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2,2'-CARBONYL-BIS(3,5-DIOXO-4-METHYL-1,2,4-OXADIAZOLIDINE) : I-A NEW REAGENT FOR THE PREPARATION OF CARBAMATES AND AMIDES, APPLICATION TO THE SYNTHESIS OF DIPEPTIDES.

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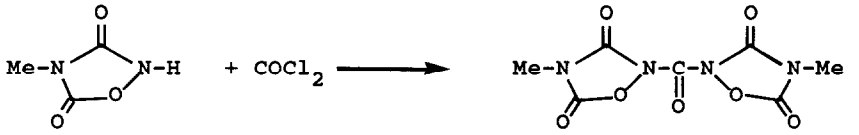
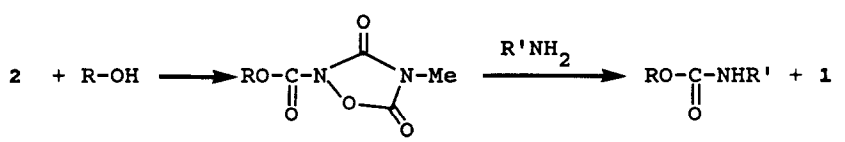
Abstract : *2,2'-Carbonyl bis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) was prepared and used for the synthesis of various carbamates and dipeptides.*

3,5-Dioxo-1,2,4-oxadiazolidines have been found as a part of the natural excitatory aminoacid quisqualic acid and their synthesis has been extensively studied by Zinner and co-workers[1]. In particular, 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine **1** is now readily available by numerous methods[1,2]. While exploring the chemistry of 2-acyl-3,5-dioxo-1,2,4-oxadiazolidines, we discovered that the heterocyclic moiety **1** is a very good leaving group. This led us to the design of the symmetrical 2,2'-carbonyl-bis(3,5-dioxo-4-methyl-1,2,4-dioxazolidine) **2** as a new coupling reagent which could be used for the preparation of carbamates and amides, and especially for the synthesis of the peptide linkage.



1 **2**

3,5-Dioxo-4-methyl-1,2,4-oxadiazolidine[1,2] **1** readily reacts with phosgene in refluxing toluene to yield the expected **2** as a white crystalline solid[3] (82% ; mp=204°C). The reaction is catalyzed by the addition of 0.5 mole% of hexamethylguanidinium chloride[4]. **2** readily reacts with hydroxy compounds to yield the already known 2-alkoxycarbonyl-5-dioxo-1,2,4-oxadiazolidines[5]. These intermediates do not need to be isolated and are reacted with an excess of amine to give the corresponding carbamate in good yield (Table 1)

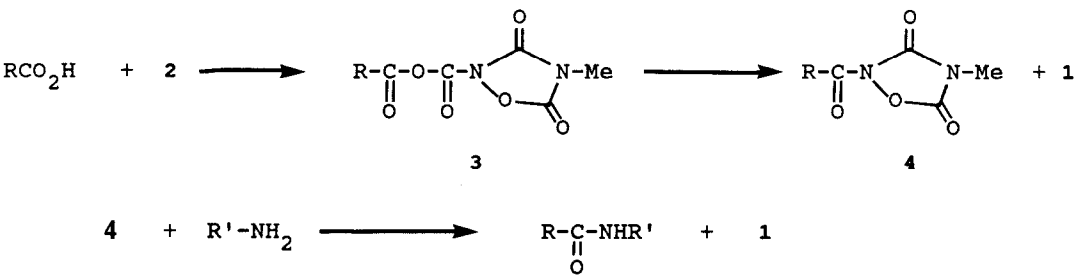


Attempts to prepare BOC- or Z-aminoacids from the isolated 2-t-butoxycarbonyl or 2-benzyloxycarbonyl-3,5-dioxo-4-methyl-1,2,4-oxadiazolidine were successful but were found of little synthetic interest mainly because of the sensitivity of 2-alkoxycarbonyl-3,5-dioxo-4-methyl-1,2,4-oxadiazolidines toward hydrolysis and because of the difficulty to remove traces of 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine from the protected amino acid. However, Z-amino acids were obtained in medium yields and were found to be free of dipeptide impurities.

Table 1 - Preparation of carbamates[6]

Carbamate[3]	Yield	m.p. or b.p.	Literature data[3]
$EtO-\overset{\overset{O}{\|}}{C}-NH-nC_8H_{17}$	90%	90°C/0.2mm Hg	
$PhOPhO-\overset{\overset{O}{\|}}{C}-NHMe$	88%	107°C	-
$Me_2\underset{SMe}{C}-CH=N-O-\overset{\overset{O}{\|}}{C}-NHMe$	85%	99-100°C	98-100°C[7]

2 also reacts with carboxylic acids to give the unstable mixed anhydride 3, which is rapidly decarboxylated to the intermediate 2-acyl-3,5-dioxo-1,2,4-oxadiazolidine[8]. As described above, 4 is not isolated but is reacted in situ with an amine to yield the corresponding amide.



