One-step synthesis of β-lactams using cyanuric fluoride

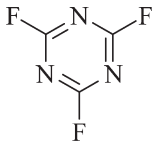
Maaroof Zarei*

Department of Chemistry, College of Sciences, Hormozgan University, Bandar Abbas 71961, Iran

Cyanuric fluoride works as an efficient acid activator reagent for the direct [2+2] ketene–imine cycloaddition of substituted acetic acids and imines in a one-pot synthesis under mild conditions. The yields are good to excellent and the reaction conditions are mild, simple and efficient.

Keywords: β-lactam, 2-azetidinone, Staudinger reaction, cyanuric fluoride, ketene, imine

2,4,6-Trifluoro-1,3,5-triazine **1** with the common name cyanuric fluoride, was prepared from cyanuric chloride and a fluorinating agent.[1] It is also commercially available. Cyanuric fluoride is used for the mild and direct conversion of carboxylic acids to acyl fluorides.[1]



1

β-Lactam antibiotics remain the main drugs to treat infections caused by bacteria. These molecules disturb the final step of bacterial cell wall biosynthesis by inhibiting penicillin binding proteins (PBPs) involved in the cross linking of peptidoglycan strands.[2] Ezetimibe is a new drug, which has the 2-azetidinone skeleton and selectively inhibits the absorption of cholesterol.[3] Besides the antibacterial and cholesterol absorption inhibitory activities, β-lactams show various other biological activities.[4] They are also used as intermediates and synthons in the synthesis of several organic compounds.[5]

Many synthetic methods have been developed for the preparation of the β-lactam ring.[6] The Staudinger reaction ([2+2] ketene–imine cycloaddition reaction)[7] is regarded as one of the most fundamental and versatile methods for the synthesis of structurally diverse 2-azetidinone derivatives.[8–12]

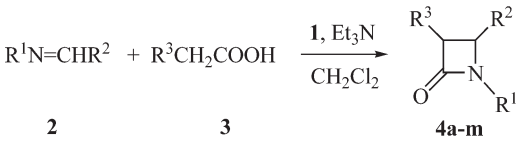
Commonly, ketenes are prepared *in situ* by reaction of acyl halides with tertiary amines.[13–15] However, the application of acyl halides for the preparation of ketenes has some disadvantages such as low availability, instability and difficulty of preparation. To solve these problems, acid activators have been used for the one-pot synthesis of 2-azetidinones from imines and carboxylic acids.[16–22]

In the present work, cyanuric fluoride is investigated as an acid activator in the synthesis of 2-the azetidinone ring by the ketene–imine cycloaddition.

Schiff bases were synthesised by reaction of the corresponding amines and aldehydes in refluxing ethanol or by stirring overnight in the presence of anhydrous Na_2SO_4 in dry CH_2Cl_2. In a model study, the solution of 4-methoxy-*N*-(4-methylbenz ylidene)aniline **2a** (1.0 mmol) and 4-methoxyacetic acid **3a** (1.0 mmol) in dry CH_2Cl_2 was treated with cyanuric fluoride in the presence of Et_3N at room temperature. After 18 hours, 2-azetidinone **4a** was obtained in 72% yield as a white solid after crystallisation from EtOAc. Spectral data confirmed the structure of **4a**. The reaction was easy, clean and simple aqueous workup removed the byproduct salts.

Table 1 Optimisation of reaction condition in the synthesis of **4a**

Entry	Solvent	Temp/°C	Cyanuric fluoride /mmol	Yield/%
1	CH_2Cl_2	rt	1.0	72
2	Dioxane	rt	1.0	44
3	DMF	rt	1.0	52
4	THF	rt	1.0	47
5	CH_2Cl_2	0	1.0	69
6	CH_2Cl_2	rt	1.5	89
7	CH_2Cl_2	rt	2.0	86

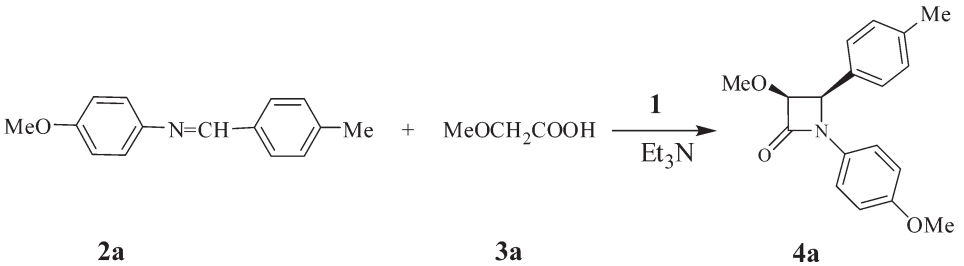


2 **3** **4a-m**

Scheme 1 Synthesis of 2-azetidinones **4a–m**.

