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ARTICLE *in* MONATSHEFTE FUER CHEMIE/CHEMICAL MONTHLY · JUNE 2015

Impact Factor: 1.22 · DOI: 10.1007/s00706-015-1438-3

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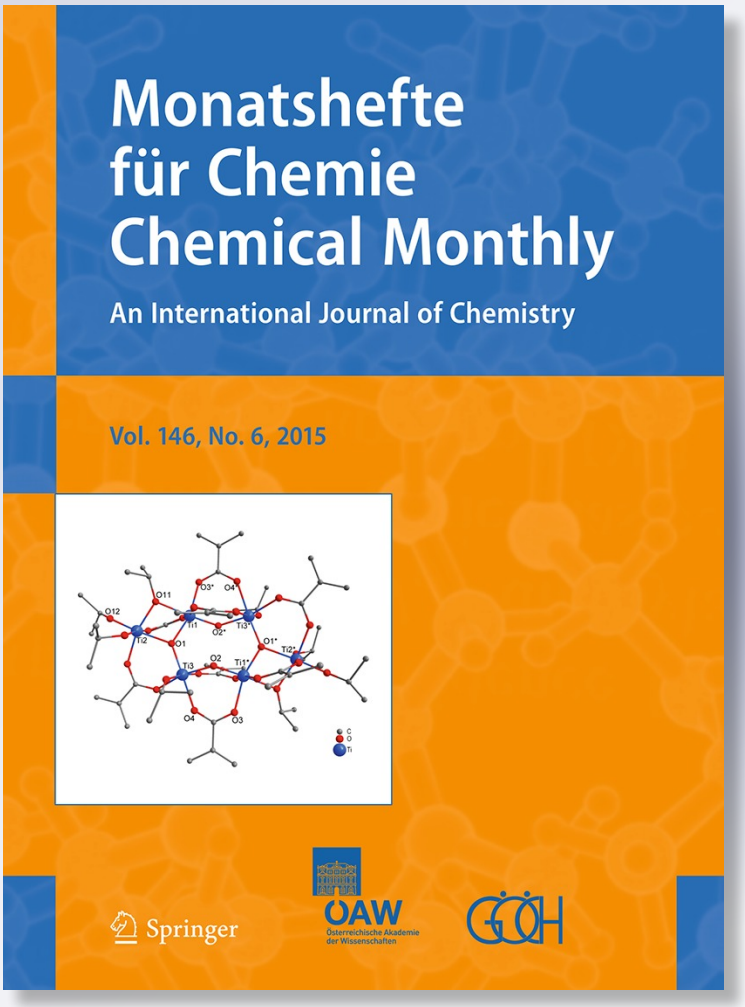
Monatshefte für Chemie - Chemical Monthly
An International Journal of Chemistry

ISSN 0026-9247
Volume 146
Number 6

Monatsh Chem (2015) 146:931-939
DOI 10.1007/s00706-015-1438-3



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ORIGINAL PAPER

Synthesis of spiro 2-(5-amino-2,3-dihydro-3-oxopyrrol-4-yl)-1,3-dialkylbenzimidazolium chlorides

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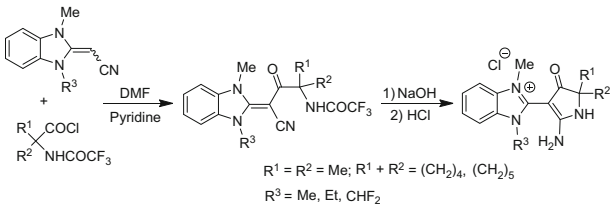
Received: 6 November 2014 / Accepted: 17 February 2015 / Published online: 2 April 2015

Abstract The interaction of 1,3-dialkyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-ylidenemethyl cyanides with *N*-trifluoroacylated acid chlorides gave the desired (3-cyano-2-oxo-3-hetarylpropyl)-2,2,2-trifluoroacetamides that upon detrifluoroacetylation provided the target 2-(5-amino-2,3-dihydro-3-oxopyrrol-4-yl)-1,3-dialkylbenzimidazolium chlorides.

Graphical abstract



A. V. Dobrydnev (✉) · Y. M. Volovenko · A. V. Turov · T. A. Volovnenko
Chemistry Department, Taras Shevchenko National University of Kiev, Vladimirskaya street 60, Kiev 01601, Ukraine
e-mail: alexey.pierrot@gmail.com

A. V. Dobrydnev
State Centre of Innovation Biotechnologies, Donetska Street 30, Kiev 03151, Ukraine

V. V. Medviediev · O. V. Shishkin
Division of Functional Materials Chemistry, SSI "Institute for Single Crystals" National Academy of Science of Ukraine, Lenina avenue 60, Kharkiv 61001, Ukraine

O. V. Shishkin
Department of Inorganic Chemistry, V. N. Karazin Kharkiv National University, Svobody square 4, Kharkiv 61202, Ukraine

Keywords Pyrroles · Cyclization · Spiro compounds · Antitumor agents · Lanthanide shift reagent · X-ray structure determination

Introduction

As a part of a program designed to study the antitumor properties of 2-amino-3-hetarylpyrrolin-4-ones [1], certain corresponding quaternary salts were required as pre-production models with significant water solubility.

In our previous works [2–6], a facile route to aminopyrroles **1**, bearing a benzoazole substituent at the suitable position, has been developed. Continuing our research in this field the corresponding quaternary salts **2** were also obtained [3] (Fig. 1). In light of these results, we prepared previously unreported spiro derivatives of pyrrolinones with quaternary benzoazole substituent **3**.

Among the many methods available for constructing the aminopyrroles, the cyclization of 4-aminobutanenitriles has proven to be a very powerful tool [2–12]. It is known that the reaction of 4-halobutanenitriles with primary amines is a convenient method for aminopyrrole preparation [7]. This approach, although reasonably effective, suffers from several drawbacks and not very efficient for the amination of tertiary halogenides. Consequently, our synthetical pathway includes the interaction of nitriles containing an active α-carbon atom with α-aminocarbonyl derivatives to proceed smoothly providing the required 4-aminobutanenitriles.

Recently we have introduced a strategy [13] for the construction of spiro-2-amino-3-hetarylpyrrolin-4-one system through an acylation of hetarylacetonitriles with acid chlorides of *N*-trifluoroacylated cyclic α-amino acids in the presence of pyridine in DMF. The isolated key

intermediates undergo a cyclization reaction (NaOH in 1-propanol) to spiro-2-amino-3-hetarylpyrrolin-4-ones through an intramolecular condensation mechanism.

