Effective and Variable Functionalization of Pyrazolo[1,5-*a*]pyridines Involving Palladium-Catalyzed Coupling Reactions

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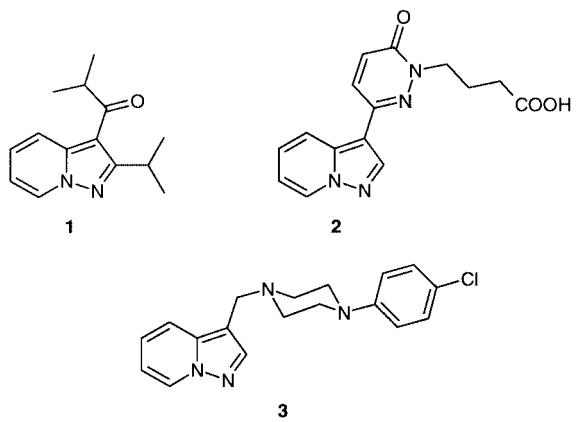
Abstract: Various 7-substituted pyrazolo[1,5-*a*]pyridines were synthesized by palladium-mediated cross-coupling reactions. Starting from the corresponding 7-iodo derivatives, incorporation of phenyl, vinyl, ethynyl, cyano, and amino was accomplished. Pyrazolo[1,5-*a*]pyridine-7-ylzinc iodide could be reacted under Negishi conditions to afford the coupling product **16**.

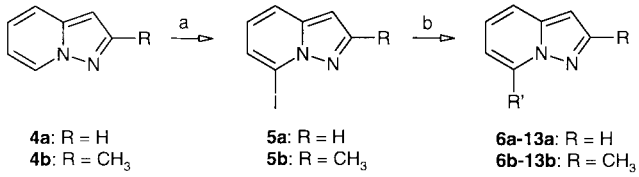
Key words: pyrazolo[1,5-*a*]pyridine, regiodirected metallation, cross coupling, Stille reaction, Suzuki reaction

The indole nucleus plays an important role as a pharmacophoric element in a wide variety of natural and synthetic bioactive compounds.[1] In order to circumvent problems arising from the metabolic instability of indoles, suitable bioisosteres are of considerable interest in the field of medicinal chemistry. The most promising candidate seems to be the pyrazolo[1,5-*a*]pyridine framework representing a stable and easily available 7a-aza analogue. Thus, the antiallergic and cerebroactive agent ibudilast (**1**)[2] and the novel adenosine A_1 receptor antagonist **2**[3] proved interesting pharmacological profiles (Figure). Furthermore, the highly potent dopamine D4 receptor ligand FAUC 113 (**3**) shows superior subtype selectivity when compared to the corresponding indole derivative.[4] As an extension of our structure activity relationship studies on FAUC 113 including the synthesis of precursors for receptor imaging by SPECT, it was necessary to establish a flexible and efficient methodology for the functionalization of the pyrazolo[1,5-*a*]pyridine moiety at position 7.



Figure

Based on a previous communication reporting on a regioselective lithiation and alkylation of pyrazolo[1,5-*a*]pyridine,[5] we envisioned to synthesize the 7-iodo derivatives **5a**, **b**, which should serve as central intermediates for a variety of coupling products (Scheme 1).



(a) *n*-BuLi, ICH_2CH_2I, THF, −78 °C, 3.5 h (82−90%); (b) see, Table

Scheme 1

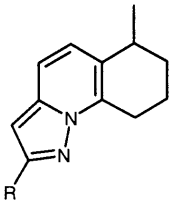
In practice, lithiation of the 8-azaindole (**4a**)[6] and the 2-methyl derivative **4b**[7] by BuLi at dry-ice temperature, followed by treatment with 1,2-diiodoethane afforded the 7-iodopyrazolopyridines **5a** and **5b**, respectively. Following the valuable methodologies elaborated by Stille, Suzuki, Sonogashira, Sakamoto, Hartwig and others, we planned to synthesize 7-alkenyl, alkinyl, aryl, amino, and cyano derivatives.

