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SYNTHETIC STUDIES CONNECTED WITH THE PREPARATION OF *N*-[3-(3-CYANOPYRAZOLO[1,5-*a*]PYRIMIDIN-5-YL)PHENYL]-*N*-ETHYLACETAMIDE, A ZALEPLON REGIOISOMER

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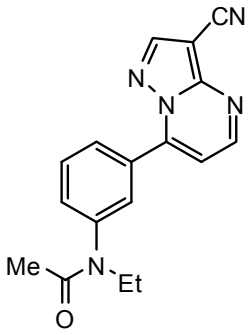
Dedicated to Prof. Akira Suzuki on the occasion of his 80th birthday in recognition of his outstanding contributions to the science of chemistry, which also make this work possible.

Abstract – *N*-[3-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-5-yl)phenyl]-*N*-ethyl-acetamide, a principal impurity of zaleplon, is prepared by Suzuki-Miyaura cross coupling reaction of the corresponding boronic acid and/or boronates with 5-chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**7**). Various methods of preparation of both components are described, as well as approaches based on the final modification of the 5-(3-aminophenyl)-pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile moiety prepared by Suzuki-Miyaura cross coupling. All the prepared compounds were unambiguouesly identified by NMR techniques. Spectral characteristics (IR, UV, MS) of these compounds are also given.

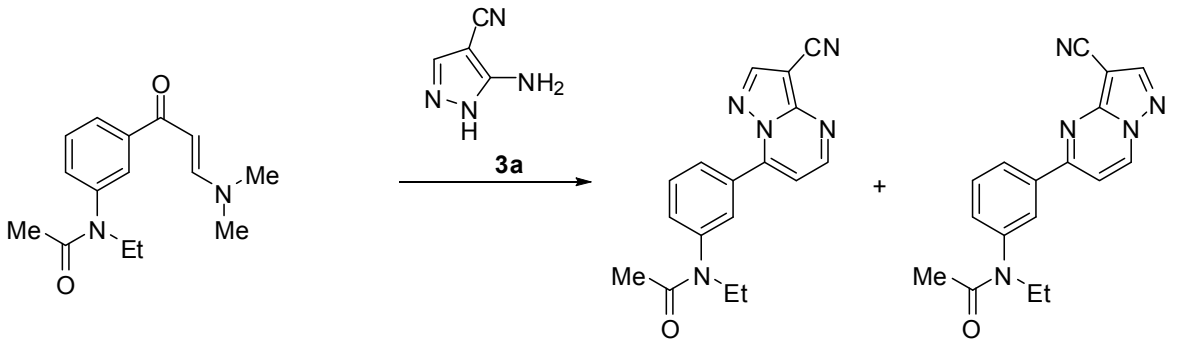
INTRODUCTION

Zaleplon (**1**) is a nonbenzodiazepine hypnotic belonging with zolpidem and zopiclon to the so called Z-hypnotic class.[1,2] Clinical results have shown that zaleplon is efficacious in the treatment of insomnia where difficulty in falling asleep is the primary problem. Zaleplon unlike many other hypnotic drugs does not interfere with sleep architecture and can be administered for up to 5 weeks without the risk of dependence or rebound insomnia upon discontinuation.[3]



zaleplon (1)

Most of the described methods[4-7] of preparation of zaleplon are based on reaction of *N*-[3-(3-dimethyl-amino-acryloyl)-phenyl]-*N*-ethyl-acetamide (**2**) with 5-amino-1*H*-pyrazol-4-carbonitrile (**3a**) under acidic conditions. The original patent[4] describes the reaction in anhydrous acetic acid, but under these conditions considerable amounts of the corresponding isomer **4** is formed. Much better results are achieved using aqueous acetic[5] or formic[6] acids. Probably the best results regarding purity and yields are obtained when the reaction is done in aqueous alcohols in the presence of hydrochloric acid[7,8] (Scheme 1).



2 **1** **4**

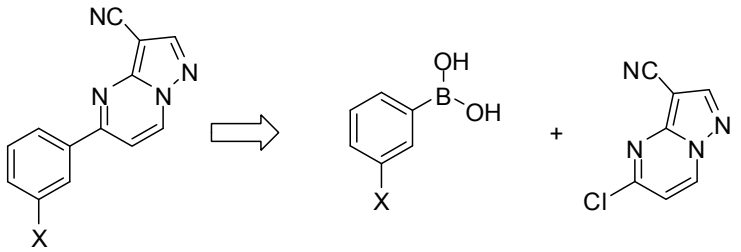
Scheme 1

One of the principal parts of documentation of any active pharmaceutical ingredient (API) is description of impurities and/or degradation products which can be present. Identified impurities should be included in the specification when they are present at a level higher than the identification threshold, which is usually 0.10 %. These impurities must be not only identified but also either isolated or independently synthesized for determination of their response factor for analytical determination.

Several impurities of zaleplon, including zaleplon regioisomer **4**, have recently been isolated and identified.[9] To the best of our knowledge, no report on its synthesis has been published and therefore we decided to synthetize this impurity as a standard.

RESULTS AND DISCUSSION

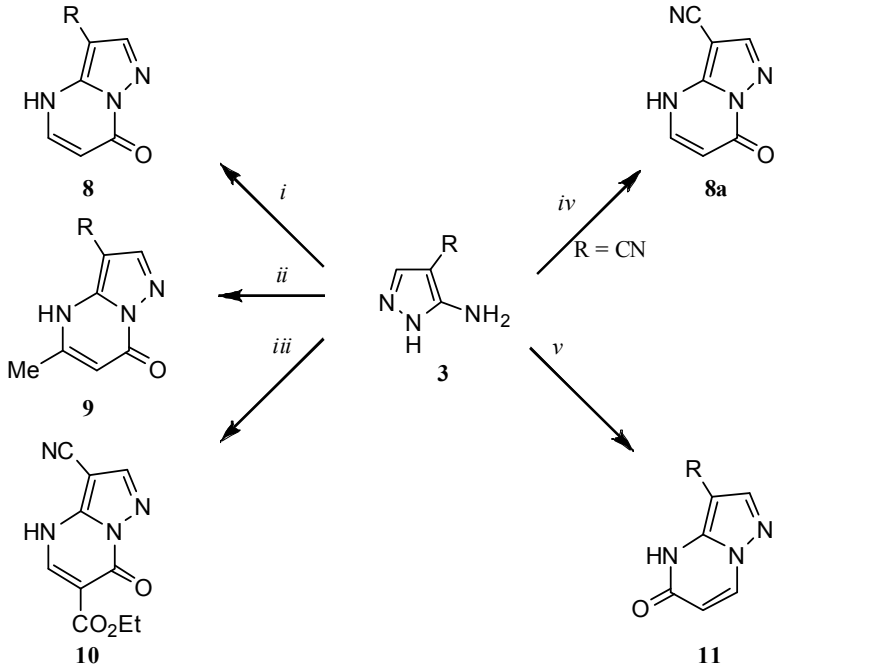
Our retrosynthetic analysis is shown in Scheme 2. Our approach is based on Suzuki-Miyaura cross-coupling reaction of boronic acids **6**, containing suitable substituent X, with 5-chloropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**7**), which should be easily obtained from the corresponding oxo derivative.



