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Reactions of 1*H*-pyrano[3,4-*c*]pyran-7-ium perchlorates with ammonium acetate and amines: synthesis of 2,7-naphthyridines and pyrano[3,4-*c*]pyridinium salts

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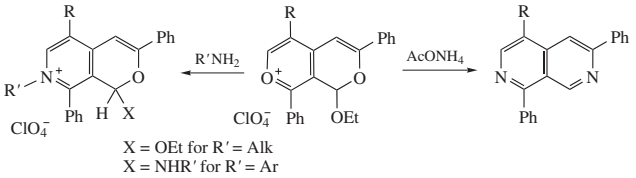
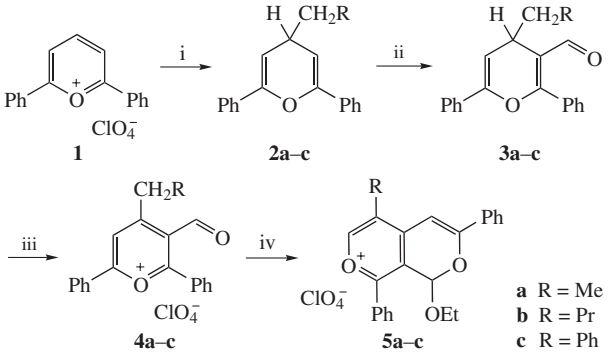
The reaction of 1*H*-pyrano[3,4-*c*]pyran-7-ium perchlorates with ammonium acetate gives 2,7-naphthyridines, while in their reaction with primary amines pyrano[3,4-c]pyridinium salts are formed. The structure of 7-[2-(dimethylamino)ethyl]-1-ethoxy-5-methyl-3,8-diphenyl-1*H*-pyrano[3,4-*c*]pyridin-7-ium perchlorate was established by X-ray diffraction.



Previously,[1] starting from 2,6-diphenylpyrylium perchlorate **1**, we obtained a representative of a new class of fused pyrylium salts, namely, 1-ethoxy-5-methyl-3,8-diphenyl-1*H*-pyrano[3,4-*c*]-pyran-7-ium perchlorate **5a**, whose formation was accompanied by the intramolecular rearrangement of the initial 3-formylpyrylium salt **4a** under the action of triethylorthoformate (Scheme 1). The reactions of the monocyclic pyrylium salts are used to synthesize a variety of heterocycles, in particular compounds of the pyridine series.[2] 1*H*-Pyrano[3,4-*c*]pyran-7-ium salts **5a–c** contain two pyran rings not equal in reactivity. This gives a challenge to alternately manipulate with different cycles to obtain various bicyclic systems. However, the properties of salts **5a–c** have not been investigated.

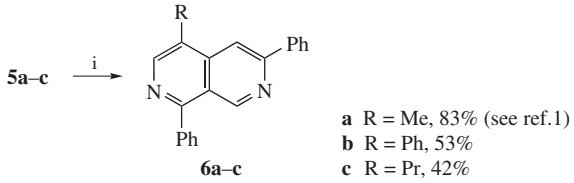
The purpose of this work was to study the reactions of salts **5a–c** with ammonia and amines. In the case of recyclization of both rings in the system **5**, such reactions should lead to 2,7-naphthyridine derivatives with potent biological activity (*cf.* refs. 3–6). The recyclization of only one ring of salts **5** should lead to pyrano[3,4-*c*]pyridine derivatives which can also be promising (*cf.* refs. 7,8). In addition to known salt **5a**, its new analogues **5b**,**c** were synthesized according to the previously described method[1] (see Scheme 1).



Scheme 1 *Reagents and conditions*: i, RCH_2MgX; ii, $Me_2NCHO/POCl_3$; iii, $TrClO_4$; iv, $CH(OEt)_3$.

The reaction of 2,6-diphenylpyrylium perchlorate **1** with organomagnesium compounds led to unstable 4*H*-pyrans **2a–c** which were then subjected to the Vilsmeier formylation without purification. Further reaction of 3-formylpyrans **3a–c** with trityl perchlorate afforded 3-formylpyrylium salts **4a–c**. Finally, the action of triethyl orthoformate resulted in 1*H*-pyrano[3,4-*c*]pyran-7-ium perchlorates **5a–c** (*cf.* ref. 1).

Reaction of salts **5b**,**c** with an ammonium acetate excess in the same manner as in the case of perchlorate **5a**[1] led to recyclization of both rings to form naphthyridines **6b**,**c** (Scheme 2).

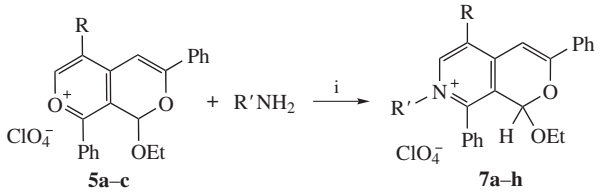


Scheme 2 *Reagents and conditions*: i, $AcONH_4$, AcOH, Δ, 1 h.

