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Facile carbamoylation of 3,4-dihydropyridin-2-one with *N*-chlorosulfonyl isocyanate

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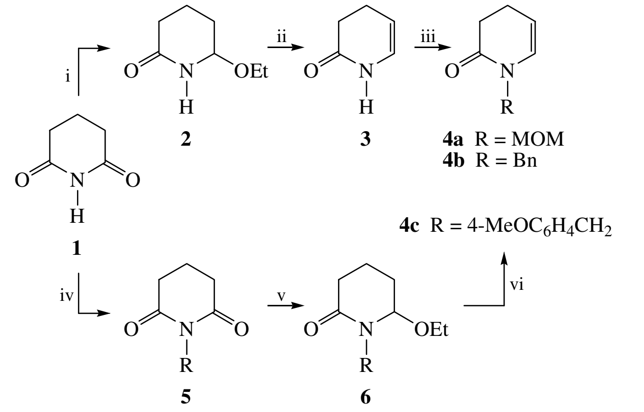
3,4-Dihydro-2-pyridone-5-carboxylic acid amides were prepared by carbamoylation at the C-5 position of 3,4-dihydropyridin-2-one with *N*-chlorosulfonyl isocyanate.

The dihydropyridone ring system possesses a prominent structural feature frequently found in naturally occurring compounds and potent insecticidal and antifungal alkaloids.[1] It is a versatile building block for the synthesis of natural piperidine, indolizidine and quinoline alkaloids.[2] It is also of interest not only in the synthesis of natural products but also in combinatorial libraries with these heterocyclic templates.[3]

3,4-Dihydro-2-pyridone-5-carboxylic acid was isolated and characterised in the degradation of nicotinic acid by a clostridium.[4] Although there are many methods for preparing dihydropyridone derivatives by the reductive elimination of glutarimides, the Birch reduction of pyridinium salts and the ring closure metathesis of acrylamides,[5] the synthesis of 5-carboxy-3,4-dihydropyridin-2-one has not been explored widely. The reported synthesis includes the Michael-type condensation of enamines with α,β-unsaturated acid chlorides and the Diels–Alder cycloaddition of 2-aza-1,3-dienes with acrylates, respectively.[6] The lack of general and efficient methods for the preparation of such systems prompted us to investigate a facile route to 3,4-dihydro-2-pyridone-5-carboxylic acid starting from glutarimide. Here, we report the carbamoylation of 3,4-dihydropyridin-2-one at the C-5 position with *N*-chlorosulfonyl isocyanate (CSI).

The key intermediate, 2-pyridone **3**, was prepared *via* reductive elimination starting from glutarimide **1**, as shown in Scheme 1.[5(a)] Thus, the sodium borohydride reduction of **1** in the presence of ethanolic hydrogen chloride followed by treatment with *p*-TsOH gave pyridone **3**. The N-protection of **3** was conveniently carried out with corresponding halides by treatment with sodium hydride to give **4a** and **4b**, respectively. Alternatively, **4c** was prepared in a similar fashion described above. Pyridone derivatives **4a–c** were easily identified by the presence of olefin signals in their ^{1}H and ^{13}C NMR spectra.[†]

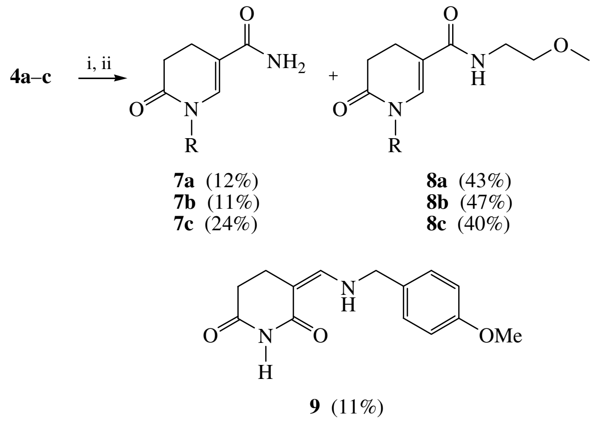


Scheme 1 *Reagents and conditions*: i, ii, see ref. 5(*a*); iii, NaH, THF, room temperature, 12 h, MOMCl, 64% (**4a**); BnBr, 81% (**4b**); iv, NaH, DMSO, room temperature, 12 h, *p*-methoxybenzyl chloride, 82%; v, $NaBH_4$, EtOH–HCl, 5 °C, 4 h; vi, toluene, molecular sieves 4A, reflux, 10 h, 78% (for two steps).

