Synthesis of Triethylammonium 4-Aryl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates: 1-Cyanoacetyl-3,5-dimethylpyrazole as an Effective Alternative to Cyanoacetic Ester in Guareschi Reaction

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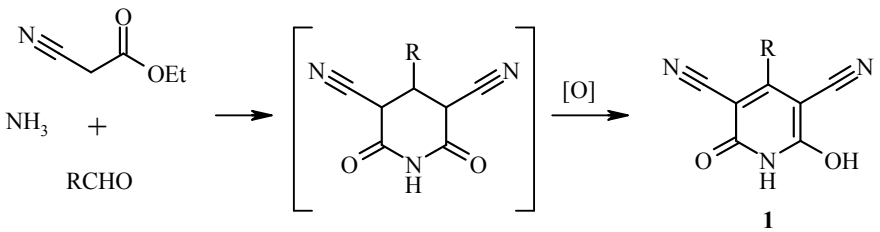
Abstract: Triethylammonium 4-aryl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates were obtained by reaction of (*E*)-3-aryl-2-cyanoacrylamides with 1-cyanoacetyl-3,5-dimethylpyrazole in the presence of 1.5 eq. of Et_3N (20 °C, acetone) in 55-98% yields.

Keywords: Guareschi reaction, Guareschi imides, 1-cyanoacetyl-3,5-dimethylpyrazole, Michael addition, active methylene compounds.

Introduction

Guareschi imides (2,6-dioxopiperidine-3,5-dicarbonitriles) are of a practical interest due to anticonvulsive, sedative and analgesic properties [1], as well as perspective building blocks for synthesis of bispidine (3,7-diazabicyclo[3.3.1]nonane) derivatives and related compounds [2, 3]. The most concise approach to 2,6-dioxopiperidine-3,5-dicarbonitriles is Guareschi reaction of cyanoacetic ester with carbonyl compounds and ammonia [4-8]. An alternative variant is based on the reaction of 2-cyanoacrylates with cyanoacetamide [9-12]. The classic Guareschi synthesis has some drawbacks – varying yields, prolonged reaction time and some scope limitations. Thus, ketones were successfully used as carbonyl components in the reaction to yield 4,4-disubstituted Guareschi imides. Much less is known, however, on the application of aldehydes in the reaction. Guareschi imides tend to oxidize readily *in situ*, as evidenced from the literature [13], so the sole products derived from the reaction of aldehydes, cyanoacetic ester and ammonia were reported to be 4-R-6-hydroxy-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1** or their salts [14-18] (*Scheme 1*):



1

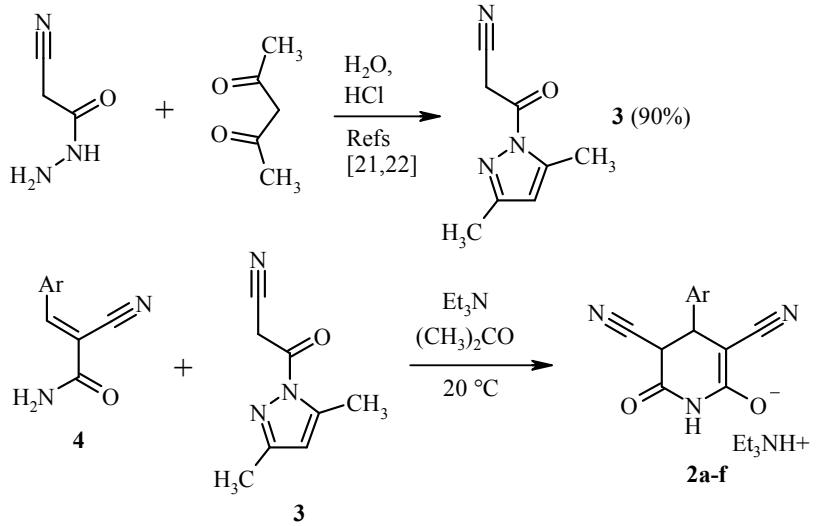
Generally, the only reported procedures [1, 19, 20] for preparation of 4-R-2,6-dioxopiperidine-3,5-dicarbonitriles or their salts are tedious, require exotic reagents such as Li_3N as a source of NH_3, or give low yields. In this

communication we present our preliminary results on the synthesis of Guareschi imides by reaction of (*E*)-3-aryl-2-cyanoacrylamides with 1-cyanoacetyl-3,5-dimethylpyrazole.