Unlike ammonia, amines react with salts **5a–c** in a different way, namely, only the pyrylium ring undergoes recyclization and the second pyran ring remains unaffected. The product composition of this reaction depends on the nucleophile type. Aliphatic amines form only the recyclization products **7a–f** (Scheme 3). Displacement of the ethoxy group is not observed even when a 2–3-fold excess of amine is used.

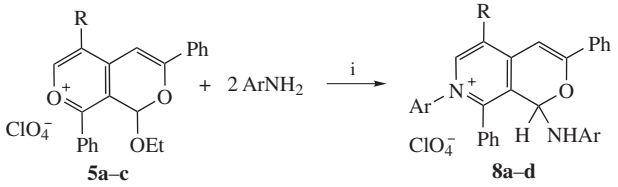
Aromatic amines give reaction products **8a–d** (Scheme 4) with 2 equiv. of nucleophile. One mole of the amine is consumed in the formation of pyridinium ring, the second one would displace the ethoxy group.

The structures of all products were confirmed by ^1H and ^{13}C NMR spectra. The structure of compound **7a** was additionally proved by X-ray diffraction (Figure 1).†



7a R = Me, R′ = $Me_2N(CH_2)_2$, 66%
7b R = Me, R′ = 2-morpholinoethyl, 43%
7c R = Me, R′ = 2-(3-indolyl)ethyl, 63%
7d R = Me, R′ = Cy, 67%
7e R = Ph, R′ = $Me_2N(CH_2)_2$, 76%
7f R = Ph, R′ = 2-morpholinoethyl, 45%
7g R = Ph, R′ = 2-(3-indolyl)ethyl, 62%
7h R = Ph , R′ = Cy, 60%

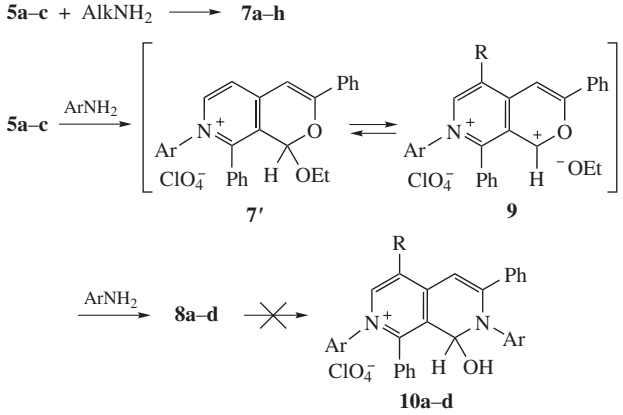
Scheme 3 *Reagents and conditions*: i, EtOH, Δ, 1.5–2 h.



8a R = Me, Ar = 4-MeC_6H_4, 49%
8b R = Me, Ar = 4-$MeOC_6H_4$, 61%
8c R = Ph, Ar = 4-MeC_6H_4, 54%
8d R = Ph, Ar = 3-$F_3CC_6H_4$, 74%

Scheme 4 *Reagents and conditions*: i, EtOH, Δ, 1.5–2 h.

Since the reactions of 1*H*-pyrano[3,4-*c*]pyran-7-ium perchlorates with ammonium acetate led to recyclization of both pyran cycles, it has been suggested that in the case of amines, both rings can be transformed to give products **10a–d** (Scheme 5) with replacing both oxygen atoms with nitrogen. Using ^{1}H NMR spectroscopy, it is not possible to distinguish structures **8** and **10**. To clarify the structure of the products, a two-dimensional correlation NMR spectrum {^{15}N, ^{1}H} of compound **8c** was recorded (see Online Supplementary Materials). In this spectrum, there is a correlation of a charged nitrogen atom (δ 201.32 ppm) with the C–H proton of the pyridinium ring as a cross-peak with the coordinates N, H {201.32, 8.10} ppm and a correlation between the nitrogen of the NH group and the *ortho*-protons of the *para*-tolyl group as a doublet with the coordinates N, H {85.52, 6.79; 85.52, 6.77} ppm. The correlation of the uncharged nitrogen atom (δ 85.52 ppm) and the proton of the NH group appears as a doublet of doublets with coordinates N, H {85.52, 6.60; 85.52, 6.58; 85.52, 6.45; 85.52, 6.43} ppm (J_{CH} = 8.57 Hz, J_{NH} = 92.4 Hz). This correlation should not fit for the structure **10c**. Thus, in reactions with aromatic amines products **8a–d** are formed. The difference between the results of reactions with aliphatic and aromatic amines can be explained as follows (see Scheme 5). Initially, the reaction with both amine types occurs on the charged ring and is accompanied with the recyclization to form products **7** or **7′**. Obviously, the ethoxy group will be substituted by the S_N1 mechanism through the formation of dication **9**. The addition of the second mole of the amine will be controlled by the ease of its generation.



