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Synthesis of Chlorinated Bicyclic C-Fused Tetrahydrofuro[3,2-*c*]azetidin-2-ones

Ram N. Ram,* Neeraj Kumar, and Nem Singh†

Department of Chemistry, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi 110016, India. †Contributed to the analysis of crystallographic data.

rnram@chemistry.iitd.ernet.in

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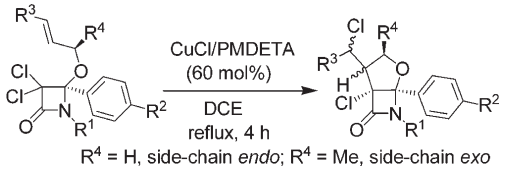

Some bicyclic C-fused chlorinated tetrahydrofuro[3,2-*c*]azetidin-2-ones were prepared by a fairly general route involving Staudinger reaction of allylic/propargylic imidates with dichloroketene followed by highly diastereoselective CuCl/PMDETA-catalyzed 5-exo-trig/dig chlorine atom transfer radical cyclization. An oxepan-fused β-lactam was also prepared similarly by 7-endo-trig cyclization. Synthetic application of the side chain chlorine atom of the products was demonstrated by its substitution in one of the products with azide followed by azide−alkyne click reaction with phenylacetylene to obtain a 1,2,3-triazolyltetrahydrofuro[3,2-*c*]azetidin-2-one.

The well-known antibacterial and most of the nonantibacterial[1] activities of β-lactams rest on some additional activation of the β-lactam ring toward nucleophilic enzymatic ring-opening. This additional activation is brought in by a pyramidal lactam nitrogen through 1,4-fusion (N-fusion) with another ring, electron-withdrawing (-R or -I) N-substituent, and/or a nucleofugal group.[1] A chlorine substituent at the α position of the β-lactam ring is expected to increase its chemical reactivity[2] and modify its biological activity. Accordingly, some apparently otherwise nonactivated monocyclic *N*-aryl-α-chloro-β-lactams[3] have been reported to exhibit promising antibacterial,[3a−e] antifungal,[3a−e] and antitubercular[3e] activities and activities against nonmicrobial diseases such as antitumor,[1a] anticonvulsant,[3f] anti-Parkinson,[3f] CNS,[3f] and HLE inhibitory activities.[3g] Some 6-chloropenams possess β-lactamase inhibitory activities[4] and 7-chlorocephems display anticancer[5] and HLE- and PPE-inhibitory[1a] activities.

3,4-Fused (C-fused) bicyclic β-lactams, in which the lactam nitrogen is not pyramidal, are apparently nonactivated and have received much less attention[6] as compared to their celebrated N-fused analogues. They have rather been used as intermediates for the synthesis of the N-fused bicyclic β-lactams.[7] However, some activated β-lactams C-fused with a cyclopentene,[8a] pyrrolidine,[8b,c] or thiazolidine[7b] ring were found to possess promising β-lactamase inhibitory activities, and recently, some otherwise additionally nonactivated bicyclic β-lactams C-fused with carbocycles and a sugar unit[9] have been reported to exhibit promising nonclassical biological activities against malaria,[9a] leishmaniasis,[9b] and several types of cancer.[9c] Moreover, new applications in the synthesis of non-β-lactam molecules of biological significance have also been discovered.[6a,10] Although the tetrahydrofuran structural unit is abundant in bioactive natural and

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synthetic molecules,[11] very few examples of C-fused tetrahydrofuro-β-lactams are known in the literature. They are mostly tetrahydrofuro[2,3-*c*]azetidin-2-ones having a C3−O linkage.[6a−f,10c] The isomeric tetrahydrofuro[3,2-*c*]azetidin-2-ones with a C4−O linkage which are also isomeric to oxapenams are scarcely known.[12]

Therefore, in view of the importance of the α-chlorine substituent on the β-lactam ring and the emerging prospect of the C-fused β-lactams, we wish to report the synthesis of some chlorinated C-fused tetrahydrofuro[3,2-*c*]azetidin-2-ones in this paper. The synthesis uses Cu(I)-catalyzed chlorine atom transfer radical cyclization (ATRC)[13] as the key step for the construction of the tetrahydrofuran ring on a preformed β-lactam ring.[14] Copper(I)-catalyzed ATRC does not suffer from the limitations of the organotin hydride-mediated radical cyclizations prevalent[6a−c,g−i,15] in bicyclic β-lactam synthesis, namely tedious separation of the product from the toxic tin residues, direct reduction of the halide precursor, and loss of the valuable halogen functionality, which may otherwise be useful for further transformation of the product.