The cycloaddition of an alkene across the C=N bond of an isocyanate is a useful method for the synthesis of β-lactams. Such a reaction requires the activation of the alkene by electron-releasing substituents such as enol ether and vinyl sulfide.[7] Dihydropyridone **4** unlikely gives the cycloadduct by the reaction with isocyanate, since the enamide can be regarded as a deactivated enamine. Cycloaddition and the subsequent reversal of alkene species with isocyanate often produces α,β-unsaturated amide.[8] Moreover, the carbamoylation of vinylogous amides with isocyanates has been achieved in cases of uracil and quinoxalinone.[9] Thus, the direct carbamoylation at the C-5 position of 3,4-dihydropyridin-2-one with CSI would offer a more concise route to the target compound, 3,4-dihydro-2-pyridone-5-carboxamide.

A 2-pyridone derivative was treated in anhydrous toluene at –70 °C with a slight excess of CSI, and then the reaction mixture was quenched with Red-Al to remove the *N*-chlorosulfonyl group, as shown in Scheme 2. The reaction of **4a** with CSI followed by reductive removal of the *N*-chlorosulfonyl group produced 2-pyridone-5-carboxamide **7a** in 12% yield and *N*-2-methoxyethyl amide **8a** in 43% yield. The formation of **8a**, obviously derived from Red-Al, was not surprising, and the formation of β-lactam was not observed in this reaction. Analogously, the reaction with **4b** yielded corresponding dihydropyridone-5-carboxamides **7b** and **8b** in combined 58% yield. In contrast, treatment of *N*-4-methoxybenzyl pyridone **4c** with CSI yielded expected carboxamides **7c** (24%) and **8c** (40%), as well as rearranged product **9** (11%).[‡]

A suggested pathway for the product distributions from the reaction of **4c** with CSI is depicted in Figure 1. The [2 + 2] cycloaddition and subsequent decomposition[8] or the direct carbamoylation[9] of **4c** with CSI eventually produces a zwitterion, even though the mechanism remains unclear. Zwitterion **10** can be irreversibly deprotonated *via* pathway A to produce caboxamide **7c**, which is converted to *N*-2-methoxyethyl amide **8c** by the addition of Red-Al. This observation is apparently general for all of the 2-pyridone derivatives examined. The unexpected formation of glutarimide **9** can be explained by a rearrangement *via* pathway B, where both the stabilizing effect of the *p*-methoxybenzyl group on intermediate **10** and the participation of the nitrogen anion of the *N*-chlorosulfonyl group may facilitate the rearrangement.



Scheme 2 *Reagents and conditions*: i, CSI, Na_2CO_3, toluene, –70 °C, 2 h; ii, Red-Al (1 M solution in toluene), –70 °C, 15 min.

[†] *Spectroscopic data of dihydropyridone derivatives* **4a**–**c**.

4a: ^{1}H NMR, δ: 2.23–2.40 (m, 2H, C*H*$_2$CH), 2.54 (t, 2H, CH_2CO, *J* 7.8 Hz), 3.38 (s, 3H, OMe), 4.84 (s 2H, NCH_2O), 5.18 (dt, 1H, CH$_2$C*H*, J_1 7.8 Hz, J_2 4.4 Hz), 6.16 (d, 1H, NCH, *J* 7.8 Hz). MS, *m*/*z*: 141 (M$^+$, 66%).

4b: ^{1}H NMR, δ: 2.25–2.43 (m, 2H, C*H*$_2$CH), 2.58 (t, 2H, CH_2CO, *J* 8.0 Hz), 4.68 (s, 2H, NCH_2), 5.13 (dt, 1H, CH$_2$C*H*, J_1 7.6 Hz, J_2 4.6 Hz), 6.01 (dt, 1H, NCH, J_1 7.6 Hz, J_2 1.6 Hz), 7.23–7.41 (m, 5H, aryl). ^{13}C NMR, δ: 20.3, 31.3, 48.8, 106.4, 127.4, 127.5, 128.6, 129.4, 137.2, 169.3. MS, *m*/*z*: 187 (M$^+$, 60%).

