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3-TRIFLUOROMETHANESULFONYLOXY-4,7-DIHYDROPYRAZOLO- [1,5-*a*]PYRIDINE VIA RING-CLOSING METATHESIS: SYNTHESIS AND TRANSFORMATION TO WITHASOMNINE HOMOLOGS

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Abstract – 3-Trifluoromethanesulfonyloxy-4,7-dihydropyrazolo[1,5-*a*]pyridine (**9**) was successfully synthesized from the starting material, pyrazole, via a sequence of reactions containing ring-closing metathesis as a key step. Suzuki-Miyaura coupling of **9** with various arylboronic acids, followed by oxidation or hydrogenation, readily afforded pyrazolo[1,5-*a*]pyridines (**11**) or 3-aryl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridines (**12**), respectively. Compounds **12** were found to be withasomnine homologs.

INTRODUCTION

The syntheses of pyrazoles with various types of substituents and of pyrazole-fused heterocyclic compounds have been studied because of the expected bioactivities of these compounds, including antitumor, antiviral, and antifungal effects.^{1,2} It is, therefore, important to develop new synthetic methods for such hetero-bicyclic systems.³ The pyrazolo[1,5-*a*]pyridine system is one of the most important of these, and many such molecules are patented. Some bioactive pyrazolo[1,5-*a*]pyridines and tetrahydropyrazolo derivatives are shown in Figure 1. Ibudilast,⁴ which has a pyrazolo[1,5-*a*]pyridine skeleton, is an anti-inflammatory drug because of its phosphodiesterase inhibiting effect, and pyraclonil,⁵ with a tetrahydropyrazolo[1,5-*a*]pyridine core, is used as a rice herbicide because it facilitates the inhibition of protoporphyrinogen-IX oxidase. Other pyrazolo[1,5-*a*]pyridines include a dopamine D4 antagonist,⁶ an anti-mycobacterial agent (TB47),⁷ and a 5-HT₄ receptor partial antagonist (Figure 1).⁸ We have studied functionalization of pyrazoles at the C4-position via several types of metal-catalyzed coupling reactions, including the synthesis of oxygen-containing pyrazole heterobicyclic systems **4**

(Scheme 1), which was developed using ring-closing metathesis (RCM) as the cyclization step.⁹⁻¹¹ In those studies, the *N*-1 position of the pyrazole ring was protected by a trityl or benzyl group. Provided the *N*-1 position was protected by an appropriate substituent group, RCM would, thus, enable the construction of various different types of pyrazole-fused hetero-bicyclic compounds.

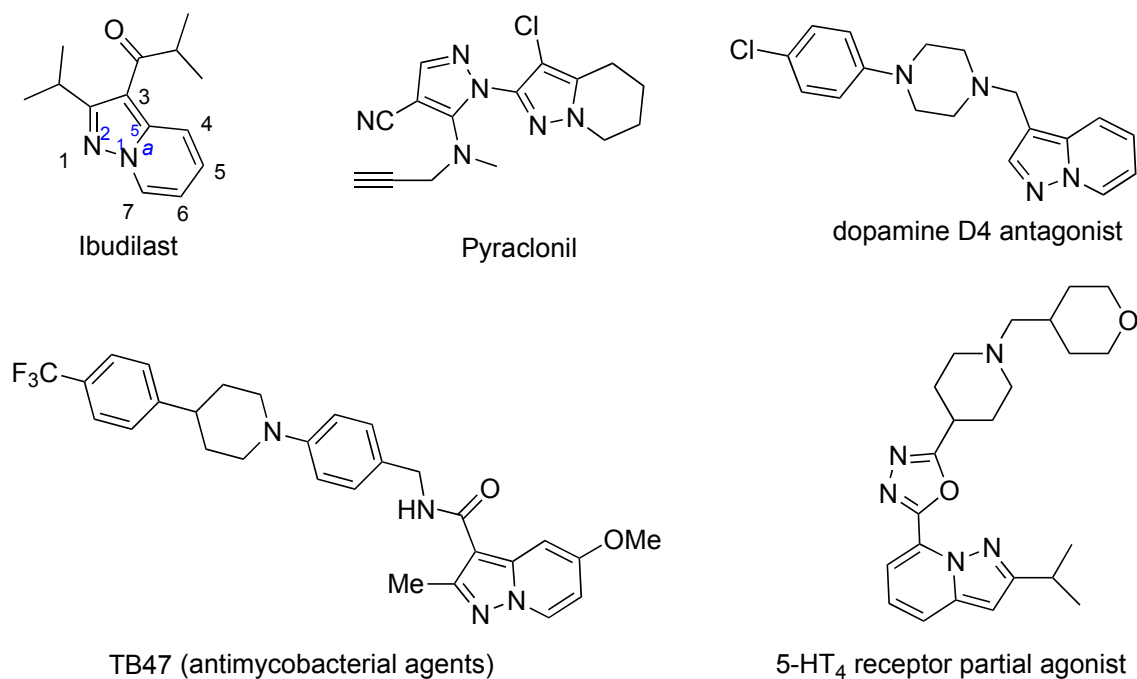
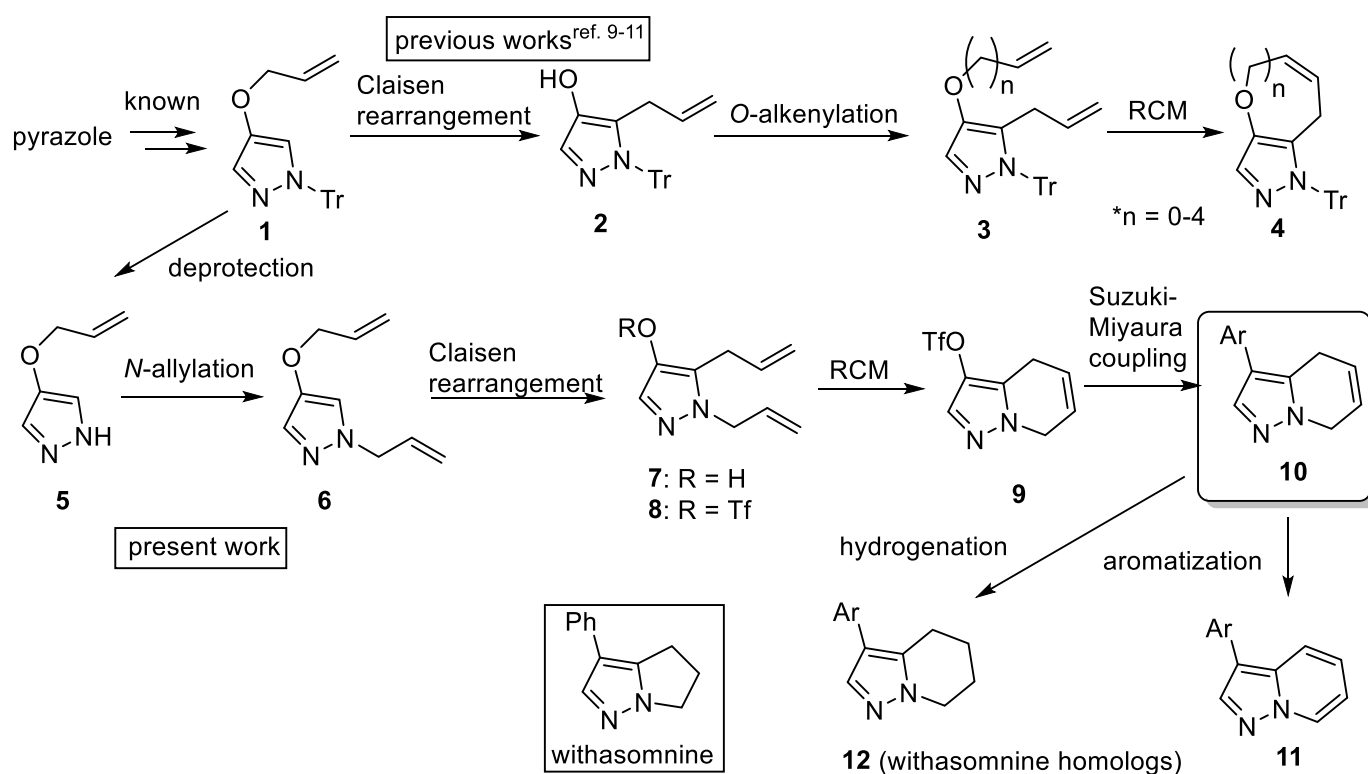


