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Note

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Controlled Dimroth Rearrangement in the Suzuki–Miyaura Cross Coupling of Triazolopyridopyrimidines

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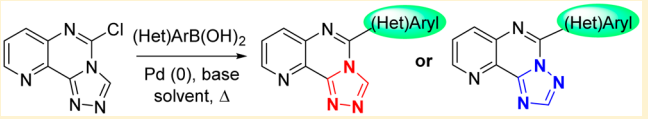
Supporting Information

ABSTRACT: Polynitrogen heterocycles are often subject to Dimroth rearrangement which consists of ring opening, bond rotation, and ring closure. In this note, we report a synthesis of two new families of triazolopyridopyrimidines. Successful functionalization via a Suzuki–Miyaura coupling was performed with total control of triazole (Dimroth) isomerization based on the judicious choice of reaction conditions.



Polynitrogen heterocycles, especially bicyclic structures, continue to be privileged scaffolds in medicinal chemistry. Among them, pyridopyrimidines **I** (Figure 1), which possess

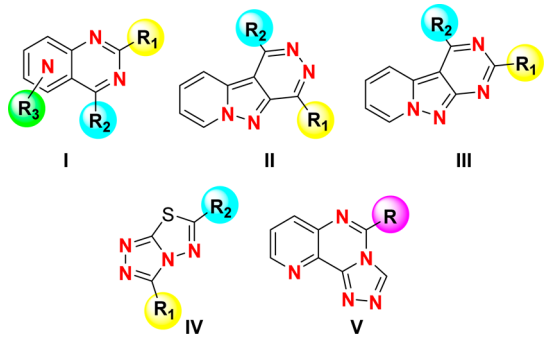


Figure 1. Some representative polynitrogen heterocycles **I**–**V**.

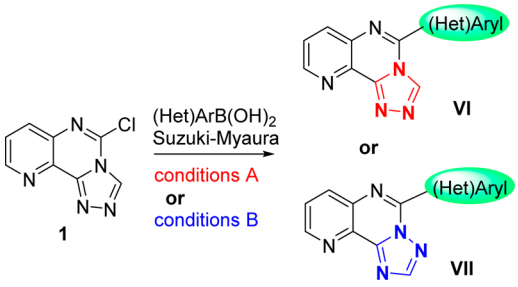
three nitrogen atoms, have received considerable attention due to their originality and biocompatibility.[1] Several groups, including ours, have been involved in developing robust methods for their preparation and functionalization in the search for new active drugs.[2−10] Our efforts have also been focused on the four nitrogen atom pyrido-pyrazolo- pyridazine/pyrimidine **II**/**III** series.[11] Functionalization of these rare fused [6,5,6] heterocyclic systems was possible with the creation of mostly C−C bonds using conventional and nonconventional bond activation. A ring contraction to a [5,5] fused system and the incorporation of a thiadiazole/triazole moiety as in the triazolothiadiazole **IV**[12] series has led to the discovery of unprecedented N−N bond disruption with organometallics and a cyanide release.

Thus, as part of a continuing effort to explore the functionalization of polynitrogen heterocycles, we focused our attention on compound **V**, an accessible but rare triazole analog of **I**. A major problem in this series is the unsolicited Dimroth rearrangement which can occur under various conditions.[13−15] Such rearrangements are well documented in 1,2,4-triazolo[4,3-*c*]pyrimidine series and are largely uncontrolled.[16,17] We felt that it would be useful to develop versatile methodology able to generate new C−C bonds as well as simultaneously manage the Dimroth rearrangement in similar heterocyclic systems.

The first syntheses of pyrido[2,3-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidines of type **V** was briefly reported in the 1970s.[18,19] Neglected for more than 15 years, the preparation of different triazolopyridopyrimidines again appeared in the literature in the early 1980s.[20,21] During these investigations, the conversion of several pyrido[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines into their [1,5-*c*] regioisomers was observed.

We report here the synthesis and regioselective functionalization of the tricyclic derivative **1** with or without Dimroth isomerization. Fine tuning the Suzuki–Myiaura palladium-catalyzed coupling gives a 5-(het)arylpyrido[2,3-*e*][1,2,4]triazole [4,3-*c*] (**VI**) or an isomerized [1,5-*c*] pyridopyrimidine ring system (**VII**) (Scheme 1). Controlled rearrangement was successfully

Scheme 1. Functionalization of Triazole 1 with or without Rearrangement



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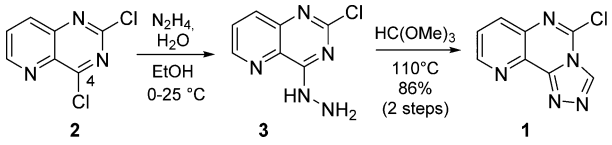
achieved, and for the first time, crystallographic data formally established the tridimensional structure of the two isomers. The relative positions of the triazole nitrogen atoms as well as that of the newly introduced heteroaryl group in C-5 were clearly identified.

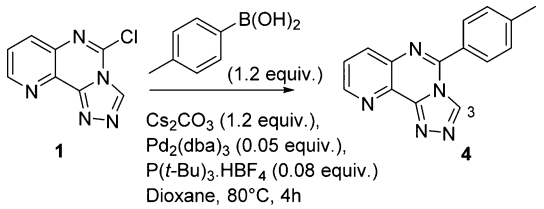
Previous work in our laboratory has described the efficient C-4 amination of 2,4-dichloropyrido[3,2-*d*]pyrimidine **2**.[2−4] For this novel study, regioselective substitution with hydrazine, followed by triazole formation using methyl formate, easily gave the desired 5-chloro triazole derivative **1** (Scheme 2) in satisfying global yield.

Scheme 2. Synthesis of the Key Chlorinated Triazole 1



Inspired by Fu's conditions for Suzuki cross coupling of aryl chlorides,[22] we were pleased to observe the formation of pyrido[2,3-*e*][1,2,4]triazolo[4,3-*c*] **4** in 86% yield using a tris(dibenzylideneacetone)dipalladium(0) $[Pd_2(dba)_3]/P(t\text{-}Bu)_3\cdot HBF_4$ catalytic system in dioxane at 80 °C (Scheme 3). ^1H NMR analysis showed a strongly deshielded singlet proton at δ 9.07 ppm which is characteristic of *H*-3 in the [4,3-*c*] isomer.[20,21,23,24] Formation of this exclusive unrearranged product **4** was reproduced at 100 °C or in toluene with no significant variation in yield.

