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Synthesis of 6,7-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazines via palladium-catalyzed heteroannulation

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Abstract—A concise and efficient method for the preparation of 6,7-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazines via a palladium-catalyzed heteroannulation is reported. Both conventional and microwave heating were used to perform the reactions, with the latter showing dramatically improved results.

The indole ring system is ubiquitous in nature and also in pharmaceutical products, and has attracted the attention of medicinal chemists due to its wide ranging biological activities and interesting structural variations.[1] Due to the wide range of activities, much attention has also been spent on finding surrogates for this structural class. The pyrrolo[2,3-*b*]pyridine (azaindole) core structure has surfaced over the past few years due to its potential as a pharmaceutical agent.[2]

The pyrrolo[2,3-*b*]pyrazine ring structure has recently received much attention from the pharmaceutical industry, both as a surrogate structure for the indole or azaindole, and as a novel kinase inhibitor.[3] However, even though the popularity of these compounds has increased, references to their synthesis are still scarce,[4] especially for the 6,7-disubstituted variants.[3c] The most general methodology for these compounds involves the reaction of an appropriately chosen 2-alkyl substituted pyrazine with an aryl nitrile (Fig. 1). However, this reaction sequence is still relatively undesirable due to the few commercially available 2-alkyl substituted pyrazines, the low reaction yields, and the need for an arylnitrile partner.

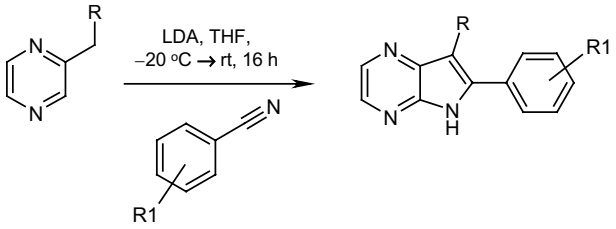

Figure 1. Synthesis of 6,7-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazines by base mediated cyclization.[3c]

The dearth of publications on the synthesis of 6,7-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazines led us to investigate the extension of our recently reported methodology to include these compounds.[5] Our methodology takes advantage of previously published work for the synthesis of 2,3-disubstituted indoles and 2,3-disubstituted-pyrrolopyridines.[6] We were able to overcome the need for an arylnitrile coupling partner and include alkyl substituents in the 6-position. Herein we report the synthesis of 6,7-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazines via a palladium-catalyzed heteroannulation, utilizing both conventional and microwave heating.

In this work we again started with *N*-(3-chloropyrazin-2-yl)-methanesulfonamide **1**.[7] Thus, our first attempts used the optimized reaction conditions that were previously reported ($Cl_2Pd(dppf)$, LiCl, Na_2CO_3) while heating at 100 °C in DMF[8] (Table 1). The reaction

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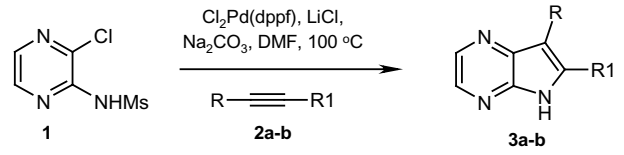
Table 1. Synthesis of 6,7-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazines via conventional heating



Entry	R	R1	Product	Time (h)	Yield (%)
1	Me	Ph	**3a**	18	10[a]
2	$-(CH_2)_2CH_3$	Ph	**3b**	84	26[b]

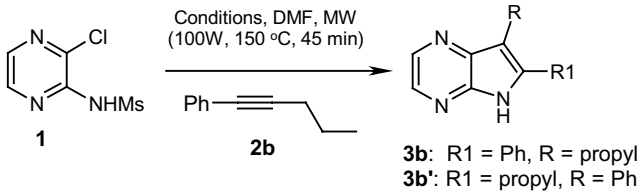
[a] 3:1 mixture of regioisomers (^{1}H NMR).
[b] 3.8:1 mixture of regioisomers (^{1}H NMR).

proceeded but the time required was considerably longer than previous examples. Also, the reaction yield was quite low with a large amount of starting material recovered. The following trial was allowed to proceed for a longer time (84 h) resulting in a higher yield, but the time was prohibitive. Also, the differentially substituted alkynes gave mixtures of regioisomers, which were not observed in the analagous reactions with indoles and azaindoles.[6]

Taking note of a recent publication by Senanayake and co-workers[9] detailing work using *o*-chloroanilines to synthesize 2,3-disubstituted indoles, we next decided to investigate alternative conditions for the reaction. Senanayake and co-workers utilized electron-rich phosphine ligands in order to affect the transformation. Thus, we tried a variety of electron-rich ligands (Table 2). Due to the long reaction times encountered using conventional heating, we explored the reaction using microwave irradiation in an attempt to shorten the reaction times to a more reasonable level. Our initial entry, from our previously optimized reaction, proved to be optimal in this reaction sequence also. Even the optimized reaction conditions for the indole equivalent[9] (Table 2, entry 8) proved inferior using our substrate, confirming our previously reported conditions for the synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines.[5] We were unable to attain the same levels of regiochemistry as that reported for the indole substrates. This lack of specificity observed may be due, in part, to the methanesulfonyl protecting group on the nitrogen. However, we did not see any of the amination/dimer coupling product as seen in the reaction of the *o*-chloroaniline substrate.[9]

