Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3809–3812

TETRAHEDRON LETTERS

Direct conversion of 4-amino-2-phenyl-2-oxazolines into either 2-arylimino-1,3-oxazolidine or 2-arylimino-1,3-thiazolidine hydrochlorides

Antonio Guirado,[a,*] Raquel Andreu[a] and Jesús Gálvez[b]

[a]*Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, 30071-Murcia, Apartado 4021, Spain*

[b]*Departamento de Química Física, Facultad de Química, Universidad de Murcia, Campus de Espinardo, 30071-Murcia, Apartado 4021, Spain*

Received 14 January 2003; accepted 14 March 2003

Abstract—A novel heterocycle–heterocycle inter-conversion is reported. It enables direct and efficient syntheses of either polysubstituted 2-arylimino-1,3-oxazolidine or 2-arylimino-1,3-thiazolidine hydrochlorides by a one-pot treatment of 4-amino-2-phenyl-2-oxazolines with arylisocyanates or arylisothiocyanates, respectively, followed by addition of hydrochloric acid.

We recently developed an efficient new preparative procedure for 2-oxazolines[1] that provided the first synthesis of 4-amino-2-aryl-2-oxazolines **1**. On exploring the reactivity of these compounds, we found that they undergo direct and remarkably fast conversions to imidazolidinones **4** by reaction with *p*-toluenesulfonyl isocyanate at room temperature[2] (Scheme 1). It was taken into account that the first generated arylsulfonylureido derivatives **2**, which have a relatively highly acidic centre, were not detected. The participation in this transformation of the reactive intermediate **3** was postulated. A protonic autoactivation of **2** would lead to **3**. Hence, a ring opening of the normally stable 2-oxazoline system with a simultaneous ring closure to give the corresponding imidazolidinones **4** would occur easily in this way. By working at low temperature, two of these labile ureido compounds **2** were recently isolated[3] and consistently showed a remarkable proclivity to undergo a quantitative conversion to the corresponding products **4**. The chemistry of 2-oxazolines has been extensively studied,[4] with there being few examples of transformation into other heterocycles. The reported work on this subject mainly corresponds to either hydrogenation or dehydrogenation of starting compounds to give products retaining the original ring system.[4e]