Figure 1. Examples of bioactive pyrazolo[1,5]pyridines and tetrahydropyrazolo[1,5]pyridines

Although the construction of pyrazolo[1,5-*a*]pyridines has thus far been carried out by cycloaddition between an aminopyridinium salt and an alkyne or alkene,¹²⁻¹⁴ our interest was directed toward the functionalization of pyrazole, as discussed above. When *N*-1 of 4-allyloxy-1*H*-pyrazole **5**,⁹ previously derived from pyrazole, was protected by an allyl group, the resulting 1-allyl-4-allyloxy-1*H*-pyrazole **6** might lead to the formation of new dihydropyrazolo[1,5-*a*]pyrazoles (**10**) via the reaction sequence Claisen rearrangement-RCM-Suzuki-Miyaura coupling, as shown in Scheme 1. Furthermore, **10** could be converted to 3-arylpyrazolo[1,5-*a*]pyridines **11** by oxidation or to 3-aryltetrahydropyrazolo[1,5-*a*]pyrazoles **12** by hydrogenation (Scheme 1).

In addition, the introduction of various aryl groups at C-3 of **10** by a Suzuki-Miyaura coupling reaction followed by hydrogenation might lead to the formation of withasomnine homologs **12** with a [5,6]-ring system, in contrast to the parent withasomnine bearing a [5,5]-ring system (Scheme 1).¹⁵ Withasomnine is a pyrazole-containing natural alkaloid from *Withania somnifera* Dunn., and is known to exhibit properties such as CNS and circulatory system depression, mild analgesic effects, and TBL₄, COX-1, and COX-2 inhibitory activities.¹⁶⁻¹⁹ Syntheses of the analogs 3-phenylpyrazolo[1,5-*a*]pyrazole (**11a**²⁰⁻²²; Ar = Ph) and

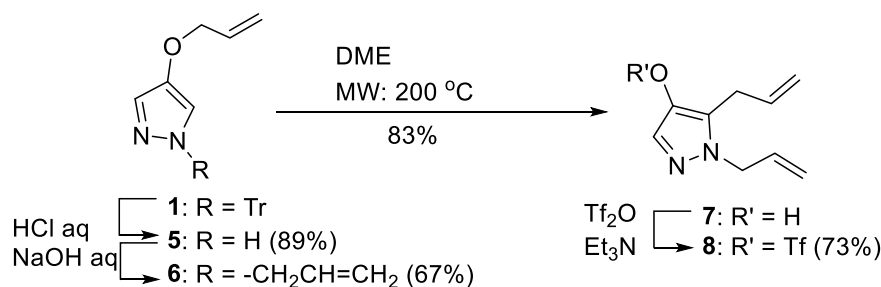
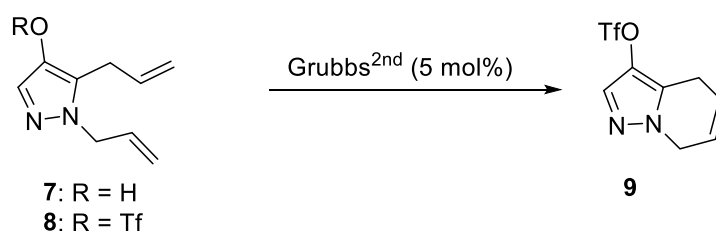
4,5,6,7-tetrahydro-3-phenylpyrazolo[1,5-*a*]pyrazole (**12a**²³; Ar = Ph) have been reported previously. In particular, **12a** exhibited COX-2 inhibitory activity (IC₅₀: 74.7 μM). Hence, development of a new synthetic pathway based on RCM to form withasomnine homologs **12** with the [5,6]-ring system is attractive. Herein, we describe a new synthesis of 4,7-dihydropyrazolo[1,5-*a*]pyridine derivatives **10** from 4-allyloxy-1*H*-pyrazole **5** via RCM as a key step, and their further modification to C3-aromatic compounds **11** or withasomnine homologs **12** with the [5,6]-ring system.



Scheme 1. Concept of this work

RESULTS AND DISCUSSION

Synthesis of the RCM substrates **7** and **8** was performed as shown in Scheme 2. 4-Allyloxy-1*H*-1-tritylpyrazole (**1**) was deprotected by aqueous HCl to give 4-allyloxy-1*H*-pyrazole (**5**) in 89% yield along the literature.¹⁹ Compound **5** was *N*-allylated into **6** in 67% yield, using allyl bromide with NaOH as the base. Compound **6** was selectively converted via Claisen rearrangement into 1,5-diallyl-4-hydroxy-1*H*-pyrazole (**7**) in 83% yield as the sole product, by heating at 200 °C in 1,2-dimethoxyethane (DME) under microwave (MW) irradiation. The alcohol **7** obtained was then *O*-triflated in the usual way to afford 4-triflated pyrazole **8** in 73% yield.

Scheme 2. Synthesis of RCM substrates **7** and **8** from 4-allyloxy-1*H*-1-tritylpyrazole (**1**)**Table 1.** Construction of dihydropyrazolo[1,5-*a*]pyridine via RCM

