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# Facile stereoselective synthesis of 1,3-disubstituted-4-trichloromethyl azetidin-2-ones

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**Abstract**—The highly stereoselective synthesis of 1,3-disubstituted-4-trichloromethyl azetidin-2-ones by the [2+2] cycloaddition of ketenes with imines derived from chloral is described.


Apart from the substructure of widely used antibiotics[1–3] such as penicillin, cephalosporins, monobactams, etc., azetidin-2-ones (β-lactams) are important building blocks in stereoselective syntheses of biologically important compounds.[4] Some of the synthetic β-lactams display interesting biological activities such as inhibition of prostate specific antigens,[5] thrombin,[6] human cytomegalovirus protein,[7] cholesterol absorption,[8] human leukocyte elastase[9] and cysteine protease.[10] As a consequence, the interest of organic chemists in the synthesis of new β-lactam derivatives remains high. There are numerous methods available for the construction of the β-lactam ring. However, a widely used method is via the [2+2] cyclocondensation of ketenes to imines, a process known as the Staudinger reaction.[11,12] In particular, this method has provided useful and economic entries to β-lactams, mainly due to the availability of both Schiff's bases and ketenes.

In continuation of our efforts towards the synthesis of substituted β-lactams via the Staudinger reaction[13] and their utility as synthons[14] for the synthesis of various biologically important compounds, we were interested in the preparation of β-lactams with a 4-trichloromethyl substituent as it can serve as a masked carboxylic acid equivalent,[15] it can be replaced by other groups[16] and can also be transformed into a chlorovinyl group.[17] Also, a trihalomethyl group at the C-4 position of the β-lactam ring will increase the susceptibility of the lactam ring towards nucleophilic attack, which may improve the antibacterial activity of these compounds.[18] To our surprise there was no general method available for the synthesis of such β-lactams bearing a trichloromethyl group at the C-4 position, except for a single report[19] on the cycloaddition of stabilized *N*-(propanesulfonyl)chloral imine and reactive trimethylsilylketene. This may be due to the fact that chloral forms stable aminols[20] when reacted with amines and in some cases oligomerizes[21] in the presence of amines. We herein report a simple and efficient preparation of various chloral imines and their application in the synthesis of 4-trichloromethyl β-lactams.

Initially, a solution of anhydrous chloral in dichloromethane was treated with aniline at 0–5 °C in the presence of a dehydrating agent such as anhydrous $MgSO_4$ or 4 Å molecular sieves and then stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was subjected to standard Staudinger reaction conditions for β-lactam formation by reaction with the ketene generated from phenoxyacetyl chloride in the presence of triethylamine. However, we did not obtain the desired β-lactam and the product was found to be *N*-phenyl phenoxyacetamide **4** (R = Ph). This probably arises via *N*-acylation of the aminol **2** followed by rearrangement as shown in Scheme 1. However, we were able to prepare the required chloral imines **3** by refluxing the aminol in toluene or dichloroethane with removal of the water formed in the reaction. Moreover, the chloral imine was also prepared directly by refluxing a mixture of anhydrous chloral and amine in toluene or dichloroethane with the removal of water. Chloral imines **3a–d** were prepared by this method (Table 1) in very good

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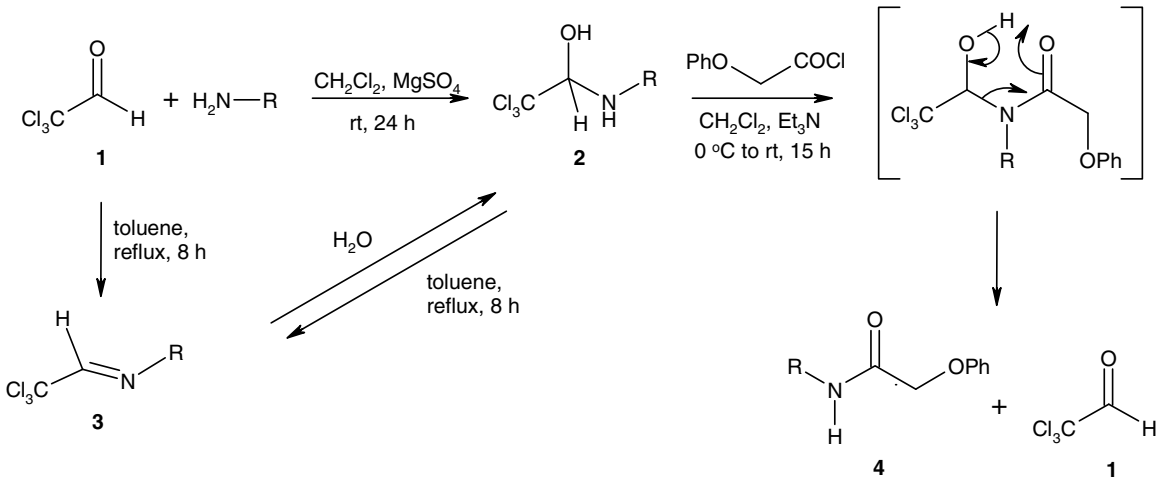



