Triazolopyridines 22.[1] Description of new 7,9-di(2-pyridyl)[1,2,3]triazolo[5',1':6,1]pyrido[3,2-*d*]pyrimidines

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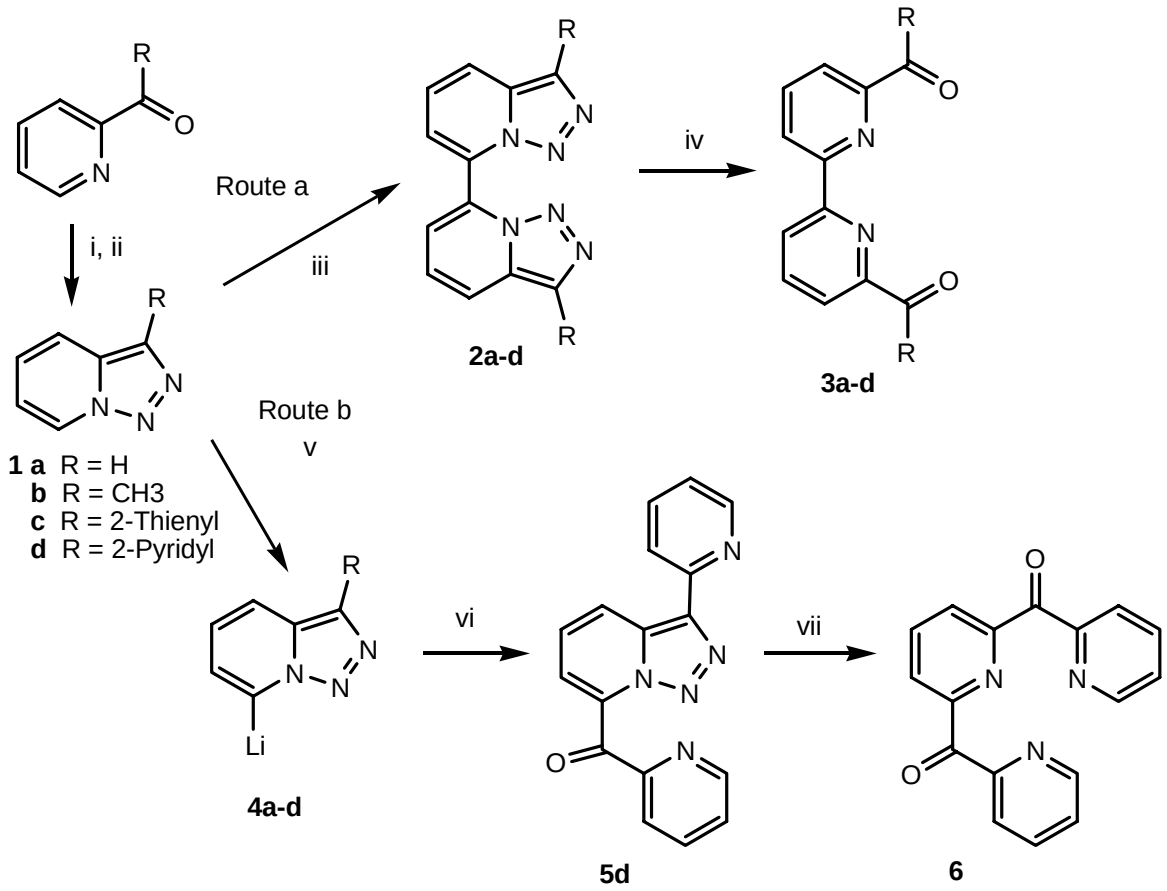
Abstract

The new heteroaromatic compounds, 7,9-di(2-pyridyl)[1,2,3]triazolo[5',1':6,1]pyrido[3,2-*d*] pyrimidines **11a-c**, were synthesized in two steps from readily available triazolopyridines **1a-c**. Regioselective lithiation of **1a-c** followed by treatment with 2-cyanopyridine gave a mixture of compounds **5a-c**, and **11a-c** in moderate to low yields, together with gums. Similar reactions with the triazolopyridine **1d** gave as the only identified compound the triazolopyridine derivative **5d**.

Keywords: Nitrogen heterocycles, helicating ligands, lithiation

Introduction

The synthetic chemical mimicry of the double-helix structural motif is an interesting area of research with intense activity in recent years.[2] Oligopyridines and related compounds are very useful helicating ligands.[2,3] We have recently discovered a facile route to new potential helicating ligands **2a-d, 3a-d, 5d,** and **6** from triazolopyridines **1a-d** (scheme 1).[4,5] Following this study we have designed new ligands **7-10**, which can be easily accessible from compound **5d** if the methodology summarized above is applicable (see scheme 2). The understanding that the availability of **5d** is important to success, led us to try its synthesis in an attempt to improve the reported yield.[5] We wish to report here our results in this project, and the discovery of a new heterocyclic system, [1,2,3]triazolo[5',1':6,1]pyrido[3,2-*d*]pyrimidine **11**, when we have tested the generality of the studied reaction.

