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The reaction of 4-amino-2-oxazolines with isocyanates and isothiocyanates. Synthesis and X-ray structures of polysubstituted 2-imidazolidinones, 1,3-oxazolidines and 1,3-thiazolidines

Antonio Guirado,[a,*] Raquel Andreu,[a] Bruno Martiz,[a] Delia Bautista,[a] Carmen Ramírez de Arellano[b] and Peter G. Jones[c]

[a]*Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, 30071 Murcia, Apartado 4021, Spain*
[b]*Departamento de Química Orgánica, Universidad de Valencia, 46100 Valencia, Spain*
[c]*Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Postfach 3329, 38023 Braunschweig, Germany*

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Abstract—Reactions of 4-alkylamino-2-phenyl-2-oxazolines **1** with isocyanates and isothiocyanates provide unprecedented efficient and regioselective heterocycle–heterocycle transformations. Compounds **1** reacted rapidly with tosyl isocyanate yielding directly 3-alkyl-4-benzamido-1-tosyl-2-imidazolidinones **4** in almost quantitative yields. The corresponding ureido intermediates **2** were not isolable species. However, the reactions with non-sulfonylated isocyanates or isothiocyanates were slower, leading to the expected ureido and thioureido derivatives **5**, which were easily and efficiently transformed to either polysubstituted 2-imino-1,3-oxazolidine or 2-imino-1,3-thiazolidine hydrochlorides **7**, respectively, by treatment with hydrochloric acid. The possible reasons for this disparity in chemical behaviour are discussed. X-ray crystallographic structures for 4-benzamido-3-methyl-1-tosyl-2-imidazolidinone **4b**, 4-[1-isopropyl-3-(4-nitrophenyl)ureido]-2-phenyl-2-oxazoline **5e**, (*Z*)-3-benzyl-4-benzamido-2-phenylimino-1,3-oxazolidine hydrochloride **7a** and (*Z*)-3-benzyl-4-benzamido-2-phenylimino-1,3-thiazolidine hydrochloride **7b** have been determined.

1. Introduction

2-Oxazolines are remarkably versatile synthetic intermediates.[1–4] The vast number of transformations[1] reported over the last few years have led to a renewed interest in the chemistry of these compounds. However, only a few examples of transformations of 2-oxazolines into other heterocycles have been described; most work on this subject has been focused on either hydrogenation or dehydrogenation processes to give products retaining the original ring system.[1]

As a result of our research project on new methods for the synthesis of heterocyclic compounds, based on using chloral as a key starting material, we developed an efficient and general preparative procedure that provided novel 4-amino-2-aryl-2-oxazolines[5,6] **1** from chloralamides. Continuing this project, we focused the work on the reactions of these compounds with isocyanates and isothiocyanates. Given the peculiar structural arrangement of the expected ureido and thioureido derivatives, it was considered that these reactions could be the starting point for attractive approaches to novel heterocyclic compounds. In preliminary communication[7,8] we reported the successful application of this synthetic methodology for preparing novel 2-imidazolidinones, 1,3-oxazolidines and 1,3-thiazolidines. In this paper we describe full details of this work and new results of the preparative procedures, together with spectral and X-ray crystallographic data for the hitherto unknown classes of compounds newly accessed. Differences in chemical behaviour observed for ureido and thioureido intermediates may be attributed to crucial electronic effects associated with the presence or absence of the sulfonyl group.

2. Results and discussion

4-Alkylamino-2-aryl-2-oxazolines **1** were treated with *p*-toluenesulfonyl isocyanate in ether solution at room temperature (Scheme 1). The reactions occurred quickly under such mild experimental conditions. The instantaneous formation of a white solid precipitate was observed in all cases. The resulting voluminous crude solid products were isolated by filtration and identified by the usual analytical methods

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* Corresponding author. Tel.: +34 968367490; fax: +34 968364148; e-mail: anguir@um.es

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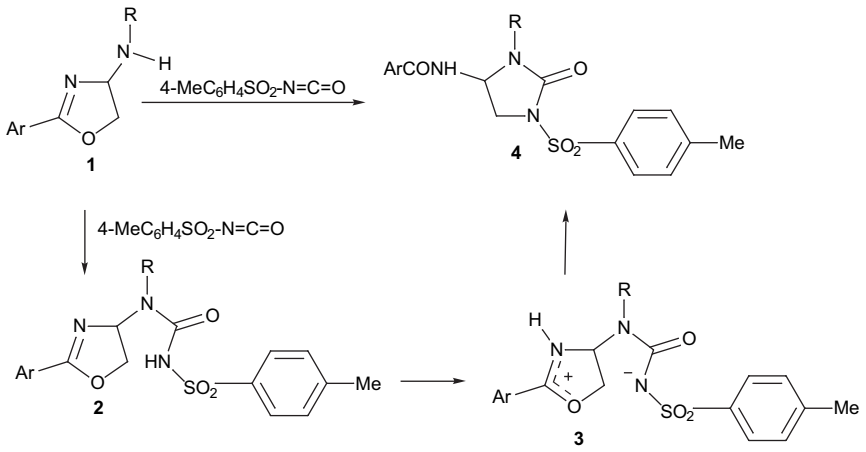