Previously cyanuric chloride has been used for activation of acids in the synthesis of 2-azetidinones, although generally this method requires the cooling of the mixture below 0 °C[23,24] and the yields using cyanuric chloride above 0 °C are low.[25] However, synthesis of 2-azetidinones using cyanuric fluoride, unlike cyanuric chloride and some other acid activators, was performed at room temperature with high yield of products under simple and mild conditions.

After this successful result, the effects of solvents, temperature of reaction and quantity of reagent in the synthesis of **4a** were investigated. According to Table 1, among the dry solvents examined, CH_2Cl_2 showed the best results. It was also found that the yields were almost identical at 0 °C and room temperature. The amounts of methoxyacetic acid and the reagent were used for optimisation of the quantity of reagent.



2a **3a** **4a**

* Correspondent. E-mail: maaroof1357@yahoo.com; mzarei@hormozgan.ac.ir

As shown in Table 1, 1.5 mmol of cyanuric fluoride was needed to complete the reaction (TLC monitoring of disappearance of the imine) in CH_2Cl_2 at room temperature. The yield of 2-azetidinone **4a** did not increase when 2.0 mmol of cyanuric fluoride and methoxyacetic acid were used

Based on the above results, 2-azetidinones **4a–m** were synthesised by treatment of 1.0 mmol of the corresponding Schiff bases **2**, 1.5 mmol of acetic acid derivatives **3** and 1.5 mmol cyanuric fluoride in the presence of triethylamine in dry CH_2Cl_2 (Scheme 1, Table 2). Purification of β-lactams **4a–m** was performed by crystallisation from EtOAc. All products were characterised by spectroscopic data and elemental analyses. The indicated *cis* and *trans* stereochemistry of the products was judged from the coupling constants of H-3 and H-4 of β-lactam ring in ^{1}H NMR ($J \geq 4.0$ for the *cis* and $J \leq 3.0$ for the *trans* stereoisomer).

The stereochemistry is mainly dominated by the electronic effect and the steric hindrance of the ketene and imine substitutents.[26] The mechanism is similar to our previously reported mechanism for the Staudinger reaction from acetic acid derivatives and imines using methoxymethylene-*N,N*-dimethyliminium salt via formation of an activated form of a carboxylic acid.[20] It is suggested that the reaction is performed by *in situ* generation of a ketene from the activated ester (Scheme 2), then nucleophile attack of the imine followed by ring closure of the zwitterionic intermediate to the β-lactam. The relative (*cis/trans*) stereoselectivity is generated as a result of the competition between the direct ring closure and the isomerisation of the imine moiety in the zwitterionic intermediate.[16,20]

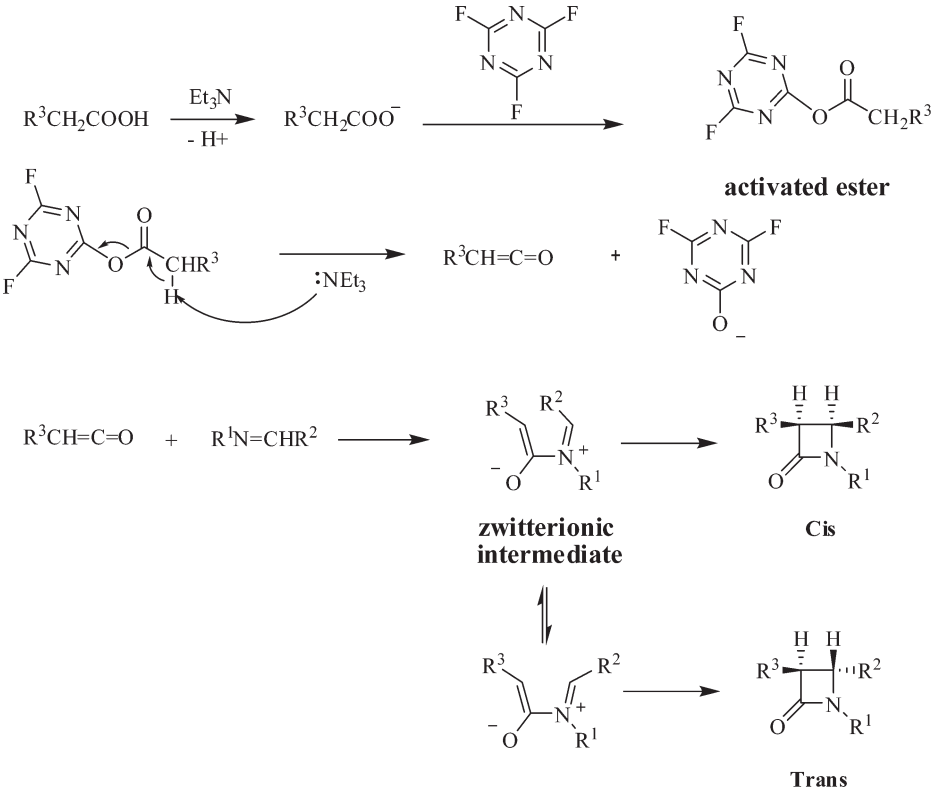
This paper describes the use of cyanuric fluoride to activate the substituted acetic acids in the synthesis of 2-azetidinones *via* a ketene–imine cycloaddition reaction. The remarkable versatility of this method is the mild condition reactions, availability of the reagents, easy purification and high yield of the products.