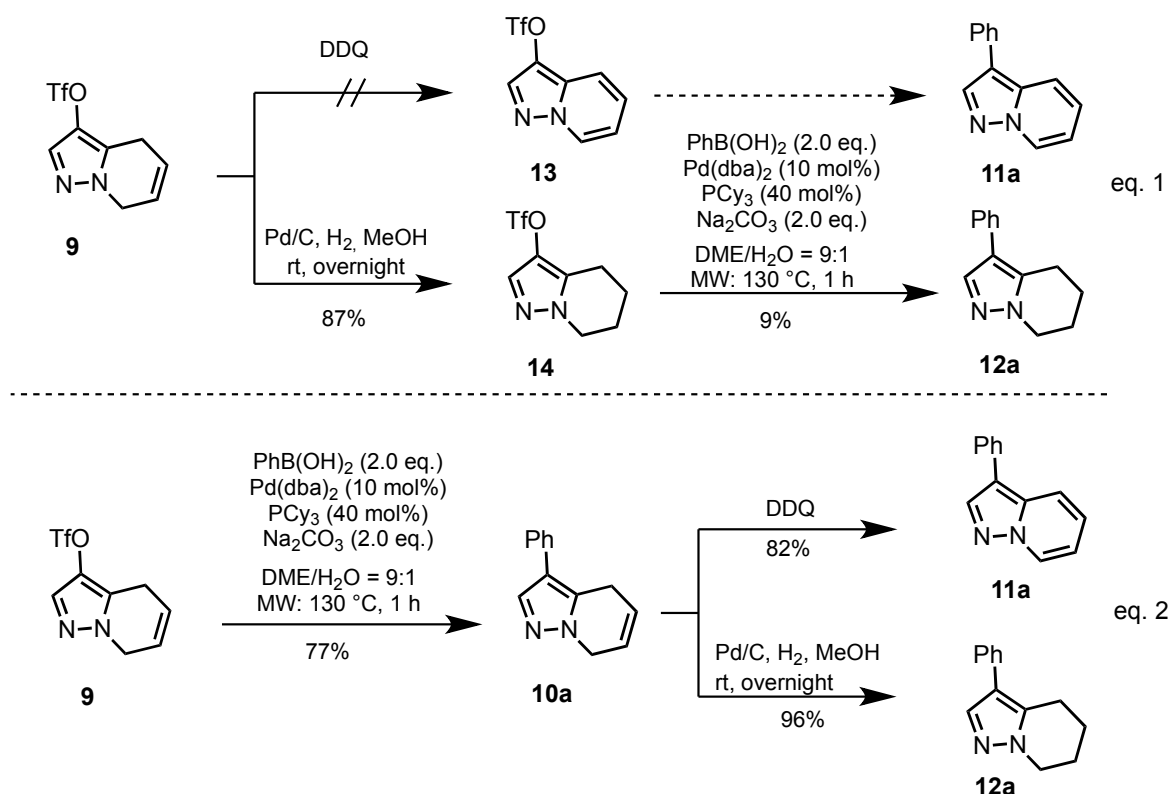
entry	substrate	solvent	reaction time	reaction temperature	product, yield
1 ^a	7	CH ₂ Cl ₂	48 h	rt	0%
2 ^a	7	CH ₂ Cl ₂	30 min	100 °C (MW)	0%
3	8	CH ₂ Cl ₂	18 h	rt	9 (14%)
4 ^b	8	CH ₂ Cl ₂	1 h	80 °C (MW)	9 (8%)
5	8	CH ₂ Cl ₂	1 h	100 °C (MW)	9 (7%)
6	8	toluene	1 h	100 °C (MW)	9 (74%)
7 ^b	8	toluene	1 h	100 °C (MW)	9 (89%)

a. Grubbs^{2nd} (10 mol%) was used as a catalyst. b. CuI (2.5 mol%) was added.

With the two substrates **7** and **8** in hand, RCM using the Grubbs second-generation catalyst (Grubbs^{2nd}) was investigated, as summarized in Table 1. The reaction of **7** in CH₂Cl₂ did not give the expected RCM product even with 10 mol% Grubbs^{2nd} and MW heating (entries 1 and 2). When triflate **8** was subjected to RCM with a reduced amount of the catalyst at room temperature (rt) for 18 h, the desired product **9** was obtained, but in only 14% yield (entry 3). Even when MW heating was applied during the reaction, the desired product was still obtained in poor yields (entries 4 and 5). However, changing the solvent to toluene improved the yield remarkably, to 74% (entry 6), and CuI addition resulted in an even higher yield (89%, entry 7).²⁴

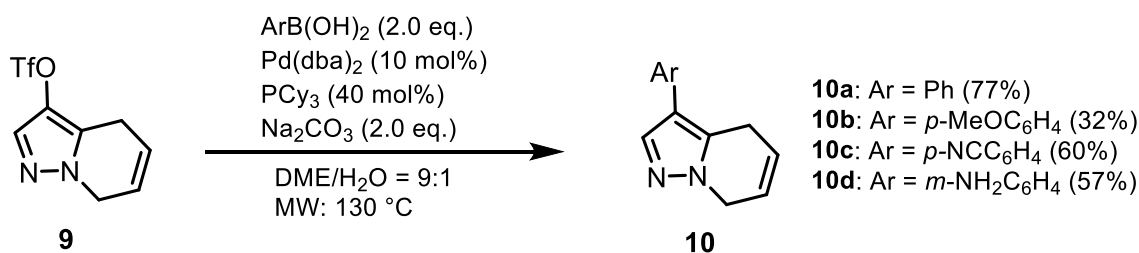
Next, aromatization and hydrogenation of 3-trifluoromethanesulfonyloxy-4,7-dihydropyrazolo[1,5-*a*]pyridine (**9**) were examined, as shown in Scheme 3. For aromatization, oxidation of substrate **9** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as well as with chloranil was attempted under various conditions without success. Hydrogenation of substrate **9** proceeded smoothly to give the desired product **14** in 87% yield, but subsequent bis(dibenzylideneacetone)palladium(0) (Pd(dba)₂) catalyzed

Suzuki-Miyaura coupling with phenylboronic acid, under the conditions previously reported in the synthesis of natural withasomnines,¹⁹ afforded the desired coupling product **12a** in only a disappointing 9% yield. We then tried changing the order of the reaction sequence. Suzuki-Miyaura coupling of **9** with phenylboronic acid provided the desired product **10a** in 77% yield under the same conditions, and subsequent DDQ oxidation and hydrogenation were successful, affording the desired aromatized and saturated products **11a** and **12a** in 82% and 96% yield, respectively. A synthetic route to the target molecules was, thus, confirmed.



Scheme 3. Comparison of synthetic routes to 3-phenylpyrazolo[1,5-*a*]pyridine (**11a**) and 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (**12a**) from **9**

Suzuki-Miyaura coupling of **9** with four different arylboronic acids under the reported conditions¹⁹ was performed, as summarized in Scheme 4. With substituted-arylboronic acids, the chemical yields of products **10** were lower than the corresponding results for withasomnine derivatives achieved in our previous work, particularly in the case of *p*-methoxyphenylboronic acid (**10b**: 32%). A major problem in this coupling reaction is the amount of tricyclohexylphosphine required (PCy₃, 40 mol%), which made it difficult to purify **10** by silica gel column chromatography.



Scheme 4. Suzuki-Miyaura coupling of triflate **9** and arylboronic acids using the reported conditions

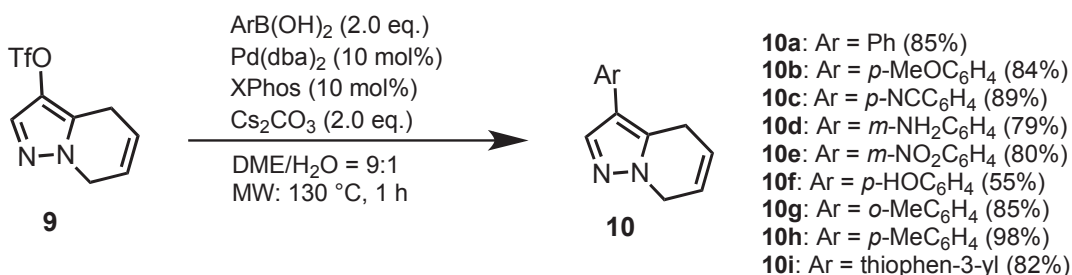
The reaction conditions for the Suzuki-Miyaura coupling of **9** with phenylboronic acid were, therefore, re-examined, with the amount of the phosphine ligand reduced to 10 mol%. Results with different choices of base and ligand are summarized in Table 2. First, the reaction was carried out with sodium carbonate (Na_2CO_3) and 10 mol% of PCy_3 , affording the desired **10a** in 20% yield (entry 1). Changing the ligand to 1,1'-bis(diphenylphosphino)ferrocene (dppf)²⁵ gave a trace of **10a**, which was inseparable and was only observed in the ¹H-NMR spectrum of the crude residue (entry 2). Using 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos)²⁶ (10 mol%) as the ligand improved the chemical yield to 42% (entry 3). Replacing Na_2CO_3 with potassium *tert*-butoxide (*t*-BuOK), again with XPhos , gave a similar yield (entry 4); however, a combination of cesium carbonate (Cs_2CO_3) and XPhos improved the yield dramatically, to 85% (entry 5). Reducing the amount of phenylboronic acid or reducing the reaction time led to lower yields of **10a** (entries 6 and 7).

