Tetrahedron Letters 50 (2009) 790–792

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile one-pot synthesis of 3-unsubstituted-2,4-oxazolidinediones via in situ generation of carbamates from α-hydroxyesters using trichloroacetyl isocyanate

Yue H. Li [a,*], Li Zhang [c], Pei-San Tseng [b], Yongliang Zhang [c], Yu Jin [c], Jingkang Shen [c], Jian Jin [b]

[a] Discovery Medicinal Chemistry, GlaxoSmithKline, 1250 S. Collegeville Rd., Collegeville, PA 19426, USA
[b] Cardiovascular & Urogenital CEDD, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA
[c] State Key Laboratory of Drug Discovery, Shanghai Institute of Materia Medica, Shanghai Institute of Biological Science, Chinese Academy of Science, 555 Zuchongzhi Rd., Shanghai, 201203, PR China

ARTICLE INFO

Article history:
Received 6 February 2008
Revised 25 November 2008
Accepted 29 November 2008
Available online 6 December 2008

Keywords:
3-Unsubstituted-2,4-oxazolidinedione
Trichloroacetyl isocyanate
α-Hydroxyester
Carbamate

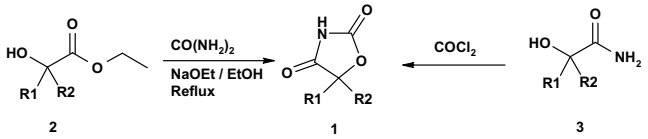
ABSTRACT

A convenient, high yield one-pot methodology for the synthesis of pharmaceutically interesting 3-unsubstituted-2,4-oxazolidinediones from α-hydroxyesters is described. A primary carbamate was generated in situ from the corresponding α-hydroxyester and trichloroacetyl isocyanate, then converted to the desired 3-unsubstituted 2,4-oxazolidinedione via intramolecular ring closure. This method is amenable to scale-up and requires no chromatographic purification.

3-Unsubstituted-2,4-oxazolidinediones (Fig. 1) are an important heterocyclic template found in many substances of pharmaceutical interest. This class of compounds displays a wide range of biological activities; examples of such are aldose reductase inhibitors,[1] hypoglycemic and hypolipidemic agents,[2] muscarinic agonists,[3] and insulin sensitizers with anti-diabetic activities.[4] Furthermore, spiro oxazolidinediones were found to be aldose reductase inhibitors.[5] In addition, 5,5-dimethyloxazolidine-2,4-dione (DMO) was described as an indicator of intracellular pH due to its weak acidic properties.[6]

Because of the importance of 3-unsubstituted-2,4-oxazolidinediones, a number of synthetic methods have been reported in the literature.[3,4,7] However, upon closer inspection, it became apparent to us that among these synthetic methods, two were typically used (Scheme 1). The first widely used method involves the reaction of α-hydroxyester **2** with urea and base, preferably sodium ethoxide. The second method involves the reaction of α-hydroxycarboxamide **3** with phosgene or phosgene equivalent reagents. In many cases, both methods have been reported to give desired products with good yields (60–80%) (Scheme 1).

In a recent drug discovery effort, we engaged in a structure–activity relationship (SAR) study around a lead compound containing a 3-unsubstituted-2,4-oxazolidinedione moiety. Using the above-mentioned urea approach from the α-hydroxyester precursor, we experienced consistently low yields during the 2,4-oxazolidinedione ring formation step. Specifically, we regularly observed the formation of α-hydroxyacid derived from hydrolysis of the α-hydroxyester starting material under highly basic reaction conditions. The formation of this hydrolysis byproduct corresponded to significantly lowered product yield and complicated purification, thereby negatively effecting subsequent steps. The amount of byproduct could be reduced using strictly anhydrous reaction conditions, but its formation could not be eliminated completely. As for the phosgene approach, in addition to the disadvantage of low yield, we wanted to avoid the use of highly toxic phosgene or its equivalent reagents. Moreover, the starting material, α-hydroxycarboxamide **3**, is typically prepared via hydrolysis of its nitrile precursor, which requires using very toxic cyanide reagents in its own preparation.[8]



Scheme 1. Two typical methods for preparation of 3-unsubstituted-2,4-oxazolidinediones (**1**).