Experimental

All required chemicals were purchased from Merck, Fluka, and Acros. The melting points were determined on a Buchi 535 apparatus and are uncorrected. IR spectra were measured on a Galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded on a Bruker spectrometer (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz) using tetramethylsilane as an internal standard and coupling constants are given in cycles per second

Table 2 Synthesis of 2-azetidinones **4a–m** with cyanuric fluoride

Entry	R^1	R^2	R^3	Stereochemistry	Product	Yield/%
1	4-$MeOC_6H_4$	4-MeC_6H_4	MeO	*cis*	**4a**	89
2	4-MeONaphthyl	4-MeC_6H_4	PhO	*cis*	**4b**	92
3	$C_6H_5CH_2$	4-$NO_2C_6H_4$	PhO	*cis*	**4c**	84
4	4-$EtOC_6H_4$	4-$MeOC_6H_4$	2-naphthO	*cis*	**4d**	90
5	C_6H_5	4-$NO_2C_6H_4$	2-naphthO	*cis*	**4e**	93
6	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	2,4-$Cl_2C_6H_3O$	*cis*	**4f**	94
7	C_6H_5	4-ClC_6H_4	2,4-$Cl_2C_6H_3O$	*cis*	**4g**	91
8	4-$EtOC_6H_4$	4-MeC_6H_4	PhthN	*trans*	**4h**	85
9	4-$EtOC_6H_4$	4-ClC_6H_4	PhthN	*trans*	**4i**	82
10	4-ClC_6H_4	4-$MeOC_6H_4$	MeS	*cis*	**4j**	87
11	4-$EtOC_6H_4$	4-$MeOC_6H_4$	MeS	*cis*	**4k**	85
12	4-MeONaphthyl	4-ClC_6H_4	MeO	*cis*	**4l**	93
13	4-$MeOC_6H_4CH_2$	4-$NO_2C_6H_4$	2,4-$Cl_2C_6H_3O$	*cis*	**4m**	90



Scheme 2

(Hz). Elemental analyses were run on a Vario EL III elemental analyser. TLC was carried out on silica gel 254 analytical sheets obtained from Fluka. Spectral data for **4a–f** and **4h–j** have been previously reported.[14,16,20,27,28]

*Synthesis of 2-azetidinones (**4a–m**); general procedure*

Cyanuric fluoride (1.5 mmol) was added to a solution of substituted acetic acids (1.5 mmol), imines (1.0 mmol) and triethylamine (5.0 mmol) in dry CH_2Cl_2 (20 mL) at room temperature and the mixture was stirred overnight. The reaction mixture was washed successively with saturated $NaHCO_3$ (20 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed to give the crude product, which was purified by crystallisation from EtOAc to give pure β-lactams **4a–m**.

1-(4-Methoxyphenyl)-3-methoxy-4-p-tolylazetidin-2-one (**4a**): White solid; m.p. 152–154 °C (lit.[20] 151–153 °C).

1-(4-Methoxynaphthalen-1-yl)-3-phenoxy-4-p-tolyl-azetidin-2-one (**4b**): White crystalline solid; m.p. 180–182 °C (lit.[27] 182–184 °C).

1-Benzyl-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (**4c**): White solid; m.p. 127–129 °C (lit.[20] 130–32 °C).