Table 2. Optimization of the reaction conditions for the Suzuki-Miyaura coupling of triflate **9** with phenylboronic acid

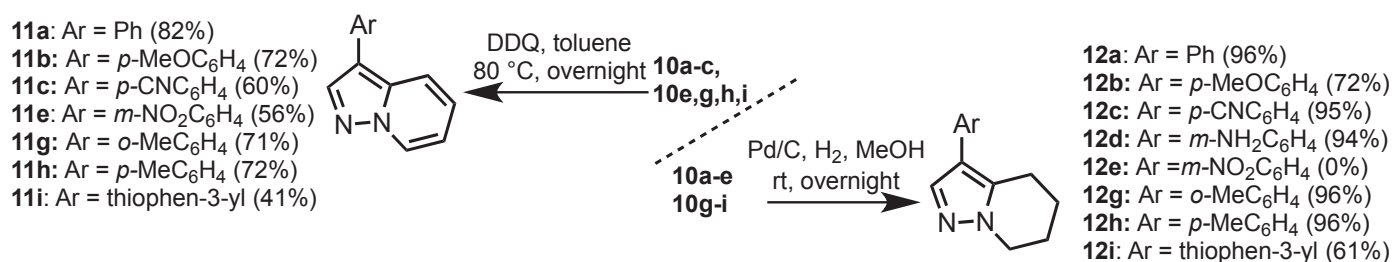
entry	ligand	base	amount of PhB(OH)_2	reaction time	10a , yield
1	PCy_3	Na_2CO_3	2.0 eq.	1 h	20%
2	dppf	Na_2CO_3	2.0 eq.	1 h	trace
3	Xphos	Na_2CO_3	2.0 eq.	1 h	42%
4	Xphos	<i>t</i> BuOK	2.0 eq.	1 h	41%
5	Xphos	Cs_2CO_3	2.0 eq.	1 h	85%
6	Xphos	Cs_2CO_3	1.1 eq.	1 h	68%
7	Xphos	Cs_2CO_3	2.0 eq.	30 min	69%

Using the optimized conditions (entry 5 in Table 2), Suzuki-Miyaura coupling of **9** with various arylboronic acids was then carried out, as summarized in Scheme 5. The chemical yields of **10b-d** were improved compared to those stated in Scheme 4.

Scheme 5. Suzuki-Miyaura coupling of **9** with various arylboronic acids under the optimal conditions



Finally, each arylated-dihydropyrazolo[1,5-*a*]pyridine **10** was smoothly oxidized with DDQ or hydrogenated in the presence of Pd-C as catalyst, as summarized in Scheme 6. However, the hydrogenation of **10e** afforded, not the desired **12e**, but **12d** (Scheme 6).



Scheme 6. Conversion of dihydropyrazolo[5,1-*a*]pyridines **10** to aromatized or saturated analogs **11**, **12**

CONCLUSION

We have achieved the preparation of pyrazolo[1,5]pyridine derivatives in three different oxidation states. Construction of a 4,7-dihydropyrazolo[1,5-*a*]pyridine system via RCM was realized with the help of heating by MW irradiation in toluene. Addition of a catalytic amount of CuI improved the chemical yields of the RCM products. Furthermore, reaction of the 3-trifluoromethanesulfonyloxy derivative **9** with various arylboronic acids in the presence of Pd(dba)₂ (catalyst), XPhos (ligand) and Cs₂CO₃ (base) under optimal reaction conditions led efficiently to the 3-aryl-4,7-dihydropyrazolo[5,1-*a*]pyridines **10**. Finally, **10** was aromatized with DDQ to 3-arylpyrazolo[5,1-*a*]pyridines **11** or hydrogenated to 3-aryl-5,6,7,8-tetrahydropyrazolo[5,1-*a*]pyridines **12** in the presence of catalytic Pd-C.

EXPERIMENTAL

NMR spectra were recorded at 27 °C on Agilent 400- and 600-MR-DD2 spectrometers in CDCl₃ with tetramethylsilane (TMS) as an internal standard. HRMS was determined with a JEOL JMS-700 (2) mass spectrometer. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Liquid column chromatography was conducted over silica gel (Fuji Silysia FL-60D). Analytical TLC was performed on precoated Merck glass plates (silica gel 60 F₂₅₄) and the compounds were detected by dipping the plates in an ethanol solution of phosphomolybdic acid, followed by heating. All microwave-aided reactions were carried out with a Biotage Initiator[®] (Switzerland).

Synthesis of 1-allyl-4-(allyloxy)-1*H*-pyrazole (**6**)

To a solution of **5** (716.2 mg, 5.8 mmol) in acetone (10 mL) was added 20% NaOH aq (1.7 mL, 8.7 mmol) at rt with stirring. After 5 min, allyl bromide (0.8 mL, 8.66 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 1 h. The reaction was quenched by addition of sat. NH₄Cl aq. (5 mL) and the product extracted with CH₂Cl₂ (10 mL × 3). The organic layer was washed with brine (5 mL × 2), dried over MgSO₄, filtered, and concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (eluent: Hexane/AcOEt = 2:1) to afford **6** (634.9 mg, 67%). **6**: Oil; ¹H-NMR (600 MHz, CDCl₃): δ 4.03 (2H, dt, *J* = 5.3, 1.5 Hz, -CH₂CH=CH₂), 4.64 (2H, dt, *J* = 5.8, 1.5 Hz, -OCH₂CH=CH₃), 5.21 (1H, dq, *J* = 17.0, 1.5 Hz, -CH₂CH=CHH), 5.26 (1H, ddd, *J* = 10.6, 2.7, 1.2 Hz, -CH₂CH=CHH), 5.27 (1H, ddd, *J* = 10.5, 2.6, 1.2 Hz, -CH₂CH=CHH), 5.38 (1H, ddd, *J* = 17.0, 2.9, 1.8 Hz, -CH₂CH=CHH), 5.95-6.46 (2H, m, ArCH=CH₂, -OCH₂CH=CH₂), 7.09 (1H, d, *J* = 0.9 Hz, pyrazole-H), 7.26 (1H, d, *J* = 0.5 Hz, pyrazole-H); ¹³C-NMR (150 MHz, CDCl₃): δ 24.8, 55.4, 72.6, 114.9, 118.5, 127.5, 132.9, 133.3, 145.5; HREIMS *m/z* Calcd for C₉H₁₂N₂O (M⁺) 164.0950, Found 164.0950.

