The Michael-type Addition of 1-Cyanoacetyl-3,5-dimethylpyrazole to Arylmethylenecyanoacetamides

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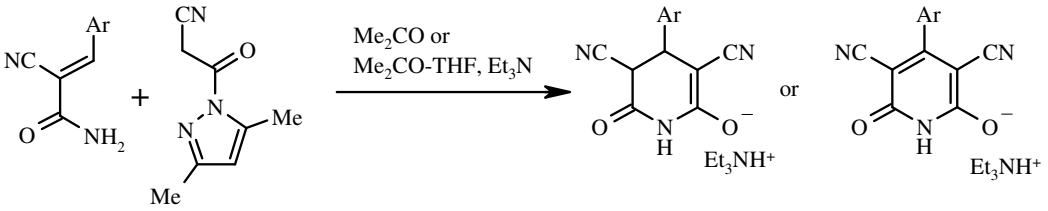
Abstract: The Et_3N-promoted reaction of (*E*)-3-aryl-2-cyanoacrylamides (arylmethylene cyanoacetamides) with 1-cyanoacetyl-3,5-dimethylpyrazole was thoroughly studied. It was found that either triethylammonium 4-aryl-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-olates **1** (salts of Guareschi imides) or their oxidation products – triethylammonium 4-aryl-3,5-dicyano-6-oxo-1,6-dihydropyridine-2-olates **2** were formed, depending on the nature of substituents in the 3-aryl fragment of starting acrylamides. Thus, when Ar = *ortho*-, *meta*-substituted phenyl or hetaryl such as 2-furyl, 3-thienyl etc., only Guareschi imides salts **1** were obtained in good to excellent yields. In the case of *para*-substituted or unsubstituted phenyl, pyridine-2-olates **2** were isolated as major products due to fast oxidation of Guareschi intermediates. The influence of reaction conditions and the nature of the base on the structure of final products is discussed.

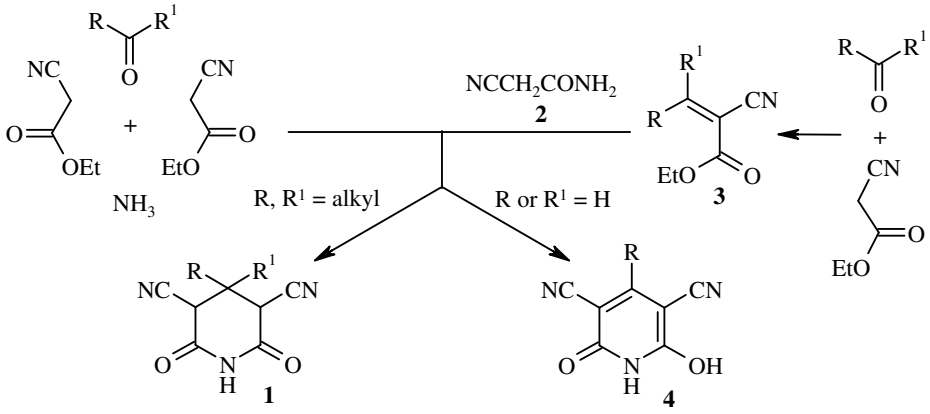
Keywords: azolides, cyanoacetylpyrazole, Michael addition, Guareschi imides, glutarimides, pyridines, oxidation, 2,6-dioxopiperidin-3,5-dicarbonitriles, 2-cyanoacrylamides, ethyl cyanoacetate.



Introduction

In the 1890s, Ichilio Guareschi had described [1-5] the ternary condensation of ketones with cyanoacetic ester and ammonia, giving rise to 4,4-disubstituted 2,6-dioxopiperidine-3,5-dicarbonitriles (**1**) (also known as β,β'-dialkyl-α,α'-dicyano-glutarimides, or Guareschi imides). The discovery of the analeptic and sedative action of compounds **1** [6-11] stimulated the study of their preparation and properties. However, it has been found that the classic Guareschi method has some drawbacks, *e.g*. varying yields and long reaction times [11]. To overcome the drawbacks, McElvain & Clemens have developed [12] a modified two-stage

procedure, based on the condensation of ketones with cyanoacetic ester followed by Michael-type addition of cyanoacetamide **2** to the resulted unsaturated esters **3**. The scope of the approach was demonstrated in papers [13-16].



