A Mild and Efficient Route to 2-Azetidinones Using the Cyanuric Chloride–DMF Complex

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Abstract: Efficient conversion of Schiff bases and carboxylic acids to β-lactams can be carried out at room temperature in CH_2Cl_2, using a cyanuric chloride–*N*,*N*-dimethyl formamide complex. The complex is easily prepared by reaction of cyanuric chloride and DMF, an inexpensive reagent, at room temperature. Optimization of conditions and comparison of yield with cyanuric chloride were performed.

Key words: 2-azetidinone, β-lactam, Staudinger reaction, cyanuric chloride, Schiff base

β-Lactams (2-azetidinones) have a long and illustrious history in the field of antibacterial chemistry and are still the main drugs to treat infections caused by bacteria.[1] Amoxicillin, for example, remains one of the most prescribed antibiotics in the United States, with approximately 49.5 million prescriptions filled in 2009.[2] Ezetimibe is an example of a 2-azetidinone-containing drug, commercialized for cholesterol absorption control, owing to its potency for inhibiting cholesterol acyl transferase and was marketed as Zetia in 2002.[3] A literature survey reveals that 2-azetidinone and its derivatives possess a broad spectrum of biological activities[4] which include human cytomegalovirus (HCMV) inhibition,[5] human leukocyte elastase (HLE) inhibition,[6] thrombin inhibition,[7] porcine pancreatic elastase (PPE) inhibition,[8] HIV-1 protease inhibition,[9] cysteine protease inhibition,[10] and anticancer,[11] antifungal,[12] potential antimalarial,[13] anti-influenza virus,[14] antihyperglycemic,[15] central nervous system (CNS),[16] neurological[17] and antiproliferative activities.[18] Besides their biological activities, the importance of β-lactams as synthetic intermediates has been widely recognized in the preparation of various heterocyclic compounds of biological significance,[19] for example, in the semisynthesis of Taxol and Taxotere.[20]

Microorganisms have built up resistance against the most traditional β-lactam antibiotics due to excess use of antibiotics.[21] The need for new β-lactam antibiotics and other applications of 2-azetidinones has motivated chemists and scientists to design new synthetic methods for the preparation of β-lactams.

Given the importance of β-lactams in heterocyclic and medicinal chemistry, many different methods for the synthesis of these compounds have been reported.[22] The formation of the 2-azetidinone ring via [2+2] cycloaddition of an imine with a ketene is termed the Staudinger reaction.[23] This method is generally accepted as the most versatile and efficient route for the construction of the β-lactam skeleton.[24] Several methods have been reported for preparation of ketenes, but reaction of acyl halides with tertiary bases is commonly used for in situ generation of ketenes.[25] Difficulty of preparation and handling, low availability and instability of acyl halides are some drawbacks of the latter method. Consequently, acid activators have been reported in the synthesis of 2-azetidinones from Schiff bases and acetic acid derivatives.[26]

Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) is a stable, nonvolatile, inexpensive, commercially available, and easy-to-handle reagent. Over the past few years, there has been considerable interest in using TCT or its derivatives in organic synthesis.[27] An empirical observation is that monosubstitution of chlorine occurs below or at 0 °C.[27c] A search of the literature revealed that the use of TCT as an acid activator in the synthesis of 2-azetidinones via ketene–imine cycloaddition has been published,[26l,28] although the procedure implied cooling the mixture below 0 °C.

TCT and DMF (TCT–DMF adduct)[29] have been used for the conversion of primary alcohols to the corresponding formate esters,[30] Beckmann rearrangement of oximes,[31] conversion of alcohols to alkyl chlorides,[32] and preparation of α-glycosyl chlorides.[33]

On this basis, and as part of an ongoing program directed to the development of efficient reagents for the synthesis of β-lactams under mild conditions, we report herein a mild and efficient procedure for the synthesis of β-lactams from imines and acetic acid derivatives in the presence of TCT–DMF adduct.