Results and discussion

Given these results, we hypothesized that hetarylylideneacetonitriles subjected to the same chemical reactions and conditions might yield the corresponding quaternary salts of spiro-2-amino-3-hetarylpyrrolin-4-ones **3**.

To apply such a reaction for our purpose, the readily available nitriles **4a**–**4c** [14] and amino acids **5a**–**5c** were selected as starting materials. The cyclic α-amino acids were shown to behave like disubstituted α-amino acids, thus presumably yielding corresponding spiro-aminopyrrolinones in similar reaction sequences. Therefore, α-aminoisobutanoic acid (**5a**) was used as a model substance for developing of aminopyrrolinones.

The trifluoroacylation of α-amino acids **5a**–**5c** was carried out with satisfactory yields using the noted method [13]. The corresponding acid chlorides of *N*-trifluoroacylated α-amino acids were prepared in the following pathway by interaction with thionyl chloride (Scheme 1)

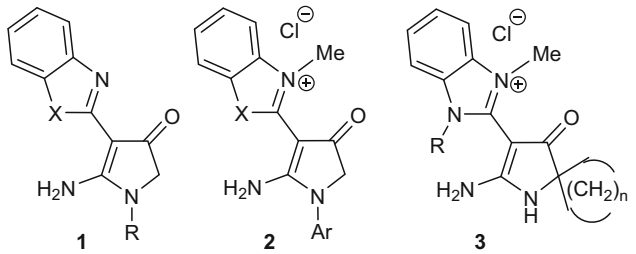


Fig. 1 The structure of pyrrolinone derivatives **1**, **2**, and **3**

using several modifications of the conditions described in References [15, 16].

However, when nitriles **4a**–**4c** were forced to react with chlorides **7a**–**7c** in the presence of pyridine, satisfactory yields of corresponding acylated nitriles **8a**–**8g** were obtained, and the products were readily isolated (Scheme 2). It was found to be advantageous to allow the reaction mixture to remain warm at least overnight to ensure completion of the acylation process.

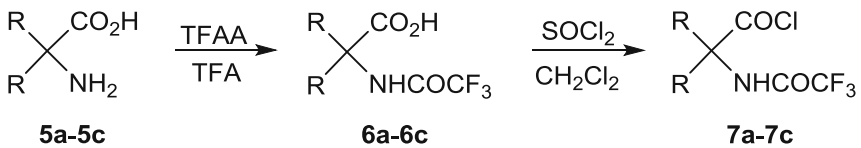
An unforeseen result was obtained during the course of reaction. A single products, either the (*Z*)- or the (*E*)-isomers, **8d**–**8g**, were obtained by acylation of isomer mixture **4b** and **4c** with the acid chlorides **7**. The configurations of acylated nitriles **8f** and **8g** were established through ^{1}H NMR spectroscopy using lanthanide shift reagent (LSR). Thus the use of Eu(FOD)$_3$ showed that in compound **8f** the CN group is in a *trans* position relative to the NMe fragment, while in compound **8g** the CN group and NMe fragment are in a *cis* position (Fig. 2). The similarity in structure of compounds **8f** and **8d**, **8e** respectively permits the supposition that the latter have similar configurations.

The only alternative interpretation of the observed data evident to the authors was that, perhaps, the electrostatic repulsion between the negative charges created on CN and CHF_2 groups, which forced CHF_2 group to exist in trans position with respect to Me group.

The reaction was assumed to proceed via initial addition of acyl chloride across the exocyclic double bond in **4a**–**4c** yielding an intermediate (Fig. 3), followed by loss of proton, which was accompanied by the charge transfer from the benzoazole moiety and exocyclic double bond reconstruction.

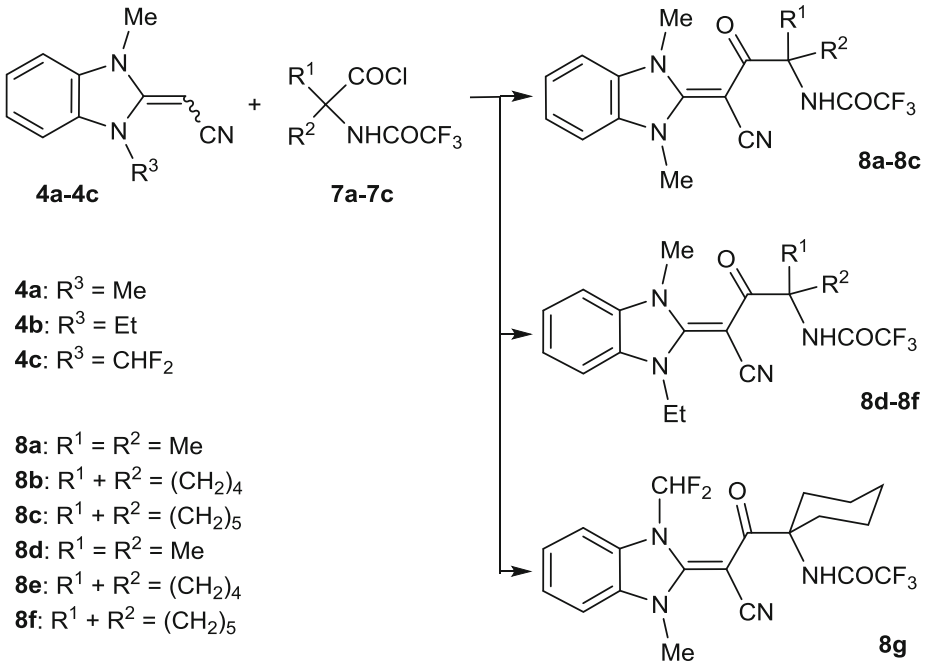
The structure of compounds **8a**–**8g** was established based on the spectral data. Thus, the IR showed the presence of strong conjugate carbonyl band at 1619–1601 cm^{-1} as well as carbonyl stretching vibration at 1714–1703 cm^{-1} from the trifluoroacetamide fragment. The nitrile group absorption is situated at 2183–2168 cm^{-1}. The ^{1}H NMR spectrum indicated the

Scheme 1



5a, **6a**, **7a**: R = Me
5b, **6b**, **7b**: R + R = $(CH_2)_4$
5c, **6c**, **7c**: R + R = $(CH_2)_5$