4c: ^{1}H NMR, δ: 2.25–2.49 (m, 2H, C*H*$_2$CH), 2.55 (t, 2H, CH$_2$C*H*, *J* 5.3 Hz), 3.76 (s, 3H, OMe), 4.60 (s, 2H, NCH_2), 5.10 (dt, 1H, CH$_2$C*H*, J_1 7.8 Hz, J_2 4.0 Hz), 5.99 (dt, 1H, NCH, J_1 7.8 Hz, J_2 1.6 Hz), 6.84 (d, 2H, aryl, *J* 8.6 Hz), 7.18 (d, 2H, aryl, *J* 8.6 Hz). ^{13}C NMR, δ: 20.3, 31.3, 48.2, 55.2, 106.3, 113.7, 113.9, 129.0, 129.2, 158.9, 169.2. MS, *m*/*z*: 217 (M$^+$, 9%).

[‡] *General procedure. N*-Chlorosulfonyl isocyanate (114 μl, 1.3 mmol) was added to a suspension of anhydrous Na_2CO_3 (0.15 g) in dry toluene (2 ml). The mixture was stirred with cooling to –70 °C, and then a solution of N-protected 3,4-dihydro-2-pyridone (1 mmol) in dry toluene (2 ml) was added dropwise. The temperature of the mixture was allowed to rise to –30 °C, and it was maintained for 1.5 h. The mixture was then cooled to –70 °C, diluted with toluene (6 ml), treated with Red-Al (1 M solution in toluene, 1.3 ml), and left for 30 min while maintaining the temperature. The cooling bath was removed, and water (0.2 ml) was added at 0 °C. After intense stirring for 15 min, the suspension was filtered through Celite 545; the solvent was evaporated, and the residue was purified by column chromatography on silica gel to give products.

7a: ^{1}H NMR, δ: 2.65 (s, 4H, CH_2CH_2), 3.34 (s, 3H, OMe), 4.94 (s, 2H, NCH_2), 7.43 (s, 1H, NCH). MS, *m*/*z*: 184 (M$^+$, 10%). Found (%): C, 52.58; H, 6.48; N, 15.52. Calc. for $C_8H_{12}N_2O_3$ (%): C, 52.17; H, 6.57; N, 15.21.

7b: ^{1}H NMR, δ: 2.52 (t, 2H, C*H*$_2$CH$_2$, *J* 4.2 Hz), 2.60 (t, 2H, CH$_2$C*H*$_2$, *J* 4.2 Hz), 4.66 (s, 2H, NCH_2), 5.95 (br. s, 2H, NH_2), 7.13–7.34 (m, 5H, aryl), 7.39 (s, 1H, NCH). ^{13}C NMR, δ: 20.4, 30.5, 50.0, 109.8, 127.7, 128.0, 128.9, 136.3, 137.9, 168.6, 169.1. MS, *m*/*z*: 230 (M$^+$, 30%).

7c: ^{1}H NMR, δ: 2.40–2.70 (m, 4H, CH_2CH_2), 3.78 (s, 3H, OMe), 4.66 (s, 2H, NCH_2), 5.56 (br. s, 2H, NH_2), 6.84 (d, 2H, aryl, *J* 8.4 Hz), 7.17 (s, 1H, NCH), 7.18 (d, 2H, aryl, *J* 8.4 Hz). ^{13}C NMR, δ: 20.4, 30.6, 49.3, 55.2, 110.2, 114.2, 128.4, 129.2, 137.2, 159.3, 168.4, 169.0. MS, *m*/*z*: 260 (M$^+$, 2%). Found (%): C, 64.58; H, 6.08; N, 11.02. Calc. for $C_{14}H_{16}N_2O_3$ (%): C, 64.60; H, 6.20; N, 10.76.