5 **6** **7**

Scheme 2

It is well documented[10-16] that reaction of 5-amino-1*H*-pyrazoles **3** with formylacetates, β-ketoesters or their equivalents, e.g., ethoxymethylenemalonates, provides the corresponding pyrazolo[1,5-*a*]-pyrimidin-7(4*H*)-ones **8**, **9**, and **10**, respectively. Similarly, reaction of 5-amino-1*H*-pyrazol-4-carbonitrile

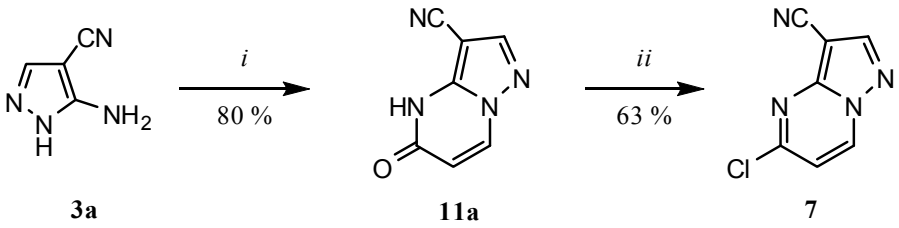


i, O=CHCH$_2$CO$_2$Et or Me2NCH=CHCO$_2$Et; *ii*, MeCOCH$_2$CO$_2$Et; *iii*, MeOCH=C(CO$_2$Et)$_2$, *iv*, HC≡CCO$_2$Et; *v*, EtOCH=CHCO$_2$Et, Cs$_2$CO$_3$

Scheme 3

(**3a**) with ethyl propiolate is reported[15,16] to provide 7-oxo derivative **8a**. However, similar reports on pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-ones are really scarce. Recently Gavrin *et al.*[14] reported that 5-amino-1*H*-pyrazoles **3** treated with ethyl 3-ethoxyacrylate in the presence of cesium carbonate yielded exclusively the corresponding 5-oxo derivatives **11** (Scheme 3).

Our synthesis of **7** started from commercially available 5-amino-1*H*-pyrazol-4-carbonitrile (**3a**), which treated with ethyl 3-ethoxyacrylate in the presence of cesium carbonate yielded the 5-oxo derivative **11a**. Its structure was fully proven by NMR techniques and the data was in accordance with data described for similar compounds.[17] Treatment of compound **11a** with phosphorus oxychloride provided intermediate **7** in good yields (Scheme 4).



3a **11a** **7**

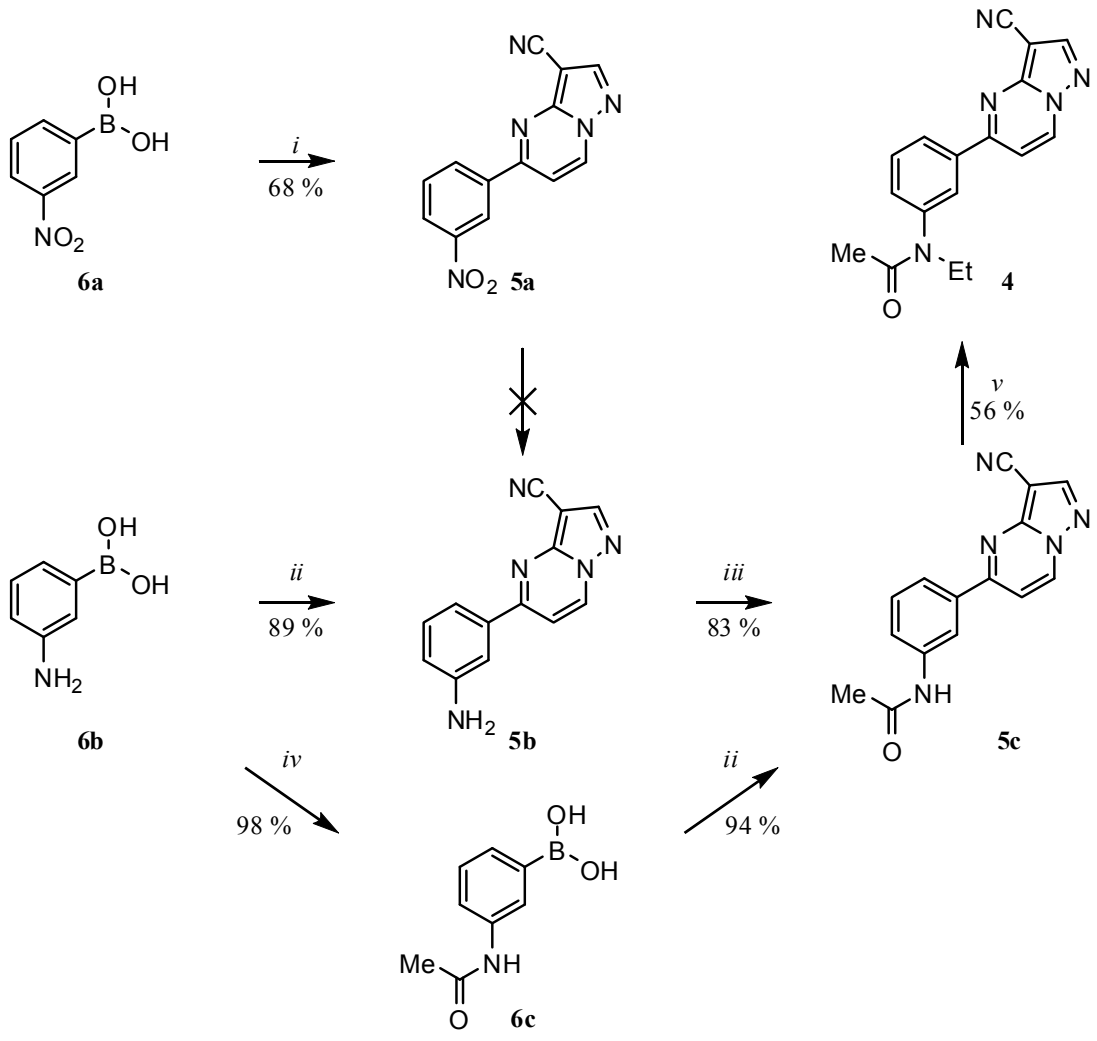
i, $MeOCH{=}CHCO_2Et$, Cs_2CO_3; *ii,* $POCl_3$

Scheme 4

Comercially available boronic acids **6a** and **6b** were chosen as the suitable intermediates. 3-Nitrophenylboronic acid (**6a**) treated with **7** using $(Ph_3P)_4Pd$, Na_2CO_3 in DMF at 100 °C, provided good yield of the corresponding coupling product **5a**. Due to the limited solubility of this compound even in DMF and DMSO, we failed to reduce the compound to the corresponding amino derivative **5b**. In the literature, there are several examples of successful Suzuki-Miyaura cross-coupling reactions using 3-aminophenylboronic acid (**6b**). When we applied the standard conditions used by Jagusch *et al.,*[18] a complex mixture not containing the required product (LCMS) was obtained. There are several reports on successful application of aqueous Suzuki-Miyaura cross-coupling reactions with 3-aminophenylboronic acid (**6b**) using water-soluble ligands, for example sodium 2-(dicyclohexylphosphino)--2',6'-dimethoxybiphenyl-3'-sulfonate[19] or trisodium triphenylphosphine- -3,3‘,3“-trisulphonate (TPPTS).[20,21] We have applied the latter conditions and obtained good yields of **5b** as the single product.

This compound was again insoluble in suitable solvents and attempts to acetylate it by heating in a mixture of acetic anhydride and acetic acid provided a complex mixture containing only traces of acetyl derivative **5c**. However, stirring a suspension of **5b** in acetic anhydride provided moderate yields of the desired product.

