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A new route for the synthesis of 5,6-dihydropyridin-2(1*H*)-ones, 2-pyridones and (4-hydroxy-2-oxopiperid-3-yl)pyridinium chlorides by intramolecular cyclization of *N*-3-oxoalkylchloroacetamide derivatives

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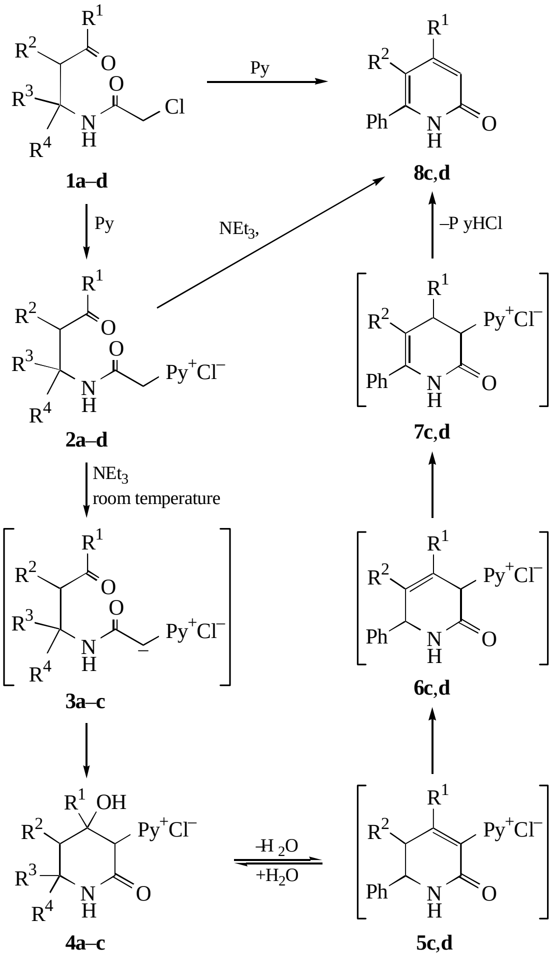
The intramolecular cyclization of triphenylphosphonium and pyridinium derivatives of *N*-3-oxoalkylchloroacetamides leads to 5,6-dihydropyridin-2(1*H*)-ones, 2-pyridones and (4-hydroxy-2-oxopiperid-3-yl)pyridinium chlorides.

We have recently reported[1] on the intramolecular cyclization of *N*-3-oxoalkylphenylacetamides into 5,6-dihydropyridin-2-ones under the influence of bases. The presence of active hydrogen at the -carbamoyl position is a necessary condition for the reaction to proceed. The *N*-3-oxoalkylamides are very promising precursors for the synthesis of pyridine derivatives, due to both the wide range of preparative synthetic methods[2–6] available and the convenience of these methods. Increasing -carbamoyl position acidity can be achieved either by transformation of the -carbamoyl group into a -thiocarbamoyl group,[7] or by placing an electron-attracting group in that position, *e.g.* pyridinium or triphenylphosphonium cations.

In order to investigate the synthesis of 5,6-dihydropyridin-2(1*H*)-ones and 2-pyridones based on *N*-3-oxoalkylchloroacetamides we have prepared the appropriate 1-(3-oxoalkylcarbamoylmethyl)pyridinium and -(triphenyl)phosphonium chlorides.



a $R^1 = R^3 = R^4 =$ Me, $R^2 =$ H
b $R^1 = R^4 =$ Me, $R^2 = R^3 =$ H
c $R^1 = R^4 =$ Ph, $R^2 = R^3 =$H
d R^1, $R^2 = (–CH_2–)_4$, $R^3 =$ H, $R^4 =$ Ph

Scheme 1

Reactions of pyridinium ylides leading to formation of a variety of heterocyclic compounds are well known.[8–12] Most of the pyridinium ylide heterocyclizations investigated proceed *via* an intermolecular Michael addition followed by cyclization of the intermediate into a heterocycle. The intramolecular cyclization of pyridinium ylides is also known,[13] but its application for the synthesis of heterocycles is not widespread.

We have obtained 1-(3-oxoalkylcarbamoylmethyl)pyridinium chlorides **2a–d**[†] by interaction of *N*-3-oxoalkylchloroacetamides **1a–d** with pyridine. Compounds **2a–c** with triethylamine in DMF at room temperature give 1-(4-hydroxy-2-oxopiperid-3-yl)pyridinium chlorides **4a–c**[‡] in high yields. Heating of both *N*-3-oxoalkylchloroacetamides **1c**,**d** in a mixture of pyridine with DMF and compounds **2c**,**d** with triethylamine in methanol leads to 2-pyridones **8c**,**d**.[§] By contrast, 1-(1-methyl-3-oxobutylcarbamoylmethyl)pyridinium chloride **2b** under the same conditions does not form the corresponding 4,6-dimethyl-2-pyridone, but (4-hydroxy-4,6-dimethyl-2-oxopiperid-3-yl)pyridinium chloride **4b** does (Scheme 1).