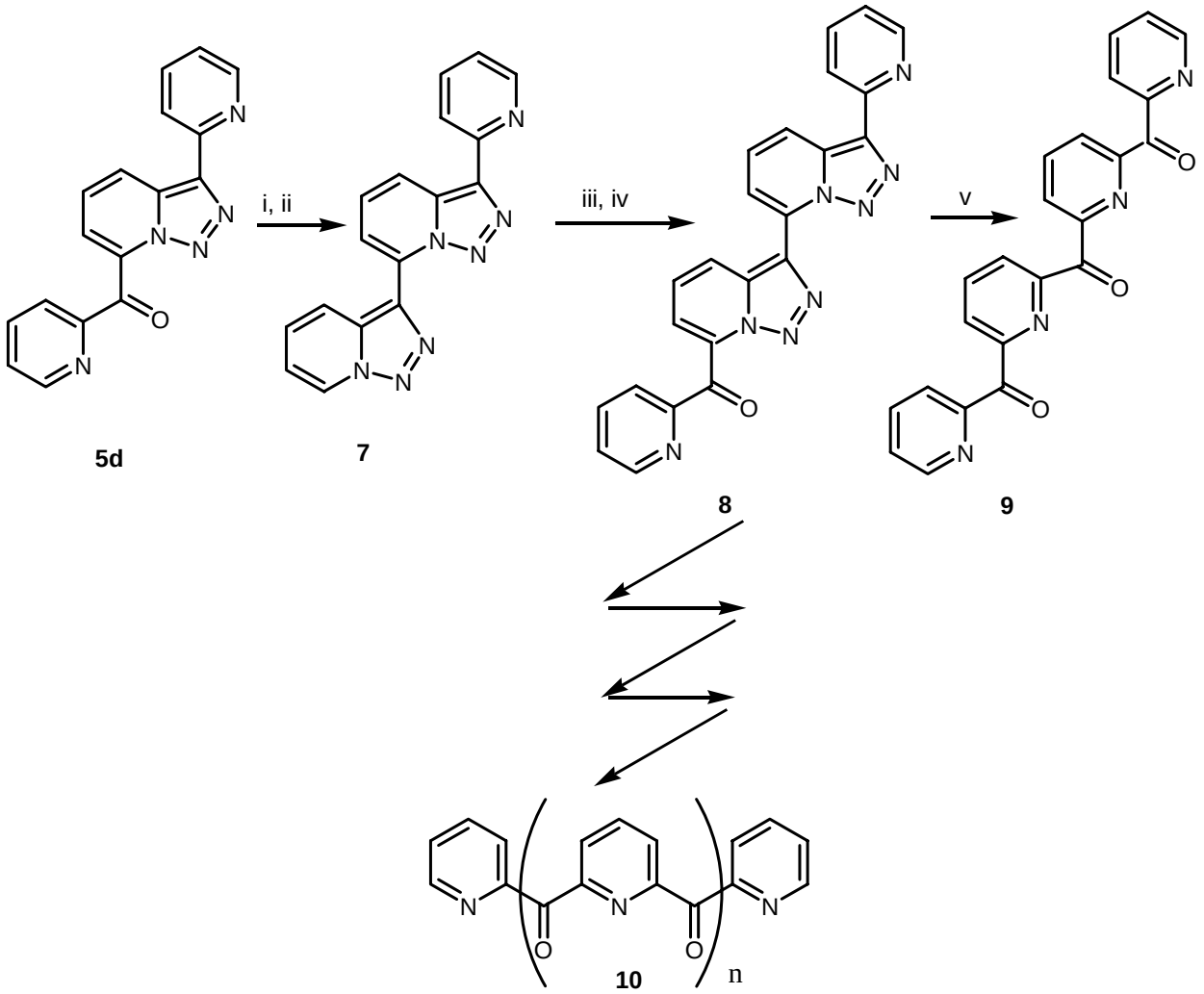


i) N_2H_4 ; ii) MnO_2 ; iii) LDA,THF, -70ºC; iv) SeO_2;
v) LDA, THF, -40ºC; vi) 2-PyCHO/air; vii) SeO_2