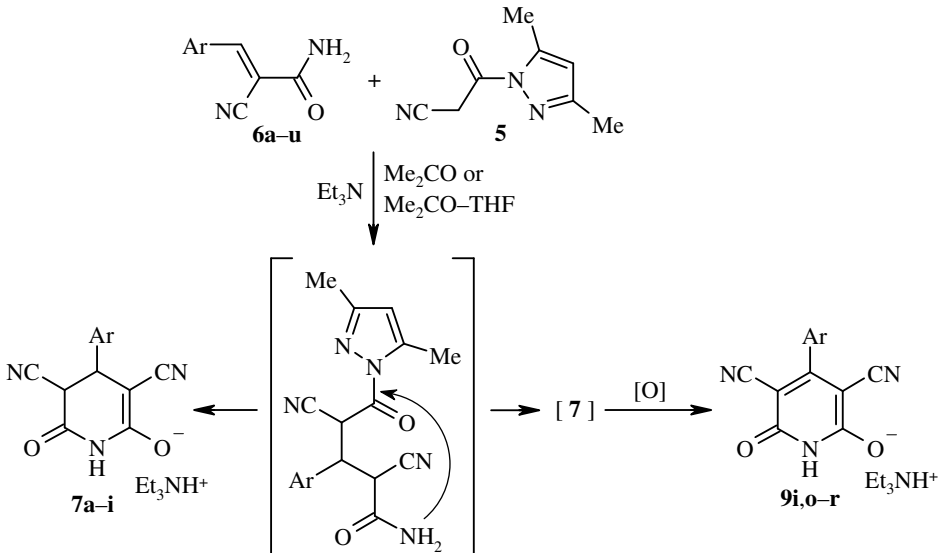
Both the Guareschi and McElvain–Clemens approaches have another limitation which is due to the low variability of a carbonyl component. In general, the Guareschi reaction proceeds smoothly when simple unbranched dialkyl ketones, cycloalkanones or certain heterocyclic ketones are used. The successful result in the synthesis of glutarimides **1** strongly depends on the steric hindrance of substituents of the carbonyl compounds: thus, the reaction does not proceed or gives very low yields in the case of alkyl aryl ketones or with ketones bearing bulky, long-chain alkyl groups (C_3-C_4 or higher) [11]. On the other hand, the reaction also fails when far less hindered aldehydes were used. The only known reports of the Guareschi imides synthesis from aldehydes [17-21] either demand the use of exotic reactants such as Li_3N as a source of NH_3 [19], 3-hydroxy-2-benzofuran-1(3*H*)-one as a masked aldehyde [21], or give low yields of target glutarimides **1** [17]. The most reasonable reason is that compounds **1** might be oxidized by air [22]. As it was noted in one of the earliest Guareschi works [23] and has been repeatedly confirmed by later observations [24-32], even under mild conditions the reaction of aldehydes with cyanoacetic ester and ammonia leads to pyridine-2(1*H*)-ones **4** as the products of oxidation of the first-formed Guareschi intermediates **1**. As it was reported [17], 4-aryl-substituted glutarimides have a marked anticonvulsant, analgesic and sedative activity, so the development of preparative method for synthesis of 4-aryl-monosubstituted Guareschi imides is of a practical interest. However, this problem cannot be solved efficiently by the methods known to date.

Results & Discussion

In preliminary communications we have reported the synthesis of triethylammonium salts of 4-aryl-monosubstituted Guareschi imides [33, 34] as well as their sulfur [35, 36] and selenium analogs [37] by Michael-type reaction of 3-aryl-2-cyanoprop-2-enechalcogenamides with 1-cyanoacetyl-3,5-dimethyl-pyrazole (**5**) in the presence of Et_3N. Azolide **5** can be easily obtained with ~90 % yield by reaction of cyanoacethydrazide with acetylacetone [38]. Cyanoacetylpyrazole **5** was recognized as a cheap, effective cyanoacetylating

agent considerably more active than ethyl cyanoacetate, it was also proved to be superior to cyanoacetyl chloride and cyanoacetyl azide in terms of stability and convenience [39]. Only a few examples of the use of cyanoacetylpyrazole **5** as an active methylene compound were reported to date [39].