	Ar	R
a	C_6H_5	$C_6H_5CH_2$
b	C_6H_5	CH_3
c	C_6H_5	$(CH_3)_2CH$
d	3-ClC_6H_4	$C_6H_5CH_2$
e	3,4,5-$(CH_3O)_3C_6H_2$	$C_6H_5CH_2$

Scheme 1.

as highly pure 3-alkyl-4-benzamido-1-tosyl-2-imidazolidinones **4**. Yields were nearly quantitative. IR and NMR spectra for crude and recrystallized products showed negligible differences.

The structural assignment of these compounds was corroborated by X-ray crystallographic analysis of 4-benzamido-3-methyl-1-tosyl-2-imidazolidinone **4b**. The molecular structure is illustrated in Figure 1. Selected intramolecular distances (crystallographic numbering of atoms) and selected bond angles are given in Table 1. Suitable single crystals for this analysis were obtained from hexane/chloroform and contained one molecule of chloroform per molecule of **4b**. A thermogravimetric analysis of this compound showed a sharp peak at 106.2 °C, corresponding to quantitative loss of chloroform. The crystallographic analysis showed the crystal packing to be determined by N–H···O and Cl···O interactions.

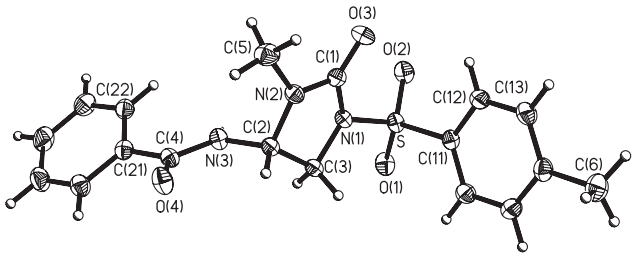

Figure 1. Molecular structure of product **4b**, showing the crystallographic numbering system used.

A particularly facile rearrangement of the ureido intermediates **2** to imidazolidinones **4** appears as a key step in this transformation (Scheme 1). However, ureido derivatives are, in general, stable crystalline compounds that can be used for the separation and characterization of amines. In contrast, 2-oxazolines are characterized by a high reluctance to undergo alteration of the ring system by nucleophilic attacks, and are indeed commonly used as protecting or activating groups in strongly nucleophilic media.[9] Therefore, the pronounced lability evidenced by intermediates **2** indicates the existence of some special factors that promote a remarkable enhancement of electrophilic activity at C-5. A reasonable explanation for this might be a protonic autoactivation induced by the sulfonyl group, which would generate an internal acidic centre. In conjunction with the cogeneration of a benzamido group, this would strongly facilitate an

Table 1. Selected bond lengths and bond angles in crystal structure of **4b**

Lengths (Å)

O(3)–C(1)	1.213(2)	O(4)–C(4)	1.229(2)
N(1)–C(1)	1.418(2)	N(1)–C(3)	1.474(2)
N(2)–C(1)	1.349(2)	N(2)–C(5)	1.453(2)
N(2)–C(2)	1.458(2)	N(3)–C(4)	1.351(2)
N(3)–C(2)	1.449(2)	C(2)–C(3)	1.537(2)

Angles (°)

C(1)–N(1)–C(3) 110.l9(13)	C(3)–N(1)–S 120.49(11)	C(1)–N(2)–C(2) 113.88(13)
C(4)–N(3)–C(2) 122.79(14)	O(3)–C(1)–N(2) 127.28(16)	N(3)–C(2)–N(2) 112.19(13)
N(2)–C(2)–C(3) 102.29(12)	C(1)–N(1)–S 122.86(11)	C(1)–N(2)–C(5) 121.19(14)
C(5)–N(2)–C(2) 123.46(14)	O(3)–C(1)–N(2) 127.3(2)	N(2)–C(1)–N(1) 106.57(13)
N(3)–C(2)–C(3) 112.11(13)	N(1)–C(3)–C(2) 102.25(13)	