Synthesis of New Flat Polyheterocyclic Systems Potential DNA Intercalating Agents Diazines Part 47

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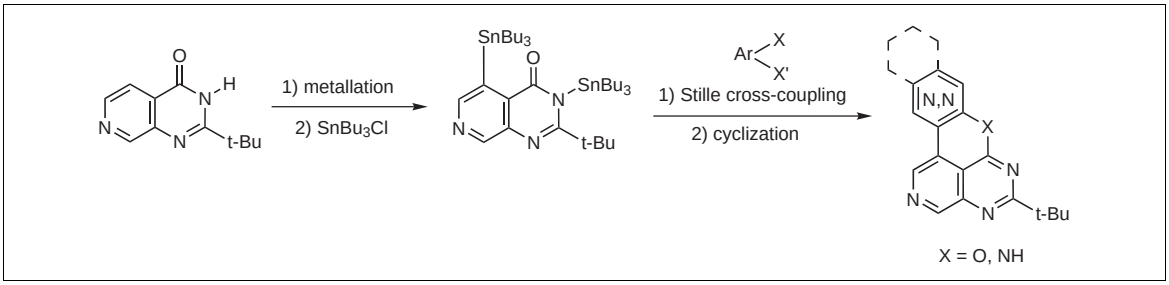

Using a regioselective metallation in connection with Stille cross-coupling reaction, we report here an original synthetic route to obtain in few steps various flat tetra- or pentaheterocyclic compounds which could be potential intercalating DNA agents.

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Introduction.

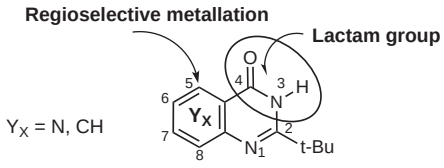
Among the antitumor drugs, DNA intercalating agents are one of the most important types. They are generally flat aromatic or heteroaromatic polycyclic molecules. In the literature, many polyheterocyclic compounds isolated from marine organisms are mentioned and have shown cytotoxic activity [1]. Among them acridines, pyridoacridines, actinomycines and anthracyclines have been well characterized as intercalors of DNA [2]. Other tetracyclic compounds with quinoline, naphthyridine, or cinnoline moiety condensed to benzopyranes or benzothiopyranes were previously synthesized and reported to have promising antitumor activity or analgesic properties [3]. The therapeutic importance of this kind of structures enthused chemists to prepare these compounds. They are usually synthesized using base-catalyzed condensation reactions and ring-annelations.

The use of metallation in connection with cross-coupling reactions, allowed us to synthesize new polyazabenzo[*de*]anthracenes.

In previous papers, we have reported a convenient method to functionalize *via* metallation reaction the benzene moiety of benzodiazines [4] or the pyridine moiety of the pyridopyrimidines [5]. For such compounds, a regioselective metallation at the C_5 position, *peri* position of the carbonyl group of the lactam function of the diazine ring was described (Scheme 1).

There is a widespread interest in the synthesis of new conjugated oligoarenes containing electron-deficient heterocycles in their backbone. Oligomers incorporating pyridine, bipyridine, quinoline, triazine and more recently pyrazine moieties have been previously described mainly for the elaboration of electronic devices [1-5].

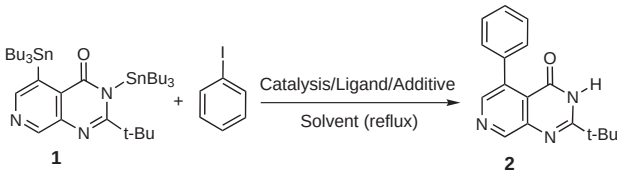
Scheme 1



Results and discussion

The lithiation at the C_5 position of the pyridopyrimidin-4(3*H*)-ones followed by reaction with tributyltin chloride as the electrophile, led to the corresponding distannyl derivatives [5a] which could react with aryl iodides under Stille conditions. With this aim, we have first tested various experimental conditions to synthesize 2-*tert*-butyl-5-phenyl pyrido[3,4-*d*]-pyrimidin-4(*3H*)-one **2** by coupling reaction of compound **1** with iodobenzene (Scheme 2).

Scheme 2



Various palladium catalysts ($Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or Pd_2dba_3) have been tried under reflux of various solvents (toluene, dioxane or DMF); in all cases no coupling reaction was observed and the starting reagent was recovered. By use of 1 equivalent of $Pd(PPh_3)_4$ in toluene, compound **2** was obtained in 50% yield besides the starting material. To increase the efficiency of the palladium catalyst, we used LiCl or CsF as additive. Attempts with LiCl were unsuccessful, while use of 2.2 equivalents of CsF and 10% of $Pd(PPh_3)_4$ gave **2** in very good yield (95%).

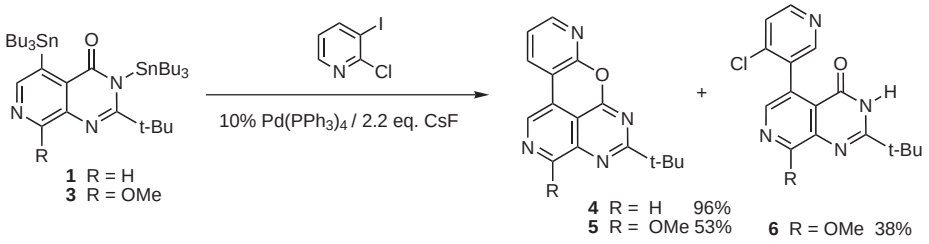
Under these experimental conditions, reaction of 2-chloro-3-iodopyridine with **1** and **3** gave one-pot, the tetracyclic compounds **4**, and **5** in moderate to good yields (Scheme 3).