Synthesis of 1,5-diallyl-1*H*-pyrazol-4-ol (**7**)

A solution of **6** (277.0 mg, 1.69 mmol) in DME (2 mL) in a MW vial was sealed and heated under MW irradiation at 200 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude residue which was purified by silica gel column chromatography (eluent: Hexane/AcOEt = 2:1) to afford **7** (230.3 mg, 83%). **7**: Colorless oil; ¹H-NMR (600 MHz, CDCl₃): δ 3.38 (2H, ddd, *J* = 6.2, 1.8, 1.5 Hz, -CH₂CH=CH₂), 4.60 (2H, ddd, *J* = 5.6, 1.8, 1.5 Hz, -NCH₂CH=CH₂), 5.01 (1H, ddd, *J* = 17.0, 3.0, 1.8 Hz, -CH₂CH=CHH), 5.09 (1H, dq, *J* = 17.0, 1.8 Hz, -CH₂CH=CHH), 5.16 (1H, ddd, *J* = 10.0, 4.0, 1.5 Hz, -CH₂CH=CHH), 5.18 (1H, ddd, *J* = 10.3, 2.7, 1.5 Hz, -CH₂CH=CHH), 5.85-5.95 (2H, m, -CH=CH₂ and -NCH₂CH=CH₂), 7.21 (1H, s, pyrazole-H5); ¹³C-NMR (150 MHz, CDCl₃): δ 27.2, 52.5, 117.0, 117.2, 125.8, 128.3, 133.3, 133.5, 138.3; HREIMS *m/z* Calcd for C₉H₁₂N₂O (M⁺) 164.0950, Found 164.0951.

Synthesis of 1,5-diallyl-1*H*-pyrazol-4-yl trifluoromethanesulfonate (**8**)

To a solution of **7** (450.0 mg, 2.72 mmol) in CH₂Cl₂ (10 mL) in an ice bath was added triethylamine (0.4 mL, 3.01 mmol, 1.1 eq.). After stirring the reaction mixture for 10 min, trifluoromethanesulfonic anhydride (0.7 mL, 4.11 mmol, 1.5 eq.) was added dropwise at 0 °C. After stirring for 1 h at rt, the reaction was quenched by addition of sat. NH₄Cl aq. (2 mL), and extracted with CH₂Cl₂ (10 mL × 3). The organic layer was washed with brine (5 mL × 2), dried over MgSO₄, filtered, and concentrated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (eluent: Hexane/AcOEt = 2:1) to afford **8** (588.8 mg, 73%). **8**: Colorless oil; ¹H-NMR (400 MHz, CDCl₃): δ 3.43 (2H, dt, *J* = 6.1, 1.3 Hz, -CH₂CH=CH₂), 4.68 (2H, dt, *J* = 5.5, 1.5 Hz, -NCH₂CH=CH₂), 5.00 (1H, d, *J* = 17.0 Hz, -CH₂CH=CHH), 5.09 (1H, dd, *J* = 17.0, 0.8 Hz, -CH₂CH=CHH), 5.20 (1H, br d, *J* = 10.1 Hz, -CH₂CH=CHH), 5.25 (1H, br d, *J* = 10.1 Hz, -CH₂CH=CHH), 5.81 (1H, ddt, *J* = 17.0, 10.1, 6.1 Hz, -CH=CH₂CH₃), 5.93 (1H, ddt, *J* = 17.0, 10.1, 5.5 Hz, -NCH₂CH=CH₂), 7.50 (1H, s, pyrazole-H5); ¹³C-NMR (100 MHz, CDCl₃): δ 27.0, 53.0, 118.1, 118.2, 118.6 (q, ¹*J*_{C-F} = 321.2 Hz), 130.2, 131.1, 131.6, 132.0; HREIMS *m/z* Calcd for C₁₀H₁₁F₃N₂O₃S (M⁺) 296.0442, Found 296.0440.

RCM of **8** (Table 1)

Typical procedure (Table 1, entry 7): To a solution of **8** (123.0 mg, 4.15 × 10⁻¹ mmol) in toluene (10 mL) in a MW vial were added Grubbs^{2nd} (8.8 mg, 2.08 × 10⁻⁴ mmol, 5 mol%) and CuI (1.6 mg, 1.04 × 10⁻³ mmol, 2.5 mol%). The reaction vial was sealed and heated at 100 °C for 1 h under MW irradiation. The reaction mixture was concentrated under reduced pressure to give a crude residue which was purified by silica gel column chromatography (eluent: Hexane/AcOEt = 4:1) to afford 3-trifluoromethanesulfonyloxy-4,7-dihydropyrazolo[1,5-*a*]pyridine (**9**) (99.3 mg, 89%). **9**: Colorless oil; ¹H-NMR (400 MHz, CDCl₃): δ 3.46-3.50 (2H, m, -NCH₂CH=CHCH₂-), 4.69-4.73 (2H, m, -NCH₂CH=CHCH₂-), 5.94-6.04 (2H, m, -NCH₂CH=CHCH₂-), 7.54 (1H, s, pyrazole-H); ¹³C-NMR (100 MHz, CDCl₃): δ 21.9, 47.5, 118.7 (q, ¹*J*_{C-F} = 321.1 Hz), 120.1, 120.5, 128.6, 129.2, 130.5; HREIMS *m/z* Calcd for C₈H₇F₃N₂O₃S (M⁺) 268.0130, Found 268.0125.

Synthesis of 3-aryl-4,7-dihydropyrazolo[1,5-*a*]pyridines (**10**) (Table 2, Scheme 5)

Typical procedure (Table 2, entry 5): To a solution of **9** (25.0 mg, 9.32 × 10⁻² mmol) in DME/H₂O = 9 : 1 (3 mL) in a MW vial, were added XPhos (4.4 mg, 9.32 × 10⁻³ mmol, 10 mol%), Pd(dba)₂ (5.4 mg, 9.32 × 10⁻³ mmol, 10 mol%), cesium carbonate (60.7 mg, 1.86 × 10⁻¹ mmol, 2.0 eq.), and phenylboronic acid (22.7 mg, 1.86 × 10⁻¹ mmol, 2.0 eq.). The sealed vial was heated under MW irradiation at 130 °C for 1 h.

The cooled reaction mixture was quenched with sat. NH_4Cl aq (2 mL) and extracted with CH_2Cl_2 (10 mL \times 3). The organic layer was washed with brine (5 mL \times 2), dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure to give a crude residue which was purified by silica gel column chromatography (eluent: Hexane/AcOEt = 2 : 1) to afford 3-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyridine (**10a**) (15.6 mg, 85%). **10a**: White powder; mp 86-89 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.61-3.62 (2H, m, = CHCH_2Ar), 4.78-4.82 (2H, m, - $\text{NCH}_2\text{CH=}$), 5.96-6.04 (2H, m, - $\text{NCH}_2\text{CH=CH-}$, - $\text{CH=CHCH}_2\text{-}$), 7.21-7.25 (1H, m, Ph-H), 7.36-7.45 (4H, m, Ph-H), 7.77 (1H, s, pyrazole-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 24.8, 47.3, 118.0, 120.7, 121.5, 125.9, 126.7, 128.7, 132.8, 133.5, 137.6; HREIMS m/z Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_2$ (M^+) 196.1000, Found 196.0995.

3-(4-Methoxyphenyl)-4,7-dihydropyrazolo[1,5-*a*]pyridine (**10b**): White powder; mp 133-137 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.56-3.58 (2H, m, = CHCH_2Ar), 3.81 (3H, s, - OCH_3), 4.75-4.78 (2H, m, - $\text{NCH}_2\text{CH=}$), 5.97-5.99 (2H, m, - $\text{NCH}_2\text{CH=CH-}$, - $\text{CH=CHCH}_2\text{-}$), 6.91 (2H, br d, $J = 8.8$ Hz, Ph-H), 7.33 (2H, br d, $J = 8.8$ Hz, Ph-H), 7.86 (1H, s, pyrazole-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 24.6, 47.3, 55.3, 114.2, 117.7, 120.5, 121.5, 126.1, 127.9, 132.2, 137.4, 157.9; HREIMS m/z Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ (M^+) 226.1106, Found 226.1103.