Scheme 1

Results and Discussion

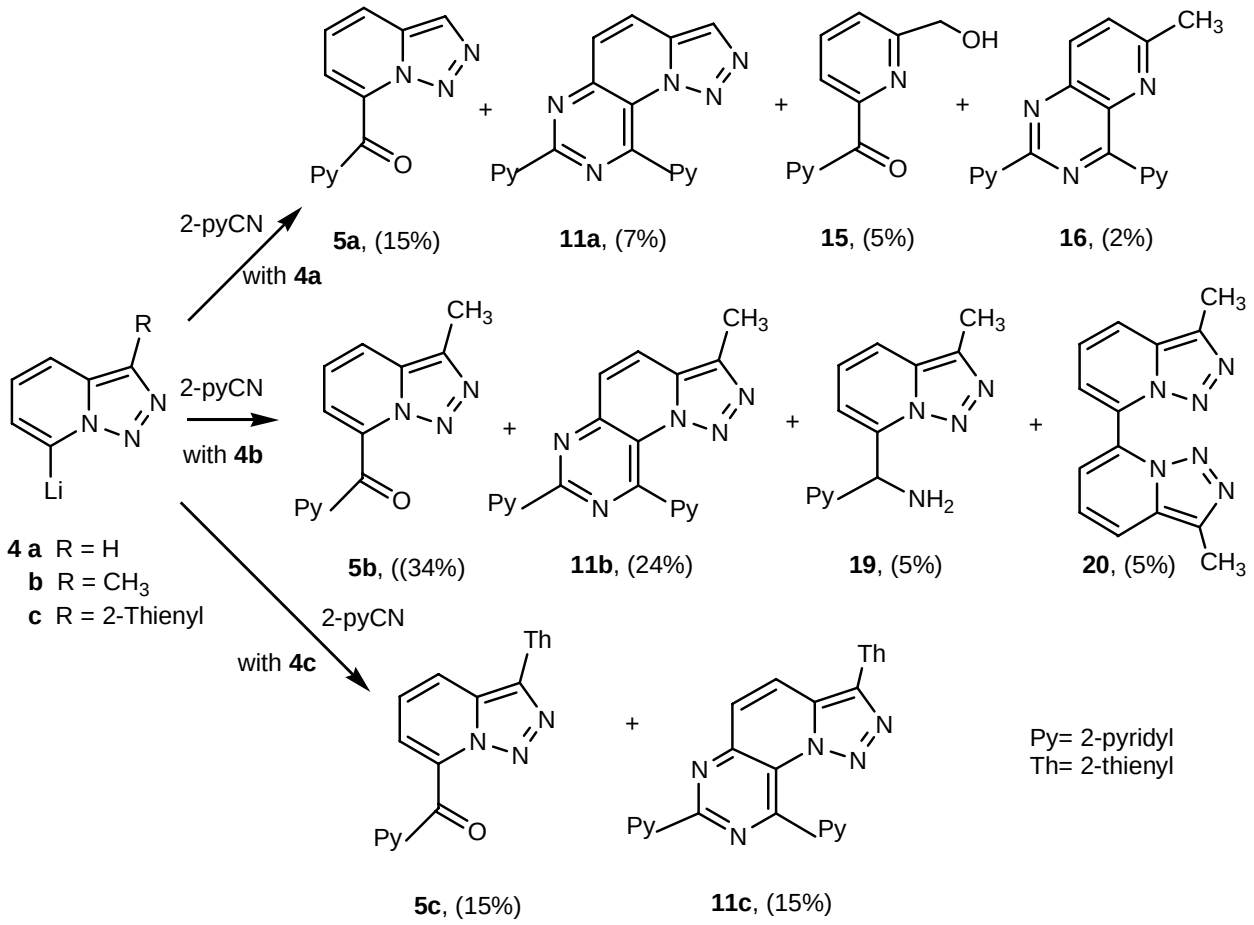
We have reported that reaction of triazolopyridine **1d** in THF solution at –40ºC with LDA gave the 7-lithio derivative **4d** which reacted with 2-pyridine carbaldehyde to form an unstable diarylmethyl alkoxide intermediate, which provides rapid access to ketone **5d** by spontaneous air oxidation in work-up, with 35% yield.[5] As we have found later that lithiation reactions of triazolopyridines **1** give better results using toluene as solvent and n-BuLi as lithiating agent,[6] we thought that in these conditions, and with 2-cyanopyridine as coreagent, we could improve the yield of **5d**. However the new reaction gave, as only characterized product, the compound **5d** in almost the same yield.



i) N_2H_4 ; ii) MnO_2,Cl_2CH_2 ; iii) LDA,-40°C; iv) 2-Py-CHO/air ; v) H_2SO_4,SeO_2

