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A Novel Synthesis of 1-Nosyl 3,3-Dichloro-β-Lactams and Derivatives

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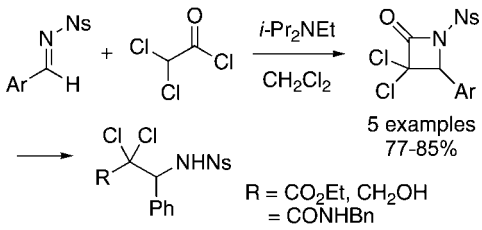
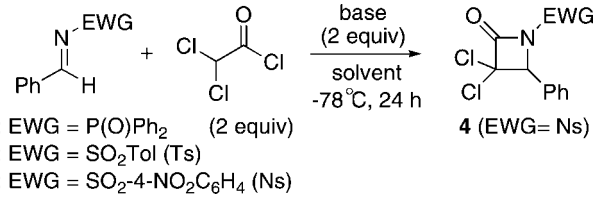


We report herein an efficient and simple route to synthesize 1-nosyl 3,3-dichloro-β-lactams using a Staudinger reaction between *N*-nosyl imines and dichloroketene. The resulting dichloroazetidines were opened to afford highly functionalized building blocks.

The reaction between imines and ketenes to form the corresponding β-lactams[1] through a formal [2 + 2]-cycloaddition was discovered by Staudinger[2] over a century ago. This method represents one of the most effective routes for preparing these compounds,[3] and recently, catalytic asymmetric versions have been developed.[4] In addition, the chemistry of β-lactams has received significant attention due to their selective functionalization[5] and their biological activities, especially as antibacterial agents.[6]

SCHEME 1. Synthesis of Lactams 4



1: EWG = $P(O)Ph_2$ (2 equiv)
2: EWG = SO_2Tol (Ts)
3: EWG = SO_2-4-$NO_2C_6H_4$ (Ns)

4 (EWG= Ns)

Generally, the Staudinger reaction uses ketenes bearing alkyl or aryl groups. Surprisingly, the use of dichloroketene[7] as the starting material has received much less attention, and its reactivity has been studied only for *N*-alkyl[8] or *N*-aryl imines.[9] The latter method provided 3,3-dichloroazetidin-2-one, which creates room for additional functionalization at the site bearing the halogen substituents.[10] Harmoniously with our continuing interest in the reactivity of dichloroketene,[11] this finding has led us to examine the Staudinger reaction with imines possessing an electron-withdrawing group, which thereafter could be easily removed.

The preparation of dichloroketene, which is unstable and polymerizes readily,[12] has been performed by a dehydrohalogenation reaction of dichloroacetyl chloride (2 equiv) in the presence of a Lewis base (2 equiv). Initially, various benzylidenimines with different electron-withdrawing groups attached to the nitrogen atom were investigated (Scheme 1 and Table 1).

Although phosphinoylimines **1** and tosylimines **2** did not react as expected (Table 1, entries 1 and 2),[13] we found that the use

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(5) For leading references on the chemistry of β-lactams, see: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (b) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889. (c) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921. (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, 4437.

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(13) The dehalogenation reaction of trichloroacetyl chloride in the presence of the Zn−Cu amalgam did not afford satisfactory results due to the decomposition of starting imines **1**−**3**.

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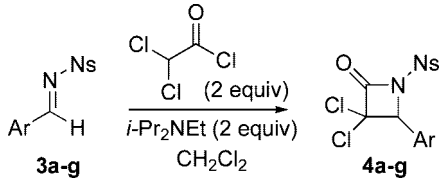
TABLE 1. Reaction Conditions for the Synthesis of Lactams 4

entry	imine	base	solvent	% conv.[a]
1	**1**	*i*-Pr_2NEt	CH_2Cl_2	0
2	**2**	*i*-Pr_2NEt or Et_3N	CH_2Cl_2	0
3	**3**	*i*-Pr_2NEt	CH_2Cl_2	96
4	**3**	*i*-Pr_2NEt	toluene	60
5	**3**	*i*-Pr_2NEt	THF	62
6	**3**	Et_3N	CH_2Cl_2	95
7	**3**	Me_2NEt	CH_2Cl_2	97
8	**3**	Cy_2NMe	CH_2Cl_2	93
9	**3**	pempidine[b]	CH_2Cl_2	47
10	**3**	BEMP[c]	CH_2Cl_2	89

[a] Estimated by ^1H NMR. [b] 1,2,2,6,6-Pentamethylpiperidine. [c] 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine.