The synthesis of the chlorinated C-fused bicyclic β-lactams **3** is shown in Scheme 1. The allylic imidates **1** were prepared by reaction of easily accessible imidoyl chlorides with allylic alcohols in the presence of NaH in quantitative yields. Staudinger reaction[16] of the crude sensitive allylic imidates **1** without further purification with dichloroacetyl chloride in the presence of Et_3N in benzene at ambient temperatures (25−30 °C) followed by purification of the product by column chromatography furnished the α,α-dichloro-β-lactams **2** in good yields. The CuCl-catalyzed ATRC of the lactams **2** was found to be influenced by the nature of the substituent at the lactam nitrogen and the nature of the ligand used (Table 1). Thus, the cyclization of the lactams **2b** and **2d** as representatives of *N*-alkyl and *N*-aryl β-lactams in DCE at reflux under a nitrogen atmosphere using up to 60 mol % (1:1 molar equiv mixture) of CuCl and 2,2′-bipyridine (bpy), tetramethylethylenediamine (TMEDA), or pentamethyldiethylenetriamine (PMDETA) as the ligand revealed that bpy was ineffective, while TMEDA was effective in the case of the *N*-phenyl-β-lactam **2d**. Only PMDETA was found to be a suitable ligand for the cyclization of both **2b** and **2d**. Subsequently, all the lactams **2** listed in Table 2 and the lactam **4** were successfully cyclized with CuCl/PMEDTA (60 mol %, 1:1 molar equiv mixture) in DCE under reflux for 4 h by 5-exo-trig radical cyclization in a highly diastereoselective manner to afford the bicyclic β-lactams **3** and **5**, respectively, in good yields. In most of the cases, only one diastereomer was isolated. The structures of all the compounds were well supported by ^{1}H and ^{13}C NMR, IR, and

SCHEME 1. Synthesis of Chlorinated Monocyclic and C-Fused Bicyclic β-Lactams via Copper(I)-Catalyzed ATRC

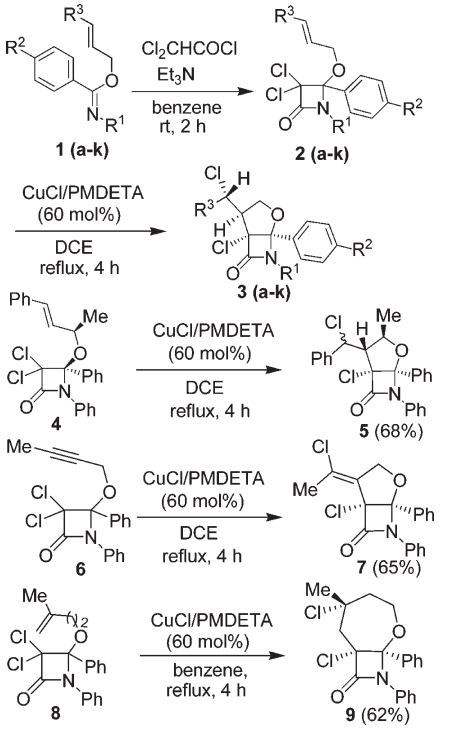

TABLE 1. Ligand Screening for ATRC of Representative β-Lactams[a]

entry	lactam **2**	ligand	time (h)	product **3** yield (%)	recovered **2** (%)
1	**b**	bpy	4		84
2	**d**	bpy	4		86
3	**b**	TMEDA	12	15	62
4	**d**	TMEDA	4	68	
5	**b**	PMDETA	4	75	
6	**d**	PMDETA	4	79	

[a]The yields are for the reactions performed with 10 mmol of **2** and 60 mol % each of CuCl and the ligand in DCE at reflux under a nitrogen atmosphere.

