Reaction of Imines with Trichloroacetic Esters or Anhydride Promoted by Iron Carbonyl or Microwave Irradiation. Preparation of 3,3-Dichloro-β-Lactams†

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Mohammad S. Khajavi,* Fatemeh Sefidkon and S. S. Sadat Hosseini

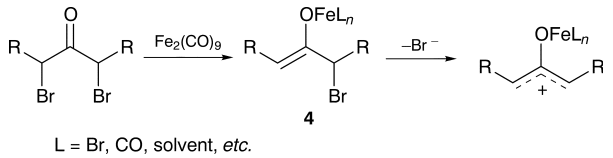
Department of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran, Iran

The synthesis of 3,3-dichloroazetidin-2-ones by the reaction of imines and methyl or trimethylsilyl trichloroacetate promoted by diiron nonacarbonyl or by microwave irradiation of imines and trichloroacetic anhydride is described.

Monocyclic β-lactams are an important class of heterocyclic compounds because of their use in the synthesis of biologically active classical or non-classical β-lactam antibiotics.[1] The cycloaddition of substituted acetic acid derivatives with imines has become one of the major routes for the synthesis of β-lactams.[2] Here we wish to report a novel method for the synthesis of 3,3-dichloro-β-lactams by the condensation of an imine with the methyl or trimethylsilyl ester of trichloroacetic acid (**1a**,**b**) promoted by diiron nonacarbonyl through an enolate intermediate (**2**).

The preparation of 3,3-dihalo-β-lactams by the reaction of a Schiff base with trimethylsilyl trihaloacetate and triphenylphosphine has been described previously.[3]

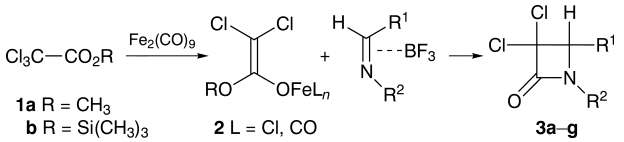
Noyori *et al*. have described the reaction of dibromo ketones with iron carbonyls to produce an oxyallyl-iron(II) complex by the mechanism outlined in Scheme 1.[4]



Scheme 1

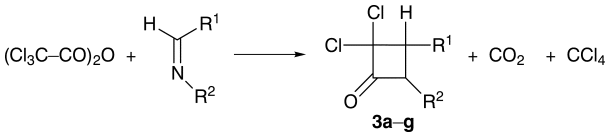
Accordingly, we decided to extend this successful iron carbonyl reduction of α,α′-dihalo ketones to iron(II) dichloro enolate (**2**) formation. Our initial experiments showed that imines reacted with methyl trichloroacetate in the presence of diiron nonacarbonyl to afford poor yields of β-lactams (**3**). Subsequently, it was found that the yields of the desired β-lactams increase when the imines were treated with boron trifluoride etherate. In the presence of BF_3 the imines, to some extent, cannot form a complex with diiron nonacarbonyl.[5] Kamiya has utilized the BF_3 complex of monomeric formaldehyde imines for the preparation of 4-unsubstituted β-lactams.[6] Thus, it was found that when a mixture of methyl or trimethylsilyl trichloroacetate (**1a**,**b**) and diiron nonacarbonyl in dry benzene was treated with an equimolar amount of the *N*-benzylideneaniline–boron trifluoride complex at 50 °C, 3,3-dichloro-1,4-diphenyl azetidin-2-one (**3c**) was isolated in 65% yield. A number of 3,3-dichloro-β-lactams with various substituents were prepared by this procedure (Table 1). To the best of our knowledge, there have been no studies on the synthesis of diahalo-β-lactams using the ester of trichloroacetic acid promoted by iron carbonyl.

