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Recyclization reactions of 1-alkylpyrimidinium salts

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Abstract

The reaction of 4-amino-2-benzyl-1-methyl-5-ethoxycarbonylpyrimidinium iodide (**3**) with alcoholic methylamine resulted in the formation of the methylimine of 2-amino-4-hydroxy-6-methylamino-5-phenylpyridine-3-carbaldehyde (**5**). Heating of the same pyrimidinium salt in benzylamine gave a mixture of products of two C–C recyclizations: 2-benzyl-4-benzylamino-5-carbamoylpyrimidine (**7**) and the benzylimine of 4-amino-2-benzyl-6-benzylaminopyrimidine-5-carbaldehyde (**8**). The reaction of 2-amino-1,4-dimethyl-5-ethoxycarbonylpyrimidinium iodide (**10**) with KOH ethanolic solution gave a single product of C–C-recyclization: 2-amino-5-acetyl-4-hydroxypyrimidine (**11**).

Keywords: pyrimidinium salt; recyclization.

Introduction

Some of the frequently used pyrimidine ring modifications are the recyclization reactions (Danagulyan, 2005; El Ashry et al., 2010), the most frequently studied of which is the Dimroth rearrangement (Brown, 1968; El Ashry et al., 1999) involving the replacement of a nitrogen ring by an exocyclic nitrogen atom (*N–N* recyclizations). This reaction is widely used in the synthesis of various compounds that are unavailable by other methods and has become an important method in organic synthesis industry applications for the creation of various biologically active compounds and drugs (Suzuki et al., 1992; Nicolai et al., 1994; Lai et al., 1996; Fujii and Itaya, 1998, 1999; Nandeeshaiah and Ambekar, 1998; Loakes et al., 1999; Anaflous et al., 2004). We have studied the transformations of pyrimidines into pyridine derivatives ('Kost-Sagitullin rearrangement', Sagitullin et al., 1978; Danagulyan et al., 2000, 2001; Danagulyan and Sahakyan, 2004) in which the nitrogen atom of a pyrimidine ring is substituted by the exocyclic carbon atom in the second position. Recently we reported a new type of nucleophilic recyclization of pyrimidines–substitution of the endocyclic carbon atom by the exocyclic carbon atom (C–C recyclization), see Figure 1 (Vardanyan et al., 2005).

Results and discussion

To further investigate possibilities of pyrimidine ring recyclizations, we have studied transformations of pyrimidinium salts that can potentially be able to competitively undergo various types of recyclizations: Dimroth rearrangement, Kost-Sagitullin rearrangement and the new C–C recyclization that we have found. The necessary structural requirements in the model compounds are the presence of a 5-ethoxycarbonyl group, a quaternized nitrogen atom in the pyrimidine ring, and an exocyclic amine or methylene group in the α-position.

One of the appropriate model compounds, which satisfies the above-mentioned requirements, is 4-amino-2-benzyl-1-methyl-5-ethoxycarbonylpyrimidinium iodide (**3**). It was synthesized in quantitative yield by the reaction of phenylacetamidine with ethyl(ethoxy-methylene)cyanoacetate (**1**) followed by alkylation of the 4-amino-2-benzyl-5-ethoxycarbonylpyrimidine (**2**) obtained with methyl iodide, resulting in the formation of **3** (Scheme 1).

For this pyrimidinium salt **3**, we assumed the Kost-Sagitullin type rearrangement and C–C recyclization. As a result of the reaction of pyrimidinium salt **3** with alcoholic methylamine, i.e., under conditions of the Kost-Sagitullin rearrangement (Danagulyan et al., 2000, 2001; Danagulyan and Sahakyan, 2004), we have isolated the methylimine of 2-amino-4-hydroxy-6-methylamino-5-phenylpyridine-3-carbaldehyde (**5**), which is the product of a Kost-Sagitullin-type rearrangement (Scheme 2).