Scheme 2

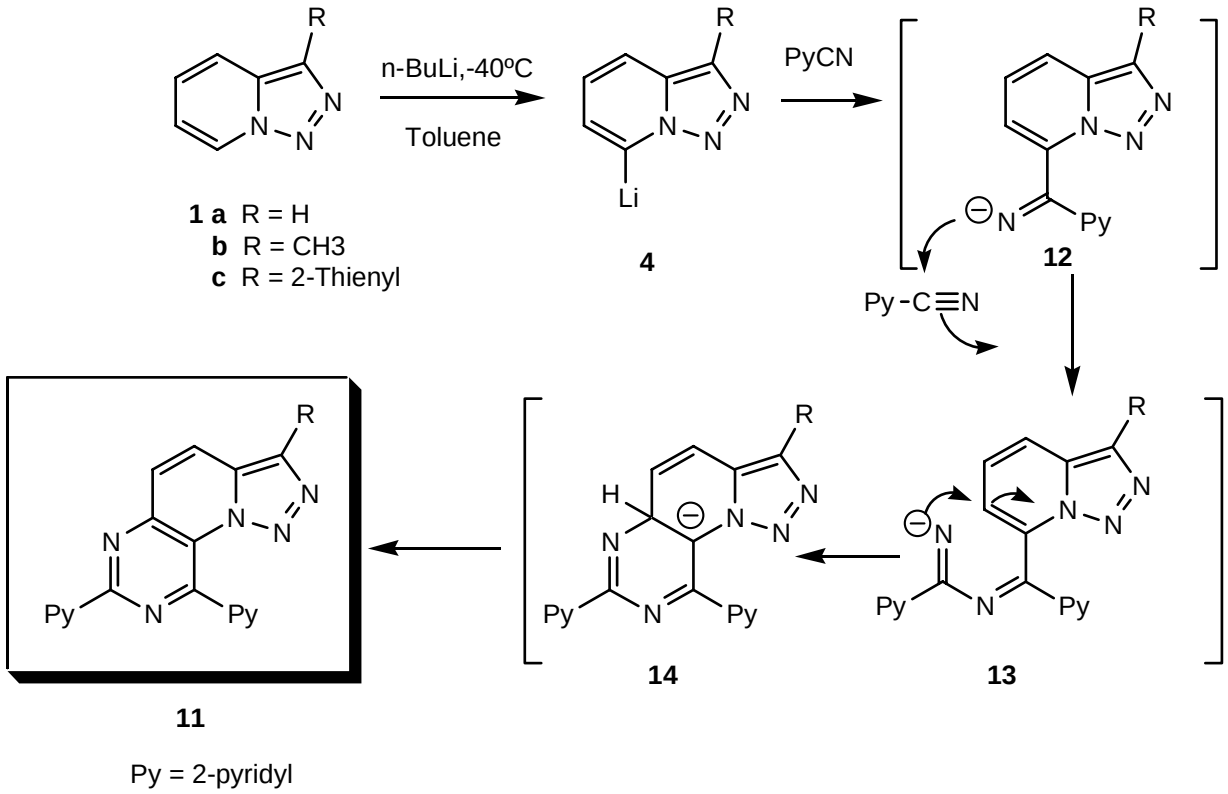
In the context of our research with triazolopyridines it was also interesting to know the scope of this type of reaction, and it was performed with compounds **1a-c**. In the conditions above indicated, the 7-lithio derivatives **4a-c** were formed. Subsequent reactions with 2-cyanopyridine gave the corresponding 7-pyridylcarbonyl derivatives **5a-c** together with other compounds (scheme 3). In all cases a new compound was found. A careful study of their analytical and spectroscopic data suggests that this was a novel triazolopyridopyrimidine system **11**.



Scheme 3

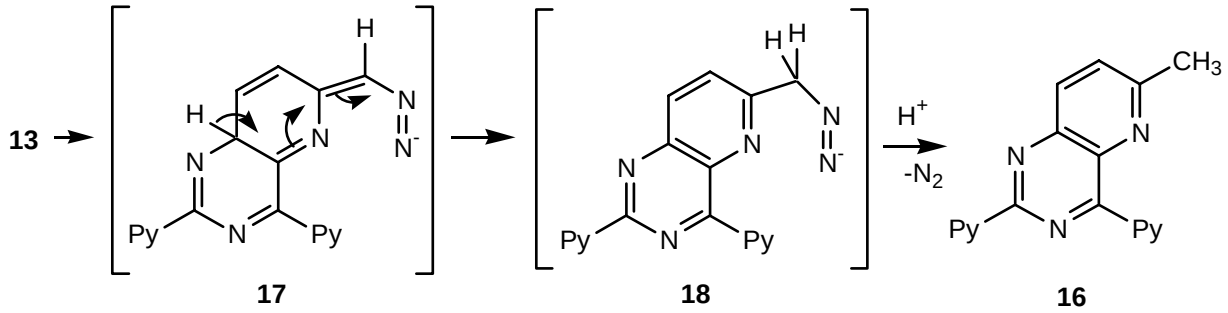
We will discuss the more interesting features for compound **11b** with molecular weight of 339.1233 consistent with a molecular formula of $C_{19}H_{13}N_7$. The ^{13}C NMR spectrum showed the expected 19 signals. The ^{1}H and ^{13}C NMR spectra showed the characteristic pattern of two different 2-substituted pyridines. In addition, in the ^{1}H NMR spectrum, contains an interesting AB pair of doublets at δ 8.65 and 7.51 with a coupling constant of 9.6 Hz, corresponding to H4 and H5 protons in a triazolo[1,5-*a*]pyridine ring.