**Scheme 1.**

**Table 1.** Synthesis of imines **3a**–**d** from chloral and various amines

| Entry | Imine | R | Yield (%)[b] | Mp (°C) |
|---|---|---|---|---|
| 1 | **3a** | –$CH_2Ph$ | 82 | Oil |
| 2 | **3b** | –Ph | 78 | Oil |
| 3 | **3c** | –PMP[a] | 82 | 57 |
| 4 | **3d** | –Cyclohexyl | 80 | Oil |

[a] PMP = *p*-methoxyphenyl.
[b] Isolated yield.

yields. Most of these imines were highly moisture sensitive and reverted to the aminols. Imines **3a**–**d** were further used in the synthesis of β-lactams via the Staudinger reaction.[22]

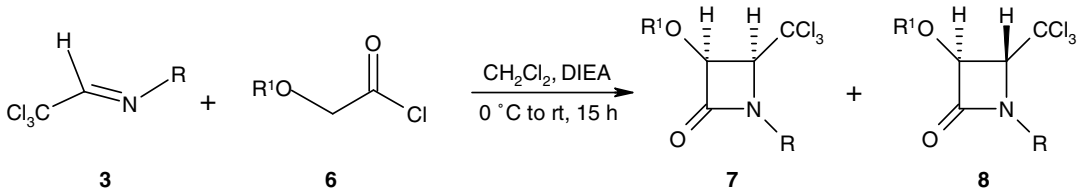
The cycloaddition reaction of the imines **3a**–**d** with acid chlorides (phenoxyacetyl chloride, acetoxyacetyl chloride, benzyloxyacetyl chloride, methoxyacetyl chloride and phthalimidoacetyl chloride) in the presence of excess *N*-ethyldiisopropylamine (0 °C to rt, 15 h) provided a mixture of *cis*- and *trans*-4-trichloromethyl-β-lactams (**7a**–**k** and **8a**–**k**) in moderate to good yields (Table 2, Scheme 2). $^1$H NMR spectral analysis of the crude reaction mixtures revealed that in all cases, the *cis*-isomer was obtained as the major product ($J$ = 4–5 Hz for the C3–C4 protons of the *cis*-isomer and $J$ = 1–2 Hz for the *trans*-isomer). In the case of imines derived from aliphatic amines and chloral, exclusive *cis*-β-lactam formation was observed in the ketene–imine cycloaddition reaction (Table 2, **7a**–**c**, **7e**–**h** and **7k**). However, imines derived from aromatic amines and chloral gave mixtures of *cis*- and *trans*-β-lactams in the cycloaddition reaction with ketenes (Table 2, **7d**, **7i**–**j** and **8d**, **8i**–**j**). Further transformation of the 4-trichloromethyl group into synthetically useful targets is in progress.

In conclusion, we have demonstrated a simple and efficient method for the preparation of chloral imines. Cycloaddition of these imines with ketenes derived from