This methodology afforded polyheterocyclic structures with formation of a pyrane ring by establishment of an oxygen bridge. With the aim to build polyazaheterocycles, we have investigated coupling reaction of **1** with an iodo aromatic substituted by an amino group at the *ortho* position.

The reaction with *o*-iodoaniline was first tested with **1** under the previous conditions. Formation of the tetracyclic derivative **8** was obtained in 57% yield besides the unexpected compound **2** resulting from a coupling with a phenyl group probably provided by the catalyst (Scheme 5).

When **1** was reacted with a protected amine such as 3-iodo-4-pivaloylaminopyridine, we obtained the expected uncyclized compound **9** besides compound **2** in similar ratio with those previously observed. To induce the

Scheme 3



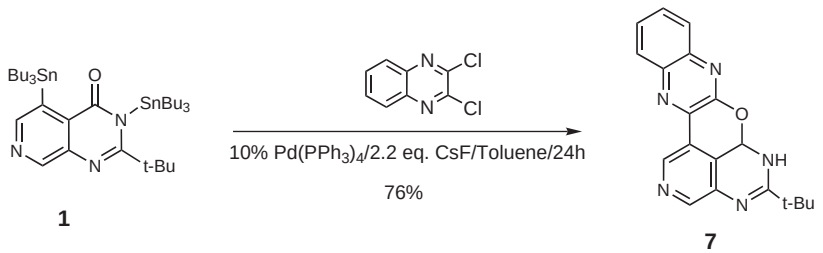
In the Stille cross-coupling reaction, the iodine atom is known to be more reactive than the chlorine one. In the case of the 2-chloro-3-iodopyridine, the iodine atom gave the aryl-aryl linkage formation, whereas, the chlorine atom at the C_2 position more sensitive to the nucleophilic substitution allowed the subsequent cyclization. With compound **3**, the tetracyclic compound **5** was obtained in 53% yield besides the uncyclized compound **6** in 38% yield.

When compound **1** was reacted with 2,3-dichloroquinoxaline under the same conditions, the pentacyclic derivative **7** was obtained in 76% yield (Scheme 4).

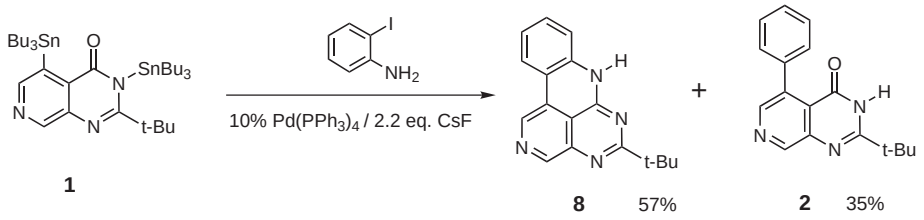
cyclization reaction of compound **9**, it was reacted with pyridine hydrochloride at 210° for 45 minutes; under these conditions, the tetracyclic compound **10** was obtained in very good yield (96%) (Scheme 6).

In order to extend this synthetic method to other polycyclic systems, we studied the metallation of benzo-[*c*][2,5]naphthyridin-1(2*H*)-one **11**. This compound previously described in the literature, has been prepared either starting from 1,6-phenanthroline [6a] or by the intramolecular cyclisation of an N-substituted *o*-cyano-benzamide [6b]. According to a strategic way, using metallation and cross-coupling reactions, compound **11** was obtained by a Suzuki coupling of 2-pivaloylamino-

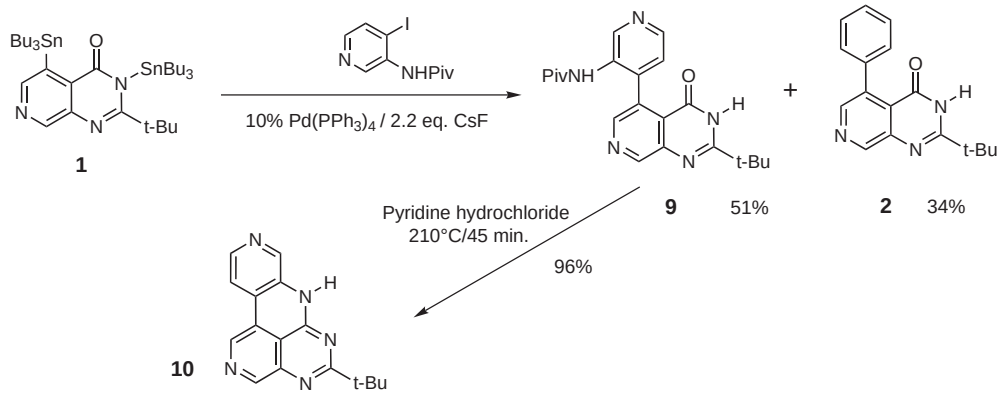
Scheme 4



Scheme 5

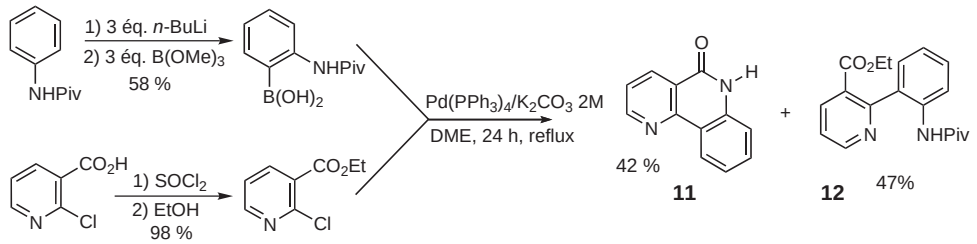


Scheme 6



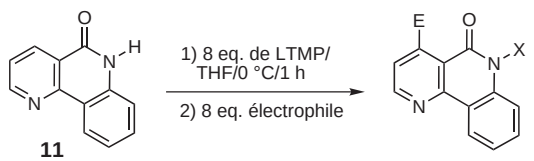
phenylboronic acid with ethyl 2-chloronicotinate and subsequent cyclization with 42% yield besides the uncyclized compound **12** (47%) (Scheme 7).

