Tetrahedron Letters,Vol.27,No.21,pp 2361-2364,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

N,N-DIALKYLAMINOMETHYLTRIBUTYLTINS AS PRECURSORS OF (N,N-DIALKYLAMINOMETHYL) KETONES

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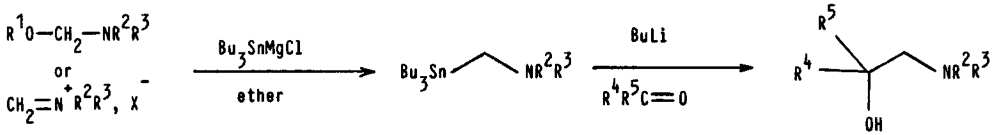
ABSTRACT : *(N,N-Dialkylaminomethyl) ketones have been obtained in good yields (64-87%) by reacting (N,N-dialkylaminomethyl) tributyltins with acyl chlorides. The mildness of the experimental conditions is compatible with the presence of functionnal groups like acetals, aldehydes or nitriles.*

Due to their importance as substances of biological interest or in preparative organic chemistry, α-amino ketones have received considerable attention and numerous methods have been proposed for their synthesis. The more usual one is the reaction of α-halogeno ketones with amines (1) but other procedures have been proposed as for instance the Neber rearrangement of ketoxime tosylates (2) or the Dakin-West reaction of α-amino acids (3). However most of these procedures are not generally applicable or suffer from moderate yields or hardly accessible starting materials. In this situation, numerous attempts to improve the preparation of α-amino ketones have been described (4-11) and an interesting advance in the search for new synthetic methods has been the use of α-metallo amine synthetic equivalents (12). Thus, deprotonation of nitrosamines (13) or α-amino nitriles (14) has led to the metallo derivatives which have been used for the preparation of α-amino ketones. Although efficient, these two methods suffer from the carcinogenic or toxic properties of the intermediates or of the species which are evolved.

Our recent improvements in the preparation of aminomethyltributyltin derivatives starting from aminoacetals (15) or immonium salts (16) allow a ready access to this class of compounds which are known to afford the corresponding organolithium reagents via transmetallation. The latter give a ready access to β-aminoalcohols upon reaction with aldehydes or ketones (15-18) :



However, when the desired compound is the α-amino ketone (for instance in view of a further stereochemical control at the carbon bearing the hydroxyl group), an interesting alternative would be the use of a direct reaction avoiding the transmetallation step. This type of direct reactivity has been previously observed in the case of α-stannylnitrosamines and acyl cyanides (19) suggesting the possibility of a similar reaction between (N,N-diorganoaminomethyl)tributyltins and acyl chlorides according to :

In the case of liquid acyl chlorides the reaction occurs spontaneously upon mixing between 0 and 20°C and affords the expected α-amino ketones in good yields (cf table, entries 1-7). On another hand when solid acyl chlorides are used, the reaction is performed in dry THF under gentle warming (~60°C over a period of 30 mn) and affords also α-amino ketones in high yields.

It is worth to notice that these mild experimental conditions are compatible with functionnalized substrates as exemplified by entries 11-13.

Nevertheless, a surprising result has been observed with acetyl chloride where expected amino ketones have not been obtained. The reaction proceeds exothermically and is believed to involve a dehydrohalogenation of acetyl chloride (with formation of ketene) as already observed with (N,N-dimethylaminomethyl)trimethylsilane (20).

Further experiments are in progress in view of the synthesis of α-substituted α-amino ketones.

AKNOWLEDGMENTS

The authors are grateful to Prof.M. PEREYRE for fruitful discussions and to SCHERING-FRANCE for gift of starting organotin materials.

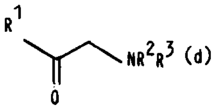
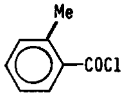
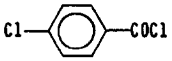
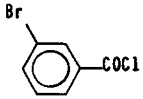
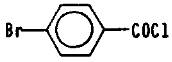
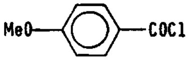
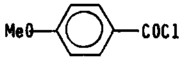
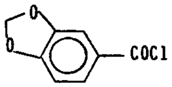
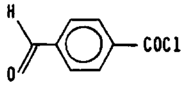
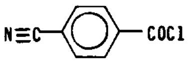
Entry	R^1COCl	$Bu_3SnCH_2NR^2R^3$		Experimental conditions[a]	 (d)
		R^2	R^3		yields
1	EtCOCl	Et	Et	0°C,then 20°C (15 mn)	65% [b]
2	iPrCOCl	Et	Et	0°C, then 20°C (15 mn)	64% [b]
3	PhCOCl	Et	Et	20°C, 15 mn	82% [b]
4	PhCOCl	Me	CH_2Ph	20°C, 15 mn	84% [b]
5		Et	Et	20°C, 15 mn	85% [b]
6		Et	Et	20°C, 15 mn	76% [b]
7		Et	Et	20°C, 15 mn	82% [b]
8		Et	Et	60°C, THF, 30 mn	87% [c]
9		Et	Et	60°C, THF, 30 mn	83% [c]
10		$-(CH_2)_5-$		60°C, THF, 30 mn	77% [c]
11		Et	Et	60°C, THF, 30 mn	84% [c]
12		Et	Et	60°C, THF, 30 mn	81% [c]
13		Et	Et	60°C, THF, 30 mn	78% [c]

Table : Synthesis of N,N dialkylaminomethylketones from N,N-dialkylaminomethyltributyltins and acyl chlorides

a) Equimolar amounts of organotin derivative and acyl chloride (10 mmoles) were mixed as neat compounds (entries 1-7) or in a THF solution (20 ml) (entries 8-13)

b) Isolated yields after addition of HCl (3N), extraction of tributyltin chloride with ether, regeneration of amino ketone with NaOH (3N) and ether extraction

c) Isolated yields after dry HCl bubbling in the THF solution, subsequent elimination of tributyltin chloride, via ether extraction and regeneration of amino ketone from the chlorhydrate

d) The α-amino ketones were unambiguously identified on the basis of their physicochemical data (RMN, IR, MS)

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(Received in France 4 April 1986)