4-(4,7-Dihydropyrazolo[1,5-*a*]pyridin-3-yl)benzotrile (**10c**): White powder; mp 154-156 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.64-3.65 (2H, m, = CHCH_2Ar), 4.79-4.82 (2H, m, - $\text{NCH}_2\text{CH=}$), 6.00-6.06 (2H, m, - $\text{NCH}_2\text{CH=CH-}$, - $\text{CH=CHCH}_2\text{-}$), 7.53 (2H, d, $J = 8.2$ Hz, Ph-H), 7.65 (2H, d, $J = 8.2$ Hz, Ph-H), 7.83 (1H, s, pyrazole-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 25.0, 47.4, 109.0, 116.4, 119.1, 120.8, 121.0, 126.6, 132.6, 133.8, 137.8, 138.4; HREIMS m/z Calcd for $\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_3$ (M^+) 221.0953, Found 221.0951.

3-(4,7-Dihydropyrazolo[1,5-*a*]pyridin-3-yl)aniline (**10d**): White powder; mp 113-115 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.59-3.62 (2H, m, = CHCH_2Ar), 3.71 (2H, br, - NH_2), 4.77-4.76-4.80 (2H, m, - $\text{NCH}_2\text{CH=}$), 5.95-6.04 (2H, m, - $\text{NCH}_2\text{CH=CH-}$, - $\text{CH=CHCH}_2\text{-}$), 6.56-6.59 (1H, m, Ph-H), 6.76 (1H, s, Ph-H), 6.83 (1H, d, $J = 7.6$ Hz, Ph-H), 7.17 (1H, t, $J = 7.6$ Hz, Ph-H), 7.73 (1H, s, pyrazole-H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 24.8, 47.3, 112.9, 113.3, 117.2, 118.1, 120.7, 121.5, 129.6, 132.7, 134.6, 137.7, 146.7; HREIMS m/z Calcd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_3\text{S}$ (M^+) 211.1110, Found 211.1107.

3-(3-Nitrophenyl)-4,7-dihydropyrazolo[1,5-*a*]pyridine (**10e**): Yellow powder; mp 143-145 °C; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.72-3.73 (2H, m, = CHCH_2Ar), 4.80-4.83 (2H, m, - $\text{NCH}_2\text{CH=}$), 5.89-6.06 (2H, m, - $\text{NCH}_2\text{CH=CH-}$, - $\text{CH=CHCH}_2\text{-}$), 7.54 (1H, t, $J = 8.0$ Hz, Ph-H), 7.74 (1H, br d, $J = 7.8$ Hz, Ph-H), 7.86 (1H, s, pyrazole-H), 8.07 (1H, br d, $J = 8.2$ Hz, Ph-H), 8.25 (1H, t, $J = 1.8$ Hz, Ph-H); $^{13}\text{C-NMR}$ (100

MHz, CDCl₃): δ 24.8, 47.4, 116.1, 120.70, 120.76, 120.9, 128.9, 129.7, 132.3, 133.9, 135.2, 137.4, 148.7; HREIMS m/z calcd for C₁₃H₁₁N₃O₂ (M⁺) 241.0851, Found 241.0847.

4-(4,7-Dihydropyrazolo[1,5-*a*]pyridin-3-yl)phenol (**10f**): Colorless needles (CH₂Cl₂); mp 164-168 °C; ¹H-NMR (400 MHz, CD₃OD): δ 3.54-3.57 (2H, m, =CHCH₂Ar), 4.69-4.72 (2H, m, -NCH₂CH=), 5.97-6.06 (2H, m, -NCH₂CH=CH-, -CH=CHCH₂-), 6.81 (2H, br d, *J* = 8.8 Hz, Ph-H), 7.27 (2H, br d, *J* = 8.8 Hz, Ph-H), 7.65 (1H, s, pyrazole-H); ¹³C-NMR (100 MHz, CD₃OD): δ 23.9, 46.9, 115.1, 118.2, 120.1, 121.2, 124.3, 127.6, 132.5, 136.5, 155.6; HREIMS m/z Calcd for C₁₃H₁₂N₂O (M⁺) 212.0950, Found 212.0944.

3-(*o*-Tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyridine (**10g**): Dark brown oil; ¹H-NMR (400 MHz, CDCl₃): δ 2.27 (3H, s, CH₃Ar), 3.35 (2H, t, *J* = 5.3 Hz, =CHCH₂Ar-), 4.81 (2H, t, *J* = 5.3 Hz, -NCH₂CH=), 5.54-6.62 (2H, m, -CH=CH-, -CH=CHCH₂-), 7.16-7.28 (4H, m, Ph-H), 7.54 (1H, s, pyrazole-H); ¹³C-NMR (100 MHz, CDCl₃): δ 20.3, 23.7, 47.4, 117.4, 120.8, 121.6, 125.6, 127.0, 130.2, 130.3, 132.6, 133.4, 136.9, 139.0; HREIMS m/z Calcd for C₁₄H₁₄N₂ (M⁺) 210.1157, Found 210.1157.

3-(*p*-Tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyridine (**10h**): White powder; mp 116-119 °C; ¹H-NMR (400 MHz, CDCl₃): δ 2.37 (3H, s, CH₃Ar), 3.59-3.63 (2H, m, =CHCH₂Ar-), 4.77-4.81 (2H, m, -NCH₂CH=), 5.59-6.01 (2H, m, -CH=CH-, -CH=CHCH₂-), 7.20 (2H, d, *J* = 8.0 Hz, Ph-H), 7.33 (2H, d, *J* = 8.0 Hz, Ph-H), 7.74 (1H, s, pyrazole-H); ¹³C-NMR (100 MHz, CDCl₃): δ 21.1, 24.7, 47.3, 118.0, 120.7, 121.5, 126.6, 129.4, 130.6, 132.5, 135.6, 137.5; HREIMS m/z Calcd for C₁₄H₁₄N₂ (M⁺) 210.1157, Found 210.1155.

3-(Thiazol-3-yl)-4,7-dihydropyrazolo[1,5-*a*]pyridine (**10i**): White powder; mp 83-84 °C; ¹H-NMR (400 MHz, CDCl₃): δ 3.57-3.62 (2H, m, =CHCH₂Ar-), 4.76-4.81 (2H, m, -NCH₂CH=), 5.96-6.05 (2H, m, -NCH₂CH=CHCH₂-), 7.17 (1H, dd, *J* = 2.7, 1.2 Hz, thiazole-H), 7.25 (1H, dd, *J* = 5.0, 0.8 Hz, thiazole-H), 7.37 (1H, dd, *J* = 5.0, 3.0 Hz, thiazole-H), 7.42 (1H, s, pyrazole-H); ¹³C-NMR (100 MHz, CDCl₃): δ 24.8, 47.3, 113.6, 118.1, 120.8, 121.2, 125.7, 126.4, 132.5, 133.8, 137.4; HREIMS m/z Calcd for C₁₁H₁₀N₂S (M⁺) 202.0565, Found 202.0561.