Scheme 7



Several experimental conditions for the metallation of **11** have been tested and the best results were obtained with an excess of metallating agent (8 equiv. LTMP), in THF at 0°C with a one hour reaction time. As previously, we observed the regioselective metallation at C_5, *peri* of the carbonyl of the lactam group. Under the same experimental conditions, lithiation of **11** with LTMP followed by reaction with various electrophiles led to compounds **13**-**17** in good yields (Scheme 8).

Scheme 8



13 X= H E = MeCH(OH) 96%
14 X= H E = PhCH(OH) 82%
15 X= H E = PhS 87%
16 X= H E = Cl 85%
17 X= E = $SnBu_3$ 88%

Using the previous conditions, Stille cross-coupling reacting was tested with compound **17** and several aryl iodides (iodobenzene, *o*-iodoanisole, *o*-iodoaniline), unfortunately all these attempts failed, only the destannylation was observed and the compound **11** was recovered. This result could be due to the relative position of the stannyl group, at the *para* position of nitrogen of the pyridine moiety.

The geometry of the molecules **5**, **7**, **8**, **10**, **11**, **13**-**15** was optimized by using Sybyl, *i.e*. Tripos force field and

PM3 from MOPAC package [7]. Only molecules **8** and **10** present a low twisted angle of about 10° while all the other are perfectly coplanar.

Conclusion.

We have extended the regioselective metallation at C_5 position of the benzo[*c*][2,5]naphthyridin-1(2*H*)-one, highlighting a general method to functionalize the *peri* position to a carbonyl of a lactam group.

In pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones series, the metallation reaction followed by a Stille cross-coupling allowed us to develop an original synthetic way to obtain in few steps, with good yields, various flat tetra or pentaheterocyclic compounds which could be potential intercalating DNA agents.

EXPERIMENTAL

Melting points were determined on an Electrothermal 1100 instrument. The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AC 300 (300 MHz ^{1}H, 75 MHz ^{13}C) instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin-Elmer 16 PC FT-IR spectrometer. Mass spectra were recorded on an ATI-Unicam Automass® apparatus.

General Procedure A for cross-coupling of Heteroaryl Halides with Tributylstannylheteroarene under Stille Conditions.

A solution of 2-*tert*-butyl-5-(tri-*n*-butylstannyl)pyrido[3,4-*d*]pyrimidin-4(3-tri-*n*-butylstannyl)-one (**1**) [5a] (0.050 g, 0.064 mmole) or 2-*tert*-butyl-5-(tri-*n*-butylstannyl)-8-methoxypyrido-[3,4-*d*]pyrimidin-4(3-tri-*n*-butylstannyl)-one (**3**) [5a] (0.050 g, 0.062 mmole), arylhalide (1.2-1.5 equiv.), cesium fluoride (2.2 equiv.) and tetrakis(triphenylphosphine)-palladium(0) $Pd(PPh_3)_4$ (0.10 equiv.) in degassed toluene (5 ml) was heated under reflux under nitrogen atmosphere for 24 hours. After cooling, a mixture of water (10 ml) and dichloromethane (10 ml) was added. The organic phase was extracted with dichloromethane (3x20 ml). The combined organic extracts were then dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel.

General Procedure B for Metallation of Benzo[*c*][2,5]naph-thyridin-1(2*H*)-one by Lithium 2,2,6,6-tetramethylpiperidide.

A solution of *n*-butyllithium (1.27 mL, 1.6 *M* in hexane, 2.0 mmoles) was added to cold (–78°), stirred and anhydrous mixture of THF (15 mL) and 2,2,6,6-tetramethylpiperidine (TMPH) (0.35 ml, 2.1 mmoles) under an atmosphere of dry nitrogen. The mixture was warmed to 0° and after 30 minutes, the mixture temperature was colded to –78° and added to a cold (–78°) solution of the benzo[*c*][2,5]naphthyridin-1(2*H*)-one (0.050 g, 0.25 mmol) in THF (10 mL). Then, the mixture was stirred for 5 min. and heated to 0°. After 45 minutes of stirring at 0°, the temperature was decreased to –78° and the electrophile introduced and stirring was continued for one hour at this temperature. Hydrolysis was then carried out at –78° using a solution of water and ethanol (1:1). At room temperature, water (10 mL) was added to the mixture and THF was removed under reduced pressure. The aqueous layer was extracted with dichloromethane or ethyl acetate (3x20 mL), the combined organic extracts were then dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

2-*tert*-Butyl-5-phenylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (**2**).

