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A new and direct synthesis of 1-acylamino-2,6-diaryl pyridinium salts

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Abstract: We described a facile one pot reaction of carboxonium salts **1** with acylhydrazines to give high yields of functionalized 1-aminopyridinium salts **3** throught an intramolecular cyclization of N-(5-ethoxy 1,5-diaryl-2,4 pentadienylidene) N'-(acyl) hydrazinium salts **2**. The synthesis of di- and tri-pyridinio substituted polycarboxamides **3e-g** demonstrate the validity of the method. The kinetics of the process indicate that the limiting rate of the reaction is the all *trans* - all *cis* interconversion of **2**. A single crystal determination confirm the structure of **3b.**

Keywords: cyanines; hydrazinium salts; aminopyridinium salts; X ray crystal structure; kinetics.

N-aminopyridinium salts are useful intermediates for the synthesis of pyridinium-betaines, metallocomplexes and biologically active compounds [1]. Although several methods for the formation of 1-aminopyridinium derivatives are reported [2], polyfunctional 1-(acylamino)-2,6-diaryl pyridinium salts are still difficult to obtain. To exploit the synthetic applications of the pentamethinium salts we achieved the regioselective synthesis of (5-ethoxy 1,5-diaryl 2,4-pentadienylidene) hydrazinium salts **2** (hemicarboxonium salts) via the reaction of N-(5-ethoxy 1,5-diaryl 2,4-pentadienylidene) ethyloxonium perchlorate **1** (carboxonium perchlorates) with N-alkyl and N-acylhydrazines [3]. In a further development of the polymethine salts chemistry, we describe herein i) the intramolecular cyclization of compounds **2** and an easy one pot route to functionalized 1-aminopyridinium salts **3**, ii) the kinetics of the reaction studied with compound **2b**.

As previously described for **2b** [3] the various monohydrazides (**a-d**) react with carboxonium salts **1**[+] at room temperature to give hydrazinium derivatives **2a-d** in excellent yields. The latter could be isolated as analytically pure orange-yellow solids after work-up and crystallization. Proton NMR spectroscopy of the compounds clearly demonstrated that the reactions exclusively afforded the isomers with a *trans-trans* configuration in the polyenic chain. The large vicinal proton coupling constants of 12-14 Hz between H_2, H_4 and H_3 indicate that these protons are all *trans* in the polymethine moiety. Nevertheless compounds **2a-d** are easily transformed in solution into 1-(acylamino) 2,6-diarylpyridinium salts **3a-d** (Scheme 1) upon standing at room temperature during several days or by heating in acetonitrile during 2-3 h. The method has a general application pattern in carboxyhydrazide

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+ (5-Ethoxy 1,5-di(4-methylphenyl) 2,4-pentadienylidene) ethyloxonium triflate was prepared from 4-methylphenyl acetophenone, $HC(OEt)_3$ and CF_3SO_3H according to the standard procedure: Pikus A.L., Feigel'man V.M., Mezheritzkii V.V., Zh.Obshch. Khim. 1989, 25, 2603.

