DECARBAMOYLATION OF N-ALKOXY-N-(4-DIMETHYLAMINOPYRIDIN-1-IUM-1-YL)UREA CHLORIDES IN DIMETHYLSULFOXIDE AS A ROUTE TO 1-ALKOXYAMINO-4-DIMETHYLAMINOPYRIDINIUM CHLORIDES


Keywords: N-alkoxy-N-(pyridin-1-iium-1-yl)urea chlorides; decarbamoylation; 1-alkoxyamino-4-dimethylaminopyridinium chlorides; structure; O-N-N geminal systems; dimethylsulfoxide.

Decarbamoylation of N-alkoxy-N-(4-dimethylaminopyridin-1-iium-1-yl)urea chlorides in dimethylsulfoxide takes place with the formation of 1-alkoxyamino-4-dimethylaminopyridinium chlorides. The nature of N-alkoxy substituents has a great influence on decarbamoylation efficiency.

Decarbamoylation of N-n-butyloxy-N-(4-dimethylaminopyridin-1-iium-1-yl)urea chloride at 20 ºC occurs with the selective formation of 1-n-butyloxyamino-4-dimethylaminopyridinium chloride. N-Methoxy-N-(4-dimethylaminopyridin-1-iium-1-yl)urea chloride is stable in dimethylsulfoxide at 20 ºC, but it forms selectively 1-methoxyamino-4-dimethylaminopyridinium chloride at 82 ºC in 1 h. N-Ethoxy-N-(4-dimethylaminopyridin-1-iium-1-yl)urea chloride is also stable in dimethylsulfoxide at 20 ºC, but it converts into 1-ethoxyamino-4-dimethylaminopyridinium chloride at 100 ºC under heating for 3 h.

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INTRODUCTION

Five types of 1-alkoxyaminopyridinium salts are known: N-alkoxy-N-(pyridin-1-iium-1-yl)-N-tert-alkylamine salts (1),[1,3] N-alkoxy-N-(pyridin-1-iium-yl)urea salts (2),[3-6] N-alkoxy-N-(1-pyridinium)carbamate chlorides(3),[7] N-alkoxy-N-(pyridin-1-iium-1-yl)benzamide chlorides(4) and unsubstituted 1-alkoxyamino-4-dimethylamino-pyridinium salts(5).[5,8] (Figure 1).

Compounds 1–4 were synthesized by the interaction of appropriate N-alkoxy-N-chloroamines and N-alkoxy-N-chloroamides with pyridines.[1-9] (Figure 2).

1-Alkoxyamino-4-dimethylaminopyridinium salts 5 were synthesized by the reaction of methyl N-alkoxy-N-chlorocarbamates with 4-dimethylaminopyridine (DMAP).[8,9] Evidently, this reaction carries out via formation of unstable intermediates 3′ (Figure 3).[8]

There are other synthesis methods for preparation of compounds 5, for example, decarbamoylation of urea derivatives 2 with bases as sodium acetate and ammonia, or potassium fluoride 8or the reaction of AcONa and benzamide 4a (Figure 4).

Figure 1. The known types of 1-alkoxyaminopyridinium salts 1-5

Figure 2. Synthesis of compounds 1 – 4

Figure 3. The most convenient synthesis of 1-alkoxyamino-4-dimethylaminopyridinium salts 5,8,9

1-Butyloxyamino-4-dimethylaminopyridinium chloride (5a).