Reaction of iodobenzene (0.010 ml, 0.09 mmole.) with (**1**) according to the procedure A gave after purification by column chromatography (silica, eluent dichloromethane:ethyl acetate (1:1)) 0.017 g (95%) of **2** as a brown solid, mp 249-250°, ^{1}H nmr (deuteriochloroform): δ 1.10 (s, 9H, *tert*-butyl), 7.27 (m, 2H, Ph), 7.34 (m, 3H, Ph), 8.34 (s, 1H, H_6), 9.03 (s, 1H, H_8), ^{13}C nmr : δ 28.4 ($3Me_{tert\text{-butyl}}$), 37.7 (CMe_3), 122.7 (C_{py}), 127.9 (CH_{Ph}), 128.1 ($2CH_{Ph}$), 129.5 ($2CH_{Ph}$), 135.6 (C_{py}), 138.0 (C_{Ph}), 144.7 (C_{py}), 147.8 (CH_{py}), 151.4 (CH_{py}), 163.1 (C_{py}), 165.1 (C_{py}) ir (potassium bromide): 3182, 3120, 3065, 2925, 2854, 1679, 1606, 1436, 1402, 1370, 1289, 1402, 1370, 1289, 1208, 976, 882, 819, 762, 698, 618, 545, 516 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}N_3O$ (279.34): C, 73.10; H, 6.13; N, 15.04. Found: C, 72.87; H, 6.34; N, 15.38.

5-*tert*-Butyl-7-oxa-2,4,6,8-tetraaza-benzo[*de*]anthracene (**4**).

Reaction of 2-chloro-3-iodopyridine (0.017 g, 0.07 mmole) with (**1**) according to the procedure A gave after purification by column chromatography (silica, ethyl acetate) 0.017 g (96%) of **4** as a brown solid, mp >250°, ^{1}H nmr (deuteriochloroform): δ 1.42 (s, 9H, *tert*-butyl), 7.32 (dd, $J_{H10\text{-}H9}$ = 4.5 Hz et $J_{H10\text{-}H11}$ = 7.5 Hz, 1H, H_{10}), 8.36 (dd, $J_{H11\text{-}H10}$ = 7.5 Hz et $J_{H11\text{-}H9}$ = 1.9 Hz, 1H, H_{11}), 8.44 (dd, $J_{H9\text{-}H10}$ = 4.9 Hz et $J_{H9\text{-}H11}$ = 1.9 Hz, 1H, H_9), 9.01 (s, 1H, H_1), 9.25 (s, 1H, H_3), ^{13}C nmr (deuteriochloroform): δ 28.2 ($3Me_{tert\text{-butyl}}$), 39.2 (CMe_3), 112.5 (C_{arom}), 112.9 (C_{arom}), 120.0 (C_{arom}), 121.0 (CH_{arom}), 131.7 (CH_{arom}), 134.1 (CH_{arom}), 144.8 (C_{arom}), 148.9 (CH_{arom}), 149.3 (CH_{arom}), 156.0 (C_{arom}), 163.5 (C_{arom}), 177.0 (C_{arom}). ir (potassium bromide): 3065, 2962, 2925, 2854, 1686, 1633, 1593, 1556, 1484, 1460, 1431, 1398, 1375, 1259, 1220, 1163, 1137, 1096, 1086, 1028, 971, 930, 892, 814, 764, 672 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_4O$ (278.31): C, 69.05; H, 5.07; N, 20.13. Found: C, 69.32; H, 4.83 N, 20.10.

5-*tert*-Butyl-3-methoxy-7-oxa-2,4,6,8-tetraaza-benzo[*de*]-anthracene (**5**).

Reaction of 2-chloro-3-iodopyridine (0.017 g, 0.07 mmole) with (**3**) according to the procedure B gave after purification by column chromatography (silica, dichloromethane:ethyl acetate (7:3)) 0.010 g (53%) of **5** as a brown solid, mp 248-250°, ^{1}H nmr (deuteriochloroform): δ 1.43 (s, 9H, *tert*-butyl), 4.15 (s, 3H, OMe), 7.23 (dd, $J_{H10\text{-}H9}$ = 4.5 Hz et $J_{H10\text{-}H11}$ = 7.5 Hz, 1H, H_{10}), 8.20 (dd, $J_{H11\text{-}H10}$ = 7.5 Hz et $J_{H11\text{-}H9}$ = 1.5 Hz, 1H, H_{11}), 8.31 (dd, $J_{H9\text{-}H10}$ = 4.5 Hz et $J_{H9\text{-}H11}$ = 1.5 Hz, 1H, H_9), 9.46 (s, 1H, H_1), ^{13}C nmr (deuteriochloroform): δ 29.7 ($3Me_{tert\text{-butyl}}$), 40.7 (CMe_3), 55.3 (OMe), 115.1 (C_{arom}), 115.2 (C_{arom}), 115.5 (C_{arom}), 122.2 (CH_{arom}), 131.9 (CH_{arom}), 132.2 (CH_{arom}), 138.0 (C_{arom}), 149.1 (CH_{arom}), 156.6 (C_{arom}), 158.8 (C_{arom}), 156.0 (C_{arom}), 164.9 (C_{arom}), 178.1 (C_{arom}). ir (potassium bromide): 2958, 2926, 2854, 1624, 1591, 1551, 1481, 1402, 1377, 1336, 1294, 1243, 1221, 1169, 1067, 1047, 1026, 978, 806, 760, 720, 620 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_4O_2$ (308.34): C, 66.22; H, 5.23; N, 18.17. Found: C, 66.58; H, 5.13 N, 18.64.

2-*tert*-Butyl-8-methoxy-5-(2-chloro-3-pyridyl)-pyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (**6**).