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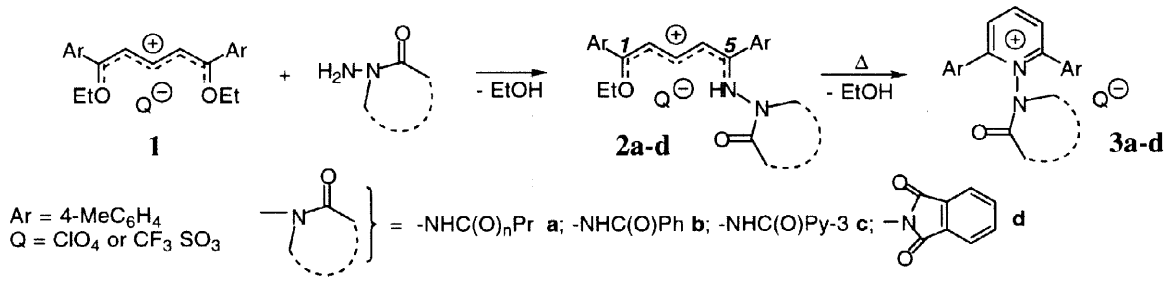
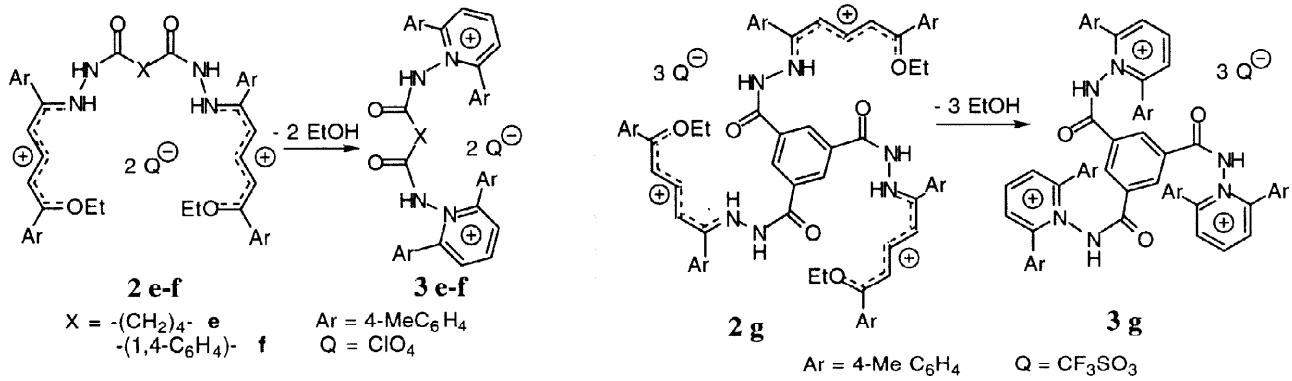
series. This is illustrated by the synthesis of the *bis* (**3e-f**) and *tris* **3g** pyridinio-functionalized derivatives from hydrazides of di- (**2e-f**) and tricarboxylic acids **2g**. Thus, the open-chain intermediate **2e-g** obtained from carboxonium salts **1** and polycarbohydrazides were converted into **3e-g** by heating at 60 °C for 3 hours in CH_3CN (Scheme 2).



Scheme 1: Synthesis of 1-(acylamino) 2,6-diarylpyridinium salts **3a-d**



Scheme 2: Cyclization of *bis* (**2e-f**) and *tris* (**2g**) hemicarboxonium intermediates

Transformation of **1** to **3** may be carried out by a one pot procedure without isolation of **2** [see exp. part]. Solvents of various polarity and basicity were used (THF, 1,2-dimethoxyethane, CH_2Cl_2, CH_3CN) and the best results from the viewpoint of yields and purity were obtained with acetonitrile. All new compounds were characterized by microanalysis (C, H, N), NMR (^1H; ^{13}C), UV-vis spectra and mass spectrometric parameters. For the purpose of unequivocal characterization, the structure of the compound **3b** was determined by single crystal X-ray analysis (Fig. 1).

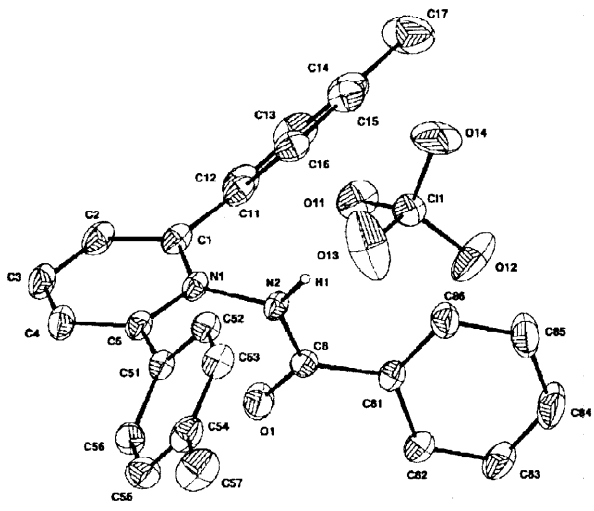
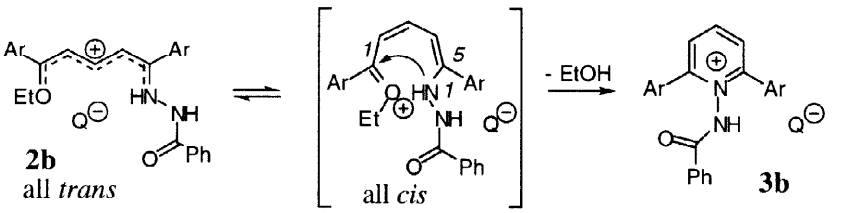