SCHEME 2. Synthesis of β-Lactams 4a−g



of a nosyl group[14] (**3**) substituted on the nitrogen atom afforded the corresponding β-lactams in very high conversion degrees (entry 3) when the reaction was performed in CH_2Cl_2.[15]

The use of both more polar solvent and less polar solvents gave a significant decrease in conversion (entries 4 and 5). We studied the effect of several amine bases, modulating both the steric bulk and basicity of each. It was found that the bases Et_3N, Me_2NEt, and Cy_2NMe led to the formation of β-lactam **4** in similarly high conversion (entries 6−8). However, a decrease in the reaction conversion was observed for the pempidine base (entry 9), probably due to a lower efficiency in the ketene formation. Moreover, the bulkiest amine BEMP (entry 10) unexpectedly gave the β-lactam **4** also in high conversion.

The scope of the reaction was then explored with several substituted aromatic *N*-nosyl imines (Scheme 2 and Table 2),[16] using the previously optimized conditions: Hünig's base (2 equiv) and dichloroacetyl chloride (2 equiv) in CH_2Cl_2 at different temperatures.

The conversion was very high for the β-lactam **4a** at −78 °C (Table 2, entry 1). Other imines provided the corresponding β-lactams in only moderate conversion.[17] Nevertheless, this could be improved by performing the reaction at 0 °C or room temperature, leading to very high conversion in both cases, and the reaction times of 3 and 1 h, respectively (Table 2, entries 2 and 3). For the imine **3b**, the conversion was higher at lower temperature (−78 °C) than at 0 °C or room temperature (Table 2, entries 4−6), probably due to the decomposition of the ketene. Decomposition can be partially avoided by a slow addition of dichloroacetyl chloride over 3 h (Table 2, entry 7). The best results were obtained when the reaction was carried out at −40 °C using 3 equiv of base and dichloroacetyl chloride (Table 2, entry 8). A similar result was obtained with imine **3c** (Table 2, entry 11). However, all the attempts to synthesize β-lactam **4d** or **4e** were unsuccessful due to the insolubility of the imines **3d** and **3e**, which were recovered. On the other hand, the presence of an electron-withdrawing group (3-CN and 2-F) enhanced the reactivity. Thus, the imines **3f** and **3g** gave the corresponding β-lactams **4f** and **4g** with complete conversion (Table 2, entries 14−17).

TABLE 2. Synthesis of 3,3-Dichloro-β-Lactams

entry	Ar (imine)	compound	time (h)	temp (°C)	conv.[a] (yield)[b]
1	Ph (**3a**)	**4a**	24	−78	96
2	Ph (**3a**)	**4a**	3	0	100 (80)
3	Ph (**3a**)	**4a**	1	rt	100
4	2-naphthyl (**3b**)	**4b**	24	−78	84
5[c]	2-naphthyl (**3b**)	**4b**	10	0	44
6[c]	2-naphthyl (**3b**)	**4b**	4	rt	39
7[d]	2-naphthyl (**3b**)	**4b**	10	0	67
8[d,e]	2-naphthyl (**3b**)	**4b**	15	−40	100 (82)
9[d]	4-*i*-Pr-C_6H_4 (**3c**)	**4c**	24	−78	86
10[c]	4-*i*-Pr-C_6H_4 (**3c**)	**4c**	4	rt	28
11[d,e]	4-*i*-Pr-C_6H_4 (**3c**)	**4c**	15	−40	100 (77)
12	4-Me_2N-C_6H_4 (**3d**)	**4d**	15	−40	0
13	2-MeO-C_6H_4 (**3e**)	**4e**	15	−40	0
14	3-CN-C_6H_4 (**3f**)	**4f**	16	−78	99
15	3-CN-C_6H_4 (**3f**)	**4f**	2	0	100 (85)
16	3-CN-C_6H_4 (**3f**)	**4f**	0.3	rt	100
17	2-F-C_6H_4 (**3g**)	**4g**	2	0	100 (79)

[a] Estimated by ^1H NMR. [b] Isolated yield (%) after crystallization. [c] No further conversion was observed at longer reaction times. [d] Slow addition of dichloroacetyl chloride for 3 h. [e] Three equivalents of base and dichloroacetyl chloride were used.

