SHORT PAPER

J. Chem. Research (S), 2000, 440–441

The preparation of 3-substituted 1-chlorocarbonyl-imidazolidin-2-ones using bis(trichloromethyl) carbonate†

Weike Su[a,b] and Yongmin Zhang[b]*

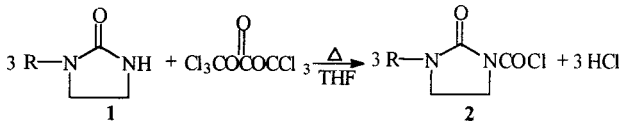
[a]*Department of Pharmaceutical Engineering, Zhejiang University of Technology, Hangzhou 310014, P.R. China*

[b]*Department of Chemistry, Zhejiang University at Xixi Campus, Hangzhou 310028, P.R. China*

A novel synthesis of 3-substituted 1-chlorocarbonyl-imidazolidin-2-ones using bis(trichloromethyl) carbonate is reported. The bis(trichloromethyl)carbonate is used to generate phosgene *in situ* in stoichiometric amounts. The yields and purity of the products obtained are better than those obtained by a conventional way using phosgene.

3-Substituted 1-chlorocarbonyl-imidazolidin-2-ones are very important intermediates for the semi-synthesis of β-lactam antibiotics[1–17]. Since 1964, when Ulrich *et al.* published the preparation of 1-chlorocarbonyl-imidazolidin-2-one and its derivatives[18], many procedures have been reported for the synthesis of these compounds.[1–17, 20] All of those methods employ phosgene in an organic solvent that circumvents the need for an excess of this gas. As we know, phosgene is a toxic gas, so its transport and storage pose considerable dangers. On the other hand, bis(trichloromethyl) carbonate is a stable solid (m.p.: 79–80°C, b.p.: 205–207°C; only slight decomposition to phosgene occurs at its boiling point[19]), so it is convenient to transport and to store.

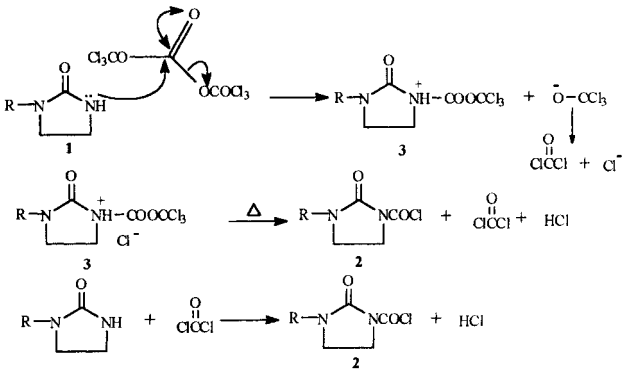
Here we report the preparation of 3-substituted 1-chlorocarbonylimidazolidin-2-ones using bis(trichloromethyl) carbonate as chlorocarbonylating reagent. (Scheme 1). Bis(trichloromethyl) carbonate can be easily prepared by exhaustive chlorination of dimethyl carbonate.[19]



Scheme 1

It was found in our studies that our method is useful and efficient for the synthesis of 3-substituted 1-chlorocarbonyl-imidazolidin-2-ones. During the reaction, one equivalent of bis(trichloromethyl) carbonate can generate three equivalents of phosgene *in situ* without catalyst. Moreover, bis(trichloromethyl) carbonate is easily soluble in the typical recrystallization solvents such as THF, chloroform and ethyl acetate, so the product can be purified by recrystallization during which any residual reagent is removed. Although the exact mechanism of above reaction is not fully clarified, the products **2** formation could be described as shown in Scheme 2.

In Scheme 2 *N*-substituted imidazolidin-2-ones **1** attack the carbonyl carbon of bis(trichloromethyl) carbonate to produce intermediates **3** and the trichloromethoxy anion (Cl_3CO^-) which loses chloride anion and generates phosgene *in situ*. On the other hand, the intermediates **3** can decompose further to yield the product **2**, phosgene and hydrogen chloride as byproduct. The phosgene generated *in situ* reacts immediately with *N*-substituted imidazolidin-2-one **1** to form the products **2**, so there is no excess phosgene remaining in solution.