Results and Discussion

We found that triethylammonium salts of Guareschi imides **2** could be easily synthesized by Michael addition of 1-cyanoacetyl-3,5-dimethylpyrazole **3** to 2-cyanoacrylamides **4** (Scheme 2). Pyrazolide **3** is readily accessible by reaction of cyanoacethydrazide with acetylacetone [21, 22] and has been known to react rather as mild cyanoacetylating agent [23]. Prior to our studies, pyrazolide **3** was never used as active methylene compound superior to cyanoacetic ester.

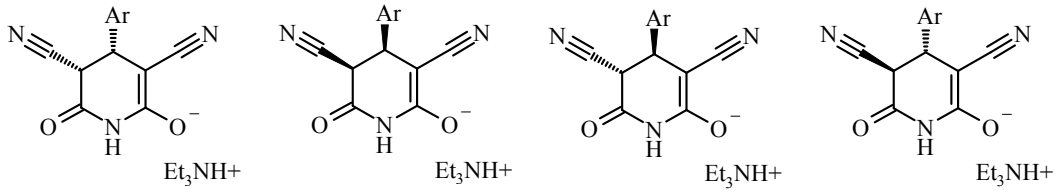
Scheme 2:



2,**4**: a) Ar = 2-ClC_6H_4; b) 2-thienyl; c) 2-$NO_2C_6H_4$; d) 4-BrC_6H_4; e) 2-MeC_6H_4; f) 2-$CF_3C_6H_4$.

The reaction proceeds under mild conditions (20 °C) and provides the salts **2** in good yields (55-98%) as mixtures of pairs of *cis*- and *trans*-diastereomers (Figure 1) in a nearly 1:1 *cis*/*trans* ratio. As revealed by ^{1}H NMR data, the reaction products lacked the impurities of oxidation products.

Fig. 1. Stereoisomers of triethylammonium 4-aryl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates **2**.



cis *cis* *trans* *trans*

Triethylammonium 4-aryl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates are white crystalline solids sparingly soluble in acetone, readily soluble in DMF or DMSO, and insoluble in THF or ether. The structures of the compounds obtained were confirmed by IR, ^{1}H- and ^{13}C-NMR spectroscopy as well as elemental analysis data.

Conclusions

In summary, we have developed new and effective approach to the synthesis of triethylammonium 4-aryl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates, based on the reaction of (*E*)-3-aryl-2-cyanoacrylamides with 1-cyanoacetyl-3,5-dimethylpyrazole **3** in the presence of Et_3N. A replacement of cyanoacetic ester for pyrazolide **3** is crucial for successful synthesis of salts of Guareschi imides, probably due to the facts that pyrazolide is much more active than ethyl cyanoacetate and reaction conditions are milder than those originally reported [14-18]. No oxidation products **1** were isolated or found.

Experimental

Melting points were measured on a Electrothermal Mel-Temp 3.0 apparatus. Elemental analyses for C, H, and N were conducted using Carlo-Erba 1106 elemental analyser, accuracy ±0.25 %. IR spectra were recorded on a FTIR Shimadzu IRPrestige-21 spectrophotometer (KBr pellets) excepting **2a** recorded on an IKS-29 spectrophotometer in Nujol mulls. The ^{1}H NMR spectra were performed on Bruker DRX-400 (400.40 MHz) spectrometer in DMSO-d_6 solutions, excepting for **2a** recorded on Bruker DRX-500 (500.07 MHz) in DMSO-d_6 with Me_4Si as the internal standard. ^{13}C NMR spectrum of **2a** was recorded on Bruker DRX-500 (125.76 MHz) spectrometer in DMSO-d_6 with Me_4Si as the internal standard. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent – Silpearl, large-pore silicagel after Pitra with luminiscent indicator for UV 254 on the aluminium foil, binder – starch) in the acetone–hexane (1:1) system; spots were visualized with iodine vapors and UV light.