In the present work, we wish to report the results of detailed studies of the new approach. It was found that the reaction of 3-aryl-2-cyanoprop-2-enamides **6** with cyanoacetylpyrazole **5** (1.2 equiv.) and an excess of Et_3N led to the triethylammonium salts of Guareschi imides **7a**-**i** in 50-98% yield, or (after acidification) to the Guareschi imides **8j**-**n**, or to the oxidation products – pyridin-2-olates **9i,o**-**r**, depending on the structure of the substrate and the conditions (Table 1). Pure acetone or acetone-THF mixtures were found to be the most convenient solvents for the reaction. The choice of the solvent was determined: (1) by the low nucleophilicity, which excluded a solvolysis of azolide **5**, and (2) by the solubility of the starting amide **6** (addition of THF helps to dissolve those amides **6** that were sparingly soluble in pure acetone). Since the products are usually poorly soluble in acetone and THF, they precipitated from the reaction mixture upon cooling, while 3,5-dimethylpyrazole remained in the mother liquor. In those cases when salts **7a**-**i** and **9i,o**-**r** appeared to be soluble in acetone, the reaction mixtures were treated with HCl to give either glutarimides **8j**-**n** or pyridin-2(1*H*)-one **4s**.



It has been found that the resistance of compounds **7** towards oxidation depends strongly on the structure of 4-aryl substituent. In general, heteroaromatic C-(4) substituents (2-furyl, 2-thienyl, 3-thienyl), as well as *ortho*- or *meta*-substituted phenyls were found to stabilize the alicyclic system of Guareschi imides. In most of these cases, the presence of an inert atmosphere (argon) is not required; compounds **7a,e** were formed under air atmosphere in the same yields.

Moreover, when the salts **7b,c** with 4-(*ortho*-R)-aryl substituents were maintained in DMSO for 4 days at 25 °C, they revealed no significant oxidation.

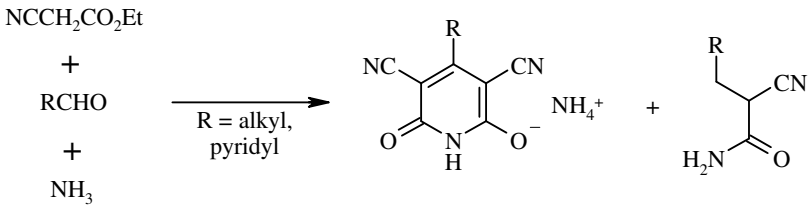
Table 1. The products of the reaction of amides 6a–u with cyanoacetylpyrazole 5

Starting amide	Ar	Conditions*	Products**	Yield, %
6a	2-ClC_6H_4	A	**7a**	79
		B		76 [34]
6b	2-MeC_6H_4	A	**7b**	88
6c	2-$O_2NC_6H_4$	A	**7c**	84
6d	2-$F_3CC_6H_4$	A	**7d**	83
6e	2,3-$(MeO)_2C_6H_3$	A	**7e**	89
		B		97
6f	2-thienyl	A	**7f**	98
6g	3-$O_2NC_6H_4$	B	**7g**	48
6h	4-BrC_6H_4	A	**7h**	55
6i	4-MeC_6H_4	A	**7i**	50
		B	**7i + 9i** (1:5)** (2:5)***	72
6j	2-furyl	C	**8j**	45
6k	3-thienyl	C	**8k**	83
6l	3-$MeOC_6H_4$	C	**8l**	54
6m	4-$BuOC_6H_4$	C	**8m**	73
6n	3-$PhCH_2O$-4-$MeOC_6H_3$	D	**8n**	55
6o	Ph	A	**7o + 9o** (1:3)***	53
		B	**9o**	57
6p	4-$MeOC_6H_4$	A	**6p + 9p** (3:2)***	16
		B	**6p + 9p** (10:14)***	21
6q	3,4-$(MeO)_2C_6H_3$	B	**7q + 9q** (1:5)***	60
6r	4-$O_2NC_6H_4$	B	**9r**	64
6s	4-*i*-PrC_6H_4	D	**4s + 8s** (55:45)** (1:1)***	15
6t	2,4-$(MeO)_2C_6H_3$	A	(no reaction)	0
6u	4-HOC_6H_4	A	(resinification)	–