* Corresponding author. Tel.: +1 610 917 6999; fax: +1 610 917 7391.
E-mail address: yue.h.li@gsk.com (Y.H. Li).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.124

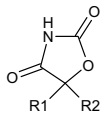


Figure 1. 3-Unsubstituted 2,4-oxazolidinediones.

It is known that 3-substituted-2,4-oxazolidinediones can be prepared by reacting a α-hydroxyester with an isocyanate.[3,9] We were able to prepare the desired 3-unsubstituted-2,4-oxazolidinediones through this route using a protecting group approach (Scheme 2). However, the added de-protection step not only resulted in decreased yield, but also limited the efficiency of our SAR exploration. This prompted us to develop a new, mild, and more robust synthetic method.

Known as one of the most reactive isocyanates, trichloroacetyl isocyanate has been reported to generate primary ureas in good yield via formation of trichloroacetyl carboxamides, followed by hydrolysis under neutral conditions.[10] This reagent has also been reported to react readily with tertiary alcohols to prepare trichloroacetyl carbamates, which can be readily converted to primary carbamates under mild conditions,[11] indicating that the trichloroacetyl group is a good nitrogen-protecting group, which can be readily cleaved under mild conditions.

We hypothesized that by taking advantage of the unique structure of the α-hydroxyester, an intramolecular cyclization could be favored, leading to the formation of the desired 3-unsubstituted 2,4-oxazolidinedione. The α-hydroxyl group could be converted to the primary carbamate, and the ester group could serve as a good leaving group. Thus, we decided to apply this strategy in our investigation. By treating the α-hydroxyester **2** with trichloroacetyl isocyanate, the expecting trichloroacetyl carbamate was formed, which was monitored by LC–MS. To our delight, we were able to obtain the desired 3-unsubstituted 2,4-oxazolidinedione **1** while attempting to deprotect the trichloroacetyl group with a weak base under refluxing conditions. Clearly, under these conditions, the formation of the thermodynamically stable five-member ring system was facile.

Herein, we report our discovery of this mild and efficient synthetic method of preparing 3-unsubstituted-2,4-oxazolidinediones using trichloroacetyl isocyanate as the key reagent as shown in Scheme 3.

As shown in Scheme 3, α-hydroxyester **2** was first treated with trichloroacetyl isocyanate at 0 °C to room temperature to form the trichloroacetyl carbamate. Typically, the reaction was complete within 30 min, as monitored by LC–MS. After quenching the excess trichloroacetyl isocyanate with methanol, the reaction solvent was evaporated from the crude trichloroacetyl carbamate intermediate. The residue was heated to reflux overnight in the presence of a base, such as triethyl amine, sodium ethoxide, or 10% aqueous K_2CO_3 solution, to form the desired 3-unsubstituted 2,4-oxazolidinedione as the sole product.[12]

As shown in Table 1, this new method works well for a variety of α-hydroxyesters. In most cases, the reactions were clean and resulted in the formation of the desired 3-unsubstituted-2,4-oxazolidinediones. Further purification, if needed, could be achieved through recrystallization from ethanol. In addition, this method is very robust and amenable to scale up. Our program team was able to use this methodology to scale up key intermediates to 100 g scale.

