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REACTION OF LITHIO TERT-BUTYL TRIMETHYLSILYLACETATE WITH ACYL IMIDAZOLES. A SYNTHESIS OF β-KETO ESTERS.

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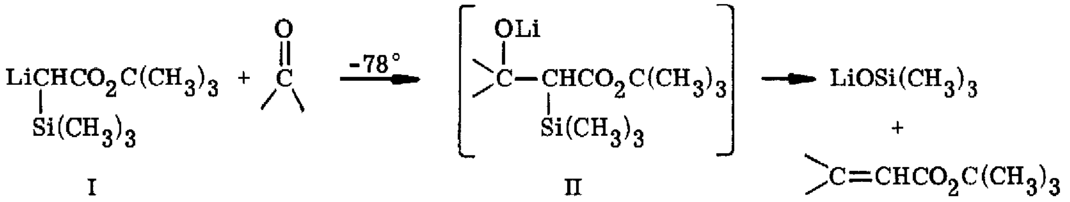
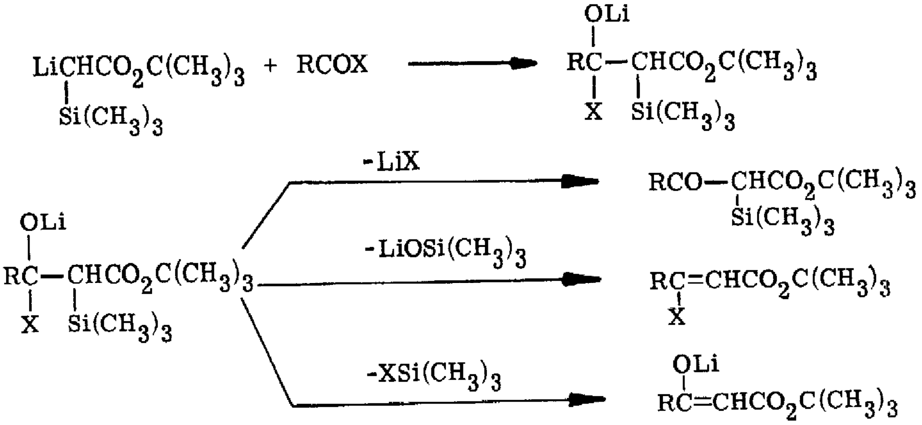
Lithio *tert*-butyl trimethylsilylacetate, I, reacts with aldehydes or ketones to give α,β-unsaturated esters (eq 1).[2] The products are assumed to form by loss of lithium trimethylsilyl oxide from intermediate II. It is remarkable that this elimination occurs rapidly at dry-ice temperatures. Evidently, the carboalkoxy group in II renders the adjacent trimethylsilyl group highly labile.[3]



$$\underset{\text{I}}{\mathrm{Li}\underset{\mathrm{Si(CH_3)_3}}{\mathrm{CH}}\mathrm{CO_2C(CH_3)_3}} + \mathrm{>C{=}O} \xrightarrow{-78^\circ} \underset{\text{II}}{\left[\mathrm{>}\overset{\mathrm{OLi}}{\mathrm{C}}-\underset{\mathrm{Si(CH_3)_3}}{\mathrm{CH}}\mathrm{CO_2C(CH_3)_3}\right]} \longrightarrow \mathrm{LiOSi(CH_3)_3} + \mathrm{>C{=}CHCO_2C(CH_3)_3} \qquad (1)$$

Granted this high lability, the reaction of I with acylating reagents, RCOX, could conceivably take three different paths, two of which involve elimination of the trimethylsilyl group (eq 2, 3, and 4).



