Short communication

One-pot, Three-component Synthesis of Dialkyl 4-(alkylamino)-7-alkoxy-5-oxo-1-pyridine-2-yl-1,5-dihydrofuro[3,4-b]pyridine-2,3-dicarboxylate

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Abstract

A one-pot isocyanide-based three-component reaction of 2-aminopyridine and acetylenic esters with alkyl isocyanides afforded tetraalkyl 4-(alkylamino)-2*H*-1,2'-bipyridine-2,3,5,6-tetracarboxylate and dialkyl 4-(alkylamino)-7-alkoxy-5-oxo-1-pyridin-2-yl-1,5-dihydrofuro[3,4-*b*]pyridine 2,3-dicarboxylate in good to high yields under mild reaction conditions.

Keywords: 2-aminopyridine, alkyl isocyanide, acetylenic esters, 1,2'-bipyridine, three-component synthesis

1. Introduction

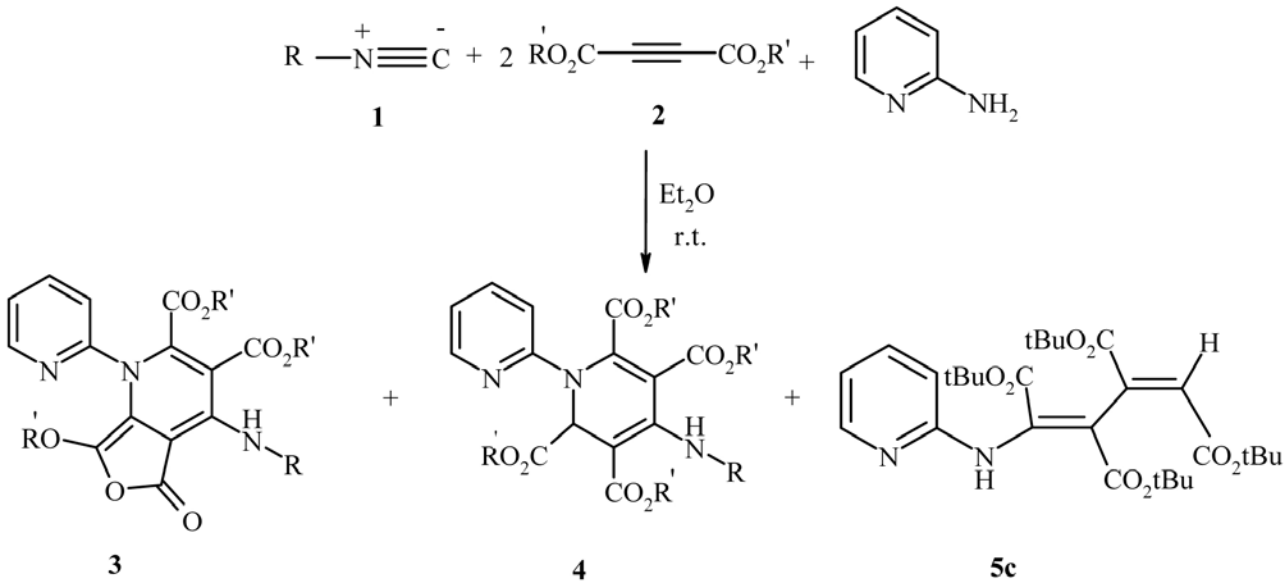
1,2-Dihydropyridines are useful intermediates for synthetic transformations. They undergo selective electrophilic substitutions[1] like formylation[2] and are also good dienes. Furthermore, Diels–Alder reactions of 1,2-dihydropyridines provided the starting point for the synthesis of several alkaloids and aminosugars.[3] The majority of synthetic methods to prepare 1,2-dihydropyridines relies on nucleophilic addition to N-acyl or N-alkyl pyridinium salts.[4,5] A good example of a synthetically useful application of this kind of reaction is provided by the reduction of pyridine in the presence of chloroformate esters.[6] Recently, other strategies for the synthesis of 1,2-dihydropyridines have been reported.[7] However, lack of general synthetic approaches for the regioselective synthesis of fully functionalized 1,2-dihydropyridines and their synthetic potential remains largely unexplored. In a recent study, Yavari et al. reported the syntheses of the functionalized 1,2-dihydropyridines from primary alkyl amines, alkyl isocyanides, and acetylenic esters.[8] In line with our general interest in the syntheses of heterocyclic compounds,[9–13] we report here on a simple and efficient method for the preparation of novel 1,2'-dihydropyridine derivatives.