1-(4-Ethoxyphenyl)-4-(4-methoxyphenyl)-3-(naphthalen-2-yloxy)-azetidin-2-one (**4d**): White solid; m.p. 163–165 °C (lit.[20] 162–164 °C).

3-(Naphthalen-2-yloxy)-4-(4-nitrophenyl)-1-phenyl-azetidin-2-one (**4e**): Light-yellow solid; m.p. 188–190 °C (lit.[16] 189–191 °C).

3-(2,4-Dichlorophenoxy)-1-(4-methoxyphenyl)-4-(4-nitro-phenyl)-azetidin-2-one (**4f**): White crystalline solid; m.p. 188–190 °C (lit.[20] 187–189 °C).

4-(4-Chlorophenyl)-3-(2,4-dichlorophenoxy)-1-phenylazetidin-2-one (**4g**). White solid; m.p. 195–197 °C. IR (KBr) cm^{-1}: 1750 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 5.21 (H-4, d, 1H, *J* = 4.8), 5.53 (H-3, d, 1H, *J* = 4.8), 6.86–7.52 (ArH, m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.5 (C-4), 82.9 (C-3), 113.7, 115.0, 118.3, 122.9, 126.6, 127.1, 127.9, 130.3, 130.7, 131.4, 131.7, 136.4, 150.8, 155.8 (aromatic carbons), 162.7 (CO, β-lactam); Anal. Calcd for $C_{21}H_{14}Cl_3NO_2$: C, 60.24; H, 3.37; N, 3.35. Found: C, 60.37; H, 3.52; N, 3.28%.

2-(1-(4-Ethoxyphenyl)-2-oxo-4-p-tolylazetidin-3-yl)isoindoline-1,3-dione (**4h**): Light-yellow solid; m.p. 205–207 °C (lit.[14] 202–204 °C).

2-(2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**4i**): Light-yellow solid; m.p. 211–213 °C (lit.[14] 211–213 °C).

1-(4-Chlorophenyl)-4-(4-methoxyphenyl)-3-(methylthio)azetidin-2-one (**4j**): White solid; m.p. 64–66 °C (lit.[28] 64–66 °C).

1-(4-Ethoxyphenyl)-4-(4-methoxyphenyl)-3-(methylthio)azetidin-2-one (**4k**): White solid; m.p. 63–65 °C. IR (KBr) cm^{-1}: 1743 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (Me, t, 3H, *J* = 7.0), 2.23 (S-Me, s, 3H), 3.55 (OMe, s, 3H), 4.05 (OCH_2, q, 2H, *J* = 7.0), 4.67 (H-4, d, 1H, *J* = 4.5), 5.17 (H-3, d, 1H, *J* = 4.5), 6.64–8.01 (ArH, m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0 (Me), 15.9 (S-Me), 56.4 (OMe), 61.3 (OCH_2), 62.9 (C-3), 63.7 (C-4), 110.1, 116.9, 122.0, 122.6, 133.9, 142.4, 149.7, 155.9 (aromatic carbons), 161.3 (CO, β-lactam). Anal. Calcd for $C_{19}H_{21}NO_3S$: 66.45; H, 6.16; N, 4.08; S, 9.34. Found: C, C, 66.38; H, 6.29; N, 4.14; S, 9.27%.

4-(4-Chlorophenyl)-3-methoxy-1-(4-methoxynaphthalen-1-yl)azetidin-2-one (**4l**): White solid; m.p. 148–150 °C. IR (KBr) cm^{-1}: 1746 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 3.37, 3.60 (2OMe, s, 6H), 4.71 (H-4, d, 1H, *J* = 4.9), 5.33 (H-3, d, 1H, *J* = 4.9), 6.80–7.94 (ArH, m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 57.6 (OMe), 62.3 (C-4), 83.4 (C-3), 110.2, 110.9, 111.8, 112.4, 116.5, 120.2, 122.6, 128.2, 131.3, 132.7, 134.9, 144.0, 150.1, 155.3 (aromatic carbons), 163.7 (CO, β-lactam); Anal. Calcd for $C_{21}H_{18}ClNO_3$: C, 68.57; H, 4.93; N, 3.81. Found: C, 68.64; H, 5.06; N, 3.88%.