SCHEME 3. Asymmetric Synthesis of β-Lactam 4a

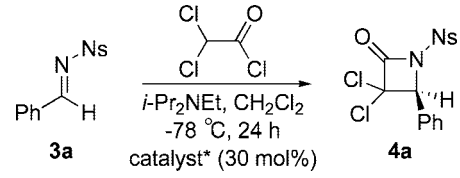


TABLE 3. Reaction in the Presence of Chiral Lewis Bases

entry	catalyst	conv. (%)[a]	ee (%)[b]
1	sparteine	79	0
2	benzoylquinidine	75	0
3	quinidine	80	8
4	TMS-quinidine	77	20

[a] Estimated by ^1H NMR. [b] Enantiomeric excess was determined by HPLC analysis (Daicel IC).

The asymmetric version of the Staudinger reaction is described in the literature for alkyl and arylketenes, usually employing catalytic amounts of a chiral Lewis base.[4] With this idea in mind, we have attempted the preparation of 3,3-dichloro-β-lactam **4a** in the presence of enantiopure tertiary amines such as sparteine or quinidine derivatives in the presence of Hünig's base (Scheme 3 and Table 3).[18]

The use of sparteine or benzoylquinidine did not provide any enantiomeric excess (Table 3, entries 1 and 2). However, in

(14) *N*-Nosyl imines were also used in the Staudinger reaction with arylalkylketenes: Sereda, O.; Wilhelm, R. *Synlett* **2007**, *19*, 3032.

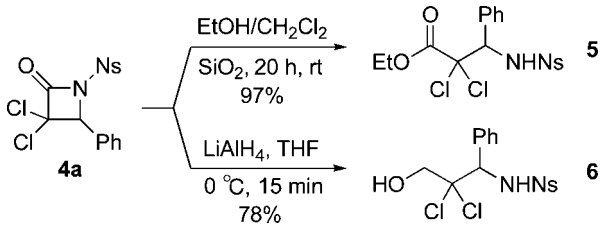
(15) The best conditions were obtained using 2 equiv of base and slowly adding acetyl chloride (2 equiv) for 2 h, in order to avoid the decomposition and polymerization of dichloroketene.

(16) Aromatic *N*-nosyl imines were prepared by reaction between 4-nitrobenzenesulfonamide and aldehydes (see Supporting Information), catalyzed by $(EtO)_4Si$ at high temperature (73−89% yield): (a) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Love, B. E.; Raje, P. S.; Williams, T. C., II. *Synlett* **1994**, 493.

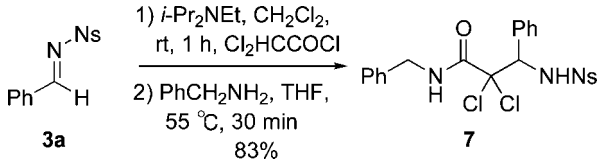
(17) The purification on both silica gel and aluminum oxide was not effective due to the decomposition of most products. Simple crystallization was more efficient.

(18) This base should not attack the ketene because of its steric hindrance: Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248.

SCHEME 4. Derivatization of β-Lactam 4a



SCHEME 5. Synthesis of β-Aminoamide 7



the presence of quinidine, some stereoselectivity was observed, affording the product in 8% ee (Table 3, entry 3). An improvement in stereoselectivity to 20% ee was accomplished with the use of TMS-quinidine (Table 3, entry 4).[19]

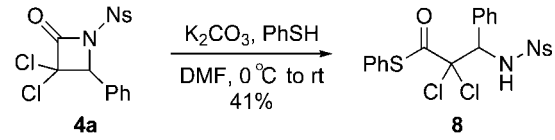
Next, we studied the possibility of derivatizing these compounds through simple reactions, such as opening the β-lactam ring by esterification to obtain β-aminoester **5** and reduction to prepare the 1,3-aminoalcohol **6** (Scheme 4).

We previously observed the unstability of the β-lactams during purification on silica gel. Therefore, we used this solid support as an acid catalyst to perform the esterification. Thus, when silica gel was added to a solution of compound **4a** in EtOH, β-aminoester **5** was obtained in 97% yield. Treatment of β-lactam **4a** with $LiAlH_4$ provided its complete reduction to afford the corresponding 1,3-aminoalcohol **6** in 78% yield. Finally, the preparation of the β-aminoamide **7** was also accomplished in the presence of benzylamine in 83% yield without any purification of the intermediate (Scheme 5).