The presence of the azomethine moiety in product **5** is another important observation of this reaction. This means that the C–N recyclization proceeds as a result of the nucleophile being attacked at position 6 of the pyrimidine ring rather than at position 4. In our previous studies (Vardanyan et al., 2005) we have shown that for a similar transformation of pyrimidine that is non-alkylated at the nitrogen atom, the nucleophilic attack takes place at position 4 of the pyrimidine ring. Actually, quaternization of the pyrimidine nitrogen atom results in a shift of electron density in the heterocycle and, as a consequence, a change in direction of the initial attack on the nucleophile that leads to formation of the imine in position 5. The possible scheme for the rearrangement is presented in Figure 2. It includes the opening of the pyrimidine ring at the N(1)–C(6) bond followed by synchronous rotation around both the C(2)–N(3) and C(4)–C(5) bonds, and then cyclization, which completes the rearrangement process–formally, we can speak of two simultaneous rearrangements: a Kost-Sagitullin rearrangement (N–C) and (C–C) recyclizations.

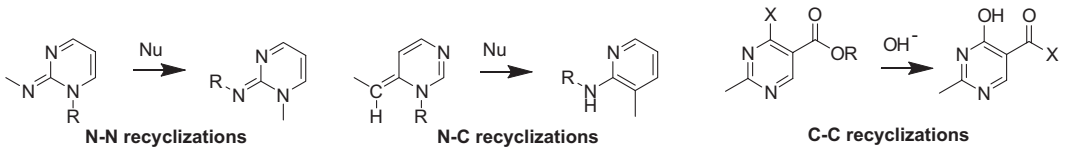
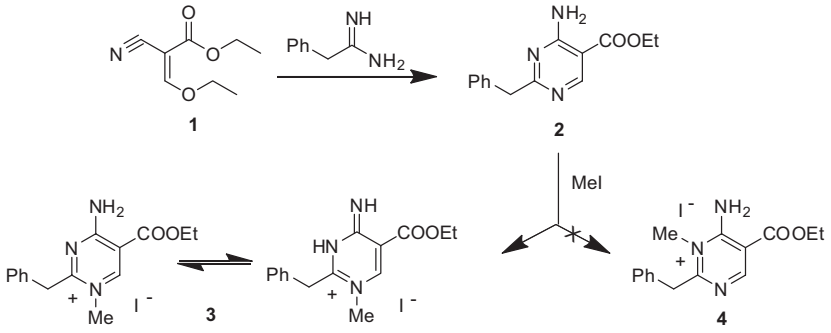
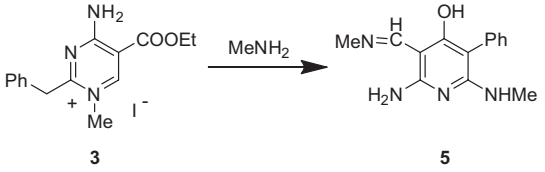


Figure 1 Pyrimidine ring recyclizations.



Scheme 1 Synthesis of the starting model compound **4**.



Scheme 2 Kost-Sagitullin rearrangement.

Heating the pyrimidinium salt **3** in benzylamine (Scheme 3) gave a mixture of acyclic product **6** and two products of C–C recyclizations: 2-benzyl-4-benzylamino-5-carbamoylpyrimidine (**7**) and the benzylimine of 4-amino-2-benzyl-6-benzylaminopyrimidine-5-carbaldehyde (**8**). The reaction of 2-amino-1,4-dimethyl-5-ethoxycarbonylpyrimidinium iodide (**10**) with KOH ethanolic solution (Scheme 4) gave a single product of C–C recyclization: 2-amino-5-acetyl-4-hydroxypyrimidine (**11**).

Conclusions

4-Amino-2-benzyl-1-methyl-5-ethoxycarbonylpyrimidinium iodide (**3**), when heated in benzylamine, is transformed into a mixture of three products: the product of destructive aminolysis **6** and two products of C–C recyclization, **7** and **8**.

On the other hand, heating 2-amino-1,4-dimethyl-5-ethoxycarbonylpyrimidinium iodide (**10**) with alcoholic KOH yields 2-amino-5-acetyl-4-hydroxypyrimidine (**11**) as the sole product. In this case, the product is derived from C–C recyclization of the pyrimidinium salt.

