Tetrahedron 71 (2015) 252–258

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of new 4-aza-indoles via acyl azides

Sengul Dilem Doğan [a,b], Eren Demirpolat [c], Mükerrem Betül Yerer Aycan [c], Metin Balci [a,*]

[a] Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey
[b] Department of Pharmaceutical Basic Sciences, Faculty of Pharmacy, Erciyes University, 38039 Kayseri, Turkey
[c] Department of Pharmacology, Faculty of Pharmacy, Erciyes University, 38039 Kayseri, Turkey

ARTICLE INFO

Article history:
Received 3 October 2014
Received in revised form 10 November 2014
Accepted 24 November 2014
Available online 29 November 2014

Keywords:
Acyl azide
Azaindole
Azaoxindole
Curtius rearrangement
Cytotoxic activity

ABSTRACT

We hereby report the preparation of new azaindole derivatives starting from 2-(2-ethoxy-2-oxoethyl) nicotinic acid. Conversion of a half ester into acyl azide followed by *Curtius* rearrangement gave the corresponding isocyanate. Trapping of the isocyanate with different nucleophiles produced urea and urethane derivatives. Intramolecular cyclization reactions gave the target compounds.

1. Introduction

Indole is a well-known privileged core in natural products and many derivatives show important biological activities.[1] The azaindole moieties **1**–**4**, also known as pyrrolopyridine exhibit excellent potential as a bioisostere of the indole ring system, differing from indole only by the presence of an additional ring nitrogen, whose position can vary on the benzene ring.[2] In contrast to indole, the azaindole structural motif is not widely distributed in natural products (Fig. 1).

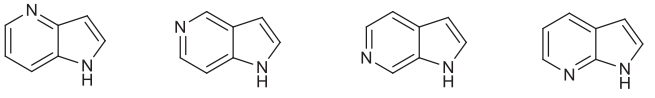


Fig. 1. Structures of isomeric azaindoles.

The 7-azaindole structure **4** was discovered in only a few natural products such as alkaloid variolin D **5**[3] from the variolin family (Fig. 2).[4] Preliminary studies on the biological activity of these compounds indicated that variolin B **6** was the most cytotoxic in the P388 murine leukemia cell line assay.

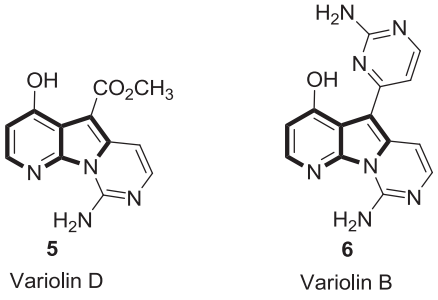


Fig. 2. Structures of variolin D and variolin B.

7-Azaindole derivatives have attracted much attention due to their physicochemical and pharmacological properties. Contrary to their 7-azaindole analogs, the 4-, 5- and 6-azaindoles have been studied less in terms of their inorganic properties.[2e] During the last two decades, with the development of transition-metal catalysis and lithiation chemistry,[2b] a number of new synthetic methodologies have been created for substituted azaindole derivatives. A novel Fischer reaction was applied to the synthesis of the bisfunctionalized 4-azaindole building block in one step.[5] Various synthetic methods such as Pd-catalyzed heterocyclization,[6] the Reissert-type procedure,[7] the Leimgruber–Batcho reaction,[8] and

* Corresponding author. Tel.: +90 535 388 8276, +90 312 210 5140; e-mail address: mbalci@metu.edu.tr (M. Balci).

http://dx.doi.org/10.1016/j.tet.2014.11.057
0040-4020/

others[9] were successfully applied to the synthesis of azaindoline derivatives.

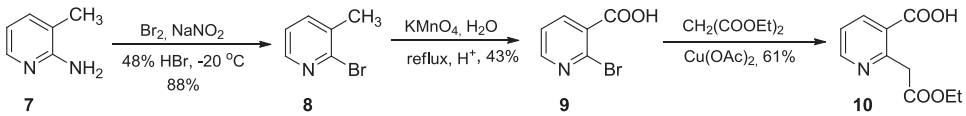
Azaindoles exhibit significant biological activity and help facilitate the generation of new therapeutic leads. Many of these compounds have shown potential as selective CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) antagonists,[10] potent MAPK p38 inhibitors,[11] anti-inflammatory agents,[12] thrombin inhibitors,[13] factor VIIa complex inhibitor,[14] and PKs (protein kinase) inhibitor.[15] Therefore, access to functionalized azaindoles is a continuous synthetic challenge for organic chemists. A part of our research program is currently dedicated to the design of new compounds containing a 4-azaindole core. In this paper we describe a new methodology for the synthesis of substituted 4-azaindoles and their biological activities.

2. Results and discussion

For the synthesis of the desired heterocyclic ring systems, i.e. azaindole derivatives, ethyl 2-(2-ethoxy-2-oxoethyl)nicotinic acid **10** was used as the key compound. Bromination of commercially available 2-amino-3-methylpyridine (**7**) in the presence of HBr at low temperature gave the bromination product **8** (Scheme 1).[16] Oxidation of **8** to 2-bromonicotinic acid (**9**)[17] was performed by using $KMnO_4$ in water. The coupling of 2-bromonicotinic acid (**9**) with diethyl malonate in the presence of $Cu(OAc)_2$ resulted in the formation of **10**[18] in good yield (Scheme 1).