Noteworthy is that changing the trichloroacetate from methyl (**1a**) to trimethylsilyl (**1b**) did not greatly improve the yields of the desired β-lactams. A possible mechanism for this dichloro-β-lactam formation is suggested in Scheme 2. The formation of iron(II) dichloro enolate (**2**) from the methyl or trimethylsilyl ester of trichloroacetic acid has an analogy in the mechanism of Noyori[4] for the formation of the iron enolate (**4**) in Scheme 1. The reaction of the *in situ* prepared **2** with imines would be similar to the condensation of lithium ester enolates with imines.[7]



Scheme 2

Furthermore, Sekiya[8] has reported that the reaction of trichloroacetic anhydride with imines in refluxing xylene over a period of 1–8 h, led to 3,3-dichloro-β-lactams. As part of our programme to study the highly accelerated synthesis of heterocyclic compounds under microwave irradiation,[9] we examined this reaction under such irradiation and it was found that the reaction of trichloroacetic anhydride with the imines results in the rapid formation of β-lactams (**3a**–**g**) in high yield when the reactions were conducted in a tall beaker covered with a stemless funnel in a microwave oven. The results are summarized in Table 1.



In conclusion, we have developed a new procedure for the synthesis of 3,3-dichloro-β-lactams by the condensation of iron(II) dichloro-enolate and imines; this is a rapid method under microwave irradiation. Work is continuing in this area to extend these reactions to other tri- and di-haloacetic esters.

Experimental

IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC 80 or JEOL-EX-90 instrument. Microwave irradiations were carried out in a National oven, Model 5250, at 2450 MHz. Melting points are uncorrected and were determined in open capillary tubes using Mel-Temp apparatus. Benzene and *m*-xylene were dried over sodium and freshly distilled before use. Diiron nonacarbonyl (Aldrich), trichloroacetic anhydride (Fluka) and methyl trichloroacetate (Aldrich) were used as received. Trimethylsilyl trichloroacetate was readily prepared by the reaction of hexamethyldisilazane and trichloroacetic acid.[11]

For safety reasons all experiments with microwave ovens should be performed in an efficient hood to avoid contact with vapours. If

*To receive any correspondence. *Present address*: Organization for the Prohibition of Chemical Weapons, Johan de Wittlaan 32, 2517 JR, The Hague, The Netherlands.

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Table 1 β-Lactams from trichloroacetic esters or anhydride and imines

Entry	Product	R^1	R^2	Method A	Method B, irradiation conditions[b]					Mp	Lit. mp
				Yield (%)[a]	(1)*P*/W	*t*/min	(2)*P*/W	*t*/min	Yield (%)[a]	(*T*/°C)	(*T*/°C)
1	**3a**	$MeOC_6H_4$	$PhCH_2$	60	70	1	210	1.5	72	104–106	–
2	**3b**	Ph	$PhCH_2$	64	70	1	210	1.5	68	46–48	45–46[8]
3	**3c**	Ph	Ph	65	70	2	210	1.5	80	162–164	164[10]
4	**3d**	Ph	$MeOC_6H_4$	75	70	1.5	210	1.5	84	110–111	110.5–112[8]
5	**3e**	Ph	ClC_6H_4	68	70	2	210	2	74	129–131	131–132[8]
6	**3f**	$MeOC_6H_4$	Ph	72	70	1.5	210	2	79	155–156	154–155[8]
7	**3g**	ClC_6H_4	Ph	78	70	2	210	2	77	130–132	130–131[8]

[a]Yield of pure, isolated product based on imines. [b] To control the reaction the irradiation was carried out in two stages, with a cooling period between each irradiation.

a tall beaker covered with a watch glass or a small stemless funnel is used and the microwave irradiation period is interrupted with a 5 min cooling period there is little vaporization and very high conversions can be observed.