Employing $Pd(PPh_3)_4$ as a catalyst, Stille reaction[8] of **5a**, **b** with phenyl- or vinyltributylstannane in refluxing toluene gave the coupling products **6a**, **b** and **7a**, **b** in 60−82% yield (Table). Interestingly, dimerization resulting in formation of the cycloaddition products **8a**, **b** was observed when the vinylation was performed in the presence of $PdCl_2(PPh_3)_2$ using NMP as a solvent. Reaction of the iodide **5a**, **b** with 4-fluorophenylboronic acid under typical Suzuki conditions[9] afforded the 7-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridines **9a**, **b**. In addition, Sonogashira reaction[10] of the aryl iodide with trimethylsilylacetylene (TMSCCH) in the presence of CuI and $Pd(PPh_3)_4$ gave the coupling products **10a**, **b**, which were desilylated upon treatment with Bu_4NF to furnish the 7-ethynylpyrazolo[1,5-*a*]pyridines **11a**, **b**. The central intermediates **5a**, **b** also underwent palladium catalyzed cross coupling reaction with CuCN[11] to afford the aryl nitriles **12a**, **b** in excellent yields. Finally, aminations using conditions described by Nishiyama, Buchwald and Hartwig [$Pd_2(dba)_3$, P(*t*-Bu)$_3$ and NaO*t*-Bu][12] gave access to the benzylpiperazines **13a**, **b**.

Table Synthesis of 7-Substituted Pyrazolo[1,5-*a*]pyridines by Palladium–Mediated Cross-Coupling Reactions

Entry	Substrate	Coupling Partner	Conditions	Time	Product	R	R'	Yield (%)
1	**5a**	$C_6H_5SnBu_3$	$Pd(PPh_3)_4$, toluene, reflux	16 h	**6a**	H	$-C_6H_5$	82
2	**5b**	$C_6H_5SnBu_3$	$Pd(PPh_3)_4$, toluene, reflux	16 h	**6b**	CH_3	$-C_6H_5$	80
3	**5a**	H_2C=CHSnBu_3	$Pd(PPh_3)_4$, toluene, reflux	2 h	**7a**	H	-CH=CH_2	62
4	**5b**	H_2C=CHSnBu_3	$Pd(PPh_3)_4$, toluene, reflux	2 h	**7b**	CH_3	-CH=CH_2	60
5	**5a**	H_2C=CHSnBu_3	$PdCl_2(PPh_3)_2$, NMP, 120 °C	16 h	**8a**	H	-X*	83
6	**5b**	H_2C=CHSnBu_3	$PdCl_2(PPh_3)_2$, NMP, 120 °C	16 h	**8b**	CH_3	-X*	76
7	**5a**	4-$FC_6H_5B(OH)_2$	$Pd(PPh_3)_4$, toluene, EtOH, H_2O, $NaHCO_3$, reflux	3 h	**9a**	H	$-C_6H_4$-4-F	85
8	**5b**	4-$FC_6H_5B(OH)_2$	$Pd(PPh_3)_4$, toluene, EtOH, H_2O, $NaHCO_3$, reflux	3 h	**9b**	CH_3	$-C_6H_4$-4-F	80
9	**5a**	TMSCCH	1. $Pd(PPh_3)_4$, CuI, $EtMe_2N$, THF, r.t. 2. Bu_4NF, THF, 0 °C	1 h 0.5 h	**10a** **11a**	H H	-CCTMS -CCH	70 80
10	**5b**	TMSCCH	1. $Pd(PPh_3)_4$, CuI, $EtMe_2N$, THF, r.t. 2. Bu_4NF, THF, 0 °C	1 h 0.5 h	**10b** **11b**	CH_3 CH_3	-CCTMS -CCH	66 78
11	**5a**	CuCN	$Pd_2(dba)_3$, dppf, dioxane, reflux	6 h	**12a**	H	-CN	95
12	**5b**	CuCN	$Pd_2(dba)_3$, dppf, dioxane, reflux	6 h	**12b**	CH_3	-CN	95
13	**5a**	4-Bn-piperazine	$Pd_2(dba)_3$, P(*t*-Bu)$_3$, *t*-BuONa, toluene, 120 °C	16 h	**13a**	H	4-Bn-piperazine	52
14	**5b**	4-Bn-piperazine	$Pd_2(dba)_3$,P(*t*-Bu)$_3$, *t*-BuONa, toluene, 120 °C	16 h	**13b**	CH_3	4-Bn-piperazine	50

