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Use of Chiral Glycerol 2,3-Carbonate in the Synthesis of 3-Aryl-2-oxazolidinones

S. Jegham*, A. Nedelec, Ph. Burnier, Y. Guminski[1], F. Puech, J.J. Koenig and P. George

Synthélabo Recherche, Direction de Recherche SNC,
10 rue des carrières, 92504, Rueil-Malmaison, France

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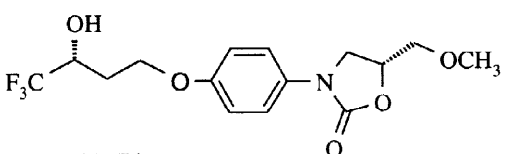
Abstract: Substituted chiral 3-aryl-2-oxazolidinones were readily prepared *via* regiospecific opening of cyclic carbonates with *N*-arylcarbamates and subsequent cyclization.

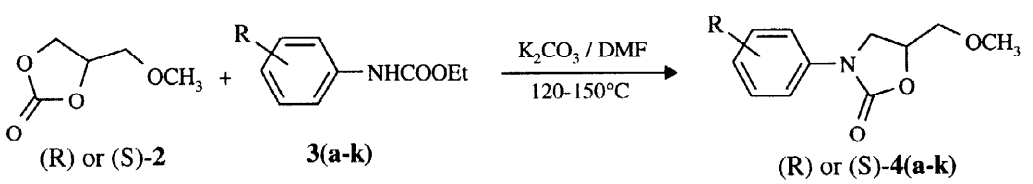
The aryloxazolidinones[2], represented by the prototype molecule of befloxatone **1**, are a new class of potent, selective and reversible inhibitors of monoamine oxidase A (MAO, E.C.1.4.3.4), an important enzyme implicated in the degradation of various amines neurotransmitters[3,4].



1 *(R,R)*, befloxatone

With the aim of searching new reversible inhibitors of MAO's, we focussed our chemical program on the synthesis of analogues of **1**. To access to a large number of derivatives to be screened in biological assays, we needed a general and efficient method to build the phenyloxazolidinone moiety without using phenylisocyanates and epoxides, that are used in the main classical synthesis of this type of compounds[5,6].

We here report on the use of the commercially available 4-nizmethoxymethyl-1,3-dioxolane-2-ones (*R*) and (*S*)-**2**[7] as key intermediates in the synthesis of chiral oxazolidinones **4(a-k)** by reaction with substituted *N*-phenylcarbamates **3(a-k)** (Scheme1).



(R) or (S)-**2** **3(a-k)** (R) or (S)-**4(a-k)**

Scheme 1

The use of elevated temperature is necessary to complete the reaction. A similar[8] opening of cyclic carbonates with isocyanates, at lower temperatures (about 70°C), results in the formation of an intermediate characterized as a molecular complex of the isocyanate and the carbonate. This complex, when heated, decomposes, carbon dioxide being evolved, leading to the formation of the oxazolidinone.

* Fax : +33.1.41.39.13.03

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Several phenyloxazolidinones (**4a-k**) were obtained (table 1).

Entry	R	Conf.	t (h)	yield(%)	*4a-k*	
					mp(°C)	Rotation (c = 1)
3a	H	*R*	4	33	oil	-50 (CH_2Cl_2)
3b	H	*S*	7	19	oil	+52.5 (CH_2Cl_2)
3c	*p*-I	*R*	1	66	96	-38 (CH_2Cl_2)
3d	*p*-CH_3	*R*	1	56	75	-47 (CH_2Cl_2)
3e	*p*-Ph	*R*	2	70	154	-58 (MeOH)
3f	*p*-OPh	*R*	3	52	68	-45 (CH_2Cl_2)
3g	*o*-OBn	*R*	3	44	66	-34 (CH_2Cl_2)
3h	*p*-OBn	*R*	3	71	100	-43 (CH_2Cl_2)
3i	*m*-OCH_3	*R*	2	73	36	-60 (MeOH)
3j	*p*-OCH_3	*R*	2	72	90	-67 (MeOH)
3k	*p*-(3-C_5H_5N)	*R*	2	55	118	-74 (MeOH)

Table 1: 3-Phenyl-5-methoxymethyl-2-oxazolidinones **4(a-k)** prepared following scheme 1.

It is important to note that this methodology has been also applied successfully to the synthesis of a wide range of aryloxazolidinones starting from different *N*-arylcarbamates and *N*-heteroarylcarbamates, including naphthyl, pyridyl, quinolyl, and different other heterocycles.

In conclusion, this paper describes a new method for the regiospecific synthesis of chiral 3-phenyl-5-methoxymethyl-2-oxazolidinones in good chemical and optical yields, using a chiral glycerol-2,3-carbonate derivative as an epoxide equivalent.This key intermediate is readily available and could be of interest in the synthesis of other chiral 2-oxazolidinone moeities as well as in the enantiospecific synthesis of chiral compounds in general.

Acknowledgement

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References and Notes

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