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Quaternisation of pyridines with 2-methyl- and 2-amino-4-(chloromethyl)thiazoles

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Quaternisation of pyridines and picolines with 2-methyl- and 2-amino-4-(chloromethyl)thiazoles furnished new highly functionalised pyridinium salts. Three-component reaction of 2-amino-4-(chloromethyl)thiazole, acetic anhydride and pyridine afforded 1-[2-(acetylamino)thiazol-4-yl]methylpyridinium chloride.

Key words: pyridine, 2- and 4-picolines, 2-amino-(4-chloromethyl)thiazole, quaternisation, *N*-substituted pyridinium salts

INTRODUCTION

N-Substituted pyridinium salts are important heterocyclic derivatives due to their practical applications in various areas of advanced technologies. Recently, products of quaternisation of pyridines by long-chain haloalkanes were employed as carriers for DNA delivery into cells [1], preparation of nanocomposites[2] and ultrathin films[3]. Alkylation of pyridines with functionalized methylene derivatives furnished synthons, which can be transformed to more complex structures, including the derivatives of medicinally important indolizines. For example, the reaction of pyridines with 2-bromoacetophenones afforded 1-(benzoylmethyl)pyridinium bromides. Action of bases on them generated pyridinium ylides that easily took part in [3+2] dipolar cycloaddition with dimethyl acetylenedicarboxylate to yield indolizines[4]. A similar synthesis protocol, where 1-(*N*-phenylcarbamoyl)methylpyridinium bromides were employed as a source of ylides, afforded indolizines with a functional carbamoyl group on the pyrrole ring[5]. The preparation of the functionalized indolizines should have interesting effects on their chemical and biological properties. It has been recently reported recently that 2-bromomethyl-5,6-dicyanopyrazine was successfuly used for the alkylation of pyridines. The following [3+2] cycloaddition reaction formed 3-(pyrazin-2-yl)indolizine[6].

The aim of the current work was to investigate the quaternisation of pyridines with 4-(chloromethyl)thiazoles. The thiazole ring is an important pharmacophore[7], and its coupling with a pyridine nucleus could furnish new biologically active compounds. The highly functionalized 1-(thiazolylmethyl)pyridinium salts could serve also as useful building blocs for more complex systems.

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RESULTS AND DISCUSSION

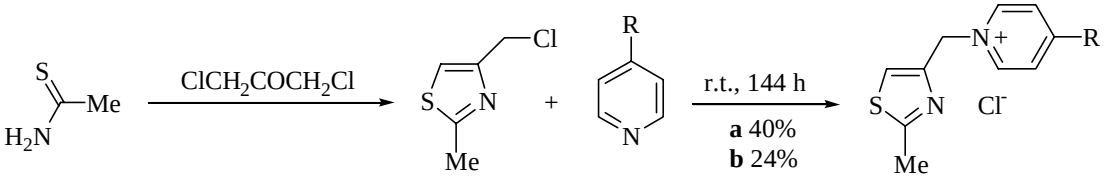
2-Methyl- and 2-amino-4-(chloromethyl)thiazoles have been chosen as alkylating agents for pyridine and picolines. Both chloromethylthiazoles can be easily prepared by the Hantsch type reaction of 1,3-dichloroacetone with thioacetamide (**1**)[8] and thiourea (**5**)[9]. 2-Amino-(4-chloromethyl)thiazole was obtained in the form of crystalline hydrochloride (**6**, yield 70%) by a simple stirring of the corresponding reagents in ethanol at room temperature. The original procedure when acetone was used as a solvent gave a lower yield (58%)[9].

The best results of the quaternisation of azines were achieved when 4-chloromethyl-2-methylthiazole (**2**) was dissolved in an excess of pyridines **3 a, b** and the reaction mixture was stirred for several days at room temperature. The structure of **4a** was confirmed by the presence of singlets at 2.68 (CH_3), 5.98 (CH_2) and 7.86 (5-H of thiazole). The signals of piridinium protons appeared in the area of ~8.20–9.20 ppm.

