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CONDENSATIONS OF β-KETO AMIDES AT THE γ-POSITION VIA DIANIONS

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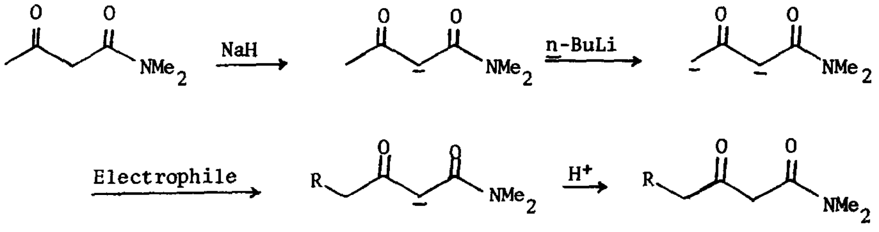
The dianions of β-keto esters have been used extensively to introduce substituents at the γ-position,[1] but the utility of these intermediates has been limited by a self-condensation of the keto esters which involves nucleophilic attack of the keto ester dianion on the ester group of the monoanion.[2,3] The problem is particularly severe with condensations which are inherently slow such as with electrophiles bearing negative charge. In an attempted condensation of the dianion of methyl acetoacetate with acetoacetaldehyde monoanion, the major product was methyl orsellinate, arising from self-condensation of methyl acetoacetate.[3] A similar result has been obtained from treatment of methyl acetoacetate dianion with ethyl benzoylacetate monoanion.[4] This problem can be minimized through use of β-keto esters having more bulky alkoxy groups which hinder nucleophilic attack on the carboxyl group; for example, condensation of tert-butyl acetoacetate dianion with acetoacetaldehyde monoanion proceeds satisfactorily.[3] We now wish to report, as an alternative to hindered β-keto esters for these reactions, the use of β-keto N,N-dialkylamides in which resonance inhibits nucleophilic attack on the carboxamido group. One example of the formation of a dianion of a β-keto N,N-dialkylamide and subsequent alkylation was reported previously but the potential synthetic advantage relative to β-keto esters was not recognized.[5]

N,N-Dimethylacetoacetamide (I) was converted to its dianion either by treatment with two equivs of lithium diisopropylamide in THF (-20°) or by treatment with one or more equivs of NaH in THF (20°) to form the monoanion followed by one equiv of n-butyl lithium (0°). Condensations of the sodium-lithium salt of I with an alkyl halide, a ketone and four esters are shown in the Table. Work-up of the condensation reactions involved removal of solvent in vacuo, acidification, and extraction from a minimum volume of water, followed by chromatography (2% MeOH-$CHCl_3$) on a short column of acid-washed TLC silica gel. All products gave satisfactory spectra and elemental analyses.



Condensations of Electrophiles with Sodio-lithio-N,N-dimethylacetoacetamide

Electrophile	Dianion:Electrophile Ratio	Reaction Conditions	Product	Yield
$C_6H_5CH_2Cl$	1:1	20°, 1 hr	$C_6H_5CH_2CH_2COCH_2CONMe_2$	92%
$(C_6H_5)_2CO$	1:1	20°, 1 hr	$(C_6H_5)_2C(OH)CH_2COCH_2CONMe_2$	79%
CH_3CO_2Et	2:1	0°, 15 min	$CH_3COCH_2COCH_2CONMe_2$	54%
$C_6H_5CO_2Me$	2:1	0°, 15 min	$C_6H_5COCH_2COCH_2CONMe_2$	88%
$CH_3COCH(Na)CO_2Me$	2:1	45°, 72 hr	$CH_3COCH_2COCH_2COCH_2CONMe_2$	56%
$C_6H_5COCH(Na)CO_2Et$	2:1	67°, 48 hr	$C_6H_5COCH_2COCH_2COCH_2CONMe_2$	68%

The alkylation of I with benzyl chloride,[1c] aldol condensation with benzophenone[1b] and acylation with ethyl acetate[2] gave results comparable with the corresponding reactions of acetoacetate esters; the other condensations were superior. Most significant was the condensation of the dianion of I with ethyl benzoylacetate monoanion which gave the corresponding aryl triketo amide in 68% yield uncontaminated by N,N-dimethyl-3,5,7-trioxocaprylamide or cyclization products thereof which would have resulted from self-condensation of I. The condensation of the dianion of I with methyl acetoacetate anion gave 56% of triketo amide after 72 hr at 45° uncontaminated by methyl 3,5,7-trioxooctanoate or methyl orsellinate. Although the triketo amide might have arisen by a self-condensation of I (dianion with monoanion), this was shown not to be the case. An equimolar mixture of monoanion and dianion of I was refluxed in THF for 48 hr but gave only 10-15% of the triketo amide; the dianion itself was stable under these conditions for at least 96 hr. The condensation of methyl benzoate with the dianion of I is noteworthy; the corresponding acylation of methyl acetoacetate dianion gives a mixture of diketo ester and diketo acid.[2]

The triketo amides are significantly more stable than the corresponding triketo esters. Methyl 3,5,7-trioxooctanoate is difficult to isolate from reaction mixtures because aldol cyclization to methyl orsellinate is so facile.[6] Steric interactions in the transition state retard aldol cyclization of the dimethylamide.

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