

TITANIUM-MEDIATED DIECKMANN CONDENSATION

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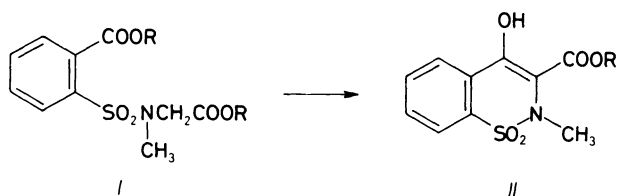
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The Dieckmann condensation of alkyl 2-(N-methyl-N-(alkoxycarbonylmethyl)sulfamoyl)-benzoates *Ia* and *Ib* with titanium tetrachloride-tert-amine or butyltitanium ate complex *III* affords alkyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxides *IIa* and *IIb* which are the piroxicam intermediates.

Transition-metal-mediated synthetic methods are bringing about a revolution in the manufacture of pharmaceuticals, agrichemicals, and other fine chemicals. The explosive growth of organotitanium chemistry over the past ten years can be attributed to the specific reactions of organotitanium compounds¹, e.g., the chemo- and enantioselective addition of organotitanium reagents to carbonyl compounds²⁻⁴, the Sharpless enantioselective epoxidation of allyl alcohols^{5,6}, and the titanium-mediated aldol⁷ and Claisen⁸ condensations. In particular, the last mentioned synthetic application of titanium compounds has increased tremendously in recent years. For some time Mukaiyama⁷ has utilized titanium(IV) chloride in crossed-aldol reactions of silyl enol ethers, enol ethers, or enol esters with carbonyl compounds, acetals, or ketals. More recently Harrison⁹ described the aldol condensation mediated by titanium(IV) chloride in the presence of triethylamine. In the course of expanding our studies



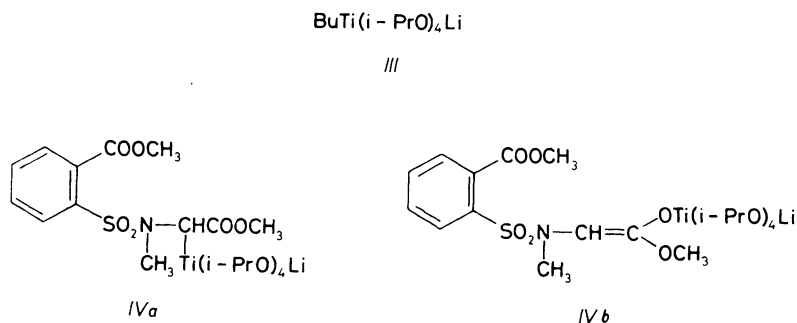
In formulae I and II: a, R = CH₃ b, R = CH₂CH₂OCH₃

SCHEME I

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on the Dieckmann condensation of some intermediates for the antiinflammatory drug piroxicam¹⁰, we became interested in the titanium complexes as a possible route to esters *II* (Scheme 1).

In this communication, we report our results with the Dieckmann condensation of esters *Ia* and *Ib* mediated by the titanium compounds such as titanium(IV) chloride and butyltitanium ate complex *III*. We have found that the esters *Ia* and *Ib* undergo the Dieckmann condensation upon treatment with titanium(IV) chloride in the presence of tertiary amines. The results of these reactions are given in Table I. As shown in Table I, the influence of molar ratio of reactants and reaction temperature on the yield of esters *II* was examined. The best results were obtained at -78°C when molar ratio *I*: titanium(IV) chloride: amine was 1 : 2.2 : 3. It should be noted that good yields could be obtained only when the amine was added dropwise over 1 h. Concerning the influence of amine structure, it was found that the yields of esters *II* are almost independent of the type of tert-amines used for this reaction. Fortunately, 2-methoxyethyl ester *Ib* also affords product *Iib* in good yield. This fact is very encouraging because from the point of view of the target product it is advantageous to carry out the preparation with alkoxyethyl esters of the type *II* (ref.¹⁰).