Scheme 2



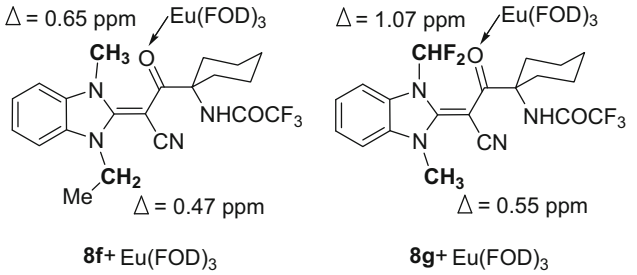


Fig. 2 Values of lanthanide induced shifts of the signals of *N*-aliphatic substituents in ^{1}H NMR spectra of compounds **8f** and **8g** in the presence of Eu(FOD)$_3$

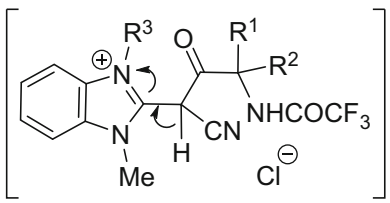


Fig. 3 The structure of intermediate with single bond between CN and heterocyclic fragment

absence of exocyclic CH proton signals. The presence of NH protons at 9.04–9.97 ppm was confirmed by exchange with D_2O. Also, the mass spectrum revealed molecular ion peaks that correspond to the molecular formulae. These data were all consistent with the desired structure.

The elaboration of the acylated nitriles **8a**–**8g** into the target aminopyrrolinones **3** was achieved without difficulty. Thus, treatment of these precursors with the solution of NaOH in 2-propanol, produces the saponification of the trifluoroacetamide fragment and the subsequent intramolecular addition of the primary amino group in the intermediate to the nitrile group followed by consequent pyrrolinone ring formation (Scheme 3).

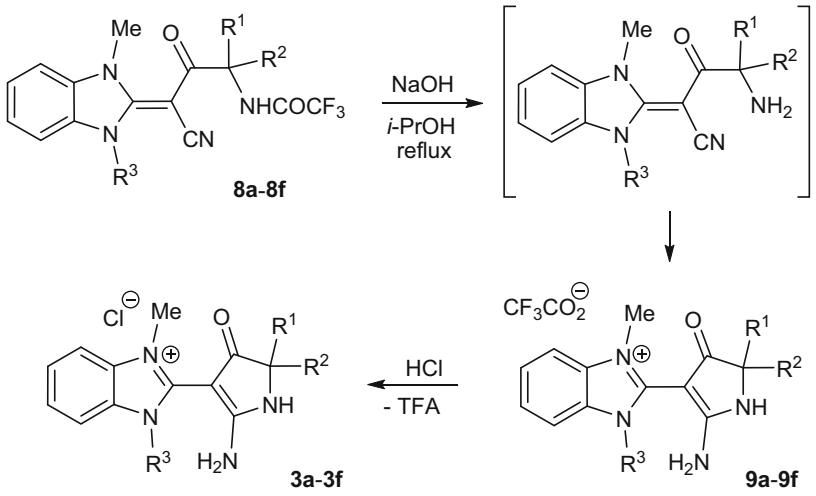
The quaternary salts could be isolated as either chlorides **3a**–**3f** or trifluoroacetates **9a**–**9f**. However, pyrrolinones with chloride counterion exhibits higher usability, water solubility, and stability upon storage.

The structures of pyrrolinones **3a**–**3f** were confirmed by ^{1}H, ^{13}C, ^{19}F NMR, IR, and mass spectral data. Particularly, presence of the amino group signals observed at 7.55–8.05 ppm, absence of nitrile absorption both in IR and ^{13}C NMR spectra and absence of signals from trifluoroacetamide fragment both in ^{13}C, ^{19}F NMR, and IR spectra clearly indicated the ring closure.

In order to confirm the structure of product **9c** in the solid state, a X-ray crystal structure determination was carried out. Figure 4 shows the molecular structure together with the atomic numbering scheme of **9c**.

According to XRD data compound **9c** is a salt of organic cation with CF_3COO^- anion. Almost equal values of the C–N bond lengths within imidazole ring (Table 1) and rotation of two planar heterocycles with respect to each other [the N1–C7–C8–C9 torsion angle is −46.4(4)°] agree

Scheme 3



3a, **8a**, **9a**: $R^1 = R^2 = R^3 = Me$
3b, **8b**, **9b**: $R^1 + R^2 = (CH_2)_4$, $R^3 = Me$
3c, **8c**, **9c**: $R^1 + R^2 = (CH_2)_5$, $R^3 = Me$
3d, **8d**, **9d**: $R^1 = R^2 = Me$, $R^3 = Et$
3e, **8e**, **9e**: $R^1 + R^2 = (CH_2)_4$, $R^3 = Et$
3f, **8f**, **9f**: $R^1 + R^2 = (CH_2)_5$, $R^3 = Et$

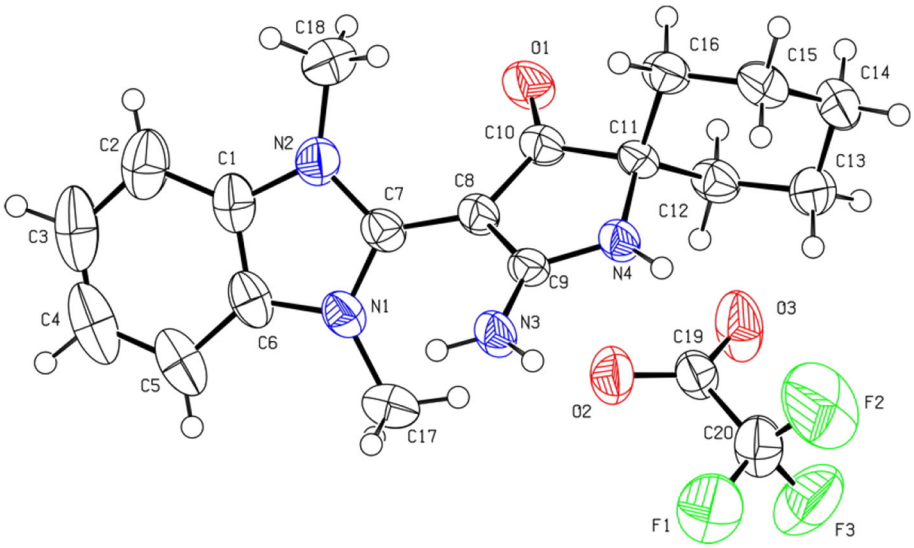


Fig. 4 Molecular structure together with the atomic numbering scheme of **9c** according to X-ray diffraction data

well with chemical formula of cation **9c** depicted in Scheme 3. However, detailed analysis of bond lengths demonstrates considerably more complex and stronger delocalization of electron density within cation. Besides imidazole ring equalization of bonds is observed for the C–C and C–N bonds within the C7–C8–C9 and N3–C9–N4 fragments, respectively (Table 1). This indicates strong delocalization of electron density within these fragments (Fig. 5).

