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A CONVENIENT METHOD FOR THE SYNTHESIS OF α-ALKOXYCARBOXAMIDE DERIVATIVES

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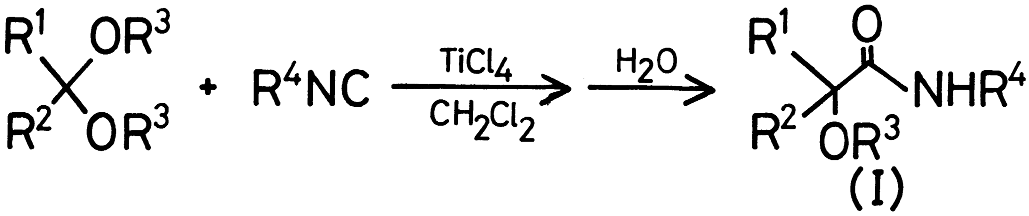
It was established that, in the presence of $TiCl_4$, isocyanides react with acetals to afford α-alkoxycarboxamide derivatives in good yields.

In the previous papers,$^{1a-d)}$ it was shown that acetals react with various nucleophiles such as silyl enol ethers, enol acetates and so on to afford the condensation products in good yields by the promotion of $TiCl_4$. On the other hand, isocyanides,$^{2a)}$ stable divalent carbon compounds, are widely utilized as powerful nucleophiles as well as electrophiles. Therefore, many reports$^{2a)}$ have been published about the reaction of carbonyl compounds with isocyanides, in which the Passerini reaction,$^{2a-c)}$ the preparation of α-acyloxycarboxamide derivatives from isocyanides, aldehydes or ketones and carboxylic acids, is the most useful synthetic method.

In this communication, we wish to report the preparation of α-alkoxycarboxamide derivatives (I) by the equimolar reaction of acetals with isocyanides in the presence of $TiCl_4$.



(I)

For example, to a stirred CH_2Cl_2 solution (4 ml) of cyclohexyl isocyanide (1 mmol) and benzaldehyde dimethyl acetal (1 mmol), $TiCl_4$ (1.1 mmol) in CH_2Cl_2 (0.3 ml) was added at -70°C under argon atmosphere. The reaction mixture was stirred for 3 hr at -70°C and then saturated aqueous sodium bicarbonate was added to the solution. After the usual work-up, N-cyclohexyl-α-methoxyphenylacetamide was obtained in 90% yield. In a similar manner, the reaction of isocyanides with various acetals afforded the corresponding α-alkoxycarboxamide derivatives(I)in good yields as shown in Table I.

The formation of I may be explained by assuming an active complex (II) from acetal and $TiCl_4$. Then isocyanide attacks the highly electrophilic carbon atom of II to form an imidoyl chloride intermediate (III), which affords I after the subsequent hydrolysis.

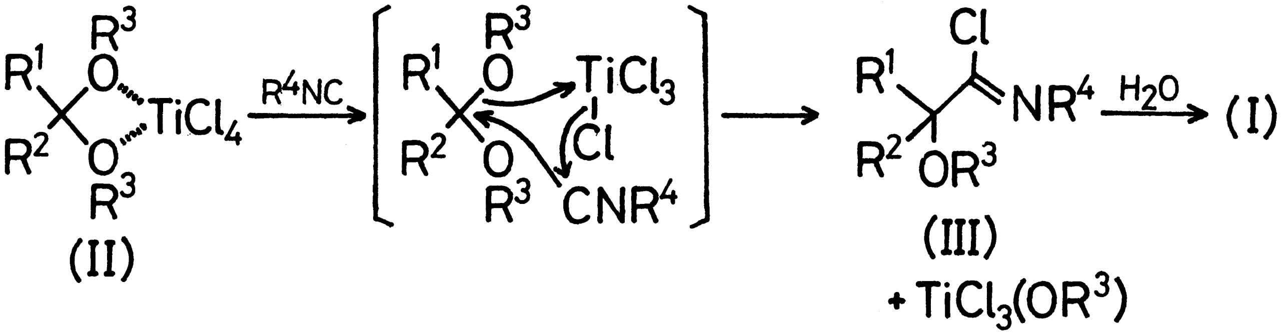
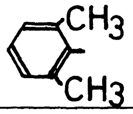


Table I Yields of α-Alkoxycarboxamide derivatives (I)

Acetal			Isocyanide	Reaction	Conditions	
R^1	R^2	R^3	R^4	Temp. (°C)	Time (hr)	Yield(%)
C_6H_5	H	CH_3	C_6H_{11}[b)]	-70	3	90
C_6H_5	H	C_2H_5	C_6H_{11}	-40 ∿ -50	3	89
$C_6H_5CH_2CH_2$	H	C_2H_5	C_6H_{11}	-40 ∿ -50	3	82
CH_3	H	C_2H_5	C_6H_{11}	-30 ∿ -40	2	90
$C_6H_5CH=CH-$[a)]	H	C_2H_5	C_6H_{11}	-30 ∿ -40	2.5	85
$CH_3CH=CH-$[a)]	H	CH_3	C_6H_{11}	-40 ∿ -50	3	80
$C_6H_5CH_2CH_2$	CH_3	CH_3	C_6H_{11}	-40 ∿ -50	3	66
$C_6H_5CH_2CH_2$	H	C_2H_5		-40 ∿ -50	3	81

a) trans-isomer b) cyclohexyl

In summary, it is noted that the equimolar reaction of acetals with isocyanides proceeds smoothly at low temperature to afford α-alkoxycarboxamide derivatives in good yields by the promotion of $TiCl_4$. The present result indicates that $TiCl_4$ is a useful Lewis acid for the activation of acetals toward nucleophiles as isocyanides.

Further development is now under investigation.

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