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2,2'-CARBONYL-BIS(3,5-DIOXO-4-METHYL-1,2,4-OXADIAZOLIDINE) : II-REAGENT FOR THE DIRECT ESTERIFICATION OF CARBOXYLIC ACIDS.

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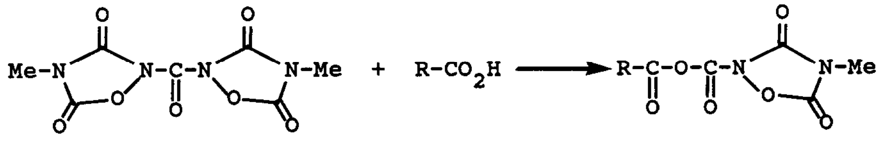
Abstract : *Reaction of carboxylic acids including N-protected α-amino acids with 2,2'-carbonyl bis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) and alcohols affords the corresponding esters under mild conditions.*

Among the numerous methods available in organic synthesis for the esterification of carboxylic acids, the use of coupling agents is by far the most convenient. Following the pionneering work of Staab with 2,2'-carbonyl diimidazole[1], symetrical esters of sulfurous[2], phosphoric[3] and especially carbonic[4-6] acids have been widely used for this purpose, the latter being particularly attractive because the only acidic by-product is the volatile carbon dioxide. Recently, reactive carbonates such as N,N'-disuccinimidyl carbonate[5] and di-2-pyridyl carbonate[6] have gained particular attention, especially for the synthesis of aminoacids esters.

We now wish to report the use of the newly available 2,2'-carbonyl bis-(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) [7] **1** for the one pot esterification of carboxylic acids, especially aminoacids under mild conditions. In a typical experiment, **1** (11 mmoles) and the appropriate alcohol (10mmoles) are added within 5 min., to a solution of the acid (10 mmoles), triethylamine (11 mmoles) and DMAP (1 mmole) in dichloromethane (20 ml) and the reaction mixture is stirred at room temperature for 2 hours. Conventional acidic and basic washes afford the corresponding ester in good yield.



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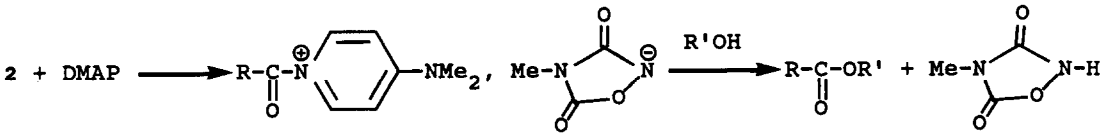

3 **4**

The reaction was efficient with both primary and secondary alcohols. Providing that an excess of the alcohol is added, tertiary alcohols are esterified in medium, but still satisfactory yields (Table). The reaction is catalyzed with DMAP ; however no base was necessary if the alcohol already contained a pyridine function. We assume that the reaction goes through the intermediate 2-acyl-3,5-dioxo-4-methyl-1,2,4-oxadiazolidine **2** since it could be easily activated by DMAP through the unstable **3**. Finally, we have examined the extent of racemization in the synthesis of amino acids esters. No sign of racemization was detected when looking for the presence of diastereoisomers in the ^{13}C NMR spectra of the cholesteryl ester of BOC-L-Phenylalanine.

Table-Esterification of carboxylic acids[8]

Acid	Alcohol	Base	Yield (%)	m.p.(°C)	$[\alpha]_D$ [a]
3-pyridyl-CO_2H	^{t}-BuOH (10 equ.)	DMAP	56	oil	-
Z-Ala	p-NO_2-Ph-CH_2OH	TEA	50	95-96	-12
Z-Ala	p-NO_2-Ph-CH_2OH	TEA/DMAP	89	95-96	-12
Z-Ala	4-pyridyl-CH_2OH	-	67	103-105	-21
BOC-Ala	p-NO_2-Ph-CH_2OH	TEA/DMAP	77	96-97	-19
BOC-Val	p-NO_2-Ph-CH_2OH	TEA/DMAP	92	60-61	-13
BOC-Trp	p-NO_2-Ph-CH_2OH	TEA/DMAP	77	112-114	+5
BOC-Met	p-NO_2-Ph-CH_2OH	TEA/DMAP	87	47-50	+3
BOC-Phe	L- menthol	TEA/DMAP	77	49-52	-42
BOC-Phe	cholesterol	TEA/DMAP	95	118-119	-13

a) c=1, EtOH except for BOC-Met-OCH_2Ph-NO_2 : c=1, $CHCl_3$

References and notes-

1)H. A. Staab and A. Mannschreck, *Chem. Ber.*, **1957**, *95*, 1326.
2)S. Kim and K.Y. Yi, *Bull. Korean Chem. Soc.*, **1986**, *7*, 87.
3)T. Gracia, A. Arrieta and C. Palomo, *Synth. Commun.*, **1982**, *12*, 681.
4)M. Ueda, H. Oikawa and T. Teshirogi, *Synthesis*, **1983**, 908.
5)H. Ogura, T. Kobayashi, K.Shimizu, K. Kawabe, and K. Takeda, *Tetrahedron Lett.*, **1979**, 4745.
6)S. Kim, J.I Lee and Y.K. Ko, *Tetrahedron Lett.*, **1984**, 4943.
7)M. Dénarié, D. Grenouillat, T. Malfroot, J.P. Senet, G. Sennyey and P. Wolf preceding paper.
8)All new compounds gave satisfactory spectral and analytical data.

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