



Synthesis of N-unsubstituted β -lactams from N-alkoxyphenyl- β -lactams with cobalt(III) fluoride

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ABSTRACT

Mild and efficient oxidative N-dearylation of N-alkoxyphenyl- β -lactams with cobalt(III) fluoride proceeded in good to excellent yields to afford the corresponding N-unsubstituted β -lactams. Optimization of the solvent, molar ratio of reagents, time, and temperature are described.

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2-Azetidinones (β -lactams) are of interest to synthetic and medicinal chemists, as they are biologically significant.¹ In addition, 2-azetidinones show many important non-antibiotic biological activities.² They are also being used increasingly as valuable starting materials to develop new synthetic methodologies.³

N-unsubstituted β -lactams have been used as intermediates in the synthesis of β -lactam antibiotics⁴ such as nocardicins and monobactams, and the glutamine synthase inhibitor, tabtoxin.⁵ The importance of N-unsubstituted β -lactams for the semisynthesis of the novel anticancer agents Taxol and Taxotere is also well documented.⁶ N-unsubstituted β -lactams have been prepared by several methods,⁷ but N-deprotection of N-alkoxyphenyl- β -lactams is an established method in β -lactam chemistry (Scheme 1).⁸ Ceric ammonium nitrate (CAN) is the most frequently used reagent for this purpose.⁹

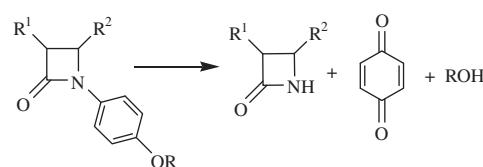
Due to the high molecular weight of CAN (548) and the use of three equivalents per mole of substrate, it has some disadvantages especially when the reaction is run on a large scale.¹⁰

Cobalt(III) fluoride (CoF_3) has been used for oxidative couplings to give biaryl.¹¹ Nakata and co-workers reported oxidative demethylation of hydroquinone dimethyl ethers to quinones with CoF_3 .¹² According to the standard reduction potential table,¹³ Co(III) has a larger value than that of Ce(IV). Furthermore, the hydrogen fluoride liberated, as the reaction proceeds, is a weak acid and hence a milder medium would be anticipated throughout the reaction.¹² The toxicity of CAN and CoF_3 is almost comparable.

We report herein the first example of oxidative N-dearylation of β -lactams using CoF_3 under mild conditions.

2-Azetidinone **1a** was selected as a model compound. According to the procedure for N-dearylation of β -lactams with CAN, 3 equiv of CoF_3 were added, at room temperature, to 2-azetidinone **1a** in 1,4-dioxane. Next, water was added and the reaction mixture was stirred vigorously for 2 h at room temperature. The corresponding N-unsubstituted 2-azetidinone **2a** was obtained in 64% yield after purification by recrystallization from diethyl ether. To find the optimum reaction conditions, we firstly evaluated the influence of the solvent and reaction time using 3 equiv of CoF_3 at room temperature (Table 1). As shown in Table 1, acetonitrile proved to be the best solvent and 1 h was required to complete the reaction.

The effect of the oxidant/substrate molar ratio and different temperatures on this oxidation was next studied in $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (3:1) for 1 h (Table 2). The solubility of several substrates was not good at 0 °C and the best results were obtained when the reactions were performed at room temperature. It was found that 3.5 equiv of CoF_3 were needed for the complete consumption of **1a**.



Scheme 1.

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Table 1
Solvent and reaction time optimization

Entry	Solvent	Time (h)	Yield (%)
1	1,4-Dioxane-H ₂ O (3:1)	0.5	51
		1	66
		2	64
2	DMF-H ₂ O (3:1)	0.5	43
		1	58
		2	61
3	CH ₃ CN-H ₂ O (3:1)	0.5	60
		1	78
		2	75
4	THF-H ₂ O (3:1)	0.5	47
		1	51
		2	55
5	CH ₂ Cl ₂ -H ₂ O (19:1)	0.5	— ^a
		1	— ^a
		2	0 ^b

^a Not determined.^b No product was observed.