Figure 1 : X-Ray molecular structure of compound **3b** shown by CAMERON drawing [4] with thermal ellipsoids (50% probability).

Selected bonds lengths (Å); C(1)-C(2) 1.383(4), C(2)-C(3) 1.367(4), C(3)-C(4) 1.371(4), C(4)-C(5) 1.380(4), C(5)-N(1) 1.369(3), N(1)-C(1) 1.375(3), N(1)-N(2) 1.407, N(2)-C(6) 1.373(3). Selected bonds angles (°); N(2)-N(1)-C(1) 116.9(2), N(2)-N(1)-C(5) 118.3(2), C(1)-N(1)-C(5) 123.6(2), N(1)-N(2)-H(1) 119.0(19), N(1)-N(2)-C(6) 115.0(2), C(6)-N(2)-H(1) 125.9(19).

$[C_{26}H_{23}N_2O][ClO_4]$, M = 478.93, Triclinic, a = 10.401(2) Å, b = 10.826(2) Å, c = 11.229(2) Å, α = 84.13(2)°, β = 72.62(2)°, γ = 83.93(2)°, V = 1197.6(9) $Å^3$, ρ_{calcd} = 1.33 $g.cm^{-3}$, μ(Mo-Kα) = 1.95 cm^{-1}. Crystal size) 0.6*0.5*0.3 mm, 9336 reflections collected, (3382 independent) Rav = 0.02.

From a mechanistic point of view, transformation **2** → **3** should include an all *trans* - all *cis* interconversion of the pentamethine chain in **2** followed by an intramolecular condensation due to the nucleophilic attack of the nitrogen N_1 on the electrophilic C_1 carbon (Scheme 3).



Scheme 3

To ascertain this assumption, the kinetics of this reaction was followed by UV-vis spectroscopy with compound **2b** as a model. The evolution with the time (3 hours) of the absorption spectra of **2b** in acetonitrile (10^{-5} M) was recorded between 250 and 550 nm at 35 °C (Fig. 2). The isosbestic point at λ = 362 nm indicates that there is no accumulation of the all *cis* intermediate which is readily transformed into **3b**. Moreover the characteristic absorption band of the *trans* conformation at λ_{max} = 437 nm decreases following a first order kinetic. A series of time drive experiments at λ_{max} in a 25-55 °C temperature range served to determine the kinetic and thermodynamic parameters of the transformation [values for k (mn^{-1}) are 1.23 x 10^{-3}, 3.06 x 10^{-3}, 4.80 x 10^{-3} and 22.15 x 10^{-3} for T °C of 25, 35, 40 and 55 respectively whereas $\Delta G^{0\ddagger}$ = 45.96 kJ x mol^{-1}, $\Delta H^{0\ddagger}$ = 32 kJ x mol^{-1} and $\Delta S^{0\ddagger}$ = -189.47 J x mol^{-1} x K^{-1} for T = 25 °C]. The standard $\Delta G^{0\ddagger}$ value comes from the Eyring equation with k at 25 °C, and the entalpy and entropy ones derives from an Arrhenius plot (Log k/T = f(1/T)). These values, characteristic of the kinetics of the disappearance of compound **2b** by intramolecular formation of **3b**, correspond to the limiting step which consists in partial double bonds rotations. Product **2b** is not *stricto sensu* a cyanine dye but an hemicarboxonium salt. Nevertheless it seems reasonable, due to its charged polyenic behaviour, to observe that the kinetic data are consistent with the ones obtained for cyanines dyes by means of variable temperature proton NMR [5].