8a: ^{1}H NMR, δ: 2.56 (s, 4H, CH_2CH_2), 3.27 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.62 (s, 2H, NHC*H*$_2$), 4.21 (s, 2H, OCH_2), 4.67 (s, 2H, NCH_2), 7.44 (s, 1H, NCH). ^{13}C NMR, δ: 19.9, 30.7, 49.1, 56.4, 58.7, 68.2, 70.3, 115.5, 137.2, 171.3, 173.7. MS, *m*/*z*: 210 (M$^+$ – MeOH, 9%), 184 (17%).

8b: ^{1}H NMR, δ: 2.47 (s, 4H, CH_2CH_2), 3.22 (s, 3H, OMe), 3.49 (m, 2H, OCH_2), 4.12 (m, 2H, NHC*H*$_2$), 4.63 (s, 2H, NCH_2), 6.4 (br. s, 1H, NH), 7.12–7.37 (m, 5H, aryl), 7.34 (s, 1H, NCH). ^{13}C NMR, δ: 20.0, 30.8, 49.8, 50.4, 58.5, 67.9, 70.2, 115.2, 127.5, 128.6, 136.8, 138.1, 164.8, 170.3. MS, *m*/*z*: 288 (M$^+$, 1%).

8c: ^{1}H NMR, δ: 2.46 (br. s, 4H, CH_2CH_2), 3.24 (s, 3H, OMe), 3.50 (br. s, 2H, OCH_2), 3.72 (s, 3H, OMe), 4.18 (br. s, 2H, NHC*H*$_2$), 4.55 (s, 2H, NCH_2), 6.78 (d, 2H, aryl, *J* 8.5 Hz), 7.14 (d, 2H, aryl, *J* 8.5 Hz), 7.35 (s, 1H, NCH). ^{13}C NMR, δ: 19.9, 30.7, 49.5, 55.3, 58.7, 68.5, 70.2, 114.1, 128.7, 129.2, 136.4, 159.2, 170.5. MS, *m*/*z*: 318 (M$^+$, 1%). Found (%): C, 64.18; H, 7.18; N, 9.08. Calc. for $C_{17}H_{22}N_2O_4$ (%): C, 64.13; H, 6.97; N, 8.80.

9: ^{1}H NMR, δ: 2.42 (s, 4H, CH_2CH_2), 3.70 (s, 3H, OMe), 4.55 (s, 2H, NCH_2), 6.86 (d, 2H, aryl, *J* 8.8 Hz), 7.18 (d, 2H, aryl, *J* 8.4 Hz), 7.36 (s, 1H, NCH), 9.63 (s, 1H, NH, disappeared with D_2O). ^{13}C NMR, δ: 17.5, 28.6, 47.8, 53.2, 108.5, 112.2, 126.7, 127.4, 137.4, 157.4, 165.6, 168.2. MS, *m*/*z*: 260 (M$^+$, 2%). Found (%): C, 64.08; H, 6.68; N, 11.02. Calc. for $C_{14}H_{16}N_2O_3$ (%): C, 64.60; H, 6.20; N, 10.76.

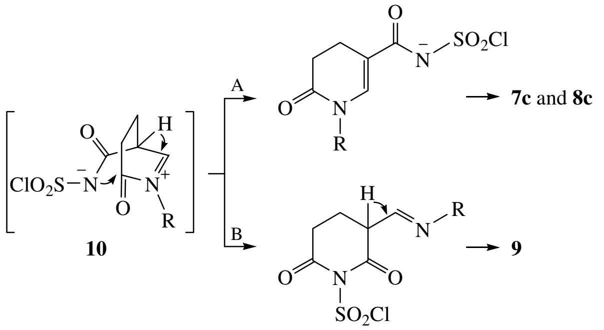


Figure 1

In conclusion, we found a facile carbamoylation at the C-5 position of vinylogous amide, which is promising for the one-step preparation of a nicotinic acid metabolite from 3,4-dihydropyridin-2-one. Interestingly, the treatment of **4c** with CSI yielded expected 2-pyridone-5-carboxamides, **7c** and **8c**, as well as rearranged product **9**. We believe that the formation of **9** likely involves the stabilization of an iminium ion by the electronic character of the *p*-methoxybenzyl group.

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