Scheme 2

The molar ratio of bis(trichloromethyl) carbonate to *N*-substituted imidazolidin-2-one has been examined in our studies. Theoretically, 1/3 mole of bis(trichloromethyl) carbonate should be enough to react with one mole of *N*-substituted imidazolidin-2-one because one mole of bis(trichloromethyl)carbonate yields three moles of phosgene. However, even when a 1% excess of bis(trichloromethyl) carbonate was allowed to react with *N*-substituted imidazolidin-2-one, 5% of *N*-substituted imidazolidin-2-one remained unconverted. The use of a 2-3% excess of bis(trichloromethyl) carbonate resulted in total conversion of *N*-substituted imidazolidin-2-one to the 3-substituted 1-chlorocarbonylimidazolidin-2-ones.

The results are summarized in Table 1. It was found that the chlorocarbonylation reaction using bis(trichloromethyl) carbonate can be accomplished within 2-4 hours and gives the products **2** in high yields. Using phosgene, however, a several-fold excess is required, and even then the yields are usually only moderate (except for 1-chlorocarbonyl-imidazolidin-2-one). Another advantage in using bis(trichloromethyl) carbonate instead of phosgene is that the former, as a solid, can be easily handled. Furthermore, owing to its relatively low volatility, only the usual safety precautions are necessary.

Experimental

Melting points were obtained with a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an IR-408 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC-80 spectrometer using TMS as internal standard. The purity was determined on a Bio-rad HPLC (column: GL Sciences Inc. Inertsil ODS-80-A 4.6 × 250mm).

General procedure for synthesis of 2-substituted 1-chlorocarbonyl-imidazolidin-2-ones: Into a 4-neck 500 ml reaction vessel equipped with a heating mantle, a reflux condenser, a thermometer, a stirrer and a graduated addition funnel was charged 100 ml dry chloroform and 16.5g N-methylsulphonyl-imidazolidin-2-one. The mixture was

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Preparation of 3-substituted 1-chlorocarbonyl-imidazolidin-2-ones using bis(trichloromethyl)carbonate

Product	R	Solvent	T(h)	Yields(%)[b]
2a	$MeSO_2$	$CHCl_3$	3-4(lit.[1] 84)	88.5(lit.[1] 70)
2b	H	THF	2(lit.[20] 3)	95.6(lit.[20] 93)
2c	MeCO	C_6H_6	2-3(lit.[1] 30)	93.8(lit.[1] 81)
2d	$EtSO_2$	$Cl(CH_2)_2Cl$	2.5(lit.[14] 84)	85.0
2e	$PhSO_2$	$CHCl_3$	2-3	83.5(lit.[14] 64)
2f	$NC(CH_2)_2CO$	$CHCl_3$	2-3	65.0(lit.[14] 44)
2g	MeOCO	C_6H_6	2-3(lit.[1] 30)	90.3(lit.[1] 72)
2h	*m*-ClC_6H_4	THF	2.5(lit.[2] 20)	85.5(lit.[2] 65)
2i	*m*-CNC_6H_4	THF	2.5(lit.[2] 20)	82(lit.[2] 59.8)
2j	*p*-$MeOC_6H_4$	THF	3-4(lit.[2] 20)	84.2(lit.[2] 64)
2k	*o*-$MeOC_6H_4$	THF	3-4(lit.[2] 20)	81.0(lit.[2] 60)

[a]The purity of products was determined by HPLC and was no less than 98.5%. [b]Isolated yields based on *N*-substituted imidazolidin-2-ones. [c]All reactions were carried out at the same molar ratio, *i.e.: N*-substituted imidazolidin-2-ones : $Cl_3COCO_2CCl_3$ = 3 : 1.00–1.02.

heated to 55–60°C and a solution of 9.9g bis(trichloromethyl)carbonate in 100 ml dry chloroform was added dropwise within 1 hour to the mixture in such a way that the internal temperature was kept at 55–60°C. The mixture was stirred for 2–3 hours at this temperature. After cooling to 20°C, it was evaporated under reduced pressure to dryness and the product was recrystallized from boiling acetone to give white crystals of 2-substituted 1-chlorocarbonyl-imidazolidin-2-ones (entry 2a, purity: 99.6%).