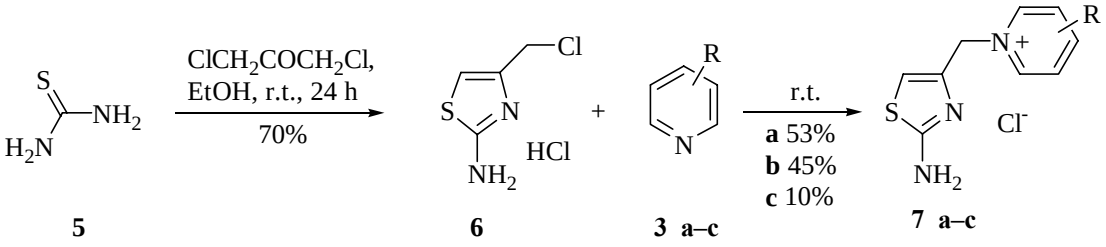
We next focused on the quaternisation of pyridines with 2-amino-4-(chloromethyl)thiazole. The latter has been used previously in reactions with various nucleophiles[9, 10]. X-ray structure of bis(2-amino-4-chloromethylthiazolium) tetrachlorocuprate is described in paper[11]. However, this is the first study on the use of 2-amino-4-(chloromethyl)thiazole hydrochloride **6** for the quaternisation of azines.

The reaction of compound **6** with pyridine was carried out in analogous conditions as for the model compound **2**. However, due the to high insolubility of the

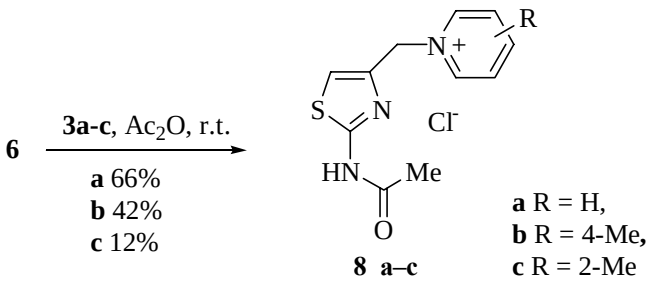
Scheme 1



Scheme 2



Scheme 3



starting hydrochloride **6**, a large excess of pyridine, which also served as a solvent was used. The reaction furnished 1-[(2-aminothiazol-4-yl)methyl]pyridinium chloride (**7a**) the structure of which was confirmed by spectral data. The ^{1}H NMR spectrum of **7a** in methanol-d_4 revealed singlets at 5.84 (CH_2) and 7.27 (5-H of the thiazole ring), and multiplets in the range of 8.12–9.10 ppm (pyridine ring protons). The ^{13}C NMR spectra showed the characteristic signals of the methylene bridge carbon at 57.33 (CH_2), pyridine ring carbons in the area ~130–150 and the carbon (C-2) of thiazole nucleus at 172.79 ppm. Quaternisation of 4- and 2-picolines with **6** gave pyridinium chlorides **7 b**, **c**. The low yield (10%) of **7c** can be explained by steric reasons.

The synthesis of 1-[(2-acetylaminothiazol-4-yl)methyl]pyridinium chlorides **8 a–c** was based on a one-pot procedure. Stiring at room temperature of a mixture of chloromethyl compound **6**, acetic anhydride and pyridine (or 4- and 2-picolines) turnished quaternary pyridinium chlorides **8 a–c**, respectively. Their ^{1}H NMR spectra contained the singlet for the methyl protons of the acetyl goup at ~2.10–2.20 ppm, while ^{13}C NMR spectra showed the characteristic signal for the carbonyl carbon at ~160–162 ppm. IR spectrum of **8b** exhibited the characteristic secondary amide moiety absorption bands at 3369 (N-H), 1676 cm^{-1} (C=O) and 1567 cm^{-1} (amide II).

EXPERIMENTAL

Melting points were determined on a *Kleinfeld* melting point apparatus. IR spectra were recorded on a Perkin–Elmer Spectrum BXII spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz on a Varian Unity Inova instrument. Tetramethylsilane was used as the internal standard. HPLC–MS analysis was performed and mass spectra were recorded on a Waters ZQ 2000 instrument (ion spray). For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Separation by flash chromatography was performed on silica gel Merck, 9385, 230–400 mesh.