Scheme 3. Suzuki−Miyaura Coupling Conditions Leading to Compound 4

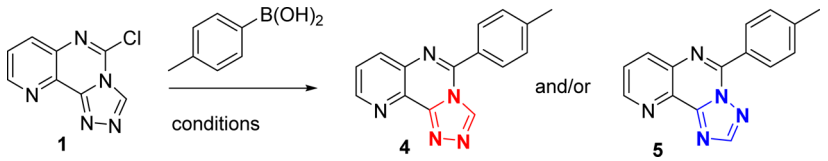


To voluntary induce the arylation/triazole rearrangement and exclusively obtain the type **VII** isomer, various conditions were screened (Table 1). For example, changing the catalyst/ligand pair to the widely used $Pd(OAc)_2$/XantPhos system gave mostly degradation and a separable mixture of isomeric products **4** and **5**, albeit in low yield (Table 1, entry 1). The two isomers were easily identified by their ^1H NMR spectra, the less polar compound **5** showed a singlet at δ 8.58 ppm characteristic of the rearranged triazole proton as compared to the signal at δ 9.07 ppm for compound **4**.

The switch to $Pd(PPh_3)_4$ in the presence of K_2CO_3 in toluene or dioxane at 100 °C induced selective arylation and isomerization but with recovered starting material (Table 1, entries 2−4). The use of a stronger base such as Cs_2CO_3 (entry 5) increased the yield of **5** (56%) but again with recovered starting material (12%). An increase in the amount of palladium catalyst (10%) drove the reaction to completion with a notably decreased reaction time and excellent yield (entry 6). It is noteworthy that the presence of compound **4** was undetected at 100 °C (entry 6) but was exclusive at 80 °C (entry 7). In light of these experimental observations, it is difficult to clearly separate the factors that control isomerization. Our results seem to imply that the cross coupling reaction and the triazole isomerization are concomitant and are dependent on both the temperature and the catalytic system. The barrier for ring opening and subsequent closure to give the Dimroth product is favored with only a minimal temperature change in toluene.

We were now able to selectively form C-5 arylated derivatives **VI** or **VII** from a unique chlorinated platform **1**. To evaluate reaction scope, a variety of boronic acid derivatives were used (Table 2). The use of $Pd_2(dba)_3/P(t\text{-}Bu)_3\cdot HBF_4$ in dioxane at 80 °C (conditions A) promoted coupling while retaining the initial triazole configuration. With tolyl boronic acids (entries 1−3), products were formed in good yields and short reaction times. A slight steric effect was observed with the *o*-tolyl derivative **7** (entry 3). Difficulties were encountered with donating OCH_3 groups (entries 4−6), as reaction time increased to 24 h and formation of compound **10** was not detected. With a weak electron-withdrawing group such as CF_3, reaction time remained correct with a slightly lower yield (entry 7). The use of phenyl boronic acid gave an excellent

Table 1. Optimization of the Suzuki−Miyaura Coupling and Triazole Isomerization



						yield (%)[a,b]		
entry	base	catalytic system	solvent	time (h)	temp (°C)	**4**	**5**	**1**
1	K_2CO_3 (2.0 equiv)	$Pd(OAc)_2$/ Xantphos (0.1/0.2 equiv)	toluene	6	110	15	20	ND
2	K_2CO_3 (1.5 equiv)	$Pd(PPh_3)_4$ (0.05 equiv)	toluene	24	100	ND	17	46
3	K_2CO_3 (1.5 equiv)	$Pd(PPh_3)_4$ (0.05 equiv)	toluene	48	100	ND	44	23
4	K_2CO_3 (1.5 equiv)	$Pd(PPh_3)_4$ (0.05 equiv)	dioxane	48	100	ND	17	48
5	Cs_2CO_3 (1.5 equiv)	$Pd(PPh_3)_4$ (0.05 equiv)	toluene	24	100	ND	56	12
6	Cs_2CO_3 (1.5 equiv)	$Pd(PPh_3)_4$ (0.1 equiv)	toluene	3	**100**	ND	**92**	ND
7	Cs_2CO_3 (1.5 equiv)	$Pd(PPh_3)_4$ (0.1 equiv)	toluene	3	**80**	**79**	traces	ND

[a]Reactions were stopped when complete disappearance of starting material **1** was observed by TLC. [b]Yields are indicated after purification by flash chromatography. ND: Not detected.

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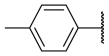
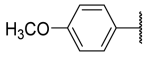
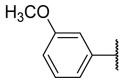
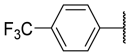
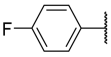
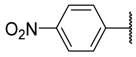
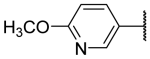
Table 2. Coupling of Different Boronic Acids and Controlled Rearrangement[a]

Entry	R-B(OH)$_2$	Conditions A[b] Time (h)	Conditions A[b] Triazole **VI** Yield (%)	Conditions B[c] Time (h)	Conditions B[c] Triazole **VII** Yield (%)
1		4	**4** (86)	3	**5** (92)
2		3.5	**6** (81)	6	**17** (82)
3		6	**7** (79)	24	**18** (82)
4		24	**8** (60)	24	**19** (68)
5		24	**9** (71)	24	**20** (79)
6		24	**10** (ND)	24	**21** (79)
7		3	**11** (60)	24	**22** (24)
8		5	**12** (89)	24	**23** (64)
9		24	**13** (76)	24	**24** (75)
10		24	**14** (52)[d]	24	**25** (ND)
11		3.5	**15** (89)	24	**26** (16)
12		3	**16** (64)	24	**27** (49)[e]

[a]Reactions were stopped after full disappearance of starting material **1**. Yields are indicated as isolated compounds. [b]Conditions A: RB(OH)$_2$ (1.2 equiv), Cs_2CO_3 (1.2 equiv), $Pd_2(dba)_3$ (0.05 equiv), P(*t*-Bu)$_3$·HBF$_4$ (0.08 equiv), dioxane 80 °C. [c]Conditions B: RB(OH)$_2$ (1.5 equiv), Cs_2CO_3 (1.5 equiv), Pd(PPh$_3$)$_4$ (0.1 equiv), toluene, 100 °C. [d]22% of rearranged triazole. [e]35% of unrearranged triazole.

result with respect to both time and yield (entry 8). An intermediate behavior was observed with a fluorine group (entry 9), whereas the strongly electron-withdrawing nitro group combined the negative time and yield effects (entry 10). Finally, conditions A are compatible with heterocyclic boronic acids such as thiophenyl and pyridinyl groups (entries 11 and 12).