* Reaction conditions: **A**: acetone or acetone–THF, under argon, 15-20 ° C; **B**: acetone, 15-20 ° C, air; **C**: acetone, THF– acetone, under argon, 20 ° C, then HCl; **D**: acetone, 20 ° C, air, then HCl.
** By HPLC / MS. *** According to the ^{1}H NMR data.

But less clear is the situation in those cases when the substituents at the 4-position are either phenyl or *para*-substituted phenyls. Thus, in the case when Ar = Ph, the corresponding oxidation product, pyridine-2-olate **9o**, was isolated even when the reaction was conducted under argon atmosphere. Under the same conditions we obtained the mixture of starting amide **6p** and pyridine **9p** when Ar was 4-$MeOC_6H_4$. The unexpected formation of the oxidation products **9** under an oxygen-free atmosphere can be explained by the possible oxidizing effects of

amides **6** with respect to Guareschi imides **1** as it was previously described by Brunskill [26, 28]:



However, an inert atmosphere is required for the synthesis of Guareschi imide salt **7i** (Ar = 4-MeC_6H_4); we succeeded to isolate the salt **7i** when the reaction was conducted under argon, whereas compound **9i** becomes the predominant product under air atmosphere. Similar results (a mixture of Guareschi imides and oxidized products) were obtained when amides **6q** (Ar = 3,4-$(MeO)_2C_6H_3$) and **6s** (Ar = 4-*i*-PrC_6H_4) were put into the reaction. However, in the case of amides **6m,n** (Ar = 4-$BuOC_6H_4$, 3-$PhCH_2O$-4-$MeOC_6H_3$) only Guareschi salts **8m,n** were isolated. In the case of amide **6r** (Ar = 4-$O_2NC_6H_4$), the salt **9r** was obtained in a good yield. Amide **6t** (Ar = 2,4-$(MeO)_2C_6H_4$) was recovered unchanged, probably due to the strong electron-donating effect of the aryl substituent in combination with steric factors. When we attempted to introduce the amide **6u** (Ar = 4-HOC_6H_4) into the reaction with pyrazolide **5** and Et_3N, only intractable tar was obtained, and the expected products **7**-**9u** could not be isolated.
All these results are in good agreement with previously reported data [17]; as it was shown, amides **6** with strong donating substituents in the 3-aryl moiety does not react with ethyl cyanoacetate. Thus, the course of the Michael addition and the oxidative resistance of di- and tetrahydropyridine systems was in a good agreement with the known effects of (C-4)-aryl substituents [40].
The structures of the obtained compounds were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, and also by the results of elemental analysis and HPLC-MS. In the IR spectra of salts **7a**-**i**, two absorption bands were detected for the CN groups, a strong one in the range of 2179-2164 cm^{-1} (3-CN) and a weak band at 2255-2241 cm^{-1} (unconjugated 5-CN group), while in the spectra of the oxidized analogs **9i**,**o**-**r** one or two strong bands were present for the conjugated nitrile groups in the range of 2216-2163 cm^{-1}. In the IR spectra of compounds **7a**-**i** and **9i**,**o**-**r**, absorption bands corresponding to the stretching vibrations of the C=O group were found in the range of 1702-1665 cm^{-1}. In the IR spectra of glutarimides **8j**-**n**, absorption bands for the unconjugated nitrile (2267-2255 cm^{-1}) and carbonyl groups (1753-1702 cm^{-1}) were observed. In the mass spectra of the salts **7a**-**i**, peaks with *m*/*z* 102 $[Et_3NH]+$ and [M(**7**)-100]+ were detected.