Experimental

General

Nuclear magnetic resonance (NMR) spectra were acquired on Varian Mercury 300 with a resonance frequency of 300.08 MHz for the ^{1}H

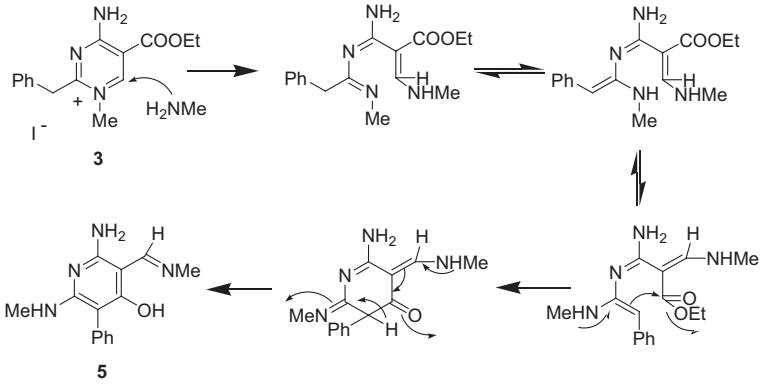
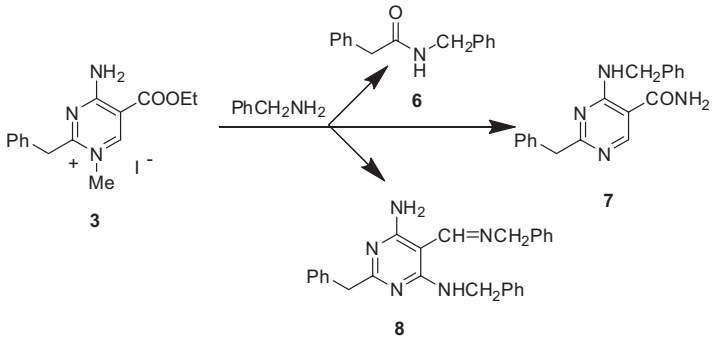
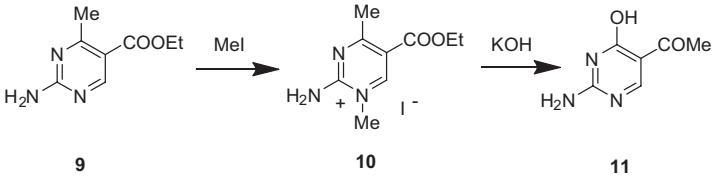


Figure 2 Proposed mechanism for the synthesis of **5** from **3**.



Scheme 3 Simultaneous rearrangements in the presence of benzylamine.



Scheme 4 Pure C–C recyclization of the pyrimidinium salt in KOH solution.

nucleus and 75.46 MHz for the ^{13}C nucleus. The sample temperature was 303 K. The coupling constants, J, are given in Hz. Thin layer chromatography (TLC) was performed on Silufol UV-254 platelets, developed by iodine vapors and Erlich reagent.

4-Amino-2-benzyl-5-ethoxycarbonylpyrimidine (2)

Here, 5.97 g (0.035 mol) of phenylacetamidine hydrochloride was added to a solution of sodium ethoxide prepared from 0.81 g (0.035 mol) of metallic sodium and 20 ml of dry ethanol. The mixture was stirred for 30 min and then the resulting sodium chloride precipitate was rapidly filtered off under reduced pressure. The residue was treated with a solution of 5.92 g (0.035 mol) of ethyl (ethoxymethylene)cyanoacetate (**1**) (Deno, 1947; Jones, 1952) in 10 ml of dry ethanol. The mixture was heated at reflux for 4 h, the alcohol was then removed and the residue thoroughly washed with acetone to afford 4.2 g (47%) of 4-amino-2-benzyl-5-ethoxycarbonylpyrimidine (**2**); mp 159–160°C, R_f 0.66 (acetone/toluene, 1:1); ^1H NMR (DMSO-d_6): δ 1.38 (3H, t, J=7.1, CH_2CH_3), 3.96 (2H, s, $CH_2C_6H_5$), 4.33 (2H, q, J=7.1, OCH_2), 7.1–7.3 (5H, m, C_6H_5), 7.5–7.6 (2H, br s, NH_2), 8.68 (1H, s, 6-H). Analysis calculated for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.64; H, 5.79; N, 16.16.