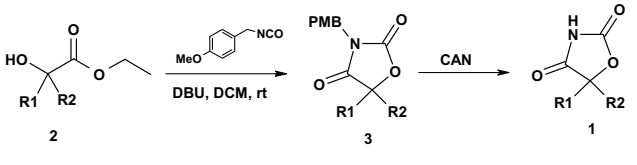
The proposed mechanism for this method is outlined in Scheme 4. Formation of compound **1e** in Table 1 was used for the mechanism study. The reaction progress was monitored by LC–MS, and the sequence of events was readily apparent by following the appearance and disappearance of the appropriate peaks. Formation of trichloroacetyl carbamate **5** occurred quickly in DCM or THF. Addition of a base was not necessary in this step. In the next stage, formation of primary carbamate **6** was observed when heating the reaction mixture in EtOH. However, formation of **1e** was not observed without the presence of a base. Thus, it was clear that this one-pot synthesis occurred via the formation of **6**, followed by ring closure, which was facilitated by thermal heating in the presence of a base.

In conclusion, we have discovered an efficient one-pot synthesis of 3-unsubstituted-2,4-oxazolidinediones via in situ generation of a primary carbamate derived from α-hydroxyesters using trichloroacetyl isocyanate and base. Subsequent heating in aqueous base facilitates carbamate deprotection and ring closure to generate the desired 3-unsubstituted-2,4-oxazolidinediones. This robust method can be readily applied toward the preparation of 3-unsubstituted-2,4-oxazolidinedione analogs and it is highly amenable to scale-

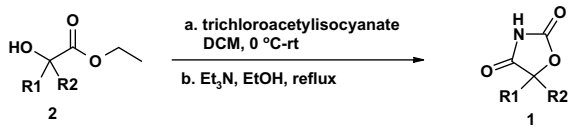
Table 1
3-Unsubstituted-2,4-oxazolidinediones synthesized via Scheme 3

Entry	R1	R2	Yield (%)	mp (°C)
1a	H	Me	67[a]	Oil[12]
1b	H	Et	87[b]	57–58[12]
1c	H	Propyl	77[b]	107–109[13]
1d	Me	Me	72[b]	61–63[14]
1e	H	Ph	87[b,18]	110–111[15]
1f	Me	Ph	91[b]	75–76[16]
1g	Ph	Ph	85[b]	136–137[16]
1h	Me	6-Chloro-2-(methyloxy)-3-pyridinyl	91[b]	214–215[17]
1i		Cyclopentyl	77[b]	120–122[16]
1j		Cyclohexyl	82[b]	107–108[16]

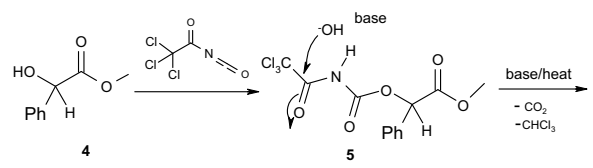
[a] Yield after running through Bond Elut® silica column.
[b] Yield after crystallization from ethanol.

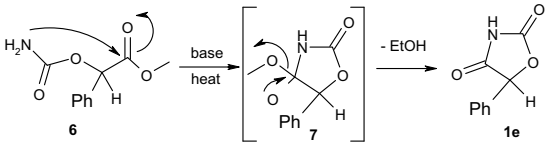


Scheme 2. Protecting group approach.



Scheme 3. One-pot preparation of 3-unsubstituted 2,4-oxazolidinediones.





Scheme 4. Proposed mechanism for preparation of 5-unsubstituted-2,4-oxazolidinedione.

up. Application of this method to the synthesis of other heterocycles, such as 3-unsubstituted-2,4-thiazolidinediones and hydantoins, is under further investigation and will be reported in due course.

Acknowledgments

Helpful discussions with Drs. Frank T. Coppo, Linda N. Casillas, Karen A. Evans, Yonghui Wang, Todd L. Graybill, and Ralph A. Rivero during the Letter preparation are gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.124.