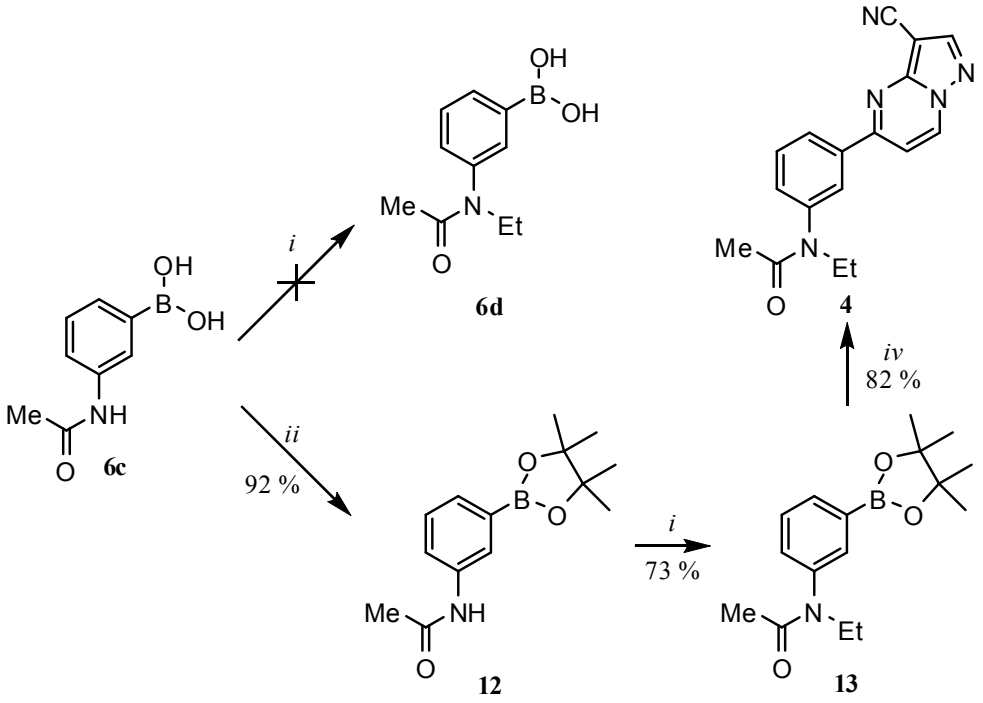
3-Aminophenylboronic acid (**6b**) was acetylated with acetic anhydride to the corresponding *N*-acetyl derivative **6c**. Its Suzuki-Miyaura cross-coupling reaction with **7** in aqueous acetonitrile provided compound **5c**. Its alkylation with iodoethane after generating the corresponding sodium salt *in situ* by sodium hydride in DMF led to the zaleplon regioisomer **4** (Scheme 5).



i, **7**, $(Ph_3P)_4Pd$, Na_2CO_3, DMF, 100 °C; *ii,* **7**, $Pd(OAc)_2$, TPPTS, Cs_2CO_3, aq. MeCN; *iii*, Ac_2O, rt ; *iv*, Ac_2O, AcOH, rt; *v*, (a) NaH, DMF, (b) EtI

Scheme 5

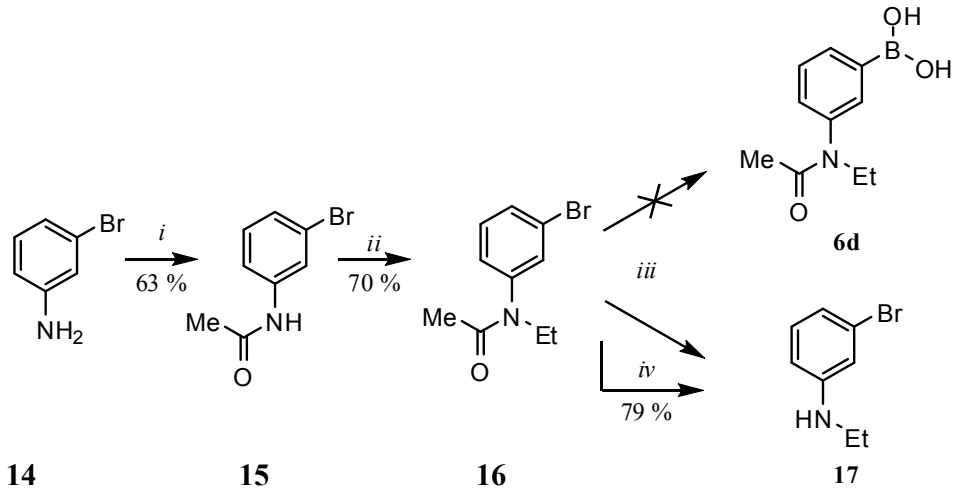
Attempts to prepare *N*-ethyl derivative **6d** by treating **6c** consecutivelly with excess of sodium hydride followed by iodoethane failed. However, when a suspension of **6c** in dichloromethane was treated with anhydrous pinacol at ambient temperature, the corresponding pinacol ester **12** was quantitatively formed and its alkylation using NaH/EtI provided compound **13**. Suzuki-Miyaura cross-coupling reaction of **13** with **7** catalyzed with $(Ph_3P)_4Pd$ then provided good yields of the zaleplon regioisomer **4** (Scheme 6).



i, (a) NaH, DMF, (b) EtI, rt; *ii,* $Me_2C(OH)CMe_2(OH)$, CH_2Cl_2, rt; *iv,* $(Ph_3P)_4Pd$, Na_2CO_3, toluene, 100 °C

Scheme 6

In order to develop an alternative way to either boronic acid **6d** or its pinacol ester **13**, we started with 3-bromoaniline **14**, which was acetylated with acetic anhydride and the corresponding anilide **15** was then alkylated with iodoethane to provide compound **16**. Our attempts of transformation of this compound to **6d** using one equivalent of butyllithium led nearly exclusively to deacetylation giving **17**, while using two equivalents of the base led to a complex mixture (Scheme 5). Compound **17** was also prepared by acid hydrolysis of **16** (Scheme 7).



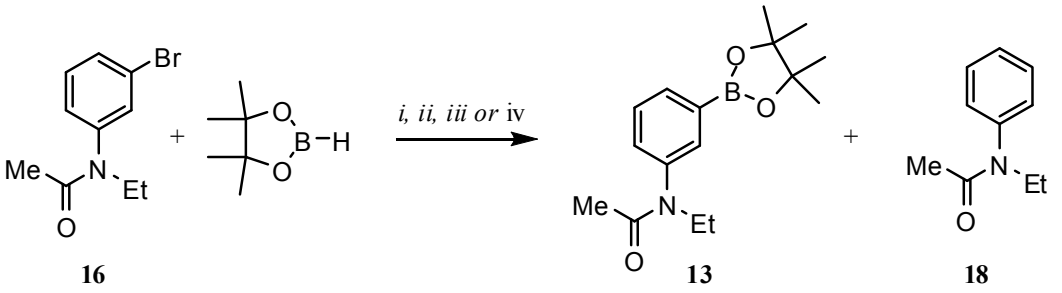
i, Ac_2O, AcOH; *ii,* NaH/DMF, EtI; *iii,* (a) BuLi, THF, (b) $B(OMe)_3$, (c) H^+; *iv*, HCl, reflux

Scheme 7

After the failure, we decided to protect the NH group in **17** by a suitable group. Surprisingly, the subject has not been widely studied. Schrer *et al.* prepared anilineboronic acids by converting the halogen substituted aniline to the corresponding *N*,*N*-dibenzyl derivatives, treating these intermediates subsequently with a metallating agent and a boronic ester.[22] A recent report[23] describing procedure of preparation of 4-amino-3-fluorophenylboronic acid transformed the starting 4-bromo-2-fluoro aniline into the corresponding bis-TMS derivative by treatment with two equivalents of butyllithium followed by addition of TMSCl. However, under these condition using one equivalent of butyllithium, partial lithium-bromine exchange in **17** occurred. Therefore we tried to utilize milder conditions using TMSCl and Et_3N[24] or TMSA,[25] but in both cases only partial silylation was observed.

An alternative method of preparing boronic acid derivatives is the transition metal-catalyzed coupling of pinacolborane with aromatic halides. Original procedure[26] using $PdCl_2$(dppf) [dpff = 1.1‘-bis(diphenylphosphino)ferrocene] is problematic for partial aryl halide reduction. An improved procedure using $Pd(dba)_2$/bis(2-di-*tert*-butylphosphinophenyl)ether (*t*-Bu-DPEPhos) as the catalyst is reported to substantially suppress this side reaction.[27] Using this system, the product contained according to GC 77.4 % of **13** and 11.3 % of the reductive product **18** (Scheme 8). Similar results were obtained with analogous 9,9-dimethyl-4,5-bis(di-*tert*-butylphosphino)xanthene (*t*-butyl-XantPhos). We have also applied a procedure using SPhos, which has just been pusblished.[28] However, even higher amount of **18** was present in the mixture. Using 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) under

analogous conditions, formation of **18** was suppressed but the mixture contained three major impurities in amounts higher than 10 % (Table 1).



i, $Pd(dba)_2$, *t*-Bu-DPEPhos, Et_3N, dioxane, 80 °C; *ii,* $Pd(dba)_2$, *t*-Bu-XantPhos, Et_3N, dioxane, 80 °C; *iii,* $PdCl_2(MeCN)_2$, SPhos, Et_3N, dioxane, 110 °C; *iv* $PdCl_2(MeCN)_2$, XPhos, Et_3N, dioxane, 110 °C

Scheme 8

Mixtures obtained by the method (entries 1-3) were used for the Suzuki-Miyaura cross-coupling reaction with **7** catalyzed with $(Ph_3P)_4Pd$ (Scheme 6). The obtained yields were lower than using pure **13**, which can be caused either by the present impurities or by lower content of **13** than indicated by GC.