Furthermore, the butyltitanium ate complex *III* was used for the reaction mentioned above. The compounds of this type have already been mentioned in literature, but their aggregation state and coordination number are currently unknown^{1,2,11}. It was assumed that with liberation of butane, the addition of *Ia* to a solution of *III* in THF affords titanium ate complex *IVa* or titanium enolate ate complex *IVb* and, after workup, desired ester *Iia*. Indeed, *III* reacts with ester *Ia* at -78°C to give a crystalline compound over a period of about 45 min. Unfortunately, spectroscopic data of this compound are not available. At about -20°C , the mixture became a clear yellow solution and after 6 h the ester *Iia* was isolated in 27% yield. It is possible that *III* (or intermediate ate complexes *IV*) dissociate to the neutral organyltitanium triisopropoxide and lithium isopropoxide prior to condensation.

For this reason, the same reaction was performed with butyltitanium triisopropoxide, lithium isopropoxide, and butyllithium. From the Table II it is evident that whatever the precise structure of the reagent may be, the reacting species is neither butyltitanium triisopropoxide nor lithium isopropoxide. It is interesting to note, that with butyllithium the ester *Ia* is obtained in a yield, which is similar to that observed for reaction with *III*. Thus, it is likely that at higher temperature (above 0°C) butyllithium could result from an equilibrium mixture according to Eq. (A)*.

TABLE I

Results of the TiCl_4 mediated Dieckmann condensation of esters *Ia* and *Ib*

Ester	Amine	$I : \text{TiCl}_4 : \text{amine}^a$	$T, ^\circ\text{C}$	Yield, %
<i>Ia</i>	Triethylamine	1 : 1·1 : 2·2	0	24
		1 : 1·1 : 3	0	30
		1 : 1·1 : 3	-78	40
		1 : 2·2 : 3	-78	65
		1 : 2·2 : 4	-78	58
<i>Ib</i>		1 : 2·2 : 3	-78	61
<i>Ia</i>	1-Ethylpiperidine	1 : 2·2 : 3	-78	64
<i>Ia</i>	N,N-Diisopropylethylamine	1 : 2·2 : 3	-78	58

^a Molar ratio.

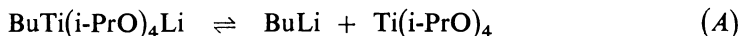
TABLE II

Results of the Dieckmann condensation of ester *Ia* using nonnitrogen bases

Base	$T, ^\circ\text{C}$	Yield, % ^a
$\text{BuTi}(\text{i-PrO})_4\text{Li}$	20	27
$\text{BuTi}(\text{i-PrO})_4\text{Li}$	-78 ^b	0
$\text{BuTi}(\text{i-PrO})_3$	20	0
$\text{Li}(\text{i-PrO})$	20	53 ^c
BuLi	-78	23
BuLi	20	24

^a 2·2 Equivalents of base, 6 h; ^b at 0°C also no reaction was observed; ^c complete transesterification (isopropylester *II* was obtained).

* Abbreviations used are as follows: Bu 1-butyl, i-Pr 2-propyl, THF tetrahydrofuran.



The actual structures of the intermediates *IV* will require further study.

EXPERIMENTAL

All amines were distilled from calcium hydride and stored over 3A molecular sieves. Dichloromethane and THF were freshly distilled from calcium hydride and sodium benzophenone ketyl, respectively, under nitrogen. Concentration of butyllithium in hexane was determined by titration with 2-propanol and 1,10-phenanthroline as indicator¹². All compounds were checked for purity by TLC on silica gel (Kieselgel 60 F 254, Merck) in toluene-ethanol-acetic acid (80 : 5 : 3). Chlorotriisopropoxytitanium was prepared according to a known procedure². Starting esters *Ia* and *Ib* were prepared from alkyl 2*H*-1,2-benzothiazolin-3-one-2-acetate 1,1-dioxides¹⁰.