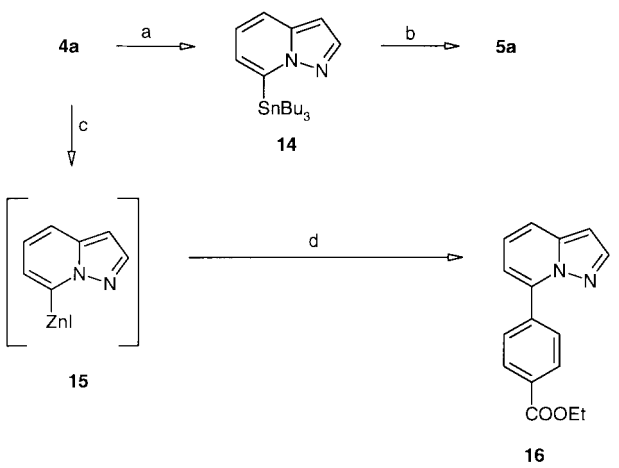
*X =



As a highly versatile alternative to the above described pathway, we envisioned to elaborate the conversion of the pyrazolopyridine **4a** into an activated intermediate capable of acting as a nucleophilic coupling partner. Thus, regiodirected deprotonation and subsequent trapping of the organolithium intermediate by $ClSnBu_3$ furnished the stannane **14**, isolated in 92% yield (Scheme 2). Reaction of **14** with I_2 under oxidative conditions affords the iodide **5a**. This iodination sequence offers an interesting alternative to the above-described methodology since oxidative iododestannylation reactions can be readily applied for the preparation of radio-labelled tracers.[13] Unfortunately, Stille coupling of the organotin derivative **14** using iodobenzene and $PdCl_2(PPh_3)_2$ as a catalyst failed. Obviously, this is due to the moderate transmetallation tendency of stannanes.[14] To circumvent this drawback, we performed the reaction under Negishi conditions[15] when the intermediately formed zincate **15** could be trapped by addition of ethyl 4-iodobenzoate in the presence of $Pd(PPh_3)_4$ resulting in formation of the biaryl **16** in 72% yield.

In conclusion, using palladium-mediated cross-coupling reactions we developed a variable synthetic approach to 7-substituted pyrazolo[1,5-*a*]pyridines, which will probably be of special interest as a bioisosteric replacement of indole derived drugs.

THF, 1,4-dioxane and toluene were distilled from Na immediately before use. All liquid reagents were purified by distillation. Unless otherwise noted, reactions were conducted under anhyd N_2. Evaporations of final product solutions were done under vacuum with a rotary evaporator. Flash chromatography was carried out with silica



(a) BuLi, $ClSnBu_3$, THF, −78 °C, 45 min (92%); (b) I_2, THF, r.t., 2 h (82%); (c) BuLi, ZnI_2, THF, −78 °C to r.t., 1 h; (d) 4-I-Ph-COOEt, $Pd(PPh_3)_4$, THF, reflux, 45 min (72% from **4a**)

Scheme 2

gel (230−400 mesh). Mps: Büchi melting point apparatus, uncorrected. IR spectra: Jasco FT/IR 410 spectrometer. Mass spectra: *FINNIGAN* MAT TSQ 70 instrument. High resolution mass spectrometry: Finnigan MAT 8200. ^{1}H NMR spectra: Bruker AM 360 spectrometer at 360 MHz. ^{13}C NMR spectra: BRUKER AC 250 spectrometer at 250 MHz. Spectra were measured in $CDCl_3$ using TMS as internal standard. Element analyses were performed by Beetz Microanalysis Laboratory and by the Organic Chemistry Department of the Friedrich-Alexander University, Erlangen-Nürnberg.

7-Iodopyrazolo[1,5-*a*]pyridine (5a)

A. A solution of BuLi (8.0 mL, 1.6 M in hexane; 12.8 mmol) was added dropwise to a solution of **4a** (1.18 g, 10 mmol) in THF (50 mL) at −78 °C. After stirring for 30 min, the mixture was treated with 1,2-diiodoethane (3.38 g, 12 mmol) in THF (50 mL) and stirred for another 3 h at −78 °C. The mixture was treated with sat. $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) to give 2.2 g (90%) of **5a** as a yellow solid, mp: 60 °C (Scheme 1).

B. A solution of **14** (120 mg, 0.29 mmol) and I_2 (76 mg, 0.30 mmol) in THF (7 mL) was stirred at r.t. for 2 h. After evaporation of the solvent, the residue was purified by flash chromatography (hexane/EtOAc, 8:2) to give 59 mg (82%) of **5a** (Scheme 2).

IR (film): ν = 3073, 1618, 1492, 1289, 1200, 781 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.76 (d, 1H, *J* = 2.1 Hz, H-3), 6.85 (dd, 1H, *J* = 8.9, 7.1 Hz, H-5), 7.33 (m, 1H, H-4 or H-6), 7.56 (br d, 1H, *J* = 8.9 Hz, H-4 or H-6), 8.05 (d, 1H, *J* = 2.1 Hz, H-2).

EIMS: *m/z* = 244 (M^+).

Anal. Calcd. for $C_7H_5N_2I$ (244.0): C, 34.45; H, 2.07; N, 11.48. Found: C, 34.40; H, 2.18, N, 11.16.

7-Iodo-2-methylpyrazolo[1,5-*a*]pyridine (5b)

Compound **5b** was prepared from **4b** (1.32 g, 10 mmol) using procedure A described for **5a** to give 2.19 g (80%) as a yellow oil.