Table 1. Results of borylation of with pinacolborane using various ligands

Entry	Ligand	GC content (%) / Yield (%)[a]	
		13	**18**
1	*t*-Bu-DPEPhos	77.4 / 58.9	11.3 / 15.2
2	*t*-butyl-XantPhos	73.5 / 61.0	12.8 / 18.8
3	SPhos	69.6 / 50.5	22.7 / 29.2
4	XPhos	37.7/30.0	0.7 / 1[b]

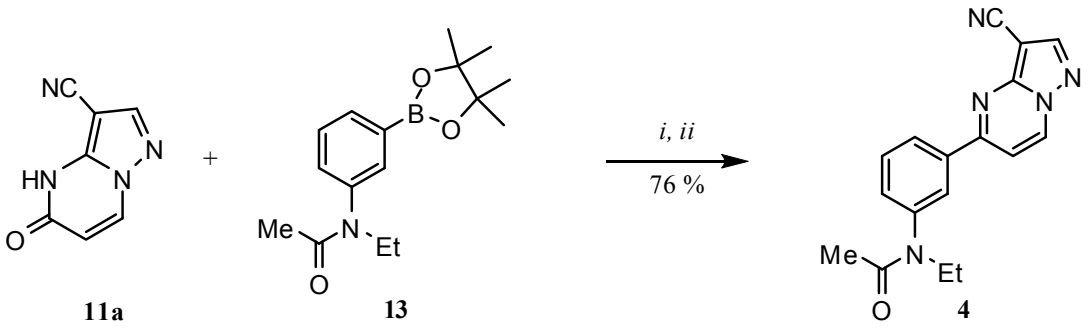
[a] GC yields are calculated on **16**.

[b] The mixture contained also three major impurities in amounts higher than 10 %.

Broutin *et al.* reported one-pot preparation of unsymmetric biaryls based on palladium-catalyzed borylation of phenyl bromides in the presence of $Pd(OAc)_2$ and DPEPhos folowed by Suzuki-Miyaura coupling.[29] We also tried to prepare compound **4** by application of this strategy starting from **16**,

pinacolborane, SPhos in the first step and using chloro derivative **7** in the second step, but the yields were substantially lower than reported by Broutin.

Kang *et al.* recently published[33] a procedure of Pd-catalyzed direct arylation of tautomerizable heterocycles with aryl boronic acids via C-OH bond activation using phosphonium salts. First we checked the methodology using the described conditions with oxo derivative **11a** and 3-nitrophenylboronic acid (**6a**). The crude product contained according the TLC the required product **5a** and an unknown impurity in about 2 : 1 ratio and due to the low solubility our attempts to purify it failed. Then we applied this method to the reaction of **11a** with pinacol ester **13** using bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP) as the phosphonium salt. While the original procedure uses 2 equivalents of the boronic acids, we used only slight excess (1.05 eq.) of the boronic ester **13** and we obtained 75 % yield of the required compound **4**. The only disadvantage of the procedure seems to be the price of the reagent.



11a **13** **4**

i, PyBroP, Et_3N, dioxane; *ii*, **13**, Na_2CO_3, $PdCl_2(PPh_3)_2$, H_2O

Scheme 9

Spectral characteristics (IR, UV, MS, ^1H NMR, ^{13}C NMR) of all new compounds have been measured. Having both zaleplon (**1**) and isozaleplon (**4**) in hands, we decided to compare their NMR spectral characteristics in details using ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz). The assignment of protons and carbons for both compounds was performed using 2D NMR techniques. Both proton and carbon spectra are very similar; comparison of aromatic regions of proton spectra for isozaleplon (**4**) and zaleplon (**1**) is shown in Figure 1. The most important difference is the value of the coupling constant (7.4 Hz) of the protons 6 and 7 of isozaleplon (**4**) while the corresponding value for protons 5 and 6 of zaleplon (**1**) is significantly lower (4.4 Hz) and was confirmed in many zaleplon analogues.[34]

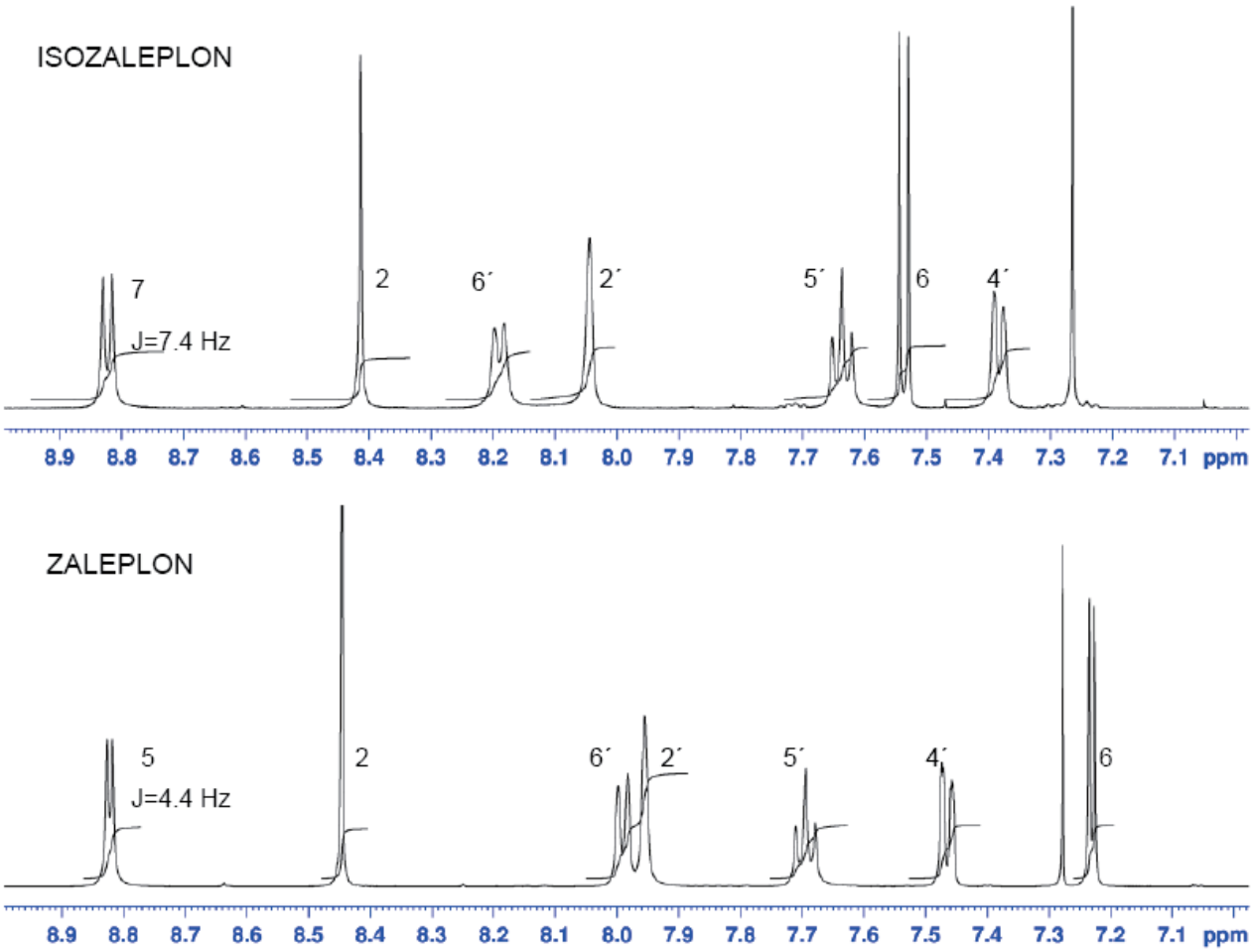


Figure 1 Comparison of aromatic regions of proton spectra for isozaleplon (**4**) and zaleplon (**1**).