A tentative mechanism of the formation of **12** and **13** is outlined in Scheme 3. It is proposed that the first step is the formation of the isocyanate **14a**. Isocyanates generally can act as a trapping agent for a variety of nucleophiles. Because of the electron-withdrawing ability of the ester group, the isocyanate **14a** may be in equilibrium with the corresponding tautomer **14b**, which increases the nucleophilicity of the methylene group. Therefore, intermediate **14b** can undergo an intramolecular cyclization reaction to yield **15**, which can tautomerize to the most stable aromatic form **13**. Under the same reaction conditions, the product **13** undergoes a further condensation reaction with the in situ formed isocyanate **14a** and forms the major product **12** (Scheme 3).

As an alternate method, to prevent the ring closure reaction of isocyanate **14a**, acyl azide **11** was treated with wet benzene and the mixture was refluxed for 3 h. The urea derivative **16** was formed as the sole isolated product in 84% yield. First acyl azide **11** was transformed to the corresponding isocyanate **14a**. Hydrolysis of this isocyanate **14a** with water, present in the reaction media, formed amine **17**. The reaction of amine **17** with isocyanate **14a** resulted in the formation of the urea derivative **16** (Scheme 4). The structure of the product **16** was characterized by NMR spectral data. The high resolution mass spectrum of **16** clearly indicates the formation of a product generated from two moles of **11**. The experimental value of M^+=385.15174 (for $C_{19}H_{22}N_4O_5$) was fully in agreement with the theoretical value, M^+=385.14935. Furthermore, the ^{13}C NMR spectrum consisting of 10 lines showed the presence of a symmetrical structure.



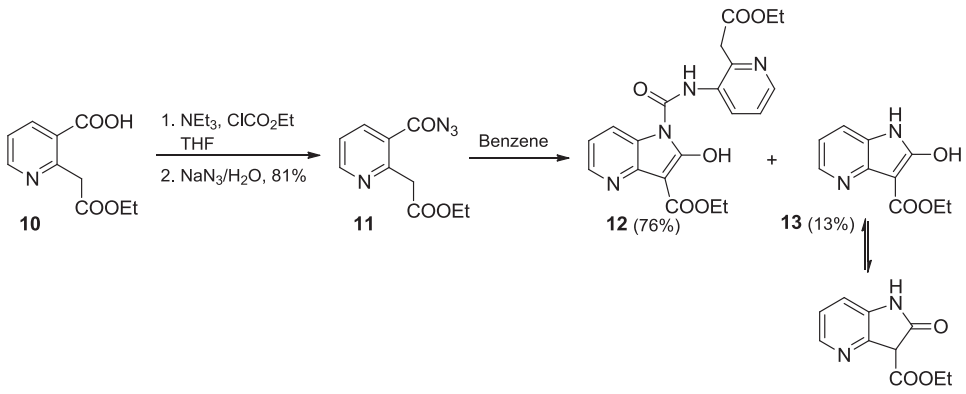
Scheme 1. Synthesis of the key compound, 2-(2-ethoxy-2-oxoethyl)nicotinic acid (**10**).

For the construction of the pyrrole moiety, half ester **10** was first converted into the corresponding azide **11**. For the azidination reaction,[19] **10** was treated with ethyl chloroformate in the presence of triethylamine followed by the addition of a solution of NaN_3 in water to give **11** in 81% yield (Scheme 2). The azide function provided a convenient handle for the generation of the corresponding isocyanate. Thus acyl azide **11** was allowed to reflux in benzene for 3 h. Unfortunately, we were not able to isolate the expected isocyanate **14a**.[20] Instead, a mixture of two 4-azaindole derivatives, **12** and **13**, was formed in 76% and 13% yields, respectively (Scheme 2). The ^1H and ^{13}C NMR spectra enabled the assignment of the structures of 4-azaindole derivatives **12** and **13**. Furthermore COSY, HMQC, DEPT, and HMBC experiments were also in agreement with the proposed structures.

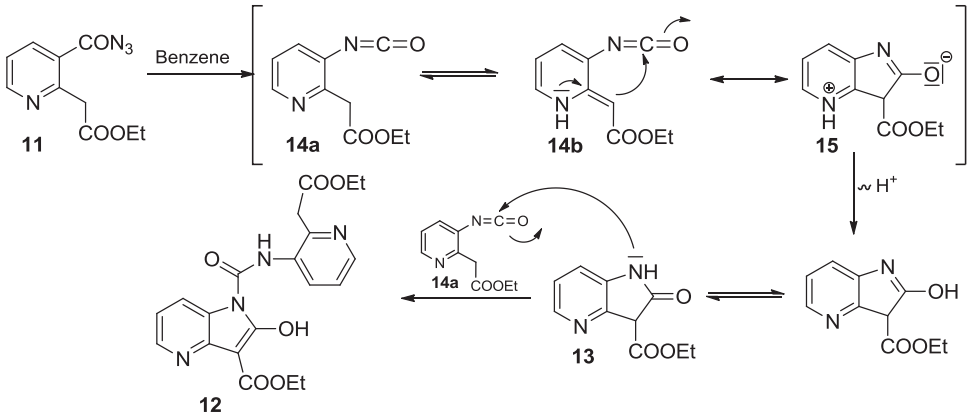
The ring-closing process of urea derivative **16** was accomplished by treatment with K_2CO_3 in acetonitrile at 60 °C (Scheme 5). NMR analysis (COSY, DEPT, HMQC, and HMBC spectra) including HRMS measurements indicated the formation of an intermolecular condensation product **18** as the major product in 44% yield along with the fragmentation product **19** in 36% yield.

The expected ring closure products **20** and **21** were not found among the isolated products (Fig. 3). However, we assume that the ring-cyclization product **20**, having a five-membered ring, is formed as an intermediate by an intramolecular cyclization reaction of **16**.