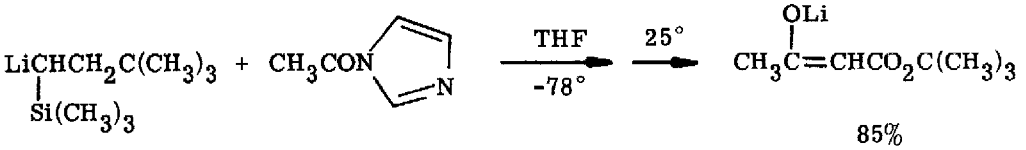
$$\mathrm{Li}\underset{\mathrm{Si(CH_3)_3}}{\mathrm{CH}}\mathrm{CO_2C(CH_3)_3} + \mathrm{RCOX} \longrightarrow \mathrm{R}\underset{\mathrm{X}}{\overset{\mathrm{OLi}}{\mathrm{C}}}-\underset{\mathrm{Si(CH_3)_3}}{\mathrm{CH}}\mathrm{CO_2C(CH_3)_3}$$

$$\mathrm{R}\underset{\mathrm{X}}{\overset{\mathrm{OLi}}{\mathrm{C}}}-\underset{\mathrm{Si(CH_3)_3}}{\mathrm{CH}}\mathrm{CO_2C(CH_3)_3} \xrightarrow{-\mathrm{LiX}} \mathrm{RCO}-\underset{\mathrm{Si(CH_3)_3}}{\mathrm{CH}}\mathrm{CO_2C(CH_3)_3} \qquad (2)$$

$$\xrightarrow{-\mathrm{LiOSi(CH_3)_3}} \mathrm{R}\underset{\mathrm{X}}{\mathrm{C}}\mathrm{{=}CHCO_2C(CH_3)_3} \qquad (3)$$

$$\xrightarrow{-\mathrm{XSi(CH_3)_3}} \mathrm{R}\overset{\mathrm{OLi}}{\mathrm{C}}\mathrm{{=}CHCO_2C(CH_3)_3} \qquad (4)$$

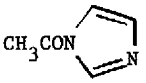
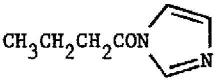
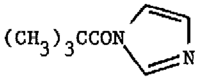
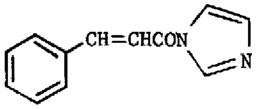
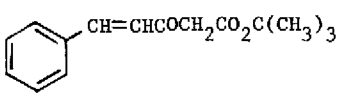
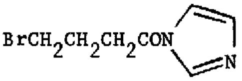
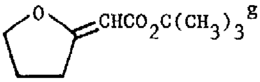
We have reacted tetrahydrofuran (THF) solutions of I with a variety of acylating reagents. With acetyl chloride, only a complicated mixture of products was obtained. With ethyl acetate or N,N-dimethylacetamide, I was recovered unchanged. However, reaction of I with acetyl imidazole gave, following removal of the solvent, an 85% yield of the lithium salt of tert-butyl acetoacetate (eq 5).[4] Alternatively, quenching the reaction mixture with dilute acid followed by workup gave tert-butyl acetoacetate in 94% yield.



(5)

We applied this latter procedure to a number of acyl imidazoles with the results shown in Table I. Although other mechanisms are clearly possible, for the present we are content to assume the β-keto esters obtained are formed as shown by eq 4 (X=imidazolide).

Table I. Reaction of Acyl Imidazoles with Lithio Tert-butyl Trimethylsilyacetate

Acyl Imidazole[a]	Product[b]	Yield, %[c]
	$CH_3COCH_2CO_2C(CH_3)_3$	94
	$CH_3CH_2CH_2COCH_2CO_2C(CH_3)_3$[d]	81
	$(CH_3)_3CCOCH_2CO_2C(CH_3)_3$[e]	70
	[f]	(50)
	[g]	75

