Tetrahedron Letters 50 (2009) 5123–5125

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of 3-alkyloxazolidin-2,4-diones using 2-chloroacetamides, carbon dioxide and 1,8-diazabicyclo[5.4.0]undecene (DBU)

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ARTICLE INFO

Article history:
Received 22 May 2009
Revised 20 June 2009
Accepted 23 June 2009
Available online 27 June 2009

Keywords:
3-Alkyloxazolidin-2,4-diones
Carbon dioxide
DBU
Amines
Chemical synthesis

ABSTRACT

Diazabicyclo[5.4.0]undecene (DBU) reacts with carbon dioxide and N-subsititued-2-chloroacetoamides in a very simple one-step procedure, to give the corresponding 3-substituted oxazolidin-2,4-diones in excellent yields.

1. Introduction

Oxazolidine-2,4-diones are used as anticonvulsants, herbicides or chemical intermediates.[1,2] Trimethadione® (3,5,5- trimethyloxazolidine-2,4-dione), Paramethadione® (5-ethyl-3,5-dimethyloxazolidine-2,4-dione) and Malidone® (3-allyl-5-methyloxazolidine-2,4-dione)[3] are important commercial products.

The preparation of 3-substituted oxazolidin-2,4-diones employs toxic and hazardous compounds such as phosgene and isocyanates.[4–7] Carbon dioxide fixation[8] offers a greener alternative to this chemistry.

The ability of amidines such as 1,8-diazabicyclo[5.4.0]undecene (DBU) to promote a new C–N bond formation in reactions involving carbon dioxide fixation, has been described recently in the synthesis of formanilide and carbanilide[9], of 2,4-dihydroquinazolines[10], of 1-*H*-quinazolines-2,4-diones[11] and of *N*-alkyl carbamates.[12]

We wish to report a very easy and highly efficient procedure to prepare 3-substituted oxazolidin-2,4-diones from primary chloroacetamides, by directly incorporating carbon dioxide in the presence of a stoichiometric amount of DBU. To the best of our knowledge, it is the first example, in the preparation of these compounds, of the use of carbon dioxide with an organic base and without electrochemical methodologies.[13–18]

2. Results and discussion

In an exploratory experiment, *N*-benzyl-2-chloroacetamide (**3a**: X = Cl; R = benzyl), prepared via the reaction of chloroacetylchloride (**2**: X = Cl) with benzylamine (1: R = benzyl) (Scheme **1**), was put into an autoclave with carbon dioxide (20 bar) and a stoichiometric amount of 1,8-diazabicyclo[5.4.0]undecene (DBU, **4**). After 4 h at 80 °C the crude reaction mixture was separated by silica gel chromatography and 3-benzyloxazolidin-2,4-dione (**6a**: R = benzyl) was obtained in excellent yield (96%).

Different primary *N*-alkylchloroacetamides gave different 3-alkyloxazolidin-2,4-diones (**6**) in excellent yields. On the contrary *N*-phenylchloroacetamide (**3h**: R = phenyl) gave the corresponding 3-phenyloxazolidin-2,4-dione (**6h**: R = phenyl) in very low yield and 3-adamantylchloroacetamide (**3g**: X = Cl, R = adamantyl) did not react (Table 1).

Using amides lacking the α–chlorine atom produced carbamate salts (**5**). In fact, upon performing the DBU-assisted carbonatation of the propionamide (**3**: X = Me) in dichloromethane, the reaction product showed an IR band at 1648 cm^{-1}, consistent with the formation of the carbamate salt (**5**: X = Me).[24]

This suggests a plausible reaction pathway involving carboxylation of the starting chloroacetamide by DBU, to form a carbamate salt (**5**: X = Cl) which undergoes intramolecular S_N2 cyclization, and where the chloride ion acts as the leaving group to give (**6**). If DBU is not present, no reaction of the chloroacetamide (**3**: X = Cl) with CO_2 is observed.

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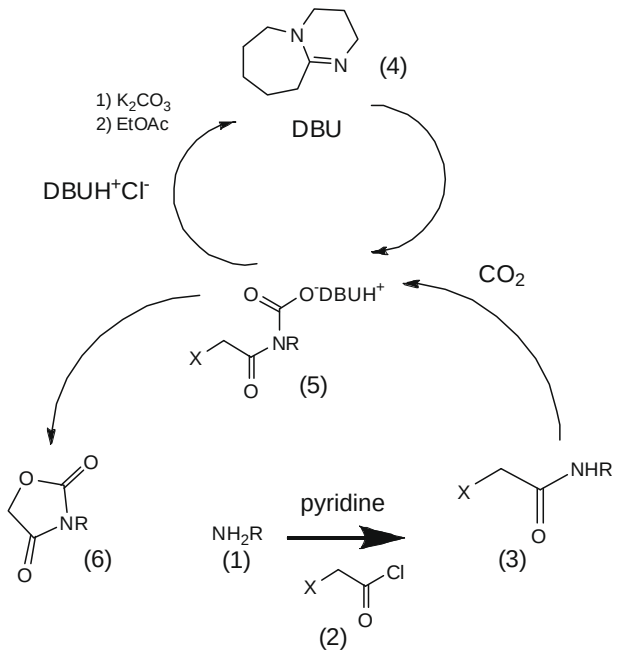
doi:10.1016/j.tetlet.2009.06.109



Scheme 1. Synthesis of 3 alkyloxazolidin-2,4-diones.