1-[(2-Methylthiazol-4-yl)methyl]pyridinium chloride (4a). A mixture of compound **2** (0.2 g, 1.36 mmol) and pyridine (3 ml) was stirred at room temperature for 6 days. Then the formed precipitate was collected by filtration, washed with ethanol–ether mixture 1:1 and dried in vacuo to yield 0.12 g (40%) of compound **4a** as an amorphous white solid. IR spectrum: 1645 cm^{-1} (C=N). ^{1}H NMR spectrum (methanol-d_4): 2.68 (s, 3H, CH_3), 5.99 (s, 2H, CH_2), 7.86 (s, 1H, CH), 8.18–8.23 (m, 2H, 2 × CH), 8.66–8.71 (m, 1H, CH), 9.18–9.20 ppm (m, 2H, 2 × CH). MS (ES+) *m/z* (rel. intensity): 191.3 (M-HCl, 20), 93.9 (100). Found: C, 53.31; H,

5.20; N, 12.20%. $C_{10}H_{11}N_2OClS$ requires: C, 52.97; H, 4.89; N, 12.36%.

4-Methyl-1-[(2-methylthiazol-4-yl)methyl]pyridinium chloride (4b). A mixture of compound **2** (0.2 g, 1.36 mmol) and 4-methylpyridine (4 ml) was stirred at room temperature for 6 days. Then the formed precipitate was collected by filtration, washed with ethanol–ether mixture 1:1 and dried *in vacuo* to yield 0.021 g (24%) of compound **4b** as an amorphous white solid. ^{1}H NMR spectrum (methanol-d_4): 2.68 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 5.86 (s, 2H, CH_2), 7.79 (s, 1H, CH), 7.99 (d, 2H, J = 6.6 Hz, 2 × CH), 8.94 ppm (d, 2H, J = 6.6 Hz, 2 × CH). MS (ES+) *m/z* (rel. intensity): 206.4 (M-HCl, 20), 94 (100). Found: C, 55.29; H, 5.87; N, 11.92%. $C_{11}H_{13}N_2ClOS$ requires: C, 54.88; H, 5.44; N, 11.64%.

2-Amino-4-(chloromethyl)thiazole hydrochloride (6). Thiourea (0.56 g, 7.4 mmol) was added to a solution of 1,3-dichloropropanone (0.945 g, 7.4 mmol) in absolute ethanol (40 ml). The mixture was stirred at room temperature for 24 h and then kept at 5 °C for 12 h. The crystalline material was collected by filtration and recrystallized from ethanol to yield 0.96 g (70%) of hydrochloride **6** with m. p. 141–143 °C. Lit.[9] m. p. 144–145 °C. ^{1}H NMR spectrum (methanol-d_4): 4.52 (s, 2H, CH_2), 6.89 ppm (s, 1H, CH). ^{13}C NMR spectrum (methanol-d_4): 37.41 (CH_2), 108.42 (CH), 137.29 (C), 172.67 ppm (C=N).

1-[(2-Aminothiazol-4-yl)methyl]pyridinium chloride (7a). A solution of compound **6** (0.2 g, 1.081 mmol) in pyridine (22 ml) was stirred at room temperature for 24 h. Then the precipitate was collected by filtration, washed with ethanol–ether mixture 1:1 and recrystallized from ethanol to yield 0.11 g (53%) of compound **7a** with m. p. 217–219 °C (decomp.). IR spectrum: 3244 cm^{-1} (NH_2). ^{1}H NMR spectrum (methanol-d_4): 5.84 (s, 2H, CH_2), 7.27 (s, 1H, CH), 8.12–8.17 (m, 2H, 2 × CH), 8.62–8.67 (m, 1H, CH), 9.08–9.10 ppm (m, 2H, 2 × CH). ^{13}C NMR spectrum (methanol-d_4): 57.33 (CH_2), 113.14 (CH), 129.84 (2 × CH), 132.79, 146.29 (2 × CH), 148.24, 172.79 ppm (C=N, thiazole). MS (ES+) *m/z* (rel. intensity): 192.4 (M-HCl, 20), 189.3 (65), 113 (100). Found: C, 47.80; H, 4.63; N, 18.67%. $C_9H_{10}ClN_3S$ requires: C, 47.47; H, 4.43; N, 18.45%.