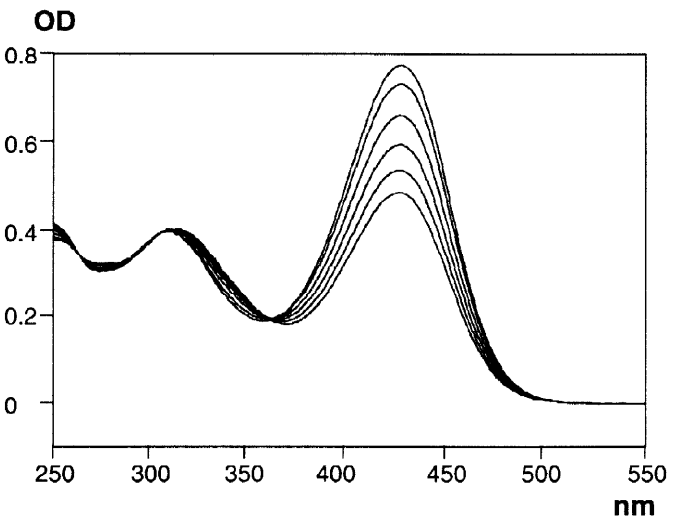


Figure 2: Evolution of the UV-vis spectra of **2b**

In summary, we have carried out an efficient way for the synthesis of 1-acylamino-2,6-diarylpyridinium derivatives, leading to various polypyridinio-substituted polycarboxamides. The possible application of this type of products as non linear optical materials is currently under investigation.

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Experimental Part

Typical experimental procedure: 1-benzoylamino 2,6-bis(4-methylphenyl) pyridinium perchlorate **3b**
The carboxonium salt **1** (0.43 g; 1 mmol) was dissolved in dry acetonitrile (10 mL) under argon. Benzoylhydrazide (0.14 g; 1 mmol) in 5 mL of acetonitrile was added dropwise and the solution stirred for 2 h. Evaporation of the volatives in vacuum gives N-(5-ethoxy 1,5-diaryl 2,4-pentadienylidene)N'-benzoylhydrazinium perchlorate **2b** in quantitative yield. More prolonged stirring at 20 °C (3 days), or heating at 60 °C for 3 h gives **3b**. Yield 0.50 g (96%), m. p. 80 °C (dec.). Satisfactory spectroscopic (^1H, ^{13}C NMR; UV-vis; mass spectrometry) and microanalytical data were obtained for all new compounds: NMR (δ ppm; J Hz); UV-vis, CH_3CN, 25 °C (λ_{max} nm, ε L x mol^{-1} x cm^{-1}) .

3a: ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.40 (t, 3H, J = 7.4, $C\underline{H}_3CH_2$), 1.07 (q, 2H, J = 7.4, $CH_3C\underline{H}_2$), 1.73 (t, 2H, J = 7.4, $C\underline{H}_2$-CO), 2.36 (s, 6H, $\underline{H}_3$C-Ar), 7.28 (d, 4H, J = 8, $\underline{H}^{3,5}$-*Ar*), 7.51 (d, 4H, J = 8, $\underline{H}^{2,6}$-*Ar*), 7.86 (d, 2H, J = 8, $\underline{H}^{3,5}$-*Py*), 8.53 (t, 1H, J = 8, $\underline{H}^4$-*Py*). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.1 ($\underline{C}H_3$), 17.0 (-$\underline{C}H_2$-), 21.6 ($H_3\underline{C}$-*Ar*), 35.1 ($\underline{C}H_2$-CO), 127.5 ($\underline{C}^1$-*Ar*), 129.0 ($\underline{C}^{3,5}$-*Py*), 142.4 ($\underline{C}^4$-*Ar*), 146.8 ($\underline{C}^4$-*Py*), 160.0 ($\underline{C}$O), 170.0 ($\underline{C}^{2,6}$-*Py*).UV-vis λ_{max} = 327, ε = 15600. FABMS (MNBA) m/z = 345 (100%) M^+. Anal. calcd for $C_{23}H_{25}N_2O_5Cl$: C, 62.09; H, 5.66; N, 6.30. Found: C, 61.21; H, 5.62; N, 5.83.