Unfortunately the $^{1}H,^{15}N$ HMBC NMR spectra did not enable the assignment of all nitrogen signals because of their overlap; only assignment of the amide nitrogen at 139.1 ppm (for NH_4^+ referencing) is unambiguous.

CONCLUSIONS

Several approaches to the synthesis of isozaleplon (**4**), a principal impurity of zaleplon, was developed. The best results were obtained using Suzuki-Miyaura cross coupling reaction of pinacol ester **13** with 5-chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**7**). Various methods of preparation of both components are described, as well as approaches based on the final modification of the 5-(3-aminophenyl)-pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile moiety prepared by Suzuki-Miyaura cross

coupling. All the prepared compounds were unambiguouesly identified by NMR techniques. Spectral characteristics (IR, UV, MS) of these compounds are also given.

EXPERIMENTAL

2,2-Bis(di-*tert*-butylphosphino)diphenyl ether (*t*-Bu-DPEPhos) vas prepared according to the literature procedure;[30] the product was purified by bulb-to-bulb distillation. *t*-Bu-XantPhos was obtained from Johnson Matthey. 3-Nitrophenylboronic acid (**6a**), 3-aminophenylboronic acid monohydrate (**6b**), triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt hydrate (TPPTS), and pinacol anhydrous were purchased from Alfa Aesar. Other chemicals used in the synthesis were purchased from Sigma-Aldrich and were used without purification.

Melting points were measured on a Kofler block and are uncorrected. The IR spectra were measured on a Perkin Elmer Spectrum BX FT-IR machine by the diffuse reflectance method (KBr), wavenumbers are given in cm^{-1}. The UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer (ethanol) in the range 190-400 nm. NMR experiments were carried out on a Bruker Avance 500 (Bruker Biospin GmbH) at 500.13 MHz (^{1}H), 125.77 MHz (^{13}C) and 50.70 MHz (^{15}N) respectively. All experiments were performed in $CDCl_3$ or DMSO-*d6* at 298K. COSY, HSQC, ^{1}H,^{13}C HMBC and ^{1}H, ^{15}N HMBC spectra were recorded using pulse programs from the Bruker NMR standard library. At 500 MHz, standard 5 mm TXO (triple-nucleus X-observe) and TBI (triple-broadband inverse) probeheads equipped with z-gradient coils were employed for all measurements. For the ^{1}H-^{13}C HSQC, a dataset was acquired with 8 scans for each t1 increment at a resolution of 2048 and 256 points in the F_2 and F_1 dimensions, respectively. The time domain data was zero-filled to 2048 and 1024 data points in F_2 and F_1 dimensions, and multiplied with a sinusoidal squared sine-bell window function in both dimensions prior to Fourier transform. The gradient-selected ^{1}H-^{13}C HMBC and ^{1}H-^{15}N HMBC data sets were recorded with 4K and 512 points in the F_2 and F_1 dimensions, respectively. The magnetization transfer in the ^{1}H-^{13}C HMBC experiment was optimized for a three-bond coupling constant $^{3}J(C,H)$ of 8 Hz. The corresponding ^{1}H-^{15}N HMBC was optimized for a long range coupling constant of 4 Hz. 1K increments of 2K data points were recorded with 128 scans for each increment. The data was subsequently processed employing zero-filling to 2K and 1K data points in the F_1 and F_2 dimensions, using a sinusoidal squared sine-bell window function for

apodization prior to Fourier transform in both dimensions.

The Mass spectra (MS/MS; ionization mode APCI(+)) were measured on an API 3000 PE machine (Sciex Instruments, Applied Biosystems). The purity of the prepared substances was evaluated by TLC on silica gel (FP KG F 254, Merck). Preparative TLC was done on pre-coated silica plates Merck 60 F_{254}, layer thickness 2 mm. Flash chromatography was performed on silica gel Merck, particle size 0.04-0.063 mm. Centrifugally accelerated axial chromatography was done using Cyclograph^{TM} instrument (Analtech) with silica gel pre-scraped rotors.

_N_-(3-Bromophenyl)acetamide (15)

3-Bromoaniline (68.8 g, 0.4 mol) was added dropwise during 1 h into the stirred mixture of acetic anhydride (80 mL) and acetic acid (80 mL) and the mixture was stirred at ambient temperature for 1 h. Residue after evaporation was crystallized from a mixture of EtOH-water (1 : 1) to give 63.2 g (73.8 %) of white crystals; mp 82-84 °C (mp 87 °C)[31].

_N_-(3-Bromophenyl)-_N_-ethylacetamide (16)

A solution of **15** (58.9 g, 0.275 mol) in DMF (250 mL) was added dropwise to a stirred mixture of 50% sodium hydride (16.7 g, 0.35 mol) and DMF (500 mL) under nitrogen and the mixture was stirred at ambient temperature for 1 h. Then the mixture was cooled at 0°C and a solution of iodoethane (56 g, 0.36 mol) in DMF (50 mL) was added at this temperature. The mixture was then stirred at ambient temperature for 6 h, poured into water (1000 mL) and extracted with CH_2Cl_2. The extract was washed with water and dried with magnesium sulfate. The residue after evaporation was then distilled to give 46.8 g (70.3 %) of slightly yellowish oil, bp 88°C/12.4 Pa). HRMS for $C_{10}H_{13}BrNO$ $(M+H)^+$ Calcd: 242.01805, found: 242.01786.

3-Bromo-_N_-ethylaniline (17)

A mixture of *N*-(3-bromophenyl)-*N*-ethylacetamide (**16**; 38.2 g, 0.158 mol), EtOH (160 mL) and concentrated HCl (160 mL) was refluxed for 24 h. The mixture was evaporated, dissolved in hot water, cooled and alkalinized with 10% NaOH. The mixture was extracted with Et_2O, the extract was dried with magnesium sulfate and the residue after evaporation was distilled to give 25.1 g (78.8 %) of yellowish oil

bp 62-64°C/4.8 Pa. HRMS for $C_8H_{11}BrN$ $(M+H)^+$ Calcd: 200.00749, found: 200.00731. ^1H NMR (500.13 MHz, $CDCl_3$) δ, ppm: 1.27 t, 3H, *J* = 7.2 (CH_3); 3.15 q, 2H, *J* = 7.2 (CH_2); 3.69 s, 1H (NH); 6.51-6.86 m, 3H (Ar-H); 7.02 t, 1H, *J* = (H-5).

3-Bromo-*N*-ethylaniline Hydrochloride (17.HCl)

A mixture of *N*-(3-bromphenyl)-*N*-ethylacetamide (**16**; 5 g, 20.7 mmol), EtOH (20 mL) and 20% HCl (10 mL) was refluxed for 48 h. The mixture was evaporated and crystallization of the residue from EtOH provided 3.5 g of white crystals (71.5 %); mp 133-140 °C. *Anal.* Calcd for $C_8H_{11}BrClN$ (236.54): C, 40.62; H, 4.69; N, 5.92. Found: C, 40.28; H, 4.72; N, 5.74.