Aromatization of **10** to 3-arylpyrazolo[1,5-*a*]pyridine (**11**) (Schemes 3 and 6)

Typical procedure (Scheme 6): To a solution of **10a** (5.9 mg, 3.0 × 10⁻² mmol) in toluene (5 mL), was added DDQ (10.2 mg, 4.5 × 10⁻² mmol, 1.5 eq.). The reaction mixture was heated at 80 °C for 18 h,

quenched by addition of sat. NaHCO₃ aq (2 mL), and extracted with CH₂Cl₂ (5 mL × 3). The organic layer was washed with brine (5 mL × 2), dried over MgSO₄, filtered, and evaporated to give a crude residue which was purified by silica gel column chromatography (eluent: Hexane/AcOEt = 4 : 1) to afford 3-phenylpyrazolo[1,5-*a*]pyridine (**11a**) (4.8 mg, 82%). **11a**²⁰⁻²²: White powder; mp 40-43 °C; ¹H-NMR (400 MHz, CDCl₃): δ 6.78-6.82 (1H, m, Ph-H), 7.16-7.20 (1H, m, Ph-H), 7.28-7.31 (1H, m, Ph-H), 7.44-7.48 (2H, m, Ph-H), 7.59-7.62 (2H, m, Ph-H), 7.82-7.84 (1H, m, Ph-H), 8.15 (1H, s, pyrazole-H), 8.49-8.51 (1H, m, Ph-H); ¹³C-NMR (100 MHz, CDCl₃): δ 112.0, 112.9, 117.5, 123.9, 126.2, 127.1, 128.98, 129.04, 133.2, 137.0, 140.4; HREIMS *m/z* calcd for C₁₃H₁₀N₂ (M⁺) 194.0844, Found 194.0845.

3-(4-Methoxyphenyl)pyrazolo[1,5-*a*]pyridine (**11b**): White powder; mp 83-84 °C; ¹H-NMR (400 MHz, CDCl₃): δ 3.86 (3H, s, -OCH₃), 6.77 (2H, br t, *J* = 6.9 Hz, Ph-H), 7.01 (1H, br dt, Ph-H), 7.14 (1H, br, Ph-H), 7.51 (2H, br t, *J* = 6.9 Hz, Ph-H), 7.76 (1H, d, *J* = 0.9 Hz, Ph-H), 8.08 (1H, s, pyrazole-H), 8.48 (1H, d, *J* = 7.0 Hz, Ph-H); ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 111.9, 112.6, 114.5, 117.4, 123.6, 125.6, 128.3, 128.9, 136.8, 140.1, 158.2; HREIMS *m/z* calcd for C₁₄H₁₂N₂O (M⁺) 224.0949, Found 224.0951.

4-(Pyrazolo[1,5-*a*]pyridin-3-yl)benzotrile (**11c**): White powder; mp 139-140 °C; ¹H-NMR (400 MHz, CDCl₃): δ 6.88 (1H, dt, *J* = 6.8, 1.0 Hz, Ph-H), 7.29 (1H, br, Ph-H), 7.68-7.73 (4H, m, Ph-H), 7.83 (1H, d, *J* = 9.0 Hz, Ph-H), 8.02 (1H, s, pyrazole-H), 8.53 (1H, d, *J* = 7.1 Hz, Ph-H); ¹³C-NMR (100 MHz, CDCl₃): δ 109.1, 111.0, 112.7, 117.1, 119.1, 125.4, 126.9, 129.4, 132.8, 137.2, 138.1, 140.8; HREIMS *m/z* calcd for C₁₄H₉N₃ (M⁺) 219.0797, Found 219.0796.

3-(*m*-Nitrophenyl)pyrazolo[1,5-*a*]pyridine (**11e**): Yellow needles (CH₂Cl₂); mp 143-145 °C; ¹H-NMR (400 MHz, CDCl₃): δ 6.89 (1H, td, *J* = 7.1, 1.0 Hz, Ar-H), 7.31 (1H, td, *J* = 6.8, 1.0 Hz, Ar-H), 7.62 (1H, t, *J* = 8.0, 1.0 Hz, Ar-H), 7.86 (1H, d, *J* = 9.0 Hz, Ar-H), 7.92 (1H, d, *J* = 7.8 Hz, Ar-H), 8.23 (1H, s, Ar-H), 8.46 (1H, s, Ar-H), 8.55 (1H, d, *J* = 7.8, 1.0 Hz, Ar-H); ¹³C-NMR (100 MHz, CDCl₃): δ 110.6, 112.7, 116.9, 120.8, 121.2, 125.2, 129.4, 129.9, 132.6, 135.0, 137.1, 140.6, 148.8; HREIMS *m/z* Calcd for C₁₃H₉N₃O₂ (M⁺) 239.0694, Found 239.0694.

3-(*o*-Tolyl)pyrazolo[1,5-*a*]pyridine (**11g**): Dark brown oil; ¹H-NMR (400 MHz, CDCl₃): δ 2.32 (3H, s, CH₃-Ar), 6.79 (1H, td, *J* = 8.0, 1.3 Hz, Ar-H), 7.12 (1H, br dd, *J* = 8.4, 6.7 Hz, Ar-H), 7.25-7.30 (2H, m, Ar-H), 7.32-7.37 (2H, m, Ar-H), 7.45 (1H, d, *J* = 9.0 Hz, Ar-H), 7.99 (1H, s, pyrazole-H), 8.51 (1H, d, *J* = 7.1 Hz, Ar-H); ¹³C-NMR (100 MHz, CDCl₃): δ 20.6, 111.9, 112.0, 117.6, 123.4, 125.9, 127.1, 128.7, 130.4, 130.6, 131.9, 136.7, 137.8, 141.5; HREIMS *m/z* Calcd for C₁₄H₁₂N₂ (M⁺) 208.1000, Found 208.1003.

3-(*p*-Tolyl)pyrazolo[1,5-*a*]pyridine (**11h**): White powder; mp 75-78 °C; ¹H-NMR (400 MHz, CDCl₃): δ 2.42 (3H, s, CH₃-Ar), 6.80 (1H, t, *J* = 6.9 Hz, Ar-H), 7.17 (1H, br dd, *J* = 8.8, 6.8 Hz, Ar-H), 7.28 (1H, d, *J* = 8.0 Hz, Ph-H), 7.51 (2H, d, *J* = 7.8 Hz, Ph-H), 7.82 (1H, d, *J* = 9.2 Hz, Ar-H), 8.13 (1H, s, pyrazole-H), 8.50 (1H, d, *J* = 6.8 Hz, Ar-H); ¹³C-NMR (100 MHz, CDCl₃): δ 21.1, 111.9, 117.5, 123.7, 127.0, 129.0, 129.7, 130.2, 136.0, 136.7, 140.3; HREIMS *m/z* Calcd for C₁₄H₁₂N₂ (M⁺) 208.1000, Found 208.0999.

3-(Thiophen-3-yl)pyrazolo[1,5-*a*]pyridine (**11i**): White powder; mp 63-66 °C; ¹H-NMR (400 MHz, CDCl₃): δ 6.80 (1H, t, *J* = 6.9 Hz, Ph-H), 7.19 (1H, dd, *J* = 8.8, 6.7 Hz, Ph-H), 7.37-7.40 (2H, m, Ar-H), 7.43-7.46 (1H, m, Ar-H), 7.79 (1H, d, *J* = 9.0 Hz, Ar-H), 8.13 (1H, s, pyrazole- or thiazole-H), 8.49 (1H, d, *J* = 7.1 Hz, Ar-H); ¹³C-NMR (100 MHz, CDCl₃): δ 108.3, 112.0, 117.5, 118.7, 123.9, 126.1, 126.8, 129.0, 133.3, 136.9, 140.3; HREIMS *m/z* Calcd for C₁₁H₈N₂S (M⁺) 200.0248, Found 200.0405.