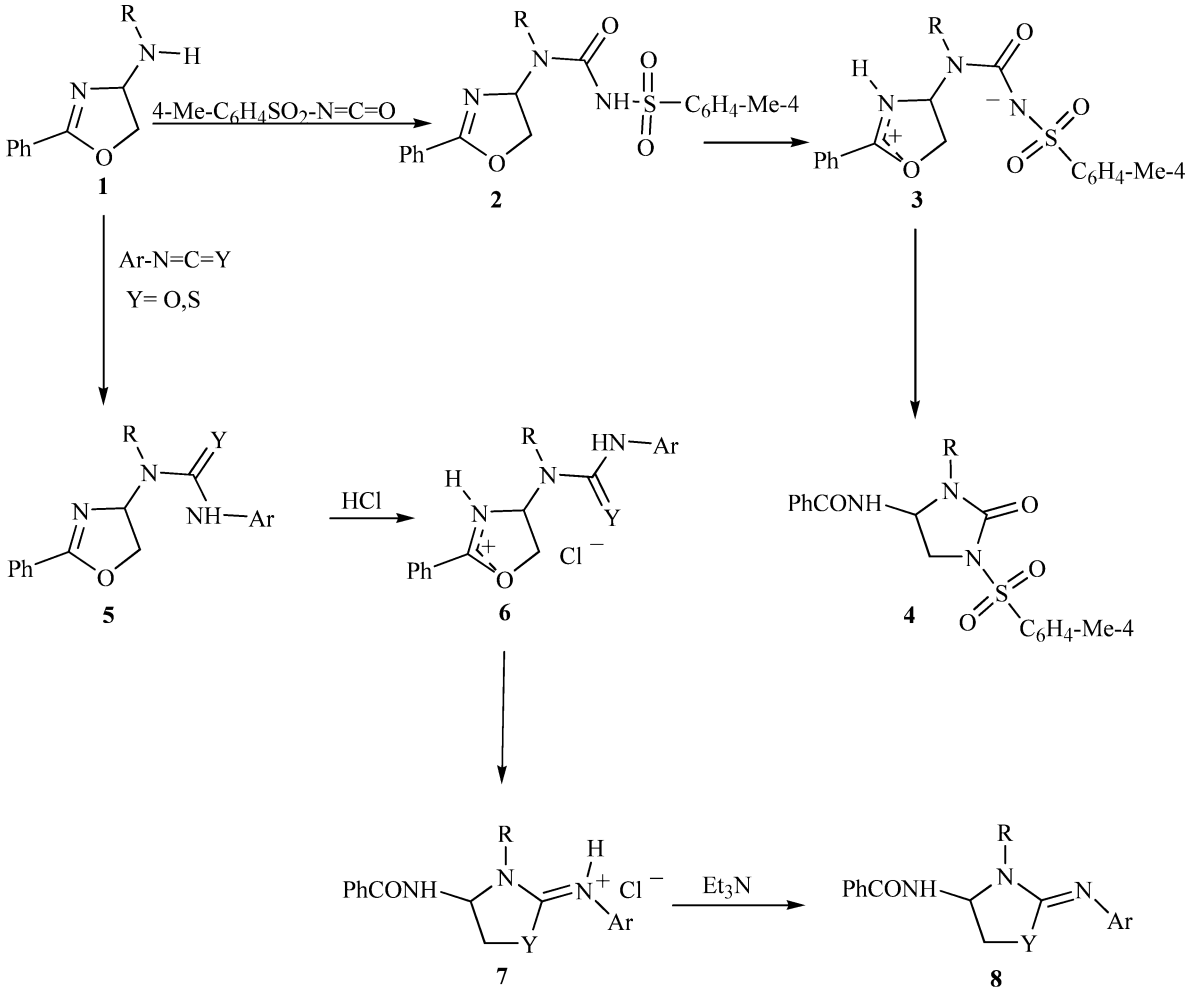
In view of the high interest of the above results, we have directed our attention to the study of reactions of 4-alkylamino-2-phenyl-2-oxazolines **1a–e** with arylisocyanates and arylisothiocyanates in order to clarify the action of the sulfonyl group in the isomerisation process. This paper deals with the dramatic change found between the behaviour of sulfonylated ureido derivatives **2** and the corresponding non-sulfonylated ureido and thioureido compounds **5** which also exhibit a high potential for the synthesis of previously unattainable heterocyclic compounds.

In contrast to the reactions with *p*-toluenesulfonyl isocyanate, which occurred almost instantaneously it was observed that compounds **1** reacted with both isocyanates or isothiocyanates over a longer time. The crude products formed were easily isolated in a high purity state[5] by simple filtration, and were crystallized and identified by IR, MS, NMR spectroscopy and elemental analysis as the corresponding ureido or thioureido derivatives **5**. Yields were near to quantitative. The molecular structure of one of these compounds: 4-[1-isopropyl-3-(4-nitrophenyl)ureido]-2-phenyl-2-oxazoline **5e**, was confirmed by X-ray crystallography.[7]

Contrary to the lability of the *N*-sulfonylureido intermediates **2**, it was found that the ureido analogs **5** were stable enough to be handled in solution and also to permit a prolonged storage without need of any special

Keywords: oxazolines; ureas; thioureas; oxazolidines; thiazolidines.
* Corresponding author. Fax +34-968364148; e-mail: anguir@um.es

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00783-4



Scheme 1.

care. This is on excellent agreement with that expected for the case of a non-favoured rearrangement motivated by the absence of the postulated protonic autoactivation.

The above facts strongly suggested that a mineral acid would have the ability to circumvent the non-presence of the sulfonyl group and, therefore, provoke a rearrangement process. This hypothesis was fully confirmed by treatment of compounds **5** with hydrochloric acid, which gave almost instantaneous reactions with the formation of solid products in high purity state[5] which were, in turn, crystallized and characterised by IR, MS, NMR spectroscopy and elemental analysis as the corresponding hydrochlorides of 2-arylimino-1,3-oxazolidines[6] **7** (Y = O) and 2-arylimino-1,3-thiazolidines[6] **7** (Y = S). Yields were almost quantitative. The molecular structure of these compounds was corroborated by X-ray crystallography of (*Z*)-3-benzyl-4-benzamido-2-phenylimino-1,3-oxazolidine hydrochloride[7] **7a** and (*Z*)-3-benzyl-4-benzamido-2-phenylimino-1,3-thiazolidine hydrochloride[7] **7b**. It was proved that this hydrochloride liberates hydrogen chloride quantitatively by treatment with an equivalent amount of thiethylamine to give the corresponding free aryliminothiazolidine **8b**.

