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Synthesis of 1-Oxacephams *via* Improved Cyclization of N-Substituted-4-formyloxyazetidin-2-ones

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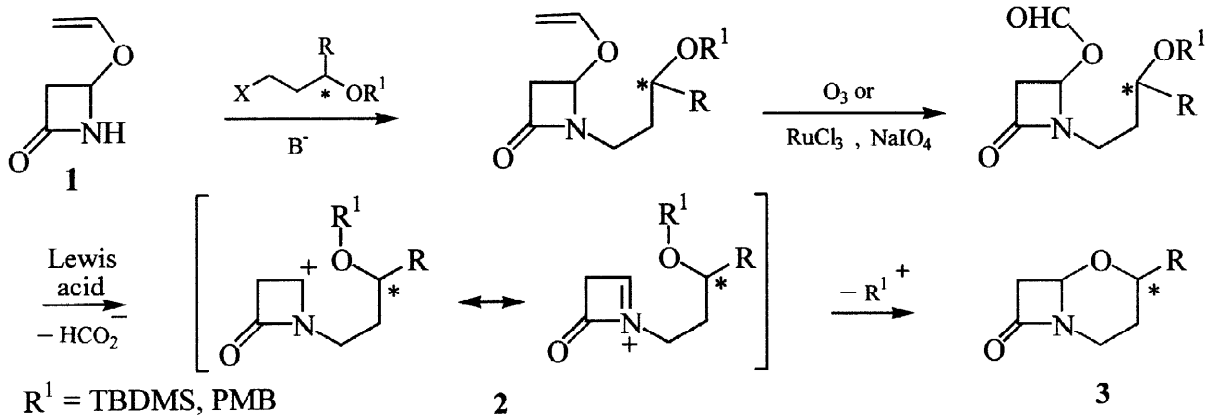
Abstract : The Lewis acid promoted cyclisation of N-substituted-4-formyloxyazetidin-2-ones, easily available from 4-vinyloxyazetidin-2-one is described. The efficiency of the ring closure reaction, to give 1-oxacephams, depends on the oxygen protected-activated group and the Lewis acid.

Keywords : azetidinones ; cyclisation ;

Recently we have reported a new strategy for stereocontrolled synthesis of 1-oxacephams from 4-benzyloxy and 4-vinyloxy-β-lactams [1,2]. The idea of the synthesis employing 4-vinyloxyazetidin-2-one **1** is shown in Scheme 1.



Scheme 1

The crucial step, Lewis acid promoted cyclisation, proceeds *via* mesomeric cation **2**. We have found that the enhancement of the nucleophilicity of the oxygen atom has a great impact upon the reaction yield [2]. Thus, the switch from t-butyldimethylsilyl ether **12b** to *p*-methoxybenzyl ether **13b** raised the yield of **18** from 15 to 52%.

Hoppe *et al.* [3] has reported the multistep synthesis of racemic 1-oxacephem **5** employing methodology related to ours (Scheme 2). Oxazolinoazetidinone **4**, having a *t*-butyl ether residue at the terminus of the nitrogen atom substituent, underwent cyclisation to give **5** in only 20 % yield. Those results prompted us to search for new *O*-substituents which would increase the efficiency of the cyclisation.

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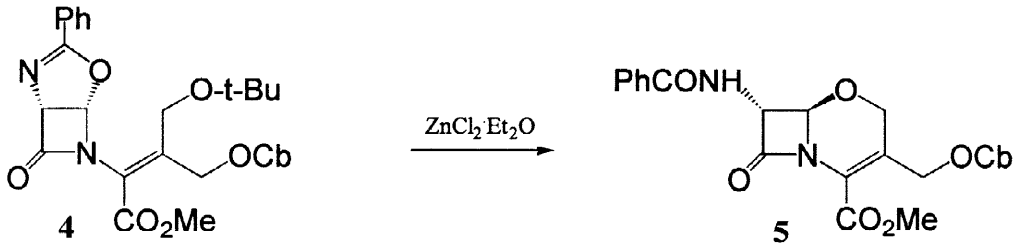
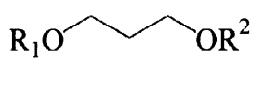
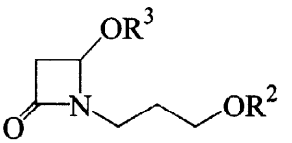