The solution of $N$-$n$-butyloxy-$N$-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride $2a$ (0.238 mmol, 68.8 mg) in freshly distilled dimethylsulfoxide (1 mL) was kept at 16 °C during 150 h, then dry benzene (13 mL) was added. The benzene-phase was separated; the liquid residue was mixed with benzene (3 mL), then after 20 h the benzene-phase was separated. The obtained residue was dried in vacuo at 20 °C (2 Hgmm for 5 h), and then it was extracted by CH$_2$Cl$_2$ (8 mL). The CH$_2$Cl$_2$-extract was evaporated in vacuo giving 1-$n$-butyloxyamino-4-dimethylaminopyridinium chloride $5a$ (50.6 mg, 80%) as a white solid, which was identified by its $^1$H NMR spectra and mass spectrum.8

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 0.901 (3H, t, $^3J$=7.4 Hz, NO(CH$_2$)$_3$Me), 1.340 (2H, sex, $^3J$=7.4 Hz, NO(CH$_2$)$_2$CH$_2$Me), 1.573 (2H, quint, $^3J$=7.4 Hz, NOCH$_2$CH$_2$CH$_2$Me), 3.302 (6H, s, NMe$_2$), 3.807–3.843 (2H, m, NOCH$_2$), 6.877 (2H, d, $^3J$=6.8 Hz, C(2,6)H Py), 11.556 (1H, NH). $^1$H NMR (400 MHz, CD$_2$OD) $\delta$ = 0.858 (3H, t, $^3J$=7.0 Hz, NO(CH$_2$)$_3$Me), 1.293 (2H, quint, $^3J$=7.0 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.532 (2H, quint, $^3J$=7.0 Hz, NOCH$_2$CH$_2$Me), 3.302 (6H, s, NMe$_2$), 3.807–3.895 (2H, m, NOCH$_2$), 6.877 (2H, d, $^3J$=6.8 Hz, C(2,6)H Py). $^1$H NMR (300 MHz, CD$_3$SO) $\delta$ = 0.86 (3H, t, $^3J$=7.5 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.27 (2H, sex, $^3J$=7.5 Hz, NOCH$_2$CH$_2$CH$_2$Me), 1.51 (2H, quint, $^3J$=7.5 Hz, NOCH$_2$CH$_2$CH$_2$Me), 3.25 (6H, s, NMe$_2$), 3.79 (2H, t, $^3J$=6.3 Hz, NOCH$_2$C$_2$H$_4$Me), 7.05 (2H, d, $^3J$=7.8 Hz, C(3,5)H Py), 8.46 (2H, d, $^3J$=7.8 Hz, C(2,6)H Py), 11.00 (s, 1H, NH). MS (FAB) m/z 210 M+ (100), 152 (62), 137 (32), 123 (73).

b) The solution of $N$-$n$-butyloxy-$N$-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride $2a$ (0.242 mmol, 69.8 mg) in freshly distilled dimethylsulfoxide (2 mL) was kept at 80 °C for 30 min, then dimethylsulfoxide was distilled off at 70 °C and 2 Torr, then benzene (20 mL) was added to the obtained residue. The reaction mixture was kept under 6 °C for 20 h, and then, the benzene-phase (upper) was separated. The residue was dried at 20 °C and 2 Torr for 4 h, yielding compound $5a$ (62.8 mg, 98%).

1-Methoxyamino-4-dimethylaminopyridinium chloride (5b).

a) The solution of N-methoxy-$N$-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride $3b$ (0.361 mmol, 89.0 mg) in freshly distilled dimethylsulfoxide (5 mL) was kept at 82 °C for 1 h, then it was concentrated to a volume of 1 mL at 65–68 °C and 2 Torr. Benzene (20 mL) was added to the residue obtained. The reaction mixture was kept under 6 °C during 20 h, and then, the upper benzene-phase was separated. The lower liquid phase was extracted by benzene (2 mL) again, and the benzene-phase was separated, too. The lower liquid phase was distilled in CH$_2$Cl$_2$ (4 mL), this CH$_2$Cl$_2$-solution was added to benzene (16 mL), this mixture was kept at 4 °C for 22 h. The obtained white precipitate was separated, dried in vacuo at 15 °C and 3 Torr for 5 h, yielding 1-methoxyamino-4-dimethylaminopyridinium chloride (5b) (51.8 mg, 70%), as colorless crystals, which were identified by $^1$H NMR and mass spectra.8