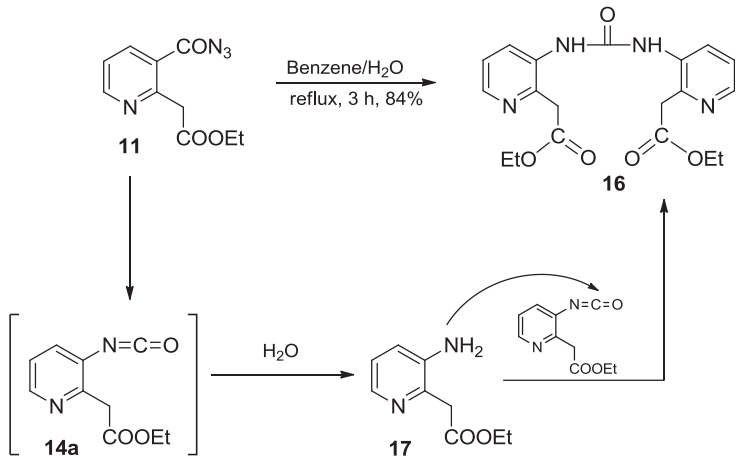
Since the methylene protons in **20** are more acidic than those in the urea derivative **16**, the reaction proceeds further and K_2CO_3 abstracts one of the methylene protons in **20** to generate a carbanion, **22** (Scheme 6). This carbanion **22** can undergo an intermolecular reaction



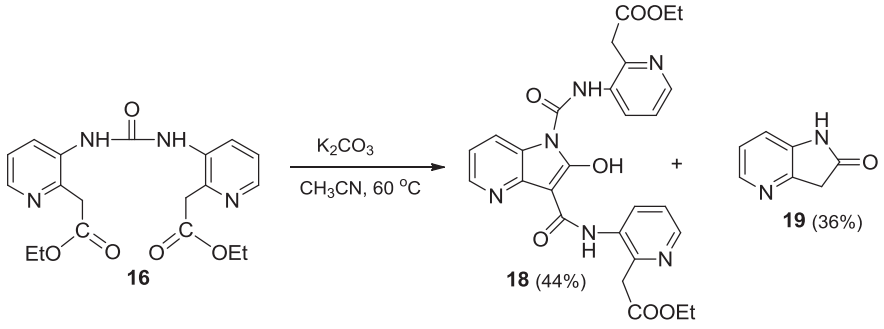
Scheme 2. Synthesis of azide **11** and its thermolysis in benzene to give **12** and **13**.



Scheme 3. Suggested mechanism for the formation of the products **12** and **13**.



Scheme 4. Synthesis of urea derivative **16** and its mechanism of formation.



Scheme 5. Ring closure reaction of **16** with K_2CO_3.

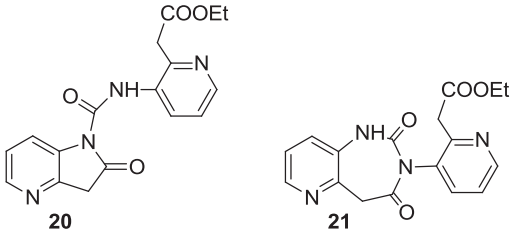
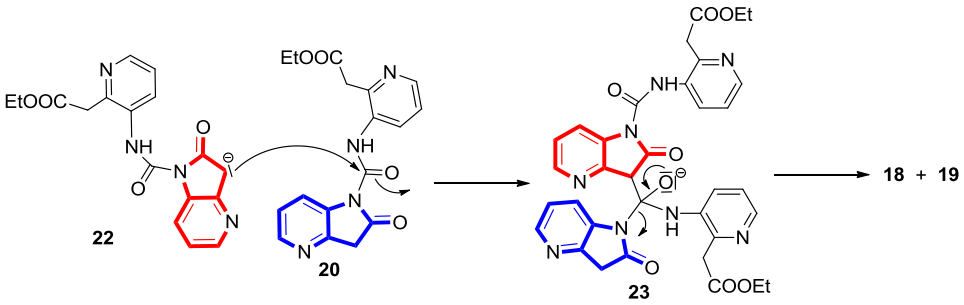


Fig. 3. Structures of **20** and **21**.

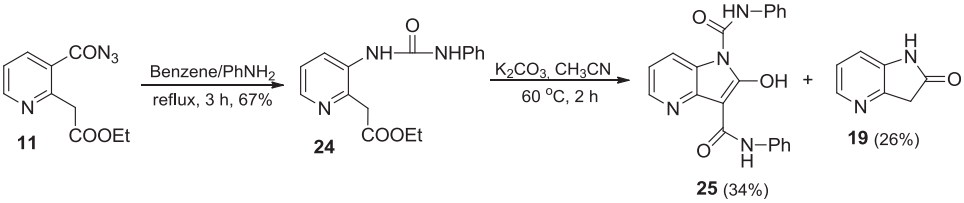
with azaindolinone derivative **20** to form **23**, which can undergo a fragmentation reaction to furnish the final products **18** and **19**.

Next, we focused our effort on the synthesis of new azaindole derivatives. The isocyanate **14a** can be trapped with different nucleophiles so that the substituents attached to *N*-atom can be controlled. Isocyanate **14a** was reacted with aniline to give the urea derivatives **24** in 67% yield (Scheme 7). Reaction of urea derivatives **24** with K_2CO_3 gave two products **19** and **25** resulting from intramolecular condensation of **24** followed by intermolecular condensation as discussed above (Scheme 6).

To prevent intermolecular condensation and synthesize further azaindole derivatives, **24** was reacted with NaH in the presence of



Scheme 6. The mechanism for the formation of the products **18** and **19**.



