

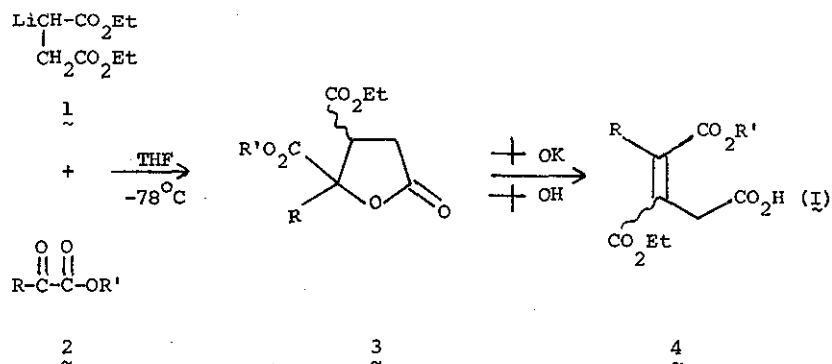
REACTION OF LITHIO DIETHYLSUCCINATE WITH CARBONYL COMPOUNDS:
STOBBE CONDENSATION OF α -KETOESTERS

Vichai Reutrakul^{*}, Kosan Kusamran and Sompong Wattanasin

Department of Chemistry, Faculty of Science, Mahidol University,
Rama VI Road, Bangkok 4, Thailand

The Stobbe condensation of α -ketoesters was successfully carried out by a two-step procedure. The reaction of lithio diethylsuccinate with α -ketoesters gave the corresponding γ -butyrolactones. Treatment of the lactones with potassium *t*-butoxide in *t*-butanol yielded the expected Stobbe products.

The Stobbe condensation is a well known reaction which has found numerous applications in organic synthesis¹. One of the limitations of this reaction is that, α -ketoesters cannot be employed as the carbonyl component due to their sensitivity to basic conditions². In this communication we wish to report the first successful Stobbe condensation of the α -ketoesters. Our novel two-step approach is as shown in equation (I).



The reaction of (1) with α -ketoester (2) gave lactone (3) in good yield. The reaction of the lactone (3) with potassium *t*-butoxide in *t*-butanol resulted in the formation of the expected Stobbe product (4) in high yield.

The following procedure is representative. α -Ketoester (1.0 equiv.) was added, at -78°C , under nitrogen, to a THF solution of lithio diethylsuccinate (1) (generated by the reaction of 2.0 equiv. of lithium diisopropylamide with 1.0 equiv. of diethylsuccinate in THF at -78°C). The reaction mixture was maintained at this temperature for 2 hr before being quenched with dilute hydrochloric acid. The aqueous mixture was extracted with ether and the crude product was purified by column chromatography on silica gel (mixture of ether-light petroleum) to give lactone (3). The formation of (4) was effected by the reaction of (3) with potassium *t*-butoxide (1.0 equiv.) in refluxing *t*-butanol. The acidic work up yielded the expected product (4). The results are summarized in Table I.

Table I

α -Ketoester	Product 3 (% Yield)	Isomer Ratio cis:trans	Product 4 (% Yield)	Isomer Ratio cis:trans
		(80.1) 2:1 ^a		(76.0) 2:1 ^{a,c}
		(71.0) 1.5:1 ^{b,c}		(76.5) - ^d
		(60.0) 1:1 ^{b,c}		(74.0) - ^d
		(24.6) 1:1 ^a		(68.8) 1:1 ^{a,b}

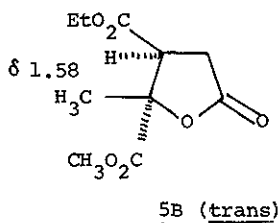
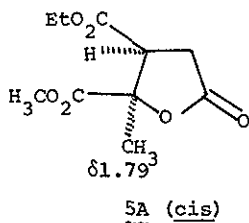
^aBy NMR

^bBy GLC as the methyl esters: on a 2 m x 6 mm glass column, packed with 2.5% SE 30 on chromosorb G A/W DMCS treated (80-100) mesh; gas flow rate = 20 ml/min; programmed temperature 150^o-180^oC.

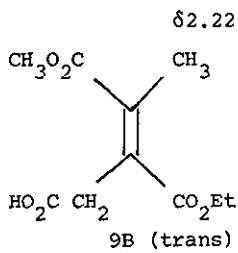
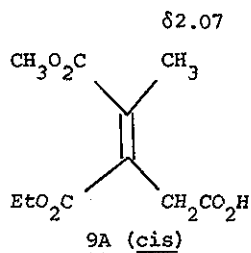
^cBy preparative thick layer chromatography (PLC).

^dIsomer ratio cannot be determined.

The assignment of isomer ratios of the lactones (5) and (8) by NMR is made possible by the observation³ that, in the γ -butyrolactone ring, the carboethoxy group exerts the shielding effect on the cis substituent, e.g. the methyl group in (5B) as compared with that in (5A). In the case of the products (9) and (12), however, the carboethoxy group deshields⁴ the

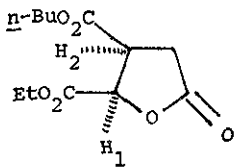


cis substituent, e.g. the methyl group in (9B) as compared with that in (9A).



$R_f = 0.16$ (ether-light petroleum 1:4) $R_f = 0.31$

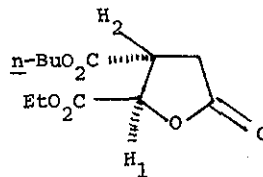
The isomer ratios of the lactones (6) and (7) were obtained from the chromatographic separation (PLC) of these compounds.



7A (cis)

$$\delta 5.19, J_{12} = 4.5 \text{ Hz}^5$$

$$R_f = 0.41 \quad (\text{ether-light petroleum 1:1})$$



7B (trans)

$$\delta 5.06, J_{12} = 8.5 \text{ Hz}^5$$

$$R_f = 0.27$$

The cis isomer (7A) (with respect to the two ester groups) is less polar (by thin layer chromatography and GLC) than the trans isomer (7B).

We are presently exploring the scope and limitation of this reaction.

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