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TABLE 2. Yields of the Monocyclic and Bicyclic β-Lactams

					yield (%)		
entry	**1**	R^1	R^2	R^3	**2**[a]	**3**[b]	**3**[c]
1	**a**	*n*-Bu	H	H	78	77	60
2	**b**	*i*-Pr	H	H	84	75	63
3	**c**	*c*-Hex	H	H	82	74	61
4	**d**	C_6H_5	H	H	78	79	62
5	**e**	4-$MeOC_6H_4$	H	H	84	72	60
6	**f**	4-ClC_6H_4	H	H	76	66	50
7	**g**	*i*-Pr	OMe	H	76	73	55
8	**h**	*i*-Pr	Cl	H	80	74	59
9	**i**	*i*-Pr	NO_2	H	78	79	62
10	**j**	C_6H_5	H	*n*-Pr	76	84[d]	64
11	**k**	C_6H_5	H	Ph	72	55[e]	40

[a]One step (1 → 2). [b]One step (2 → 3). [c]Two steps (1 → 3). [d]Mixture of diastereomers. [e]Only one diastereomer could be isolated.

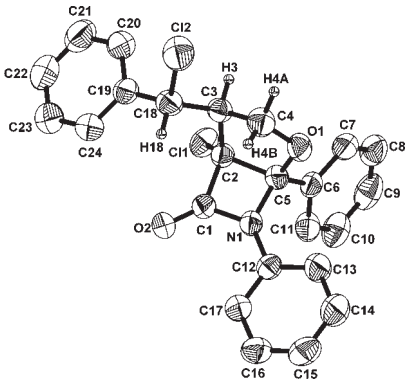
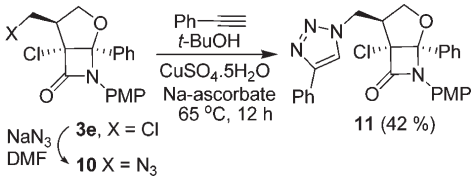


FIGURE 1. ORTEP diagram of bicyclic β-lactam **3k**.

HRMS data. Thus, in the ^{1}H NMR spectra of **3**, the THF OCH_2 protons appeared in the range δ 4.90−4.64 as a dd (J = 10.2−9.8, 7.8−7.4 Hz, 1H) and in the range δ 4.17−3.86 as a triplet (J = 11.3−10.6 Hz, 1H). In the case of **3a** and **3f**, the dd collapsed to triplet (J = 8.6 Hz). The THF CH proton appeared as a multiplet in the range δ 3.06−2.77. Understandably, it showed up as a dt (J = 11.1−10.8, 7.5 Hz) in the side-chain substituted derivatives **3j**,**k**. Single-crystal X-ray diffraction of **3d** and **3k** showed cis ring fusion and a trans relationship between the bridgehead chlorine atom and the adjacent side chain on the tetrahydrofuran ring. The similarity of their NMR spectra and the vicinal coupling constants of the THF ring protons (10.8−7.4 Hz) with those of the other bicyclic β-lactams **3** (11.3−7.5 Hz) indicated that probably all the bicyclic β-lactams **3** had similar stereostructures. In the case of **3j**, a mixture of two diastereomers was obtained in 91:9 ratio due to the formation of an additional stereogenic center in the side chain which could not be separated. However, in the case of **3k**, ^{1}H NMR indicated the formation of four diatereoisomeric products in 76:9:8:7 ratio due to different orientations (exo, endo) of the side chain and configurations of the stereogenic center in it. Of these, only the major diastereomer could be separated and purified by column chromatography in 55% yield. Its stereostructure, as shown in **3k**, was established by single-crystal X-ray diffraction. The ORTEP diagram is shown in Figure 1. Single-crystal X-ray diffraction also revealed that the monocyclic β-lactam **4** was an *RR* and *SS* enantiomeric mixture of a single diastereoisomer. Thus, it was formed by a highly diastereoselective Staudinger reaction. On ATRC, it furnished a 78:22 mixture of two not easily separable diastereomers **5**. In this