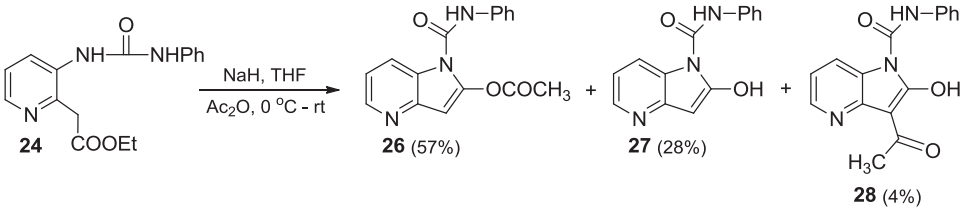
Scheme 7. Synthesis of urea **24** and its cyclization reaction to produce **25** and **19**.

acetic anhydride in THF to give three products, **26**, **27**, and **28** in yields of 57, 28, and 4%, respectively (Scheme 8). Careful examination of the reaction mixture did not reveal the formation of any trace of the intermolecular condensation products having a structure such as **25**. It is proposed that compound **27** first was formed by an intramolecular condensation reaction of **24**. Azaindole derivative **27** undergoes a proton abstraction to form a carbanion, which is then trapped by acetic anhydride to form azaindole derivative **28**. Formation of azaindole derivative **26** can be attributed to proton abstraction from the hydroxyl group and trapping of this anion with acetic acid to form **26**. The 1D- and 2D-NMR experiments facilitated the assignments of structures **24**–**27**.

None of the compounds showed inhibitory activity (IC50 values) at <10 μM against HepG2 (hepatocellular carcinoma) or Colo-25 (colorectal carcinoma) cells.

3. Conclusion

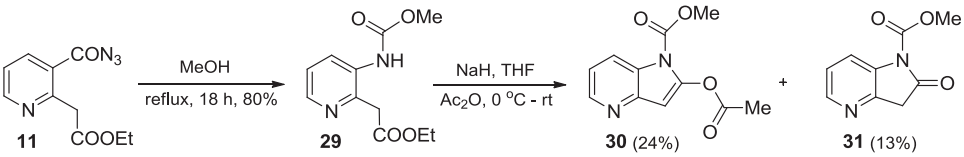
We have applied a simple and efficient method for the synthesis of new azaindole derivatives. The monoazide **11** was successfully synthesized. The conversion of **11** into the corresponding isocyanate **14a** followed by trapping with different amine bases gave the urea derivatives **12** and **24**. The base-supported condensation reaction of these products resulted in the formation of **18** and **25**.



Scheme 8. Reaction of urea **24** with NaH in the presence of acetic anhydride.

For the synthesis of new azaindole derivatives, the isocyanate **14a** was trapped with methanol at the reflux temperature of the alcohol to give the corresponding urethane derivative **29**. Reaction of **29** with NaH in the presence of acetic anhydride gave two easily separable azaindole derivatives, **30** and **31** (Scheme 9).

When the condensation reaction was carried out in the presence of a trapping reagent, acetic anhydride, the intermolecular reaction was prevented. Application of this methodology to pyridine opens up a new area for the synthesis of various substituted azaindole derivatives.



Scheme 9. Reaction of urethane **29** with NaH in the presence of acetic anhydride.

4. Experimental

4.1. General procedure

Melting points are uncorrected. Infrared (IR) spectra were recorded in the range 4000–600 cm^{-1} via ATR diamond. The ^1H and ^{13}C NMR spectra were recorded on a 400 (100) MHz spectrometer. Apparent splitting is given in all cases. High resolution mass spectra were recorded by LC–MS TOF electrospray ionization technique. Chemicals and all solvents were commercially available and used without further purification. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates.

4.2. Ethyl 2-(3-(azidocarbonyl)pyridine-2-yl)acetate (11)

To a solution of 2-(2-ethoxy-2-oxoethyl)nicotinic acid (**10**) (1.0 g, 4.78 mmol) in 10 mL THF at −5 °C, triethylamine (0.7 mL, 4.78 mmol) in THF (5 mL) was added dropwise and the resulting mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of ethyl chloroformate (0.6 mL, 5.74 mmol) in THF (5 mL) and the reaction mixture was stirred at the same temperature for additional 30 min. A solution of sodium azide (0.62 g, 9.56 mmol) in water (5 mL) was then added dropwise and the mixture was left to stir at room temperature overnight. The mixture was extracted with ethyl acetate (3×15 mL) and the organic phase was washed with saturated sodium bicarbonate (3×30 mL) and with water (2×25 mL) and dried over $MgSO_4$. After removal of ethyl acetate azide **11** (0.91 g, 81%) was obtained as pale yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, J=4.8, 1.7 Hz, 1H), 8.20 (dd, J=8.0, 1.7 Hz, 1H), 7.27 (dd, J=8.0, 4.8 Hz, 1H), 4.22 (s, 2H), 4.11 (q, J=7.1 Hz, 2H), 1.19 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 170.4, 156.4, 153.1, 138.6, 125.9, 122.4, 61.0, 43.7, 14.1. ν_{max} (ATR) 2984, 2136, 1733, 1693, 1569, 1443, 1370, 1234, 1176, 1028.

4.3. Thermolysis of 11 in benzene

Ethyl 2-(3-(azidocarbonyl)pyridin-2-yl)acetate (**11**) (1.92 g, 8.2 mmol) was heated at reflux in freshly distilled benzene (20 mL) for 3 h. The precipitate formed was filtered off to give a mixture of the products **12** and **13**. The mixture was washed with hot chloroform; **12** was soluble in hot chloroform and the other compound **13** was insoluble. Filtrate was concentrated under vacuum to give the pure compound **12** (1.28 g, 76%). The insoluble part **13** was washed with chloroform to give pure sample (0.22 g, 13%).