Table 2
Moles of CoF₃ and temperature optimization in the synthesis of **2a**

Entry	Temp (°C)	CoF ₃ (mmol)	Yield (%)
1	0	2	20
2	0	2.5	22
3	0	3	35
4	0	3.5	43
5	0	4	53
6	rt	2	40
7	rt	2.5	59
8	rt	3	78
9	rt	3.5	86
10	rt	4	85

Encouraged by this success, we next investigated the oxidative N-dearylation of several N-alkoxyphenyl-β-lactams **1a–k** to obtain NH-β-lactams **2a–k**. In all the reactions, 3.5 equiv of CoF₃ were used in aqueous acetonitrile at room temperature for 1 h, and the yields were compared with those obtained using CAN (Table 3).¹⁴

Although a larger quantity of the reagent was required in the case of CoF₃, the isolated yields of the NH-β-lactams **2a–j** (entries 1–10) were comparable to those obtained with CAN. In the case of 3-chloro-2-azetidinone **1k** (entry 11), the oxidative N-dearylation to **2k** using CAN was superior. All NH-β-lactams **2a–k** were characterized from spectral data and by elemental analyses.¹⁵

Table 3
N-dearylation of 2-azetidinones **1a–k**

Entry	Substrate	Product	Yield (%)	
			CoF ₃	CAN ^a
1	<img alt="Chemical structure of 2-azetidinone 1a: PhO-C(=O)-N(OEt)-C1=C(C=C1)C(=O)N2C=C(C=C2)C(=O)N3C=C(C=C3)C(=O)N4C=C(C=C4)C(=O)N5C=C(C=C5)C(=O)N6C=C(C=C6)C(=O)N7C=C(C=C7)C(=O)N8C=C(C=C8)C(=O)N9C=C(C=C9)C(=O)N10C=C(C=C10)C(=O)N11C=C(C=C11)C(=O)N12C=C(C=C12)C(=O)N13C=C(C=C13)C(=O)N14C=C(C=C14)C(=O)N15C=C(C=C15)C(=O)N16C=C(C=C16)C(=O)N17C=C(C=C17)C(=O)N18C=C(C=C18)C(=O)N19C=C(C=C19)C(=O)N20C=C(C=C20)C(=O)N21C=C(C=C21)C(=O)N22C=C(C=C22)C(=O)N23C=C(C=C23)C(=O)N24C=C(C=C24)C(=O)N25C=C(C=C25)C(=O)N26C=C(C=C26)C(=O)N27C=C(C=C27)C(=O)N28C=C(C=C28)C(=O)N29C=C(C=C29)C(=O)N30C=C(C=C30)C(=O)N31C=C(C=C31)C(=O)N32C=C(C=C32)C(=O)N33C=C(C=C33)C(=O)N34C=C(C=C34)C(=O)N35C=C(C=C35)C(=O)N36C=C(C=C36)C(=O)N37C=C(C=C37)C(=O)N38C=C(C=C38)C(=O)N39C=C(C=C39)C(=O)N40C=C(C=C40)C(=O)N41C=C(C=C41)C(=O)N42C=C(C=C42)C(=O)N43C=C(C=C43)C(=O)N44C=C(C=C44)C(=O)N45C=C(C=C45)C(=O)N46C=C(C=C46)C(=O)N47C=C(C=C47)C(=O)N48C=C(C=C48)C(=O)N49C=C(C=C49)C(=O)N50C=C(C=C50)C(=O)N51C=C(C=C51)C(=O)N52C=C(C=C52)C(=O)N53C=C(C=C53)C(=O)N54C=C(C=C54)C(=O)N55C=C(C=C55)C(=O)N56C=C(C=C56)C(=O)N57C=C(C=C57)C(=O)N58C=C(C=C58)C(=O)N59C=C(C=C59)C(=O)N60