The TCT–DMF adduct was prepared by reaction of DMF and TCT following a reported procedure (Scheme 1).[30–32]

In a model study, a solution of 4-ethoxy-*N*-(4-methylbenzylidene)aniline (**1a**) and 4-chlorophenoxyacetic acid (**2a**) in dry CH_2Cl_2 was treated with TCT–DMF adduct at –15 °C. Then the mixture was stirred overnight at room temperature to give 3-(4-chlorophenoxy)-1-(4-ethoxyphenyl)-4-*p*-tolylazetidin-2-one (**3a**) in high yield as a

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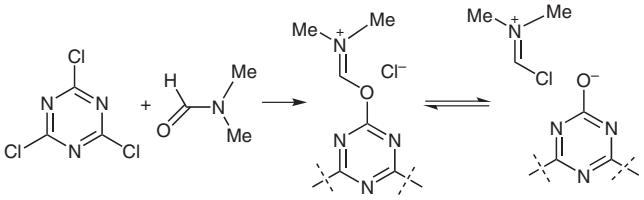
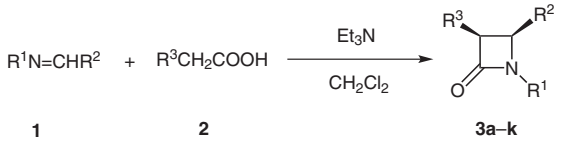


Scheme 1



Scheme 2

white solid after crystallization from EtOAc. The reaction was very simple and clean, because the triazine byproduct was removed by a simple aqueous workup. After this success, we investigated the effect of solvent, temperature, and quantity of reagent (based on mmol of TCT) in the synthesis of **3a**. In all reactions, triethylamine was used as the base. According to Table 1, CH_2Cl_2 and DMF showed the best results, but the workup from CH_2Cl_2 was much easier than DMF. It was also found that the yields were almost identical at –15 °C, 0 °C, and room temperature; whereas the yield decreased at –63 °C. The molar optimization of the reagent was also examined. As it is shown in the Tables 1, 1.2 mmol of TCT–DMF was needed to complete the reaction (TLC monitoring for disappearance of the imine) in CH_2Cl_2 at room temperature.

Table 1 Reaction Conditions in the Synthesis of **3a**

Entry	Solvent	Temp (°C)	TCT–DMF (mmol)	Yield (%)
1	CH_2Cl_2	–15	1.5	89
2	DMF	–15	1.5	86
3	toluene	–15	1.5	58
4	THF	–15	1.5	45
5	CH_2Cl_2	0	1.5	85
6	CH_2Cl_2	r.t.	1.5	90
7	CH_2Cl_2	–63	1.5	59
8	CH_2Cl_2	r.t.	1.3	87
9	CH_2Cl_2	r.t.	1.2	90
10	CH_2Cl_2	r.t.	1.0	81

Based on the above results, 2-azetidinones **3a–k** were synthesized by treatment of 1.0 mmol of the corresponding Schiff bases, 1.2 mmol of acetic acid derivatives, and 1.2 mmol TCT–DMF adduct in the presence of triethylamine in dry CH_2Cl_2 (Scheme 2, Table 2). The β-Lactams **3a–i** were purified by recrystallization from EtOAc and β-lactams **3j**,**k** by short column chromatography. All products were characterized by spectroscopic data and elemental analyses. The indicated *cis* stereochemistry of the products was judged from the coupling constants of H-3 and H-4 of the β-lactam ring in their ^{1}H NMR spectra (J > 4.0 Hz). This new procedure for the synthesis of 2-azetidinones was also compared to the TCT method at –15 °C and room temperature.

The data in Table 2 confirm that the yields using TCT–DMF adducts are higher than using TCT on its own, and the yields are almost identical at –15 °C and at room temperature using TCT–DMF. However, in the case of TCT, the yields increased at lower temperature. In particular, this method is useful for the synthesis of β-lactams **3j**,**k** with electron-withdrawing groups at C-3. When chloroacetic acid and azidoacetic acid were used as starting materials, no β-lactam formation was observed using TCT at room temperature. 3-Azido β-lactam **3k** was obtained in 13% yield using TCT at –15 °C. But 3-chloro- and azido β-lactams **3j**,**k** were prepared in better yield with TCT–DMF adducts, although the yields increased at lower temperature.