Using conditions B which involved Pd(PPh$_3$)$_4$, Dimroth triazole isomerization occurred. With the *o*-tolyl derivative, this procedure gave access to compound **21** (entry 6) in excellent yield. We encountered similar effects with Me and OMe groups (entries 1−5) , i.e., increased reaction time and steric effects. Reactivity decreased using either deactivated aryl or heteroaryl boronic acids (entries 7, 10−12) until observing a total lack of reactivity with the most electron-withdrawing NO_2 group (entry 10).

From a mechanistic point of view, the triazole Dimroth rearrangement involves ring opening, bond rotation, and ring closure to give the thermodynamically more stable isomer under acidic, basic, or thermal conditions. In our case, heating compound **4** at 100 °C in toluene in the presence or absence of the boron derivative or catalyst gave no corresponding [1,5-*c*] isomers. However, interconversion from **4** into **5** occurs successfully in the presence of the base and heating. These data converge toward a multifactorial combination depending on base, catalyst, and temperature.

Formal proof of the Dimroth rearrangement was obtained by X-ray analysis of the two crystalline 5-*m*-tolyl derivatives **17** and **6** (SI section crystallographic data). Products were clearly different in both the position of the triazole nitrogen atoms and conformation of the phenyl ring. For compound **6**, nitrogen atoms have been unambiguously identified at positions 1 and 2, while they have been clearly localized at positions 1 and 3 for compound **17**. The pyrrolopyridopyrimidine moiety as well as the phenyl ring of **17** are quasi planar, whereas the two motifs are slightly twisted in **6**. All bond lengths are consistent with the aromatic character of these units.[25]

In this note, access to a collection of both 5-(het)arylated 1,2,4-triazolo [4,3-*c*] pyridopyrimidine and [1,5-*c*]pyridopyrimidine systems was achieved via Suzuki−Miyaura coupling and controlled Dimroth rearrangement based on the judicious choice of reaction conditions. From one newly designed chlorinated platform, the choice of temperature, catalyst, and base influences triazole isomerization. X-ray analysis was used to formally prove the structure of two isomers, and reaction scope and limitation were illustrated for each set of conditions. Thus, we have successfully demonstrated that the Dimroth rearrangement is not necessarily an unwanted secondary reaction and can also be a source of increased molecular diversity within this triazolopyridopyrimidine series.

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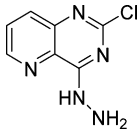
EXPERIMENTAL SECTION

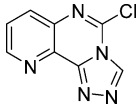
General Information. Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{19}F) were recorded at 250 or 400 MHz in $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in parts per million (δ scale), and all coupling constant (J) values are in Hertz (Hz). The following abbreviations were used to denote the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (double doublet). IR absorption spectra were recorded using an IR spectrometer (diamond plate), and values are reported in cm^{-1}. High-resolution mass spectra (HRMS) were acquired in positive mode with an ESI source on a Q-TOF mass spectrometer. Monitoring of the reactions was performed with silica gel TLC plates. Spots were visualized with UV light at 254 and 356 nm. Column chromatography was performed with silica gel 60 (0.063−0.200 mm). Reactions requiring anhydrous conditions were performed under argon.

2-Chloro-4-hydrazino-pyrido[3,2-*d*]pyrimidine 3.



The dichloronated compound **2** was prepared from commercially available 3-amino picolinic acid in two steps, by condensation with urea at high temperature,[24,26] followed by treatment of the intermediate dione with $POCl_3/PCl_5$ as previously described by our group.[3] To a solution of the dichlorinated compound **2** (1.0 g, 4.99 mmol, 1.0 equiv) in THF at 0 °C were added Et_3N (1.05 mL, 7.49 mmol, 1.5 equiv) and hydrazine hydrate (0.29 mL, 5.99 mmol, 1.2 equiv). The solution was stirred for 30 min at 0 °C. The mixture was allowed to reach room temperature and was stirred for an additional 2 h. The solvent was removed under reduced pressure, and the crude orange solid obtained was used directly in the next step without further purification. Mp 248−250 °C. IR (ATR diamond, cm^{-1}) ν 3343, 3255, 3182, 1577, 1537, 1466, 1394, 1322, 1294, 915, 872, 822, 803, 691, 606. ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.73 (dd, J = 4.3, 1.6 Hz, 1H), 8.00 (dd, J = 8.4, 1.5 Hz, 1H), 7.79 (dd, J = 8.5, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.0, 157.8, 148.9, 145.4, 134.7, 130.7, 129.1. HRMS (EI-MS): calcd for $C_7H_6ClN_5$[M + H]$^+$ m/z 196.0384, found m/z 196.0387.

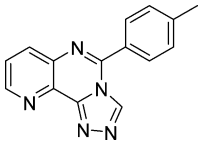
5-Chloro-pyrido[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine 1.



Trimethylorthoformate (14 mL) was added to crude **3** of under argon atmosphere. The mixture was heated to 70 °C for 40 min. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (CH_2Cl_2/Acetone, 1:0 to 7:3) to afford **1** as a light yellow solid (847 mg, 83% over 2 steps). R_f 0.27 (acetone/CH_2Cl_2 20/80). Mp 246−248 °C. IR (ATR diamond, cm^{-1}) ν 3116, 3063, 1611, 1479, 1448, 1413, 1368, 1268, 1282, 1192, 990, 840, 706, 655, 649, 612. ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.01 (dd, J = 4.5, 1.4 Hz, 2H), 8.37 (dd, J = 8.3, 1.5 Hz, 2H), 7.91 (dd, J = 8.3, 4.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.7, 148.3, 138.2, 138.1, 135.7, 134.7, 134.1, 127.4. HRMS (EI-MS): calcd for $C_8H_4ClN_5$[M + H]$^+$ m/z 206.0228, found m/z 206.0233.

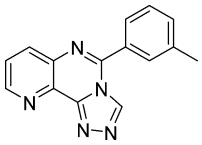
General Procedure A for the Suzuki Coupling Reaction Leading to the Unrearranged 1,2,4 Triazole Derivatives. All reactions were performed in a 10 mL vial and sealed with a Teflon cap. Compound **1** (0.070 g, 0.34 mmol, 1 equiv), Pd_2dba_3 (0.016 g, 0.017 mmol, 0.05 equiv), the boronic acid (1.2 equiv), Cs_2CO_3 (0.134 g, 0.41 mmol, 1.2 equiv), and P(t-Bu)$_3$·HBF$_4$ (0.008 g, 0.027 mmol, 0.08 equiv) were sequentially added to the reaction vial. The tube was closed, put under argon atmosphere, and degassed dioxane was added. The mixture was stirred at 80 °C (thermal heating) until disappearance of the starting material (TLC monitoring). The solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using a gradient solvent system of 100% CH_2Cl_2 up to an acetone/CH_2Cl_2 system of 30/70.