Hydrogenation of **10** to 3-aryl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (**12**) (Schemes 3 and 6)

Typical procedure (Scheme 3): To a solution of **10a** (7.7 mg, 3.9 × 10⁻² mmol) in MeOH (5 mL), was added Pd/C (0.8 mg, 10 mol%). The reaction flask was filled with H₂ gas from a balloon, and the reaction mixture was stirred at rt for 24 h under almost 1 atm. After removal of Pd/C catalyst by filtration, the filtrate was concentrated under reduced pressure to give a crude residue which was purified by silica gel column chromatography (eluent: Hexane/AcOEt = 8 : 1) to afford 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (**12a**) (7.5 mg, 96%). **12a**²³: White powder; mp 78-81 °C; ¹H-NMR (400 MHz, CDCl₃): δ 1.89-1.94 (2H, m, -CH₂CH₂CH₂-), 2.06-2.12 (2H, m, -CH₂CH₂CH₂-), 2.96 (2H, t, *J* = 6.4 Hz, -CH₂CH₂Ar), 4.21 (2H, t, *J* = 6.2 Hz, -NCH₂CH₂-), 7.21-7.25 (2H, m, Ph-H), 7.36-7.41 (3H, m, Ph-H), 7.68 (1H, s, pyrazole-H); ¹³C-NMR (100 MHz, CDCl₃): δ 20.5, 23.11, 23.16, 48.2, 118.5, 125.8, 126.8, 128.6, 133.6, 135.8, 137.2; HREIMS *m/z* calcd for C₁₃H₁₄N₂ (M⁺) 198.1157, Found 198.1154.

3-(4-Methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (**12b**): White powder; mp 105-108 °C; ¹H-NMR (400 MHz, CDCl₃): δ 1.61-1.93 (2H, m, -CH₂CH₂CH₂-), 2.05-2.11 (2H, m, -CH₂CH₂CH₂-), 2.91 (2H, t, *J* = 6.4 Hz, -CH₂CH₂Ar), 3.83 (3H, s, -OCH₃), 4.20 (2H, t, *J* = 6.2 Hz, -NCH₂CH₂-), 6.92-6.94 (2H, m, Ph-H), 7.30-7.33 (2H, m, Ph-H), 7.61 (1H, s, pyrazole-H); ¹³C-NMR (100 MHz, CDCl₃): δ 20.6, 23.0, 23.2, 48.2, 55.3, 114.1, 118.2, 126.2, 128.0, 135.3, 137.0, 157.8; HREIMS *m/z* calcd for C₁₄H₁₆N₂O (M⁺) 228.1263, Found 228.1264.

4-(4,5,6,7-Tetrahydropyrazolo[1,5-*a*]pyridin-3-yl)benzotrile (**12c**): White powder; mp 141-145 °C; ¹H-NMR (400 MHz, CDCl₃): δ 1.92-1.97 (2H, m, -CH₂CH₂CH₂-), 2.05-2.13 (2H, m, -NCH₂CH₂CH₂-),

2.96 (2H, t, $J = 6.4$ Hz, $-\text{CH}_2\text{CH}_2\text{Ar}$), 4.22 (2H, t, $J = 6.2$ Hz, $-\text{NCH}_2\text{CH}_2-$), 7.47-7.50 (2H, m, Ph-H), 7.63-7.66 (2H, m, Ph-H), 7.73 (1H, s, pyrazole-H); ^{13}C -NMR (100 MHz, CDCl_3): δ 20.3, 22.9, 23.4, 48.3, 108.8, 117.0, 119.2, 126.7, 132.5, 136.8, 137.4, 138.5; HREIMS m/z calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3(\text{M}^+)$ 223.1109, Found 223.1107.

3-(4,5,6,7-Tetrahydropyrazolo[1,5-*a*]pyridin-3-yl)aniline (**12d**): White powder; mp 138-141 °C; ^1H -NMR (400 MHz, CDCl_3): δ 1.86-1.92 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.04-2.10 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.94 (2H, t, $J = 6.3$ Hz, $-\text{CH}_2\text{CH}_2\text{Ar}$), 3.74 (2H, br, $-\text{NH}_2$), 4.19 (2H, t, $J = 6.1$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_2-$), 6.55-6.58 (1H, m, Ph-H), 6.72-6.73 (1H, m, Ph-H), 6.79-6.81 (1H, m, Ph-H), 7.14-7.18 (1H, m, Ph-H), 7.64 (1H, s, pyrazole-H); ^{13}C -NMR (100 MHz, CDCl_3): δ 20.5, 23.1, 23.2, 48.2, 112.8, 113.4, 117.3, 118.5, 129.5, 134.7, 135.8, 137.3, 146.6; HREIMS m/z calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3(\text{M}^+)$ 213.1266, Found 213.1265.

3-(*o*-Tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (**12g**): White powder; mp 96-99 °C; ^1H -NMR (400 MHz, CDCl_3): δ 1.85-1.89 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.05-2.12 (2H, m, $-\text{NCH}_2\text{CH}_2\text{CH}_2-$), 2.28 (3H, s, CH_3Ar), 2.68 (2H, t, $J = 6.3$ Hz, $-\text{CH}_2\text{CH}_2\text{Ar}$), 4.24 (2H, t, $J = 6.2$ Hz, $-\text{NCH}_2\text{CH}_2-$), 7.14-7.22 (3H, m, Ph-H), 7.24-7.27 (1H, m, Ph-H), 7.47 (1H, s, pyrazole-H); ^{13}C -NMR (100 MHz, CDCl_3): δ 20.5, 20.6, 22.4, 23.4, 48.0, 117.9, 125.5, 126.8, 130.2, 130.3, 132.7, 136.5, 136.7, 138.7; HREIMS m/z Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2(\text{M}^+)$ 212.1314, Found 212.1312.

3-(*p*-Tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (**12h**): White powder; mp 97-101 °C; ^1H -NMR (400 MHz, CDCl_3): δ 1.87-1.93 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.05-2.12 (2H, m, $-\text{NCH}_2\text{CH}_2\text{CH}_2-$), 2.37 (3H, s, CH_3Ar), 2.94 (2H, t, $J = 6.5$ Hz, $-\text{CH}_2\text{CH}_2\text{Ar}$), 4.21 (2H, t, $J = 6.2$ Hz, $-\text{NCH}_2\text{CH}_2-$), 7.19 (2H, d, $J = 7.9$ Hz, Ph-H), 7.19 (2H, d, $J = 7.9$ Hz, Ph-H), 7.65 (1H, s, pyrazole-H); ^{13}C -NMR (100 MHz, CDCl_3): δ 20.6, 21.1, 23.11, 23.14, 48.2, 118.4, 126.7, 129.3, 130.7, 135.4, 135.6, 137.2; HREIMS m/z Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2(\text{M}^+)$ 212.1314, Found 212.1311.

3-(Thiophen-3-yl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine (**12i**): White powder; mp 82-84 °C; ^1H -NMR (400 MHz, CDCl_3): δ 1.89-1.96 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.04-2.10 (2H, m, $-\text{NCH}_2\text{CH}_2\text{CH}_2-$), 2.93 (2H, t, $J = 6.4$ Hz, $-\text{CH}_2\text{CH}_2\text{Ar}$), 4.21 (2H, t, $J = 6.2$ Hz, $-\text{NCH}_2\text{CH}_2-$), 7.13 (1H, d, $J = 2.9$ Hz, thiazole-H), 7.23 (1H, d, $J = 5.1$ Hz, thiazole-H), 7.36 (1H, dd, $J = 5.1, 3.0$ Hz, thiazole-H), 7.65 (1H, s, pyrazole-H); ^{13}C -NMR (100 MHz, CDCl_3): δ 20.4, 23.0, 23.1, 48.1, 114.0, 118.1, 125.6, 126.6, 134.0, 135.5, 137.0; HREIMS m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{S}(\text{M}^+)$ 204.0722, Found 204.0721.

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