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INDIUM-MEDIATED FACILE SYNTHESIS OF 3-UNSUBSTITUTED FERROCENYL β-LACTAMS

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Abstract - A simple synthesis of some 3-unsubstituted ferrocenyl β-lactams was achieved through indium mediated reaction of imines with ethyl bromoacetate

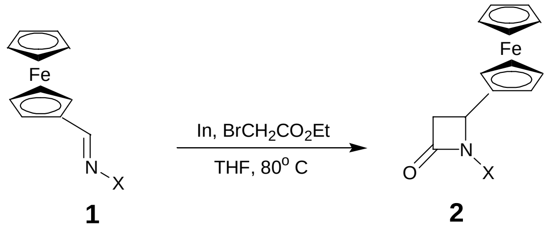
Synthesis of diversely substituted β-lactams and their use for the synthesis of several natural and non-natural products is an increasingly active area. Because of the recent developments using β-lactams as synthons for several biologically active compounds, research on this topic has gained tremendous attention in spite of the clinical resistance of some organisms to the β-lactam antibiotics.[1] Monocyclic β-lactams with diverse substituents at N_1, C_3 and C_4 have been of considerable interest to the synthetic community in the past few decades. Also, various methods have been developed for the synthesis of *N*-unsubstituted, C_3-unsubstituted and C_4-unsubstituted β-lactams.[2]

Ferrocene containing β-lactams are unique compounds because they are ideal candidates for drug design due to their low toxicity and their ability to modify the three dimensional profile of the β-lactam by bringing the metal atom in close proximity to the ring.[3] Synthesis of 3,4-disubstituted β-lactam with ferrocene moiety at C_4 has been reported and their biological activity has also been investigated.[4] Synthetic antibiotics containing ferrocene exhibit high antibiotic activity and some of them are potent β-lactamase inhibitors.[5]

In continuation of our studies on metal-induced reactions[6] and β-lactam chemistry,[7] we[8] have demonstrated a facile synthesis of 3-unsubstituted β-lactams by indium-mediated reaction of imines with bromo ester. Our interest on β-lactam derivatives has prompted us to investigate the indium-mediated reaction of readily available ferrocenyl imines with bromo ester. This study has resulted in a new synthetic method of synthesis of 3-unsubstituted ferrocenyl β-lactams. To the best of our knowledge, this is the first report for the synthesis of 3-unsubstituted ferrocenyl β-lactams.

The synthetic application of indium metal is growing and these have been documented in a number of reports.[9] For example, indium has been used for the Barbier type of reaction of the imines and addition reaction to the carbonyl compounds. It has also been shown that indium can form an intermediate with bromo derivative which is claimed to be reactive species in many reactions.[9d]

Reaction of ferrocenylimines (**1**) with ethyl bromoacetate in the presence of indium metal using anhydrous tetrahydrofuran as the solvent produced the β-lactams (**2**) (**Scheme 1**). It was found that



Scheme 1

N-ferrocenylidine-4-methoxyaniline (**1a**) produced the β-lactam (**2a**) **(Table 1)** in 66 % yield. Imines obtained from benzylamine or substituted benzylamines (**1b**), (**1c**) and (**1d**) led to the β-lactams (**2b**), (**2c**) and (**2d**) in 55-62 % yield. Yields of the β-lactams were lower in case of the imines obtained form allylamine or 1-naphthelenemethylamine (**Table 1** entries 5 and 6). Surprisingly, no intermediate β-amino ester could be detected in the reaction mixtures.[8]

In conclusion, we have demonstrated, for the first time, a simple and rapid synthesis of several 3-unsubstituted 4-ferrocenyl-β-lactams by indium-mediated reaction with ethyl bromoacetate.[10,11] Standard substitution reactions of ferrocene and base-mediated functionalization at C_3 of the β-lactams (**2**) can provide advanced intermediates for structure-activity relationship studies.