*4.3.1. Ethyl 2-hydroxy-1H-pyrrolo[3,2-b]pyridine-3-carboxylate (**13**).* White solid from chloroform, mp (decomposition) 272–274 °C. ^1H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 10.31 (s, 1H), 7.51 (t, J=6.2 Hz, 1H), 7.05 (dd, J=7.4, 0.8 Hz, 1H), 6.78 (t, J=6.9 Hz, 1H), 4.22 (q, J=7.1 Hz, 2H), 1.26 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 165.3, 164.1, 143.2, 131.1, 125.6, 111.6, 111.4, 82.7, 58.0, 14.7. ν_{max} (ATR): 3087, 2984, 1698, 1592, 1513, 1456, 1444, 1327, 1238, 1075, 1038. HRMS: m/z $[M+Na]^+$ calcd for $C_{10}H_{10}N_2O_3$: 205.06134; found: 205.06187.

*4.3.2. Ethyl 1-((2-(2-ethoxy-2-oxoethyl)pyridin-3-yl)carbamoyl)-2-hydroxy-1H-pyrrolo-[3,2-b]pyridine-3-carboxylate (**12**).* White solid from chloroform, mp (decomposition) 264–265 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.83 (s, 1H), 11.48 (s, 1H), 8.42 (dd, J=7.7, 0.7 Hz, 1H), 8.29 (dd, J=4.7, 1.5 Hz, 1H), 8.26 (dd, J=8.2, 1.4 Hz, 1H), 7.55 (t, J=5.8 Hz, 1H), 7.20 (dd, J=8.0, 5.0 Hz, 1H), 6.86 (dt, J=7.1, 1.6 Hz, 1H), 4.32 (q, J=7.1 Hz, 2H), 4.16 (q, J=7.1 Hz, 2H), 3.97 (s, 2H), 1.33 (t, J=7.1 Hz, 3H), 1.21 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 165.9, 164.8, 151.1, 147.0, 145.4, 145.3, 132.8, 130.7, 129.5, 127.3, 122.7, 121.8, 113.5, 83.4, 61.2, 60.4, 40.7, 14.6, 14.1. ν_{max} (ATR): 3287, 2979, 1723, 1592, 1557, 1413, 1383, 1329, 1264, 1179, 1131, 1077, 1021. HRMS: m/z $[M+Na]^+$ calcd for $C_{20}H_{20}N_4O_6$: 411.13101; found: 411.13273.

4.4. Diethyl 2,2′-(3,3′-(carbonylbis(azanediyl))bis(pyridine-3,2-diyl))diacetate (16)

Acyl azide (**11**) (640 mg, 2.56 mmol) was heated at reflux in a mixture of benzene (20 mL) and water (2 mL) for 3 h. The solvent was evaporated and the crude product was purified by crystallization from ethyl acetate/hexane at room temperature to give urea **16** as a white solid (390 mg, 84%), mp 147–148 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, J=4.7, 1.5 Hz, 2H), 8.30 (br s, 2H), 8.18 (dd, J=8.2, 1.5 Hz, 2H), 7.27 (dd, J=8.2, 4.7 Hz, 2H), 4.19 (q, J=7.1 Hz, 4H), 3.97 (s, 4H), 1.29 (t, J=7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 153.2, 146.2, 145.1, 134.0, 131.9, 123.2, 61.9, 42.0, 14.01. ν_{max} (ATR): 3279, 2953, 1722, 1630, 1589, 1557, 1437, 1328, 1252, 1218, 1151, 1025. HRMS: m/z $[M+Na]^+$ calcd for $C_{19}H_{22}N_4O_5$: 385.14935; found: 385.15174.

4.5. Cyclization reaction of 16 with K_2CO_3

To a solution of urea derivative **16** (340 mg, 0.88 mmol) in acetonitrile (20 mL) at 60 °C was added excess K_2CO_3 (0.6 g, 4.3 mmol). After stirring for 3 h, excess K_2CO_3 was filtered and solvent was evaporated under reduced pressure. The formed products were separated by column chromatography (silica gel, EtOAc/hexane, 99:1). The fragmentation product **19** (43 mg, 36%) was isolated as the first fraction. The major product **18** was eluted as the second fraction (210 mg, 44%).

*4.5.1. 1H-Pyrrolo[3,2-b]pyridin-2(3H)-one (**19**).*[21] Colorless viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (br s, 1H), 8.14 (dd, J=2.4, 4.4 Hz, 1H), 7.08 (br s, 1H), 7.07 (br s, 1H), 3.62 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 148.0, 143.1, 137.6, 122.7, 115.9, 37.8.

*4.5.2. Diethyl 2,2′-(3,3′-((2-hydroxy-1H-pyrrolo[3,2-b]pyridine-1,3-dicarbonyl) bis (azanediyl)) bis(pyridine-3,2-diyl))diacetate (**18**).* White crystals from EtOAc, mp 186–187 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 11.28 (s, 1H), 9.71 (s, 1H), 8.43 (dd, J=7.7, 0.9 Hz, 1H), 8.32 (dd, J=4.6, 1.4 Hz, 1H), 8.30 (dd, J=4.7, 1.4 Hz, 1H), 8.26 (dd, J=8.2, 1.5 Hz, 1H), 8.22 (dd, J=8.2, 1.4 Hz, 1H), 7.22 (dd, J=8.2, 4.7 Hz, 1H), 7.15 (dd, J=8.1, 4.7 Hz, 2H), 6.73 (dd, J=7.7, 6.6 Hz, 1H), 4.18 (q, J=7.1 Hz, 2H), 4.14 (q, J=7.1 Hz, 2H), 3.97 (s, 2H), 3.94 (s, 2H), 1.20 (t, J=7.1 Hz, 3H), 1.16 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (2C), 166.2, 163.9, 150.6, 147.3, 146.0, 145.5, 145.4, 143.3, 138.9, 133.1, 132.7, 131.5, 130.8, 128.6, 122.8, 122.7, 122.7, 113.4, 85.3, 61.3 (2C), 40.7, 40.6, 14.1. ν_{max} (ATR): 3284, 2983, 1721, 1634, 1594, 1544, 1429, 1397, 1329, 1283, 1216, 1140, 1024. HRMS: m/z $[M+Na]^+$ calcd for $C_{27}H_{26}N_6O_7$: 545.17847; found: 545.17686.

