Arch. Pharm. Res. Vol. 16, No. 2, pp. 158-160, 1993

Note

A Facile Synthetic Method of 2-Oxazolidinones and 1,3-Oxazine-2-ones, Essential Moieties of New Antiulcer Agent

Min-Soo Park[1] and Jae-Won Lee[2]

[1]*College of Phamacy, Kyungsung University, Pusan 608-736 and* [2]*Whan In Pharmaceutical Cooperation, Seoul 136-074, Korea*

(Received February 8, 1993)

2-Oxazolidinones and 1,3-oxazine-2-ones, key moieties of new antiulcer agents, were prepared successfully by treating corresponding hydroxyamide with N-bromosuccinimide (NBS) and silveracetate in acetonitrile. From the fact that the methods for the preparation of hydroxy amides are versatile and such amides could be converted to the corresponding 2-oxazolidinones and 1,3-oxazine-2-one under our reaction condition, we think that our method is very practical one for the preparation of such compounds. In addition, the above synthetic example affords a good evidence of the synthetic applicability of our improved Hofmann rearrangement.

Key words: 2-Oxazolidinone, 1,3-Oxazine-2-one, 3-Hydroxyamide, 4-Hydroxyamide, N-Bromosuccinimide, Antiulcer agent, Hofmann rearrangement

INTRODUCTION

2-Oxazolidinones have been found to be key components of biologically active compounds (Conforth, 1957). And for another recent interesting example, some N-substututed 2-oxazolidinones and 1,3-oxazine-2-ones were reported to show potent antiulcer activity (Kovayashi *et al.*, 1984). Therefore so far many methods (Dyen and Swern, 1967) available for their synthesis were developed. But in view of synthetic practicability these methods have some demerits that starting materials can not be obtained easily and the reaction path is somewhat long.

Interestingly, there was an attempt for the preparation of 2-oxazolidinones from 3-hydroxyamide by Hofmann reaction (Close, 1951). But the yields was very low owing to the hydrolysis in alkaline midium.

This fact was so impressive that we tried applying our improved Hofmann reannangement (Jew *et al.*, 1990), conducted in anhydrous and neutral condition by using NBS and silveracetate, to the preparation of those valuable heterocyclic compounds. And also we though that this synthetic trial is an interesting evidence to confirm the synthetic utility of our improved Hofmann rearrangement procedure.

As the first synthetic application of our improved Hofmann rearrangement procedure, we attempted to apply this method to the synthesis of 2-oxazolidinone and 1,3-oxazine-2-one, a part of new potent antiulcer agents, shown in Fig. 1.

Kovayashi *et al.* (1984) reported that foresaid antiulcer agent, having 2-oxazolidinone or 1,3-oxazine-2-one as a key moeity in their structure, could be synthesized by N-alkylation to the corresponding 2-oxazolidinone or 1,3-oxazine-2-one as shown in Fig. 2.

So the synthesis of 2-oxazolidinone and 1,3-oxazine-2-one was thought to be a key step for the preparation of those antiulcer agent. And we thought that the wanted 2-oxazolidinones and 1,3-oxazine-2-one could be prepared from the easily available 3- or 4-hydroxyamides by using our improved Hofmann rearrangement procedure as shown in Fig. 3.

As seen in Fig. 3, we thought that the 2-oxazolidinones and 1,3-oxazine-2-ones could be synthesized ideally by intramolecular nucleophilic addition of hydroxy group to the isocyanate, generated by treating amides with NBS and silveracetate. In this paper, we wish to report a convient method for the preparation of 2-oxazolidone and 1,3-oxazine-2-one, an essential part of new antiulcer agents, by using our improved Hofmann rearrangement as a key reaction.

MATERIALS AND METHOD

All melting points were determinted with Electronthermal melting point apparatus and uncorrected. IR spectroscopy was measured with a Beckmann infrared

Correspondene to: Min-Soo Park, College of Pharmacy, Kyungsung Univ., Daeyoun-Dong, Nam-Gu, Pusan 608-736, Korea

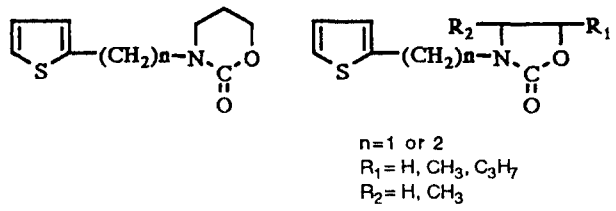


Fig. 1.

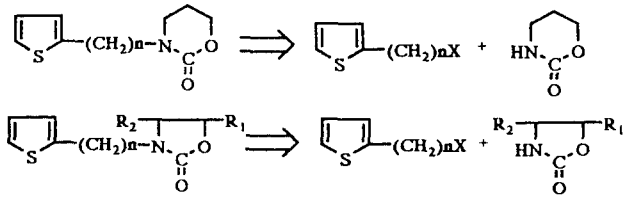


Fig. 2.