Reaction of 2-chloro-3-iodopyridine (0.16 g, 0.67 mmole) with (**3**) according to the procedure A gave after purification by column chromatography (silica, dichloromethane:ethyl acetate (7:3)) 0.08 g (38%) of **6** as a white solid, mp > 250°, ^{1}H nmr (deuteriochloroform): δ 1.16 (s, 9H, *tert*-butyl), 4.10 (s, 3H, OMe), 7.23 (dd, $J_{H5\text{-}H6}$ = 4.9 Hz et $J_{H5\text{-}H4}$ = 7.5 Hz, 1H, H_{5py}), 7.52 (dd, $J_{H4\text{-}H5}$ = 7.5 Hz et $J_{H4\text{-}H6}$ = 1.9 Hz, 1H, H_{4py}), 7.76 (s, 1H, H_{6py}), 8.37 (dd, $J_{H6\text{-}H5}$ = 4.5 Hz et $J_{H6\text{-}H4}$ = 1.9 Hz, 1H, H_{6py}), 11.66 (s, 1H, NH), ^{13}C nmr (deuteriochloroform): δ 27.0 ($3Me_{tert\text{-}butyl}$), 36.6 (CMe_3), 53.9 (OMe), 120.9 (CH_{arom}), 122.1 (C_{arom}), 123.5 (C_{arom}), 133.2 (C_{arom}), 137.1 (C_{arom}), 137.7 (CH_{arom}), 141.9 (CH_{arom}), 147.3 (CH_{arom}), 150.2 (C_{arom}), 159.5 (C_{arom}), 161.5 (C_{arom}), 163.6 (C_{arom}). ir (potassium bromide): 3181, 3042, 2925, 2854, 1666, 1599, 1561, 1473, 1391, 1262, 1217, 1061, 1025, 936, 889, 808, 767, 726, 657, 553 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}ClN_4O_2$ (344.80): C, 56.22; H, 4.97; N, 16.25. Found: C, 56.43; H, 5.01 N, 16.06.

5-*tert*-Butyl-7-oxa-2,4,6,8,13-pentaaza-benzo[*de*]naphthacene (**7**).

Reaction of 2,3-dichloroquinoxaline (0.014 g, 0.07 mmole) with (**1**) according to the procedure A gave after purification by column chromatography (silica, petroleum ether:ethyl acetate (3:1)) 0.016 g (76%) of **7** as a yellow solid, mp 222-224°, ^{1}H nmr (deuteriochloroform): δ 1.42 (s, 9H, *tert*-butyl), 7.71 (m, 2H, H_{benzo}), 7.94 (m, 1H, H_{benzo}), 8.10 (m, 1H, H_{benzo}), 9.42 (s, 1H, H_1), 9.58 (s, 1H, H_3), ^{13}C nmr (deuteriochloroform): δ 29.6 ($3Me_{tert\text{-}butyl}$), 40.8 (CMe_3), 114.7 (C_{arom}), 121.5 (C_{arom}), 128.9 (CH_{benzo}), 129.6 (CH_{benzo}), 130.5 (CH_{benzo}), 132.4 (CH_{benzo}), 135.5 (C_{arom}), 139.2 (CH_{py}), 141.6 (C_{arom}), 141.8 (C_{arom}), 145.9 (C_{arom}), 152.0 (C_{arom}), 153.0 (CH_{arom}), 163.8 (C_{arom}), 178.3 (C_{arom}). ir (potassium bromide): 2957, 2923, 2352, 1633, 1557, 1482, 1456, 1374, 1352, 1310, 1259, 1216, 1138, 1083, 957, 899, 769, 672 cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}N_5O$ (329.31): C, 69.29; H, 4.59; N, 21.20. Found: C, 69.05; H, 4.14 N, 21.03.

5-*tert*-Butyl-7*H*-2,4,6,7-tetraaza-benzo[*de*]anthracene (**8**).

Reaction of 2-iodoaniline (0.025 g, 0.11 mmole) with (**1**) according to the procedure A gave after purification by column chromatography (silica, petroleum ether:ethyl acetate (1:1)) 0.016 g (57%) of **8** as a colorless solid, mp > 250°, ; ^{1}H nmr (DMSO-d_6): δ 1.43 (s, 9H, *tert*-butyl), 7.28 (td, J = 6.8 Hz et J = 1.1 Hz, 1H, H_{benzo}), 7.51 (m, 2H, H_{benzo}), 8.35 (d, J = 7.5 Hz, 1H, H_{benzo}), 8.84 (s, 1H, H_1), 9.23 (s, 1H, H_3), ^{13}C nmr (DMSO-d_6): δ 29.7 ($3Me_{tert\text{-}butyl}$), 40.8 (CMe_3), 116.0 (C_{arom}), 118.0 (CH_{benzo}), 118.1 (C_{arom}), 123.6 (CH_{benzo}), 123.8 (CH_{benzo}), 125.3 (C_{arom}), 131.0 (CH_{benzo}), 134.8 (CH_{py}), 137.5 (C_{arom}), 144.0 (C_{arom}), 144.7 (CH_{py}), 155.7 (C_{arom}), 177.0 (C_{arom}). ir (potassium bromide): 3107, 2953, 2918, 2857, 2798, 1632, 1613, 1578, 1549, 1513, 1439, 1427, 1354, 1311, 1256, 1216, 1151, 1109, 1028, 970, 932, 869, 810, 759, 740, 695, 600 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_4$ (276.34): C, 73.89; H, 5.84; N, 20.27. Found: C, 73.64; H, 6.05 N, 20.59.

2-*tert*-Butyl-5-[3-(pivaloylamino)-4-pyridyl]pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (**9**).