This reaction has been successfully applied to the coupling of aminoacids (Table 2). Yields are generally good and the dipeptides are easily freed of by-products by simple washes. The by-product, 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine, or its sodium salt are readily soluble in water and thus are easily separated from the fully protected dipeptide. Several dipeptides were prepared and no deviations were found in their optical rotations. However,

racemization was investigated more thoroughly for aminoacids protected as carbamates or amides. Peaks due to the DL-isomers were not observed in the 250 MHz spectra of crude Z-L-Phe-Ala-OMe or Z-L-Ala-Phe-OMe examined both with simple and double irradiation[9]. In the Young test[10], reagent 2 gave Bz-Leu-Gly-OEt with an $[\alpha]_D$ -4° for the crude crystalline product, which corresponds to a 12% excess of the L-isomer. This low rotation could be also attributed to the contamination of the crude dipeptide by some optically inactive 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine. However, this side-product could not be eliminated in this case by simple recrystallization, since, as noted earlier[10], recrystallization increases the amount of racemate. Addition of hydroxy-benzotriazole to the reaction mixture does not increase significantly the excess of the L-isomer ($[\alpha]_D$ -8 ; 23% L).

Table 2-Preparation of dipeptides[8]

Dipeptide[3]	Yield %	m.p. (Lit.) °C	$[\alpha]_D^o$ (Lit.)
BOC-Phe-Gly-OEt	86	86-88 (88-89)	-4 (-4.2 c 1 EtOH[11])
Z-Val-Gly-OEt	66	165-166 (164-165)	-27 (-25.3 c 1 EtOH[12])
Z-Leu-Gly-OEt	68	97-99 (104-105)	-26 (-25.7 c 1 EtOH[12])
Z-Leu-Phe-OMe	74	80-81 (87-88)	-20 (-22.4 c 2 MeOH[13])
Z-Ala-Phe-OMe	88	96-98 (100-101)	-10 (-9.2 c 1 EtOH[13])
Z-Phe-Ala-OMe	83	127-129 (126-127)	-22 (-22.9 c 1.25 EtOH[13])
Bz-Leu-Gly-OEt	78	137-139 (153-155)	-4 (-34.0 c 3.1 EtOH[10])
BOC-Tyr(OBzl)-Gly-OEt	79	117-119	+2 (- c 0.5 EtOH)

Consequently, we think that 2 could be a valuable reagent for the coupling of aminoacids. It is a crystalline, stable and non-hygroscopic compound. The starting material 3,5-dioxo-4-methyl-1,2,4-oxadiazolidine 1 has been proposed as a building block for the synthesis of industrial products[2] thus opening opportunities for a low cost synthesis of 2. Furthermore 1 is also obtained as a by-product in the reaction and therefore can be recycled. It is water soluble and thus can be easily eliminated. Further investigations concerning the recycling of 1 and application of the reagent 2 to the solid phase synthesis of peptides are under investigation.

References and notes-

1)G. Zinner, M. Menzel, R. Sunderdiek and E. Fischer, *Arch. Pharm. (Weinheim)*, **1981**, *314*, 294 and references cited therein.
2)Belgium Patent, BE 726232 (1969/1967), BASF AG.
3)All new compounds gave satisfactory spectroscopic and analytical results.
4)W. Kantlehner and H. Hagen, DOS 2 718 275 (1977) ; C.A., **1979**, *90*, 86 777.
5)G. Zinner and M.Hitze, *Arch. Pharm.*, **1970**, *303*,139.
6)One equivalent of **2** is added to a solution of the hydroxy compound in chloroform or dichloromethane and refluxed for 2 h. After cooling to room temperature, excess gaseous methylamine is bubbled into the reaction mixture. The mixture is then stirred for 1h and worked up as usual.
7)The Pesticide Manual, 8th Ed., **1987**, 7.
8)One equivalent of **2** is added to a solution of the protected amino acid and N-methylmorpholine (2 equ.) in acetonitrile or dichloromethane and stirred at room temperature for 1 h. The aminoacid ester (or its hydrochloride) is then added and the reaction mixture is stirred for an additionnal hour. After conventional washes of the organic phase, the dipeptide is crystallized from a suitable solvent.
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