IR (film): ν = 3072, 2923, 1615, 1490, 1289, 781 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.54 (s, 3H, CH_3), 6.52 (s, 1H, H-3), 6.78 (dd, 1H, *J* = 8.5, 7.1 Hz, H-5), 7.23 (m, 1H, H-4 or H-6), 7.41 (br d, 1H, *J* = 8.5 Hz, H-4 or H-6).

EIMS: *m/z* = 258 (M^+).

Anal. Calcd. for $C_8H_7IN_2$ (258.1): C, 37.23; H, 2.73; N, 10.86. Found: C, 37.27; H, 2.78, N, 10.76.

7-Phenylpyrazolo[1,5-*a*]pyridine (6a)

A solution of **5a** (244 mg, 1.0 mmol), phenyltributyltin (459 mg, 1.25 mmol) and $Pd(PPh_3)_4$ (27 mg, 5 mol%) in toluene (10 mL) was refluxed for 2 h. The mixture was cooled, treated with Bu_4NF (2 mL, 1M in THF), and stirred for 2 h at r.t. After addition of EtOAc (10 mL), the mixture was washed with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) to give 90 mg (82%) of **6a** as a colorless oil.

IR (film): ν = 3059, 3033, 1631, 1490, 1306, 1196, 790 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 6.61 (d, 1H, *J* = 2.3 Hz, H-3), 6.81 (dd, 1H, *J* = 6.4, 1.4 Hz, H-5), 7.19 (m, 1H, H-6), 7.47−7.54 (m, 5H, Ph), 7.89 (d, 1H, *J* = 2.3 Hz, H-2), 7.98 (d, 1H, *J* = 2.3 Hz, H-2).

EIMS: *m/z* = 194 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_2$ (194.2): C, 80.38; H, 5.19; N, 14.34. Found: C, 80.38; H, 5.11, N, 14.42.

2-Methyl-7-phenylpyrazolo[1,5-*a*]pyridine (6b)

Compound **6b** was prepared from **5b** (258 mg, 1.0 mmol) using the procedure described for **6a** to give 166 mg (80%) as a colorless oil.

IR (film): ν = 3055, 1633, 1490, 1299, 1172, 791 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.48 (s, 3H, CH_3), 6.36 (s, 1H, H-3), 6.71 (dd, 1H, *J* = 7.1, 1.4 Hz, H-5), 7.14 (m, 1H, H-6), 7.39−7.52 (m, 5H, Ph), 7.93 (d, 1H, *J* = 2.3 Hz, H-4).

EIMS: *m/z* = 208 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_2$ (208.3): C, 80.73; H, 5.81; N, 13.46. Found: C, 81.10; H, 5.85; N, 13.60.

7-Vinylpyrazolo[1,5-*a*]pyridine (7a)

A solution of **5a** (244 mg, 1.0 mmol), vinyltributyltin (334 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (27 mg, 5mol%) in toluene (10 mL) was refluxed for 2 h. The mixture was cooled, treated with Bu_4NF (2 mL, 1M in THF) and stirred for 2 h at r.t. After addition of EtOAc (10 mL), the mixture was washed with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to give 90 mg (62%) of **7a** as a colorless oil.

IR (film): ν = 3095, 2925, 1631, 1453, 1308, 788 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.67 (dd, 1H, *J* = 11.3, 1.4 Hz, CH*CH*$_2$), 6.33 (dd, 1H, *J* = 17.5, 1.4 Hz, CH*CH*$_2$), 6.57 (d, 1H, *J* = 2.1 Hz, H-3), 6.95 (br d, 1H, *J* = 6.9 Hz, H-4), 7.20 (dd, 1H, *J* = 8.5, 6.9 Hz, H-5), 7.49 (m, 2H, H-6 and *CH*CH$_2$), 7.99 (d, 1H, *J* = 2.1 Hz, H-2).

EIMS: *m/z* = 144 (M^+).

Anal. Calcd. for $C_9H_8N_2$ (144.1): C, 74.98; H, 5.59, N, 19.43. Found: C, 74.89; H, 5.54; N, 19.48.

2-Methyl-7-vinylpyrazolo[1,5-*a*]pyridine (7b)

7b was prepared from **5b** (258 mg, 1.0 mmol) using the procedure described for **7a** to give 88 mg (60%) as a colorless oil.

IR (film): ν = 2926, 1633, 1483, 1301, 788 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.52 (s, 3H, CH_3), 5.64 (dd, 1H, *J* = 11.7, 1.4 Hz, CH*CH*$_2$), 6.28 (dd, 1H, *J* = 17.5, 1.4 Hz, CH*CH*$_2$),

6.33 (s, 1H, H-3), 6.95 (br d, 1H, *J* = 6.9 Hz, H-5), 7.20 (m, 1H, H-6), 7.49 (m, 2H, H-4 and $CHCH_2$).