2. Results and Discussion

2-Aminopyridine reacts with alkyl isocyanide **1** and dialkyl acetylenedicarboxylate **2** at room temperature in diethyl ether as solvent to produce compounds **3**, **4** and **5** in good to high yields (Scheme 1).

In particular, three-component reactions of 2-aminopyridine, alkyl isocyanides and double insertion of dialkyl acetylenedicarboxylates lead to dialkyl 4-(alkylamino)-7-alkoxy-5-oxo-1-(pyridin-2-yl)-1,5-dihydrofuro[3,4-*b*]pyridine-2,3-dicarboxylates (**3a-b** and **3d-e**) in good to high yields. When di-*tert*-butyl acetylenedicarboxylate is used, the reaction produces tetra-*tert*-butyl 4-(*tert*-butylamino)-2*H*-[1,2'-bipyridine]- 2,3,5,6-tetracarboxylate **4c** in good yield and (1*Z*,3*E*)-tetra-*tert*-butyl 1-(pyridin-2-ylamino)buta-1,3-diene-1,2,3,4-tetracarboxylate **5c** in low yield without the formation of **3c**.

On the basis of the established chemistry of isocyanides,[14–21] the initial Michael addition of alkyl isocyanide to acetylenic ester presumably leads to zwitterionic intermediate **6**. The intermediate **6** is protonated by the enaminoester **7**, generated *in situ* from 2-aminopyridine and acetylenic ester, to produce intermediates **8** and **9**. Ketenimine **10**, generated from the addition of **8** to **9**, undergoes a cyclization reaction to afford **11** which is converted to **4**



3,4,5	R	R '	Yield(%) of **3**	Yield(%) of **4**	Yield (%) of **5**
a	^{t}Bu	Me	90	——	——
b	^{t}Bu	Et	75	——	——
c	^{t}Bu	^{t}Bu	——	52	28
d	Cy-hexyl	Me	72	——	——
e	Cy-hexyl	Et	60	——	——

Scheme 1.

by a proton transfer from carbon to nitrogen atom. Compound **4** was tautomerized to enol **12** that undergoes a cyclization reaction, lossing alcohol, to produce compound **3** (Scheme 2).

As shown in Scheme 1, compounds **4a-b** and **4d-e** undergo cyclization reactions at room temperature to produce **3a-b** and **3d-e,** respectively, but this is not true for compound **4c** to give compound **3**. This is probably due to the existence of the hindered *tert*-butyl groups in the isocyanide and acetylenic ester molecules. However, compound **5c** was formed from the nucleophilic addition of 2-aminopyridine to two molecules of acetylenic esters followed by a proton transfer from nitrogen to carbon atom.