Preparation of 4-amino-2-benzyl-1-methyl-5-ethoxycarbonylpyrimidinium iodide (3)

A solution of 4-amino-2-benzyl-5-ethoxycarbonylpyrimidine (**2**, 2.57 g, 0.01 mol) in methyl iodide (5 ml) was heated in a sealed tube in a boiling water bath for 10 h. The resulting precipitate of **3** was washed with hot hexanes to afford 3.69 g (92%); mp 219–220°C; R_f 0.52 (isopropanol/ammonia/water, 7: 0.5:1); ^1H NMR (DMSO-d_6): δ 1.42 (3H, t, J=7.1, CH_2CH_3), 4.02 (3H, s, N–CH_3), 4.43 (2H, s, $CH_2C_6H_5$), 4.43 (2H, q, J=7.1, OCH_2), 7.34 (5H, m, C_6H_5), 8.79 (1H, br s, NH), 9.18 (1H, s, 6-H), 9.82 (1H, br s, NH). Analysis calculated for $C_{15}H_{18}N_3IO_2$: C, 45.13; H, 4.54; N, 10.53. Found: C, 45.34; H, 4.49; N, 10.66.

Reaction of 4-amino-2-benzyl-1-methyl-5-ethoxycarbonylpyrimidinium iodide (3) with methylamine

A mixture of **3** (1 g, 0.0025 mol) and alcoholic methylamine (20 ml, 10%) was heated for 10 h in a sealed tube immersed in a boiling water bath. The solvent and the excess methylamine were removed under reduced pressure. The residue was thoroughly extracted with hot benzene and after removal of the solvent the product was separated on a silica gel column eluting with benzene/acetone (1:1) to give 0.35 g (55%) of methylimine of 2-amino-4-hydroxy-6-methylamino-5-phenylpyridine-3-carbaldehyde (**5**); mp 140–141°C; R_f 0.52 (benzene/acetone, 1:1); ^1H NMR ($CDCl_3$), δ, ppm, J (Hz): 3.20 (3H, s, N–CH_3), 3.23 (3H, d, J=5.1, $NHCH_3$), 5.01 (1H, br s, NH), 5.58 (1H, br s, NH), 7.3–7.44 (5H, m, C_6H_5), 9.98 (1H, br s, $NHCH_3$), 10.17 (1H, s, CH=N). Analysis calculated for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.68; H, 6.47; N, 21.76.

Reaction of 4-amino-2-benzyl-1-methyl-5-ethoxycarbonylpyrimidinium iodide (3) with benzylamine

A mixture of **3** (0.8 g, 0.002 mol) and benzylamine (5 ml) was heated for 8 h in a sealed tube in a boiling water bath. After removal of the excess benzylamine under reduced pressure, the residue was extracted with hot benzene. The solvent was removed and products **6** to **8** obtained were separated on a silica gel column eluting with benzene/acetone (10:1).

***N*-(Benzyl)phenylacetamide (6)** Yield 0.15 g (33%); mp 117–118°C; R_f 0.76 (benzene/acetone, 1:1); ^1H NMR ($CDCl_3$): δ 3.62

(2H, s, CH_2), 4.42 (2H, d, J=5.9, CH_2NH), 5.68 (1H, br s, NH), 7.3 (10H, m, $2C_6H_5$). Analysis calculated for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.58; H, 6.49; N, 6.66.

2-Benzyl-4-benzylamino-5-carbamoylpyrimidine (7) Yield 0.18 g (28%); mp 210–211°C; R_f 0.48 (benzene/acetone, 1:1); ^{1}H NMR ($CDCl_3$), δ, ppm, J (Hz): 4.17 (2H, s, $CH_2C_6H_5$), 4.58 (2H, d, J=5.7, CH_2NH), 7.3 (10H, m, $2C_6H_5$), 7.43 (1H, br s, NH), 8.11 (1H, br s, NH), 9.02 (1H, s, 6-H). Analysis calculated for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60. Found: C, 71.58; H, 5.47; N, 17.66.