4.6. Ethyl 2-(3-(3-phenylureido)pyridin-2-yl)acetate (24)

Acyl azide (**14a**) (1.62 g, 6.5 mmol) and aniline (0.78 g, 8.4 mmol) in benzene (20 mL) were stirred at 50 °C for 1 h and then at 80 °C for 3 h. The solvent was evaporated and the crude product was purified by crystallization from chloroform/hexane to give urea **24** as white crystals (1.3 g, 43%), mp 143–144 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J=4.7, 1.4 Hz, 1H), 8.08 (dd, J=8.2, 1.4 Hz, 1H), 7.96 (s, 1H), 7.33–7.21 (m, 4H), 7.17 (dd, J=8.2, 4.7 Hz, 1H), 7.07–7.01 (m, 1H), 6.98 (s, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.84 (s, 2H), 1.16 (t, J=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 153.4, 146.2, 144.8, 138.3, 138.0, 134.2, 132.3, 129.2, 124.2, 123.2, 120.9, 120.8, 61.9, 41.5, 14.0. ν_{max} (ATR): 3289, 2981, 1722, 1660, 1602, 1541, 1435, 1318, 1239, 1191, 1026. HRMS: m/z $[M+Na]^+$ calcd for $C_{16}H_{17}N_3O_3$: 298.11971; found: 298.11666.

4.7. Reaction of urea 24 with K_2CO_3

To a solution of urea derivative **24** (780 mg, 2.61 mmol) in acetonitrile (20 mL) at 60 °C was added excess K_2CO_3 (1.5 g, 0.01 mol). After stirring for 2 h, excess K_2CO_3 was filtered and solvent was evaporated under reduced pressure. The residue was treated with chloroform, pyrrolo-prydinone **19** was soluble in chloroform and whereas the major product **25** was insoluble. Analytical pure samples were obtained by column chromatography on silica gel eluting with EtOAc/*n*-hexane (8:2) to give **19** (90 mg, 26%). The major compound **25** was purified by washing with cold methanol (333 mg, 34%).

*4.7.1. 2-Hydroxy-N^1,N^3-diphenyl-1H-pyrrolo[3,2-b]pyridine-1,3-dicarboxamide (**25**).* Brown solid, mp 194–195 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 11.28 (s, 1H), 8.26 (dd, J=7.8, 1.4 Hz, 1H), 8.14 (dd, J=5.1, 1.4 Hz, 1H), 7.75 (d, J=7.6 Hz, 2H), 7.69 (d, J=7.6 Hz, 2H), 7.43 (t, J=7.9 Hz, 2H), 7.34 (t, J=7.9 Hz, 2H), 7.15 (t, J=7.4 Hz, 1H), 7.01 (t, J=7.3 Hz, 1H), 6.87 (dd, J=7.8, 5.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 165.4, 163.2, 151.4, 147.8, 141.0, 140.7, 138.4, 129.0, 128.7, 124.4, 123.0, 121.3, 119.4, 118.5, 118.3, 113.2, 85.1. ν_{max} (ATR): 3219, 3026, 1694, 1590, 1547, 1498, 1455, 1378, 1310, 1249, 1180, 1077. HRMS: m/z [M+Na]$^+$ calcd for $C_{21}H_{16}N_4O_3$: 371.11496; found: 371.11158.

4.8. The reaction of urea 24 with NaH in the presence of acetic anhydride

To a solution of urea derivative **24** (0.48 g, 1.6 mmol) in freshly distilled THF (20 mL) at 0 °C sodium hydride (0.079 g, 3.2 mmol) was added and stirred at 0 °C for 45 min. Then acetic anhydride (0.23 g, 2.24 mmol) was added to this solution and the resulting mixture was stirred at room temperature overnight. The product **26** precipitated from the reaction medium, which was filtered off and purified by washing with chloroform and ethyl acetate (267 mg, 57%). The filtrate was concentrated under reduced pressure. The residue was treated with methanol, **26** (110 mg, 28%) was soluble in methanol and the minor product **28** was insoluble (20 mg, 4%).

*4.8.1. 3-Acetyl-2-hydroxy-N-phenyl-1H-pyrrolo[3,2-b]pyridine-1-carboxamide (**28**).* Pale yellow solid, mp (decomposition) 259–260 °C. ^{1}H NMR (400 MHz, DMSO) δ 13.70 (br s, 1H), 11.59 (s, 1H), 8.52 (dd, J=7.8, 0.8 Hz, 1H), 7.88 (d, J=6.2 Hz, 1H), 7.61 (d, J=7.7 Hz, 2H), 7.39 (t, J=7.9 Hz, 2H), 7.18 (dd, J=7.8, 6.5 Hz, 1H), 7.14 (t, J=7.4 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 191.9, 166.0, 150.0, 142.0, 137.3, 130.2, 129.1, 128.5, 123.9, 122.3, 119.8, 114.8, 93.4, 27.6. ν_{max} (ATR): 3209, 3063, 2993, 1715, 1624, 1585, 1522, 1500, 1452, 1312, 1293, 1182, 1011. HRMS: m/z [M+Na]$^+$ calcd for $C_{16}H_{13}N_3O_3$: 296.10297; found: 296.10217.