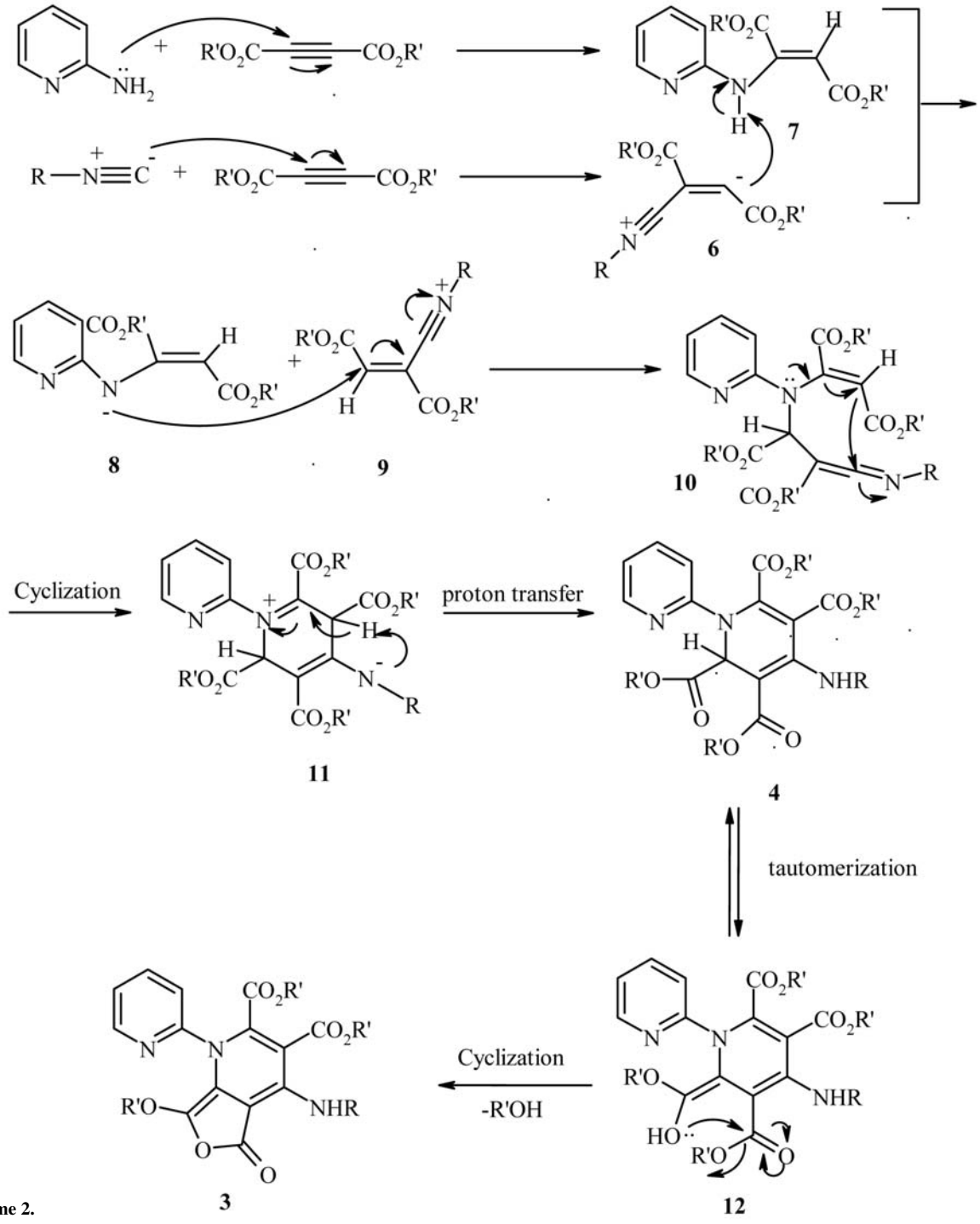
The structures of compounds **3a-b, 3d-e, 4c** and **5c** were deduced from their ^{1}H and ^{13}C NMR, IR and mass spectra as well as from elemental analyses.

^{1}H NMR spectrum of **3a** in $CDCl_3$ displayed a singlet at 1.64 ppm for the *tert*-butyl group, three singlets at 3.64, 3.79 and 3.83 ppm for the three methoxy groups and a singlet at 9.76 ppm for amino proton. The protons of the pyridine ring exhibited characteristic multiplets in the appropriate regions of the ^{1}H NMR spectrum. ^{13}C NMR spectrum of **3a** exhibited nineteen signals in agreement with the proposed structure. The partial assignment of these resonances is given in the experimental section. The IR spectrum of **3a** displayed characteristic carbonyl (1725 and 1705 cm^{-1}) and N–H (3430 cm^{-1}) stretching vibrations.

^{1}H and ^{13}C NMR spectra of **3b** and **3d-e** are similar to those of **3a** except for the alkyl groups of ester moieties and alkyl amino groups.

The mass spectra of **3a-b** and **3d-e** displayed the molecular ion peaks at the appropriate *m/z* values. The fragmentations involved the loss of side chains such as alkoxy, ester and amino groups.

^{1}H NMR spectrum of **4c** exhibited five singlets at 1.40, 1.46, 1.47, 1.48 and 1.53 ppm for four *tert*-butoxy groups and *tert*-butylamino group; a broad singlet at 4.04 ppm for the NH group, a singlet at 4.08 ppm for the methine group and four characteristic multiplets in the appropriate regions for the pyridine ring protons, consistent with the proposed structure for **4c**. ^{13}C NMR spectrum displayed twenty four sharp lines in agreement with the structure of **4c**. IR spectrum of **4c** showed two absorption bands at 3430 and 1725 cm^{-1} indicating the presence of



Scheme 2.