*5-(p-Tolyl)-pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine **4**.*



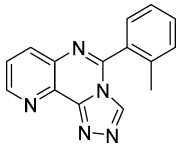
This compound was synthesized according to the general procedure A. Reaction time 4 h. Yield: 0.077 g, 86% (white solid). R_f 0.30 (acetone/CH_2Cl_2 20/80). Mp 247−249 °C. IR (ATR diamond, cm^{-1}) ν 3145, 3050, 2920, 2853, 1983, 1612, 1530, 1476, 1419, 1365, 1346, 1305, 1182, 1115, 941, 808, 722. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09−9.03 (m, 2H), 8.35 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 7.7 Hz, 2H), 7.77 (dd, J = 8.1, 4.5 Hz, 1H), 7.50 (d, J = 7.7 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 148.2, 145.7, 143.2, 137.8, 136.5, 136.1, 134.3, 130.2, 129.0, 128.5, 126.6, 21.7. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5$[M + H]$^+$ m/z 262.1087, found m/z 262.1086.

*5-(m-Tolyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine **6**.*



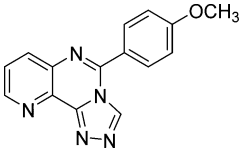
This compound was synthesized according to the general procedure A. Reaction time 3.5 h. Yield: 0.072 g, 81% (white solid). R_f 0.29 (acetone/CH_2Cl_2 20/80). Mp 239−241 °C. IR (ATR diamond, cm^{-1}) ν 3170, 3043, 2917, 2359, 1612, 1524, 1486, 1410, 1359, 1340, 1182, 1099, 795, 722. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 9.00 (s, 1H), 8.41 (d, J = 7.5 Hz, 1H), 7.90 (s, 1H), 7.83 (s, 2H), 7.54 (s, 2H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.3, 148.0, 146.5, 139.0, 138.2, 137.9, 136.4, 134.6, 132.9, 132.4, 129.9, 129.4, 127.2, 126.7, 21.4. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5$[M + H]$^+$ m/z 262.1087, found m/z 262.1086.

*5-(o-Tolyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine **7**.*



This compound was synthesized according to the general procedure A. Reaction time 6 h. Yield: 0.070 g, 79% (off-white solid). R_f 0.32 (acetone/CH_2Cl_2 20/80). Mp 225−227 °C. IR (ATR diamond, cm^{-1}) ν 3141, 3100, 3046, 2356, 1612, 1533, 1473, 1413, 1356, 1340, 1315, 1182, 1109, 947, 811, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 4.4 Hz, 1H), 8.57 (s, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.81 (dd, J = 8.3, 4.5 Hz, 1H), 7.64−7.55 (m, 2H), 7.53−7.45 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 147.7, 145.5, 137.5, 136.8, 136.5, 136.2, 134.3, 131.7, 131.6, 130.9, 128.5, 126.7, 126.6, 19.4. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5$[M + H]$^+$ m/z 262.1087, found m/z 262.1086.

*5-(4-Methoxyphenyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine **8**.*



This compound was synthesized according to the general procedure A. Reaction time 24 h. Yield: 0.057 g, 60% (off-white solid). R_f 0.24 (acetone/CH_2Cl_2 20/80). Mp 219−221 °C. IR (ATR diamond, cm^{-1}) ν 3135, 3100, 2999, 2834, 2363, 1600, 1530, 1505, 1476, 1413, 1356, 1340, 1302, 1267, 1166, 1106, 1036, 944, 821, 735. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.97 (d, J = 4.4 Hz, 1H), 8.38 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.7 Hz, 2H), 7.88 (dd, J = 8.2, 4.5 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 151.0, 148.1, 146.2, 138.2, 138.0, 136.2, 134.4, 131.4, 127.2, 124.6, 114.9, 56.1. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5O$[M + H]$^+$ m/z 278.1036, found m/z 278.1034.

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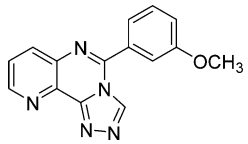
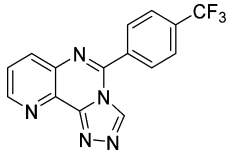
5-(3-Methoxyphenyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine ***9***.



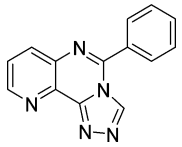
This compound was synthesized according to the general procedure A. Reaction time 24 h. Yield: 0.067 g, 71% (off-white solid). R_f 0.19 (acetone/CH_2Cl_2 20/80). Mp 246−248 °C. IR (ATR diamond, cm^{-1}) ν 3126, 3072, 3018, 2970, 2359, 1619, 1596, 1530, 1498, 1463, 1410, 1340,1245, 1182, 1112, 1033, 805, 726. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 9.01 (s, 1H), 8.43 (d, J = 7.8 Hz, 1H), 7.91 (s, 1H), 7.57 (d, J = 6.5 Hz, 3H), 7.29 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.8, 151.4, 148.0, 146.3, 138.2, 137.8, 136.4, 134.6, 133.7, 130.7, 127.2, 121.7, 118.3, 114.5, 55.9. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5O[M + H]^+$ m/z 278.1036, found m/z 278.1035.

5-(4-(Trifluoromethyl)phenyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]-pyrimidine ***11***.



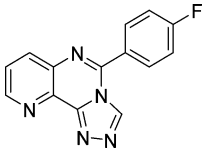
This compound was synthesized according to the general procedure A. Reaction time 3 h. Yield: 0.065 g, 60% (white solid). R_f 0.19 (acetone/CH_2Cl_2 20/80). Mp 263−265 °C. IR (ATR diamond, cm^{-1}) ν 3100, 1612, 1530, 1475, 1425, 1400, 1362, 1318, 1166, 1112, 1061, 1007, 947, 846, 719. ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.98 (dd, J = 4.5, 1.5 Hz, 1H), 8.40 (dd, J = 8.3, 1.5 Hz, 1H), 8.20 (d, J = 8.1 Hz, 2H), 8.00 (d, J = 8.3 Hz, 2H), 7.88 (dd, J = 8.3, 4.5 Hz, 1H). ^{13}C NMR (63 MHz, DMSO-d_6) δ 151.7, 147.9, 145.3, 138.1, 137.7, 136.5, 136.3, 134.7, 131.9 (q, J = 31.9 Hz), 130.6, 127.3, 126.4 (q, J = 3.9 Hz), 122.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8. HRMS (EI-MS): calcd for $C_{15}H_8F_3N_5[M + H]^+$ m/z 316.0805, found m/z 316.0804.