The Dieckmann Condensations of Esters *Ia* and *Ib* with Different Bases

TiCl₄-tertiary amine. To a cooled (0°C) solution of TiCl₄ (1.38 g, 7.3 mmol) in dichloromethane (15 ml) a solution of ester *I* (3.3 mmol) in dichloromethane (5 ml) was added. The mixture was stirred for 10 min and then cooled to -78°C. After 5 min, the tertiary amine (9.9 mmol) was added over a period of 1 h. The dark brown solution was stirred at -78°C for 4 h. Before quenching, the solution was warmed to 0°C and then brine (10 ml) and 18% HCl (10 ml) were added and the mixture was stirred for 10 min. The aqueous layer was extracted twice with dichloromethane and combined organic extracts were dried over MgSO₄. After removal of the solvent, the residue was crystallized from ethanol to give *II*. The yields are given in Table I.

Butyltitanium ate complex IV: To a solution of tetraisopropoxytitanium (2.08 g, 7.3 mmol) in THF (15 ml) butyllithium (4.8 ml, 7.3 mmol) was added dropwise at -78°C. After stirring for 10 min, the orange ate complex *III* was formed. After addition of a solution of *Ia* (1.00 g, 3.3 mmol) in THF (5 ml), the orange solution was stirred over a period of about 45 min to give an orange suspension. The mixture was allowed to warm to room temperature and after stirring for 6 h, the clear yellow solution was evaporated to dryness. The residue was treated with cold brine (10 ml) and 18% HCl (10 ml). This mixture was extracted twice with dichloromethane and combined organic extracts were dried over MgSO₄. After removal of the solvent, the residue was crystallized from ethanol to give *Ila* (0.24 g, 27%).

Butyltitanium triisopropoxide: To a solution of chlorotriisopropoxytitanium (3.4 ml, 7.3 mmol, in hexane) in THF (15 ml) butyllithium (4.8 ml, 7.3 mmol) was added dropwise at -30°C. After stirring for 30 min, the red-brown solution was formed. After addition of a solution of *Ia* (1.00 g, 3.3 mmol) in THF (5 ml), the solution was stirred for 6 h and worked up as described for the ate complex *III* to give starting ester *Ia* (0.7 g) and by-products. No ester *Ila* was detected.

Lithium isopropoxide: A solution of 2-propanol (4.39 g, 7.3 mmol) in THF (15 ml) was cooled to 0°C. Butyllithium (6.4 ml, 7.3 mmol) was added, the cooling bath was removed, and a solution of *Ia* (1.00 g, 3.3 mmol) in THF (5 ml) was added. After stirring for 6 h at room temperature, the solution was worked up as above described to give isopropyl ester *II* (0.52 g, 53%).

Butyllithium: To a solution of butyllithium (6.4 ml, 7.3 mmol) in THF (15 ml) at -78°C, the solution of *Ia* (1.00 g, 3.3 mmol) in THF (5 ml) was added, the cooling bath was removed and after stirring for 6 h at room temperature, the solution was worked up as above described to give *Ila* (0.21 g, 24%).

REFERENCES

1. Reetz M. T.: *Organotitanium Reagents in Organic Synthesis*. Springer, Berlin 1986.
2. Reetz M. T., Westermann J., Steinbach R., Wenderoth B., Peter R., Ostarek R., Maus S.: *Chem. Ber.* *118*, 1421 (1985).
3. Weidmann B., Seebach D.: *Angew. Chem., Int. Ed. Engl.* *22*, 31 (1983).
4. Seebach D., Beck A. K., Roggo S., Wonnacott A.: *Chem. Ber.* *118*, 3673 (1985).
5. Katsuke T., Sharpless K. B.: *J. Am. Chem. Soc.* *102*, 5974 (1980).
6. Sharpless K. B.: *J. Am. Chem. Soc.* *109*, 5765 (1987).
7. Mukaiyama T.: *Org. React.* *28*, 203 (1982).
8. Tanabe Y., Mukaiyama T.: *Chem. Lett.* *1986*, 1813.
9. Harrison C. R.: *Tetrahedron Lett.* *28*, 4135 (1987).
10. Pátek M., Hampl F.: *Collect. Czech. Chem. Commun.* *54*, 3267 (1989).
11. Takahashi H., Kawabata A., Niwa H., Higashiyama K.: *Chem. Pharm. Bull.* *36*, 803 (1988).
12. Watson S. C., Eastham J. F.: *J. Organomet. Chem.* *9*, 165 (1967).

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