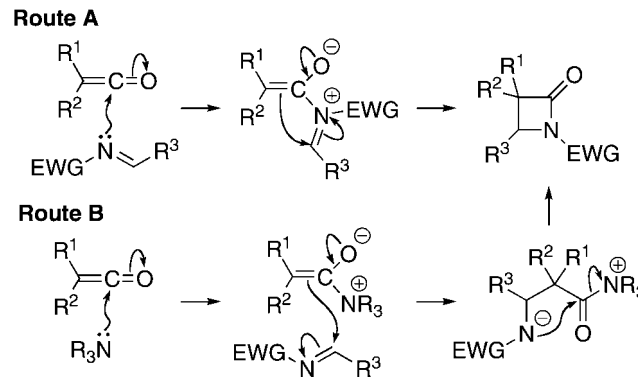
Other transformations such as the reduction of the 2-azetidinone ring to the azetidine were attempted. Several reducing agents such as AlH_2Cl,[20] $BH_3 \cdot SMe_2$,[21] $NaBH_4/I_2$,[22] or $LiEt_3BH/Et_3SiH$-$Et_2O \cdot BF_3$[23] were assayed, but all the attempts were unsuccessful, affording only the corresponding 1,3-aminoalcohol **6** in moderate yield.

Removal of the nosyl group was also examined with thiolate anion, as reported in the literature.[24] However, as could be expect, the thiolate anion reacted with the amide group of the β-lactam without deprotection of the sulfonyl group, giving the corresponding thioester **8** (Scheme 6).[25]

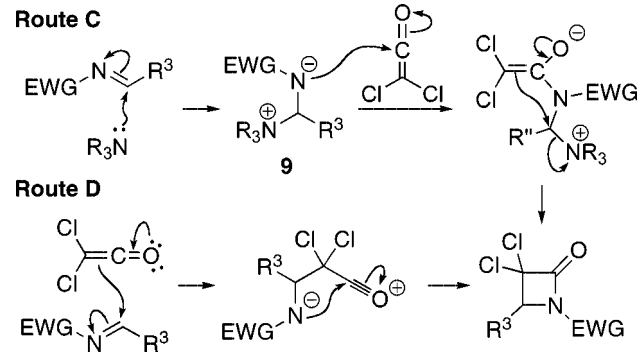
SCHEME 6. Synthesis of Thioester 8



SCHEME 7. Different Mechanistic Routes for the Staudinger Reaction



SCHEME 8. Mechanistic Routes Using Dichloroketene



We have made a step toward the understanding of the mechanism of this reaction as well as the high levels of conversion even with the bulkiest amines. Traditionally, the Staudinger reaction consists in the attack of the imine nitrogen lone electron pair to the central atom of the ketene (Scheme 7, route A). However, this only occurs with *N*-alkyl or *N*-aryl imines and stable ketenes such as diphenylketene. For the imines with electron-withdrawing groups attached at the nitrogen atom, this route is not favored due to the poor nucleophilic character of the nitrogen atom. Another possibility is that the reaction could also be promoted by the tertiary amine (used to prepare the ketene in situ), to form a zwitterionic enolate, which reacts with the electrophilic imine carbon, affording the corresponding β-lactam (Scheme 7, route B). However, route B could not explain the results obtained in this communication, as bulky amines such as *i*-Pr_2NEt should not be able to attack the ketene due to steric hindrance.[18]

Alternatively, we could consider the reaction between the imine and the tertiary amine as described by Fu with *N*-triflyl imine (Scheme 8, route C).[4h]

However, no evidence for the adduct **9** was found by ^1H NMR[26] at low temperature or by in situ IR.[27] Therefore, we propose another route wherein dichloroketene behaves as a nucleophilic species (Scheme 8, route D), able to attack the imine (through a resonance hybrid more important in dichlo-

(19) Different experimental conditions such as solvents (THF, toluene, Et_2O), bases (K_2CO_3, NaH, Bu_3N, Cy_2MeN, pempidine, BEMP, phosphazene-P_2-*t*-Bu), and catalysts (from 0.1 to 0.3 equiv) and addition modes of acyl chloride were tested. Nevertheless, no improvement in the enantiomeric excess was observed, leading to poorer results than the 20% ee achieved with TMS-quinidine. It is important to note that, in all assays, the reaction provided the β-lactam **4a** in high conversion (>85%).

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(22) Haldar, P.; Ray, J. K. *Tetrahedron Lett.* **2003**, *44*, 8229.

(23) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; Ruano, L. C. *Tetrahedron Lett.* **1994**, *35*, 2053.

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(25) The deprotection of the *N*-nosyl group of **8** was never observed even when an excess of thiolate was used.

roketene than in the case of alkylketenes), as reported with electron-poor aldehydes.[28] This route could also account for our poor results on the asymmetric induction of this reaction.