5-Phenylpyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine ***12***.



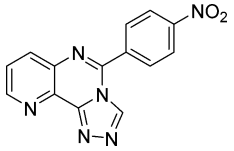
This compound was synthesized according to the general procedure A. Reaction time 5 h. Yield: 0.075 g, 89% (white solid). R_f 0.31 (acetone/CH_2Cl_2 20/80). Mp 259−261 °C. IR (ATR diamond, cm^{-1}) ν 3135, 3110, 3075, 2359, 1619, 1533, 1479, 1448, 1413, 1365, 1305, 1242, 1185, 1106, 944, 821, 719. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17−8.99 (m, 2H), 8.36 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.79 (dd, J = 8.3, 4.5 Hz, 1H), 7.75−7.67 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 148.2, 145.5, 137.7, 136.4, 136.1, 134.4, 132.4, 131.9, 129.6, 128.5, 126.6. HRMS (EI-MS): calcd for $C_{14}H_9N_5[M + H]^+$ m/z 248.0931, found m/z 248.0928.

5-(4-Fluorophenyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine ***13***.



This compound was synthesized according to the general procedure A. Reaction time 24 h. Yield: 0.069 g, 76% (white solid). R_f 0.29 (acetone/CH_2Cl_2 20/80). Mp >270 °C. IR (ATR diamond, cm^{-1}) ν 3097, 3056, 3002, 1619, 1600, 1533, 1505, 1419, 1368, 1353, 1248, 1220, 1175, 1102, 852, 814, 741. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 9.02 (dd, J = 4.5, 1.5 Hz, 1H), 8.43 (dd, J = 8.3, 1.5 Hz, 1H), 8.11 (dd, J = 8.8, 5.4 Hz, 2H), 7.92 (dd, J = 8.3, 4.5 Hz, 1H), 7.52 (t, J = 8.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.4 (d, J = 249.4 Hz), 151.4, 148.0, 145.7, 138.2, 137.9, 136.4, 134.6, 132.3 (d, J = 9.1 Hz), 129.1 (d, J = 3.4 Hz), 127.3, 116.6 (d, J = 22.1 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ −108.1. HRMS (EI-MS): calcd for $C_{14}H_8FN_5[M + H]^+$ m/z 266.0837, found m/z 266.0836.

5-(4-Nitrophenyl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine ***14***.

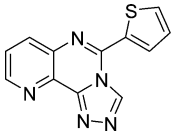


This compound was synthesized according to the general procedure A. Reaction time 12 h. Yield: 0.052 g, 52% (light yellow solid). R_f 0.24 (acetone/CH_2Cl_2 20/80).

Major isolated product **14**: Mp >270 °C. IR (ATR diamond, cm^{-1}) ν 3145, 3110, 3081, 2853, 1593, 1526, 1482, 1419, 1400, 1343, 1315, 1242, 1188, 1112, 931, 874, 821, 719. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.05 (d, J = 4.3 Hz, 1H), 8.48 (t, J = 10.1 Hz, 3H), 8.30 (d, J = 8.3 Hz, 2H), 7.94 (dd, J = 8.1, 4.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.9, 149.6, 147.9, 144.9, 138.2, 138.1, 137.7, 136.6, 134. 8, 131.3, 127.4, 124.5. HRMS (EI-MS): calcd for $C_{14}H_8N_6O_2[M + H]^+$ m/z 293.0782, found m/z 293.0780.

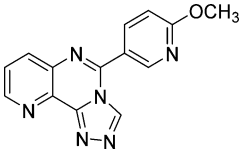
Rearranged product **25**: Yield: 0.022 g, 22% (light yellow solid). R_f 0.33 (acetone/CH_2Cl_2 20/80). Mp 247−249 °C. IR (ATR diamond, cm^{-1}) ν 3065, 2866, 2359, 1590, 1533, 1520, 1438, 1346, 1311, 1270, 1194, 1147, 1106, 859, 830, 716, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.89 (d, J = 8.4 Hz, 2H), 8.65 (s, 1H), 8.56−8.42 (m, 3H), 7.89 (dd, J = 7.8, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 152.2, 152.0, 149.7, 144.9, 138.9, 136.7, 136.6, 135.1, 131. 8, 127.1, 123.5. HRMS (EI-MS): calcd for $C_{14}H_8N_6O_2[M + H]^+$ m/z 293.0782, found m/z 293.0785.

5-(Thiophen-2-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine ***15***.



This compound was synthesized according to the general procedure A. Reaction time 3.5 h. Yield: 0.077 g, 89% (off-white solid). R_f 0.26 (acetone/CH_2Cl_2 20/80). Mp 220 °C. IR (ATR diamond, cm^{-1}) ν 3157, 3062, 2363, 1603, 1530, 1514, 1476, 1422, 1362, 1226, 1163, 1106, 1064, 836, 805, 716. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.96 (d, J = 4.1 Hz, 1H), 8.45−8.27 (m, 2H), 8.08 (d, J = 4.9 Hz, 1H), 7.88 (dd, J = 8.2, 4.5 Hz, 1H), 7.39 (t, J = 4.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.1, 148.1, 140.7, 137.9, 137.6, 135.9, 135.2, 134.4, 133.8, 132.1, 129.4, 127.3. HRMS (EI-MS): calcd for $C_{12}H_7N_5S[M + H]^+$ m/z 254.0495, found m/z 254.0494.

5-(6-Methoxypyridin-3-yl)pyrido[2,3-e][1,2,4]triazolo[4,3-c]-pyrimidine ***16***.



This compound was synthesized according to the general procedure A. Reaction time 3 h. Yield: 0.061 g, 64% (off-white solid). R_f 0.14 (acetone/CH_2Cl_2 20/80).mp 261−263 °C. IR (ATR diamond, cm^{-1}) ν 3116, 3031, 2999, 2948, 1603, 1498, 1419, 1391, 1365, 1340, 1296, 1188, 1118, 998, 941, 840, 814, 722. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 9.00 (d, J = 4.0 Hz, 1H), 8.86 (s, 1H), 8.42 (d, J = 8.2 Hz, 1H), 8.34 (dd, J = 8.7, 2.0 Hz, 1H), 7.91 (dd, J = 8.2, 4.5 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.8, 151.3, 148.7, 147.9, 144.6, 140.3, 138.2, 137.9, 136.3, 134.5, 127.2, 122.5, 111.3, 54.4. HRMS (EI-MS): calcd for $C_{14}H_{10}N_6O[M + H]^+$ m/z 279.0989, found m/z 279.0989.