3-Acetamidophenylboronic acid (6c)

A mixture of 3-aminophenylboronic acid monohydrate (**6a**; 3.1 g, 20 mmol), Ac_2O (6 mL), acetic acid (20 mL), and 4-dimethylaminopyridine (0.05 g) was stirred at ambient temperature for 24 h. The formed suspension was evaporated in vacuo and the residue was triturated with Et_2O. The insoluble portion was filtered off, washed with Et_2O and dried to give 3.5 g (97.8 %) of white solid, mp 286-288 °C [mp 274-275 °C (H_2O) [32]]. *Anal.* Calcd for $C_8H_{10}BNO_3$ (178.98): C, 53.68; H, 5.63; N, 7.83. Found: C, 53.49; H, 5.87; N, 7.50. HRMS for $C_8H_{11}BNO_3$ $(M+H)^+$ Calcd: 180.08320, found: 180.08247. ^1H NMR (500.13 MHz, DMSO-*d6*): 2.04 s, 3H (CH_3), 7,21-7,95 m, 4H (Ar-H), 9.81-9.87 m, 2H (2xOH), 11.92 bs, 1H (NH). ^{13}C NMR (125.77 MHz, DMSO): 23.94, 120.55, 124.33, 127.58, 128.32, 138.55, 168.15, 171.98. IR (KBr): ν(NH) 3306, ν(C=O) 1710, 1652, ν(C=C) + ν(C=N) 1486, 1414, δ(NH) 1553, ν(BO) 1339, 1258, δ(CH) 721 cm^{-1}. UV λ_{max} (log ε): 212 (4.48), 244 (4.12), 284 (3.51).

***N*-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (12)**

Pinacol anhydrous (1.2 g, 10 mmol) was added to a stirred suspension of 3-acetamidophenylboronic acid (**6c**; 1.79 g, 10 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred at ambient temperature for 10 h. The formed clear solution was evaporated, the residue was triturated with boiling hexane and the insoluble solid was filtered off to give 2.4 g of white crystals (91.9 %); mp 188-190 °C. *Anal.* Calcd for $C_{14}H_{20}BNO_3$ (261.12): C, 64.39; H, 7.72; N, 5.36. Found: C, 64.13; H, 7.56; N, 5.21. HRMS for $C_{14}H_{21}BNO_3$ $(M+H)^+$ Calcd: 262.16145, found: 262.16086. ^1H NMR (500.13 MHz, $CDCl_3$) δ, ppm: 1.32

s, 12H (CH_3), 2.15 s, 3H (CH_3CO), 7,32-7,70 m, 4H (Ar-H), 11.02 bs, 1H (NH). ^{13}C NMR (125.77 MHz, $CDCl_3$): 24.41, 24.81, 83.84, 123.13, 125.95, 128.44, 130.49, 137.44, 168.53, 172.13. IR (KBr): ν(NH) 3322, ν(CH) 2975, ν(C=O) 1661, δ(NH) 1548, ν(COBOC) 1355, 1138 cm^{-1}. UV λ_{max} (log ε): 216 (4.49), 246 (4.08), 286 (3.02).

_N_-Ethyl-_N_-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (13)

Method A) Sodium hydride (0.3 g, 50 % dispersion, 6.25 mmol) was added to a solution of *N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**12**; 1.3 g, 5 mmol) in dry THF (20 mL) and the mixture was stirred under nitrogen for 1 h. Then iodoethane (1 mL, 12.5 mmol) was added, the flask was closed by a stopper and the mixture was stirred for 24 h at ambient temperature. The mixture was evaporated, the residue was mixed with water (25 mL) and extracted with CH_2Cl_2. The extract was washed with brine and dried with anhydrous magnesium sulfate. The oily residue after evaporation (1.05 g, 72.6 %) was analyzed by LC-MS and used for the next step without purification. HRMS for $C_{16}H_{25}BNO_3$ $(M+H)^+$ Calcd: 290.19275, found: 290.19212.

Method B) A flask with a septum inlet was charged with $Pd(dba)_2$ (56 mg, 0.1 mmol) and *t*-Bu-DPEPhos (50 mg, 0.1 mmol) and then flushed with argon. Dry dioxane (20 mL) and Et_3N (4 mL, 28 mmol) were added via syringe, followed by *N*-(3-bromophenyl)-*N*-ethylacetamide (**16**; 2.42 g, 10 mmol) and pinacolborane (2.2 mL, 15 mmol). The mixture was then stirred for 24 h at 80 °C and the mixture was analyzed by GC. Et_2O (50 mL) was added and the solution was washed with brine (4 x 10 mL), dried with magnesium sulfate and evaporated to give 2.2 g of oily residue containing 77.4 % of **13** and 11.3 % of **18** (GC).

Method C) Analogously as Method B, using *t*-Butyl-XantPhos (48 mg, 0.1 mmol), 2.4 g of an oily residue was obtained. According to GC, the mixture contained 73.5 % of **13** and 12.8 % of **18**.

Method D) A pressure tube closed by a septum was charged with $PdCl_2(MeCN)_2$ (50 mg, 0.2 mmol) and SPhos (100 mg, 0.25 mmol) and then flushed with argon. Dry dioxane (15 mL) was added via syringe, followed by a solution of *N*-(3-bromophenyl)-*N*-ethylacetamide (**16**, 2.42 g, 10 mmol) in dry dioxane (5 mL), Et_3N (4 mL, 28 mmol) and pinacolborane (2.2 mL, 15 mmol). The septum was then replaced with a teflon screw valve and the mixture was then stirred for 4 h at 110 °C. The mixture was filtered through a pad of celite, eluted with Et_2O (10 mL) and the filtrate was diluted with Et_2O (40 mL).

The solution was washed with brine (4 x 10 mL), dried with magnesium sulfate and evaporated to give 2.1 g of oily residue containing 69.6 % of **13** and 22.7 % of **18** (GC).

Method E) Analogously as Method D, using XPhos (48 mg, 0.1 mmol), 2.3 g of an oily residue was obtained. According to GC, the mixture contained 37.7 % of **13** and 0.7 % of **18**; however, the mixture contained also three major impurities in amounts higher than 10 %.

5-Oxo-4,5-dihydropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (11a)

Ethyl 3-ethoxyacrylate (5 mL, 35 mmol) and cesium carbonate (11.4 g, 35 mmol) were consecutively added to a stirred solution of 5-amino-1*H*-pyrazole-4-carbonitrile (**3a**; 2.45 g, 22.7 mmol) in DMF (115 mL) and the mixture was stirred under nitrogen at 110 °C for 2 h. Then the mixture was evaporated, the residue was dissolved in water (100 mL) and after addition of crushed ice (30 g) the solution was acidified with 10% HCl. After cessation of carbon dioxide evolution, the formed solid was filtered off and washed with cold water to give 4.5 g of white solid (80.3 %); mp 293-305 °C. *Anal.* Calcd for $C_7H_4N_4O$ (160.13): C, 52.50; H, 2.52; N, 34.99. Found: C, 52.67; H, 2.71; N, 34.52. HRMS for $C_7H_5N_4O$ $(M+H)^+$ Calcd: 161.04634, found: 161.04596. ^{1}H NMR (500.13 MHz, DMSO-*d6*) δ, ppm: 6.28 d, 1H, *J* = 7.3 (H-6), 8.68 s, 1H (H-2), 8.73 d, 1H, *J* = 7.3 (H-7). ^{13}C NMR (125.77 MHz, DMSO-*d6*) δ, ppm: 74.60, 107.54, 112.62, 138.78, 142.33, 145.62, 160.68. IR (KBr): ν(CH) 3073, 2929, 2882, ν(CN) 2237, ν(C=O) 1705, 1680, ν(C=C) + ν(C=N) 1586, 1507, 1475, ν(C-N), 1355, 1181, δ(CH) 826 cm^{-1} . UV λ_{max} (log ε): 208 (4.15), 234 (4.45), 264 (3.93).