In conclusion, a straightforward methodology preparing 3,3-dichloro-β-lactams in high yields was developed following the Staudinger reaction between dichloroketene and *N*-nosyl imines. Additionally, the preparation of corresponding derivatives such as β-aminoesters, 1,3-aminoalcohols, and β-aminoamides was also performed in high yields by simple transformations.

Experimental Section

Typical Procedure for the Preparation of 3,3-Dichloro-β-lactams 4a, 4f, and 4g (Table 2, entry 2, β-lactam 4a as an example): Diisopropylethylamine (0.4 mmol) was added to a solution of imine **3a** (0.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C and under N_2 atmosphere. Dichloroacetyl chloride (0.4 mmol) was then added, and the reaction was stirred for 3 h. The reaction mixture was hydrolyzed with a solution of 10% HCl (2 mL), and the organic layer was washed with brine (2 mL), dried over $MgSO_4$, and evaporated under vacuum. The residue was purified by chromatography on silica gel column (acetone/pentane 1:8) to provide the desired β-lactam **4a** as a white solid in 80% yield: mp 134.1−135.5 °C (EtOAc/heptane); IR ν 3106, 1820, 1528, 1385, 1352, 1180, 1122, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 and 8.10 (AA′BB′ system, 4H), 7.50−7.35 (m, 3H), 7.22−7.15 (m, 2H), 5.49 (s, 1H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.6, 151.4, 142.5, 130.6, 130.4, 129.3, 128.8, 127.9, 124.8, 83.7, 76.3 ppm; MS (EI+) *m*/*z* 404 (0.3), 402 (2), and 400 (3) [M^+], 365 (4) and 367 (1.6) [M^+ − Cl], 301 (6) and 303 (5.5), 186 (5.4) and 188 (2.5), 172 (100) and 174 (64); HRMS calcd for $C_{15}H_{10}Cl_2N_2O_5S$ [M^+] 399.9687; found 399.9692. Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_5S$: C, 44.90; H, 2.51; N, 6.98. Found: C, 44.97; H, 2.82; N, 6,74. HPLC (Diacel IC column; CH_2Cl_2/heptane 1:1; flow: 1 mL/min): T = 9.96 and 11.04.

Typical Procedure for the Preparation of 3,3-Dichloro-β-lactams 4b and 4c (Table 2, entry 8, β-lactam 4b as an example): Diisopropylethylamine (0.6 mmol) was added to a solution of imine **3b** (0.2 mmol) in CH_2Cl_2 (2 mL) at −40 °C and under N_2 atmosphere. Dichloroacetyl chloride (0.6 mmol) in CH_2Cl_2 (1 mL) was slowly added by syringe pump for 3 h. The reaction was stirred at −40 °C for 15 h and hydrolyzed as previously indicated. After crystallization from EtOAc/heptane, β-lactam **4b** was obtained as a white solid in 82% yield: mp 167.7−169.3 °C; IR ν 3106, 1817, 1532, 1385, 1347, 1180, 1137, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 and 8.07 (AA′BB′ system, 4H), 7.91−7.64 (m, 4H), 7.52−7.52 (m, 2H), 7.18 (dd, J = 8.5 and 1.4 Hz, 1H), 5.67 (s, 1H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.7, 151.4, 142.7, 134.1, 132.7, 129.5, 128.9, 128.7, 128.2, 128.0, 127.8, 127.7, 127.3, 124.8, 124.2, 83.9, 77.3 ppm; MS (EI+) *m*/*z* 454 (6), 452 (26), and 450 (36) [M^+], 415 (30) and 417 (12) [M^+ − Cl], 340 (51), 222 (100) and 224 (65), 129 (43), 114 (99); HRMS calcd for $C_{19}H_{12}Cl_2N_2O_5S$ [M^+] 449.9844; found 449.9856.

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Supporting Information Available: Spectroscopic data (^1H and ^{13}C NMR) of the imines **3a**−**g**, β-lactams **4a**−**c**, **4f**−**g**, and the derivatization products **5**−**8**; HPLC for the β-lactam **4a** and in situ IR for β-lactam **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) ^1H NMR experiments were carried out in CD_2Cl_2 of an equimolecular mixture of imine **3a** and various bases such as Et_3N, Me_2NEt, and i-Pr_2NEt, but no variation was observed after the addition of the bases in comparison with the starting imine.

(27) We were not able to detect any intermediate by in situ IR (see Supporting Information). On the other hand, a direct and fast transformation to β-lactam **4g** was observed.

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