Apparently, the mechanism of transformation of **2a–c** into **4a–c** involves the formation of the corresponding pyridinium ylides **3a–c** (Scheme 1). The degree of conversion of **2a–d** depends on both electronic and structural factors. Transformation of **2** into **8** will be promoted by increasing both the effective

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[†] 1-(3-*Oxoalkylcarbamoylmethyl*)*pyridinium chlorides* **2a–d**: a solution of 2 mmol of *N*-3-oxoalkylchloroacetamide **1** in 3 ml of pyridine was allowed to stand at room temperature for 24 h and then the reaction mixture was diluted with 10 ml of diethyl ether. The resulting precipitate was filtered off and washed with an additional 5 ml of dry diethyl ether to give 88–96% of **2a–d**.

^{1}H NMR data for compounds **2a–c** (200 MHz, CD_3OD, TMS, δ):

2a: 9.64 (s, 1H, NH), 8.12–8.92 (m, 5H, Py), 5.40 (s, 2H, CH_2–Py), 3.01 (s, 2H, OC–CH_2), 2.10 (s, 3H, CH_3–CO), 1.40 (s, 6H, CH_3–C–CH_3).

2b: 9.44 (s, 1H, NH), 9.03–9.21 (m, 5H, Py), 5.59 (s, 2H, CH_2–Py), 4.12–4.31 (m, 1H, CH_3–CH_x–NH), 3.46 (A of ABX, 1H, CH_AH_B-CO, $^2J_{AB}$ 16.8 Hz, $^3J_{BX}$ 6.8 Hz), 3.25 (B of ABX, 1H, CH_AH_B–CO, $^2J_{AB}$ 16.8 Hz, $^3J_{AX}$ 6.8 Hz), 2.10 (s, 3H, CH_3–CO), 1.16 (d, 3H, CH_3–CH_x–NH, ^3J 6.6 Hz).

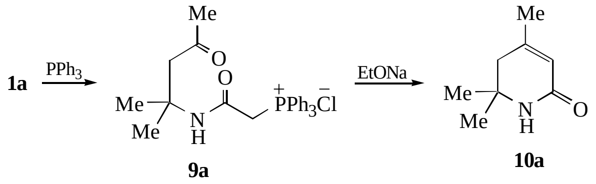
2c: 9.97 (s, 1H, NH), 7.96–8.90 (m, 5H, Py), 7.24–7.61 (m, 10H, 2Ph), 5.56 (X of ABX, 1H, Ph–CH_x–NH), 5.49 (s, 2H, CH_2–Py), 3.74 (A of ABX, 1H, CH_AH_B–CO, $^2J_{AB}$ 17.4 Hz, $^3J_{BX}$ 8.1 Hz), 3.56 (B of ABX, 1H, CH_AH_B–CO, $^2J_{AB}$ 17.4 Hz, $^3J_{AX}$ 5.8 Hz).

[‡] 1-(4-*Hydroxy*-2-*oxopiperid*-3-*yl*)*pyridinium chlorides* **4a–c**: 4 mmol of 1-(3-oxoalkylcarbamoylmethyl)pyridinium chloride **2** was dissolved in the minimum amount of DMF (3–4 ml) and treated with 0.05 ml of triethylamine at 0–5 °C. The resulting mixture was allowed to stand at room temperature for 48 h. The resulting precipitate was separated and washed with dry diethyl ether (5 ml) to give 88–90% of **4a–c**.

^{1}H NMR data for compounds **4a**,**b** (200 MHz, CD_3OD, TMS, δ):

4a: 8.13–9.00 (m, 5H, Py), 5.89 (s, 1H, 3-CH), 1.29 [s, 3H, 6-$(CH_3)_a$], 1.54 (s, 3H, 4-CH_3), 2.18 (s, 2H, 5-CH_2), 1.13 [s, 3H, 6-$(CH_3)_e$].

4b: 9.18–10.00 (m, 5H, Py), 5.90 (s, 1H, CH–Py), 3.92–4.03 (m, 1H, CH_3–CH_x–NH), 2.21 (A of ABX, 1H, CH_AH_B–CH_x–CH_3, $^2J_{AB}$ 14.3 Hz, $^3J_{AX}$ 4.5 Hz), 1.99 (B of ABX, 1H, CH_AH_B–CH_x–CH_3, $^2J_{AB}$ 14.3 Hz, $^3J_{AX}$ 11.2 Hz), 1.33 (d, 3H, CH_3–CH_x–NH, J 7.3 Hz), 1.20 (s, 3H, CH_3–C–OH).



Scheme 2

volume of the R^1 substituent, which decreases 4-hydroxy-2-piperidone stability, and the acidity of the C$_6$ position which eases isomerisation of dihydropyridin-2(1*H*)-ones **5**,**6** into intermediate **7**. The elimination of pyridinium hydrochloride from pyridinium salts such as intermediate **7** has already been described.[12,14]

5,6-Dihydropyridin-2(1*H*)-ones are widely employed in the synthesis of alkaloids and aza sugars and possess significant biological activity.[15–18] However, there are some restrictions on their synthesis such as inaccessibility of the starting reagents, low applicability of the preparation methods and difficult reaction conditions.[1,16,19,20] Therefore, it may be interesting to develop new, flexible methods which allow 5,6-dihydropyridin-2(1*H*)-ones to be obtained under mild conditions. We have studied the possibility of synthesising 5,6-dihydropyridin-2(1*H*)-ones by means of an intramolecular Wittig reaction based on *N*-3-oxoalkylchloroacetamides.

