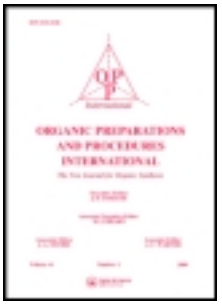

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A NOVEL SYNTHESIS OF 3-SUBSTITUTED MDAZOLIDIN-2-ONE-1-CARBONYL CHLORIDES

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A NOVEL SYNTHESIS OF 3-SUBSTITUTED IMIDAZOLIDIN-2-ONE-1-CARBONYL CHLORIDES

Submitted by
(05/31/00)

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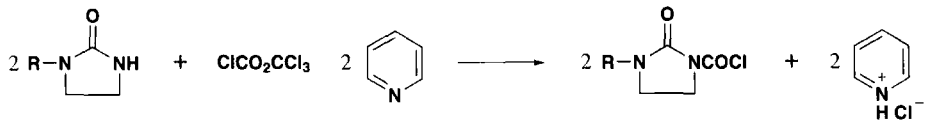
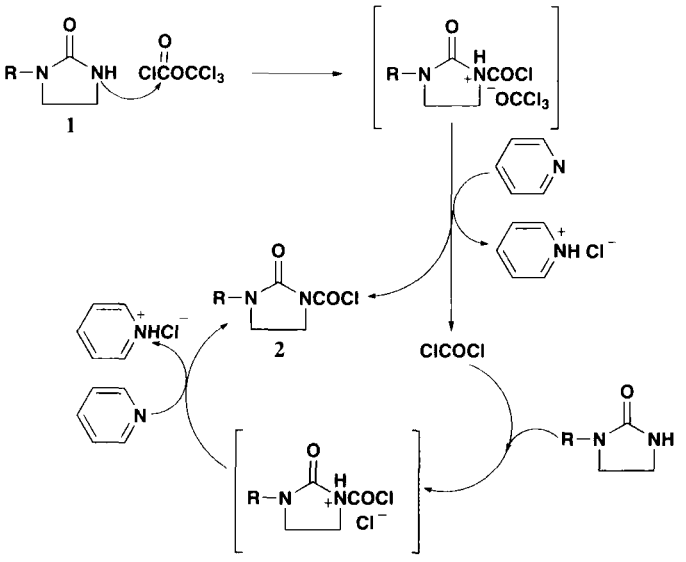
3-Substituted imidazolidin-2-one-1-carbonyl chlorides (SICs) are very important intermediates for the semi-synthesis of β-lactam antibiotics.[1-6] SICs have been conveniently prepared by the reaction of *N*-substituted imidazolidin-2-ones with phosgene.[1-5] However, phosgene has become commerically inaccessible as a common and useful reagent because it is a highly toxic, dangerous gas. Such a situation prompted us to investigate a substitute for phosgene in the synthesis of SICs.

Trichloromethyl chloroformate (TCF) has been known as a phosgene dimer and used as a substitute for phosgene in industry.[7-12] We found that TCF can replace phosgene in the synthesis of SICs and the reaction is shown in *Scheme 1*. The role of pyridine is to promote the decomposition of TCF to phosgene and to intercept the by-product HCl. Our experiment showed that without pyridine, the reaction time would be longer and the yield would be lower.



Scheme 1

A possible mechanism may be proposed as shown in *Scheme 2*. TCF undergoes nucleophilic attack at the carbonyl carbon; the trichloromethoxy (Cl_3CO^-) leaving group decomposes to the chloride anion and a molecule of phosgene, which reacts immediately with another molecule of *N*-substituted imidazolidin-2-one. As the reaction proceeds, the evolved HCl is trapped by pyridine. However, the exact mechanism is not fully clarified and a more detailed study is in progress in our laboratory.



Scheme 2

Table 1 Synthesis of 3-Substituted Imidazolidin-2-one-1-carbonyl Chlorides[a]

Product	R	Solvent	Reaction time (h)	Purity (%)[b]	Yields (%)[c]
2a	$MeSO_2$	$CHCl_3$	2-3 (*lit.*[3] 72)[d]	99.5	85 (*lit.*[3] 70)
2b	$EtSO_2$	$Cl(CH_2)_2Cl$	2-3 (*lit.*[3] 72)[d]	99.4	80
2c	MeCO	C_6H_6	2 (*lit.*[3] 18)[d]	99.6	92 (*lit.*[3] 81)
2d	MeOCO	C_6H_6	2 (*lit.*[3] 18)[d]	99.5	88 (*lit.*[3] 72)
2e	$PhSO_2$	$CHCl_3$	3-4	99.0	80 (*lit.*[2] 64)
2f	$NC(CH_2)_2CO$	$CHCl_3$	2-3	98.8	60 (*lit.*[2] 44)
2g	*m*-CNC_6H_4	THF	2 (*lit.*[6] 20)[d]	98.5	79 (*lit.*[6] 59.8)
2h	*m*-ClC_6H_4	THF	2 (*lit.*[6] 20)[d]	98.7	81 (*lit.*[6] 65.5)
2i	*p*-$MeOC_6H_4$	THF	2 (*lit.*[6] 20)[d]	99.0	78 (*lit.*[6] 64)
2j	*o*-$MeOC_6H_4$	THF	2 (*lit.*[6] 20)[d]	99.1	76 (*lit.*[6] 60)

a) All reactions were carried out at the same molar ratio, *i.e.* *N*-substituted imidazolidin-2-ones : TCF = 1 : 0.55. b) HPLC purity. c) Isolated yields based on *N*-substituted imidazolidin-2-ones. d) Time required in literature cited with phosgene.