General Procedure B for the Suzuki Coupling Reaction Leading to the Dimroth Rearangment. In a round-bottom flask,

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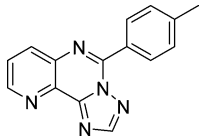
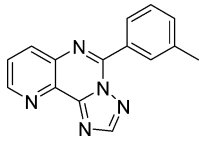
compound **1** (0.070 g, 0.341 mmol, 1 equiv) was dissolved in 10 mL of anhydrous toluene under argon atmosphere. The solution was degassed with argon for 10 min. The boronic acid (1.5 equiv), Cs_2CO_3 (1.5 equiv), and $Pd(PPh_3)_4$ (0.1 equiv) were then added. The mixture was stirred at 100 °C until disappearance of the starting material (TLC monitoring). The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography using a gradient solvent system of 100% petroleum ether (PE) up to an EtOAc/petroleum ether system of 60/40 for certain compounds.

5-(p-Tolyl)-pyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***5***.



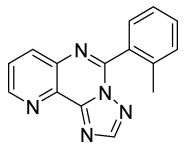
This compound was synthesized according to the general procedure B. Reaction time 3 h. Yield: 0.082 g, 92% (white solid). R_f 0.62 (acetone/CH_2Cl_2 20/80). Mp 153−155 °C. IR (ATR diamond, cm^{-1}) ν 3091, 3043, 2913, 2853, 1609, 1524, 1508, 1438, 1359, 1267, 1197, 1150, 1112, 947, 817, 729. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 3.3 Hz, 1H), 8.58 (s, 1H), 8.47 (d, J = 8.2 Hz, 2H), 8.43 (d, J = 8.4 Hz, 1H), 7.80 (dd, J = 8.4, 4.4 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 151.9, 151.2, 147.6, 143.0, 139.4, 136.4, 135.1, 130.6, 129.4, 128.4, 126.8, 21.8. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5[M + H]^+$ m/z 262.1087, found m/z 262.1084.

5-(m-Tolyl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***17***.



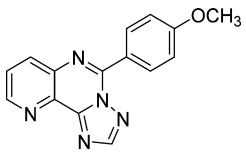
This compound was synthesized according to the general procedure B. Reaction time 6 h. Yield: 0.073 g, 82% (off-white solid). R_f 0.67 (acetone/CH_2Cl_2 20/80). Mp 165−167 °C. IR (ATR diamond, cm^{-1}) ν 3113, 3056, 2913, 2359, 1619, 1606, 1530, 1476, 1432, 1410, 1368, 1254, 1106, 963, 798, 726. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 4.2 Hz, 1H), 8.58 (s, 1H), 8.48−8.40 (m, 1H), 8.36−8.27 (m, 2H), 7.80 (dd, J = 8.4, 4.4 Hz, 1H), 7.56−7.42 (m, 2H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 154.3, 151.8, 151.3, 147.7, 139.2, 138.4, 136.3, 135.0, 132.9, 131.0, 130.9, 128.4, 127.6, 126.7, 21.6. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5$ $(M+H)^+$ m/z 262.1087, found 262.1085.

5-(o-Tolyl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***18***.



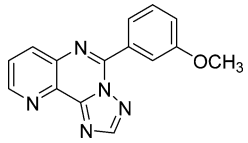
This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.073 g, 82% (off-white solid). R_f 0.64 (acetone/CH_2Cl_2 20/80). Mp 177−179 °C. IR (ATR diamond, cm^{-1}) ν 3141, 3100, 2917, 2359, 1615, 1533, 1476, 1406, 1359, 1261, 1185, 1102, 944, 735.^{1}H NMR (250 MHz, $CDCl_3$) δ 9.12 (dd, J = 4.4, 1.5 Hz, 1H), 8.52 (s, 1H), 8.45 (dd, J = 8.4, 1.5 Hz, 1H), 7.83 (dd, J = 8.4, 4.4 Hz, 1H), 7.70−7.60 (m, 1H), 7.59−7.48 (m, 1H), 7.48−7.37 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 151.6, 151.2, 149.1, 139.1, 137.4, 136.5, 135.2, 131.2(x2), 130.9, 129.5, 126.8, 126.0, 19.9. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5[M + H]^+$ m/z 262.1087, found m/z 262.1084.

5-(4-Methoxyphenyl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***19***.



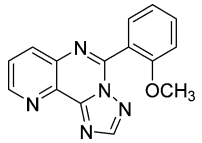
This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.064 g, 68% (white solid). R_f 0.59 (acetone/CH_2Cl_2 20/80). Mp 219−221 °C. IR (ATR diamond, cm^{-1}) ν 3120, 3046, 2961, 2838, 1609, 1533, 1508, 1479, 1438, 1368, 1311, 1254, 1185, 1153, 1099, 1014, 957, 821, 653. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, J = 4.3 Hz, 1H), 8.63 (d, J = 8.6 Hz, 2H), 8.58 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.3, 4.4 Hz, 1H), 7.11 (d, J = 8.6 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 154.2, 151.9, 150.9, 147.0, 139.3, 136.1, 134.7, 132.5, 126.7, 123.4, 113.9, 55.6. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5O[M + H]^+$ m/z 278.1036, found m/z 278.1037.

5-(3-Methoxyphenyl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***20***.



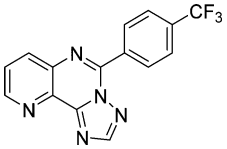
This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.075 g, 79% (off-white solid). R_f 0.64 (acetone/CH_2Cl_2 20/80). Mp 177−179 °C. IR (ATR diamond, cm^{-1}) ν 3107, 3075, 2989, 2939, 2831, 1609, 1577, 1517, 1486, 1454, 1362, 1286, 1267, 1220, 1194, 1112, 1026, 950, 817, 722. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.09 (dd, J = 4.4, 1.5 Hz, 1H), 8.59 (s, 1H), 8.45 (dd, J = 8.4, 1.5 Hz, 1H), 8.23−8.06 (m, 2H), 7.81 (dd, J = 8.4, 4.4 Hz, 1H), 7.63−7.44 (m, 1H), 7.20 (dd, J = 8.3, 2.6 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.6, 154.3, 151.9, 151.4, 147.2, 139.1, 136.4, 135.0, 132.2, 129.6, 126.7, 22.9, 118.2, 115.7, 55.6. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5O[M + H]^+$ m/z 278.1036, found m/z 278.1036.