C=C(C=C59)C(=O)N61C=C(C=C59)C(=O)N62C=C(C=C59)C(=O)N63C=C(C=C59)C(=O)N64C=C(C=C59)C(=O)N65C=C(C=C59)C(=O)N66C=C(C=C59)C(=O)N67C=C(C=C59)C(=O)N68C=C(C=C59)C(=O)N69C=C(C=C59)C(=O)N70C=C(C=C59)C(=O)N71C=C(C=C59)C(=O)N72C=C(C=C59)C(=O)N73C=C(C=C59)C(=O)N74C=C(C=C59)C(=O)N75C=C(C=C59)C(=O)N76C=C(C=C59)C(=O)N77C=C(C=C59)C(=O)N78C=C(C=C59)C(=O)N79C=C(C=C59)C(=O)N80C=C(C=C59)C(=O)N81C=C(C=C59)C(=O)N82C=C(C=C59)C(=O)N83C=C(C=C59)C(=O)N84C=C(C=C59)C(=O)N85C=C(C=C59)C(=O)N86C=C(C=C59)C(=O)N87C=C(C=C59)C(=O)N88C=C(C=C59)C(=O)N89C=C(C=C59)C(=O)N90C=C(C=C59)C(=O)N91C=C(C=C59)C(=O)N92C=C(C=C59)C(=O)N93C=C(C=C59)C(=O)N94C=C(C=C59)C(=O)N95C=C(C=C59)C(=O)N96C=C(C=C59)C(=O)N97C=C(C=C59)C(=O)N98C=C(C=C59)C(=O)N99C=C(C=C59)C(=O)N100C=C(C=C59)C(=O)N101C=C(C=C59)C(=O)N102C=C(C=C59)C(=O)N103C=C(C=C59)C(=O)N104C=C(C=C59)C(=O)N105C=C(C=C59)C(=O)N106C=C(C=C59)C(=O)N107C=C(C=C59)C(=O)N108C=C(C=C59)C(=O)N109C=C(C=C59)C(=O)N110C=C(C=C59)C(=O)N111C=C(C=C59)C(=O)N112C=C(C=C59)C(=O)N113C=C(C=C59)C(=O)N114C=C(C=C59)C(=O)N115C=C(C=C59)C(=O)N116C=C(C=C59)C(=O)N117C=C(C=C59)C(=O)N118C=C(C=C59)C(=O)N119C=C(C=C59)C(=O)N120C=C(C=C59)C(=O)N121C=C(C=C59)C(=O)N122C=C(C=C59)C(=O)N123C=C(C=C59)C(=O)N124C=C(C=C59)C(=O)N125C=C(C=C59)C(=O)N126C=C(C=C59)C(=O)N127C=C(C=C59)C(=O)N128C=C(C=C59)C(=O)N129C=C(C=C59)C(=O)N130C=C(C=C59)C(=O)N131C=C(C=C59)C(=O)N132C=C(C=C59)C(=O)N133C=C(C=C59)C(=O)N134C=C(C=C59)C(=O)N135C=C(C=C59)C(=O)N136C=C(C=C59)C(=O)N137C=C(C=C59)C(=O)N138C=C(C=C59)C(=O)N139C=C(C=C59)C(=O)N140C=C(C=C59)C(=O)N141C=C(C=C59)C(=O)N142C=C(C=C59)C(=O)N143C=C(C=C59)C(=O)N144C=C(C=C59)C(=O)N145C=C(C=C59)C(=O)N146C=C(C=C59)C(=O)N147C=C(C=C59)C(=O)N148C=C(C=C59)C(=O)N149C=C(C=C59)C(=O)N150C=C(C=C59)C(=O)N151C=C(C=C59)C(=O)N152C=C(C=C59)C(=O)N153C=C(C=C59)C(=O)N154C=C(C=C59)C(=O)N155C=C(C=C59)C(=O)N156C=C(C=C59)C(=O)N157C=C(C=C59)C(=O)N158C=C(C=C59)C(=O)N159C=C(C=C59)C(=O)N160C=C(C=C59)C(=O)N161C=C(C=C59)C(=O)N162C=C(C=C59)C(=O)N163C=C(C=C59)C(=O)N164C=C(C=C59)C(=O)N165C=C(C=C59)C(=O)N166C=C(C=C59)C(=O)N167C=C(C=C59)C(=O)N168C=C(C=C59)C(=O)N169C=C(C=C59)C(=O)N170C=C(C=C59)C(=O)N171C=C(C=C59)C(=O)N172C=C(C=C59)C(=O)N173C=C(C=C59)C(=O)N174C=C(C=C59)C(=O)N175C=C(C=C59)C(=O)N176