The formation of the new triazolopyridopyrimidine system could be explained by the following mechanism (scheme 4). Reaction of the corresponding lithio derivative with a mole of 2-cyanopyridine gives the intermediate **12** which reacts with a second mole of reagent forming a new intermediate **13** that could in turn produce **14**. Here the negative charge is delocalized through a strongly acceptor system made of two nitrogen atoms in the pyrimidine part of the structure, which permits the proposed cyclization. Then compounds **11** are formed by a hydride elimination. Another possibility is an electrocyclic process (6π) from N-protonated **13** followed by oxidation.



Scheme 4

In the reaction with triazolopyridine **1a** two minor (5% and 2%) compounds were also formed, one identified as **15** (see scheme 3), easily formed from **5a** by triazolo ring opening and loss of dinitrogen in acid medium.[7] The other one was unexpected, and it was shown by HRMS to have formula $C_{18}H_{13}N_5$. A study of their ^1H and ^{13}C NMR spectra shows the presence of two different 2-substituted pyridines. A 2,3,6-trisubstituted pyridine was also present (a pair of doublets at 9.25 and 7.42 ppm with a coupling constant of 8.5 Hz in the ^1H NMR spectrum) and a methyl group. All these data lead us to propose the structure **16** for this compound. Its formation could be explained from the same intermediate **13** proposed to interpret the formation of compounds **11**. This anion could undergo a ring-closure/triazole-ring opening leading to a diazo anion **17**, a 1,5-transfer of hydrogen in this anion to form **18** that, after protonation and nitrogen elimination, gives **16** as is shown in scheme 5. In the reaction with triazolopyridine **1b** a further compound was identified as **19** probably formed from **12b** by hydride reduction, in this reaction the known compound **20**[4] was also formed in very low yield (5%).



Scheme 5

Experimental Section

General Procedures. Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC300MHz in $CDCl_3$ as solvent. COSY experiments were done for all compounds. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). Infrared spectra were recorded in KBr discs on a Bio-Rad FTS-7.

[1,2,3]Triazolo[1,5-a]pyridine 1a, 3-methyl-[1,2,3]triazolo[1,5-a]pyridine 1b, 3-(2-thienyl)-[1,2,3]triazolo[1,5-a]pyridine 1c and 3-(2-pyridyl)-[1,2,3]triazolo[1,5-a]pyridine 1d.
Prepared as described elsewhere.[8,9,5]

General procedure for lithiation of [1,2,3]triazolo[1,5-a]pyridines 1
To a solution of the corresponding [1,2,3]triazolo[1,5-a]pyridine **1** (1g) in anhydrous toluene (50mL) at -40ºC, a solution of *n*-butyllithium in hexane (5mL, 2.5M) was added with stirring. A deep red colour developed. The mixture was kept at -40ºC (4h). Treatment with a dry toluene solution (40mL) of an equimolar amount of the 2-cyanopyridine produced a change to yellow colour. The mixture was left at room temperature overnight, treated with 10% solution of HCl (5mL), stirried for 1h and neutralised with aqueous NaOH. The organic layer was separated and the aqueous layer extracted with dichloromethane. After drying over anhydrous Na_2SO_4 and evaporation of the organic solvents, a residue was obtained which was purified. The conditions of the purification are given for each compound.
2-Pyridyl-[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanone (5a) and 7,9-di(2-pyridyl)-[1,2,3] triazolo[5',1':6,1]pyrido[3,2-d]pyrimidine (11a). Purification by alumina (IV) chromatography, elution with ethyl acetate/hexane with increasing amount of ethyl acetate gave first starting material 1a (15%), then a yellow solid identified as 5a (15% yield). Mp 158-160 ºC (AcOEt). HRMS found M^+ 224.0691; $C_{12}H_8N_4O$ requires 224.0698. ν_{max} (KBr) (cm^{-1}) 1688(CO), 1596, 1322, 1287, 814, 741. λ_{max} (nm) (log ε) 235 (4.31), 275.5 (3.99), 356.5 (3.55). ^{1}H NMR δ 8.44 (ddd, J_1= 4.71, J_2= 1.68, J_3= 0.93Hz, 1H), 8.15 (ddd, J_1= 7.71, J_2= 1.10, J_3= 0.93Hz, 1H), 8.07 (s, 1H), 7.88 (ddd, J_1= J_2= 7.71, J_3= 1.68Hz, 1H), 7.84 (dd, J_1= 8.85, J_2= 1.50Hz, 1H), 7.43 (ddd, J_1= 7.71, J_2= 4.71, J_3= 1.10Hz, 1H), 7.37 (dd, J_1= 6.78, J_2= 1.50Hz, 1H),