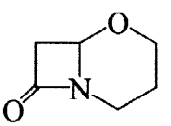
Scheme 2

We now present an optimised cyclisation of N-substituted-4-formyloxyazetidin-2-ones, leading to 1-oxacephams in high yield. In particular, the influence of the substituent at the oxygen atom and Lewis acid catalyst on the ring closure reaction is discussed.

For the present study we selected compounds **6a-11a**, easily available from 1,3-propanediol and commercially available protecting agents.[1] The highly electron rich 3,5-dimethyl-2,4,6-trimethoxybenzyl chloride was prepared according to three step procedure from 1,3,5-trimethoxybenzene [4,5]. Triflation of **6a-11a** under standard conditions Tf_2O/ 2,6-lutidine /CH_2Cl_2 gave the respective triflates **6b-11b**. The synthesis of N-alkylated β-lactams **12a-17a** was accomplished by applying the procedure described previously [2].







18

6a : R^1 = H, R^2 = TBDMS,
6b : R^1 = Tf, R^2 = TBDMS,
7a : R^1 = H, R^2 = PMB,
7b : R^1 = Tf, R^2 = PMB,
8a : R^1 = H, R^2 = Bn,
8b : R^1 = Tf, R^2 = Bn,
9a : R^1 = H, R^2 = Tr,
9b : R^1 = Tf, R^2 = Tr,
10a : R^1 = H, R^2 = PMeB,
10b : R^1 = Tf, R^2 = PMeB,
11a : R^1 = H, R^2 = DMTMB,
11b : R^1 = Tf, R^2 = DMTMB,

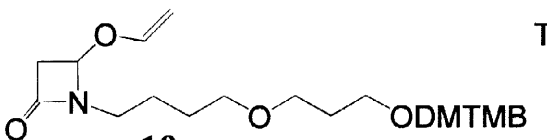
12a : R^2 = TBDMS, R^3 = vinyl
12b : R^2 = TBDMS, R^3 = formyl
13a : R^2 = PMB, R^3 = vinyl
13b : R^2 = PMB, R^3 = formyl
14a : R^2 = Bn, R^3 = vinyl
14b : R^2 = Bn, R^3 = formyl
15a : R^2 = Tr, R^3 = vinyl
15b : R^2 = Tr, R^3 = formyl
16a : R^2 = PMeB, R^3 = vinyl
16b : R^2 = PMeB, R^3 = formyl
17a : R^2 = DMTMB, R^3 = vinyl
17b : R^2 = DMTMB, R^3 = formyl

TBDMS = *t*-butyldimethylsilyl, PMB = *p*-methoxybenzyl, Tr = triphenylmethyl,
PMeB = pentamethylbenzyl, DMTMB = 3,5-dimethyl-2,4,6-trimethoxybenzyl

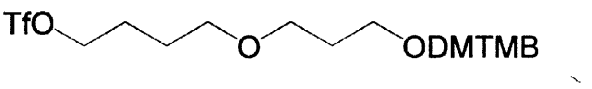
Thus, treatment of a mixture of **1** (1 equiv.) and Bu_4NHSO_4 (1.05 equiv.) in THF at -78°C with butyllithium (2.1 equiv.) followed by the addition of crude **6b-11b** gave desired **12a-17a** in 50-80% yield. N-Alkylation of **1** can also be performed in the presence of a THF soluble tetrabutylammonium salt, such as tosylate or tetrafluoroborate. When N-alkylation was carried out with tetrabutylammonium bromide, or without any ammonium salt, no alkylation product was formed and **1** underwent decomposition. It seems that the N-lithiated β-lactam is stable only at a low temperature, and in order to perform alkylations successfully, the lithium cation