3b: ^{1}H NMR (CD_3CN, 250 MHz) δ 2.36 (s, 6H, $C\underline{H}_3$-Ar), 7.21-7.54 (m, 13H, $\underline{H}_{arom}$), 8.13 (d, 2H, J = 8, $\underline{H}^{3,5}$-*Py*), 8.71 (t, 1H, J = 8, $\underline{H}^4$-*Py*). ^{13}C NMR (CD_3CN, 62.9 MHz) δ 21.5 ($\underline{C}H_3$), 128.4 ($\underline{C}^{3,5}$-*Py*), 128.7 ($\underline{C}^1$-*Ar*), 143.5 ($\underline{C}^4$-*Ar*), 148.8 ($\underline{C}^4$-*Py*), 160.1($\underline{C}$=O). UV-vis λ_{max} = 325, ε = 20000. DCIMS (NH_3) m/z =379 (90%) (M^+), m/z = 260 (100%) (2,6-Ar *Py* - H)$^+$. Anal. calcd for $C_{26}H_{23}N_2O_5Cl$: C, 65.20; H, 4.84; N, 5.85. Found: C, 65.88; H, 4.86; N, 5.55.

3c: ^{1}H NMR ($DMSOd_6$, 400 MHz) δ 2.30 (s, 6H, CH_3 -Ar), 7.30-7.70 (m, 8H, H_{arom}), 7.75-8.73 (m, 4H, *nicotinyl*), 8.12 (d, J = 8, $\underline{H}^{3,5}$-*Py*), 8.71 (t, 1H, J = 8, $\underline{H}^4$*Py*). ^{13}C NMR ($DMSOd_6$, 100.7 MHz) δ 20.8 ($C\underline{H}_3$-*Ar*) 125.5 ($\underline{C}^3$-*Py*), 129.2 ($\underline{C}^1$-*Ar*), 140.3 ($\underline{C}^4$-*Ar*), 143.3 ($\underline{C}^4$-*Py*), 155.3 (C=O), 163.0 ($\underline{C}^{2,6}$-*Py*). UV-vis λ_{max} = 337, ε = 19700. FABMS (MNBA) m/z = 380 (100%) M^+. Anal. calcd for $C_{25}H_{22}N_3O_5Cl$: C, 61.19; H, 4.64; N, 8.58. Found: C, 61.28; H, 4.75; N, 8.49.

3d: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 6H, $C\underline{H}_3$-*Ar*), 7.20-7.90 (m, 8H, $\underline{H}_{arom}$), 8.28 (d, 2H, J = 8, $\underline{H}^{3,5}$-*Py*), 8.92 (t, 1H, J = 8, $\underline{H}^4$-*Py*). ^{13}C NMR (CD_3CN, 75.5 MHz) 21.8 ($\underline{C}H_3$-*Ar*), 126.5 ($\underline{C}^{3,5}$-*Py*),127.4 ($\underline{C}^1$-*Ar*), 144.2 ($\underline{C}^4$-*Ar*), 151.2 ($\underline{C}^4$-*Py*), 160.1 ($\underline{C}$=0), 162.3 ($\underline{C}^{2,6}$-*Py*). UV-vis λ_{max} = 334, ε = 9140. FABMS (MNBA) m/z = 405 (100%) M^+. Anal. calcd for $C_{27}H_{21}N_2O_6Cl$: C, 64.23; H, 4.19; N, 5.55. Found: C, 64.02; H, 4.17; N, 5.81.