There are no precedents for the families of compounds **7** and **8**. As far as we know, this is the first time that direct conversions of 2-oxazolines into 1,3-oxazolidines or 1,3-thiazolidines have been reported. The wide variety of oxazolines **1** available[1,8] determines a high versatility in these new synthetic approaches. The preparative procedures in separate steps described could also be carried out in a one-pot process, which allows a quick and very efficient preparation of the same heterocyclic compounds (Table 1). It should be noted that the synthesis of either 2-iminooxazolidines or 2-iminothiazolidines has an especial interest because they show a range of important therapeutic and biological activities.[9]

Both the relatively highly reactivity of the sulfonylated ureides **2** and the entire change of selectivity towards each reaction mode observed can be explained on the basis of a crucial electronic effect of the sulfonyl group. Thus, it seems reasonable to postulate that in each transformation the reactive intermediates—either **3** or **6**—would participate. An internal electrophilic attack on one of the alternative heteroatoms (N or O,S) would subsequently operate.

Table 1. One-pot synthesis of compounds **7**

Entry	Y	R	Ar	Yield (%)	Mp (°C)
7a	O	$C_6H_5CH_2$	C_6H_5	92	164–165
7b	S	$C_6H_5CH_2$	C_6H_5	88	172–174
7c	S	$C_6H_5CH_2$	4-$CH_3OC_6H_4$	90	173 (dec.)
7d	S	$C_6H_5CH_2$	4-ClC_6H_4	94	167
7e	O	$(CH_3)_2CH$	4-$O_2NC_6H_4$	97	119–121

The reasons for the difference in behaviour between intermediates **2** and **5** can be explained if we consider that ureas and thioureas are attacked[10] by electrophilic agents preferentially at the oxygen or sulfur atoms, respectively. This is mainly attributable to a high electron density on such heteroatoms. This is the case for the formation of products **7** from intermediates **5**. The formation of products **4** from intermediates **2**, however, seems to be in agreement with the strong electron withdrawing effect of the sulfonyl group, which would substantially decrease the nucleophilicity of those reactive centres.

In summary, the first direct conversion of 2-oxazolines into either 1,3-oxazolidines **7** (Y = O) or 1,3-thiazolidines **7** (Y = S) is reported. Versatility, good yields, easy availability of starting materials, mildness and simple experimental procedure are noteworthy advantages of this approach, which has high prospects in the access to previously unattainable compounds. In this work a new reaction mode has been found which is associated to a peculiar molecular arrangement of 4-amino-2-oxazoline ureido derivatives. It seems feasible to extend the described synthetic methodology for preparing a wide variety of heterocyclic compounds.

One-pot synthesis of compounds **7**. Typical procedure: To a well stirred solution of aminooxazoline **1** (1 mmol) in dry ether (10 mL) a solution of the corresponding isocyanate or isothiocyanate (1 mmol) in dry ether (10 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 1 h. Then, hydrochlorid acid (0.15 mL; 35%) was added and the solid product was filtered off and crystallized from the appropriate solvent: compound **7a** (ethanol), **7b** (acetonitrile), **7c** (ethanol), **7d** (methanol), **7e** (ethanol–pentane).

Acknowledgements

This work was supported by the Ministerio de Ciencia y Tecnología (Project BQU2000-0222). We are grateful to Professor Peter G. Jones at Technische Universität Braunschweig for the X-ray crystallographic analyses.