The amount of TCF needed for complete reaction with *N*-substituted imidazolidin-2-ones has been examined. Theoretically, a half mole of TCF should be sufficient to react with a mole of the *N*-substituted imidazolidin-2-one, because one mole of TCF yields two moles of phosgene. However, even when a 5 mol% excess of TCF was allowed to react with *N*-substituted imidazolidin-2-ones, 10% of the *N*-substituted imidazolidin-2-one was left still unreacted. The use of 10% excess of TCF led total conversion to SICs and the results are summarized in *Table 1*.

Table 1 shows that the phosgenation reaction is completed within 2-3 hours and gives SICs in high yields. However, the use of phosgene requires a several-fold excess and even then, the yields are often only moderate. Furthermore, owing to the relatively low-volatility of TCF, only the usual safety precautions are necessary.

EXPERIMENTAL SECTION

Melting points were obtained in a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an IR-408 spectrometer as KBr pellet (cm^{-1}). ^1H NMR spectra were determined in a Bruker AC-80 spectrometer using TMS as internal standard. The purity of products was determined on Bio-rad HPLC (Column: GL sciences Inc. Inertsil ODS-80A 4.6 x 250 nm; mobile phase: $CH_3CN : H_2O : KH_2PO_4$ (w/w/w)= 32 : 60 : 0.2; flow rate: 1 mL/min).

General Procedure for the Preparation of SICs Using TCF.- Into a 4-neck 250 mL reaction vessel fitted with a heating mantle, a reflux condenser, a thermometer, a stirrer and a graduated addition funnel was charged 75 mL of dry solvent (*Table 1*), 8.8 mL (0.11 mol) of pyridine and 0.1 mol of *N*-substituted imidazolidin-2-one. The suspension was heated to 50°, and then 6.6 mL (0.55 mol) of TCF was added dropwise over the course of 1 hr. to the suspension at such a rate that the internal temperature was 50-55°. The mixture was then stirred further at 55° (see *Table 1*), then cooled to 20° until crystals precipitated completely. The crude product was recrystallized from 120 mL of the boiling recrystallization solvent.

2a, light yellow crystal, mp 179-180° (acetone, *lit.*[3] 178°). IR (cm^{-1}): 1810, 1718, 1360, 1160. ^1H NMR: d 3.41 (3H, s, CH_3), 3.81-4.39 (4H, m, 2 x CH_2).

2b, light pale crystal, mp 175-175.5° (acetone, *lit.*[3] 174°). IR (cm^{-1}): 1812, 1722, 1350, 1170. ^1H NMR: d 1.45 (3H, t, J=3.8Hz, CH_3), 3.60 (2H, q, J=3.8Hz, CH_2), 3.96-4.40 (4H, m, 2¥ CH_2).

2c, light pale crystal, mp 104-104.5° (acetone/petroleum ether, *lit.*[3] 104°). IR (cm^{-1}): 1800, 1742, 1692, 1665. ^1H NMR: d 2.60 (3H, s, CH_3), 3.80-4.40 (4H, m, 2 x CH_2).

2d, light yellow crystal, mp 129-130° (acetone/ petroleum ether, *lit.*[3] 129°). IR (cm^{-1}): 1818, 1740, 1695, 1265. ^1H NMR: d 3.94 (3H, s, CH_3O), 3.77-4.40 (4H, m, 2 x CH_2).

2e, light yellow crystal, mp 161-162° (acetone/ petroleum ether, *lit.*[2] 161°). IR (cm^{-1}): 1800, 1730, 1320, 1200. ^1H NMR: d 3.95-4.35 (4H, m, 2 x CH_2), 7.61-8.18 (5H, m, PhH).

2f, light yellow crystal, mp 127-130° (dec.) (acetone, *lit.*[2] 127-130°). IR (cm^{-1}): 2250, 1798, 1718, 1690. ^1H NMR: d 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 x CH_2).

2g, light yellow crystal, mp 138-138.5° (ethyl acetate, *lit.*[6] 136°). IR (cm^{-1}): 2230, 1822, 1722. ^1H NMR: d 3.82-4.10 (4H, m, 2 x CH_2), 7.06-7.95 (4H, m, ArH).

2h, light yellow crystal, mp 209-210° (ethyl acetate, *lit.*[6] 208°). IR (cm^{-1}): 1821, 1702. ^1H NMR: d 3.80-4.10 (4H, m, 2 x CH_2), 6.96-7.86 (4H, m, ArH).

2i, light yellow crystal, mp 183-183.5° (toluene, *lit.*[6] 182-183°). IR (cm^{-1}): 2850, 1815, 1707. ^1H NMR: d 3.60 (3H, s, CH_3O), 3.70-4.10 (4H, m, 2 x CH_2), 7.06-7.25 (4H, m, ArH).

2j, light yellow crystal, mp 90-91° (toluene, *lit.*[6] 88-91°). IR (cm^{-1}): 2845, 1799, 1700. ^1H NMR: d 3.90 (3H, s, CH_3O), 3.60-4.10 (4H, m, 2 x CH_2), 6.74-7.35 (4H, m, ArH).

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