Benzylimine of 4-amino-2-benzyl-6-benzylaminopyrimidine-5-carbaldehyde (8) Yield 0.2 g (25%); mp 92–93°C; R_f 0.44 (benzene/acetone, 1:1); ^{1}H NMR ($CDCl_3$): δ 3.94 (2H, s, $CH_2C_6H_5$), 4.75 (2H, d, J=6.2, CH_2NH), 5.18 (2H, s, CH_2N), 7.1–7.4 (15H, m, 3 C_6H_5), 10.2 (1H, s, CH=N), 10.24 (1H, t, J=6.2, NH); ^{13}C NMR ($CDCl_3$): δ 42.4 (2-CH_2), 44.7 (CH_2NH), 45.5 (CH_2N=), 96.7 (5-C), 134.1 (O-Ph), 136.1 (m-Ph), 138.07 (ipso-Ph), 160.7 (6-C), 163.9 (4-C), 165.2 (2-C), 190.7 (CH=N). Analysis calculated for $C_{26}H_{25}N_5$: C, 76.63; H, 6.18; N, 17.19. Found: C, 73.58; H, 5.47; N, 16.33.

2-Amino-4-methyl-5-ethoxycarbonylpyrimidine (9) Here 3.2 g (0.0335 mol) of guanidine hydrochloride was added to a solution of sodium ethoxide prepared from 2.3 g (0.1 mol) of metallic sodium and 40 ml of absolute ethanol. After 30 min the NaCl precipitate that had formed was rapidly filtered off and 5.95 g (0.032 mol) of ethyl (ethoxymethylene)acetoacetate was added to the filtrate. The mixture was heated over a steam bath for 1 h and then the solvent was removed under reduced pressure. The residue was treated with 25 ml of 10% HCl and the mixture stirred for 30 min. The resulting crystals were filtered off and washed with acetone to yield 4.9 g (85%) of product **9**; mp 210–211°C; R_f 0.68 (toluene/acetone, 3:1); ^{1}H NMR (DMSO-d_6): δ 1.28 (3H, t, J=7.1, CH_2CH_3), 2.68 (3H, s, 4-CH_3), 4.30 (2H, q, J=7.1, OCH_2), 7.2 (2H, s, NH_2), 8.62 (1H, s, 6-H). Analysis calculated for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.32; H, 5.93; N, 23.08.

2-Amino-1,4-dimethyl-5-ethoxycarbonylpyrimidinium iodide (10) Here, 4 ml of methyl iodide was added to 1.81 g (0.01 mol) of 2-amino-4-methyl-5-ethoxycarbonylpyrimidine (**9**) and the mixture heated for 10 h in a sealed ampoule over a water-bath. After the excess methyl iodide was removed, the crystals that had formed were filtered off and thoroughly washed with hot hexane to give 3.1 g (96%) of product **10**; mp 179–181°C; R_f 0.48 (isopropanol/ammonia/water, 7:0.5:1); ^{1}H NMR (DMSO-d_6): δ 1.41 (3H, t, J=7.1, CH_2CH_3), 2.78 (3H, s, 4-CH_3), 3.90 (3H, s, N-CH_3), 4.38 (2H, q, J=7.1, OCH_2), 9.18 (1H, s, 6-H), 9.18 (1H, br s, NH), 9.78 (1H, br s, NH). Analysis calculated for $C_9H_{14}N_3IO_2$: C, 33.45; H, 4.37; N, 13.00. Found: C, 33.34; H, 4.52; N, 13.24.

Reaction of 2-amino-1,4-dimethyl-5-ethoxycarbonylpyrimidinium iodide (10) with potassium hydroxide

A solution of potassium hydroxide prepared from 0.56 g (0.01 mol) of KOH and 20 ml of ethanol had 0.97 g (0.003 mol) of 2-amino-1,4-dimethyl-5-ethoxycarbonylpyrimidinium iodide (**10**) added to it. The mixture was heated under reflux for 5–6 h. The alcohol was removed, the residue dissolved in water and the solution acidified with acetic acid. The precipitated crystals were filtered off and washed with acetone to give 0.34 g (74%) of 2-amino-5-acetyl-4-hydroxypyrimidine (**11**): mp 296–298°C; R_f 0.5 (ethanol); ^{1}H NMR (DMSO-d_6): δ 2.57 (3H, s, CH_3), 6.69 (2H, br s, NH_2), 8.64 (1H, s, 6-H), 10.8–12.1 (1H, br s, OH). Analysis calculated for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 46.77; H, 4.35; N, 27.59.

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