1-[(2-Aminothiazol-4-yl)methyl]-4-methylpyridinium chloride (7b). A solution of compound **6** (0.2 g, 1.081 mmol) in 4-methylpyridine (10 ml) was stirred at room temperature for 24 h. Then the precipitate was collected by filtration, and recrystallized from ethanol–diethyl ether mixture 1:1. The yield of compound **7b** was 0.226 g (45%), m. p. 196–198 °C (decomp.). ^{1}H NMR spectrum (methanol-d_4): 2.62 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 6.99 (s, 1H, CH), 7.89 (d, 2H, J = 6.6 Hz, 2 × CH), 8.83 ppm (d, 2H, J = 6.6 Hz, 2 × CH). ^{13}C NMR spectrum (methanol-d_4): 22.14 (CH_3), 59.05 (CH_2), 110.92, 129.94 (2 × CH), 140.08, 145.03 (2 × CH), 162.18, 172.66 ppm (C=N, thiazole). MS (ES+) *m/z* (rel. intensity): 206.4 (M-HCl, 20), 93.9 (100). Found: C, 49.97; H, 5.23; N, 17.59%. $C_{10}H_{12}ClN_3S$ requires: C, 49.68; H, 5.00; N, 17.38%.

1-[(2-Aminothiazol-4-yl)methyl]-2-methylpyridinium chloride (7c). A solution of compound **6** (0.2 g, 1.081 mmol) in 2-methylpyridine (10 ml) was stirred at room temperature for 72 h. Then the white precipitate was collected by filtration, and recrystallized from ethanol–diethyl ether mixture 1:1. The yield of compound **7c** was 0.03 g (10%), m. p. 241–243 °C (decomp.). IR spectrum: 3372 cm^{-1} (NH_2). ^{1}H NMR spectrum (methanol-d_4): 2.96 (s, 3H, CH_3), 5.62 (s, 2H, CH_2), 6.82 (s, 1H, CH), 7.88–7.93 (m, 1H, CH), 7.98 (d, 1H, J = 8.1 Hz, CH), 8.42 (dt, J = 7.8 Hz, J = 1.2 Hz, 1H, CH), 8.94 ppm (dd, J = 6.3 Hz, J = 1.2 Hz, 1H, CH). ^{13}C NMR spectrum (methanol-d_4): 20.96 (CH_3), 58.27 (CH_2), 109.18, 126.90, 131.40, 143.64, 146.95, 147.12, 157.52, 172.30 ppm (C=N, thiazole). MS (ES+) *m/z* (rel. intensity): 206.4 (M-HCl, 20), 93.9 (100). Found: C, 49.87; H, 5.50; N, 17.42%. $C_{10}H_{12}ClN_3S$ requires: C, 49.68; H, 5.00; N, 17.38%.

1-[(2-Acetylaminothiazol-4-yl)methyl]pyridinium chloride (8a). Acetic anhydride (0.22 g, 0.20 ml, 2.16 mmol) was added to a solution of compound **6** (0.2 g, 1.08 mmol) in pyridine (10 ml). The reaction mixture was stirred at room temperature for 24 h. Then the white precipitate was collected by filtration and recrystallized from ethanol–diethyl ether mixture 1:1. The yield of compound **8a** was 0.192 g (66%), m. p. 272–274 °C (decomp.). ^{1}H NMR spectrum (methanol-d_4): 2.11 (s, 3H, CH_3), 5.81 (s, 2H, CH_2), 7.38 (s, 1H, CH), 8.07–8.12 (m, 2H, 2 × CH), 8.55–8.61 (M, 1H, CH), 9.07–9.10 ppm (m, 2H, 2 × CH). ^{13}C NMR spectrum (methanol-d_4): 22.67 (CH_3), 61.28 (CH_2), 115.68, 129.45 (2 × C), 143.65, 146.34 (2 x C), 147.36, 161.09 (C=O), 170.91 ppm (C=N, thiazole). MS (ES+) *m/z* (rel. intensity): 234.4 (M-HCl, 20), 191.3 (50), 157.2 (85), 115 (100). Found: C, 49.31; H, 4.82; N, 15.20%. $C_{11}H_{12}ClN_3OS$ requires: C, 48.98; H, 4.48; N, 15.58%.