References and notes

1. (a) York, B. M. U.S. Patent 4,717,725, 1988.; b York, B. M. U.S. Patent 5,070,100, 1991.
2. Sohda, T.; Ikeda, H.; Momose, Y. Eur. Patent 643050, 1995.
3. Tsukamoto, S.; Ichihara, M.; Wanibuchi, F.; Usuda, S.; Hidaka, K.; Harada, M.; Tamura, T. *J. Med. Chem.* **1993**, *36*, 2292.
4. Dow, R. L.; Bechle, B. M.; Chou, Thomas T.; Clark, D. A.; Hulin, B.; Stevenson, R. W. *J. Med. Chem.* **1991**, *34*, 1538.
5. Schnur, R. C.; Sarges, R.; Peterson, M. J. *J. Med. Chem.* **1982**, *25*, 1451.
6. Minoru, M.; Yoshihiko, T.; Toshimitsu, F.; Masaharu, K. *J. Labelled Compd. Radiopharm.* **1988**, *27*, 553.
7. (a) Nakamura, K.; Kamikawa, T. U.S. Patent 6,384,231, 2002.; (b) Zha, C.; Brown, G. B.; Brouillette, W. J. *J. Med. Chem.* **2004**, *47*, 6519; (c) Schnur, R. C.; Morville, M. *J. Med. Chem.* **1986**, *29*, 770.
8. Galvez, E.; Trigo, G. G.; Martinez, M.; Cabezas, N. *J. Heterocycl. Chem.* **1983**, *20*, 13.
9. Menendez, J. C.; Avendano, C.; Sollhuber, M. M. *Heterocycles* **1989**, *29*, 477.
10. (a) Pietsch, M.; Guetschow, M. *J. Med. Chem.* **2005**, *48*, 8270–8288; (b) Meusel, M.; Guetschow, M. *Tetrahedron Lett.* **2005**, *46*, 2231.
11. Bubert, C.; Leese, M. P.; Mahon, M. F.; Ferrandis, E.; Regis-Lydi, S.; Kasprzyk, P. G.; Newman, S. P.; Ho, Y. T.; Purohit, A.; Reed, M. J.; Potter, B. V. L. *J. Med. Chem.* **2007**, *50*, 4431.
12. Kano, S.; Yuasa, Y. *Heterocycles* **1987**, *26*, 373.
13. Spielman, M. A.; Everett, G. M. *J. Am. Chem. Soc.* **1948**, *70*, 1021–1022.
14. Stoughton, R. W. *J. Am. Chem. Soc.* **1941**, *63*, 2375.
15. Sheehan, J. C.; Laubach, G. D. *J. Am. Chem. Soc.* **1951**, *73*, 4752.
16. Garcia, M. V. *Synthesis* **1991**, *9*, 697.
17. MS: (M^+): 256.7. ^{1}H NMR (400 MHz, MeOD) δ 1.92 (s, 3H) 3.94 (s, 3H) 7.11 (d, J = 7.83 Hz, 1H) 7.82 (d, J = 7.83 Hz, 1H) ppm.
18. *General procedure*: To the stirring solution of methyl mandelate (0.2 g, 1.2 mmol) in DCM (3.0 mL) at 0 °C was added trichloroacetyl isocyanate (0.21 mL, 1.8 mmol) dropwise. After addition, the resulting mixture was allowed to stir at rt for 30 min. LC–MS of an aliquot of the reaction mixture showed 100% formation of corresponding trichloroacetyl carbamate. The excess trichloroacetyl isocyanate was quenched by methanol (1 mL). The reaction mixture was concentrated in vacuo. The residue was dissolved in EtOH (5 mL), followed by the addition of Et_3N (0.33 mL, 2.4 mmol). The reaction mixture was then heated to reflux overnight. The solvent was removed under vacuum. The residue was dissolved in water (5 mL). 1 N HCl was carefully added to adjust pH to 3. The precipitate was filtered, washed with water, and dried in vacuum to give the desired product as a while solid (0.194 g, 91%). The product was further purified by recrystallization from ethanol (0.185 g, 87%). MS: (M^+): 177.6. ^{1}H NMR (400 MHz, MeOD) δ 5.91 (s, 1H) 7.34–7.61 (m, 5H) ppm.