**Figure 4.** Other synthesis routes of 1-alkoxyaminopyridinium salts (5)

**Figure 5.** Quinonoid deformation of pyridine ring in 1-alkoxyaminopyridinium salts

**Experimental**

300 MHz $^1$H NMR spectra were recorded on a VARIAN VX8-300 spectrometer, 400 MHz $^1$H NMR spectra were recorded on a VARIAN JEMINI 400 spectrometer with Me$_3$Si as an internal standard. Mass spectrum was recorded on VG 770-70EQ spectrometer in FAB regime. The solvents were purified and dried according to standard procedures. Dimethylsulfoxide (DMSO) was distilled in vacuo at 4 Torr. Benzene was dried by boiling and distillation over Na.


DOI: 10.17628/ecb.2018.7.267-271
Decarbamoylation of N-ethoxy-N-(4-dimethylaminopyridin-1-i um-1-yl)urea chloride (2c)

a) The solution of N-ethoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride (2c) (0.1323 mmol, 34.5 mg) in dimethyl sulfoxide (0.6 mL) was kept at 19 °C for 48 h, then benzene (20 mL) was added. The obtained white precipitate was filtered off, washed by benzene (5 mL), dried at 2 Torr, yielding 28,0 mg, 81%, which was identified by its 1H NMR spectra. 1H NMR (400 MHz, CDCl3) δ = 1.313 (3H, t, J3J =7.0 Hz, NOCH2Me), 3.334 (6H, s, NMe2), 4.107 (2H, q, J3J =7.0 Hz, NOCH2Me), 7.052 (2H, d, J3J =8.0 Hz, C(3,5)H Py), 8.290 (2H, d, J3J =8.0 Hz, C(2,6)H Py). 1H NMR (300 MHz, CDCl3) δ = 3.299 (6H, s, NMe2), 3.599 (3H, s, NOME), 6.923 (2H, d, J3J =8.1 Hz, C(3,5)H Py), 8.527 (2H, d, J3J =8.1 Hz, C(2,6)H Py), 11.669 (1H, NH). 13C NMR spectrum data).

b) The solution of N-ethoxy-N-(4-dimethylaminopyridin-1-i um-1-yl)urea chloride (2b) (0.1937 mmol, 50.5 mg) in dimethyl sulfoxide (2 mL) was kept at 19 °C for 22 h, then DMSO was distilled off at 65–68 °C and 2 Torr, then the obtained residue was washed twice by benzene (10 mL and 3 mL), yielding N-ethoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride (1b) (34.0 mg, 92%) which was identified by its 1H NMR spectrum. 1H NMR (300 MHz, CDCl3) δ = 3.330 (6H, s, NMe2), 3.892 (3H, s, NOMe), 4.003 (2H, q, J3J =8.0 Hz, C(2,6)H Py), 7.074 (2H, d, J3J =6.6 Hz, C(3,5)H Py), 8.292 (2H, d, J3J =6.6 Hz, C(2,6)H Py).

b) The solution of N-ethoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride (2c) (0.2708 mmol, 70.6 mg) in dimethyl sulfoxide-d6 was kept at 19 °C for 22 h, then DMSO was distilled off at 65–68 °C and 2 Torr, then the obtained residue was washed twice by benzene (10 mL and 3 mL). The 1H NMR spectrum of compound 2c (Figure 6). At 80°C, this reaction finishes in 30 min.

Contrary to the behavior of N-n-butoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride 2a, N-alkoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)ureas salts 2b and 2c are stable in dimethyl sulfoxide medium at room temperature. Compounds 2b and 2c could be recovered in unchanged form after keeping them in DMSO at room temperature. However, N-ethoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride 2b, has been converted in DMSO in 1-methoxy-4-dimethylaminopyridinium chloride 5b on heating at 82 °C for 1 h (Figure 7).

