A One-Pot Conversion of an Aziridine to a β-Lactam using Nickel Tetracarbonyl

Wilaiporn Chamchaang and Allan R. Pinhas*

Department of Chemistry, University of Cincinnati, Cincinnati, OH 45221-0172, U.S.A.

A one-pot, inert atmosphere conversion of an aziridine to a β-lactam has been achieved, using nickel tetracarbonyl, in which the less substituted C–N bond is carbonylated.

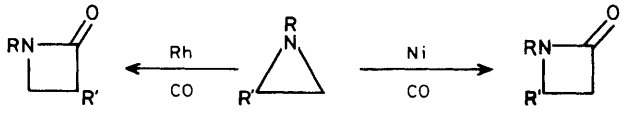
A β-lactam is the active functionality in penicillin and cephalosporin, two of the most important antimicrobial agents known.[1] The significance of these two families of compounds has stimulated the discovery of new strategies for the synthesis of both naturally-occurring and unnatural β-lactams.[1,2] These strategies include a number of novel methods using organometallic chemistry.[3—5]

Because of the ready availability of aziridines,[6] their direct carbonylation should prove to be a very convenient synthesis of β-lactams. The one known method for this chemical transformation[5] is catalytic in transition metal but, unfortunately, requires a high pressure of carbon monoxide {$[Rh(CO)_2Cl]_2$, 20 atm., C_6H_6, 90 °C}. This rhodium catalysed carbonylation reaction inserts the CO into the *more* substituted C–N bond. In this communication, a complementary reaction is reported, which uses a stoicheiometric amount of inexpensive nickel and an inert atmosphere. In the nickel reaction, it is the *less* substituted C–N bond of the aziridine which is carbonylated (Scheme 1).

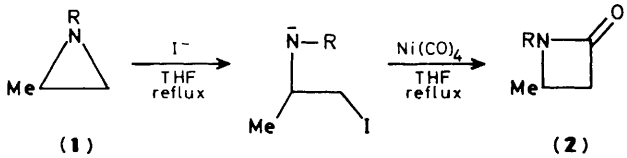
The methodology discussed here is based on two observations. (i) Lithium dialkyl amides and nickel tetracarbonyl react to generate acylate complexes,[7] and (ii) nickel acylate complexes react with methyl iodide.[8] Using these observations and starting with a benzylated aziridine (**1a**), the following scheme was postulated. Allowing the iodide ring opening step to proceed in refluxing tetrahydrofuran (THF) for 15 min, cooling the solution to room temperature, adding nickel tetracarbonyl, and then refluxing the solution under an argon atmosphere for an additional three hours, gives β-lactam (**2a**) in 51% isolated yield after purification (Scheme 2). To test the effect of added CO on this carbonylation reaction, the second step was run under one atmosphere of carbon monoxide. The resulting yield is the same as under an argon atmosphere. ^1H and ^{13}C n.m.r. spectroscopy shows that only one regioisomer of the product is formed.[3]†

To determine whether 3,4-disubstituted β-lactams may be synthesized by this methodology, and at the same time, to determine the stereochemical relationship between the aziridine and the β-lactam, 1-benzyl-*cis*-2,3-dimethylaziridine (**3**) was synthesized[9] and subjected to the $I^-/Ni(CO)_4$ reaction conditions. This reaction proceeds in 16% yield under an argon atmosphere but in 37% yield under a CO atmosphere, to give the *cis*-isomer (**4**) of the β-lactam[3]‡ in both cases (Scheme 3). Because the I^- reaction is most likely an S_N2 reaction, and thus occurs with complete inversion of configuration, attack by the intermediate nickel acylate complex on the alkyl halide must also occur with inversion of configuration to give the observed net retention of configuration between the aziridine and the β-lactam.

It also has been found that the nitrogen may be substituted with an electron withdrawing group, such as a methyl sulphone (SO_2Me). The ring opening reaction was again allowed to proceed for 15 min, the reaction mixture was cooled, nickel tetracarbonyl was added, and the solution was allowed to reflux for six hours under an argon or carbon monoxide atmosphere. This carbonylation reaction generates β-lactam (**2b**)§ in 18% yield under both sets of conditions.