3-(2,4-Dichlorophenoxy)-1-(4-methoxybenzyl)-4-(4-nitrophenyl)-azetidin-2-one (**4m**): Light-yellow solid; m.p. 84–86 °C. IR (KBr) cm^{-1}: 1344, 1557 (NO_2), 1751 (CO, β-lactam); ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (OMe, s, 3H), 3.81, 4.75 (CH_2-benzyl, 2d, 2H, *J* = 14.7), 4.93 (H-4, d, 1H, *J* = 5.0), 5.45 (H-3, d, 1H, *J* = 5.0), 6.77–8.08 (ArH, m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.9 (CH_2), 55.6 (OMe), 63.1 (C-3), 82.7 (C-4), 113.5, 114.6, 116.0, 117.2, 119.5, 120.3, 125.8, 126.2, 128.0, 128.9, 133.6, 147.5, 152.1, 155.8 (aromatic carbons), 163.6 (CO, β-lactam); Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_5$: C, 58.37; H, 3.83; N, 5.92. Found: C, 58.49; H, 3.97; N, 5.98%.

Financial support from Hormozgan University Research Centre is gratefully acknowledged.

Received 30 September 2012; accepted 1 November 2012
Paper 1201547 doi: 10.3184/174751912X13545429290478
Published online: 15 January 2013

References

1 G.A. Olah, M. Nojima and I. Kerekes, *Synthesis*, 1973, 487.
2 H. Ceric, M. Sindler-Kulyk, M. Kovacevic, M. Peric and A. Zivkovic, *Bioorg. Med. Chem.*, 2010, **18**, 3053.
3 D.A. Burnett, *Curr. Med. Chem.*, 2004, **11**, 1873.
4 P.D. Mehta, N.P.S. Sengar and A.K. Pathak, *Eur. J. Med. Chem.*, 2010, **45**, 5541.
5 B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, **107**, 4437.
6 N. Fu and T.T. Tidwell, *Tetrahedron*, 2008, **64**, 10465.
7 H. Staudinger, *Liebigs Ann. Chem.*, 1907, **356**, 51.
8 A. Jarrahpour, M. Motamedifar, M. Zarei and M. Mimouni, *Phosphorus Sulfur Silicon*, 2010, **185**, 287.
9 A. Jarrahpour and M. Zarei, *Tetrahedron Lett.*, 2009, **50**, 1568.
10 A. Jarrahpour and M. Zarei, *Tetrahedron Lett.*, 2007, **48**, 8712.
11 A. Jarrahpour, M.M. Doroodmand and E. Ebrahimi, *Tetrahedron Lett.*, 2012, **53**, 2797.
12 R.S. Keri and K.M. Hosamani, *Monatsh. Chem.*, 2010, **141**, 883.
13 R.S. Keri, K.M. Hosamani, R.V. Shingalapur and H.R.S. Reddy, *Eur. J. Med. Chem.*, 2009, **44**, 5123.
14 A. Jarrahpour and M. Zarei, *Molecules*, 2007, **12**, 2364.
15 A. Jarrahpour and M. Zarei, *Molecules*, 2006, **11**, 49.
16 M. Zarei, *Bull. Chem. Soc. Jpn*, 2012, **85**, 360.
17 M. Zarei, *J.Chem. Res.*, 2012, **36**, 118.
18 A. Jarrahpour and M. Zarei, *Synlett*, 2011, 2572.
19 A. Jarrahpour, A. Fadavi and M. Zarei, *Bull. Chem. Soc. Jpn.*, 2011, **84**, 320.
20 A. Jarrahpour and M. Zarei, *Tetrahedron*, 2010, **66**, 5017.
21 A. Jarrahpour and M. Zarei, *Tetrahedron*, 2009, **65**, 2927.
22 B.K. Banik, I. Banik and F.F. Becker, *Eur. J. Med. Chem.*, 2010, **45**, 846.
23 M.S. Manhas, A.K. Bose and M.S. Khajavi, *Synthesis*, 1981, 209.
24 W. Hinz and G. Just, *Can. J. Chem.*, 1987, **65**, 1503.
25 J.M. Van der Veen, S.S. Bari, L. Krishnan, M.S. Manhas and A.K. Bose, *J. Org. Chem.*, 1989, **54**, 5758.
26 Y. Wang, Y. Liang, L. Jiao, D.-M. Du and J. Xu, *J. Org. Chem.*, 2006, **71**, 6983.
27 M. Zarei, A. Jarrahpour, E. Ebrahimi, M. Aye and S.A. Torabi Badrabady, *Tetrahedron*, 2012, **68**, 5505.
28 M. Zarei and M. Mohamadzadeh, *Tetrahedron*, 2011, **67**, 5832.