N-Ethoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chloride 2c is more stable to decarbamoylation in DMSO solution.
Decarbamoylation of compound 2c at 82 °C occurred very slow. Heating at 100 °C for 1 h with further DMSO removing yielded the mixture of compounds 2c and 5e in molar ratio 85:15. The heating of compound 2e solution in DMSO at 100 °C for 3 h yielded the mixture of compound 5c and 4-dimethylaminopyridine hydrochloride (DMAP•HCl) in the molar ratio 3:1, the precursor 2c was absent. Apparently, in this case, after the overall conversion of urea 2c, the particular decomposition of product 5c may be occurred.

Unfortunately, in our case, the mechanism of decarbamoylation of N-alkoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)ureas salts (2) in the presence of base is not known. It may be supposed, that dimethylsulfoxide as a weak base facilitates proton elimination at high temperatures (Figure 8).

It is probable, that the differences of N-alkoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chlorides (2) activity in the decarbamoylation processes may be caused by the different degree of pyramidality of the central nitrogen atom of O–N–N+ geminal system. As it is known for compounds different degree of pyramidality of the central nitrogen atom in the decarbamoylation processes may be caused by the base facilitates to increasing the pyramidality of central nitrogen atom facilitates to increasing the growth of N–O(Ac) bond weakening.10-13

The pyramidality of the central nitrogen atom of O–N–O geminal systems of N-(4-chlorbenzoyloxy)-N-alkoxyureas (6a and 6b, R = BuO(O) (a), EtO (b)) (Figure 9) depends on the nature of N-alkoxy moiety.14 In N-4-chlorbenzoyloxy-N-n-butylxoyurea 6a, the pyramidality of the central nitrogen atom is such as great (sum of bond angles is 323.8°) as that was found in N-4-chlorbenzoyloxy-N-etoxyurea 6b (sum of bond angles is 329.3°).14

A similar influence of the nature of N-alkoxy substituent on the reactivity was found for the isopropanolation of N-acetoxy-N-alkoxyureas 7a and 7b (N-alkoxy group = BuO (a), MeO(b)).15 In isopropanol, N-acetoxy-N-n-butylxoyurea 7a selectively forms N-n-butylxoy-N-isopropylxoyurea 8 at room temperature (Figure 10). At the same time, N-acetoxy-N-methoxyurea 7b is stable towards isopropanolation at room temperature. It was proposed16 that the nitrogen pyramidality degree in N-acetoxy-N-n-butylxoyurea 7a was higher than that in N-acetoxy-N-methoxyurea 7b due to the influence of N-n-butylxoy moiety. Probably, this phenomenon facilitates the action of nO(BuO)=σ*N−OAc anomeric effect and the more weakening of N–OAc bond.15

It may be proposed that similarly to N-alkoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)urea chlorides, compound 2a has the largest nitrogen pyramidality degree which remains during forming intermediate 5a (Figure 8). Respectively, intermediate 5a′ may be more stable than intermediates 5b and 5c′. It might cause the higher reactivity of N-n-butylxoyurea 2a comparing to N-methoxyurea 2b and N-etoxyurea 2c. But the structure parameters are known only for compound 2b,3 and further XRD study of the structure of compounds 2a and 2c is needed for correct mechanism proposition.

Conclusions

Decarbamoylation of N-alkoxy-N-(4-dimethylaminopyridin-1-ium-1-yl)ureas chlorides in dimethylsulfoxide occurs with the formation of 1-alkoxyamino-4-dimethylaminopyridinium chlorides. The nature of N-alkoxy substituent’s has a significant influence on easyness of the decarbamoylation reaction.

References


Figure 8. The possible mechanism of decarbamoylation of ureas 2 by action base( AcO −, F −, NH3) and DMSO

Figure 9. The family of N-4-chlorbenzoyloxy-N-alkoxyureas 6a,b,3,4


Figure 10. Isopropanolation of N-acetoxy-N-alkoxyureas 7a,b at room temperatures16