Table 1
Yield in 3-substituted oxazolidine-2,4-diones (**6**)

Entry	R	Substrate	Product	Yield[a] (%)
1	Benzyl	**3a**	**6a**[15,17–21]	96
2	Cyclohexyl	**3b**	**6b**[19,22]	87[b]
3	*n*-Pentyl	**3c**	**6c**[19,21]	95
4	*n*-Hexyl	**3d**	**6d**	96
5	*i*-Propyl	**3e**	**6e**	88[b]
6	Allyl	**3f**	**6f**[16–18,20,21]	86
7	Adamantyl	**3g**	**6g**	0[b,c]
8	Phenyl	**3h**	**6h**[15–17,20,22,23]	5[b,c]

[a] Isolated product, reaction time 4 h.
[b] Reaction time 14 h.
[c] GC yield.

About 70% of DBU may be recovered by dissolving the reaction mixture in methylene chloride and washing the resulting solution three times with 100 mL of water. The collected aqueous extracts are treated with solid K_2CO_3 and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to recover DBU.

Other bases were also tested for their ability to promote the reaction under the same experimental conditions used with DBU: triazabicyclodecene (TBD) gave 3-benzyloxazolidin-2,4-dione (**6a)** from (**3a)** in 85% yield; 1,8-dimethylaminonaphthalene (DMAN) and triethylamine were almost ineffective; no reaction was noticed with sodium hydroxide.

In conclusion, we have described a mild and selective procedure which allows 3-substituted oxazolidine-2,4-diones (**6**) to form by a DBU-assisted carbonatation of primary chloroacetamides (**3**). Recovery of DBU after the reaction is also possible.

3. Experimental

3.1. Representative experimental procedures

(a) *N-Alkyl 2*-chloroacetamide (**3**): chloroacetyl chloride (**2,** 10 mmol) was slowly added to a mixture of amine (**1**, 10 mmol) and pyridine (10 mmol) in 150 ml of tetrahydrofuran. The solution was stirred for 4 h at room temperature, then 100 mL of ethyl acetate was added and the organic phase was washed three times with 100 mL portions of water, and then it was dried over sodium sulfate. Evaporation of the organic phase under reduced pressure gave the *N*-alkyl 2-chloroacetoamides (**3**).

(b) *3-Alkyl-oxazolidine-2,4-dione* (**6**): all the experiments were carried out in a 100 mL autoclave equipped with temperature control. In a typical experiment, 2 mmol of *N*-alkyl-2-chloroacetoamide (**3**) and 2 mmol of DBU (**4**) were dissolved in 20 mL of acetonitrile and the solution was put in a quartz reactor which was inserted into the autoclave. This was then charged with carbon dioxide (99.8%), 20 bar, placed in an oil bath and left to react for the required time at 80 °C. Then the autoclave was cooled, excess gas was released slowly and the reaction mixture was purified by column chromatography on silica gel $R = 50$ eluting with dichloromethane–ethyl acetate 1:1.

n-Pentyloxazolidine-2,4-dione: MS (EI 70 ev) *m/z*: 171 (M^+) 156, 142, 129, 115, 102, 70,56; ^{1}H NMR ($CDCl_3$, δ): 0.84–0.87 (m,3H), 1.25–1.32 (m,4H), 1.59–1.63 (m,2H), 3.48–3.52 (m,2H), 4.65 (s,2H); ^{13}C NMR ($CDCl_3$, δ): 14.0 (CH_3), 22.3 (CH_2), 27.4 (CH_2), 28.9 (CH_2), 40.4 (CH_2), 68.0 (CH_2), 156.2 (C=O), 170.9 (C=O).

n-Hexyloxazolidine-2,4-dione: MS (EI 70 ev) *m/z*: 185 (M^+), 170, 156, 115, 102, 70, 56; ^{1}H NMR ($CDCl_3$, δ): 0.82–0.85(m,3H), 1.22–1.30 (m,6H); 1.59–1.63(m,2H)); 3.48–3.52 (m,2H); 4.65 (s,2H); ^{13}C NMR($CDCl_3$, δ): 14.0 (CH_3), 22.7 (CH_2), 27.5 (CH_2), 29.1 (CH_2), 32.4 (CH_2),40.4 (CH_2), 68.0 (CH_2), 156.2 (C=O), 170.9 (C=O).