5-Chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (7)

A mixture of 5-oxo-4,5-dihydropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**11a**; 1.6 g, 10 mmol) and phosphorus oxychloride (10 mL) was stirred in a pressure tube at 150 °C for 1h. The mixture was evaporated under reduced pressure, crushed ice was added to the residue and the mixture was alkalinized with 20% aqueous sodium hydroxide. The formed solid was filtered off, washed with water and crystallized from 2-propanol (charcoal) to give 1.1 g (62.6 %) of white crystals; mp 138-142 °C. *Anal.* Calcd for $C_7H_3ClN_4$ (178.58): C, 47.08; H, 1.69; Cl, 19.85; N, 31.37. Found: C, 46.88; H, 1.51; Cl, 19.53; N, 31.42. HRMS for $C_7H_4ClN_4$ $(M+H)^+$ Calcd: 179.01245, found: 179.01307. ^{1}H NMR (500.13 MHz,

DMSO-*d6*) δ, ppm: 7.50 d, 1H, *J* = 7.3 (H-6), 8.85 s, 1H (H-2), 9.41 d, 1H, *J* = 7.3 (H-7). ^{13}C NMR (125.77 MHz, DMSO-*d6*) δ, ppm: 80.98, 112.24, 112.64, 139.82, 148.33, 148.90, 154.40. IR (KBr): ν(CH) 3109, 3091, ν(CN) 2233, ν(C=C) + ν (C=N) 1619, 1543, 1514, 1401, ν(CCl) 1074, δ(CH) 814 cm^{-1}. UV λ_{max} (log ε): 208 (4.21), 234 (4.51), 266 (3.85).

5-(3-Nitrophenyl)pyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (5a)

A mixture of 3-nitrophenylboronic acid (**6a;** 0.5 g, 3 mmol), 5-chloropyrazolo-[1,5-*a*]pyrimidin-3-carbonitrile (**7**, 0.5 g, 2.8 mmol), sodium carbonate (0.75 g) and tetrakistriphenylphosphinepalladium (0.1 g) in DMF (15 mL) was stirred under argon at 100 ºC for 3 days. Then the mixture was poured into a 10% aqueous solution of sodium carbonate (50 mL) and stirred at ambient temperature overnight. The insoluble portion was filtered off, the beige paste was stirred with water (25 mL) for 2 h and the insoluble portion was again filtered off to give yellow crystals (0.54 g, 67.9 %), mp 272-278 °C. *Anal.* Calcd for $C_{13}H_7N_5O_2$ (265.23): C, 58.87; H, 2.66; N, 26.41. Found: C, 58.64; H, 2.87; N, 26.73. HRMS for $C_{13}H_8N_5O_2$ $(M+H)^+$ Calcd: 266.06780, found: 266.06823. ^{1}H NMR (500.13 MHz, DMSO-*d6*) δ, ppm: 7.82-8.15 m, 1H (Ar-H), 8.20 d, 1H, *J* = 7.4 (H-6), 8.30-8.80 m, 2H (Ar-H), 8.84 s, 1H (H-2), 9.02 s, 1H (H-2'), 9.53 d, 1H, *J* = 7.4 (H-7). ^{13}C NMR (125.77 MHz, DMSO-*d6*) δ, ppm: 81.32, 108.46, 113.27, 122.03, 123.12, 125.88, 130.82, 131.49, 133.88, 136.88, 148.46, 149.32, 156.91. IR (KBr): ν(CH) 3078, ν(CN) 2235, ν(C=C) + ν(C=N) 1613, ν(NO) 1518, ν(NO) + ν(CN) 1355, δ(CH) 738 cm^{-1}. UV λ_{max} (log ε): 218 (4.35), 258 (4.48), 300 (3.98).

5-(3-Aminophenyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (5b)

A solution of palladium acetate (0.056 g, 0.29 mmol), TPPTS hydrate (0.71 g) in a mixture of water (10 mL) and MeCN (5 mL) was added to a stirred solution of 3-aminophenylboronic acid monohydrate (**6a**; 0.78 g, 5 mmol), 5-chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**7**, 0.86 g, 4.8 mmol), and cesium carbonate (4 g) in a mixture of water (20 mL) and MeCN (15 mL) and the mixture was refluxed for 1 h under argon. The cold reaction mixture was diluted with water (50 mL), the mixture was stirred at 0 °C for 2h and the insoluble portion was filtered off, washed with cold water (20 mL) and dried to give 1.05 g (89.3 %) of yellowish crystals, mp 160-165 °C. A small sample was crystallized from a mixture of MeCN

- DMF 9 : 1 to give beige crystals, mp 164-166 °C. *Anal.* Calcd for $C_{13}H_9N_5$ (235.24): C, 66.37; H, 3.86; N, 29.77. Found: C, 66.51; H, 3.72; N, 29.92. HRMS for $C_{13}H_{10}N_5$ $(M+H)^+$ Calcd: 236.09362, found: 236.09719. ^{1}H NMR (500.13 MHz, DMSO-*d6*) δ, ppm: 5.43 s, 2H (NH_2), 6.80 ddd, 1H, *J* = 0.9; 2.4; 7.9 (H-4'), 7.23 t, 1H, *J* = 7.9 (H-5'), 7.37-7.53 m, 2H (Ar-H), 7.80 d, 1H, *J* = 7.4 (H-6), 8.77 s, 1H (H-2), 9.32 d, 1H, *J* = 7.4 (H-7). ^{13}C NMR (125.77 MHz, DMSO-*d6*) δ, ppm: 80.54, 108.25, 112.12, 113.54, 113.65, 115.42, 117.34, 129.58, 137.67, 140.09, 148.02, 149.43, 159.98. IR (KBr): ν(NH) 3391, 3300, ν(CH) 2916, 2848, ν(CN) 2225, ν(C=C) + ν(C=N) + δ(NH) 1604, ν(C=C) + ν(C=N) 1550, 1410, δ(CH) 764 cm^{-1}. UV λ_{max} (log ε): 218 (4.41), 270 (4.37), 298 (4.08).

_N_-(3-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-5-yl)phenyl)acetamide (5c)

Method A) A suspension of 5-(3-aminophenyl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**5b;** 0.28 g, 1 mmol) in Ac_2O (10 mL) was stirred at ambient temperature for 24 h. Then the mixture was diluted with ice water (50 mL), the mixture was stirred for 1 h, the insoluble portion was filtered off and dried to give 0.23 g (82.9 %) of beige solid; mp 253 – 255 °C. A small sample was crystallized from acetic acid to give white crystals, mp 255-256 °C.

Method B) A solution of palladium acetate (10 mg, 0.05 mmol), TPPTS hydrate (0.15 g) in a mixture of water (5 mL) and MeCN (2.5 mL) was added to a stirred solution of 3-acetamidophenylboronic acid (**6c**; 0.45 g, 2.5 mmol), 5-chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**7**, 0.45 g, 2.5 mmol), and cesium carbonate (2 g) in a mixture of water (10 mL) and MeCN (5 mL) and the mixture was refluxed under argon for 2 h. The cold reaction mixture was diluted with water (25 mL), the insoluble portion was filtered off, washed with cold water (10 mL) and dried to give 0.65 g (93.8 %), mp 253-256 °C. *Anal.* Calcd for $C_{15}H_{11}N_5O$ (277.28): C, 64.97; H, 4.00; N, 25.26. Found: C, 64.39; H, 4.45; N, 25.55. HRMS for $C_{15}H_{12}N_5O$ $(M+H)^+$ Calcd: 278.10419, found: 278.10355. ^{1}H NMR (500.13 MHz, DMSO-*d6*) δ, ppm: 2.09 s, 3H (CH_3), 7.51 t, 1H, *J* = 7.9 (Ar-H), 7.86 d, 1H, *J* = 7.4 (H-6), 7.90-8.42 m, 3H (Ar-H), 8.80 s, 1H (H-2), 9.38 d, 1H, *J* = 7.4 (H-7), 10.23 s, 1H (NH). ^{13}C NMR (125.77 MHz, DMSO-*d6*) δ, ppm: 23.95, 80.81, 108.23, 113.54, 117.65, 122.12, 122.50, 129.52, 135.76, 138.05, 140.13, 148.20, 149.50, 159.06, 168.58. IR (KBr): ν(NH) 3340, ν(CH) 3072, ν(CN) 2227, ν(C=O) 1682, 1682, ν(C=C) + ν(C=N) 1620, 1596, δ(NH) 1551, δ(CH) 785 cm^{-1}. UV λ_{max} (log ε): 220 (4.36), 262 (4.55), 304 (4.00).

