Pergamon

Tetrahedron Letters 40 (1999) 8163–8165

TETRAHEDRON LETTERS

Direct conversion of 4-amino-2-oxazolines into 2-imidazolidinones

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 21 July 1999; accepted 31 August 1999

Abstract

A convenient new method for the synthesis of polysubstituted 2-imidazolidinones has been established involving the reaction of 4-alkylamino-2-aryl-2-oxazolines with arylsulfonyl isocyanates. It has been applied successfully in preparing previously unknown 3-alkyl-4-aroylamino-1-arylsulfonyl-2-imidazolidinones in high yields.

Keywords: oxazolines; ureas; imidazolidinones.

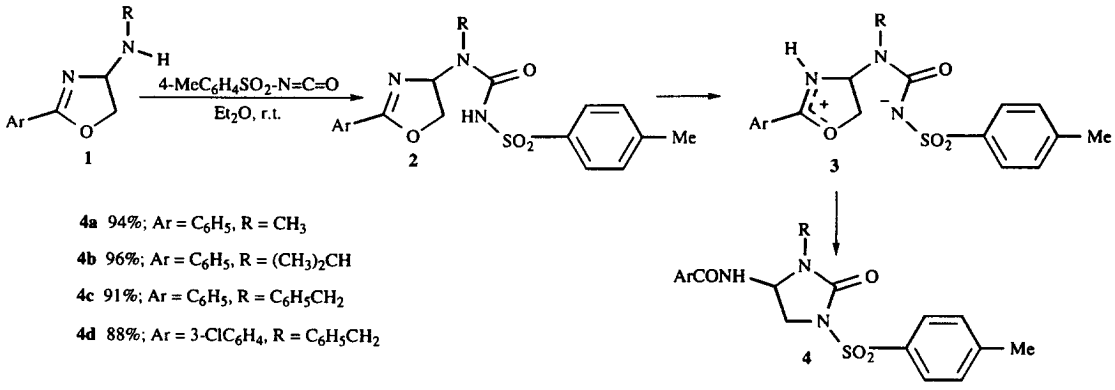
2-Imidazolidinones[1] exhibit a wide range of therapeutic[2] and other important properties.[3] These compounds are also useful as synthetic intermediates and chiral auxiliaries.[4] The most general methodology for preparing 2-imidazolidinones involves carbonylation of 1,2-diamines.[5] However, the synthesis of complex polysubstituted 2-imidazolidinones requires specific procedures.[6]

We recently reported[7] an efficient new entry to 2-oxazolines that provided previously unknown 4-alkylamino-2-aryl-2-oxazolines **1**. 2-Oxazolines are versatile synthetic intermediates[8] with extensive utility in the generation of functional groups, activation of aryl groups towards nucleophilic substitution and addition, metallation, etc. However, there are few examples of transformation into other heterocycles. The work around this subject mainly corresponds to either hydrogenation or dehydrogenation of starting materials to give products retaining the original ring system.[8] Given the interest of the development of new synthetic methods to expand the classes of 2-imidazolidinones available,[2,3,6] the conversion of oxazolines **1** into imidazolidinones **4** was attempted, as shown in Scheme 1.

4-Alkylamino-2-aryl-2-oxazolines **1** were treated with *p*-toluenesulfonyl isocyanate. Remarkably fast reactions with almost instantaneous formation of white solid precipitates were observed. The products were highly pure 2-imidazolidinones **4**. Yields were nearly quantitative. Microanalysis of

* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01682-2



Scheme 1.

4a (crystallized from hexane–chloroform) was in agreement with a $C_{19}H_{20}Cl_3N_3O_4S$ composition $\equiv C_{18}H_{19}N_3O_4S(CHCl_3)$ which was confirmed by thermogravimetric analysis. The molecular structure of **4a** was determined by X-ray crystallography.[9]

The formation of products **4** can be explained as shown in Scheme 1. Owing to the relatively high acidic centre present in the firstly formed ureido intermediates **2**, autoactivation for nucleophilic attack at 5-position by generation of species **3** should operate. Therefore, a ring opening of the oxazoline system with simultaneous ring closure leading to the corresponding imidazolidinones **4** could take place easily. As far as we know it is the first time that a direct conversion of 2-oxazolines into 2-imidazolidinones has been reported. The wide variety of 2-oxazolines **1** available[7] determines a high versatility in this new entry to 2-imidazolidinones.[10] It should be noted that the hitherto unknown products **4** are closely related with some *N*-arylsulfonyl-2-imidazolidinones with pronounced antitumor properties.[2c] It therefore seems of interest to check the biological activity of these novel compounds.