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 carboxylic acid.[26c,d]

In conclusion, the procedure reported here for the first time is a simple, high-yielding, and clean TCT–DMF one-pot synthesis of β-lactams from imines and substituted acetic acid under very mild conditions using inexpensive and readily available starting materials. In this method, no corrosive or toxic materials such as $SOCl_2$ or Me_2SO_4 are used, and the purification procedure was simple because an aqueous workup removes the triazine byproduct. Moreover, this method is convenient for the synthesis of 2-azetidinones from acetic acid derivatives that are α-substituted with electon-withdrawing substituents.

General Procedure

DMF (0.30 mL, 4.0 mmol) was added to TCT (0.22 g, 1.2 mmol), and the resulting suspension was stirred at r.t. for 5 min. The requisite Schiff base (1.0 mmol) and substituted AcOH (1.2 mmol) in dry CH_2Cl_2 solution (7 mL) were added to the TCT–DMF suspension followed by addition of dry Et_3N (0.6 mL, 4.0 mmol). The reaction mixture was stirred at r.t. overnight. The solution was washed successively with sat. $NaHCO_3$ (7 mL) and brine (7 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to give the crude product. β-Lactams **3a–i** were purified by recrystallization from EtOAc and β-lactams **3j**,**k** by short-column chromatography (hexane–EtOAc = 9:1).

3-(4-Chlorophenoxy)-1-(4-ethoxyphenyl)-4-*p*-tolyl-azetidin-2-one (3a)

Yield 90%; mp 178–180 °C. IR (KBr): 1759 (CO, β-lactam) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (Me, t, 3 H, J = 7.0 Hz), 2.33 (Me, s, 3 H), 4.02 (OCH_2, q, 2 H, J = 7.0 Hz), 5.18 (H-4, d, 1 H,

Table 2 Comparison of the Synthesis of 2-Azetidinones **3a–k** with TCT and TCT–DMF Adduct

Product	R^1	R^2	R^3	Temp (°C)	Yield (%)	
					TCT	TCT–DMF adduct
3a	4-$EtOC_6H_4$	4-MeC_6H_4	4-ClC_6H_4O	–15	72	89
				r.t.	60	90
3b	4-$EtOC_6H_4$	3,4-di$MeOC_6H_3$	PhO	–15	77	82
				r.t.	80	86
3c	4-$MeOC_6H_4$	CH=CHPh	PhthN	–15	70	88
				r.t.	51	86
3d	4-$MeOC_6H_4$	4-MeC_6H_4	MeO	–15	74	87
				r.t.	69	91
3e	4-$EtOC_6H_4$	4-$O_2NC_6H_4$	2,4-diClC_6H_3O	–15	63	85
				r.t.	48	84
3f	4-$EtOC_6H_4$	4-ClC_6H_4	2-NaphthO	–15	83	90
				r.t.	71	91
3g	Bn	4-ClC_6H_4	PhO	–15	86	89
				r.t.	75	92
3h	Me	4-MeC_6H_4	PhthN	–15	53	67
				r.t.	39	62
3i	PhN=NC_6H_4	4-$O_2NC_6H_4$	2-NaphthO	–15	79	90
				r.t.	69	93
3j	4-$MeOC_6H_4$	Ph	Cl	–15	0	55
				r.t.	0	42
3k	Ph	Ph	N_3	–15	13	69
				r.t.	0	45

J = 5.1 Hz), 5.40 (H-3, d, 1 H, *J* = 5.1 Hz), 6.84–7.61 (ArH, m, 12 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2 (Me), 22.5 (Me), 59.6 (OCH_2), 61.6 (C-4), 63.0 (C-3), 117.4, 119.1, 122.9, 123.3, 124.0, 125.6, 128.9, 129.2, 141.8, 142.5, 152.7, 156.3 (arom. C), 165.9 (CO, β-lactam). Anal. Calcd for $C_{24}H_{22}ClNO_3$: C, 70.67; H, 5.44; N, 3.43. Found: C, 70.58; H, 5.53; N, 3.38.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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