Preparation of 3,3-*Dichloro-β-lactams* (*Method A*).—The general procedure is illustrated with 1-benzyl-3,3-dichloro-4-*p*-anisylazetidin-2-one (**3a**). In a flame-dried three-necked flask, equipped with a dropping funnel, a condenser and a three-way stopcock attached to a dry nitrogen inlet tube, was placed 3.64 g, 10 mmol of diiron nonacarbonyl and the system was evacuated then flushed with nitrogen. To this were added 20 ml of dry benzene and then 1.8 g, 10 mmol of methyl trichloroacetate or 2.36 g, 10 mmol of trimethylsilyl trichloroacetate and the resultant mixture stirred at room temperature while a benzene 30 ml solution of 2.25 g, 10 mmol of *N*-*p*-methoxybenzylidenebenzylamine and an equimolar amount of boron trifluoride etherate was added dropwise over a 10 min period. The resulting reaction mixture was stirred at 50 °C for 48 h. The precipitates that formed were removed by filtration through a pad of Celite. Evaporation of benzene gave the crude product which was chromatographed on silica gel (100–200 mesh), using dichloromethane–hexane (50:50) as eluent gave the title compound in 60% yield, mp 104–106 °C (from hexane and diethyl ether) (Found: C, 61.13; H, 4.53; N, 4.13. $C_{17}H_{15}Cl_2NO_2$ requires C, 60.73; H, 4.49; N, 4.16%); ν_{max}/cm^{-1} (KBr) 1786; δ_H ($CDCl_3$) 3.75 (s, 3 H, OCH_3), 3.87 (d, 1 H, *J* 13.7 Hz), 4.82 (s, 1 H, C_4-H), 4.91 (d, 1 H, *J* 13.7 Hz), 6.87–7.46 (m, 9 H, Ar-H).

Preparation of 3,3-*Dichloro-β-lactams* (*Method B*).—The general procedure is illustrated with 3,3-dichloro-1,4-diphenylazetidin-2-one (**3c**). A mixture of *N*-benzylideneaniline (1.81 g, 10 mmol) and trichloroacetic anhydride (3.4 g, 11 mmol) in 8 ml of *m*-xylene contained in a tall beaker was placed in the microwave oven and the beaker was covered with a stemless funnel and irradiated for 2 min at 70 W, and after 10 min (during this time the mixture cools slowly to room temperature) it was irradiated again at 210 W for 1.5 min. The solvent was evaporated under reduced pressure. Trituration of the crude residue with diethyl ether led to the title compound which was recrystallized from ethanol and hexane to give an 80% yield of **3c**, mp 162–164 °C (lit.,[10] 164 °C); ν_{max}/cm^{-1} (KBr) 1767; δ_H ($CDCl_3$) 5.59 (s, 1 H, C_4-H), 7.11–7.48 (m, 10 H, Ar-H).

3b: ν_{max}/cm^{-1} (KBr) 1782; δ_H ($CDCl_3$) 3.82 (d, 1 H, *J* 13.6 Hz), 4.71 (s, 1 H, C_4-H), 4.86 (d, 1 H, *J* 13.6 Hz), 6.85–7.61 (m, 10 H, Ar-H).

3d: ν_{max}/cm^{-1} (KBr) 1776; δ_H ($CDCl_3$) 3.73 (s, 3 H, OCH_3), 5.45 (s, 1 H, C_4-H), 6.82–7.93 (m, 9 H, Ar-H).

3e: ν_{max}/cm^{-1} (KBr) 1785; δ_H ($CDCl_3$) 5.48 (s, 1 H, C_4-H), 7.21–7.67 (m, 9 H, Ar-H).

3f: ν_{max}/cm^{-1} (KBr) 1770; δ_H ($CDCl_3$) 3.78 (s, 3 H, OCH_3), 5.41 (s, 1 H, C_4-H), 6.63–7.45 (m, 9 H, Ar-H).

3g: ν_{max}/cm^{-1} (KBr) 1774; δ_H ($CDCl_3$) 5.48 (s, 1 H, C_4-H), 7.05–7.63 (m, 9 H, Ar-H).

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