Tetrahedron Letters, Vol. 22, No. 14, pp 1323 - 1326 ,1981
Printed in Great Britain

0040-4039/81/141323-04\$02.00/0

SYNTHESIS OF OPTICALLY ACTIVE TETRAORGANOTIN COMPOUNDS

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SUMMARY

Optically active tetraorganotin compounds have been synthesized by reaction of organometallic reagents on a tin cinchoninate intermediate at low temperature.

Optically active organotin compounds are potentially very interesting intermediates for organic synthesis and also for stereodynamic investigations on the tin atom. The possibility of such studies is unfortunately limited by the synthesis of the products. Till now most of them have been prepared by diastereomeric resolution of functionnal organotin compounds (1,2) ; this method was tedious and generally yielded products with poor optical activity.

The first attempt in asymmetric synthesis was carried out by TADDEI (3) to obtain methyl phenyl i-propyl benzyl tin from the non-isolated intermediate (-) menthyl methyl phenyl i-propyl tin.

$$\text{Me Ph i-Pr Sn Br} \xrightarrow{\text{Men O}^-} \text{Me Ph i-Pr Sn O Men} \xrightarrow{\text{PhCH}_2\text{MgX}} \underset{\underline{1}}{\text{Me Ph i-Pr Sn CH}_2\text{ Ph}}$$

Men = menthyl $\qquad [\alpha]^{20}_{585} = + 2.5°$ MeOH

GIELEN and co-workers used the same method to prepare methyl i-propyl neophyl trityl tin $[\alpha]^{30}_{578} = + 5.1°$ (4) ; the authors emphasized the role of temperature in the experimental procedure.

To compare our results with the described compounds $\underline{1}$ we have repeated the experiment according to TADDEI's conditions at 0°C. We have never obtained the rotatory power observed by this author. The best value obtained was $[\alpha]^{20}_{D} = + 0.6°$ (EtOH). We have checked that the optical activity stayed unchanged after distillation of the product (5).

Recently we have proposed (-) menthyl thioglycolate as an inductor leaving group (5) to synthesize the same tetraorganotin compound

$$\text{Me Ph i-Pr Sn SCH}_2\text{COO Men} \xrightarrow{\text{PhCH}_2\text{MgX}} \text{Me Ph i-Pr Sn CH}_2\text{Ph}$$

$[\alpha]^{20}_{578} = + 0.83°$ (EtOH)

Further investigation by NMR (8) showed the existence of an equilibrium between the two diastereomers $\vdots$Sn - SR $\rightleftarrows$ RS - Sn$\vdots$, slow compared to the fast equilibrium observed for $\vdots$Sn-OR $\rightleftarrows$ RO - Sn$\vdots$ (9).

We now suggest a facile route optically active tetraorganotin compounds with high optical activity. We have tested several inducting groups and the results show that the most efficient one is (+) cinchonine.

$$\begin{array}{lcl} R^1R^2R^3Sn\ O\ Cin & \xrightarrow{RM} & R^1R^2R^3Sn^{*}R\ (+) \\ \downarrow\uparrow & & \\ Cin\ O\ Sn\ R^1R^2R^3 & \longrightarrow & R^1R^2R^3Sn^{*}R\ (-) \end{array}$$

Cin = Cinchonine overall yield $\geqslant$ 80 %

M = MgX, Li

The temperature of reaction plays an important role in the activity of the products. So the optimum temperature for the first step of this synthesis (T_1) seems to be around 0° to - 5°C. On the contrary, the temperature of reaction of the intermediate cinchoninate with a Grignard reagent must be low, the lower the temperature, the higher the optical activity.

Asymmetric synthesis proceeds by an attack of the nucleophile on a system in equilibrium rather than a kinetic resolution resulting from selective reactivity on the two independent diastereomers.

Table 1 Preparation of optically active tetraorganotin compounds

$$R^1R^2R^3\ Sn\ X \xrightarrow[T_1]{^{-}O\ Cin} R^1R^2R^3SnOCin \xrightarrow[T_2]{R^4MgX} R^1R^2R^3R^4Sn^{*}$$

$R^1R^2R^3$ -	Sn -	OCin	T_1	R^4M	T_2	$(\alpha)^{20}_{578}$	$(\alpha)^{20}_{436}$	C g/100ml Et OH	Bp °C/torr
R^1	R^2	R^3		R^4					
Me	i.Pr	Ph	-5°C	$PhCH_2MgBr$	-70°C	-3.0	-7	2.6	100/0.1
"	"	"	"	BuLi	-70	-0.8	-1.5	2.11	60/0.1
"	"	"	"	BuMgX	-70	+0.3	+0.3	2.18	60/0.1
"	"	"	"	αNpMgBr	-70	+0.6	+1.3	2.3	$160/10^{-3}$
"	"	t.Bu	-30	PhMgCl	-30	+0.4	+0.7	2.12	90/1
"	t.Bu	Ph	-5	i.PrMgBr	-70	+2.1	+4.7	2.32	90/1
"	"	"	"	$PhCH_2MgBr$	-70	-9.6	-22.6	1.1	103/0.3

All the structures are checked by identification of NMR spectra with authentic racemic samples.

This reaction allows to investigate stereodynamic substitution at tin atom attached to a cinchoninate leaving group by organometallic reagents. In the same reactional conditions, butyl lithium reacting with methyl phenyl i-propyl tin cinchoninate leads to the levorotatory enantiomer while butyl magnesium chloride yields the dextrorotatory enantiomer. These results are very similar to the substitution of $>M^{*}$-OR(M=Si, Ge) by organometallics ; the lithium reagent gives an inversion of configuration, the Grignard reagent reacts with retention of configuration (6,7).

The optical purity of tetraorganotin compounds investigated in this work is not yet known. Work is in progress for the determination of enantiomeric excess and also for the determination of the absolute configuration.

Any way this one pot synthesis is easy to be carried out and allows to prepare optically active tetraorganotin compounds on a large scale; the inductor can be separated from the product without difficulty.

Preparation of optically active tetraorganotin compounds; general procedure.

To $8,10^{-3}$ mole of (+) cinchonine in 60 ml of tetrahydrofuran (THF) freshly distilled from lithium tetrahydroaluminate under argon bubbling, is added dropwise $8,10^{-3}$ mole of 2N n-butyllithium in hexane at -5-0°. The homogeneous solution is allowed to warm to room temperature for 1/2 h, then cooled to -5-0° and $7.8\ 10^{-3}$ mole of $R^1R^2R^3$ Sn X(X = Cl or I) in 20 ml of THF is added dropwise. The mixture is stirred at the same temperature for 2 h then cooled to -70° and $16,10^{-3}$ mole of Grignard reagent or n-butyllithium is added dropwise as the temperature is maintained at -70° for 2 h.

The mixture is warmed rapidly to room temperature, then poured on a saturated NH_4Cl aqueous solution and extracted with ether. The ether layer is dried over Mg SO_4 and the solvent is distilled to dryness. The residue is dissolved in pentane and filtered. The final product is purified either by chromatography through a column of silica or simply distilled without decomposition or racemisation.

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(Received in France 1 December 1980)