C=C(C=C59)C(=O)N177C=C(C=C59)C(=O)N178C=C(C=C59)C(=O)N179C=C(C=C59)C(=O)N180C=C(C=C59)C(=O)N181C=C(C=C59)C(=O)N182C=C(C=C59)C(=O)N183C=C(C=C59)C(=O)N184C=C(C=C59)C(=O)N185C=C(C=C59)C(=O)N186C=C(C=C59)C(=O)N187C=C(C=C59)C(=O)N188C=C(C=C59)C(=O)N189C=C(C=C59)C(=O)N190C=C(C=C59)C(=O)N191C=C(C=C59)C(=O)N192C=C(C=C59)C(=O)N193C=C(C=C59)C(=O)N194C=C(C=C59)C(=O)N195C=C(C=C59)C(=O)N196C=C(C=C59)C(=O)N197C=C(C=C59)C(=O)N198C=C(C=C59)C(=O)N199C=C(C=C59)C(=O)N200C=C(C=C59)C(=O)N201C=C(C=C59)C(=O)N202C=C(C=C59)C(=O)N203C=C(C=C59)C(=O)N204C=C(C=C59)C(=O)N205C=C(C=C59)C(=O)N206C=C(C=C59)C(=O)N207C=C(C=C59)C(=O)N208C=C(C=C59)C(=O)N209C=C(C=C59)C(=O)N210C=C(C=C59)C(=O)N211C=C(C=C59)C(=O)N212C=C(C=C59)C(=O)N213C=C(C=C59)C(=O)N214C=C(C=C59)C(=O)N215C=C(C=C59)C(=O)N216C=C(C=C59)C(=O)N217C=C(C=C59)C(=O)N218C=C(C=C59)C(=O)N219C=C(C=C59)C(=O)N220C=C(C=C59)C(=O)N221C=C(C=C59)C(=O)N222C=C(C=C59)C(=O)N223C=C(C=C59)C(=O)N224C=C(C=C59)C(=O)N225C=C(C=C59)C(=O)N226C=C(C=C59)C(=O)N227C=C(C=C59)C(=O)N228C=C(C=C59)C(=O)N229C=C(C=C59)C(=O)N230C=C(C=C59)C(=O)N231C=C(C=C59)C(=O)N232C=C(C=C59)C(=O)N233C=C(C=C59)C(=O)N234C=C(C=C59)C(=O)N235C=C(C=C59)C(=O)N236C=C(C=C59)C(=O)N237C=C(C=C59)C(=O)N238C=C(C=C59)C(=O)N239C=C(C=C59)C(=O)N240C=C(C=C59)C(=O)N241C=C(C=C59)C(=O)N242C=C(C=C59)C(=O)N243C=C(C=C59)C(=O)N244C=C(C=C59)C(=O)N245C=C(C=C59)C(=O)N246C=C(C=C59)C(=O)N247C=C(C=C59)C(=O)N248C=C(C=C59)C(=O)N249C=C(C=C59)C(=O)N250C=C(C=C59)C(=O)N251C=C(C=C59)C(=O)N252C=C(C=C59)C(=O)N253C=C(C=C59)C(=O)N254C=C(C=C59)C(=O)N255C=C(C=C59)C(=O)N256C=C(C=C59)C(=O)N257C=C(C=C59)C(=O)N258C=C(C=C59)C(=O)N259C=C(C=C59)C(=O)N260C=C(C=C59)C(=O)N261C=C(C=C59)C(=O)N262C=C(C=C59)C(=O)N263C=C(C=C59)C(=O)N264C=C(C=C59)C(=O)N265C=C(C=C59)C(=O)N266C=C(C=C59)C(=O)N267C=C(C=C59)C(=O)N268C=C(C=C59)C(=O)N269C=C(C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9)C(=O)N533C=C(C=C59)C(=O)N534C=C(C=C59)C(=O)N535C=C(C=C59)C(=O)N536C=C(C=C59)C(=O)N537C=C(C=C59)C(=O)N538C=C(C=C59)C(=O)N539C=C(C=C59)C(=O)N540C=C(C=C59)C(=O)N541C=C(C=C59)C(=O)N542C=C(C=C59)C(=O)N543C=C(C=C59)C(=O)N544C=C(C=C59)C(=O)N545C=C(C=C59)C(=O)N546C=C(C=C59)C(=O)N547C=C(C=C59)C(=O)N548C=C(C=C59)C(=O)N549C=C(C=C59)C(=O)N550C			