Scheme 1



(**1**) (**2**)

Scheme 2. **a**; R = CH_2Ph
b; R = SO_2Me

† A mixture of 1-benzyl-2-methylaziridine (**1a**) (1.0 mmol) and lithium iodide (1.5 mmol) in THF (30 ml) was heated at reflux for 15 min under an argon atmosphere. It was then cooled to room temperature, nickel tetracarbonyl (11.4 mmol) was added, and the solution was heated to reflux under an argon atmosphere for 3 h. The reaction mixture was then added to solid iodine (3.9 mmol). Additional iodine was added to the solution until there was no more bubbling; ether was added and the solution was stirred for 15 min. The solution was washed (saturated sodium bisulphite then 10% K_2CO_3) and dried (K_2CO_3). If the second step was under a CO atmosphere, the first step was run as above. After the solution was cooled, CO gas was bubbled into it for 15 min, nickel carbonyl was added, the flask was connected to a balloon filled with CO, and the reaction mixture allowed to reflux for 3 h.

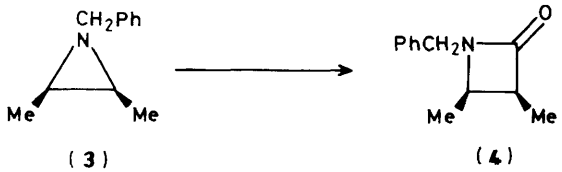
Spectral data for 1-benzyl-4-methylazetidinone (**2a**): ^1H n.m.r. ($CDCl_3$), δ 1.22 (d, 3H, *J* 6.6 Hz) 2.54 (dd, 1H, *J* 2.1, 14.4 Hz), 3.07 (dd, 1H, *J* 5.1, 14.4 Hz), 3.57—3.60 (m, 1H), 4.10 (d, 1H, *J* 15.3 Hz), 4.59 (d, 1H, *J* 15.3 Hz), 7.25—7.38 (m, 5H); ^{13}C n.m.r. ($CDCl_3$), δ 18.51(q), 44.07(d), 44.33(t), 47.04(t), 127.11—136.02, 166.89(s); i.r. ($CDCl_3$), ν 2960(w), 2920(w), 1730(s), 1460(m), 1450(m), 1375(m) cm^{-1}; m.s., *m/z* 176 (2.9%), 175 (4.9), 133 (55.0), 132 (33.6), 105 (47.1), 104 (27.6), 92 (10.8), 91 (100), 89 (4.7), 78 (7.7), 77 (11.8), 65 (23.0).

‡ This reaction was conducted under the same conditions as for the monomethyl analogue except that 1-benzyl-*cis*-2,3-dimethylaziridine (**3**) (1.0 mmol) was used and the iodide ring opening was allowed to proceed for 2 h rather than 15 min.

Spectral data for 1-benzyl-*cis*-3,4-dimethylazetidinone (**4**): ^1H n.m.r. ($CDCl_3$), δ 1.09 (d, 3H, *J* 6.3 Hz), 1.18 (d, 3H, *J* 7.5 Hz), 3.24 (dq, 1H, *J* 5.4, 7.5 Hz), 3.64 (dq, 1H, *J* 5.7, 6.0 Hz), 4.08 (d, 1H, *J* 15.3 Hz), 4.58 (d, 1H, *J* 15.3 Hz), 7.24—7.37 (m, 5H); ^{13}C n.m.r. ($CDCl_3$), δ 8.80, 13.54, 43.87, 46.98, 50.47, 127.54—136.21, 170.96; i.r. ($CDCl_3$), ν 2960(s), 2920(m), 2860(s), 1730(s), 1440(m), 1375(s), 1345(m) cm^{-1}; m.s., *m/z* 189 (23.8%), 133 (43.6), 132 (28.1), 105 (35.3), 104 (24.7), 92 (22.0), 91 (100).

§ This reaction was run under the same conditions as with (**1a**) except that 1-methylsulphone-2-methylaziridine (**1b**) (1.0 mmol) was used; the nickel tetracarbonyl reaction was allowed to proceed for 6 h; and methylene chloride was used for extraction.

Spectral data for 1-methylsulphone-4-methylazetidinone (**2b**): ^1H n.m.r. ($CDCl_3$), δ 1.61 (d, 3H, *J* 6.3 Hz), 2.74 (dd, 1H, *J* 3.7, 15.9 Hz), 3.19 (s, 3H), 3.29 (dd, 1H, *J* 6.0, 15.6 Hz), 4.29—4.38 (m, 1H); ^{13}C n.m.r. ($CDCl_3$), δ 19.94(q), 42.40(q), 44.25(t), 51.52(d), 163.97(s); i.r. ($CDCl_3$), ν 2980(w), 2930(w), 1780(s), 1345(s), 1270(m), 1200(w), 1160(s), 1140(s), 950(m), 770(m) cm^{-1}; m.s., *m/z* 124 (5.1%), 123 (3.6), 122 (100), 106 (5.1), 79 (42.4), 56 (8.9).



(3) (4)

Scheme 3. *Reagents:* I^-, then $Ni(CO)_4$.

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