SCHEME 2. Cu(I)-Catalyzed Click Reaction of 3e



case also, the two diastereomers arose probably due to the stereogenic center in the side chain. However, the side chain in these diastereomers was arguably oriented cis to the bridgehead chlorine as suggested by considerably different values of the *vicinal* coupling constants (1.8, 3.5 Hz) between the tetrahydrofuran ring protons, probably due to difference in the puckering of the THF ring. The trans relationship of the methyl and benzylic side chain in both the diastereomers was also supported by ^{1}H NOSEY and difference NOE spectra (Supporting Information). The cyclization of the β-lactam **6** having an alkynic radical trap occurred exclusively by 5-exo-dig radical cyclization to afford the lactam **7** with an *E*-exocyclic double bond.[17] The reaction of the lactam **8** having a substituted homoallyic group as the radical trap was mostly incomplete under similar conditions. The 7-endo-trig radical cyclization product **9** and the monoreductive dechlorination product were detected by ^{1}H NMR in 25:75 ratio. However, when the cyclization was carried out in benzene under reflux, no reduction product was formed and the bicyclic β-lactam **9** was isolated as a single diastereomer in 62% yield. The 7-endo-trig cyclization was probably favored due to steric hindrance for the 6-exo-trig cyclization. The stereostructures of the bicyclic β-lactams **7** and **9** were also supported by X-ray diffraction spectroscopy.

In order to demonstrate the utility of the side-chain chlorine atom in further elaboration of the bicyclic β-lactams, **3e** was converted to the azide **10** (Scheme 2) by treatment with sodium azide which on copper(I)-catalyzed azide−alkyne click reaction[18] with phenylacetylene followed by purification by column chromatography furnished the triazolyl β-lactam **11**. 1,2,3-Triazole-containing molecules possess a wide range of biological activities,[11f,18,19] and even though 1,2,3-triazolyl-β-lactam antibiotic cefatrizine,[19c] the β-lactamase inhibitors tazobactam and BRL 42715,[19a] and the anti-inflammatory coenzyme A-independent transacylase inhibitor SB 212047[19d] have been known for a long time, triazolyl-β-lactams have since been rarely revisited.[20]

Curiously, relatively few reports describe Staudinger reaction of dichloroketene,[21] very few of acyclic imidates[7a,22] and

(17) See ref 11d and references cited therein for synthetic applications of β-alkylidenetetrahydrofurans and for such a natural bioactive compound.
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practically none involving the two together.[23] Regarding exploiting the synthetic potentiality of the *gem*-dichlorofunctionality of the α,α-dichloro-β-lactams, only reductive monodehalogenation and alkylation via chlorine−lithium exchange[24] and a transformation to aziridines[25] have been reported. The present work describes the generation of a radical center for the first time.

In conclusion, Staudinger reaction of allylic imidates with dichloroketene followed by copper(I)-catalyzed ATRC constituted a diastereoselective method for the synthesis of novel chlorinated tetrahydrofuro[3,2-*c*]azetidin-2-ones. The method used readily available and inexpensive starting materials. It is quite general for the synthesis of a variety of bicyclic β-lactams C-fused with a substituted tetrahydrofuran ring and with an aliphatic or aromatic substituent at the lactam nitrogen. The synthesis involves some rarely exploited reactions in β-lactam chemistry and the products have some attractive structural attributes to merit attention.

Experimental Section

4-(Allyloxy)-3,3-dichloro-1,4-diphenylazetidin-2-one 2d: Typical Procedure for the Synthesis of Monocyclic β-Lactams. To a solution of the allylic imidate **1d** (2.37 g,10 mmol) in benzene (50 mL) was added triethylamine (2.02 g, 2.8 mL, 20 mmol) through a syringe at room temperature (22−30 °C). A solution of dichloroacetyl chloride (2.9 g, 1.9 mL, 20 mmol) in benzene (5 mL) was added to this solution dropwise over 15 min, and the reaction mixture was stirred for 2 h at the same temperature. After this time, TLC indicated the disappearance of the imidate. The reaction mixture was filtered to separate the hydrochloride salt, and the filtrate was washed with brine (3 × 10 mL), dried over Na_2SO_4, and evaporated under reduced pressure on a rotary evaporator. The residue was purified by column chromatography (neutral alumina, *n*-hexane/EtOAc = 95:5 v/v) followed by recrystallization from *n*-hexane−diethyl ether to obtain the pure 4-(allyloxy)-3,3-dichloro-1,4-diphenylazetidin-2-one **2d** (2.71 g, 78%) as a white solid: mp 62−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.19 (m, 10H), 6.03−5.90 (m, 1H), 5.39 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.25 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.74 (dd, *J* = 12.3, 4.8 Hz, 1H), 4.18 (dd, *J* = 12.3, 5.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.1 (C), 135.6 (C), 133.7 (C), 132.5 (CH), 129.7 (CH), 129.3 (CH), 128.2 (CH), 127.4 (CH), 125.9 (CH), 118.5 (CH), 117.4 (CH_2), 98.6 (C), 89.9 (C), 67.0 (CH_2); IR (KBr) ν_{max} 3063 (w), 2927 (w), 1784 (s), 1493 (m), 1371 (s), 1123 (m), 759 (m), 731 (m), 692 (m) cm^{-1}; HRMS calcd for $[C_{18}H_{15}NO_2Cl_2 + Na]^+$ 370.0378, found 370.0365.