Based on XRD data it is impossible to understand reasons of highly delocalized conjugated system in cation **9c** either it is caused by delocalization of positive charge due to protonation or induced by polar environment in the crystal phase as it was found recently for derivatives aminoiminoisoindole [17] containing similar amidine fragment. Quantum-chemical calculations of structure of cation **9c** by the M06-2X/6-311G(d,p) method demonstrated good agreement between calculated and experimental values of bond lengths (Fig. 6; Table 1). Some differences are observed only for C8–C10=O1 fragment which probably are induced by polar environment in the crystal. Thus, it is possible to suggest that strong

Table 1 Values of bond lengths/Å for cation and neutral deprotonated tautomers **A**–**C** of compound **9c** according to X-ray diffraction data and quantum-chemical calculations by M06-2X/6-311G(d,p) method

Bond	Cation		Neutral		
	Exp	Calc	A	B	C
O1–C10	1.226(3)	1.209	1.220	1.223	1.221
N1–C7	1.349(3)	1.355	1.373	1.361	1.369
N2–C7	1.356(3)	1.344	1.365	1.362	1.361
N3–C9	1.329(3)	1.345	1.393	1.281	1.282
N4–C9	1.333(3)	1.338	1.283	1.397	1.388
C7–C8	1.428(3)	1.429	1.395	1.405	1.399
C8–C9	1.417(3)	1.405	1.460	1.458	1.465
C8–C10	1.434(3)	1.452	1.447	1.430	1.435

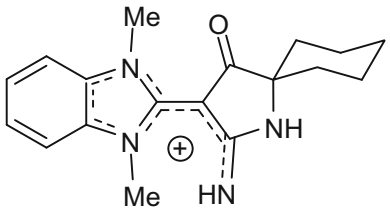


Fig. 5 The graphic illustration of wide delocalization of electron density within cation **9c**

delocalization of electron density in cation **9c** is caused by protonation of molecule.

Analysis of calculated values of bond lengths in deprotonated tautomers **A**–**C** of the cation **9c** (Fig. 6) shows absence of considerable delocalization of electron density within molecule (Table 1). Values of the C–N bond lengths within amidine fragment are usual for single and double bonds (Table 1). It is observed only some elongation of the C7–C8 bond up to 1.395–1.404 Å which may be explained by strong conjugation within planar enone fragment C7=C8–C10=O1. It is accompanied by shortening of the C8–C10 bond (Table 1). Thus, it is possible to conclude that strong delocalization of electron density in cation **9c** is caused by protonation of molecule.

Analysis of changes of atomic charges due to protonation of one of the nitrogen atom of neutral tautomers **A**–**C** indicates that positive charge in cation is mainly localized within the amidine fragment N3–C9–N4 ($\Delta q = +0.6$ e). Probably this leads to complete delocalization of electron density within this fragment creating suitable conditions for charge transfer to enone and imidazole fragments of cation.

Thus, a facile route to the quaternary salts of spiro pyrrolinones has been developed. General and convenient methods for preparation of trifluoroacylated amino acid chlorides and further acylation were elaborated. Further studies for this reaction extension and preparation of new *N*-substituted cyclic amino acids and spiropyrrolinones substituted at position 1 are currently in progress.

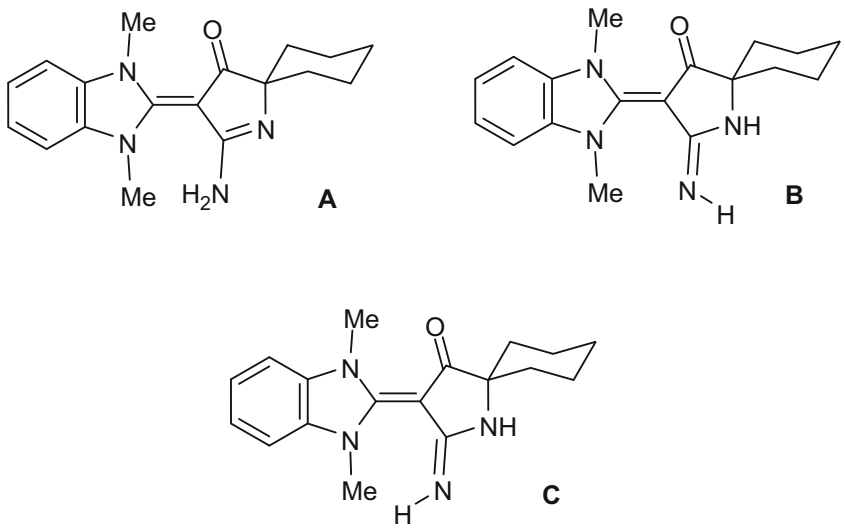
Experimental

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. *N*,*N*-Dimethylformamide was dried by distillation from phosphorus pentoxide. The other chemicals were from Aldrich or Fluka and, when necessary, chemicals were purified according to the reported procedure [18]. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Mercury 400 spectrometer at 400.45, 100.61, and 376.73 MHz, respectively, using DMSO-d_6 as solvent and Me_4Si (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standarts. IR spectra were obtained on a Perkin Elmer BX II spectrometer in KBr pellets and are reported in cm^{-1}. Mass spectra were recorded on an Agilent 1100 Series with an Agilent LC/MSD SL detector by chemical ionization (CI). All melting points were determined in open capillary tubes in a Thiele apparatus.

General method for the preparation of acid chlorides ***7a–7c***

To a magnetically stirred suspension of the *N*-trifluoroacylated amino acid **6a–6c** (0.05 mol) in 50 cm^3 of CH_2Cl_2 containing two drops of dry pyridine was added 4.04 cm^3 $SOCl_2$ (0.056 mol). The mixture was heated under reflux for 4 h and allowed to cool to room temperature. Then CH_2Cl_2 with excess of $SOCl_2$ were removed by rotary evaporation maintaining the temperature below 40 °C, yielding the crude acid chloride as solidify yellow oil. The material thus obtained was used without further purification.