*4.8.2. 2-Hydroxy-N-phenyl-1H-pyrrolo[3,2-b]pyridine-1-carboxamide (**27**).* Pale brown solid, mp 168–169 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.90 (br s, 1H), 11.88 (s, 1H), 7.98 (d, J=7.5 Hz, 1H), 7.48 (dd, J=6.5, 0.9 Hz, 1H), 7.40 (d, J=7.6 Hz, 2H), 7.20 (t, J=7.9 Hz, 2H), 6.93 (t, J=7.4 Hz, 1H), 6.52 (dd, J=7.4, 6.6 Hz, 1H), 4.92 (d, J=0.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 167.5, 150.5, 144.5, 137.8, 129.1, 128.7, 128.5, 123.5, 119.5, 118.10, 108.9, 75.7. ν_{max} (ATR): 3027, 2919, 2849, 1713, 1647, 1596, 1499, 1307, 1269, 1213, 1119, 1084. HRMS: m/z [M+Na]$^+$ calcd for $C_{14}H_{11}N_3O_2$: 252.07785; found: 252.07652.

*4.8.3. 1-(Phenylcarbamoyl)-1H-pyrrolo[3,2-b]pyridin-2-yl acetate (**26**).* Yellow solid, mp 204–206 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.53 (s, 1H), 8.03 (d, J=7.3 Hz, 1H), 7.99 (d, J=7.3 Hz, 1H), 7.58 (d, J=7.8 Hz, 2H), 7.39 (t, J=7.8 Hz, 2H), 7.14 (t, J=7.3 Hz, 1H), 6.65 (t, J=7.3 Hz, 1H), 6.28 (s, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 172.0, 169.3, 149.6, 141.3, 137.3, 132.0, 129.1, 127.2, 124.0, 119.8, 115.4, 109.1, 90.1, 23.9. ν_{max} (ATR): 3023, 2940, 1724, 1645, 1598, 1539, 1498, 1325, 1295, 1141, 1085, 1002. HRMS: m/z [M+Na]$^+$ calcd for $C_{16}H_{13}N_3O_3$: 294.08841; found: 294.08573 (negative ions).

4.9. Ethyl 2-(3-((methoxycarbonyl)amino)pyridin-2-yl)acetate (29)

Acyl azide **11** (2.1 g, 8.39 mmol) was heated at reflux in dry methanol (25 mL) for 18 h with TLC monitoring. After completion of reaction, the solvent was removed under vacuum. Chromatography of the residue (silica gel, 50 g, EtOAc/hexane, 1:1) afforded **29** (1.6 g, 80%). Pale yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J=4.8, 1.5 Hz, 1H), 8.1 (br s, 2H), 7.16 (dd, J=8.0, 4.8, Hz, 1H), 4.11 (q, J=7.2 Hz, 2H), 3.84 (s, 2H), 3.71 (s, 3H), 1.20 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.5, 145.1, 145.0, 133.9, 130.2, 123.1, 61.8, 52.5, 41.9, 14.0. ν_{max} (ATR): 3318, 2984, 1729, 1591, 1520, 1459, 1369, 1296, 1174, 1072, 1029, 931. HRMS: m/z [M+Na]$^+$ calcd for $C_{11}H_{14}N_2O_4$: 237.08808, found: 237.08730.

4.10. The reaction of 29 with NaH in the presence of Ac_2O

To a solution of urethane derivative **29** (0.5 g, 2.1 mmol) in freshly distilled THF (20 mL) at 0 °C sodium hydride (0.1 g, 4.2 mmol) was added and stirred at room temperature for 3.5 h. Then acetic anhydride (0.3 mL, 2.94 mmol) was added to this solution and stirred at room temperature overnight. The product **30** precipitated from the reaction medium, which was filtered off and purified by washing with ethyl acetate (118 mg, 24%). The filtrate was concentrated under reduced pressure to give the crude **31**, which was recrystallized from diethyl ether (50 mg, 12%).

*4.10.1. Methyl 2-acetoxy-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (**30**).* Yellow solid, mp 235–238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=7.6 Hz, 1H), 7.40 (d, J=7.7 Hz, 1H), 6.44 (s, 1H), 6.34 (t, J=7.9 Hz, 1H), 4.03 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 152.0, 145.5, 142.1, 133.9, 123.7, 111.4, 109.2, 94.4, 53.9, 23.9. ν_{max} (ATR): 3421, 3270, 2597, 2253, 1734, 1636, 1408, 1232, 1013. HRMS: m/z [M+Na]$^+$ calcd for $C_{11}H_{10}N_2O_4$: 235.0713; found: 235.0717 (positive ions).

*4.10.2. Methyl 2-oxo-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (**31**).* Pale brown solid, mp 103–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J=7.7 Hz, 1H), 7.57 (d, J=6.4 Hz, 1H), 6.94 (t, J=8.0 Hz, 1H), 4.05 (s, 2H), 4.05 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 163.1, 152.6, 129.8, 126.9, 120.4, 114.5, 53.7, 27.7. ν_{max} (ATR): 3416, 3275, 1705, 1635, 1533, 1406, 1236, 1182, 1012. HRMS: m/z [M+Na]$^+$ calcd for $C_9H_8N_2O_3$: 193.0607; found: 193.0608 (positive ions).

Acknowledgements

The authors are indebted to the Scientific and Technological Research Council of Turkey (TUBITAK, Grant No: 110-R001), the Department of Chemistry at Middle East Technical University, the Faculty of Pharmacy at Erciyes University, and the Turkish Academy of Sciences (TUBA) for their financial support of this work.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of compounds) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.11.057.