EIMS: *m/z* = 158 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_2$ (158.1): C, 75.92; H, 6.37, N, 17.71. Found: C, 75.93; H, 6.31; N, 17.83.

6-Pyrazolo[1,5-*a*]pyridin-7-yl-6,7,8,9-tetrahydropyrazol[1,5-*a*]quinoline (8a)

A solution of **5a** (244 mg, 1.0 mmol), vinyltributyltin (417 mg, 1.25 mmol) and $Pd(PPh_3)_2Cl_2$ (35 mg, 5 mol%) in NMP (2.5 mL) was heated in a sealed tube for 16 h at 120 °C. The mixture was cooled, treated with Bu_4NF (2 mL, 1M in THF) and stirred for 2 h at r.t. After addition of EtOAc (10 mL), the mixture was washed with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) to give 120 mg (83%) of **8a** as a yellow oil.

IR (film): ν = 2955, 1636, 1446, 1306, 789 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 3.07−3.17 (m, 1H, CH_2-8), 3.39−3.47 (m, 2H, CH_2-7), 5.27 (m, 2H, CH_2-9), 6.14 (m, 1H, CH-6), 6.57 (d, 1H, *J* = 2.1 Hz, H-3), 6.62 (d, 1H, *J* = 2.1 Hz, H-3'), 6.82 (d, 1H, *J* = 8.9 Hz, H-5), 6.97−7.26 (m, 2H, H-5' and H-6'), 7.41 (d, 1H, *J* = 9.1 Hz, H-4), 7.48 (dd, 1H, *J* = 8.9, 1.1 Hz, H-4'), 8.02 (d, 1H, *J* = 2.1 Hz, H-2), 8.06 (d, 1H, *J* = 2.5 Hz, H-2').

^{13}C NMR (90 MHz, $CDCl_3$): δ = 29.2 (C-8), 29.3 (C-7), 38.0 (C-9), 97.2 (C-3), 97.3 (C-3'), 112.4 (C-6), 115.5 (C-5), 115.9 (C-6'), 119.2 (C-4'), 122.2 (C-4), 126.5 (C-5'), 138.3 (C-11), 139.4 (C-10 and C-13), 140.6 (C-8'), 141.2 (C-2 and C-7'), 144.4 (C-2').

EIMS: *m/z* = 288 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_4$ (288.1): C, 74.98; H, 5.59, N, 19.43. Found: C, 74.67; H, 5.77; N, 19.26.

2-Methyl-6-(2-methylpyrazolo[1,5-*a*]pyridin-7-yl-6,7,8,9-tetrahydropyrazol[1,5-*a*]quinoline (8b)

Compound **8b** was prepared from **5b** (258 mg, 1.0 mmol) using the procedure described for **8a** to give 120 mg (76%) as a yellow oil.

IR (film): ν = 2927, 1637, 1489, 1295, 788 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.55 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.04−3.12 (m, 1H, CH_2-8), 3.33−3.40 (m, 2H, CH_2-7), 5.20 (m, 2H, CH_2-9), 6.01 (m, 1H, CH-6), 6.32 (s, 1H, H-3), 6.36 (s, 1H, H-3'), 6.75 (d, 1H, *J* = 9.1 Hz, H-5), 6.87 (dd, 1H, *J* = 1.7, 7.1 Hz, H-6'), 7.26−7.34 (m, 3H, H-4' and H-5).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 14.1 (CH_3), 14.2 (CH_3), 25.0 (C-8), 25.5 (C-7), 37.8 (C-9), 96.6 (C-3 and C-3'), 111.4 (C-6), 114.5 (C-5), 115.1 (C-6'), 122.7 (C-4'), 122.9 (C-4), 126.2 (C-5'), 137.8 (C-11), 138.0 (C-10), 140.6 (C-8'), 141.7 (C-13), 143.8 (C-7'), 151.0 (C-2), 151.1 (C-2').

EIMS: *m/z* = 316 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_4$ (316.2): C, 75.92; H, 6.37, N, 17.71. Found: C, 75.62; H, 6.43; N, 17,58.

7-(4-Fluorophenyl)pyrazolo[1,5-*a*]pyridine (9a)

A solution of **5a** (244 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (54 mg, 0.1 mmol) in toluene (10mL) was stirred for 30 min at r.t. After addition of 4-fluorophenylboronic acid (210 mg, 1.5 mmol) in EtOH (30 mL), the mixture was treated with sat. $NaHCO_3$ (15 mL), refluxed for 3 h, cooled to r.t., and poured into sat. NaCl. The aqueous layer was separated and washed with EtOAc (30 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) to give 180 mg (85%) of **9a** as a colorless oil.