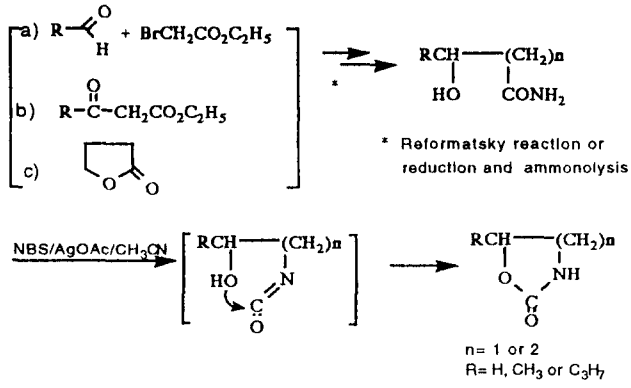


Fig. 3.

20A Spectrometer and ^{1}H-NMR spectra were recorded on Perkin-Elmer R-32 NMR spectrometer using TMS as an internal standard. All yields refered to chromatographically homogeneous material.

Ethyl 3-hydroxybutanoate

To a solution of $NaBH_4$ (145 mg, 383 mmol) in absolute ethanol (10 ml), ethylacetoacetate (1.0 g, 7.68 mmol) was added, and the reaction solution was stirred at 0℃ for 3 hrs. Then the reaction mixture was acidified with 5% H_2SO_4 and evaporated; extracted with 200 ml of EtOAc; washed with sat. $NaHCO_3$ (20 ml×2), H_2O (20 ml×2) and sat. NaCl (20 ml×2) successively; dried over anhydrous $MgSO_4$; and evaporated to give 1.03 g of pale yellow oil. This was purified with silicagel column chromatography (EtoAc : Hexane =1 : 3) to give 984 mg of colorless oil (97%).

IR(neat) cm^{-1}: 3300, 1720.

3-Hydroxybutanamide

To excess ammonia water, ethyl 3-hydroxybutanoate (1.00 g, 76.0 mmol) was added, then stirred at room temperature for 6 hrs. It was evaporated under reduced pressure to give 1.2 g of semisolid material. Then this was crystalized with EtOAc and Hexan and filtered to give 1.10 g of white solid (quant.), mp: 78-80℃ [lit. (Simons, 1973) 82.9-84℃].

IR(nujol) cm^{-1}: 3350, 3200, 1660, 1630.

Ethyl 3-hydroxyhexanoate

To the suspension of powered Zn (940 mg, 14.3 mmol) in 20 ml of diethylether, the mixed solution of ethylbromoacetate (2.00 g, 11.9 mmol) and n-butylaldehyde (1.03 g, 14.3 mmol) in diethylether (15 ml) and benzene (15 ml) was added dropwise, then the reaction mixture was refluxed for 12 hrs. It was cooled to 0℃, acidified with cold 5% H_2SO_4 and extracted with 300 ml of diethylether; washed with 10% Na_2CO_3 (20 ml×2), 5% H_2SO_4 (20 ml×1), H_2O (20 ml×2) and sat. NaCl (20 ml×2) successively; dried over anhydrous $MgSO_4$ and evaporated to give 2.20 g of yellow oil. It was distillated in vacuo to give 1.56 g of yellow oil (65%).

IR(neat) cm^{-1}: 3400, 1720.

3-Hydroxy hexanamide

To excess ammonia water ethyl 3-hydroxyhexanoate (1.00 g, 6.25 mmol) was added, then the mixture was stirred at room temperature for 6 hrs. Then the reaction mixture was evaporated in vacuo to give 980 mg of caramel. It was purified with column chromatogrphy (EtOAc) to give 900 mg of pale yellow caramel (quant.).

IR(neat) cm^{-1}: 3400, 3200, 1660, 1620.

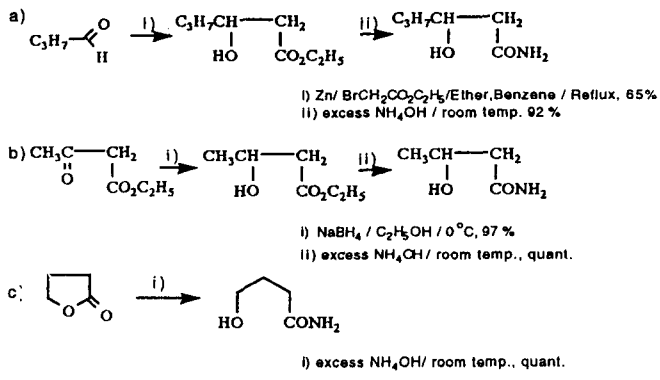
4-Hydroxybutanamide

To excess ammonia water γ-butyrolactone (1.00 g, 11.6 mmol) was added, and stirred ar room temperature overnight. Then this was evaporated to give 1.20 g of caramel. This was purified with column chromatography (EtOAc) to give 970 mg of caramel (quant.).