Scheme 5

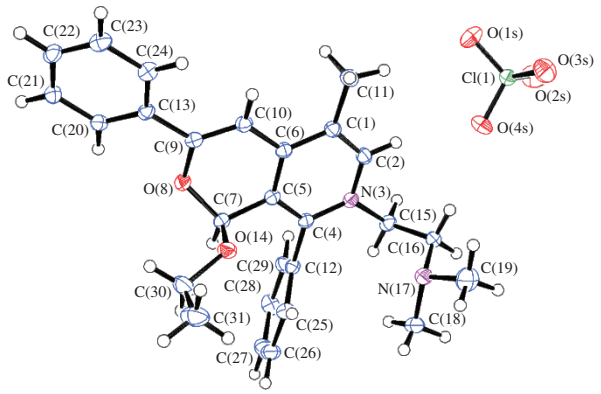


Figure 1 Molecular structure of compound **7a** (thermal ellipsoids are drawn at the 50% probability level).

Quantum chemical methods were used to compare the kinetic and thermodynamic characteristics of formation of cations of type **9** (model structures **12** with R = Me and R = Ph, Scheme 6). It turned out that the elimination of methanol from phenyl derivative **11** is 18.7 kcal mol^{-1} more advantageous than in the case of methyl derivative **13**. The activation energy of the structure $\mathbf{12}^{Ph}$ formation in the case of the *N*-phenyl derivative is also 20.2 kcal mol^{-1} lower than that for the corresponding *N*-methyl dication $\mathbf{12}^{Me}$. The calculations were carried out taking into account the solvation effects in ethanol (Scheme 6).‡

Hence, the calculations showed that cation **9** in the case of aromatic amines would form faster and easier. This explains the reaction route towards products **8a–d**.

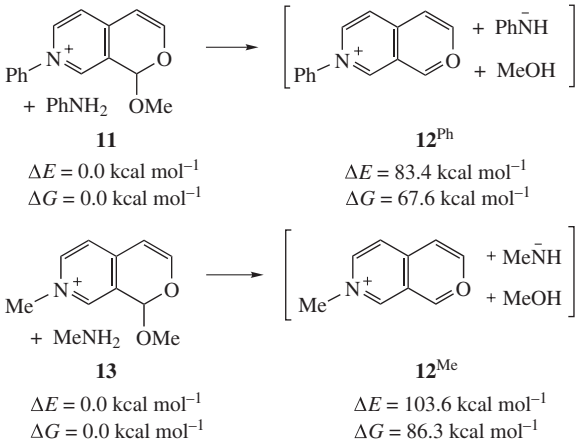
In summary, pyrano[3,4-*c*]pyranium salts react with ammonium acetate, forming 2,7-naphthyridines the recyclization products of both pyran rings. In reactions with primary amines, only the

† *Crystal data for* **7a**. $C_{27}H_{31}ClN_2O_6$ (M = 515.01), monoclinic, space group $P2_1/n$, a = 15.5795(15), b = 10.3847(10) and c = 16.6676(17) Å, β = 106.076(2)°, V = 2591.2(4) Å^3, Z = 4, d_{calc} = 1.3201 g cm^{-3}, μ = = 0.192 cm^{-1}, $2\theta_{max}$ = 58°, 31135 reflections collected (6894 independent reflections, R_{int} = 0.0477), R_1 = 0.0440 [for $I \geqslant 2\sigma(I)$], wR_2 = 0.1473 (for all data), largest difference peak and hole 0.39/–0.56 e Å^{-3}.

The X-ray datasets for compound **7a** were collected on a Bruker SMART APEX II CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 56°$]. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the isotropic-anisotropic approximation. The positions of hydrogen atoms were calculated from geometrical point of view and refined with the riding model. All calculations were performed using SHELXTL PLUS 5.0 software package.

CCDC 1882688 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

‡ Quantum chemical calculations were performed by density functional theory (DFT) using 6-31G** basis set and B3LYP functional, including the Becke three-parameter exchange functional[9] and the Lee–Young–Parr correlation functional.[10] Complete geometry optimization for structures corresponding to stationary points on minimum energy paths was continued until the gradient value reached 10^{-7} hartree/bohr, using Gaussian 03 software suite[11] running on a Silver cluster at the Deparment of Chemistry of the Southern Federal University. The nature of stationary points was established by calculation of the normal vibration frequencies (Hesse matrices).[12] The solvation effects were accounted for using the polarized continuum model (PCM).[13]



Scheme 6

pyrylium ring is recyclized; aliphatic amines form only the products of recyclization, while aromatic amines – products of recyclization and displacement of the ethoxy group. The reactions revealed can serve as methods for the synthesis of 2,7-naphthyridines and pyrano[3,4-*c*]pyridinium salts.

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Online Supplementary Materials

Supplementary data associated with this article (details of experimental procedures and NMR spectra) can be found in the online version at doi: 10.1016/j.mencom.2019.07.026.

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