Salts **7a-i** and glutarimides **8j-n** are finely crystalline solids, insoluble in EtOH and ether, sparingly soluble in acetone and readily soluble in DMF and DMSO. Pyridin-2-olates **9i,o-r** are colorless or yellow crystals, insoluble in EtOH and acetone, slightly soluble in DMF and DMSO.

Conclusion

In summary, long-time known Guareschi condensation could be vastly improved if ethyl cyanoacetate was replaced by more reactive 1-(cyanoacetyl)-3,5-dimethylpyrazole. It was found that the structure of the final products depends on the reaction conditions and the structure of the aromatic substituents at C-4 position of Guareschi glutarimides.

Experimental

IR spectra were recorded on a FTIR spectrophotometer Shimadzu IRPrestige-21 (compounds **7a, b, d, f, h, i, 8j-m, 9i**) and Fourier spectrometer Infralum FT-801 (the other compounds) in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DPX-400 (400 MHz) spectrometer in DMSO-d_6, internal standard - TMS. ^{13}C NMR spectra were recorded on Brucker Avance DPX spectrometer 300 (75 MHz), in DMSO-d_6, internal standard - TMS. HPLC-MS analysis was performed on a liquid chromatograph Shimadzu LC-10AD with Shimadzu SP D-10A UV-Vis (254nm) detector and Sedex 75 ELSD detector, combined with PE SCIEX API 150EX mass spectrometer, ionization mode – ES-API. Elemental analysis was performed on Carlo-Erba 1106 Elemental Analyser. Purity of the obtained compounds was controlled by TLC on Sorbfil PTSKh-AF-V-UV plates, eluent was acetone–hexane, 1:1, visualization with iodine vapor or UV light. Melting points were determined on an Electrothermal Mel-Temp 3.0 apparatus. Cyanoacetylpyrazole **5** [38] and (*E*)-3-(het)aryl-2-cyanoacrylamides **6a**-**u** [41] were obtained by literature procedures.

Synthesis of triethylammonium 4-aryl-6-oxo-3,5-dicyano-1,4,5,6-tetrahydro-pyridine-2-olates (7), 4-aryl-2,6-dioxo-3,5-dicarbonitriles (8) and triethylammo-nium 4-aryl-6-oxo-3,5-dicyano-1,6-dihydropyridin-2-olates (9). General Procedure. Acrylamide **6a**-**s** (1.50 mmol) was placed in an Erlenmeyer flask, and acetone (10 ml) was added. The mixture was stirred under argon stream (Table 1, conditions A, C) or in air (Table 1, conditions B, D) until complete dissolution of the amide. If solubility was inadequate, THF (5-10 ml) was added dropwise to the stirred suspension, with gentle heating if necessary (~40°C). Cyanoacetylpyrazole **5** (300 mg, 1.84 mmol, ~1.2 equiv.) and Et_3N (dried over KOH, 0.3-0.4 ml, 2.2-2.9 mmol, ~1.4-1.9 equiv.) were added to the obtained solution. The solution was stirred for 4-6 h, maintained at 20°C for 24-48 h, and then in a freezer at -18°C for 2-3 h. In the case of salts **7a**-**i** or **9i**,**o**-**r**, the crystalline solid was filtered off, washed with THF and with Et2O. In the case of amides **6j**-**n**,**s**, no solid formed. To isolate the product, the solvent was evaporated in vacuum, the residue was treated with EtOH (10 ml) and with 18% HCl to pH 2 and left for 3-5 days to complete crystallization. Guaraschi imides **8j**-**n** or 6-hydroxy-4-(4-iso-propylphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**4s**) were obtained.