IR (film): ν = 3079, 1631, 1503, 1307, 1223, 786 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 6.61 (d, 1H, *J* = 2.2 Hz, H-3), 6.79 (dd, 1H, *J* = 7.1, 1.2 Hz, H-6), 7.16−7.26 (m, 5H, H-5 and Ph), 7.56 (dd, 1H, *J* = 8.9, 1.2 Hz, H-4), 7.98 (d, 1H, *J* = 2.2 Hz, H-2).

EIMS: *m/z* = 212 (M^+).

Anal. Calcd. for $C_{13}H_9FN_2$ (212.2): C, 73.57; H, 4.27; N, 13.20. Found: C, 73.69; H, 4.35, N, 12.97.

7-(4-Fluorophenyl)-2-methylpyrazolo[1,5-*a*]pyridine (9b)

Compound **9b** was prepared from **5b** (258 mg, 1.0 mmol) using the procedure described for **9a** to give 181 mg (80%) as a colorless oil.

IR (film): ν = 2925, 1630, 1503, 1307, 1233, 786 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.48 (s, 3H, CH_3), 6.37 (s, 1H, H-3), 6.68 (dd, 1H, *J* = 7.1, 1.3 Hz, H-6), 7.11 (dd, 1H, *J* = 8.8, 7.1 Hz, H-5), 7.20−7.26 (m, 2H, Ph), 7.41 (dd, 1H, *J* = 8.8, 1.3 Hz, H-4), 7.91−7.95 (m, 2H, Ph).

EIMS: *m/z* = 226 (M^+).

Anal. Calcd. for $C_{14}H_{11}FN_2$ (226.1): C, 74.31 4.90, N, 12.39. Found: C, 74.05; H, 4.88, N, 12.48.

7-(1-Trimethylsilyl)ethynylpyrazolo[1,5-*a*]pyridine (10a)

Ethynyltrimethylsilane (118 mg, 1.2 mmol) was added to a stirred mixture of **5a** (244 mg, 1.0 mmol), CuI (13 mg, 7 mol%), $Pd(PPh_3)_4$ (27 mg, 5 mol%) and ethyldimethylamine (219 mg, 3.0 mmol) in THF (10 mL). Stirring was continued for 1 h at r.t., and the solvent was evaporated under reduced pressure. After addition of hexane (15 mL), the mixture was filtered through a layer of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 95:5) to give 150 mg (70%) of **10a** as a colorless oil.

IR (film): ν = 3077, 2960, 2161, 1619, 1517, 1307, 787 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 0.34 [s, 9H, $Si(CH_3)_3$], 6.59 (d, 1H, *J* = 2.3 Hz, H-3), 7.04−7.26 (m, 2H, H-5 and H-6), 7.55 (br d, 1H, *J* = 8.9 Hz, H-4), 8.05 (d, 1H, *J* = 2.3 Hz, H-2).

EIMS: *m/z* = 214 (M^+).

2-Methyl-7-(1-trimethylsilyl)ethynylpyrazolo[1,5-*a*]pyridine (10b)

Compound **10b** was prepared from **5b** (258 mg, 1.0 mmol) using the procedure described for **10a** to give 151 mg (66%) as a colorless oil.

IR (film): ν = 3077, 2960, 2161m, 1619, 1517, 1307, 787 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 0.34 [s, 9H, $Si(CH_3)_3$], 2.53 (s, 3H, CH_3), 6.34 (s, 1H, H-3), 6.94−7.26 (m, 2H, H-5 and H-6), 7.41 (br d, 1H, *J* = 8.9 Hz, H-4).

EIMS: *m/z* = 228 (M^+).

7-Ethynylpyrazolo[1,5-*a*]pyridine (11a)

A solution of **10a** (107 mg, 0.5 mmol) in THF (5 mL) was treated with Bu_4NF (1 mL, 1 M in THF, 1.0 mmol) and stirred for 30 min at r.t. After addition of aq $NaHCO_3$ (5%, 10 mL), the mixture was extracted with Et_2O (3 x 10 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) yielding 55 mg (80%) of **11a** as a colorless oil.

IR (film): ν = 3287, 3202, 2109, 1620, 1517, 1309, 788 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 3.79 (s, 1H, ArC*CH*), 6.62 (d, 1H, *J* = 2.4 Hz, H-3), 7.05−7.10 (m, 2H, H-5 and H-6), 7.45 (br d, 1H, *J* = 9.0 Hz, H-4), 8.05 (d, 1H, *J* = 2.4 Hz, H-2).

EIMS: *m/z* = 142 (M^+).