References and notes

1. (a) Sundberg, R. J. *Indoles*; Academic: London, UK, 1996; (b) Sharma, V.; Kumar, P.; Pathak, J. *Heterocycl. Chem.* **2010**, *47*, 491–502; (c) Sadig, J. E. R.; Willis, M. C. *Synthesis* **2011**, 1–22.
2. (a) Merour, J. V.; Routier, S.; Suzenet, F.; Joseph, B. *Tetrahedron* **2013**, *69*, 4767–4834; (b) Ila, H.; Markiewiczb, J. T.; Malakhovb, V.; Knochel, P. *Synthesis* **2013**, *45*, 2343–2371; (c) Zhihui, W.; Xiao, W. *Prog. Chem.* **2012**, *24*, 1974–1982; (d) Zhao, S.-B.; Wang, S. *Chem. Soc. Rev.* **2010**, *39*, 3124–3156; (e) Popowycz, F.; Mérour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689–8807; (f) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120–1132; (g) Le Hyaric, M.; Vieira de Almeida, M.; Nora de Souza, M. V. *Quim. Nova* **2002**, *25*, 1165–1171; (h) Merour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471–506.
3. (a) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987–3992; (b) Trimurtulu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993–4000.
4. Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080–3098.
5. (a) Wang, T.; Yang, Z.; Zhang, Z.; Gong, Y.-F.; Riccardi, K. A.; Lin, P.-F.; Parker, D. D.; Rahematpura, S.; Mathew, M.; Zheng, M.; Meanwell, N. A.; Kadow, J. F.; Bender, J. A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 213–217; (b) Pin, F.; Buron, F.; Saab, F.; Colliandre, L.; Bourg, S.; Schoentgen, F.; Guevel, R. L.; Guillouzod, C.; Routier, S. *Med. Chem. Commun.* **2011**, *2*, 899–903; (c) Hou, Z.; Suzuki, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Tetrahedron* **2012**, *68*, 1695–1703.
6. (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680; (b) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307–3310; (c) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152–5160.
7. (a) Curtis, N. R.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M. P.; Emms, F.; Freedman, S. B.; Patel, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 585–588; (b) Dodd, R. H.; Ouannès, C.; Robert-Gréco, M.; Potier, P. *J. Med. Chem.* **1989**, *32*, 1272–1276; (c) Dodd, R. H.; Doisy, X.; Potier, P. *Heterocycles* **1989**, *28*, 1101–1113.
8. Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29*, 359–367.
9. (a) Whelligan, D. K.; Thomson, D. W.; Taylor, D.; Hoelder, S. *J. Org. Chem.* **2010**, *75*, 11–15; (b) Moustafa, M. M. A. R.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 3168–3171; (c) Gorugantula, S. P.; Carrero-Martínez, G. M.; Dantale, S. W.; Soderberg, B. C. G. *Tetrahedron* **2010**, *66*, 1800–1805; (d) Cooper, C. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K.-L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1233–1236.
10. Simard, D.; Leblanc, Y.; Berthelette, C.; Zaghdane, M. H.; Molinaro, C.; Wang, Z.; Gallant, M.; Lau, S.; Thao, T.; Hamel, M.; Stocco, R.; Sawyer, N.; Sillaots, F. G.; Houle, R.; Levesque, J.-F. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 841–845.
11. (a) Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, D. E.; Fahmy, B.; Olini, G. O.; Davis, J. E.; Pellegrino-Gensey, J. L.; Schafer, P. H.; Siekierka, J. J. *J. Med. Chem.* **1998**, *41*, 4196–4198; (b) James, R. H.; Dodd, J. H. *Tetrahedron Lett.* **1998**, *39*, 8763–8764.
12. Shumaila, A. M. A.; Puranik, V. G.; Kusurkar, R. S. *Tetrahedron* **2011**, *67*, 936–942.
13. Takeuchi, K.; Bastian, J. A.; Gifford-Moore, D. S.; Harper, R. W.; Miller, S. C.; Mullaney, J. T.; Sall, D. J.; Smith, G. F.; Zhang, M.; Fisher, M. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2347–2351.
14. Hu, H.; Kolesnikov, A.; Riggs, J. R.; Wesson, R. S.; Leahy, E. M.; Shrader, W. D.; Sprengeler, P. A.; Green, M. J.; Sanford, E.; Nguyen, M.; Gjerstad, E.; Cabuslay, R.; Young, W. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4657–4670.
15. Ganser, C.; Lauermann, E.; Maderer, A.; Stauder, T.; Kramb, J.-P.; Plutizki, S.; Kindler, T.; Moehler, M.; Dannhardt, G. *J. Med. Chem.* **2012**, *55*, 9531–9540.
16. Mandal, A. B.; Augustine, J. K.; Quattropani, A.; Bombrun, A. *Tetrahedron Lett.* **2005**, *46*, 6033–6036.
17. Meier, P.; Legraverant, S.; Müller, S.; Schaub, J. *Synthesis* **2003**, *4*, 551–554.
18. (a) Ames, D. E.; Dodds, W. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 705–710; (b) Deady, L. W.; Rodemann, T. *J. Heterocycl. Chem.* **2001**, *38*, 1185–1190.
19. Scriven, E. F. V. *Chem. Rev.* **1988**, *88*, 297–368.
20. For formation of isocyanate on similar systems see: (a) Ozcan, S.; Sahin, E.; Balci, M. *Tetrahedron Lett.* **2007**, *48*, 2151–2154; (b) Özcan, S.; Balci, M. *Tetrahedron* **2008**, *64*, 5531–5540; (c) Kilikli, A. A.; Dengiz, C.; Özcan, S.; Balci, M. *Synthesis* **2011**, *22*, 3697–3705; (d) Koza, G.; Karahan, E.; Balci, M. *Helv. Chim. Acta* **2010**, *93*, 1698–1704; (e) Koza, G.; Balci, M. *Tetrahedron* **2011**, *67*, 8679–8684.
21. Daisley, R. W.; Hanbali, J. R. *Synth. Commun.* **1981**, *11*, 743–749.