7.29 (dd, J_1= 8.85, J_2= 6.78Hz, 1H). ^{13}C NMR δ 188.60 (CO), 153.38 (C), 149.58 (CH), 137.80 (CH), 134.96 (C), 134.41 (C), 128.14 (CH), 126.23 (CH), 125.01 (CH), 124.27 (CH), 121.08 (CH), 118.84 (CH). MS m/z (%), 224 (45), 196 (80), 168 (16), 132 (36), 106 (55), 78 (100), 63 (11). Further elution gave the alcohol 15 as a yellow solid. (5% yield). Mp 211-212 ºC (DMSO). HRMS found M^+ 214.0744; $C_{12}H_{10}N_2O_2$ requires 214.0742. ν_{max} (KBr) (cm^{-1}) 3523, 3434(OH), 1669(CO), 1591, 1322, 989, 952, 826, 748. λ_{max} (nm) (log ε) 204.5 (4.06), 239.0 (4.13), 280.5 (4.22), 291.5 (4.21). ^{1}H NMR δ 8.74 (d, J= 4.5, 1H), 8.19-8.06 (m, 4H), 7.88 (d, J= 8.28Hz, 1H), 7.72-7.67 (m, 1H), 7.06 (br s, 1H), 6.64 (s, 2H). ^{13}C NMR δ 193.64 (CO), 149.45 (CH), 142.17 (C), 141.05 (CH), 138.12 (CH), 137.49 (CH), 127.29 (CH), 125.08 (CH), 123.63 (CH), 122.37 (CH), 60.52 (CH_2). MS m/z (%), 214 (100), 213 (8), 185 (33), 169 (56), 108 (34), 78 (93). Then compound 16 was eluted as an oil (2% yield). HRMS found M^+ 299.1177; $C_{18}H_{13}N_5$ requires 299.1171. ν_{max} (KBr) (cm^{-1}) 3057, 1600, 1555, 1463, 1371, 1336, 1269, 999, 796, 750. ^{1}H NMR δ 9.25 (d, J= 8.5, 1H), 8.83-8.82 (m, 2H), 8.75 (ddd, J_1= 4.89, J_2= 1.70, J_3= 0.75Hz, 1H), 8.47 (dd, J_1= 7.92, J_2= 0.93Hz, 1H), 7.93-7.81 (m, 2H), 7.42 (d, J= 8.5Hz, 1H), 7.44-7.35 (m, 2H), 2.80 (s, 3H). ^{13}C NMR δ 168.65 (C), 166.53 (C), 162.61 (C), 160.26 (C), 156.31 (C), 155.21 (C), 150.39 (CH), 149.12 (CH), 137.98 (CH), 137.94 (CH), 137.32 (CH), 126.35 (CH), 125.42 (CH), 125.35 (CH), 125.11 (CH), 124.84 (CH), 115.83 (C), 26.41 (CH_3). The last compound eluted was 11a. Yellow solid. (7% yield). Mp 256-258 ºC (EtOH). HRMS found M^+ 325.1078; $C_{18}H_{11}N_7$ requires 325.1076. ν_{max} (KBr) (cm^{-1}) 1608, 1562, 1532, 1511, 1395, 1373, 776, 719. λ_{max} (nm) (log ε) 237.0 (4.35), 285.5 (4.40), 359.0 (4.17). ^{1}H NMR δ 8.87 (ddd, J_1= 4.71, J_2= 1.70Hz, J_3= 0.96, 1H), 8.84 (d, J= 7.92Hz, 1H), 8.77 (d, J= 9.60Hz, 1H), 8.77 (dd, J_1= 1.7, J_2= 0.96Hz, 1H), 8.52 (d, J= 7.92, 1H), 8.16 (s, 1H), 7.97-7.87 (m, 2H), 7.64 (d, J= 9.61Hz, 1H), 7.48-7.40 (m, 2H). ^{13}C NMR δ 164.10 (C), 161.70 (C), 155.55 (C), 153.65 (C), 150.40 (CH), 149.21 (C), 148.91 (CH), 137.66 (CH), 137.22 (CH), 134.13 (C), 128.44 (CH), 126.08 (CH), 125.64 (CH), 125.21 (CH), 125.09 (CH), 124.46 (CH), 117.14 (CH), 113.35 (C). MS m/z (%), 325 (57), 297 (100), 271 (16), 193 (22), 78 (22).