To conclude, a convenient new method for the synthesis of polysubstituted 2-imidazolidinones is reported. Versatility, good yields, easy availability of starting materials, mildness and simple experimental procedure are noteworthy advantages of this approach, which provides access to previously unattainable compounds.

Typical experimental procedure: A solution of *p*-toluenesulfonyl isocyanate (1 mmol) in dry ether (3 mL) was added dropwise at room temperature to a stirred solution of the appropriate aminooxazoline **1** (1 mmol) in dry ether (5 mL). An almost instantaneous formation of a white solid precipitate was observed. The solid product was filtered off, washed with cold ether and crystallized from a mixture of hexane–chloroform or hexane–dichoromethane.[11] All compounds gave satisfactory IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analyses.[12]

References

1. For brief reviews, see: *Rodd's Chemistry of Carbon Compounds*; Coffey, S; Ansell, M. F., Eds.; Elsevier: Amsterdam, 1986; Vol. 4, Part C. *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; Imidazole and its derivatives, Part I; Interscience Publishers Inc.: New York, 1953.
2. See, for example: (a) Hussain, M. H.; Lien, E. J. *J. Heterocyclic Chem.* **1971**, *8*, 507; (b) Aelony, D.; McKillip, W. J. *J. Heterocyclic Chem.* **1972**, *9*, 687; (c) US 5,270,329; CA 120: 124875; (d) US 5,789,425; CA 123: 228184; (e) US 5,494,927; CA 116: 128921; (f) US 4,410,540; CA 99: 194958.
3. For example, see: (a) US 5,746,946; CA 125: 275878; (b) US 4,749,403; CA 108: 6018.
4. For a recent review, see: Roos, G. H. P. *S. Afr. J. Chem.* **1998**, *51*, 7.

5. Nomura, R.; Hasegawa, Y.; Ishimoto, M.; Toyosaki, T.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 7339, and references cited therein.
6. For example, see: (a) Nadir, U. P.; Basu, N. *Tetrahedron* **1993**, *49*, 7787; (b) VanVerst, M. E.; Bell, C. L.; Bauer, L. *J. Heterocyclic Chem.* **1979**, *16*, 1329; (c) Milcent, R.; Barbier, G. *J. Heterocyclic Chem.* **1992**, *29*, 1081; (d) Talaty, E. R.; Yusoff, M. M.; Ismail, A. A.; Gomez, J. A.; Keller, C. E.; Younger, J. M. *Synlett* **1997**, 683.
7. Guirado, A.; Andreu, R.; Gálvez, J. *Tetrahedron Lett.* **1998**, *39*, 1071.
8. For a general review, see: Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
9. Details of the structure determination will be reported in a future full paper.
10. The study of reactions with aryl and alkyl isocyanates and isothiocyanates is now in progress.
11. Compound **4a**: mp 216–218°C; Compound **4b**: mp 222–224°C; Compound **4c**: mp 215–216°C; Compound **4d**: mp 220–221°C.
12. Compound **4a**: ^{1}H NMR δ ($CDCl_3$, 300 MHz): 2.45 (s, 3H), 2.79 (s, 3H), 3.90 (dd, 1H, *J*=8.4, *J*=5.1 Hz), 4.05 (dd, 1H, *J*=5.2, *J*=2.4 Hz), 5.87 (td, 1H, *J*=8.4, *J*=2.4 Hz), 7.29 (d, 2H, *J*=8.1 Hz), 7.42 (t, 2H, *J*=7.8 Hz), 7.55 (t, 1H, *J*=7.5 Hz), 7.83 (d, 2H, *J*=8.4 Hz), 7.97–8.03 (m, 3H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 21.68, 28.00, 48.73, 59.69, 127.68, 127.92, 128.50, 129.82, 132.05, 133.31, 134.51, 145.04, 153.41, 168.00; ms; *m/z* (%): 373 (M^+, 1), 252 (19), 218 (20), 155 (13), 105 (100), 97 (60), 91 (47), 77 (41); IR (nujol): 3310, 1732, 1667, 1537, 1464, 1366, 1265, 1171, 1134, 857, 814, 760, 666 cm^{-1}.