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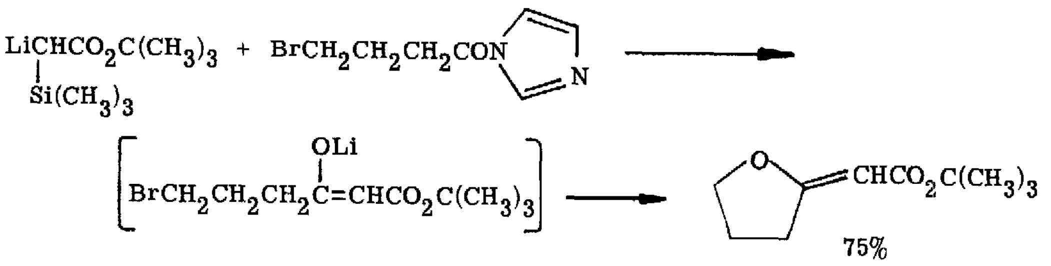
[a] Prepared from imidazole and acid chloride (ref. 7). [b] Products are mixtures of keto and enol forms. [c] GLPC yields, isolated yields in parentheses. [d] PMR spectrum (CCl_4): singlet δ3.16 (2H), multiplet δ2.60-2.30 (2H), singlet δ1.46 (9H), multiplet δ1.06-0.70 (5H). [e] PMR spectrum (CCl_4): singlet δ4.83 (1H), singlet δ3.93 (1H), singlet δ3.26 (2H), overlapping singlets δ1.46-1.43 (9H), singlet δ1.13 (9H). [f] PMR spectrum (CCl_4): multiplet δ7.80-6.70 (2H), multiplet δ7.73-7.26 (5H), singlet δ3.60 (2H), singlet δ1.5 (9H). [g] PMR spectrum (CCl_4): singlet δ5.13 (1H), triplet δ4.13-3.96 (2H), multiplet δ4.13-3.96 (2H), multiplet δ2.16-1.86 (2H), singlet δ1.43 (9H).

The preparation of β-keto esters by direct acylation of ester enolates is normally complicated by the acidic nature of the products.[5] This usually results in the neutralization of 50% of the starting enolate. The present procedure avoids this difficulty by generating the anion of the β-keto ester directly. This also offers obvious advantages when further synthetic sequences with the anion are desired. For example, reaction of I with 4-bromo-butanoyl imidazole[6] gave in one step a 75% yield of tert-butyl 2-tetrahydrofurylideneacetate (eq 6).



(6)

The following procedure for the conversion of cinnamoyl imidazole into tert-butyl cinnamoylacetate is representative. A 100 ml, round-bottomed flask equipped with magnetic stirring, septum inlet and mercury bubbler is flushed with nitrogen and immersed in an ice-water bath. The flask is charged with a hexane solution of n-butyllithium (12.5 ml, 25 mmol) and 3.6 ml (25 mmol) of diisopropylamine is injected over a 2 minute period. Following complete addition, the hexane is removed under vacuum and the residue of lithium diisopropylamide is dissolved in 25 ml of THF. The flask is immersed in a dry-ice acetone bath and tert-butyl trimethylsilylacetate[2] (5.5 ml, 25 mmol) is added dropwise over a 2 minute period. After an additional 10 minutes of stirring, a warm solution of cinnamoyl imidazole[7] (4.95 g, 25 mmol) in 25 ml of THF is added dropwise. The red reaction mixture is stirred for an hour and then allowed to reach room temperature and quenched by the addition of 25 ml of 3N hydrochloric acid. Addition of 100 ml pentane followed by separation and evaporation of the organic phase gave 5.85 g (95%) of a yellow solid. Recrystallization from methanol gave pure tert-butyl cinnamoylacetate; 3.1 g, (50%), mp 87-87.5°.

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3. For example, sodium salts of intermediates similar to II but lacking the carboalkoxy group, eliminate only sluggishly at 50°: D.J. Peterson, J. Org. Chem., **33**, 780 (1968).

4. Physical and spectral properties of the salt were identical to authentic samples prepared from *tert*-butyl acetoacetate.
5. M.W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971).
6. Tetrahydrofuran solutions of this acyl imidazole were prepared from 4-bromobutanoyl chlori and imidazole and used directly.
7. H.A. Staab, *Angew. Chem. Internat. Edit.*, **1**, 351 (1962).