3-Chloro-4-chloromethyl-1,6-diphenyltetrahydrofuro[3,2-*c*]azetidin-2-one 3d: Typical Procedure for the Synthesis of Bicyclic β-Lactams. A flame-dried, two-necked, round-bottom flask was charged with 4-(allyloxy)-3,3-dichloro-1,4-diphenylazetidin-2-one **2d** (3.48 g,10 mmol), CuCl (0.6 g, 6 mmol), and degassed DCE (40 mL) under a N_2 atmosphere using Schlenk techniques. Into this suspension was injected PMDETA (1.04 g, 1.25 mL, 6 mmol), and the mixture was heated with stirring for 4 h. The mixture was then cooled and filtered. The filtrate was evaporated under reduced pressure, and the residual mass was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 90:10 v/v) followed by recrystallization from *n*-hexane−diethyl ether to obtain 3-chloro-4-chloromethyl-1,6-diphenyltetrahydrofuro[3,2-*c*]azetidin-2-one **3d** (2.8 g, 79%) as a white solid: mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.43 (m, 7H), 7.30−7.25 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 4.74 (dd, *J* = 10.1, 7.4 Hz, 1H), 4.04 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.91 (t, *J* = 10.8 Hz, 1H), 3.72 (t, *J* = 11.4 Hz, 1H), 3.06−2.96 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.5 (C), 134.7 (C), 131.6 (C), 130.0 (CH), 129.2 (CH), 128.7 (CH), 127.2 (CH), 125.5 (CH), 118.5 (CH), 101.7 (C), 81.3 (C), 70.3 (CH_2), 51.3 (CH), 40.7 (CH_2); IR (KBr) ν_{max} 3008 (w), 2923 (w), 1770 (s), 1501 (m), 1384 (m), 1055 (m), 748 (m), 690 (w) cm^{-1}; HRMS calcd for $[C_{18}H_{15}NO_2Cl_2 + Na]^+$ 370.0378, found 370.0372.

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Supporting Information Available: Detailed experimental procedures, spectral data, and NMR spectra of all the new and relevant compounds, CIF and ORTEP diagrams of **3d**, **3k**, **4**, **7**, and **9**. This material is available free of charge via the Internet http://pubs.acs.org.

(23) We could find only one report which described two examples of cycloaddition of ethyl formimidates with dichloroketene to form the corresponding 3,3-dichloro-β-lactams in negligible yields (7%). (a) Katagiri, N.; Niwa, R.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 2899. A few reports described cycloaddition of dichloroketene to some endocyclic imidates (5,6-dihydro-1,3-oxazines): (b) Stajer, G.; Virag, M.; Szabo, A. E.; Bernath, G.; Sohar, P.; Sillanpaa, R. *Acta Chem. Scand.* **1996**, *50*, 922. (c) Sohar, P.; Stajer, G.; Pelczer, I.; Szabo, A. E.; Szunyog, J.; Bernath, G. *Tetrahedron* **1985**, *41*, 1721. Exocyclic imidates (maleic isoimides) have also been described: (d) Capraro, H. G.; Winkler, T.; Martin, P. *Helv. Chim. Acta* **1983**, *66*, 362. These compounds form N-fused bicyclic and spirocyclic β-lactams, respectively.

(24) Dejaegher, Y.; Denolf, B.; Stevens, C. V.; De Kimpe, N. *Synthesis* **2005**, 193.

(25) Dejaegher, Y.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 2075.