IR(neat) cm^{-1}: 3400, 3200, 1660, 1630.

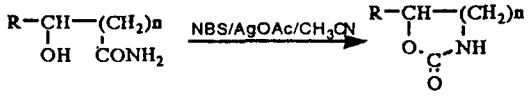
5-Methyl-2-Oxazolidinone

To the suspension of 3-hydroxyamide (1.00 g, 9.70 mmol) and AgOAc (1.94 g, 11.6 mmol) in 10 ml of acetonitrile, the NBS (2.02 g, 11.6 mmol) solution in 30 ml of acetonitrile was added at 0℃ under Ar atmosphere, then stirred for 2 hrs at 0℃ and 10 hrs at room temperature. After 12 hrs acetonitrile was evaporated; extracted with 300 ml of ethylacetate; washed with 10% Na_2CO_3 (30 ml×2), 5% HCl (30 ml×2), H_2O (30 ml×1) and sat. NaCl (30 ml×2); dried over anhydrous $MgSO_4$ and evaporated to give 1.02 g of oil, then purified with column chromatography (EtOAc) to give 860 mg of pale yellow oil (87%).



Scheme 1.

Table I.



R	n	Yields (%)
CH_3	1	87
C_3H_7	1	90
H	2	90

IR(neat) cm^{-1}: 3300, 1650; ^{1}H-NMR ($CDCl_3$) δ; 1.10 (d, 3H, CH_3), 3.05-3.30 (m, 2H, CH_2N), 3.50-3.83 (m, 1H, CHO), 4.50-4.90 (br, 1H, NH).

5-Propyl-2-Oxazolidinone

3-hydroxyhexanamide (1.00 g, 7.60 mmol), AgOAc (1.52 g, 9.12 mmol), NBS (1.63 g, 9.12 mmol); yield (882 mg, 90%) oil.

IR(neat) cm^{-1}: 3300, 1735; ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, CH_3, J=7.0 Hz), 1.10-1.75 (m, 4H, CH_2×2), 3.05-3.30 (m, 2H, CH_2N), 3.40-3.80 (m, 1H, CHO), 4.30-4.70 (br, 1H, NH).

1,3-Oxazine-2-one

4-hydroxybutanamide (1.00 g, 9.70 mmol), AgOAc (1.94 g, 11.6 mmol), NBS (1.72 g, 11.6 mmol): yield (890 mg, 90%) mp: 82-84℃.

IR(nujol) cm^{-1}: 3250, 1680; ^{1}H-NMR ($CDCl_3$) δ: 1.10-1.75 (m, 2H, CH_2), 3.05-3.30 (m, 2H, CH_2N), 3.40-3.80 (m, 2H, CH_2O), 4.30-4.70 (br, 1H, NH).

RESULT AND DISCUSSION

A number of 3-hydroxyamides and 4-hydroxyamide for this reaction were prepared by various methods as shown in Scheme 1.

Then these amides were conducted in our improved Hofmann rearrangement to afford the corresponding 2-oxazolidinone or 1,3-oxazine-2-one, a part of new antiulcer agent, as a sole product in tlc.

As seen in Table 1, both 3- and 4-hydroxyamide were converted into the corresponding 2-oxazolidinone and 1,3-oxazine-2-one in high yields without any side products in our reaction procedure.

From the above results, it is clear that intranucleophilic addition of 3- or 4-hydroxy group of these amides to isocyanate take place ideally as soon as the formation of isocyanate, generated by treating amide with NBS and silveracetate in a similar mode to Hofmann rearrangement. Especially, it was known that 2-oxazolidinone and 1,3-oxazine-2-one are labile to alkali. But in our rection procedure, carried out in neutral condition, such trouble could be prevented.

In addition, the vesatility of methods for the preparation of hydroxy amides and their stability compared to some other precursors of 2-oxazolidone and 1,3-oxazine-2-one are the advantages of this method.

Conculsion

2-Oxazolidinone and 1,3-oxazine-2-one, a key moeity of antiulcer agents, could be obtained successfully from the corresponding hydroxyamides by using our improved Hofmann rearrangement procedure.

Especially, 2-oxazolidinone and 1,3-oxazine-2-one were known to be very labile to alkali, but in our reaction procedure, conducted in neutral condition, such trouble could be prevented. In addition, the facility of the preparation of these amides and their stability are also advantage of our method.

ACKNOWLEDGEMENT

This work was in part supported by Whan In Pharmaceutical Cooperation.

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