Fig. 6 Tautomers of deprotonated cation **9c**



*General method for the acylation of nitriles **4a–4c***

The corresponding acid chloride **7a**, **7c**, **7d** (0.016 mol) was added gradually to stirred solution of nitrile **4a–4c** (0.015 mol) and 3.3 cm^3 pyridine (0.04 mol) in 10 cm^3 dry DMF, and left overnight at 40 °C. The solvent with excess of pyridine was evaporated in vacuum and 15 cm^3 water was added. The resulting precipitate was triturated, filtered off, and recrystallized from the corresponding solvent.

N-[3-Cyano-3-(1,3-dimethyl-2,3-dihydro-1H-benzo-[d]imidazol-2-ylidene)-1,1-dimethyl-2-oxopropyl]-2,2,2-trifluoroacetamide (**8a**, $C_{17}H_{17}F_3N_4O_2$)
Yield 74 %; m.p.: 257 °C (HOAc); ^{1}H NMR: $\delta = 1.57$ (s, 6H, CH_3), 3.76 (s, 6H, NCH_3), 7.55 (m, 2H, H-5 and H-6), 7.73 (m, 2H, H-4 and H-7), 9.45 (br. s, 1H, *NH*$COCF_3$) ppm; ^{13}C NMR: $\delta = 24.28$, 32.75, 54.01, 59.84, 111.60, 115.74 (q, $^1J_{C,F} = 287$ Hz), 120.76, 124.66, 131.67, 153.51, 154.81 (q, $^2J_{C,F} = 36$ Hz), 188.98 ppm; ^{19}F NMR: $\delta = -74.56$ (s, CF_3) ppm; IR: $\overline{\nu} = 3232$ (*NH*$COCF_3$), 2179 (C≡N), 1712 (NH*CO*CF_3), 1606 (C=O) cm^{-1}; MS (CI): $m/z = 367.2$ ($[M+H]^+$).

N-[2-Cyano-2-(1,3-dimethyl-2,3-dihydro-1H-benzo-[d]imidazol-2-ylidene)acetyl]cyclopentyl-2,2,2-trifluoroacetamide (**8b**, $C_{19}H_{19}F_3N_4O_2$)
Yield 85 %; m.p.: 272 °C (*n*-BuOH); ^{1}H NMR: $\delta = 1.64$ (m, 2H, cyclopentane), 1.75 (m, 2H, cyclopentane), 2.06 (m, 2H, cyclopentane), 2.33 (m, 2H, cyclopentane), 7.41 (m, 2H, H-5 and H-6), 7.65 (m, 2H, H-4 and H-7), 9.62 (br. s, 1H, *NH*$COCF_3$) ppm; ^{13}C NMR: $\delta = 24.20$, 32.78, 35.44, 54.46, 70.12, 111.40, 115.81 (q, $^1J_{C,F} = 286$ Hz), 120.79, 124.48, 131.67, 153.74, 155.26 (q, $^2J_{C,F} = 35$ Hz), 188.69 ppm; ^{19}F NMR: $\delta = -74.14$ (s, CF_3) ppm; IR: $\overline{\nu} = 3223$ (*NH*$COCF_3$), 2186 (C≡N), 1705 (NH*CO*CF_3), 1603 (C=O) cm^{-1}; MS (CI): $m/z = 393.2$ ($[M+H]^+$).

N-[2-Cyano-2-(1,3-dimethyl-2,3-dihydro-1H-benzo-[d]imidazol-2-ylidene)acetyl]cyclohexyl-2,2,2-trifluoroacetamide (**8c**, $C_{20}H_{21}F_3N_4O_2$)
Yield 88 %; m.p.: 273–275 °C (*n*-BuOH); ^{1}H NMR: $\delta = 1.33$ (m, 1H, cyclohexane), 1.61 (m, 5H, cyclohexane), 1.98 (m, 2H, cyclohexane), 2.08 (m, 2H, cyclohexane), 3.74 (s, 6H, NCH_3), 7.44 (m, 2H, H-5 and H-6), 7.71 (m, 2H, H-4 and H-7), 9.09 (br. s, 1H, *NH*$COCF_3$) ppm; ^{13}C NMR: $\delta = 21.41$, 25.01, 31.22, 32.75, 54.23, 62.85, 111.60, 115.73 (q, $^1J_{C,F} = 288$ Hz), 120.76, 124.64, 131.68, 153.86, 155.22 (q, $^2J_{C,F} = 36$ Hz), 189.29 ppm; ^{19}F NMR: $\delta = -70.88$ (s, CF_3) ppm; IR: $\overline{\nu} = 3238$ (*NH*$COCF_3$), 2179 (C≡N), 1703 (NH*CO*CF_3), 1620 (C=O) cm^{-1}; MS (CI): $m/z = 407.2$ ($[M+H]^+$).

N-[3-Cyano-3-(1-ethyl-3-methyl-2,3-dihydro-1H-benzo-[d]imidazol-2-ylidene)-1,1-dimethyl-2-oxopropyl]-2,2,2-trifluoroacetamide (**8d**, $C_{18}H_{19}F_3N_4O_2$)
Yield 83 %; m.p.: 220–221 °C (*n*-BuOH); ^{1}H NMR: $\delta = 1.45$ (t, $J = 7.2$ Hz, 3H, $NCH_2\underline{CH_3}$), 1.58 (s, 6H, CH_3), 3.72 (s, 3H, NCH_3), 4.40 (q, $J = 7.2$ Hz, 2H, NCH_2CH_3), 7.46 (m, 2H, H-5 and H-6), 7.75 (m, 2H, H-4 and H-7), 9.42 (br. s, 1H, *NH*$COCF_3$) ppm; ^{13}C NMR: $\delta = 13.27$, 24.21, 32.80, 40.61, 53.08, 59.80, 111.73, 111.89, 115.75 (q, $^1J_{C,F} = 287$ Hz), 121.10, 124.72, 124.85, 130.46, 131.99, 152.76, 154.82 (q, $^2J_{C,F} = 36$ Hz), 189.03 ppm; ^{19}F NMR: $\delta = -74.59$ (s, CF_3) ppm; IR: $\overline{\nu} = 3234$ (*NH*$COCF_3$), 2171 (C≡N), 1715 (NH*CO*CF_3), 1612 (C=O) cm^{-1}; MS (CI): $m/z = 381.2$ ($[M+H]^+$).