2-Pyridyl-3-methyl-[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanone (5b) and 3-methyl-7,9-di(2-pyridyl)[1,2,3]triazolo [5',1':6,1]pyrido[3,2-d]pyrimidine (11b). Purification by chromatotron, elution with ethyl acetate/hexane with increasing amount of ethyl acetate gave first starting material 1b (15%), then an oil identified as 19 (5% yield). HRMS found M^+ 239.1171; $C_{13}H_{13}N_5$ requires 239.1171. ν_{max} (KBr) (cm^{-1}) 3367 (broad), 1638, 1591, 1470, 1436. ^{1}H NMR δ 8.46 (d, J= 4.71, 1H), 7.60-7.59 (m, 2H), 7.46 (dd, J_1= 8.85, J_2= 1.14Hz, 1H), 7.13-7.09 (m, 2H), 6.68 (d, J= 6.96, 1H), 5.95 (s, 1H), 4.75 (br s, 2H), 2.53 (s, 3H). ^{13}C NMR δ 159.25 (C), 143.95 (CH), 141.21 (C), 136.78 (CH), 134.66 (C), 132.05 (C), 124.01 (CH), 123.03 (CH), 122.73 (CH), 115.93 (CH), 112.42 (CH), 56.10 (CH), 10.44 (CH_3). MS m/z (%), 239 (3), 211 (59), 107 (100). This was followed by a yellow solid identified as 5b (34% yield). Mp 165-167 ºC (AcOEt). HRMS found M^+ 238.0853; $C_{13}H_{10}N_4O$ requires 238.0854. ν_{max} (KBr) (cm^{-1}) 3048, 1692(CO), 1580, 1544, 1437, 1315, 1285, 1020, 775, 745. ^{1}H NMR δ 8.45 (ddd, J_1= 4.71, J_2= 1.70, J_3= 0.93Hz, 1H), 8.15 (ddd, J_1= 7.71, J_2= 1.32, J_3= 0.93Hz, 1H), 7.88 (ddd, J_1= J_2= 7.71, J_3= 1.70Hz, 1H), 7.73 (dd, J_1= 8.64, J_2= 1.11Hz, 1H), 7.43 (ddd, J_1= 7.71, J_2= 4.71, J_3= 1.32Hz, 1H), 7.34

(dd, J_1= 6.78, J_2= 1.11Hz, 1H), 7.23 (dd, J_1= 8.64, J_2= 6.78Hz, 1H), 2.57 (s, 3H). ^{13}C NMR δ 188.71 (CO), 153.53 (C), 149.54 (CH), 137.73 (CH), 135.09 (C), 134.79 (C), 132.39 (C), 127.99 (CH), 124.26 (CH), 123.38 (CH), 120.80 (CH), 118.89 (CH), 10.79 (CH_3). MS m/z (%), 238 (42), 210, (100), 209 (57), 182 (22), 181 (98), 156 (15), 155 (9), 106 (8), 104 (23), 78 (57). Further elution gave 20 (5% yield). Mp 238-240 ºC (AcOEt/hexane), lit.[4] 238-240 ºC (AcOEt/hexane). The last compound eluted was 11b. Yellow solid. (24% yield). Mp 255-257 ºC (AcOEt). HRMS found M^+ 339.1233; $C_{19}H_{13}N_7$ requires 339.1232. ν_{max} (KBr) (cm^{-1}) 1618, 1561, 1547, 1377, 776. λ_{max} (nm) (log ε) 232.0 (5.35), 285.5 (5.33), 374.5 (4.12). ^{1}H NMR δ 8.87 (ddd, J_1= 4.71, J_2= 1.68, J_3= 0.93Hz, 1H), 8.81 (ddd, J_1= 7.89, J_2= 1.71, J_3= 0.93 Hz, 1H), 8.77 (ddd, J_1= 4.71, J_2= 1.71, J_3= 0.75 Hz, 1H), 8.65 (d, J= 9.6Hz, 1H), 8.49 (ddd, J_1= 7.89, J_2= 1.68, J_3= 0.75Hz, 1H), 7.97-7.86 (m, 2H), 7.51 (d, J= 9.6Hz, 1H), 7.48-7.40 (m, 2H), 2.64 (s, 3H). ^{13}C NMR δ 163.75 (C), 161.40 (C), 155.65 (C), 153.68 (C), 150.33 (CH), 149.38 (C), 148.89 (CH), 137.59 (CH), 137.59 (C), 137.19 (CH), 131.50 (C), 125.87 (CH), 125.59 (CH), 125.12 (CH), 125.00 (CH), 122.80 (CH), 117.00 (CH), 113.51 (C), 10.36 (CH_3). MS m/z (%), 339 (13), 311 (100), 206 (10).