5-(2-Methoxyphenyl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***21***.



This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.075 g, 79% (white solid). R_f 0.60 (acetone/CH_2Cl_2 20/80). Mp 196−198 °C. IR (ATR diamond, cm^{-1}) ν 3116, 3031, 3005, 2951, 2359, 2321, 1983, 1603, 1498, 1416, 1387, 1359, 1318, 1302, 1254, 1191, 1115, 992, 950, 840, 814, 719. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (dd, J = 4.4, 1.5 Hz, 1H), 8.51 (s, 1H), 8.47 (dd, J = 8.4, 1.5 Hz, 1H), 7.83 (dd, J = 8.4, 4.4 Hz, 1H), 7.68−7.59 (m, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 154.4, 151.4, 150.9, 147.8, 139.2, 136.5, 135.4, 132.9, 130.5, 126.5, 121.2, 120.9, 111.7, 55.8. HRMS (EI-MS): calcd for $C_{15}H_{11}N_5O[M + H]^+$ m/z 278.1036, found m/z 278.1033.

5-(4-(Trifluoromethyl)phenyl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]-pyrimidine ***22***.



This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.026 g, 24% (white solid). R_f 0.63 (acetone/CH_2Cl_2 20/80). Mp 191−193 °C. IR (ATR diamond, cm^{-1}) ν 3094, 2925, 2359, 1611, 1528, 1432, 1401, 1324, 1171, 1103, 1069, 1014, 841, 724. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.10 (dd, J = 4.4, 1.5 Hz, 1H), 8.71 (d, J = 8.5 Hz, 2H), 8.59 (s, 1H), 8.45 (dd, J = 8.4, 1.5 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.83−7.77 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 154.5, 151.9, 145.9, 139.0, 136.6, 135.1, 134.3, 133.9, 133.4, 131.0, 125.8, and 121.5 (part of the quartet CF_3, J = 275.2 Hz), 125.5 (q, J = 3.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ

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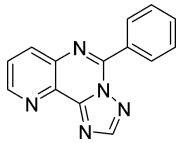
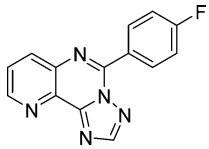
−63.1. HRMS (EI-MS): calcd for $C_{15}H_8F_3N_5[M + H]^+$ m/z 316.0805, found m/z 316.0806.

5-Phenylpyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***23***.



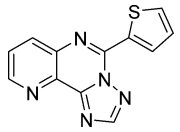
This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.054 g, 64% (off-white solid). R_f 0.64 (acetone/CH_2Cl_2 20/80). Mp 181−183 °C. IR (ATR diamond, cm^{-1}) ν 3145, 3091, 3050, 2359, 1603, 1520, 1454, 1406, 1362, 1267, 1197, 1106, 944, 789, 722. ^1H NMR (400 MHz, $CDCl_3$) δ 9.11−9.05 (m, 1H), 8.59 (s, 1H), 8.58−8.51 (m, 2H), 8.45 (dd, J = 8.4, 1.2 Hz, 1H), 7.80 (dd, J = 8.4, 4.4 Hz, 1H), 7.68−7.55 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 151.9, 151.4, 147.4, 139.2, 136.4, 135.0, 132.1, 131.1, 130.5, 128.5, 126.7. HRMS (EI-MS): calcd for $C_{14}H_9N_5[M + H]^+$ m/z 248.0931, found m/z 248.0930.

5-(4-Fluorophenyl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine ***24***.



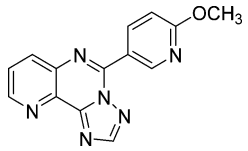
This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.068 g, 75% (white solid). R_f 0.68 (acetone/CH_2Cl_2 20/80). Mp 217−219 °C. IR (ATR diamond, cm^{-1}) ν 3097, 3065, 1606, 1530, 1508, 1438, 1403, 1359, 1261, 1248, 1232, 1197, 1156, 954, 840, 732. ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 4.1 Hz, 1H), 8.73−8.65 (m, 2H), 8.61 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 8.1, 4.2 Hz, 1H), 7.37−7.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (d, J = 254.3 Hz), 133.1 (d, J = 8.9 Hz), 115.8 (d, J = 21.9 Hz), 154.3, 151.9, 151.4, 146.2, 139.1, 136.3, 134.9, 133.1 (d, J = 8.9 Hz), 127.2 (d, J = 3.2 Hz), 126.8, 115.8 (d, J = 21.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.3. HRMS (EI-MS): calcd for $C_{14}H_8FN_5[M + H]^+$ m/z 266.0837, found m/z 266.0834.

5-(Thiophen-2-yl)pyrido[2,3-e][1,2,4]triazolo[1,5-*c*]-pyrimidine 26.



This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.014 g, 16% (off white solid). R_f 0.67 (acetone/CH_2Cl_2 20/80). Mp deg. at 110 °C. IR (ATR diamond, cm^{-1}) ν 3443, 3117, 3072, 2917, 1597, 1530, 1501, 1426, 1270, 1182, 1109, 1049, 821, 716. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 3.4 Hz, 1H), 8.97 (d, J = 3.0 Hz, 1H), 8.66 (s, 1H), 8.42 (d, J = 8.3 Hz, 1H), 7.87−7.74 (m, 2H), 7.39−7.31 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 151.6, 150.8, 142.3, 139.3, 135.9, 134.9, 134.6, 134.1, 133.5, 128.6, 126.7. HRMS (EI-MS): calcd for $C_{12}H_7N_5S[M + H]^+$ m/z 254.0495, found m/z 254.0495.

5-(6-Methoxypyridin-3-yl)pyrido[2,3-e][1,2,4]triazolo[1,5-c]-pyrimidine ***27***.



