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

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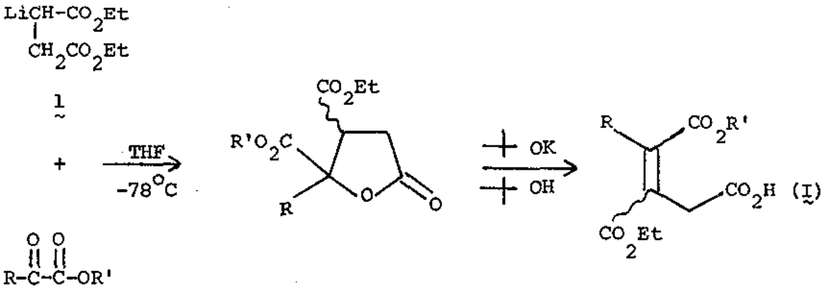
The Stobbe condensation of α-ketoesters was successfully carried out by a two-step procedure. The reaction of lithio diethylsuccinate with α-ketoesters gave the corresponding γ-butyrolactones. Treatment of the lactones with potassium t-butoxide in t-butanol yielded the expected Stobbe products.

The Stobbe condensation is a well known reaction which has found numerous applications in organic synthesis[1]. One of the limitations of this reaction is that , α-ketoesters cannot be employed as the carbonyl component due to their sensitivity to basic conditions[2]. 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).

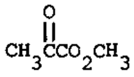
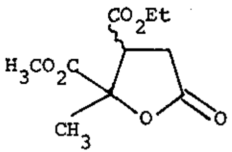
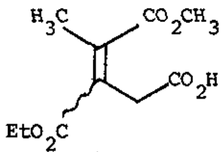
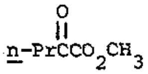
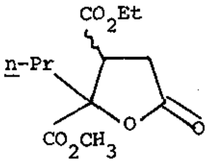
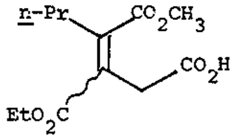
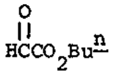
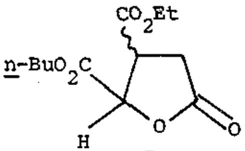
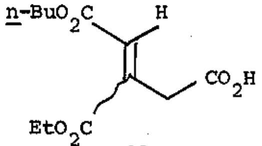
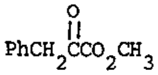
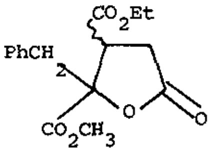
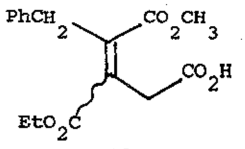


2 3 4

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 diethyl succinate 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
 $CH_3\overset{O}{\overset{\|}{C}}CO_2CH_3$	 **5** (80.1)	2:1[a]	 **9** (76.0)	2:1[a,c]
 $\underline{n}\text{-}Pr\overset{O}{\overset{\|}{C}}CO_2CH_3$	 **6** (71.0)	1.5:1[b,c]	 **10** (76.5)	-[d]
 $H\overset{O}{\overset{\|}{C}}CO_2Bu^{\underline{n}}$	 **7** (60.0)	1:1[b,c]	 **11** (74.0)	-[d]
 $PhCH_2\overset{O}{\overset{\|}{C}}CO_2CH_3$	 **8** (24.6)	1:1[a]	 **12** (68.8)	1:1[a,b]

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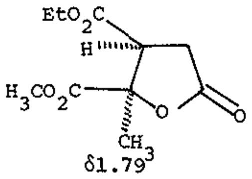
[a] By NMR

[b] By 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°-180°C.

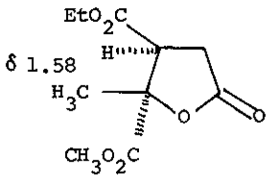
[c] By preparative thick layer chromatography (PLC).

[d] Isomer ratio cannot be determined.

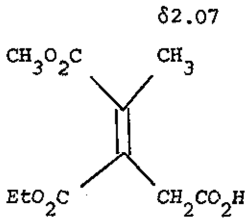
The assignment of isomer ratios of the lactones (5) and (8) by NMR is made possible by the observation[3] that, in the γ-butyrolactone ring, the carboethoxy group exerts the *shielding* effect on the *cis* substituent, e.g. the methyl group in (5B) as compared with that in (5A). In the case of the products (9) and (12), however, the carboethoxy group deshields[4] the *cis* substituent, e.g. the methyl group in (9B) as compared with that in (9A).



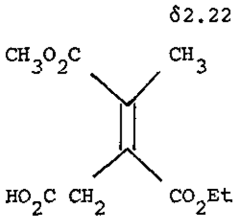
5A (*cis*)



5B (*trans*)



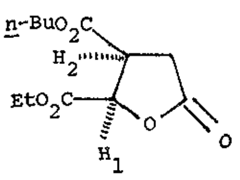
9A (*cis*)



9B (trans)

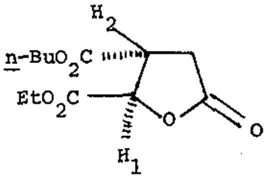
$R_f = 0.16$ (ether-light petroleum 1:4) $R_f = 0.31$

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



7A (*cis*)

δ5.19, J_{12} = 4.5 Hz[5]



7B (*trans*)

δ5.06, J_{12} = 8.5 Hz[5]

R_f = 0.41 (ether-light petroleum 1:1) 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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