1965).
5. For example, treatment of 8 with 3M HCL for 10 min at room temperature gave the β-keto amide in quantitative yield.
6. K. Shimoj, H. Taguchi, K. Oshima, H. Yamamoto and H. Nazaki, J. Amer. Chem. Soc., 96, 1620 (1974). S.L. Hartzell, D.F. Sullivan and M.W. Rathke, Tetrahedron Lett., 1403 (1974). S.L. Hartzell and M.W. Rathke, Tetrahedron Lett., 2737 (1976).