Triethylammonium 4-aryl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates (2a-f). General procedure. A 50 mL Erlenmeyer flask equipped with a magnetic stirring bar was charged with 1.0 mmol of corresponding (*E*)-3-aryl-2-cyanoacrylamide **4a-f** and 10-20 mL of solvent (pure acetone or acetone:THF 1:3) and flushed with dry argon. The reaction mixture was stirred continuously while the temperature was kept constant at 20-25 °C until a homogenic solution formed. After 10 min, 1-cyanoacetyl-3,5-dimethylpyrazole **3** (196 mg, 1.2 mmol) and triethylamine (0.20-0.22 ml, 1.5-1.6 mmol, dried over KOH) were added, the mixture was flushed with argon, a flask was sealed. The mixture was stirred at 20 °C for 24 h and then kept in freezer for 2-3 h. A white crystalline solid mass was filtered off, washed with a plenty of THF or ether to give salts **2a-f** which were found to be pure enough for analytical purposes.

Triethylammonium 4-(2-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olate (2a). (*Caution! Irritant*). Yield 76%, mp > 210 ºC, R_f = 0.69 (acetone-hexane 1:1). IR, ν, cm^{-1}: 3550-3400 (NH^+), 3240 (NH), 2255 (non-conjugated C≡N), 2175 (C≡N), 1695 (C=O). ^{1}H NMR (500 MHz), δ, ppm (*J*, Hz): 1.16 (t, 9 H, ^3J = 7.1, 3 C<u>H</u>$_3$CH$_2$); 3.05 (q, 6 H, ^3J = 7.1, 3 CH$_3$C<u>H</u>$_2$); 4.19-4.79 (m, 2 H, C(4)H & C(5)H signals of diastereomers overlapped); 7.27-7.50 (m, 4 H, 2-ClC_6H_4); 9.71 (broadened s, 1 H, NH). Signal of NH^+-proton was not detected, probably due to proton-deuterium exchange. ^{13}C NMR (125 MHz), δ, ppm: 9.34;

37.30, 41.78, 46.31; 128.07; 128.17; 129.10; 129.32; 129.75; 129.97; 133.13; 133.70; 138.47; 140.50; 164.32; 164.51. Found, %: C 61.14; H 6.24; N 14.90. $C_{19}H_{23}ClN_4O_2$ (M = 374.86). Calculated, %: C 60.88; H 6.18; N 14.95.

Triethylammonium 3,5-dicyano-6-oxo-4-(2-thienyl)-1,4,5,6-tetrahydropyridine-2-olate (2b). Yield 98%, mp 157.5-162.5 ºC. IR, ν, cm^{-1}: 3547-3416 (NH^+), 3238 (NH), 2253 (non-conjugated C≡N), 2164 (C≡N), 1690 (C=O). ^{1}H NMR (400 MHz), δ, ppm (*J*, Hz): 1.16 (t, 9 H, ^3J = 7.2, 3 C$\underline{H}_3$CH$_2$); 2.96 (q, 6 H, ^3J = 7.2, 3 CH$_3$C$\underline{H}_2$); 3.87-4.80 (m, 2 H, C(4)H & C(5)H signals of diastereomers overlapped); 6.95 (m, 1 H, thienyl); 6.96 (m, 1 H, thienyl); 7.29 (m, 1 H, thienyl); 9.31 (broadened s, 1 H, NH). Signal of NH^+-proton was not detected, probably due to proton-deuterium exchange. Found, %: C 59.14; H 6.36; N 16.29. $C_{17}H_{22}N_4O_2S$ (M = 346.45). Calculated, %: C 58.94; H 6.40; N 16.17.