Anal. Calcd. for $C_9H_6N_2$ (142.1): C, 76.04; H, 4.25; N, 19.71. Found: C, 76.35; H, 4.01, N, 19.55.

7-Ethynyl-2-methylpyrazolo[1,5-*a*]pyridine (11b)
Compound **11b** was prepared from **10b** (129 mg, 0.5 mmol) using the procedure described for **11a** to give 60 mg (78%) as a colorless oil.

IR (film): ν = 3289, 3198, 2110, 1621, 1525, 1301, 789 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.55 (s, 3H, CH_3), 3.77 (s, 1H, ArC*CH*), 6.38 (s, 1H, H-3), 6.98−7.04 (m, 2H, H-5 and H-6), 7.37 (br d, 1H, *J* = 9.0 Hz, H-4).

EIMS: *m/z* = 156 (M^+).

Anal. Calcd. for $C_{10}H_8N_2$ (156.1): C, 76.89; H, 5.17; N, 17.94. Found: C, 76.83; H, 5.09, N, 17.94.

7-Cyanopyrazolo[1,5-*a*]pyridine (12a)
A mixture of **5a** (244 mg, 1.0 mmol), CuCN (358 mg, 4.0 mmol), $Pd_2(dba)_3$ (37 mg, 4 mol%) and diphenylphosphinoferrocene (dppf, 89 mg, 0.16 mmol) in anhyd 1,4-dioxane (5 mL) was refluxed for 6 h. The mixture was cooled to r.t., diluted with EtOAc (10 mL), and filtered through a Celite pad. The filtrate was washed with aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) yielding 136 mg (95%) of **12a** as a pale yellow solid.

IR (film): ν = 3147, 3070, 3028, 2231, 1625, 1457, 1315, 797 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 6.73 (d, 1H, *J* = 2.5 Hz, H-3), 7.15 (dd, 1H, *J* = 9.0, 7.1 Hz, H-5), 7.16 (br d, 1H, *J* = 7.1 Hz, H-6), 7.82 (br d, 1H, *J* = 9.0 Hz, H-4), 8.12 (d, 1H, *J* = 2.5 Hz, H-2).

EIMS: *m/z* = 143 (M^+).

HRMS: *m/z* calc for $C_8H_5N_3$ (M^+): 143.0483. Found: 143.0484.

7-Cyano-2-methylpyrazolo[1,5-*a*]pyridine (12b)
Compound **12b** was prepared from **5b** (129 mg, 0.5 mmol) using the procedure described for **12a** to give 149 mg (95%) as a pale yellow solid.

IR (film): ν = 3070, 2232, 1624, 1479, 1300, 802 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.55 (s, 3H, CH_3), 6.48 (s, 1H, H-3), 7.08 (dd, 1H, *J* = 8.9, 7.1 Hz, H-5), 7.23 (br d, 1H, *J* = 7.1 Hz, H-6), 7.67 (br d, 1H, *J* = 8.9 Hz, H-4).

EIMS: *m/z* = 157 (M^+).

HRMS: *m/z* calc for $C_9H_7N_3$ (M^+): 157.0640. Found: 157.0643.

7-(4-Benzylpiperazin-1-yl)pyrazolo[1,5-*a*]pyridine (13a)
A mixture of **5a** (244 mg, 1.0 mmol), *N*-benzylpiperazine (246 mg, 1.4 mmol), *t*-BuONa (134 mg, 1.4 mmol), $Pd_2(dba)_3$ (46 mg, 5 mol%) and P(*t*-Bu)$_3$ (8 mg, 4 mol%) in toluene (5 mL) was heated in a sealed tube at 120 °C for 16 h. The mixture cooled to r.t., diluted with Et_2O (10 mL), and filtered through a Celite pad. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc, 1:1) yielding 152 mg (52%) of **13a** as a yellow oil.

IR (film): ν = 3084, 2822, 1625, 1520, 1453, 1295, 779 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.77 (m, 4H, N*CH*$_2$CH$_2$), 3.45 (m, 4H, CH$_2$*CH*$_2$N), 3.63 (s, 2H, Ph*CH*$_2$N), 6.17 (dd, 1H, *J* = 7.2, 1.0 Hz, H-6), 6.50 (d, 1H, *J* = 2.2 Hz, H-3), 7.08 (dd, 1H, *J* = 9.0, 7.2 Hz, H-5), 7.22−7.39 (m, 6H, H-4 and Ph), 7.97 (d, 1H, *J* = 2.2 Hz, H-2).

EIMS: *m/z* = 292 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_4 \cdot {}^1/_4\ H_2O$: C, 72.82; H, 6.96; N, 18.87. Found: C, 72.65; H, 6.75, N, 19.01.