Reaction of 3-pivaloylamino-4-iodopyridine (0.44 g, 1.44 mmole) with (**1**) according to the procedure A gave after purification by column chromatography (silica, ethyl acetate: ethanol (9:1)) 0.256 g (51%) of **9** as a colorless solid, mp 200-202°, ^{1}H nmr (deuteriochloroform): δ 0.88 (s, 9H, *tert*-butyl), 1.21 (s, 9H, *tert*-butyl), 5.80 (m, 1H, NH), 7.10 (s, 1H, NH), 7.12 (d, $J_{H5\text{-}H6}$ = 4,9 Hz, 1H, H_{5py}), 8.33 (s, 1H, H_6), 8.42 (d, $J_{H6\text{-}H5}$ = 4.9 Hz, 1H, H_{6py}), 9.05 (s, 1H, H_{2py}), 9.15 (s, 1H, H_8), ^{13}C nmr (deuteriochloroform): δ 26.1 ($3Me_{tert\text{-}butyl}$), 26.8 ($3Me_{tert\text{-}butyl}$), 36.6 (CMe_3), 121.5 (C_{arom}), 123.0 (CH_{arom}), 127.0 (C_{arom}), 131.5 (C_{arom}), 137.9 (C_{arom}), 143.0 (C_{arom}), 144.2 (CH_{arom}), 144.8 (CH_{arom}), 145.7 (CH_{arom}), 151.9 (CH_{arom}), 161.5 (C_{arom}), 164.7 (C=O), 171.9 (C=O). IR (potassium bromide) 3368, 3232, 2960, 1666, 1607, 1512, 1499, 1435, 1398, 1288, 1261, 1211, 1173, 1096, 1056, 979, 937, 862, 817, 807, 690, 618, 574 cm^{-1}.

Anal. Calcd. for $C_{21}H_{25}N_5O_2$ (379.47): C, 66.47; H, 6.64; N, 18.46. Found: C, 66.26; H, 6.87; N, 17.93.

5-*tert*-Butyl-7*H*-2,4,6,7,9-pentaaza-benzo[*de*]anthracene (**10**).

A mixture of (**9**) (0.10 g, 0.26 mmole) and 1.0 g of pyridine hydrochoride was warmed at 210° for 45 minutes. After cooling, the mixture was poured on 10 mL of water and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were then dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, ethyl acetate:ethanol (9:1)) to give 0.063g (90%) of **10** as a brown solid mp > 250°, ^{1}H nmr (DMSO-d_6): δ 1.44 (s, 9H, *tert*-butyl), 8.30 (d, $J_{H5\text{-}H6}$ = 5.3 Hz, 1H, H_{5py}), 8.44 (d, $J_{H6\text{-}H5}$ = 4.9 Hz, 1H, H_{6py}), 8.79 (s, 1H, H_{2py}), 8.95 (s, 1H, H_6), 9.38 (s, 1H, H_8), 12.17 (s, 1H, NH), ^{13}C nmr (DMSO-d_6): δ 29.3 ($3Me_{tert\text{-}butyl}$), 40.1 (CMe_3), 116.9 (CH_{5py}), 117.5 (C_{arom}), 123.6 (C_{arom}), 124.4 (C_{arom}), 136.0 (C_{arom}), 136.6 (CH_8), 143.3 (CH_{6py}), 144.2 (CH_{2py}), 144.5 (C_{arom}), 146.4 (CH_6), 155.4 (C_{arom}), 176.1 (C_{arom}). ir (potassium bromide): 3436, 2964, 2864, 1633, 1601, 1544, 1459, 1434, 1416, 1348, 1310, 1297, 1220, 1154, 936, 875, 830, 815, 695, 674, 549 cm^{-1}.

Anal. Calc for $C_{16}H_{15}N_5$ (277.33): C, 69.30; H, 5.45; N, 25.25. Found: C, 69.33; H, 5.26 N, 25.22.

Benzo[*c*][2,5]naphthyridin-1(2*H*)-one (**11**).

A mixture of the ethyl 2-chloro-nicotinate (0.37 g, 2 mmoles), the 2-pivaloylaminophenylboronic acid (4.77 g, 1.3 equiv.), tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) (0.70g, 0.10 equiv.), aqueous 2 *M* potassium carbonate (11 mL, 2 equiv.) and ethanol (1 mL) in degassed dimethoxyethane (DME) (40 mL) was heated under reflux and under nitrogen for 24 h. The reaction mixture was cooled, diluted with 15 ml of water and dichloromethane (1:1) and the organic layers separated. The aqueous layer was extracted with dichloromethane (3x15 mL), the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography (silica gel, eluent dichloromethane: diethylether (95:5)) to give 0.887g (42%) of (**11**) as a colorless solid, mp > 250 °C; ^{1}H nmr (DMSO d_6): δ 7.39 (t, J = 7.9 Hz, 1H, H_{benz}), 7.46 (d, J = 7.9 Hz, 1H, H_{benz}), 7.66 (td, J = 8.3 Hz et J = 1.1 Hz, 1H, H_{benz}), 7.75 (q, $J_{H3\text{-}H2}$ = 4.5 Hz et $J_{H3\text{-}H4}$ = 7.9 Hz, 1H, H_3), 7.68 (m, 2H, H_{benz} et H_4), 9.13 (q, $J_{H2\text{-}H3}$ = 4.5 Hz et $J_{H2\text{-}H4}$ = 1.9 Hz, 1H, H_2), 11.97 (s, 1H, NH); ^{13}C nmr (DMSO d_6): δ 116.2 (CH), 119.1 (C_{arom}), 121.5 (C_{arom}), 122.7 (CH), 123.7 (CH), 124.3 (CH), 131.5 (CH), 136.1 (CH), 138.2 (C_{arom}), 150.8 (C_{arom}), 154.4 (CH), 161.2 (C=O). ir (potassium bromide): 3033, 2982 (CH), 1679 (C=O), 1605, 1585, 1455 cm^{-1}.

Anal. Calcd. for $C_{12}H_8N_2O$ (196.21): C, 73.46; H, 4.11, N, 14.28.. Found: C, 73.49; H, 3.98; N, 14.33.

2-(Pivaloylaminophenyl)nicotinic ethyl ester (**12**).