Cyclization of 1,1-dimethyl-3-oxobutylcarbamoylmethyl(triphenyl)phosphonium chloride **9a**[¶] by treatment with sodium ethylate at room temperature leads to 5,6-dihydro-4,6,6-trimethylpyridin-2(1*H*)-one **10a**[††] in 90% yield (Scheme 2).

Thus, we have shown that 5,6-dihydropyridin-2(1*H*)-ones, 2-pyridones and (4-hydroxy-2-oxopiperid-3-yl)pyridinium chlorides can be obtained by cyclization of the pyridinium and triphenylphosphonium derivatives of available *N*-3-oxoalkylchloroacetamides.

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[§] 4,6-*Diphenylpyridin*-2(1*H*)-*one* **8c** and 4,5,6,7-*tetrahydro*-8-*phenyl*-2-*isoquinolone* **8d**:

Method *A*. 4 mmol of *N*-3-oxoalkylchloroacetamide **1** was dissolved in a mixture of 0.5 ml pyridine with 0.5 ml DMF and refluxed for 3 h. After the reaction time had elapsed, the resulting mixture was poured into 30 ml of water. The resulting precipitate was filtered off, washed with an additional portion of water and dried *in vacuo* to give 42% of **8c** and 24% of **8d**.

Method *B*. To a solution of 4 mmol of 1-(3-oxoalkylcarbamoylmethyl)pyridinium chloride **2** in 3 ml of methanol was added 0.15 ml of triethylamine. The resulting mixture was refluxed for 1 h. Methanol was removed under reduced pressure and the residue was washed with water, filtered off and dried *in vacuo* to give 79% of **8c** and 58% of **8d**.

^{1}H NMR data for compounds **8c**,**d** (200 MHz, [^{2}H$_6$]DMSO, TMS, δ):

8c: 7.28–7.80 (m, 10H, 2Ph), 6.84 (d, 1H, 3-CH, $^4J_{35}$ 1.6 Hz), 6.50 (d, 1H, 5-CH, $^4J_{35}$ 1.6 Hz).

8d: 7.41–7.45 (m, 5H, Ph), 6.13 (s, 1H, 3-CH), 2.65 (m, 2H, 7-CH$_2$), 1.57–1.65 (m, 4H, 5-CH$_2$ and 6-CH$_2$), 2.31 (m, 2H, 4-CH$_2$).

Mp **8c** 211–212 °C, in agreement with the literature.[21]

[¶] 1,1-*Dimethyl*-3-*oxobutylcarbamoylmethyl* (*triphenyl*) *phosphonium chloride* **9a**: *N*-(1,1-dimethyl-3-oxobutyl)chloroacetamide **1a** (3.21 g, 16.7 mmol) and triphenylphosphine (4.84 g, 18.4 mmol) in dry dioxane (20 ml) were refluxed for 16 h. The resulting mixture was cooled and the resulting precipitate was filtered off, dried *in vacuo* and recrystallized from benzene–ethanol (5:1) to give 7.60 g (65%) of **9a**.

^{1}H NMR (200 MHz, CDCl$_3$, TMS,) δ: 9.68 (s, 1H, NH), 7.67–7.91 (m, 15H, 3Ph), 1.28 (s, 6H, CH$_3$–C–CH$_3$), 5.07 (d, 2H, C*H*$_2$–$^+$PPh$_3$, $^2J_{\text{HP}}$ 14.4 Hz), 2.79 (s, 2H, OC–CH$_2$), 2.04 (s, 3H, CH$_3$–CO).

[††] 5,6-*Dihydro*-4,6,6-*trimethylpyridin*-2(1*H*)-one **10a**: Compound **9a** (1.400 g, 3.2 mmol) was dissolved in absolute ethanol (20 ml). To this solution was added, dropwise and with stirring over 5 min at room temperature, a solution of sodium ethylate which was first prepared by dissolving 0.074 g of sodium in absolute ethanol (5 ml). The reaction mixture was stirred for 1 h and filtered from the precipitated NaCl. The filtrate was evaporated and the residue was treated with 10 ml of pentane–ether (1:1) and filtered again. The pentane–ether filtrate was evaporated and from the resulting residue after column chromotography (SiO$_2$, CHCl$_3$–AcOEt 3:1) 0.125 g (90% yield) of 5,6-dihydro-4,6,6-trimethylpyridin-2(1*H*)-one **10a** was obtained.

^{1}H NMR (200 MHz, CDCl$_3$, TMS) δ: 6.33 (s, 1H, NH), 5.72 (m, 1H, 3-CH), 2.23 (s, 2H, 5-CH$_2$), 1.91 (s, 3H, 4-CH$_3$), 1.28 [s, 6H, 2(6-CH$_3$)].

Mp **10a** 117–118 °C, in agreement with the literature.[22]