3e: ^{1}H NMR (CD_3CN, 300 MHz) δ 0.51 (m, 4H, -$C\underline{H}_2CH_2$-), 1.44 (m, 4H, -$C\underline{H}_2$CO), 2.34 (s, 12H, $C\underline{H}_3$-*Ar*) 7.29 (d, 8H, J = 8, $\underline{H}^{3,5}$-*Ar*), 7.45 (d, 8H, J = 8, $\underline{H}^{2,6}$-*Ar*), 7.90 (d, 4H, J = 8, $\underline{H}^{3,5}$-*Py*), 8.54 (t, 2H, J = 8, $\underline{H}^4$-*Py*). ^{13}C NMR (CD_3CN, 75.5 MHz) δ 22.4 (CH_3-*Ar*) 23.3 ($\underline{C}H_2CH_2$), 32.8 ($\underline{C}H_2$CO), 128.4 ($\underline{C}^1$-*Ar*), 130.0 ($\underline{C}^3$-*Py*); 143.3 ($\underline{C}^4$-*Ar*), 148.0 ($\underline{C}^4$-*Py*), 160.5 ($\underline{C}$O), 169.9 ($\underline{C}^{2,6}$-*Py*). UV-vis λ_{max} = 328, ε = 24000. FABMS (MNBA) m/z = 759 (15%) (M^{++}, ClO_4^-)$^+$, m/z = 659 (87%) (M-H)$^+$, m/z = 259 (100%) (2, 6-Ar *Py* $^{+\bullet}$). Anal. calcd for $C_{44}H_{44}N_4O_{10}Cl_2$: C, 61.47; H, 5.16; N, 6.52. Found: C, 60.70; H, 5.05; N, 6.27.

3f: ^{1}H NMR (CD_3CN, 400 MHz) δ 2.37 (s, 12H, $C\underline{H}_3$-*Ar*), 7.20-7.60 (m, 20H, $\underline{H}_{arom}$), 8.16 (d, 4H, J = 8, $\underline{H}^{3,5}$-*Py*), 8.72 (t, 2H, J = 8, $\underline{H}^4$-*Py*). ^{13}C NMR (CD_3CN, 100.6 MHz) δ 21.2 ($\underline{C}H_3$-*Ar*), 127.6 ($\underline{C}^1$-*Ar*), 143.2 ($\underline{C}^4$-*Ar*), 148.6 ($\underline{C}^4$-*Py*), 159.6 (C=O), 164.3 ($\underline{C}^{2,6}$-*Py*). UV-vis λ_{max} = 330, ε = 31500. FABMS (MNBA) m/z = 779 (10%) (M^{++}, ClO_4^-)$^+$, m/z = 679 (100%) (M^{++}-H^+)$^{+\bullet}$. Anal. calcd for $C_{44}H_{40}N_4O_{10}Cl_2$: C, 62.80; H, 4.58; N, 6.37. Found: C, 62.14; H, 4.60; N, 6.20.

3g: ^{1}H NMR (CD_3CN, 400 MHz) δ 2.30 (s, 18H, $C\underline{H}_3$-*Ar*), 7.25-7.60 (m, 24+3, $\underline{H}_{arom}$), 8.13 (d, 6H, J = 8, $\underline{H}^{3,5}$-*Py*), 8.73 (t, 3H, J = 8, $\underline{H}^4$-*Py*). ^{13}C NMR (CD_3CN, 100.6MHz) δ 21.3 ($\underline{C}H_3$-*Ar*), 128.2 ($\underline{C}^1$-*Ar*), 131.5 ($\underline{C}^{3,5}$-*Py*), 143.1($\underline{C}^4$-*Ar*), 148.6 ($\underline{C}^4$-*Py*), 159.4 (C=O), 162.9 ($\underline{C}^{2,6}$-*Py*). UV-vis λ_{max} = 328, ε = 35900. FABMS (MNBA) m/z = 1279 (4%) (M^{+++}, 2 $CF_3SO_3^-$)$^+$, m/z = 1129 (42%) (M^{+++}- 2H)$^+$, m/z = 461 (100%) (M- 2H- 2*Py*). Anal. calcd for $C_{69}H_{57}N_6O_{12}F_9S_3$: C, 57.98; H, 4.02; N, 5.88. Found: C, 56.62; H, 4.02; N, 5.82.

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