REPRESENTATIVE EXPERIMENTAL

A mixture of imine (**1a**) (0.305 g, 0.96 mmol), indium powder (0.24 g, 2.1 mmol) and ethyl bromoacetate (0.32 g, 1.92 mmol) in anhydrous THF (10 mL) was heated at 80° C with vigorous stirring under argon for 12 h. The reaction mixture was cooled, saturated NH_4Cl solution (0.5 mL) added and diluted with CH_2Cl_2. It was filtered through a pad of celite, dried (Na_2SO_4) and concentrated. Column chromatography over silica gel with 15% EtOAc : hexane and recrystallization with ether-hexane afforded the β-lactam (**2a**) (0.227 g, 66%); mp 140-142° C. IR (cm^{-1}): 1736, 1509. ^1H NMR (300 MHz): δ 3.26 (dd, 1H, J = 14.9 and 2.7 Hz), 3.49 (dd, 1H, J = 14.9 and 5.5 Hz), 3.73 (s, 3H), 4.17 (s, 5H), 4.18-4.22 (m, 2H), 4.25-4.27 (m, 1H), 4.32-4.33 (m, 1H), 4.79 (dd, 1H, J = 5.5 and 2.7 Hz), 6.78 (d, 2H, J = 9 Hz), 7.29 (d, 2H, J = 9 Hz); ^{13}C NMR (75 MHz): δ 44.69 ($\mathit{C}H_2$), 50.9 (*C*H), 55.43 ($O\mathit{C}H_3$), 65.93 (*C*H), 68.05 (*C*H), 68.6 (*C*H), 69.39 (*C*H), 70.22 (*C*H), 84.93, 114.19 (*C*H), 118.51 (*C*H), 131.45, 155.99, 164.48.

ACKNOWLEDGMENTS

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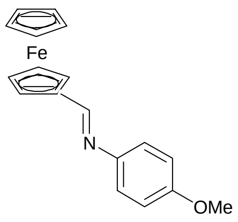
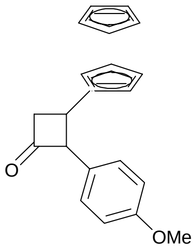
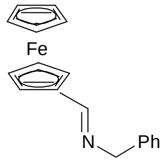
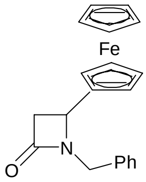
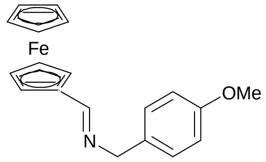
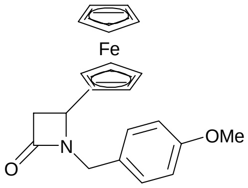
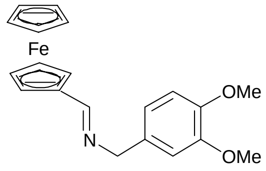
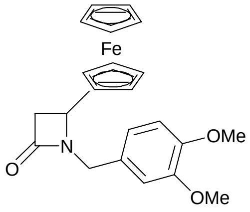
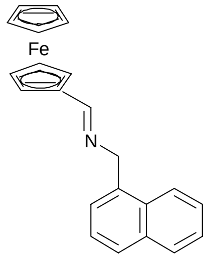
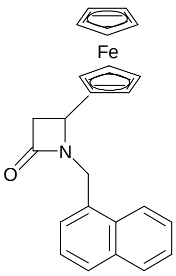
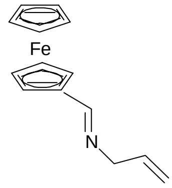
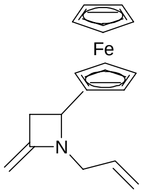
Table 1: Indium mediated synthesis of 3-unsubstituted ferrocenyl β-lactams

Entry	Imine	β - lactam	Yield (%)[a]	Time (h)	Analysis
1	 **1a**	 **2a**	66	7	Calcd for $C_{20}H_{19}NO_2Fe$ C, 66.5; H, 5.3; N, 3.9 Found C, 66.32; H, 5.3; N, 3.91
2	 **1b**	 **2b**	62	8	Calcd for $C_{20}H_{19}NOFe$ C, 69.6; H, 5.5; N, 4.1 Found C, 69.95; H, 5.7; N, 4.16
3	 **1c**	 **2c**	57	8	Calcd for $C_{21}H_{21}NO_2Fe$ C, 67.2; H, 5.6; N, 3.7 Found C, 66.55; H, 5.57; N, 3.67
4	 **1d**	 **2d**	55	8	Calcd for $C_{22}H_{23}NO_3Fe$ C, 65.2; H, 5.7; N, 3.5 Found C, 65.1; H, 5.71; N, 3.26
5	 **1e**	 **2e**	45	14	Calcd for $C_{24}H_{21}NOFe$ C, 72.9; H, 5.4; N, 3.5 Found C, 72.52; H, 5.3; N, 3.48
6	 **1f**	 **2f**	41	12	Calcd for $C_{16}H_{17}NOFe$ C, 65.1; H, 5.8; N, 4.7 Found C, 65.14; H, 5.89; N, 4.77