N-[2-Cyano-2-(1-ethyl-3-methyl-2,3-dihydro-1H-benzo-[d]imidazol-2-ylidene)acetyl]cyclopentyl-2,2,2-trifluoroacetamide (**8e**, $C_{20}H_{21}F_3N_4O_2$)
Yield 79 %; m.p.: 263 °C (*n*-BuOH); ^{1}H NMR: $\delta = 1.44$ (t, $J = 7.2$ Hz, 3H, NCH_2CH_3), 1.64 (m, 2H, cyclopentane), 1.75 (m, 2H, cyclopentane), 2.07 (m, 2H,

cyclopentane), 2.33 (m, 2H, cyclopentane), 3.69 (s, 3H, NCH_3), 4.39 (q, $J = 7.2$ Hz, 2H, NCH_2CH_3), 7.44 (m, 2H, H-5 and H-6), 7.72 (m, 2H, H-4 and H-7), 9.61 (br. s, 1H, *NH*$COCF_3$) ppm; ^{13}C NMR: $\delta = 13.29$, 24.14, 32.85, 35.36, 40.54, 53.51, 70.09, 111.59, 111.77, 115.80 (q, $^1J_{C,F} = 287$ Hz), 121.11, 124.61, 124.74, 130.50, 132.02, 153.00, 155.27 (q, $^2J_{C,F} = 36$ Hz), 188.73 ppm; ^{19}F NMR: $\delta = -74.18$ (s, CF_3) ppm; IR: $\overline{\nu} = 3247$ (*NH*$COCF_3$), 2168 (C≡N), 1711 (NH*CO*CF_3), 1610 (C=O) cm^{-1}; MS (CI): $m/z = 407.2$ ($[M+H]^+$).

N-[2-Cyano-2-(1-ethyl-3-methyl-2,3-dihydro-1H-benzo-[d]imidazol-2-ylidene)acetyl]cyclohexyl-2,2,2-trifluoroacetamide (**8f**, $C_{21}H_{23}F_3N_4O_2$)
Yield 88 %; m.p.: 249–250 °C (*n*-BuOH); ^1H NMR: $\delta = 1.34$ (m, 1H, cyclohexane), 1.44 (t, $J = 7.2$ Hz, 3H, NCH_2CH_3), 1.62 (m, 5H, cyclohexane), 1.97 (m, 2H, cyclohexane), 2.09 (m, 2H, cyclohexane), 3.71 (s, 3H, NCH_3), 4.40 (q, $J = 7.2$ Hz, 2H, NCH_2CH_3), 7.46 (m, 2H, H-5 and H-6), 7.74 (m, 2H, H-4 and H-7), 9.04 (br. s, 1H, *NH*$COCF_3$) ppm; ^{13}C NMR: $\delta = 13.26$, 21.46, 25.03, 31.27, 32.78, 40.53, 53.31, 62.79, 111.73, 111.91, 115.75 (q, $^1J_{C,F} = 287$ Hz), 121.11, 124.73, 124.86, 130.47, 132.00, 153.12, 155.23 (q, $^2J_{C,F} = 36$ Hz), 189.32 ppm; ^{19}F NMR: $\delta = -73.86$ (s, CF_3) ppm; IR: $\overline{\nu} = 3222$ (*NH*$COCF_3$), 2178 (C≡N), 1706 (NH*CO*CF_3), 1618 (C=O) cm^{-1}; MS (CI): $m/z = 421.2$ ($[M+H]^+$).

N-[2-Cyano-2-[1-(difluoromethyl)-3-methyl-2,3-dihydro-1H-benzo[d]imidazol-2-ylidene]acetyl]cyclohexyl-2,2,2-trifluoroacetamide (**8g**, $C_{20}H_{19}F_5N_4O_2$)
Yield 90 %; m.p.: 281 °C (*n*-BuOH); ^1H NMR: $\delta = 1.37$ (m, 1H, cyclohexane), 1.62 (m, 5H, cyclohexane), 2.03 (m, 4H, cyclohexane), 3.84 (s, 3H, NCH_3), 7.52 (m, 2H, H-5 and H-6), 7.56 (t, 1H, $^2J_{H,F} = 56.4$ Hz, *CH*F_2), 7.75 (d, 1H, $J = 7.6$ Hz, H-7), 7.81 (d, 1H, $J = 7.6$ Hz, H-4), 9.52 (br. s, 1H, *NH*$COCF_3$) ppm; ^{13}C NMR: $\delta = 21.40$, 24.94, 31.15, 33.16, 56.23, 62.79, 110.67 (t, $^1J_{C,F} = 247$ Hz), 112.60, 112.84, 115.62 (q, $^1J_{C,F} = 286$ Hz), 119.21, 125.81, 125.90, 126.83, 132.46, 153.42, 155.76 (q, $^2J_{C,F} = 36$ Hz), 191.30 ppm; ^{19}F NMR: $\delta = -73.94$ (s, 3F, CF_3), −97.15 (d, 2F, $^2J_{H,F} = 56.5$ Hz, CHF_2) ppm; IR: $\overline{\nu} = 3246$ (*NH*$COCF_3$), 2184 (C≡N), 1706 (NH*CO*CF_3), 1619 (C=O) cm^{-1}; MS (CI): $m/z = 443.1$ ($[M+H]^+$).

*General method for the preparation of aminopyrrolinones **3a–3c***

The corresponding acylated hetarylylideneacetonitrile **8a–8c** (0.005 mol) and 0.26 g NaOH (0.007 mol) were dissolved in 20 cm^3 *i*-PrOH and this mixture was refluxed for 3 h. The resulting solution was evaporated to dryness and triturated with 8 cm^3 water. The precipitate thus obtained was the corresponding trifluoroacetate of pyrrolinones **9a–9c**. It was filtered off, washed with water (2 × 2 cm^3) and dissolved in 15 cm^3 of 4 N HCl. Evaporation of the solution and subsequent recrystallization (if necessary) from aq. *i*-PrOH led to 2-(5-amino-2,3-dihydro-3-oxopyrrol-4-yl)-1,3-dimethylbenzimidazolium chlorides **3a–3c**.