1-[(2-Acetylaminothiazol-4-yl)methyl]-4-methylpyridinium chloride (8b). Acetic anhydride (0.22 g, 0.20 ml, 2.16 mmol) was added to a solution of compound **6** (0.2 g, 1.081 mmol) in 4-methylpyridine (8 ml). The reaction was stirred at room temperature for 24 h. Then the white precipitate was collected by filtration and recrystallized from ethanol–diethyl ether mixture 1:1. The yield of compound **8b** was 0.129 g (42%), m. p. 218–220 °C. ^{1}H NMR spectrum (methanol-d_4): 2.08 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 5.67 (s, 2H, CH_2), 7.31 (s, 1H, CH), 8.62 (d, 2H, J = 6.6 Hz, 2 × CH), 8.85 ppm (d, 2H, J = 6.6 Hz, 2 × CH). ^{13}C NMR spectrum (methanol-d_4): 22.23 (CH_3), 22.53 (CH_3), 60.56 (CH_2), 115.55, 129.97 (2 × CH), 142.39, 145.36 (2 × CH), 162.0 (C=O), 171.08 ppm (C=N, thiazole). MS (ES+) *m/z* (rel. intensity): 248.4 (M-HCl, 20), 94 (100). Found: C, 51.03; H, 5.12; N, 14.64%. $C_{12}H_{14}ClN_3OS$ requires: C, 50.80; H, 4.97; N, 14.81%.

1-[(2-Acetylaminothiazol-4-yl)methyl]-2-methylpyridinium chloride (8c). Acetic anhydride (0.44 g, 0.41 ml,

4.32 mmol) was added to a solution of compound **6** (0.2 g, 1.08 mmol) in 2-methylpyridine (7 ml). The reaction mixture was stirred at room temperature for 72 h. Then the white precipitate was collected by filtration and recrystallized from a mixture of ethanol–diethyl ether, 1:1. The yield of compound **3c** was 0.036 g (12%), m. p. 241–243 ˚C (decomp.). IR spectrum: 3408 (N-H), 1683 cm^{-1} (C=O). ^{1}H NMR spectrum (methanol-d_4): 2.19 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 5.88 (s, 2H, CH_2), 7.41 (s, 1H, CH), 7.98–8.08 (m, 2H, 2 ´ CH), 8.49 (m, 1H, CH), 9.07–9.09 ppm (m, 1H, CH). ^{13}C NMR spectrum (methanol-d_4): 19.67 (CH_3), 21.40 (CH_3), 57.0 (CH_2), 113.60, 125.74, 130.24, 142.14, 145.89, 146.23, 156.45, 159.94 (C=O), 169.77 ppm (C=N, thiazole). MS (ES+) *m/z* (rel. intensity): 248.4 (M-HCl, 24), 155.2 (33), 94 (100). Found: C, 50.9; H, 5.2; N, 14.64%. $C_{12}H_{14}ClN_3OS$ requires: C, 50.8; H, 4.97; N, 14.81%.

CONCLUSIONS

This is the first study demonstrating that 2-amino- and 2-methyl-4-(chloromethyl)thiazoles can serve as versatile alkylating agents for the quaternization of pyridines and picolines. Eight new quaternary pyridinium chlorides possessing at the nitrogen atom a thiazolylmethyl substituent have been synthesized. The structures of the obtained heterocyclic adducts were proved by chemical and spectral analyses.

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PIRIDINŲ KVATERNIZACIJA 2-METIL- IR 2-AMINO-4-(CHLORMETIL)TIAZOLAIS

Santrauka

Alkilinant piridinus ir pikolinus 2-metil- ir 2-amino-4-(chlormetil)tiazolais, gaunamos naujos funkcionalizuotos piridinio druskos. Trijų komponentų reakcija, kai reakcijos mišinyje vienu metu reaguoja 2-amino-4-(chlormetil)tiazolas, acto rūgšties anhidridas ir piridinas arba pikolinai, įgalina lengvai gauti 1-[2-(acetilamino)tiazol-4-il]metilpiridinio chloridus.