The selected spectral data

Triethylammonium 3,5-dicyano-6-oxo-4-[2-(trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyridin-2-olate (7d). White, finely crystalline powder, mp 167-171°C, R_f 0.14. FTIR spectrum, ν, cm^{-1}: 3553-3416 (NH+), 3238 (NH), 2241 (5-C≡N), 2174 (3-C≡N), 1697 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz)*: 1.16 (9H, t, *J* = 7.2, $N(CH_2CH_3)_3$); 2.97 (6H, q, *J* = 7.2, $N(CH_2CH_3)_3$); 4.16-4.94 (2H, m, 4,5-CH); 7.43-7.80 (4H, m, H Ar); 9.41 (1H, br. s, NH). ^{13}C NMR spectrum δ, ppm (*J*, Hz)**: 8.8 ($N(CH_2CH_3)_3$); 36.2 and 38.0 (C-4); 42.7 and 52.8 (C-5); 45.8 ($N(CH_2CH_3)_3$); 116.7 (C≡N); 125.1, 125.2, 125.3 (C Ar); 126.5 (q, ^3JC–F = 29.5, C-2 Ar); 126.7 (q, ^2JC–F = 271.5, CF3); 127.5, 127.6, 128.6, 129.6, 132.8, 133.08 (C Ar); 140.2 (C-2(3)); 143.3 (C-3(2)); 163.4 (C=O); 163.8 (C=O). Found, %: C 58.58; H 5.70; N 13.80. $C_{20}H_{23}F_3N_4O_2$. Calculated, %: C 58.82; H 5.68; N 13.72. *The signal of an NH+ proton is not displayed, evidently as a result of deuterium exchange. **Double asterisk denotes a spectrum in which doubled signals are assigned to *cis* and *trans* diastereomers.

Triethylammonium 3,5-dicyano-6-oxo-4-(thiophen-2-yl)-1,4,5,6-tetrahydropyridin-2-olate (7f). White, finely crystalline powder, mp 158-163°C, R_f 0.45. FTIR spectrum, ν, cm^{-1}: 3547-3416 (NH+), 3238 (NH), 2253 (5-C≡N), 2164 (3-C≡N), 1690 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz)*: 1.16 (9H, t, *J* = 7.2, $N(CH_2CH_3)_3$); 2.96 (6H, q, *J* = 7.2, $N(CH_2CH_3)_3$); 4.12-4.72 (2H, m, 4.5-CH); 6.95-6.96 (2H, m, H-3,4 Th); 7.36-7.40 (1H, m, H-5 Th); 9.61 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz)**: 8.7 ($N(CH_2CH_3)_3$); 36.7 and 37.5 (C-4); 43.1 and 52.1 (C-5); 45.7 ($N(CH_2CH_3)_3$); 118.6 (C≡N); 124.7, 124.9, 125.9, 126.7, 126.9, 127.1, 128.3, 129.0 (C Ar); 135.5 (C-3); 146.3, 146.4 (C-2); 163.2 (C=O); 163.6 (C=O). Found, %: C 59.14; H 6.36; N 16.29. $C_{17}H_{22}N_4O_2S$. Calculated, %: C 58.94; H 6.40; N 16.17. *The signal of an NH+ proton is not displayed, evidently as a result of deuterium exchange. **Double asterisk denotes a spectrum in which doubled signals are assigned to *cis* and *trans* diastereomers.

Triethylammonium 3,5-dicyano-4-(4-methylphenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-olate (7i). Pale-yellow, finely crystalline powder, mp 172-178°C, R_f 0.33. IR spectrum, ν, cm^{-1}: 3428-3402 (NH+), 2254 (5-C≡N), 2167 (3-C≡N), 1668 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz)*: 1.12 (9H, t, *J* = 7.1, $N(CH_2CH_3)_3$); 2.27 (3H, s, $ArCH_3$); 2.97 (6H, q, *J* = 7.1, $N(CH_2CH_3)_3$); 3.71-4.90 (2H, m, 4,5-CH); 7.09-7.27 (4H, m, H Ar); 9.31 (1H, br. s, NH). Found, %: C 67.65; H 7.52; N 15.95. $C_{20}H_{26}N_4O_2$. Calculated, %: C 67.77; H 7.39; N 15.81. A mixture of compounds **7i** and **9i** was obtained in a ratio of ~1:5 (HPLC-MS), or ~2:5 (according to ^{1}H NMR spectrum) when the reaction was carried out under air atmosphere (conditions B). The oxidation product – **triethylammonium 3,5-dicyano-4-(4-methylphenyl)-6-oxo-1,6-dihydropyridin-2-olate** (**9i**) was identified by the following signals in the ^{1}H NMR spectrum, δ, ppm: 2.36 (3H, s, CH_3); 7.26-7.29 (4H, m, H Ar); 10.56 (1H, br. s, NH). In the IR spectra, two absorption bands were detected at ν 2210 and 2171 cm^{-1} (2C≡N). Mass spectrum, *m*/*z*: 102.3 [Et_3NH]+, 252.3 [(M(**9i**)-Et_3N+H)]+, 254.1 [(M(**7i**)-Et_3N+H)]+.