This compound was synthesized according to the general procedure B. Reaction time 24 h. Yield: 0.046 g, 49% (0.033 g, 35% nonrearranged product **16**) (off-white solid). R_f 0.47 (acetone/CH_2Cl_2 20/80). Mp 195−197 °C. IR (ATR diamond, cm^{-1}) ν 3449, 3113, 3091, 2939, 2321, 1666, 1603, 1505, 1435, 1387, 1327, 1267, 1191, 1020, 950, 817, 726, 650. ^1H NMR (250 MHz, $CDCl_3$) δ 9.51 (s, 1H), 9.00 (d, J = 3.3 Hz, 1H), 8.79 (dd, J = 8.9, 2.3 Hz, 1H), 8.53 (s, 1H), 8.36 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 8.4, 4.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.2, 154.3, 151.9, 151.2, 150.6, 145.3, 140.3, 139.2, 136.2, 134.9, 126.8, 120.8, 110.7, 54.1. HRMS (EI-MS): calcd for $C_{14}H_{10}N_6O[M + H]^+$ m/z 279.0989, found m/z 279.0986.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site at DOI: The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02357.

Copies of ^1H and ^{13}C NMR spectra of all new products (PDF)

Additional crystallographic data (CIF)

Details of crystallographic analysis and data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Buron, F.; Mérour, J. Y.; Akssira, M.; Guillaumet, G.; Routier, S. *Eur. J. Med. Chem.* **2015**, *95*, 76.

(2) Tikad, A.; Routier, S.; Akssira, M.; Guillaumet, G. *Org. Biomol. Chem.* **2009**, *7*, 5113.

(3) Tikad, A.; Routier, S.; Akssira, M.; Leger, J.-M.; Jarry, C.; Guillaumet, G. *Synlett* **2006**, *2006*, 1938.

(4) Tikad, A.; Routier, S.; Akssira, M.; Leger, J.-M.; Jarry, C.; Guillaumet, G. *Org. Lett.* **2007**, *9*, 4673.

(5) Saurat, T.; Buron, F.; Rodrigues, N.; de Tauzia, M.-L.; Colliandre, L.; Bourg, S.; Bonnet, P.; Guillaumet, G.; Akssira, M.; Corlu, A.; Guillouzo, C.; Berthier, P.; Rio, P.; Jourdan, M.-L.; Bénédetti, H.; Routier, S. *J. Med. Chem.* **2014**, *57*, 613.

(6) Innocenti, P.; Woodward, H.; O'Fee, L.; Hoelder, S. *Org. Biomol. Chem.* **2015**, *13*, 893.

(7) Henry, J. R.; Kaufman, M. D.; Peng, S.-B.; Ahn, Y. M.; Caldwell, T. M.; Vogeti, L.; Telikepalli, H.; Lu, W.-P.; Hood, M. M.; Rutkoski, T. J.; Smith, B. D.; Vogeti, S.; Miller, D.; Wise, S. C.; Chun, L.; Zhang, X.; Zhang, Y.; Kays, L.; Hipskind, P. A.; Wrobleski, A. D.; Lobb, K. L.; Clay, J. M.; Cohen, J. D.; Walgren, J. L.; McCann, D.; Patel, P.; Clawson, D. K.; Guo, S.; Manglicmot, D.; Groshong, C.; Logan, C.; Starling, J. J.; Flynn, D. L. *J. Med. Chem.* **2015**, *58*, 4165.

(8) Andrs, M.; Korabecny, J.; Jun, D.; Hodny, Z.; Bartek, J.; Kuca, K. *J. Med. Chem.* **2015**, *58*, 41.

(9) Lacbay, C. M.; Mancuso, J.; Lin, Y.-S.; Bennett, N.; Götte, M.; Tsantrizos, Y. S. *J. Med. Chem.* **2014**, *57*, 7435.

DOI: 10.1021/acs.joc.6b02357
J. Org. Chem. 2016, 81, 12506−12513

(10) Dehbi, O.; Tikad, A.; Bourg, S.; Bonnet, P.; Lozach, O.; Meijer, L.; Aadil, M.; Akssira, M.; Guillaumet, G.; Routier, S. *Eur. J. Med. Chem.* **2014**, *80*, 352.
(11) Belaroussi, R.; El Hakmaoui, A.; Percina, N.; Chartier, A.; Marchivie, M.; Massip, S.; Jarry, C.; Akssira, M.; Guillaumet, G.; Routier, S. *Eur. J. Org. Chem.* **2015**, *2015*, 4006.
(12) Othman, R. B.; Massip, S.; Marchivie, M.; Jarry, C.; Vercouillie, J.; Chalon, S.; Guillaumet, G.; Suzenet, F.; Routier, S. *Eur. J. Org. Chem.* **2014**, *2014*, 3225.
(13) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, 2005.
(14) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Assafir, H. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: Amsterdam, The Netherlands, 1999; Vol. 75, p 79.
(15) Dimroth, O. *Justus Liebigs Ann. Chem.* **1909**, *364*, 183.
(16) Shaban, M. A. E.; Morgaan, A. E. A. In *Advances in Heterocyclic Chemistry*; Alan, R. K., Ed.; Academic Press: Amsterdam, The Netherlands, 1999; Vol. 75, p 243.
(17) Shaban, M. A. E.; Morgaan, A. E. A. In *Advances in Heterocyclic Chemistry*; Academic Press: Amsterdam, The Netherlands, 2000; Vol. 77, p 345.
(18) Godefroy, L.; Decormeille, A.; Queguiner, G.; Pastour, P. *C. R. Acad. Sci. Paris* **1974**, *278*, 1421.
(19) Godefroy, L.; Queguiner, G.; Pastour, P. *J. Heterocycl. Chem.* **1973**, *10*, 1077.
(20) Petrič, A.; Tišler, M.; Stanovnik, B. *Monatsh. Chem.* **1983**, *114*, 615.
(21) Petrič, A.; Tišler, M.; Stanovnik, B. *Monatsh. Chem.* **1985**, *116*, 1309.
(22) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387.
(23) Tang, C.; Li, Z.; Wang, Q. *Beilstein J. Org. Chem.* **2013**, *9*, 2629.
(24) Salgado, A.; Varela, C.; García Collazo, A. M.; García, F.; Pevarello, P.; Alkorta, I.; Elguero, J. *J. Mol. Struct.* **2011**, *987*, 13.
(25) Crystallographic data has been deposited in the Cambridge Crystallographic Data Centre (CCDC 1450525−1450526). Copies of these data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax: + 44 1223 336 033 or http://www.ccdc.cam.ac.uk/data_request/cif).
(26) Wustrow, D.; Zhou, H. J. Fused Pyrimidines as inhibitors of p97 complex. Patent WO2015109285, July 23, 2015.

DOI: 10.1021/acs.joc.6b02357
J. Org. Chem. 2016, 81, 12506−12513