1. Compounds **6a** and **9a** were obtained by a selective protection of 1,3-propanediol (4 equiv.) dissolved in pyridine and treated with TBDMS chloride (1 equiv.) or TrCl (1 equiv.), respectively. Compounds **7a**, **8a**, **10a** and **11a** were obtained from 1,3-propanediol (4 equiv.) by a treatment with sodium hydride (4 equiv.) in DMF followed by the addition of benzyl chloride (1 equiv.). All new compounds gave satisfactory spectroscopic and analytical data.

must be exchanged for an ammonium one. Tetrabutylammonium bromide is insoluble in THF, so such an exchange does not take place. Tetrabutylammonium hydrogen sulphate is also insoluble in THF, but probably reacts with butyllithium to form a soluble lithium-ammonium salt. Slow dissolution of suspended Bu_4NHSO_4 during the reaction provides an evidence for such a process. Products of N-alkylation **12a-17a** were sometimes accompanied by a small amount of a more polar compound, which in one case (reaction of **1** with **11b**) was isolated and characterised as **19**. Probably, triflate **11b** dissolved in freshly distilled, warm THF opens the tetrahydrofuran ring to form **20**, which reacts with **1** to give **19**. Such cleavage of ethers by alkyl triflate [6] or triflic anhydride [7] is well known. The formation of undesired products derived from THF could be avoided by dissolving triflates **6b-11b** in small amount of cold THF or toluene just before addition to the solution of the N-anion.



19



20

Ozonolysis of β-lactams **12a-17a** at -78° C in CH_2Cl_2, followed by reductive workup with dimethyl sulfide, gave respective formates **12b-17b**. High yields, and reproducibility of ozonolysis was achieved by the inclusion of a small amount of ozonizable dye (Sudan red 7B) as an internal standard, which indicated the reaction end point [8]. 4-Formyloxyazetidin-2-ones **12b-17b** were subjected to cyclisation in the presence of Lewis acid to afford 1-oxacepham **18**[2] (Table 1). Compounds **13b**, **16b** and **17b** treated with a catalytic amount of $BF_3{\cdot}Et_2O$ (20% molar) gave **18** in 51, 48 and 50%, respectively. The application of the equimolar amount of $BF_3{\cdot}Et_2O$ (Entries 2, 6, 12, 15 and 18) resulted in the shortening of the reaction time and provided a slightly higher yield of **18**. Tin (II) chloride activated by TMS chloride, invented by Mukaiyama [10,11] is a mild Lewis acid, has been shown to be a very effective catalyst for carbon-carbon bond forming reactions such as the aldol reaction of acetals or aldehydes with silyl enol ethers and the Michael reaction of α, β-unsaturated ketones with silyl enol ethers. We found, that Mukaiyama's catalytst system can also be successfully applied to nucleophilic displacement at C-4 of the azetidin-2-one ring.[3] Thus, β-lactams **12b** and **13b** treated with tin (II) chloride (0.2 equiv.) in combination with TMS chloride (1.0 equiv.) gave **18** in 16 and 51% yield (Entries 3 and 7). Use of the equimolar amount of tin (II) chloride and TMS chloride (4.0 equiv.) (Entries 4, 8, 13, 16 and 19) resulted in a further increase in yield of **18** up to 80% (Entries 8).

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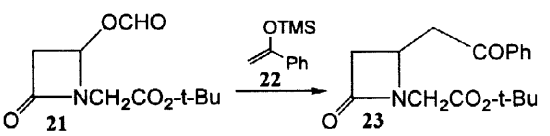
2. All reactions were run using a 0.5 mmol scale of β-lactams **12b-17b**, in dry CH_2Cl_2 (6 mL) at room temperature, except entries 1and 2. General procedure for the preparation of **18** : To a stirred solution of β-lactam (**12b-17b**) was added $BF_3{\cdot}Et_2O$ (0.1 equiv.) in one portion. Stirring was continued until TLC showed disappearance of substrate. The reaction was quenched by the addition of 2 M solution of Na_2CO_3 (2 ml), the organic phase was separated, dried and evaporated. Crude **18** was purified on silica gel. The cyclization reaction run with equimolar amount of $BF_3{\cdot}Et_2O$ (Entries 2, 6, 10, 12, 15, and 18) or $SnCl_2$ activated by a TMS-Cl (Entries 3, 4, 7, 8, 11, 13, 16, and 19) was performed with the addition of molecular sieves A-4 (200 mg).