Table 3 (continued)

Entry	Substrate	Product	Yield (%)	
			CoF_3	CAN ^a
5			85	87
6			80	74
7			76	79
8			77	80
9			82	76
10			80	81
11			71	88

^a CAN (3 equiv) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (3:1) for 1 h.

In conclusion, the use of CoF_3 for the oxidative N-dearylation of *N*-alkoxyphenyl- β -lactams under mild conditions has been reported. The method is simple and versatile. The solvents, molar ratio of reagent, time, and temperature have been optimized.

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References and notes

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- General procedure:** To a solution of 2-azetidinone **1a–k** (1.0 mmol) in 16 mL of $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (3:1), CoF_3 (0.41 g, 3.5 mmol) was added at room temperature. The reaction mixture was stirred for 1 h, then water (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layer washed with 10% aqueous (NaHCO_3) (20 mL). The aqueous layer of NaHCO_3 was extracted again with EtOAc (10 mL) and all the organic layers were combined and washed successively with 10% NaHSO_3 (2 × 10 mL) and brine (20 mL), and then dried over Na_2SO_4 . After filtration and evaporation of the solvent in vacuo, the crude product was purified by recrystallization from Et_2O .
- 4-(4-Chlorophenyl)-3-(5-norbornene-2,3-dicarboxyloylimido)-azetidin-2-one (2j):** White solid. Yield: (80%), mp: 225–227 °C IR (KBr) cm^{-1} : 1743, 1770 (CO, imide), 1787 (CO, β -lactam), 3424 (NH); ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ 1.46, 1.64 (H-11, d, 2H, J = 8.5), 3.22 (H-5, d, 1H, J = 7.7), 3.30 (H-10, d, 1H, J = 7.7), 3.42–3.51 (H-6 and H-9, m, 2H), 4.71 (H-4, dd, 1H, J = 2.3, 3.5), 5.12 (H-3, d, 1H, J = 2.3), 6.06–6.21 (H-7 and H-8, m, 2H), 6.53–7.13 (ArH, m, 4H), 8.94 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, $\text{DMSO}-d_6$) δ 40.0, 40.9 (C-5, C-10), 43.7, 44.4 (C-6, C-9), 50.6 (C-11), 58.1 (C-4), 63.5 (C-3), 117.3–151.1 (C=C, aromatic carbons), 163.8 (CO, β -lactam), 177.9, 178.4 (CO, imide); GC-MS m/z = 344 [M^+ , ^{37}Cl], 342 [M^+ , ^{35}Cl]. Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 62.91; H, 4.55; N, 8.03. **3-Chloro-4-phenylazetidin-2-one (2k):** White solid. Yield: (71%), mp: 71–73 °C IR (KBr) cm^{-1} : 1767 (CO, β -lactam), 3417 (NH); ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ 4.33 (H-4, d, 1H, J = 4.7), 4.87 (H-3, dd, 1H, J = 2.2, 4.7), 6.63–7.09 (ArH, m, 5H), 9.03 (NH, br s, 1H); ^{13}C NMR (62.9 MHz, $\text{DMSO}-d_6$) δ 58.6 (C-4), 69.4 (C-3), 111.7–150.3 (aromatic carbons), 161.4 (CO, β -lactam); GC-MS m/z = 183 [M^+ , ^{37}Cl], 181 [M^+ , ^{35}Cl]. Anal. Calcd for $\text{C}_9\text{H}_8\text{ClNO}$: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.60; H, 4.62; N, 7.65.
- Characterization data for all compounds have been reported previously, except for **2j–k**. (a) Jarrahpour, A.; Motamedifar, M.; Zarei, M.; Mimouni, M. *Phosphorus Sulfur Silicon* **2010**, *185*, 287–297; (b) Jarrahpour, A.; Zarei, M. *Tetrahedron* **2009**, *65*, 2927–2934; (c) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2007**, *48*, 8712–8714; (d) Jarrahpour, A.; Zarei, M. *Molecules* **2006**, *11*, 49–58; (e) Jarrahpour, A.; Zarei, M. *Tetrahedron Lett.* **2009**, *50*, 1568–1570; (f) Jarrahpour, A.; Zarei, M. *Synlett* **2008**, 381; (g) Jarrahpour, A.; Zarei, M. *Synth. Commun.* **2008**, *38*, 1837–1845; (h) Jarrahpour, A.; Zarei, M. *Phosphorus Sulfur Silicon* **2009**, *184*, 1738–1749.