NH and carbonyl groups, respectively. The mass spectrum of **4c** exhibited molecular ion peak at *m/z* 629 and base peak at *m/z* 57 for the *tert*-butyl group. The fragmentations involved the loss of side chains such as alkoxy, ester and amino groups.

^{1}H NMR spectrum of **5c** exhibited four singlets at 1.50, 1.51, 1.52 and 1.58 ppm for four *tert*-butoxy groups, a singlet at 6.00 ppm for methine group, a doublet at 6.82 ppm ($^3J_{HH}$ = 8.0 Hz) for CH group of the pyridine ring, a multiplet at 6.86–6.89 ppm for the CH group of the pyridine ring, a doublet of doublet of doublet at 7.56 ppm ($^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 6.8 Hz and $^4J_{HH}$ = 1.6) for CH group of the pyridine ring, a doublet of doublet at 8.15 ppm ($^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.6 Hz) for the CH group of the pyridine ring and a broad singlet at 11.15 ppm for the NH group. ^{13}C NMR spectrum of **5c** displayed twenty one sharp lines in agreement with the proposed structure and IR spectrum exhibited three absorption bands at 3550,

1731 and 1667 cm^{-1} for NH, C = O and C = C groups, respectively. The mass spectrum of **5c** exhibited molecular ion peak at *m/z* 546 and base peak at 57 in agreement with the existence of *tert*-butyl group. The fragmentations also involved the loss of side chains such as alkoxy, ester and amino groups.

Elemental analyses also confirmed the proposed formula of the compounds.

3. Experimental

2-Aminopyridine, *tert*-butyl isocyanide, cyclohexyl isocyanide, dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate and di-*tert*-butyl acetylenedicarboxylate were purchased from Merck and Fluka without further purification. NMR spectra were recorded with a Brucker DRX-400 AVANCE instrument (400.13 MHz and 100.6 MHz for ^1H and ^{13}C) with $CDCl_3$ as solvent. Melting points were measured on an Electrotermal 9100 apparatus. Mass spectra were recorded on a Finniga-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure for preparation of compounds 3, 4c and 5c

To a magnetically stirred solution of 2-aminopyridine (2 mmol, 0.18 g) and dialkyl acetylenedicarboxylate (4 mmol) in diethyl ether (10 ml), alkyl isocyanide (2 mmol) in diethyl ether (4 ml) was added dropwise over 30 min at room temperature. The reaction mixture was stirred for 3 hours at room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography using hexane:ethyl acetate (4:1) as eluent. The solvent was removed under reduced pressure and the solid product was recrystallized from diethyl ether. Products **3a-b, 3d-e** and **4c** and **5c** were obtained with high purity as yellow powders.

Dimethyl 4-(*tert*-butylamino)-7-methoxy-5-oxo-1-(pyridin-2-yl)-1,5-dihydrofuro[3,4-*b*]pyridine-2,3-dicarboxylate (3a).

Yellow powder, yield: 90%; mp 145–147 °C; IR (KBr) ν 3430 (NH), 1720 and 1667 (C=O), 1614 cm^{-1} (C=C); ^1H NMR (400.1 MHz, $CDCl_3$): δ (ppm) 1.64 (s, 9H, CMe_3), 3.64, 3.79, 3.83 (3s, 9H, 3OCH_3), 6.92 (td, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 7.29 (td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 7.57 (d, $^3J_{HH}$ = 8.8 Hz, 1H, CH) 8.80 (d, $^3J_{HH}$ = 7.2 Hz, 1H, CH), 9.76 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 30.9, 51.3, 52.5, 52.9, 54.4, 80.8, 105.5, 113.5, 117.5, 122.3, 126.1, 127.4, 131.6, 143.2, 156.3, 166.7, 168.7, 169.6, 172.8; MS*: m/z* (%) 430 (M^+), 313, 282, 257, 231, 205, 179, 149, 57. Anal. Calcd for $C_{21}H_{23}N_3O_7$ (429.42): C, 58.74; H, 5.40; N, 9.79. Found: C, 58.67; H, 5.35; N, 9.71.