7-(4-Benzylpiperazin-1-yl)-2-methylpyrazolo[1,5-*a*]pyridine (13b)
Compound **13b** was prepared from **5b** (129 mg, 0.5 mmol) using the procedure described for **13a** to give 153 mg (50%) as yellow oil.

IR (film): ν = 3026, 2930, 2820, 1627, 1529, 1301, 779 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.49 (s, 3H, CH_3), 2.76 (m, 4H, N*CH*$_2$CH$_2$), 3.45 (m, 4H, CH$_2$*CH*$_2$N), 3.63 (s, 2H, Ph*CH*$_2$N), 6.07 (dd, 1H, *J* = 7.2, 1.0 Hz, H-6), 6.25 (d, 1H, *J* = 2.2 Hz, H-3), 7.01 (dd, 1H, *J* = 8.9, 7.2 Hz, H-5), 7.09 (br d, 1H, *J* = 8.9 Hz, H-4), 7.25−7.39 (m, 5H, Ph).

EIMS: *m/z* = 306 (M^+).

Anal. Calcd. for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24; N, 18.28. Found: C, 74.20; H, 7.40, N, 18.19.

7-(Tributylstannyl)pyrazolo[1,5-*a*]pyridine (14)
To a solution of **4a** (200 mg, 1.70 mmol) in THF (8 mL) was added BuLi (1.1 mL, 1,6 M in *n*-hexane, 1,76 mmol) at −78 °C. After stirring for 30 min, a solution of tributyltin chloride (0.46 mL, 1.7 mmol) in THF (1 mL) was added. The mixture was stirred for another 15 min, treated with sat. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 9:1) to give 635 mg (92%) of **15** as an colorless liquid.

IR (film): ν = 2955, 2923, 2852, 1613, 1500, 1300, 779 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 0.87 (t, 9H, *J* = 7.0 Hz, 3 × CH$_2$*CH*$_3$), 1.22 (t, 6H, *J* = 8.0 Hz, Sn*CH*$_2$CH$_2$), 1.33 (tq, 6H, *J* = 7.0, 7.0 Hz, CH$_2$*CH*$_2$CH$_3$), 1.50−1.62 (m, 6H, CH$_2$*CH*$_2$CH$_2$), 6.43 (d, 1H, *J* = 2.0 Hz, H-3), 6.76 (br d, 1H, *J* = 6.5 Hz, H-4 or H-6), 6.99 (dd, 1H, *J* = 8.5, 6.5 Hz, H-5), 7.45 (br d, 1H, *J* = 8.5 Hz, H-4 or H-6), 7.87 (d, 1H, *J* = 2.0 Hz, H-2).

EIMS: *m/z* = 407 (M^+).

Anal. Calcd. for $C_{19}H_{32}N_2Sn$ (408.2): C, 55.86; H, 7.90; N, 6.86. Found: C, 56.15; H, 7.98, N, 6.86.

Pyrazolo[1,5-*a*]pyridin-7-yl-benzoic Acid Ethyl Ester (16)
To a solution of **4a** (130 mg, 1.10 mmol) in THF (5 mL) was added BuLi (0.7 mL, 1.6 M in hexane, 1.12 mmol) at −78 °C. After stirring for 15 min, a solution of ZnI_2 (370 mg, 1.15 mmol) in THF (5 mL) was added and stirring was continued while warming up to r.t. 4-Iodobenzoic acid ethyl Ester (336 mg, 1.20 mmol) and $Pd(PPh_3)_4$ (60 mg, 0.11 mmol) were added and the mixture was refluxed for 45 min. After cooling to r.t., the solution was diluted with Et_2O (10 mL) and washed with aq $NaHCO_3$ (15 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/ hexane/EtOAc, 3:3:1) yielding 211 mg (72%) of **16** as a colorless oil.

IR (film): ν = 2980, 1715, 1629, 1609, 1275, 1105, 770 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.42 (t, 3H, *J* = 7.2 Hz, CH_3), 4.42 (q, 2H, *J* = 7.2 Hz, CH_2), 6.63 (d, 1H, *J* = 2.4 Hz, H-3), 6.79 (dd, 1H, *J* = 7.0, 1.4 Hz, H-6), 7.20 (dd, 1H, *J* = 8.9, 7.0 Hz, H-5), 7.59 (dd, 1H, *J* = 8.9, 1.4 Hz, H-4), 7.97−8.01 (m, 3H, H-2 and Ph), 8.17−8.21 (m, 2H, Ph).

EIMS: *m/z* = 266 (M^+).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.1): C, 72.15; H, 5.30; N, 10.52. Found: C, 71.89; H, 5.38, N, 10.68.

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