2-(5-Amino-2,2-dimethyl-3-oxo-2,3-dihydro-1H-4-pyrrolyl)-1,3-dimethyl-3H-benzo[d]imidazol-1-ium chloride (**3a**, $C_{15}H_{19}ClN_4O$)
Yield 64 %; m.p.: >300 °C; ^1H NMR: $\delta = 1.32$ (s, 6H, CH_3), 3.85 (s, 6H, NCH_3), 7.58 (m, 2H, H-5 and H-6), 7.89 (m, 4H, H-4 and H-7, NH_2), 8.57 (br. s, 1H, NH-pyrroline) ppm; ^{13}C NMR: $\delta = 24.27$, 32.46, 63.09, 74.11, 112.38, 125.34, 131.80, 147.43, 164.71, 194.04 ppm; IR: $\overline{\nu} = 3451$ (NH_2, asym), 3401 (NH_2, sym), 3294 (NH-pyrroline), 1690 (C=O) cm^{-1}; MS (CI): $m/z = 271.2$ ($[M–Cl]^+$).

2-(3-Amino-1-oxo-4-azaspiro[4.4]non-2-en-2-yl)-1,3-dimethyl-3H-benzo[d]imidazol-1-ium chloride (**3b**, $C_{17}H_{21}ClN_4O$)
Yield 60 %; m.p.: >300 °C; ^1H NMR: $\delta = 1.84$ (m, 6H, cyclopentane), 1.95 (m, 2H, cyclopentane), 3.85 (s, 6H, NCH_3), 7.56 (m, 2H, H-5 and H-6), 7.87 (m, 4H, H-4 and H-7, NH_2), 9.03 (br. s, 1H, NH-Pyrroline) ppm; ^{13}C NMR: $\delta = 25.00$, 32.53, 36.69, 72.92, 75.04, 112.37, 125.30, 131.80, 147.37, 165.20, 193.54 ppm; IR: $\overline{\nu} = 3361$ (NH_2, asym), 3293 (NH_2, sym), 3266 (NH-pyrroline), 1636 (C=O) cm^{-1}; MS (CI): $m/z = 297.4$ ($[M–Cl]^+$).

2-(3-Amino-1-oxo-4-azaspiro[4.5]dec-2-en-2-yl)-1,3-dimethyl-3H-benzo[d]imidazol-1-ium chloride (**3c**, $C_{18}H_{23}ClN_4O$)
Yield 75 %; m.p.: >300 °C; ^1H NMR: $\delta = 1.31$ (m, 1H, cyclohexane), 1.55 (m, 3H, cyclohexane), 1.63 (m, 3H, cyclohexane), 1.78 (m, 3H, cyclohexane), 3.84 (s, 6H, NCH_3), 7.57 (m, 2H, H-5 and H-6), 7.73 (br. s, 2H, NH_2), 7.88 (m, 2H, H-4 and H-7), 9.37 (br. s, 1H, NH-pyrroline) ppm; ^{13}C NMR: $\delta = 21.78$, 24.57, 32.45, 32.89, 66.25, 74.71, 112.37, 125.33, 131.80, 147.42, 165.51, 193.50 ppm; IR: $\overline{\nu} = 3339$ (NH_2, asym), 3277 (NH_2, sym), 3204 (NH-pyrroline), 1631 (C=O) cm^{-1}; MS (CI): $m/z = 311.2$ ($[M–Cl]^+$).

*General method for the preparation of aminopyrrolinones **3d-3f***

The corresponding acylated hetarylylideneacetonitrile **8a–8c** (0.005 mol) and 0.26 g NaOH (0.007 mol) were dissolved in 20 cm^3 *i*-PrOH and this mixture was refluxed for 3 h. The resulting solution was evaporated to dryness and diluted with 5 cm^3 water. The bottom phase was separated, washed with water (2 × 2 cm^3) and dissolved in 8 cm^3 *i*-PrOH. An addition of fresh saturated solution of HCl in *i*-

PrOH produced the crystallization of 2-(5-amino-2,3-dihydro-3-oxopyrrol-4-yl)-1-ethyl-3-methylbenzimidazolium chlorides **3d**–**3f**. This quaternary salt was collected on a suction filter and washed with *i*-PrOH. The products thus obtained were pure and no further purification was required.

2-(5-Amino-2,2-dimethyl-3-oxo-2,3-dihydro-1H-4-pyrrolyl)-1-ethyl-3-methyl-3H-benzo[d]imidazol-1-ium chloride (**3d**, $C_{16}H_{21}ClN_4O$)
Yield 56 %; m.p.: >300 °C; ^{1}H NMR: $\delta = 1.33$ (s, 6H, CH_3), 1.41 (t, $J = 6.8$ Hz, 3H, NCH_2CH_3), 3.83 (s, 3H, NCH_3), 4.36 (m, 2H, NCH_2CH_3), 7.57 (m, 2H, H-5 and H-6), 7.91 (m, 2H, H-4 and H-7), 7.97 (br. s, 2H, NH_2), 8.66 (br. s, 1H, NH-pyrroline) ppm; ^{13}C NMR: $\delta = 14.06$, 24.28, 32.23, 41.06, 63.07, 73.73, 112.52, 112.79, 125.38, 125.47, 130.66, 132.15, 146.62, 164.86, 193.96 ppm; IR: $\overline{\nu} = 3448$ (NH_2, asym), 3404 (NH_2, sym), 3313 (NH-pyrroline), 1635 (C=O) cm^{-1}; MS (CI): $m/z = 285.2$ ([M–Cl]$^+$).

2-(3-Amino-1-oxo-4-azaspiro[4.4]non-2-en-2-yl)-1-ethyl-3-methyl-3H-benzo[d]imidazol-1-ium chloride (**3e**, $C_{18}H_{23}ClN_4O$)
Yield 61 %; m.p.: >300 °C; ^{1}H NMR: $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H, NCH_2CH_3), 1.87 (m, 6H, cyclopentane), 1.97 (m, 2H, cyclopentane), 3.86 (s, 3H, NCH_3), 4.39 (m, 2H, NCH_2CH_3), 7.59 (m, 2H, H-5 and H-6), 7.93 (m, 4H, H-4 and H-7, NH_2), 9.10 (br. s, 1H, NH-pyrroline) ppm; ^{13}C NMR: $\delta = 14.02$, 24.98, 32.29, 36.66, 41.10, 72.96, 74.76, 112.53, 112.78, 125.37, 125.45, 130.67, 132.15, 146.48, 165.27, 193.35 ppm; IR: $\overline{\nu} = 3410$ (NH_2, asym), 3232 (NH_2, sym), 3132 (NH-pyrroline), 1678 (C=O) cm^{-1}; MS (CI): $m/z = 311.2$ ([M–Cl]$^+$).