3. Preliminary experiments show the advantage of the Mukaiyama's catalyst system over the commonly used Lewis acids for promoting the nucleophilic substitution at C-4 of azetidin-2-one ring. For example, condensation of **21** with **22** in the presence of $SnCl_2$ (1 equiv.) and TMS-Cl (4 equiv.) in CH_2Cl_2, at r. t., for 1 h, afforded compound **23** in 83% yield, in comparison to only 40% yield when TMS triflate was applied [1].



Surprisingly, *t*-butyldimethylsilyl ether **12b**, which required an elevated temperature and relatively long cyclization time with $BF_3{\cdot}Et_2O$, (Entries 1 and 2) reacted in the presence of Mukaiyama's Lewis acid instantly at room temperature to give **18** in an acceptable 57% yield. Benzyl ether **14b** was shown to be unreactive in all reaction conditions (Entries 5, 6 and 7).

	Entry	Lewis acid	Reaction time [min]	Yield of 18 [%]
12b	1	$BF_3{\cdot}Et_2O$ 0.2 equiv.	90, reflux	15
	2	$BF_3{\cdot}Et_2O$ 1.0 equiv.	30, reflux	18
	3	$SnCl_2$ 0.2 equiv. TMS-Cl 1 equiv.	10	16
	4	$SnCl_2$ 1.0 equiv. TMS-Cl 4 equiv.	5	57
13b	5	$BF_3{\cdot}Et_2O$ 0.2 equiv.	20	51
	6	$BF_3{\cdot}Et_2O$ 1.0 equiv.	10	63
	7	$SnCl_2$ 0.2 equiv. TMS-Cl 1 equiv.	70	51
	8	$SnCl_2$ 1.0 equiv. TMS-Cl 4 equiv.	10	80
14b	9	$BF_3{\cdot}Et_2O$ 0.2 equiv.	90	0
	10	$BF_3{\cdot}Et_2O$ 1.0 equiv.	90	0
	11	$SnCl_2$ 1.0 equiv. TMS-Cl 4 equiv.	90	0
15b	12	$BF_3{\cdot}Et_2O$ 1.0 equiv.	50	44
	13	$SnCl_2$ 1.0 equiv. TMS-Cl 4 equiv.	50	43
16b	14	$BF_3{\cdot}Et_2O$ 0.2 equiv.	60	48
	15	$BF_3{\cdot}Et_2O$ 1.0 equiv.	10	53
	16	$SnCl_2$ 1.0 equiv. TMS-Cl 4 equiv.	15	55
17b	17	$BF_3{\cdot}Et_2O$ 0.2 equiv.	15	50
	18	$BF_3{\cdot}Et_2O$ 1.0 equiv.	10	55
	19	$SnCl_2$ 1.0 equiv. TMS-Cl 4 equiv.	30	58

Table 1

In conclusion, a simple and efficient procedure for the synthesis of the 1-oxacepham skeleton from readily available 4-vinyloxyazetidin-2-one was elaborated. It was shown that the crucial step of the methodology, involving a ring closure reaction can be achieved by the use of an activator at the oxygen atom which forms a stable cation and enhances nucleophilicity of the oxygen atom in β-lactam side chain. Many popular protective groups such as *t*-butyldimethylsilyl, *p*-methoxybenzyl, 3,5-dimethyl-2,4,6-trimethoxybenzyl and trityl ethers are suitable for this purpose. Mukaiyama's mild Lewis acid, a combination of tin (II) chloride and TMS chloride, was found to be a very effective catalyst of the cyclization.

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