2-Pyridyl-3-(2-thienyl)[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanone 5c and 7,9-di(2-pyridyl)-3-(2-thienyl)-[1,2,3]triazolo [5',1':6,1]pyrido[3,2-d]pyrimidine (11c). Purification by chromatotron, elution with ethyl acetate/hexane with increasing amount of ethyl acetate gave first starting material 1c (15%), then a yellow solid identified as 5c (15% yield). Mp 172-174 ºC (AcOEt). HRMS found M^+ 306.0575; $C_{16}H_{10}N_4OS$ requires 306.0575. ν_{max} (KBr) (cm^{-1}) 1679(CO), 1578, 1438, 1311, 1216, 825, 725. λ_{max} (nm) (log ε) 249.5 (4.29), 281.0 (4.30), 401.0 (3.71). ^{1}H NMR δ 8.45 (ddd, J_1= 4.71, J_2= 1.68, J_3= 0.93Hz, 1H), 8.16 (ddd, J_1= 7.89, J_2= 1.11, J_3= 0.96Hz, 1H), 8.09 (dd, J= 5.1, J_2= 0.96, 1H), 7.89 (ddd, J_1= J_2= 7.74, J_3= 1.61Hz, 1H), 7.52 (dd, J_1= 3.75, J_2= 1.11Hz, 1H), 7.44 (ddd, J_1= 7.74, J_2= 4.79, J_3= 1.11Hz, 1H), 7.38 (d, J= 5.1, 1H), 7.38 (d, J= 4.89, 1H), 7.32 (dd, J_1= 5.10, J_2= 1.11Hz, 1H), 7.11 (dd, J_1= 4.53, J_2= 3.57Hz, 1H). ^{13}C NMR δ 188.24 (CO), 152.94 (C), 149.22 (CH), 137.32 (CH), 135.04 (C), 133.60 (C), 132.94 (C), 129.93 (C), 127.78 (CH), 127.72 (CH), 125.28 (CH), 125.13 (CH), 124.20 (CH), 123.67 (CH), 120.86 (CH), 118.33 (CH). MS m/z (%), 306 (9), 278 (100), 249 (15), 200 (8), 172 (26), 78 (24). The last compound eluted was 11c. Yellow solid. (15% yield). Mp 248-250 ºC (cyclohexane). HRMS found M^+ 407.0968; $C_{22}H_{13}N_7S$ requires 407.0953. ν_{max} (KBr) (cm^{-1}) 1609, 1573, 1558, 1507, 1462, 1427, 1378, 777, 723. λ_{max} (nm) (log ε) 247.0 (4.36), 288.0 (4.41), 408.0 (4.05). ^{1}H NMR δ 8.88 (ddd, J_1= 4.71, J_2= 1.70Hz, J_3= 0.96, 1H), 8.84 (d, J= 9.60Hz, 1H), 8.83 (d, J= 7.89Hz, 1H), 8.78 (ddd, J_1= 4.89, J_2= 1.68, J_3= 0.93Hz, 1H), 8.53 (d, J= 7.92, 1H), 7.97-7-91 (m, 2H), 7.86 (d, J= 9.60Hz, 1H), 7.64 (dd, J_1= 3.57, J_2= 1.11Hz, 1H), 7.48-7.42 (m, 2H), 7.39 (dd, J_1= 5.07, J_2= 1.11Hz, 1H), 7.15 (dd, J_1= 5.07, J_2= 3.57Hz, 1H). ^{13}C NMR δ 163.78 (C), 161.74 (C), 155.47 (C), 153.59 (C), 150.35 (CH), 149.38 (C), 148.90 (CH), 137.60 (CH), 137.22 (CH), 136.33 (C), 132.12 (C), 129.42 (C), 127.96 (CH), 126.00 (2CH), 125.67 (CH), 125.26 (CH), 125.21 (CH), 125.10 (CH), 124.73 (CH), 117.36 (CH), 113.65 (C). MS m/z (%), 407 (8), 379 (100), 378 (25), 334 (6), 284 (6), 78 (6).

2-Pyridyl-3-(2-pyridyl)-[1,2,3]triazolo[1,5-a]pyridin-7-ylmethanone 5d.

Compound 5d was obtained with 38% yield. Two crystalline phases can be obtained from AcOEt/hexane. At 194-195 ºC there is a phase transition forming needles that melt at 220-221ºC. lit.[5] m.p.194-195 ºC (AcOEt/hexane).

Acknowledgements

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