Cyclohexyloxazolidine-2,4-dione: MS (EI 70 ev) *m/z*: 183 (M^+),102; ^{1}H NMR ($CDCl_3$, δ): 1.22–1.39 (m,4H), 1.48–73 (m,6H); 2.02–2.14 (m,1H); 3.82–3.88 (m,2H); 4.65 (s,2H); ^{13}C NMR($CDCl_3$, δ): 24.6 (CH_2), 22.7(CH_2), 27.5(CH_2), 29.1(CH_2), 32.4(CH_2), 40.2 (CH), 68.0 (CH_2), 156.2 (C=O), 170.9 (C=O).

i-Propyloxazolidine-2,4-dione: MS (EI 70 ev) *m/z*: 143 (M^+), 128, 102, 70, 56; ^{1}H NMR ($CDCl_3$, δ): 1.40 (d, $J = 7$ Hz, 6H), 3.42–3.53 (m, 1H); 4.58 (s, 2H); ^{13}C NMR($CDCl_3$, δ: 19.8 (CH_3), 38.2 (CH), 68.0 (CH_2), 156.2 (C=O), 170.9 (C=O).

Acknowledgements

A special thanks to INOXRIVA s.r.l. for providing us with stainless steel components and instrumental assembly for pressure control. We would also like to thank Giovanni Bosetti for technical support, and Daniel Ehman, Emma Page, Moira Pringle and our students Benedetto Putomatti Andrea Agnelli, Giusy Cardinale, for their collaboration.

References and notes

1. Clark-Lewis, J.-W. *Chem. Rev.* **1958**, *58*, 63–99.
2. Biliaz, R. *Fruits* **1965**, *20*, 371–381.
3. Mercier, J.. In *Anticonvulsant Drugs in International of Pharmacology and Therapeutics*; Mercier, J., Ed.; Pergamon Press: Oxford, 1973; Vol. 1, pp 213–215.
4. Casadei, M. A.; Inesi, A.; Rossi, L. *Tetrahedron Lett.* **1977**, *38*, 3565–3568.
5. Buchanan, J. G.; Sable, H. Z.. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, pp 1–95.
6. Lyle, F. R., U.S. Patent 5 973 257, 1985; *Chem. Abstr.* **1985**, *65*, 2870.
7. Pianka, M.; Potton, D. J. *J. Chem. Soc.* **1960**, 983–989.
8. Aresta, M.; Di Benedetto, A. *Dalton Trans.* **2007**, 2975–2992.
9. Munshi, P.; Heldebrant, D. J.; McKoon, E . P.; Kelly, P. A.; Tai, C.-G.; Jessop, P. G. *Tetrahedron Lett.* **2003**, *44*, 2725–2727.
10. Mizuno, T.; Okamoto, N.; Ito, T.; Miyata, T. *Tetrahedron Lett.* **2000**, *41*, 1051–1053.
11. Mizuno, T.; Ishino, Y. *Tetrahedron* **2002**, *58*, 3155–3158.
12. Perez, E. R.; Odnicki, M.; da Silva, V.; Costa, C.; Rodrigues-Filho, U. P.; Franco, D. W. *Tetrahedron Lett.* **2002**, *43*, 4091–4093. and reference cited therein.
13. Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron* **1994**, *50*, 6549–6558.
14. Heldebrant, D. J.; Jessop, P. G.; Thomas, C. A.; Eckert, C. A.; Liotta, C. L. *J. Org. Chem.* **2005**, *70*, 5335–5338.
15. Rossi, L.; Feroci, M.; Verdecchia, M.; Inesi, A. *Lett. Org. Chem.* **2005**, *2*, 731–741.

16. Cesa, S.; Mucciante, V.; Rossi, L. *Tetrahedron* **1999**, *55*, 193–200.
17. Casadei, M. A.; Cesa, S.; Micheletti Moracci, F.; Inesi, A.; Feroci, M. *J. Org. Chem.* **1996**, *61*, 380–383.
18. Casadei, M. A.; Cesa, S.; Inesi, A. *Tetrahedron* **1995**, *51*, 5891–5900.
19. Galliani G, Orlandi M, Rindone B, Terraneo A, Patent WO 2006122782, PCT Int. Appl. 2006.
20. Shapiro, S. L.; Rose, I. M.; Testa, F. C.; Roskin, E.; Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 6498–6504.
21. Davies, J. S. H.; Fitzgerald, M. E. H.; Hook, W. H. *J. Chem. Soc.* **1950**, 34–36.
22. Heuer, L. (Bayer A.-G., Germany). Ger. Offen. 1997, p 9 CODEN: GWXXBX DE 19613333 A1 19971009.
23. Patton, T. L. *J. Org. Chem.* **1967**, *32*, 383–388.
24. Phan, L.; Andreatta, J. R.; Horvey, L. K.; Edie, C. F.; Luco, A.; Mirchandani, A.; Darensbourg, D. J.; Jessop, P. G. *J. Org. Chem.* **2008**, *73*, 127–132.