**Table 2.** Synthesis of 4-trichloromethyl β-lactams **7** and **8** from chloral imines (**3a**–**d**)

| β-Lactams | | R | $R^1$ | Ratio **7**:**8** | Yield (%)[b] | Mp (°C) |
|---|---|---|---|---|---|---|
| **7** and **8** | | | | | | |
| **7a** | **8a** | –$CH_2Ph$ | Ph | 100:00 | 68 | 127 |
| **7b** | **8b** | –Cyclohexyl | Ph | 100:00 | 67 | 175 |
| **7c** | **8c** | –Allyl | Ph | 100:00 | 62 | 99 |
| **7d** | **8d** | –PMP[a] | Ph | 96:4 | 61 | 214[c] |
| **7e** | **8e** | –$CH_2Ph$ | $PhCH_2$ | 100:00 | 61 | 63–64 |
| **7f** | **8f** | –$CH_2Ph$ | Me | 100:00 | 65 | oil |
| **7g** | **8g** | –$CH_2Ph$ | Ac | 100:00 | 63 | 103–104 |
| **7h** | **8h** | –Cyclohexyl | Ac | 100:00 | 65 | 172–173 |
| **7i** | **8i** | –PMP | Ac | 72:28 | 62 | 204[c] |
| **7j** | **8j** | Ph | Ac | 55:45 | 45 | 180–182[c] |
| **7k** | **8k** | –$CH_2Ph$ | PhthN[a] | 100:00 | 52 | 221 |

[a] PMP = *p*-methoxyphenyl, PhthN = phthalimido.
[b] Isolated yield (based on imine consumed).
[c] Mp of *cis*-isomer.




**Scheme 2.**

various acid chlorides provided selectively *cis*-4-trichloromethyl azetidin-2-ones in moderate to good yields.

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22. Typical procedure for the synthesis of Benzyl-(2,2,2-trichloroethylidene) amine **3a**: To a stirred solution of chloral (0.75 g, 5 mmol) in anhydrous ethylene dichloride (15 mL), benzylamine (0.54 g, 5 mmol) in dry EDC (5 mL) was added slowly at 0–5 °C and the reaction mixture was then allowed to warm to rt and stirred for 30 min. It was then refluxed for 5–8 h with removal of water using molecular sieves (4 Å). The reaction mixture was then cooled and concentrated under vacuum to give the crude product, which was purified by column chromatography to yield the imine **3a** (0.98 g, 82%) as a pale yellow oil.
IR (neat): 1666, 1496, 1454 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 4.87 (s, 2H), 7.35–7.45 (m, 5H), 7.85 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 61.38 (*C*$H_2$Ph), 94.02 (*C*$Cl_3$), 127.39 (Ar*C*), 127.80 (Ar*C*), 128.50 (Ar*C*), 136.66 (*ipso C*–$CH_2$, Ar), 157.17 (N=*C*H).
Typical procedure for the synthesis of 1-benzyl-3-phenoxy-4-trichloromethyl-azetidin-2-one **7a**: To a solution of imine (0.236 g, 1 mmol) and *N*-ethyldiisopropylamine (0.58 g, 4.5 mmol) in anhydrous $CH_2Cl_2$ (20 mL) was added dropwise a solution of phenoxyacetyl chloride (0.25 g, 1.5 mmol) in dry DCM (5 mL) at 0 °C. Following addition the reaction mixture was allowed to warm to room temperature and was stirred for an additional 12 h. The reaction mixture was then washed successively with water (20 mL), saturated sodium bicarbonate solution (2 × 15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give the crude product, which on purification by crystallization from methanol furnished **7a** as a white crystalline solid (0.252 g, 68%). Mp 127 °C; IR ($CHCl_3$): 1774 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 4.35 (d, $J$ = 15.1 Hz, 1H), 4.55 (d, $J$ = 4.9 Hz, 1H), 5.10 (d, $J$ = 15.1 Hz, 1H), 5.35 (d, $J$ = 4.9 Hz, 1H), 7.00–7.20 (m, 3H), 7.30–7.50 (m, 7H); $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 44.74 (*C*$H_2$Ph), 69.48 (*C*4), 81.31 (*C*3), 97.08 (*C*$Cl_3$), 116.05 (Ar*C*), 122.63 (Ar*C*), 128.07 (Ar*C*), 128.32 (Ar*C*), 128.84 (Ar*C*), 129.35 (Ar*C*), 134.28 (*ipso C*–$CH_2$, Ar), 157.55 (*ipso C*–O, Ar), 166.37 (N–*C*=O). MS (EI) *m*/*z* $M^+$ (369); Analysis $C_{17}H_{14}NO_2Cl_3$ requires C, 55.08; H, 3.80; N, 3.77; Cl, 28.69. Found: C, 55.22; H, 3.76; N, 3.80; Cl, 28.60.