2a, light yellow crystals, m.p. 179–180°C (acetone, lit.[1] 178°C); ν_{max} (cm^{-1}): 1810, 1718, 1360, 1160; δ_H ($CDCl_3$) 3.41(3H, s, CH_3), 3.81–4.39(4H, m, 2 × CH_2).

2b, light yellow crystals, m.p. 153–154°C (acetone, lit.[20] 153°C); ν_{max} (cm^{-1}): 1795, 1708, 1270, 1150; δ_H ($CDCl_3$) 3.53(2H, t, *J*=6.5 Hz, CH_2), 4.15(2H, t, *J*=6.5 Hz, CH_2), 6.33(1H, br s, NH).

2c, light pale crystals, m.p. 104–104.5°C (acetone/petroleum ether, lit.[1] 104°C); ν_{max}(KBr)/cm^{-1} 1800, 1742, 1692, 1665; δ_H ($CDCl_3$) 2.60(3H, s, CH_3), 3.80–4.40(4H, m, 2 × CH_2).

2d, light pale crystal, m.p. 175–175.5°C (acetone, lit.[1] 174°C); ν_{max}(KBr)/cm^{-1} 1812, 1722, 1350, 1170; δ_H ($CDCl_3$) 1.45(3H, t, J=6.0 Hz, CH_3), 3.60(2H, q, J=6.0 Hz, CH_2), 3.96–4.40(4H, m, 2 × CH_2).

2e, light yellow crystals, m.p. 161–162°C (acetone/petroleum ether, lit.[14] 161°C); ν_{max}(KBr)/cm^{-1} 1800, 1730, 1320, 1200; δ_H ($CDCl_3$) 3.95–4.35(4H, m, 2 × CH_2), 7.61-8.18(5H, m, PhH).

2f, light yellow crystals, m.p. 127–130°C (dec.) (acetone, lit.[14] 127–130°C); ν_{max}(KBr)/cm^{-1} 2250, 1798, 1718, 1690; δ_H ($CDCl_3$) 2.90 (2H, t, *J*=5.0Hz, CH_2), 3.12(2H, t, *J*=5.0Hz, CH_2), 3.83–3.90(4H, m, 2 × CH_2).

2g, light yellow crystals, m.p. 129–130°C (acetone/pentane, lit.[1] 129°C); ν_{max}(KBr)/cm^{-1} 1818, 1740, 1695, 1265; δ_H ($CDCl_3$) 3.94(3H, s, CH_3O), 3.77–4.40(4H, m, 2 × CH_2).

2h, light yellow crystals, m.p. 209–210°C (acetic ether, lit.[2] 208°C); ν_{max}(KBr)/cm^{-1} 1821, 1702; δ_H (DMSO-d_6) 3.80–4.10(4H, m, 2 × CH_2), 6.96–7.86(4H, m, ArH).

2i, light yellow crystals, m.p. 138–138.5°C (ethyl acetate, lit.[2] 136°C); ν_{max}(KBr)/cm^{-1} 2230, 1822, 1722; δ_H (DMSO-d_6) 3.82–4.10(4H, m, 2 × CH_2), 7.06–7.95(4H, m, ArH).

2j, light yellow crystasl, m.p. 183-183.5°C (toluene, lit.[2] 182–183°C); ν_{max}(KBr)/cm^{-1} 2850, 1815, 1707; δ_H (DMSO-d_6) 3.60(3H, s, OCH_3), 3.70–4.10(4H, m, 2 × CH_2), 7.06–7.25(4H, m, ArH).