References

1. (a) Guirado, A.; Andreu, R.; Gálvez, J. *Tetrahedron Lett*. **1998**, *39*, 1071; (b) Guirado, A.; Andreu, R.; Gálvez, J.; Jones, P. G. *Tetrahedron* **2002**, *58*, 9853.
2. Guirado, A.; Andreu, R.; Gálvez, J. *Tetrahedron Lett*. **1999**, *40*, 8163.
3. Unpublished results.
4. For reviews, see: (a) Wiley, R. H.; Bennett, L. L. *Chem. Rev*. **1949**, *44*, 447; (b) Seeliger, W.; Aufderhaar, E.; Diepers, W.; Feinauer, R.; Nehring, R.; Their, W.; Hellmann, H. *Angew. Chem., Int. Ed. Engl*. **1966**, *5*, 875; (c) Frump, J. A. *Chem. Rev*. **1971**, *71*, 483; (d) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 270; (e) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837; (f) Maryanoff, B. E. In *Chemistry of Heterocyclic Compounds*; Turchi, I., Ed. Oxazoles. John Wiley & Sons: Chichester, 1986; Vol. 45, p. 963; (g) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
5. IR and ^{1}H NMR spectra for crude and crystalline products were recorded showing negligible differences.
6. All compounds gave satisfactory microanalyses. Spectral data for **7a** and **7b** are reported as examples of spectroscopic properties of these classes of compound. Compound **7a**: ^{1}H NMR δ (DMSO-d_6, 200 MHz): 4.63 (d, 1H, J = 16.1 Hz), 4.84 (dd, 1H, J = 9.6 Hz, J = 3.6 Hz), 5.10 (t, 1H, J = 9.3 Hz), 5.52 (d, 1H, J = 16.0 Hz), 6.00 (td, 1H, J = 9.4 Hz, J = 3.3 Hz), 7.23–7.60 (m, 13H), 7.90 (d, 2H, J = 7.0 Hz), 9.82 (d, 1H, J = 8.1 Hz); ^{13}C NMR δ (DMSO-d_6, 50.4 MHz): 45.46 (CH_2), 64.87 (CH), 74.02 (CH_2), 119.58 (CH), 124.07 (CH), 126.51 (C), 126.95 (CH), 127.68 (CH), 128.10 (CH), 128.47 (CH), 128.68 (CH), 129.23 (CH), 132.26 (CH), 132.87 (C), 134.07 (C), 158.71 (C=N), 166.90 (CO); MS; m/z (%): 371 (M^+–HCl, 1), 250 (1), 226 (2), 181 (2), 145 (77), 117 (63), 105 (43), 90 (100), 77 (61); IR (Nujol): 3212, 3185, 1682, 1665, 1596, 1531, 1462, 1378, 1278, 1153, 1070, 997, 944, 839, 767 cm^{-1}. Compound **7b**: ^{1}H NMR δ (DMSO-d_6, 200 MHz): 3.46 (dd, 1H, J = 11.9 Hz, J = 2.8 Hz), 3.91 (dd, 1H, J = 11.9 Hz, J = 7.8 Hz), 4.71 (d, 1H, J = 15.9 Hz), 5.49 (d, 1H, J = 15.9 Hz), 6.17 (td, 1H, J = 8.0 Hz, J = 2.8 Hz), 7.33–7.63 (m, 14H), 7.91 (d, 2H, J = 7.1 Hz), 9.75 (d, 1H, J = 8.0 Hz); ^{13}C NMR δ (DMSO-d_6 50.4 MHz): 33.85 (CH_2), 48.81 (CH_2), 70.35 (CH), 125.33 (CH), 127.86 (CH), 127.99 (CH), 128.37 (CH), 128.78 (CH), 129.64 (CH), 132.10 (CH), 133.09 (C), 134.64 (C), 166.74 (CO); MS; m/z (%): 387 (M^+–HCl, 11), 266 (44), 240 (45), 182 (20), 167 (76), 148 (24), 121 (27), 105 (63), 91 (100), 77 (68), 65 (22); IR (Nujol): 3146, 2692, 1650, 1626, 1587, 1519, 1487, 1463, 1378, 1181, 766, 700 cm^{-1}.
7. Details of the structure determination will be reported in a future full paper.
8. Guirado, A.; Andreu, R.; Cerezo, A.; Gálvez, J. *Tetrahedron* **2001**, *39*, 4925.
9. See for example: Ciba-Geigy Corporation (1993), US Patent 5,229,405; Egls Gyogyszergyar (1987), US Patent 4,665,083; ICI Americas Inc. (1989), US Patent

4,877,880; ICI Americas Inc. (1990), US Patent 4,900,351; ICI Americas Inc. (1993), US Patent 5,266,701; Union Carbide Corporation (1985), US Patent 4,525,357.

10. (a) Challis, B. C.; Challis, J. A. In *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2 (Sutherland, O. I., Ed.), p. 974; (b) Andersen, K. K. In *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 3 (Jones, D. N., Ed.), p. 456; (c) Whitham, G. H. *Organosulfur Chemistry*; Oxford University Press: Oxford, 1995; p. 26.