Triethylammonium 3,5-dicyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-olate (9o). When the reaction was carried out under an argon atmosphere (conditions A), ~3:1 mixture of salt **9o** with the dihydro analog **7o** was obtained (according to ^{1}H NMR spectrum). When the reaction was carried out under air atmosphere (conditions B), only the Guareschi imide oxidation product, compound **9o**, was obtained. Colorless crystals, mp >250°C. IR spectrum, ν, cm^{-1}: 3167 (NH), 2209, 2176 (C≡N), 1688 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz)*: 1.17 (9H, t, *J* = 7.2, $N(CH_2CH_3)_3$); 3.08 (6H, q, *J* = 7.2, $N(CH_2CH_3)_3$); 7.38-7.41 (2H, m, H Ph); 7.46-7.49 (3H, m, H Ph); 10.60 (1H, br. s, NH). Found, %: C 67.50; H 6.65; N 16.43. $C_{19}H_{22}N_4O_2$. Calculated, %: C 67.44; H 6.55; N 16.56. The presence of salt **7o** was identified by the following signals in the ^{1}H NMR spectrum, δ, ppm: 3.58-4.85 (2H, m, 4,5-CH); 7.24-7.40 (5H, m, H Ph); 9.41 (1H, br. s, NH).

Triethylammonium 3,5-dicyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridin-2-olate (9p). When the reaction was carried out under an argon atmosphere (conditions A), a mixture of the starting amide **6p** and triethylammonium 3,5-dicyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridin-2-olate (**9p**) was obtained in ~3:2 ratio (according to ^{1}H NMR spectrum). When the reaction was carried out under air atmosphere (conditions B), ~10:14 mixture of compounds **6p** and **9p** was obtained. The ^{1}H NMR spectrum of salt **9p**, δ, ppm (*J*, Hz): 1.16 (9H, t, *J* = 7.3, $N(CH_2CH_3)_3$); 3.07 (6H, q, *J* = 7.3, $N(CH_2CH_3)_3$); 3.80 (3H, s, OCH_3); 7.00 (2H, *J* = 8.6, H Ar); 7.34 (2H, *J* = 8.6, H Ar); 10.51 (1H, br. s, NH). Mass spectrum, *m*/*z*: 203.6 [M(**6p**)+H]+, 268.8 [M(**9p**)+H]+, 405.9 [2M(**6p**)+H]+.

Triethylammonium 3,5-dicyano-4-(4-nitrophenyl)-6-oxo-1,6-dihydropyridin-2-olate (9r). Bright-yellow, finely crystalline powder, mp >250°C, R_f 0. FTIR spectrum, ν, cm-1: 3120 (NH), 2216, 2163 (C≡N), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz)*: 1.17 (9H, t, *J* = 7.2, $N(CH_2CH_3)_3$); 3.09 (6H, q, *J* = 7.2, $N(CH_2CH_3)_3$); 7.70 (2H, d, *J* = 7.8, H Ar); 8.33 (2H, d, *J* = 7.8, H Ar); 10.72 (1H, br. s, NH). Found, %: C 59.40; H 5.65; N 18.21. $C_{19}H_{21}N_5O_4$. Calculated, %: C 59.52; H 5.52; N 18.27. *The signal of an NH+ proton is not displayed, evidently as a result of deuterium exchange.

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