2k, light yellow crystals, m.p. 90–91°C (toluene, lit.[2] 88–91°C); ν_{max}(KBr)/cm^{-1} 2845, 1799, 1700; δ_H (DMSO-d_6) 3.90(3H, s, OCH_3), 3.60–4.10(4H, m, 2 × CH_2), 6.74–7.35(4H, m, ArH).

Received 22 March 2000; accepted 11 August 2000
Paper 00/237

References

1 Koenig, H.B.; Schroeck, W. and Metzger, K.G., *Ger. Offen. 2,152,968* (*Chem. Abstr.*, 1975, **79**, 18697y).
2 Koenig, H.B.; Metzger, K.G. and Schroeck, W., *Ger. Offen. 2,528,079* (*Chem. Abstr*., 1977, **86**, 189918v).
3 (a) Novak, L., *Czech, CS 218,030* (*Chem. Abstr.*, 1985, **104**, 148624t); (b) Novak, L., *Czech, CS 218,027* (*Chem. Abstr.*, 1985, **104**, 14825u). (c) Novak, L., *Czech, CS 218,031* (*Chem. Abstr.*, 1985, **104**, 148873y).
4 (a) Milner, P.H., *EP 114,752* (1984); (b) Milner, P.H., *EP 71,395* (*Chem. Abstr.*, 1983, **99**, 105050p).
5 Wehrli, H.; Kocsis, K. and Scartazzini, K., *EP 31,794* (*Chem. Abstr.*, 1981, **96**, 68704v).
6 Pfizer Inc., *Israeli 50,205* (*Chem. Abstr.*, 1979, **93**, 8165y).
7 Preiss, M.; Koenig, H.B.; Metzger, K.G. and Schrnit, G., *EP 3,992* (*Chem. Abstr.*, 1979, **92**, 76493h).
8 Ertel, W., *Ep 4,938* (*Chem. Abstr.*, 1979, **92**, 146750r).
9 Pfizer Inc., *Brit. 1,509,695* (*Chem. Abstr.*, 1978, **89**, 197533t).
10 Barth, W.E., *S. African 76 04,716* (*Chem. Abstr.*, 1977, **88**, 170138k).
11 Koenig, H.B.; Metzger, K.G. and Schroeck, W., *Ger. Offen. 2,548,247* (*Chem. Abstr.*, 1977, **87**, 85022c).
12 Koenig, H.B.; Metzger, K.G. and Schroeck, W., *Ger. Offen. 2,548,248* (*Chem. Abstr.*, 1977, **87**, 85023j).
13 Lilly, E., *JP 76,100,090* (*Chem. Abstr.*, 1977, **87**, 184532a).
14 Schroeck, W.; Koenig, H.B.; Preiss, M. and Metzger, K.G., *Ger. Offen. 2,407,715* (*Chem. Abstr.*, 1975, **84**, 4975d).
15 Schroeck, W.; Furtwangler, H.R.; Koenig, H.B. and Metzger, K.G., *Ger. Offen. 2,318,955* (*Chem. Abstr.*, 1974, **82**, 31313b).
16 Fosker, G.R.; Burton, G., *Ger. Offen. 2,428,139* (*Chem. Abstr.*, 1975, **82**, 17099lj);
17 Koenig, H.B.; Schroeck, W. and Metzger, K.G., *Ger. Offen. 2,152,967* (*Chem. Abstr.*, 1971, **76**, 32047t).
18 Ulrich, H.; Tilley, J.N. and Sayigh, A.A.R., *J. Org. Chem.*, 1964, **29**, 2401.
19 Marotta, D., *Gazz. Chim. Ital.*, 1929, **59**, 955.
20 Schroeck, W.; Koenig, H.B. and Metzger, K.G., *Ger. Offen.* 2,104,580 (Chem. Abstr., 1972, **77**, 126629v).