_N_-(3-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-5-yl)phenyl)-_N_-ethylacetamide (4)

Method A) A 50% sodium hydride dispersion (0.1 g, 2 mmol) was added to a solution of *N*-(3-(3-cyanopyrazolo[1,5-*a*]pyrimidin-5-yl)phenyl)acetamide (**5c**; 0.28 g, 1 mmol) in DMF (3 mL) and the mixture was stirred at ambient temperature for 1 h. Then iodoethane (0.4 mL, 5 mmol) was added and the mixture was stirred at this temperature for 24 h. The reaction mixture was evaporated, mixed with water (5 mL) and extracted with CH_2Cl_2 (4 x 5 mL). The extract was washed with water (5 mL) and dried with magnesium sulfate. The residue after evaporation (0.4 g) was purified by centrifugally accelerated axial chromatography (CH_2Cl_2 – acetone 20 : 1 to 5 : 1 v/v) to give 0.17 g (55.7 %) of **4**; mp 194-198 °C.

Method B) A mixture of *N*-ethyl-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**13**; 0.28 g, 1 mmol), 5-chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**7**; 0.18 g, 1 mmol), $(Ph_3P)_4Pd$ (0.06 g, 5 mol %), sodium carbonate (0.25 g, 2.4 mmol) and toluene (3 mL) was stirred in a vial at 100 °C for 10 h. The mixture was evaporated, mixed with water (5 mL), extracted with CH_2Cl_2 (4 x 5 mL) and the extract was dried with magnesium sulfate. The residue after evaporation (0.45 g) was crystallized from MeOH to give 0.25 g (81.9 %) of **4**; mp 197-199 °C. *Anal.* Calcd for $C_{17}H_{15}N_5O$ (305.33): C, 66.87; H, 4.95; N, 22.94. Found: C, 67.03; H, 5.09; N, 22.78. HRMS for $C_{17}H_{16}N_5O$ $(M+H)^+$ Calcd: 306.13549, found: 306.13495. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ, ppm: 1.17 t, 3H, *J* = 7.2 (CH_3), 1.87 s, 3H, (CH_3CO), 3.84 q, 2H, *J* = 7.2 (CH_2), 7.38 d, 1H, *J* = 7.8 (H-4'), 7.54 d, 1H, *J* = 7.4 (H-6), 7.64 t, 1H, *J* = 7.8 (H-5'), 8.05 s, 1H (H-2'), 8.19 d, 1H, *J* = 7.8 (H-6'), 8.41 s, 1H (H-2), 8.82 d, 1H, *J* = 7.4 (H-7). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ, ppm: 13.2 (CH_3), 22.9 (**C**H_3CO), 44.0 (CH_2), 83.4 (C-3), 107.6 (C-6), 112.7 (CN), 127.1 (C-6'), 127.4 (C-2'), 130.6 (C-5'), 131.6 (C-4'), 136.5 (C-7), 137.4 (C-1'), 144.1 (C-3'), 148.2 (C-2), 149.9 (C-3a), 158.4 (C-5), 169.6 (CO). IR (KBr): ν(CH) 3103, 2922, 2853, ν(CN) 2227, ν(C=O) 1652, ν(C=C) + ν(C=N) 1626, 1601, 1553, 1522, δ(CH) 700 cm^{-1}. UV λ_{max} (log ε): 204 (4.40), 262 (4.48), 302 (3.95).

Method C) Products obtained by Methods B, C and D of preparation of *N*-ethyl-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide containing 77.4 %, 73.5 % and 69.6 % of **13**, respectively were used. A mixture of these products (0.4 g), 5-chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**7**, 0.18 g, 1 mmol), $(Ph_3P)_4Pd$ (0.05 g, mmol), sodium

carbonate (0.25 g, mmol) and toluene (3 mL) was stirred in a vial at 100 °C for 10 h, then worked-up as in Method A to give 0.18-0.21 g of **4**.

Method D) To a mixture of $PdCl_2(MeCN)_2$ (50 mg, 0.2 mmol), SPhos (100 mg, 0.25 mmol) and dry dioxane (20 mL) was added via syringe a solution of *N*-(3-bromophenyl)-*N*-ethylacetamide (**16**; 2.42 g, 10 mmol) in dry dioxane (5 mL), Et_3N (4 mL, 28 mmol) and pinacolborane (2.2 mL, 15 mmol). The mixture was stirred for 4 h at 110 °C using a round-bottom flask with threaded joint. The mixture was stirred without heating for 1 h, then CsF (12.2 g, 80 mmol), $Pd(OAc)_2$ (0.11 g, 5 mol %) and 5-chloropyrazolo[1,5-*a*]pyrimidin-3-carbonitrile (**7**, 1.8 g, 10 mmol) were added and the mixture was stirred at 100 °C for 10 h. The mixture was filtered through a pad of Celite, eluted with dioxane (10 mL) and the filtrate was evaporated. The obtained residue was mixed with water (25 mL), extracted with CH_2Cl_2 (4 x 25 mL) and the extract was dried with magnesium sulfate. The residue after evaporation (3.2 g) was crystallized from MeOH to give 0.9 g (29 %) of **4**.

Method E) PyBroP (0.56 g, 1.2 mmol) was added to a solution of **11a** (0.16 g, 1 mmol) in dry dioxane (8 mL) and triethylamine (0.3 g) in a sealed tube and the mixture was stirred under agron for 2h. Then **13** (0.275 g, 0.95 mmol), sodium carbonate (0.53 g, 5 mmol), $PdCl_2(Ph_3P)_2$ (50 mg, 7 mol %) and water (2 mL) were added and the mixture was stirred in the sealed tube for 2 h. The mixture was stirred overnight. at room temperature and the liquid portion was diluted with EtOAc (25 mL). The insoluble portion on the walls of the sealed tube was boiled with EtOAc (2 x 25 mL), the hot solutions were decanted and combined. All the organic portions were combined, washed with water and dried with magnesium sulfate. The residue after evaporation (1.2 g) was purified by centrifugally accelerated axial chromatography (CH_2Cl_2 – acetone 20 : 1 to 5 : 1 v/v) to give 0.22 g (75.8 %) of **4**; mp 194-197 °C.

N-(3-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl)-*N*-ethylacetamide, zaleplon (1)

Standard of zaleplon (**1**) used for the spectral studies was prepared according to the patent.[8] Mp 183-185 °C (mp 186-187 °C)[4]. HRMS for $C_{17}H_{16}N_5O$ $(M+H)^+$ Calcd: 306.13548, found: 306.13477. ^1H NMR (500.13 MHz, $CDCl_3$) δ, ppm: 1.17 t, 3H, J = 7.2 (CH_3), 1.94 s, 3H (CH_3CO), 3.83 q, 2H, J = 7.2 (NCH_2), 7.22 d, 1H, J = 4.4 (H-6), 7.46 d, J = 7.9 (H-4'), 7.69 t, J = 7.9 (H-5'), 7.95 s, 1H (H-2'), 7.99 d, J = 7.9 (H-6'), 8.44 s, 1H (H-2), 8.82 d, 1H, J = 4.4 (H-5). ^{13}C NMR (125.77 MHz, $CDCl_3$)) δ, ppm: 13.1

(CH_3); 23.0 (**C**H_3CO); 44.0 (CH_2); 83.7 (C-3); 109.8 (C-6); 112.5 (CN); 128.7 (C-6'); 129.6 (C-2'); 130.3 (C-5'); 131.0 (C-1'); 131.6 (C-4'); 143.5 (C-3'); 146.9 (C-7); 147.1 (C-2); 151.3 (C-3a); 152.6 (C-5); 169.6 (CO). IR (KBr) cm^{-1}: ν(CH) 3054, 2972, ν(C=N) 2228, ν(C=O) 1644, ν(C=C) + (C=N) 1613, 1547, 1486. UV λ_{max} (log ε): 204 (4.40), 232 (4.54), 338 (3.81).

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