2-(3-Amino-1-oxo-4-azaspiro[4.5]dec-2-en-2-yl)-1-ethyl-3-methyl-3H-benzo[d]imidazol-1-ium chloride (**3f**, $C_{19}H_{25}ClN_4O$)
Yield 65 %; m.p.: 289 °C; ^{1}H NMR: $\delta = 1.34$ (m, 1H, cyclohexane), 1.40 (t, $J = 7.2$ Hz, 3H, NCH_2CH_3), 1.53 (m, 2H, cyclohexane), 1.64 (m, 4H, cyclohexane), 1.79 (m, 3H, cyclohexane), 3.83 (s, 3H, NCH_3), 4.37 (m, 2H, NCH_2CH_3), 7.58 (m, 2H, H-5 and H-6), 7.79 (br. s, 2H, NH_2), 7.92 (m, 2H, H-4 and H-7), 9.40 (br. s, 1H, NH-pyrroline) ppm; ^{13}C NMR: $\delta = 14.04$, 21.77, 24.56, 32.22, 32.93, 41.05, 66.28, 74.34, 112.51, 112.78, 125.40, 125.49, 130.66, 132.14, 146.59, 165.59, 193.41 ppm; IR: $\overline{\nu} = 3368$ (NH_2, asym), 3261 (NH_2, sym), 3232 (NH-pyrroline), 1630 (C=O) cm^{-1}; MS (CI): $m/z = 325.2$ ([M–Cl]$^+$).

X-ray diffraction study of compound ***9c***

Crystal data for **9c** at 293 K: $C_{20}H_{23}N_4O_3F_3$, $M_r = 424.42$, $a = 8.2305(12)$ Å, $b = 9.9710(15)$ Å, $c = 13.6382(17)$ Å, $\alpha = 103.550(12)°$, $\beta = 105.966(12)°$, $\gamma = 102.068(12)°$, $V = 1000.3(2)$ Å^3, space group P$\overline{1}$, $Z = 2$, $D_c = 1.409$ g cm^{-3}, μ(MoKα) = 0.115 mm^{-1}, $F(000) = 444$; 11,108 reflections measured up to $2\theta_{max} = 60.0°$, 6238 unique ($R_{int} = 0.0448$) which were used in all calculations. Refinement was converged at $wR2 = 0.1979$ (all data), $R1 = 0.0680$ [2968 reflections with $I > 2\sigma(I)$], GoF = 1.01.

Intensities of reflections were measured on an automatic Xcalibur 3 diffractometer (graphite monochromated MoKα radiation, CCD-detector ω-scaning). All structures were solved by direct method using SHELX97 package [19]. Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of carrier non-hydrogen atom ($n = 1.5$ for methyl group and $n = 1.2$ for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) deposition number CCDC 912324. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.

Quantum-chemical calculations

Molecular structure of cation **9c** and its deprotonated tautomers was optimized using M06-2X functional [20] with 6-311G(d,p) basis set. Atomic charges were calculated within Natural Bonding Orbitals theory [21]. All calculations were performed using Gaussian09 program [22].

Acknowledgments Alexey Dobrydnev acknowledges Patricia Dobrydneva for a fellowship and technical support.

References

1. Dubinina HH, Volovenko YuM (2007) Compound of 1,4-disubstituted 5-amino-1,2-dihydropyrol-3-on, having anticarcinogenic activity. Ukrainian Pat UA22204
2. Volovenko YM, Tverdokhlebov AV, Gorulya AP, Shishkina SV, Zubatyuk RI, Shishkin OV (2002) Eur J Org Chem 4:663
3. Tverdokhlebov AV, Volovenko YM, Shokol TV (1998) Chem Heterocycl Compd 34:44
4. Resnyanskaya EV, Shokol TV, Volovenko YM, Tverdokhlebov AV (1999) Chem Heterocycl Compd 35:1230
5. Resnyanskaya EV, Tverdokhlebov AV, Volovenko YM, Shokol TV (2004) Russ J Org Chem 40:368
6. Tverdokhlebov AV, Lyashenko AB, Volovenko YM, Tolmachev AA (2004) Chem Heterocycl Compd 40:1536
7. Tverdokhlebov AV, Denisenko AV, Tolmachev AA, Volovenko YM (2007) Synthesis 1811

8. Eldin AMS (2003) Heteroatom Chem 14:612
9. Gewald K, Hentschel M (1976) J Prakt Chem 318:663
10. Teuber H-J, Schiitz G, Erkenbrecher E (1980) Arch Pharm 313:851
11. Dave CG, Shah PR, Upadhyaya SP (1987) J Indian Chem Soc 64:713
12. Dave CG, Desai ND (1999) J Heterocycl Chem 36:729
13. Dobrydnev AV, Volovnenko TA, Volovenko YM, Palamarchuk GV, Shishkin OV (2012) Monatsh Chem 143:779
14. Dobridnev AV, Volovnenko TA, Turov AV, Volovenko YM (2010) Chem Heterocycl Compd 46:887
15. Nordlander JE, Payne MJ, Njoroge FG, Balk MA, Laikos GD, Vishwanath VM (1984) J Org Chem 49:4107
16. Schallenberg EF, Calvin M (1955) J Am Chem Soc 77:2779
17. Shishkin OV, Konovalova IS, Zubatyuk RI, Palamarchuk GV, Shishkina SV, Biitseva AV, Rudenko IV, Tkachuk VA, Kornilov MY, Hordiyenko OV, Leszczynski J (2013) Struct Chem 24:1089
18. Perrin DD, Armarego IF, Perrin DR (1980) Purification of laboratory chemicals, 2nd edn. Pergamon Press, New York
19. Sheldrick G (2008) Acta Cryst Sect A 64:112
20. Zhao Y, Truhlar DG (2008) Acc Chem Res 41:157
21. Foster JP, Weinhold F (1980) J Am Chem Soc 24:7211
22. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery JA Jr, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox DJ (2009) Gaussian09, Rev A.1. Gaussian Inc, Wallingford