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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.

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 antibiotics[4] 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]

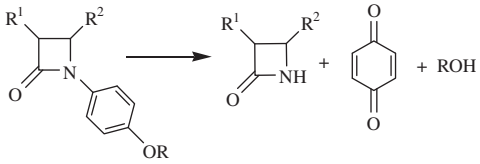
Due to the high molecular weight of CAN (548) and the use of three equivalents per mole of substrate, it has some disadvantages especially when the reaction is run on a large scale.[10]

Cobalt(III) fluoride (CoF_3) has been used for oxidative couplings to give biaryls.[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 CH_3CN–H_2O (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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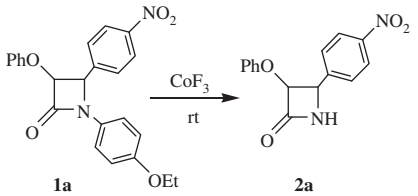
Table 1
Solvent and reaction time optimization



1a **2a**

Entry	Solvent	Time (h)	Yield (%)
1	1,4-Dioxane–H_2O (3:1)	0.5	51
		1	66
		2	64
2	DMF–H_2O (3:1)	0.5	43
		1	58
		2	61
3	CH_3CN–H_2O (3:1)	0.5	60
		1	78
		2	75
4	THF–H_2O (3:1)	0.5	47
		1	51
		2	55
5	CH_2Cl_2–H_2O (19:1)	0.5	—[a]
		1	—[a]
		2	0[b]

[a] Not determined.
[b] No product was observed.

Table 2
Moles of CoF_3 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 CoF_3 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 CoF_3, 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 analyzes.[15]

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

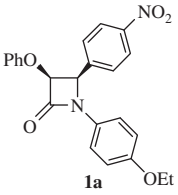
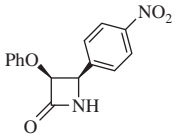
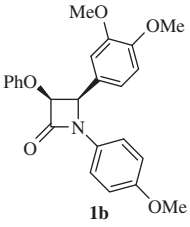
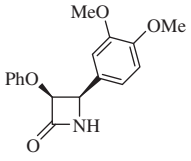
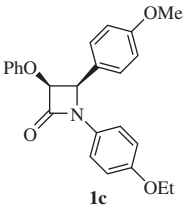
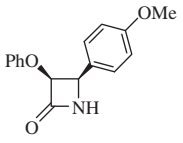
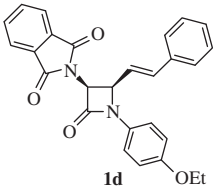
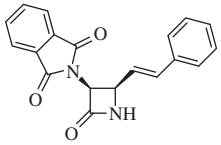
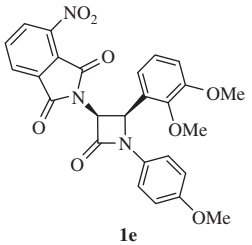
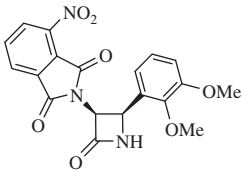
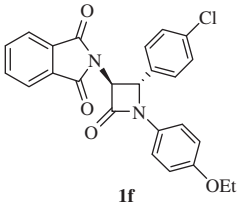
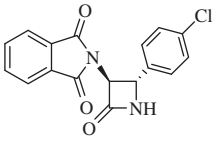
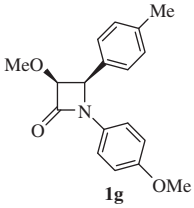
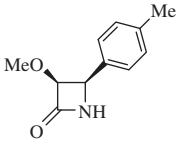
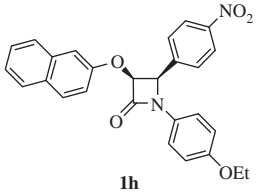
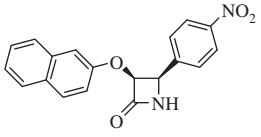
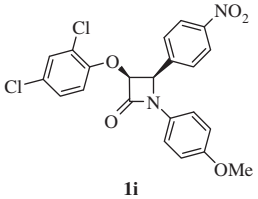
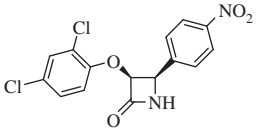
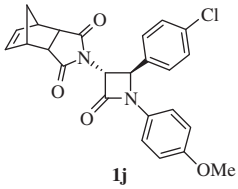
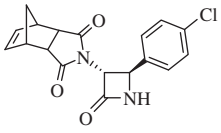
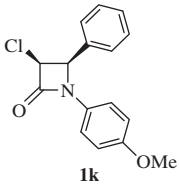
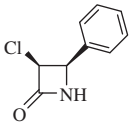
Entry	Substrate	Product	Yield (%)	
			CoF_3	CAN[a]
1	 **1a**	 **2a**	83	81
2	 **1b**	 **2b**	80	83
3	 **1c**	 **2c**	81	79
4	 **1d**	 **2d**	78	83

Table 3 (*continued*)

Entry	Substrate	Product	Yield (%)	
			CoF_3	CAN[a]
5	 **1e**	 **2e**	85	87
6	 **1f**	 **2f**	80	74
7	 **1g**	 **2g**	76	79
8	 **1h**	 **2h**	77	80
9	 **1i**	 **2i**	82	76
10	 **1j**	 **2j**	80	81
11	 **1k**	 **2k**	71	88

[a] CAN (3 equiv) in CH_3CN/H_2O (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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14. *General procedure*: To a solution of 2-azetidinone **1a**–**k** (1.0 mmol) in 16 mL of CH_3CN–H_2O (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, 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, 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 $C_{18}H_{15}ClN_2O_3$: 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, 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, 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 C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.60; H, 4.62; N, 7.65.
15. 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.