After purification by column chromatography (silica gel, eluent dichloromethane:diethylether (95:5)) 1.65g (47%) of (**12**) as a brown solid, mp 81-83 °; ^{1}H nmr (deuteriochloroform): δ 0.90 (t, J = 7.1 Hz, 3H, Me), 1.10 (s, 9H, *tert*-butyl), 4.01 (q, J = 7.1 Hz, 2H, OCH_2), 6.98 (t, J = 7.2 Hz, 1H, H_{Ph}), 7.09 (d, J = 6.4 Hz, 1H, H_{Ph}), 7.29 (m, 2H, H_{5py} et H_{Ph}), 8.08 (dd, J_{H4-H5} = 7.5 Hz et J_{H4-H6} = 1.5 Hz, 1H, H_{4py}), 8.34 (d, J = 8.3 Hz, 1H, H_{Ph}), 8.65 (dd, J_{H6-H5} = 4.5 Hz et J_{H6-H4} = 1.5 Hz, 1H, H_{6py}), 9.93 (s, 1H, NH); ^{13}C nmr 13.9 (CH_3), 27.7 (3 x $CH_{3tert-butyl}$), 40.2, 62.1 (CH_2), 122.3 (CH), 122.4 (CH), 123.4 (CH), 128.4 (C_{arom}), 129.4 (C_{arom}), 130.1 (CH), 130.5 (CH), 136.6 (C_{arom}), 139.3 (CH), 150.2 (CH), 157.4 (C_{arom}), 168.1 (C=O), 177.0 (C=O). Ir (potassium bromide): 3271, 2980, 1716, 1583, 1515, 1453, 1422, 1365, 1296, 1166, 1140, 1056, 1017, 923, 863, 752, 623, 548 cm^{-1}.

Anal. Calcd. for $C_{19}H_{22}N_2O_3$ (326,39): C, 69.92; H, 6.79; N, 8.58.. Found: C, 69.63; H, 6.86; N, 8.49

8-(1-Hydroxyethyl)benzo[*c*][2,5]naphthyridin-1(2*H*)-one (**13**).

Metallation of (**11**) according to the procedure A followed by reaction with acetaldehyde (10 equiv., 0.15 mL) in solution with anhydrous tetrahydrofurane (5 mL) gave after purification by column chromatography (silica gel, eluent ethyl acetate:dichloromethane (1:1)) 58 mg (96%) of (**13**) as a colorless solid, mp 224-226°; ^{1}H nmr (DMSO-d_6): δ 1.43 (d, J = 6.4 Hz, 3H, Me), 5.50 (d, J = 4.5 Hz, 1H, OH), 6.22 (quint, J = 4.9 Hz, 1H, C*H*OH), 7.34 (t, J = 7.2 Hz, 1H, H_{benz}), 7.42 (d, J = 7.5 H, 1H, H_{benz}), 7.63 (t, J = 8.2 Hz, 1H, H_{benz}), 7.97 (d, J = 5.3 Hz, 1H, H_3), 8.72 (d, J = 7.2 Hz, 1H, H_{benz}), 9.04 (d, J = 4.9 Hz, 1H, H_2), 11.81 (s, 1H, NH); ^{13}C nmr (DMSO-d_6) : δ 25.9 (Me), 65.0 (CHOH), 115.6 (CH), 117.7 (C_{arom}), 119.3 (C_{arom}), 120.3 (CH), 122.5 (CH), 125.0 (CH), 131.4 (CH), 137.9 (C_{arom}), 151.7 (C_{arom}), 153.7 (CH), 161.2 (C_{arom}), 161.7 (C=O). ir (potassium bromide): 3171, 3114, 3031, 2983, 2923, 2867, 1658, 1605, 1557, 1498, 1459, 1434, 1387, 1356, 1262, 1110, 805, 757, 669 cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66.. Found: C, 70.11; H, 5.22; N, 11.71.

8-(Hydroxyphenylmethyl)benzo[*c*][2,5]naphthyridin-1(2*H*)-one (**14**).

Metallation of (**11**) according to the procedure B followed by reaction with benzaldehyde (9 equiv., 0.23 ml) in solution with anhydrous tetrahydrofurane (15 mL) gave after purification by column chromatography (silica gel, eluent ethyl acetate: dichloromethane (1:1)) 0.063g (82%) of (**14**) as a colorless solid, mp 226-228°; ^{1}H nmr (deuteriochloroform): δ 6.08 (d, J = 7.2 Hz, 1H, OH), 6.53 (d, J = 7.2 Hz, 1H, C*H*OH), 7.01 (d, J = 7.9 Hz, 1H, H_{benz}), 7.27 (m, 7H, H_{Ph}, H_3 et H_{benz}), 7.46 (t, J = 8.3 Hz, 1H, H_{benz}), 8.72 (dd, J = 7.9 et 1.14 Hz, 1H, H_{benz}), 8.87 (d, J = 4.5 Hz, 1H, H_2), 11.57 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 74.7 (CHOH), 116.0 (CH), 118.9 (C_{arom}), 120.5 (C_{arom}), 124.0 (CH), 124.1 (CH), 124.2 (CH), 125.9 (CH), 127.1 ($2CH_{Ph}$), 127.9 (CH), 128.7 ($2CH_{Ph}$), 131.9 (CH), 136.6 (C_{arom}), 142.2 (C_{arom}), 153.9 (C_{arom}), 154.5 (CH), 155.2 (C_{arom}), 164.4 (C=O). ir (potassium bromide): 3315, 2922, 2853, 1657, 1607, 1567, 1551, 1500, 1455, 1391, 1241, 1152, 1035, 1023, 896, 829, 751, 702, 688, 653 cm^{-1}.