Diethyl 4-(*tert*-butylamino)-7-ethoxy-5-oxo-1-(pyridin-2-yl)-1,5-dihydrofuro[3,4-*b*]pyridine-2,3-dicarboxylate (3b).

Yellow powder, yield: 75%; mp 125–127 °C; IR (KBr) ν 3460 (NH), 1729 and 1705 (C=O), 1670 cm^{-1} (C=C); ^1H NMR (400.1 MHz, $CDCl_3$): δ (ppm) 1.10 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.23 (s, 9H, CMe_3), 1.32 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.39 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 3.93–4.11 (m, 2H, OCH_2), 4.17–4.31 (m, 2H, OCH_2), 4.32–4.41 (m, 2H, OCH_2), 6.76 (t, $^3J_{HH}$ = 6.8 Hz, 1H, CH), 7.41–7.46 (m, 2H, 2CH), 7.78 (t, $^3J_{HH}$ = 7.6, 1H, CH), 10.06 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 13.8, 14.0, 14.2, 30.7, 56.5, 60.5, 60.6, 61.8, 86.29, 100.8, 113.3, 114.2, 116.6, 134.4 143.7, 149.8, 152.9, 160.2, 165.1, 165.3, 167.0, 167.1; MS: *m/z* (%): 471 (M^+), 414, 369, 323, 296, 250, 224, 57. Anal. Calcd for $C_{24}H_{29}N_3O_7$ (471.50): C, 61.14; H, 6.2; N, 8.91. Found: C, 61.05; H, 6.14; N, 8.85%.

Dimethyl 4-(cyclohexylamino)-7-methoxy-5-oxo-1-(pyridin-2-yl)-1,5-dihydrofuro [3,4-*b*]pyridine-2,3-dicarboxylate (3d).

Yellow powder, yield: 72%; mp 140–142 °C; IR (KBr) ν 3350 (NH), 1770 and 1690 (C=O), 1610 cm^{-1} (C=C); ^1H NMR (400.1 MHz, $CDCl_3$): δ (ppm) 1.44–1.79 (m, 8H, 4CH_2), 2.07–2.09 (m, 2H, CH_2), 3.65, 3.81, 3.83 (3s, 9H, 3OCH_3), 4.26–4.32 (m, 1H, CH Cyclohexyl), 6.94 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 7.32 (td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 7.59 (dt, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, CH), 8.88 (dt, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 1.2, 1H, CH), 9.59 (d, $^3J_{HH}$ = 8.0, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 24.1, 25.4, 33.6, 50.5, 51.3, 52.5, 52.9, 80.6, 105.7, 113.7, 116.2, 117.3, 121.2, 126.4, 127.7, 134.1, 143.1, 166.7, 168.8, 169.2, 170.2; MS: *m/z* (%) 455 (M^+), 424, 372, 341, 309, 298, 267, 254, 240, 210, 182, 78. Anal. Calcd for $C_{23}H_{25}N_3O_7$ (455.46): C, 60.65; H, 5.53; N, 9.23. Found: C, 60.56; H, 5.45; N, 9.15.

Diethyl 4-(cyclohexylamino)-7-ethoxy-5-oxo-1-(pyridin-2-yl)-1,5-dihydrofuro[3,4-*b*]pyridine-2,3-dicarboxylate (3e).

Yellow powder, yield: 60%; mp 155–157 °C; IR (KBr) ν 3450 (NH), 1700 and 1690 (C=O), 1640 and 1440 cm^{-1} (C=C); ^1H NMR (400.1 MHz, $CDCl_3$): δ (ppm) 1.23 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.35 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.40–1.79 (m, 8H, 4CH_2), 2.07–2.10 (m, 1H, CH_2), 4.10 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2), 4.21–4.30 (m, CH–N, 5H, 2 OCH_2), 6.92 (td, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 7.31 (td, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 7.58 (d, $^3J_{HH}$ = 9.2 Hz, 1H, CH), 8.98 (dd, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 9.62 (d, $^3J_{HH}$ = 8.0 Hz, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 13.8, 14.1, 14.2, 24.1, 25.4, 33.7, 50.5, 60.2, 61.4, 62.1, 81, 108.7, 113.5, 116.1, 117.2, 126.2, 126.3 128.0, 134.1, 144.0, 166.4, 168.3, 169.0, 170.2; MS: *m/z* (%) 497 (M^+), 451, 413, 377, 326, 224, 196, 78.