[a] Isolated yield

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and Related Microbial Products, ed. by G. Lukacs, Springer-Verlag, New York, 1993, vol. 2, p. 551. (b) Ultrasound promoted synthesis of 3-unsubstituted β-lactam was reported, for example see: A. K. Bose, K. Gupta, and M. S. Manhas, *J. Chem. Soc., Chem. Commun.* 1984, 86.

11. **2b**; IR (cm^{-1}): 1747. ^1H NMR (300 MHz, $CDCl_3$): δ 3.04 (dd, 1H, J = 14.5 and 2.3 Hz), 3.3 (dd, 1H, J = 14.5 and 5.1 Hz), 3.78 (d, 1H, J = 15.2 Hz), 4.01 (m, 1H), 4.09 (s, 5H), 4.14-4.2 (m, 3H), 4.27 (dd, 1H, J = 5.1 and 2.3 Hz), 4.66 (d, 1H, J = 15.2 Hz), 7.17-7.34 (m, 5H). **2c**; IR (cm^{-1}): 1743, 1611, 1509. ^1H NMR (300 MHz, $CDCl_3$): δ 3.02 (dd, 1H, J = 14.4 and 2.4 Hz), 3.28 (dd, 1H, J = 14.4 and 5.1 Hz), 3.72 (d, 1H, J = 15 Hz), 3.79 (s, 3H), 4.01-4.02 (m, 1H), 4.1 (s, 5H), 4.16-4.2 (m, 3H), 4.24 (dd, 1H, J = 5.1 and 2.4 Hz), 4.6 (d, 1H, J = 15 Hz), 6.81-6.86 (m, 2H), 7.08-7.12 (m, 2H). **2d**; IR (cm^{-1}): 1740, 1592, 1515. ^1H NMR (300 MHz, $CDCl_3$): δ 3.04 (dd, 1H, J = 14.5 and 2.3 Hz), 3.3 (dd, 1H, J = 14.5 and 5.1 Hz), 3.76 (d, 1H, J = 14.9 Hz), 3.84 (s, 3H), 3.87 (s, 3H), 4.01-4.02 (m, 1H), 4.11 (s, 5H), 4.15-4.21 (m, 3H), 4.25 (dd, 1H, J = 5.1 and 2.3 Hz), 4.56 (d, 1H, J = 14.9 Hz), 6.67-6.73 (m, 2H), 6.79 (d, 1H, J = 8 Hz). **2e**; IR (cm^{-1}): 1743. ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (dd, 1H, J = 14.5 and 2.4 Hz), 3.23 (dd, 1H, J = 14.5 and 5.1 Hz), 3.90-3.92 (m, 1H), 4.03 (s, 5H), 4.02-4.17 (m, 5H), 5.13 (d, 1H, J = 14.9 Hz), 7.22-7.25 (m, 1H), 7.35-7.39 (m, 1H), 7.47-7.58 (m, 2H), 7.78-7.87 (m, 2H), 8.09 (d, 1H, J = 8.3 Hz). **2f**; IR (cm^{-1}): 1747. ^1H NMR (300 MHz, $CDCl_3$): δ 3.0 (dd, 1H, J = 14.5 and 2.4 Hz), 3.35 (dd, 1H, J = 14.5 and 5.1 Hz), 3.4 (dd, 1H, J = 15.8 and 7 Hz), 3.96-4.03 (m, 1H), 4.13-4.22 (m, 9H), 4.42 (dd, 1H, J = 5.1 and 2.4 Hz), 5.09-5.16 (m, 2H), 5.61-5.74 (m, 1H).