Anal. Calcd. for $C_{19}H_{14}N_2O_2$ (302.33): C, 75.48; H, 4.67; N, 9.27.. Found: C, 75.48; H, 4.81; N, 9.13.

8-Phenylsulfanylbenzo[*c*][2,5]naphthyridin-1(2*H*)-one (**15**).

Metallation of (**11**) according to the procedure B followed by reaction with diphenyl disulfide (9 equiv., 0.501 g) in solution with anhydrous tetrahydrofurane (15 mL) gave after purification by column chromatography (silica gel, eluent ethyl acetate: dichloromethane (1:3)) 0.067g (87%) of (**15**) as a colorless solid, mp > 250°; ^{1}H nmr (DMSO-d_6) : δ 6.63 (d, J = 5.3 Hz, 1H, H_3), 7.34 (t, J = 7.9 Hz, 1H, H_{benz}), 7.43 (d, J = 7.9 Hz, 1H, H_{benz}), 7.67 (m, 6H, H_{Ph} et H_{benz}), 8.64 (m, 2H, H_2 et H_{benz}), 12.00 (s, 1H, NH); ^{13}C nmr (DMSO-d_6) : δ 115.9 (CH), 117.1 (C_{arom}), 119.0 (C_{arom}), 119.0 (CH), 122.7 (CH), 125.2 (CH), 130.6 (CH), 130.7 (C_{arom}), 130.8 ($2CH_{Ph}$), 131.8 (CH), 136.1 ($2CH_{Ph}$), 137.9 (C_{arom}), 152.1 (C_{arom}), 152.1 (CH), 155.9 (C_{arom}), 161.8 (C_{arom}). ir (potassium bromide): 3169, 3015, 2981, 2901, 2854, 1662, 1602, 1541, 1454, 1435, 1373, 1361, 1157, 877, 823, 789, 753, 695, 654, 533, 463 cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}N_2O_2S$ (304.37): C, 71.03; H, 3.97; N, 9.20; S, 10.54.. Found: C, 71.04; H, 4.17; N, 9.42; S, 10.32.

8-Chlorobenzo[*c*][2,5]naphthyridin-1(2*H*)-one (**16**).

Metallation of (**11**) according to the procedure B followed by reaction with hexachloroethane (8 equiv., 0.483 g) in solution with anhydrous THF (5 mL) gave after purification by column chromatography (silica gel, eluent ethyl acetate: dichloromethane (1:1)) 0.049g (85%) of (**16**) as a colorless solid, mp > 250°; ^{1}H nmr (DMSO-d_6): δ 7.37 (m, 2H, H_{benz}), 7.66 (t, J = 8.3 Hz, 1H, H_{benz}), 7.78 (d, J = 5.3 Hz, 1H, H_3), 8.66 (d, 1H, H_{benz}), 8.95 (d, 1H, H_2), 11.93 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 115.7 (C_{arom}), 118.3 (CH), 118.6 (CH), 122.7 (C_{arom}), 125.3 (C_{arom}), 126.2 (C_{arom}), 132.2 (C_{arom}), 138.2 (CH), 145.2 (CH), 153.6 (C_{arom}), 153.7 (CH), 159.4 (CH). ir (potassium bromide): 2922, 2854, 1681, 1605, 1563, 1453, 1375, 1260, 1063, 868, 838, 795, 753, 655, 602, 528, 455 cm^{-1}.

Anal. Calcd. for $C_{12}H_7N_2OCl$ (230.65): C, 62.49; H, 3.06; N, 12.15.. Found: C, 62.55; H, 2.99; N, 12.11.

8-Bis(tri-*n*-butylstannyl)benzo[*c*][2,5]naphthyridin-1(2*H*)-one (**17**).

Metallation of (**11**) according to the procedure B followed by reaction with tributyltin chloride (9 equiv., 0.63 mL) in solution with anhydrous THF (5 mL) gave after purification by column chromatography (silica gel, eluent dichloromethane) 0.107 g (88%), of (**17**) and as a colorless solid, mp 150-151°; ^{1}H nmr (deuteriochloroform): δ 0.78 (m, 18H, Me), 1.08 (m, 24H, CH_2), 1.51 (m, 12H, $SnCH_2$), 7.32 (m, 2H, H_{benz}), 7.48 (t, J = 7.2 Hz, 1H, H_{benz}), 7.69 (td, J_{H3-H2} = 4.5 Hz et J_{H3-Sn} = 19.2 Hz, 1H, H_3), 8.75 (d, J = 7.9 Hz, 1H, H_{benz}), 8.84 (q, J_{H3-H2} = 4.5 Hz et J_{H3-Sn} = 10.2 Hz, 1H, H_2), 11.20 (s, 1H, NH); ^{13}C nmr (deuteriochloroform) : δ 10.7 (CH_2), 12.59 (Me), 12.6 (Me), 16.4 (CH_2), 25.8 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 28.2 (CH_2), 114.8 (CH), 119.8 (C_{arom}), 122.3 (CH), 124.1 (CH), 125.1 (C_{arom}), 129.6 (CH), 130.8 (CH), 135.5 (C_{arom}), 149.7 (C_{arom}), 150.7 (CH), 157.1 (C_{arom}), 163.7 (C_{arom}). ir (potassium bromide): 3177, 3114, 3022, 2922, 1660, 1602, 1540, 1505, 1455, 1363, 1258, 1149, 1073, 1018, 961, 873, 841, 818, 754, 670, 642, 599, 523 cm^{-1}.

Anal. Calcd. for $C_{36}H_{60}N_2OSn_2$, H_2O (792.32): C, 54.47; H, 7.86; N, 3.54. Found: C, 54.62; H, 7.85; N, 3.74.

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