Anal. Calcd for $C_{26}H_{31}N_3O_7$ (497.54): C, 62.76; H, 6.28; N, 8.45. Found: C, 62.68; H, 6.21 ; N, 8.39.

Tetra-*tert*-butyl 4-(*tert*-butylamino)-2*H*-[1,2'-bipyridine]-2,3,5,6-tetracarboxylate (4c).

Yellow powder, yield: 52%; mp 135–137 °C; IR (KBr) ν 3430 (NH), 1725 (C=O), 1660 cm^{-1} (C=C); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ (ppm) 1.40, 1.46, 1.47, 1.48, 1.53 (5s, 45H, 5 CMe_3), 4.04 (bs, 1H, NH), 4.08 (s, 1H, CH), 6.63–6.67 (m, 1H, CH), 7.06–7.14 (m, 1H, CH), 7.38–7.40 (m, 1H, CH), 7.82 (d, $^3J_{HH}$ = 6.8, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 27.7, 27.8, 27.9, 28.1, 30.0, 52.3, 55.1, 80.3, 81.7 , 82.1, 82.5, 82.7, 100.0, 114.9, 123.4, 137.7, 141.4, 146.0, 147.8, 164.1, 164.9, 165.2, 165.9, 166.1; MS: *m/z* (%) 629 (M^+), 572, 516, 445, 389, 342, 277, 180, 154, 57. Anal. Calcd for $C_{34}H_{51}N_3O_8$ (629.78): C, 64.84; H, 8.16; N, 6.67. Found: C, 64.74; H, 8.09; N, 6.59.

(1*Z*,3*E*)-tetra-*tert*-butyl 1-(pyridin-2-ylamino)buta-1,3diene-1,2,3,4-tetracarboxylate (5c).

Yellow powder, yield: 28%; mp 160–162 °C, IR (KBr) ν 3550 (NH), 1731 (C=O), 1667 and 1608 cm^{-1} (C=C); ^{1}H NMR (400.1 MHz, $CDCl_3$): δ (ppm) 1.50, 1.51, 1.52, 1.58 (4s, 36H, 4 CMe_3), 6.00 (s, 1H, CH), 6.82 (d, $^3J_{HH}$ = 8.0 Hz, 1H, CH), 6.86–6.89 (m, 1H, CH), 7.56 (ddd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.6, 1H, CH), 8.15 (dd, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.2 Hz, 1H, CH), 11.15 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) 27.8, 28.0, 28.1, 28.2, 80.9, 81.2, 81.8, 83.5, 112.0, 112.1, 117.6, 130.5, 133.7, 137.3, 137.8, 146.9, 151.2, 162.1, 164.6, 164.8, 168.7; MS: *m/z* (%) 546 (M^+), 445, 313, 277, 260, 215, 187, 143, 57. Anal. Calcd for $C_{29}H_{42}N_2O_8$ (546.65): C, 63.72; H, 7.74; N, 5.12. Found: C, 63.61; H, 7.68; N, 5.04.

4. Conclusions

In summary, we reported a one-pot, three-component synthesis of tetra-alkyl 4-(alkylamino)-1,2'-bipyridine-2,3,5,6-tetracarboxylate and dialkyl 4-(alkylamino)-7-alkoxy-5-oxo-1-pyridine-2-yl-1,5-dihydrofuro[3,4-*b*]pyridine 2,3-dicarboxylate which are of potential synthetic interest. The mild reaction conditions, good yields and use of simple starting materials are the main advantages of this approach.

5. Acknowledgements

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Povzetek

Avtorji v prispevku poročajo o učinkoviti enostopenjski trokomponentni reakciji med 2-aminopiridinom, estri acetilena in alkil izocianidi. Pri reakciji pod milimi pogoji nastanejo tetraalkil 4-(alkilamino)-2*H*-[1,2'-bipiridin]-2,3,5,6-tetrakarboksilati in dialkil 4-(alkyiamino)-7-alkoksi-5-okso-1-(piridin-2-il)-1,5-dihidrofuoro[3,4-*b*]piridin 2,3-dikarboksilati z visokimi izkoristki.