Triethylammonium 3,5-dicyano-4-(2-nitrophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-olate (2c). (*Caution! Irritant*). Yield 84%, mp 177-178 ºC. IR, ν, cm^{-1}: 3549-3416 (NH^+), 3237 (NH), 2255 (non-conjugated C≡N), 2172 (C≡N), 1670 (C=O), 1521 (NO_2, N–O *symm* stretch), 1346 (NO_2, N–O *asymm* stretch). ^{1}H NMR (400 MHz), δ, ppm (*J*, Hz): 1.17 (t, 9 H, ^3J = 7.2, 3 C$\underline{H}_3$CH$_2$); 3.01 (q, 6 H, ^3J = 7.2, 3 CH$_3$C$\underline{H}_2$); 4.09 and 4.39 (each d, 1 H, ^3J = 7.4, C(4)H and C(5)H signals of *trans*-diastereomers); 4.67-4.96 (m, 1 H, C(4)H & C(5)H signals of *cis*-diastereomers overlapped); 7.50-7.94 (m, 4 H, Ar); 9.38 and 9.43 (both are broadened s, 1 H, NH peaks of *cis*- and *trans*-diastereomers). Signal of NH^+-proton was not detected, probably due to proton-deuterium exchange. Found, %: C 59.48; H 6.04; N 18.33. $C_{19}H_{23}N_5O_4$ (M = 385.42). Calculated, %: C 59.21; H 6.01; N 18.17.

Triethylammonium 4-(4-bromophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olate (2d). Yield 55%, mp > 210 ºC. IR, ν, cm^{-1}: 3553-3416 (NH^+), 3238 (NH), 2255 (non-conjugated C≡N), 2170 (C≡N), 1672 (C=O). ^{1}H NMR (400 MHz), δ, ppm (*J*, Hz): 1.14 (t, 9 H, ^3J = 7.2, 3 C$\underline{H}_3$CH$_2$); 2.93 (q, 6 H, ^3J = 7.2, 3 CH$_3$C$\underline{H}_2$); 3.79-4.85 (m, 2 H, C(4)H & C(5)H signals of diastereomers overlapped); 7.18-7.62 (m (two dd overlapped), 4 H, 4-BrC$_6$H$_4$); 9.29 and 9.31 (both are broadened s, 1 H, NH peaks of *cis*- and *trans*-diastereomers). Signal of NH^+-proton was not detected, probably due to proton-deuterium exchange. Found, %: C 54.01; H 5.55; N 13.38. $C_{19}H_{23}BrN_4O_2$ (M = 419.32). Calculated, %: C 54.42; H 5.53; N 13.36.

Triethylammonium 3,5-dicyano-4-(2-methylphenyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-olate (2e). Yield 76%, mp 166-168 ºC. IR, ν, cm^{-1}: 3553-3416 (NH^+), 3238 (NH), 2241 (non-conjugated C≡N), 2174 (C≡N), 1695 (C=O). ^{1}H NMR (400 MHz), δ, ppm (*J*, Hz): 1.10 (t, 9 H, ^3J = 7.2, 3 C$\underline{H}_3$CH$_2$); 2.41 (s, 3 H, CH$_3$); 2.81 (q, 6 H, ^3J = 7.2, 3 CH$_3$C$\underline{H}_2$); 3.98-4.75 (m, 2 H, C(4)H & C(5)H signals of diastereomers overlapped); 7.11-7.49 (m, 4 H, Ar); 9.27 (broadened s, 1 H, NH). Signal of NH^+-proton was not detected, probably due to proton-deuterium exchange. Found, %: C 68.00; H 7.36; N 15.11. $C_{20}H_{26}N_4O_2$ (M = 354.45). Calculated, %: C 67.77; H 7.39; N 15.18.

Triethylammonium 3,5-dicyano-4-[2-(trifluoromethyl)phenyl]-6-oxo-1,4,5,6-tetrahydropyridine-2-olate (2f). Yield 83%, mp 167-171 ºC. IR, ν, cm^{-1}: 3553-3416 (NH^+), 3238 (NH), 2241 (non-conjugated C≡N), 2174 (C≡N), 1697 (C=O). ^{1}H NMR (400 MHz), δ, ppm (*J*, Hz): 1.16 (t, 9 H, ^3J = 7.2, 3 $C\underline{H}_3CH_2$); 2.97 (q, 6 H, ^3J = 7.2, 3 $CH_3C\underline{H}_2$); 4.16-4.94 (m, 2 H, C(4)H & C(5)H signals of diastereomers overlapped); 7.43-7.74 (m, 4 H, Ar); 9.41 (broadened s, 1 H, NH). Signal of NH^+-proton was not detected, probably due to proton-deuterium exchange. Found, %: C 58.58; H 5.70; N 13.80. $C_{20}H_{23}F_3N_4O_2$ (M = 408.42). Calculated, %: C 58.82; H 5.68; N 13.72.

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