After having settled on the optimized conditions for the reaction, the first entries were performed on the same substrates as the conventional heating for a direct comparison. As can be seen in Table 3, the use of microwave irradiation dramatically shortened the reaction times and improved the yields to a more synthetically useful level (entries 1 and 2). The use of microwave reaction conditions allowed the cyclization to proceed in a matter of minutes versus hours (and even days) under conventional heating, and also improved the reaction yields. As can be seen in Table 3, the reaction proceeds with a variety of substrates utilizing alkyl, aryl, and heteroaryl substituents and even a free alcohol (entry 7). When the phenyl

Table 2. Optimization of reaction conditions



Entry	Conditions	**3b**:**3b′**	Yield (%)
1	$Cl_2Pd(dppf)$, Na_2CO_3, LiCl	3:1	36
2	$Cl_2Pd(PPh_3)_2$, Na_2CO_3, LiCl	—	Dec.
3	$Pd(OAc)_2$, PCy_3, K_2CO_3	3.6:1	6
4	$Pd(OAc)_2$, P*t*-Bu_3, K_2CO_3	3.7:1	15
5	$Pd(OAc)_2$, **6**, K_2CO_3	2.4:1	27
6	$Pd(OAc)_2$, **7**, K_2CO_3	3.3:1	18
7	$Pd(OAc)_2$, **8**, K_2CO_3	3.6:1	5
8	$Pd(OAc)_2$, **9**, K_2CO_3	4.5:1	12
9	$Pd(OAc)_2$, **4**, K_2CO_3	4.6:1	8
10	$Pd(OAc)_2$, **5**, K_2CO_3	3.8:1	8.5
11	$Pd(OAc)_2$, **10**, K_2CO_3	—	Dec.

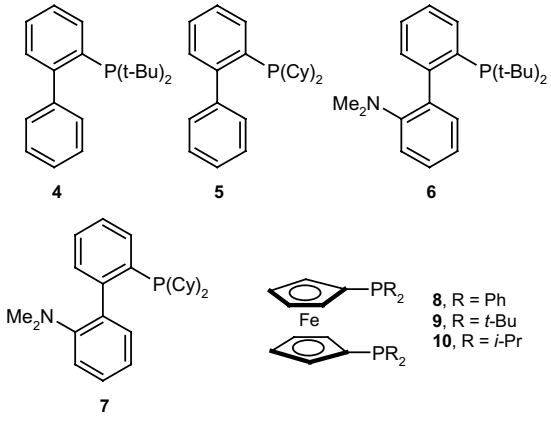
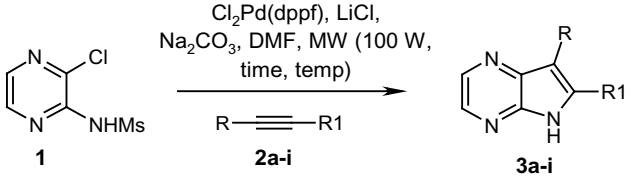


Table 3. Synthesis of 6,7-disubstituted-5*H*-pyrrolo[2,3-*b*]pyrazines via microwave conditions



Entry[a]	R	R1	Product	Yield (%)
1	Me	Ph	**3a**	37[b]
2	$-(CH_2)_2CH_3$	Ph	**3b**	36[c]
3	Ph	Ph	**3c**	41
4	$-(CH_2)_3CH_3$	Ph	**3d**	45[b]
5	Me	TMS	**3e**	Dec.
6	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	**3f**	42
7	$-CH(OH)CH(CH_3)_2$	Ph	**3g**	39
8	$-(CH_2)_3CH_3$	2-Thiazole	**3h**	37
9	$-(CH_2)_3CH_3$	2-Thiophene	**3i**	40

[a] Reactions were run for 45 min and 150 °C, except entry 2, which was run at 175 °C.
[b] 5:1 mixture of regioisomers (^{1}H NMR).
[c] 3:1 mixture of regioisomers (^{1}H NMR).

substituted alkyl alkynes were used (entries 1, 2, and 4), the products were isolated as regioisomeric mixtures.[10] However, using the heteroaryl substituted alkyl alkynes (entries 8 and 9) only one regioisomer was isolated. This could be due to the electron-rich nature of the heterocyclcs biasing one position of the alkyne to insertion.[9]

Noting the use of silyl-protected internal alkynes in previous palladium-catalyzed cyclizations led us to investigate this useful group as a potential surrogate for further manipulation. We have previously tried using silyl alkynes[5a] and observed that the products undergo desilylation after cyclization. However, using the internal silylated alkyne, there was no product observed either with or without the silyl group. It was suspected that the TMS group was just too labile for these conditions; however, use of either TIPS or TBDMS groups gave the same result. Even though a variety of groups are tolerated under these reaction conditions (alkyl, hydroxy, aryl, heteroaryl), silyl groups to this point do not participate and only lead to undesired byproducts.

Representative example:[11] *N*-(3-Chloropyrazin-2-yl)-methanesulfonamide **1** (179.6 mg; 0.8650 mmol), 1-phenyl-1-propyne (130 μL; 1.03 mmol), $Cl_2Pd(dppf)$ (37.9 mg; 0.0464 mmol), LiCl (44.8 mg; 1.06 mmol), and Na_2CO_3 (188.1 mg; 1.775 mmol) were dissolved in DMF (4.0 mL) and the resulting mixture was degassed by passing an N_2 stream through the sample. After 10 min, the reaction vessel was reacted under microwave conditions (100 W, 150 °C, 45 min). The reaction mixture was cooled to rt, diluted with H_2O, and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (10 g pre-packed SiO_2 column from ISCO; 50% EtOAc/heptane eluent) to yield 66.5 mg (0.319 mmol; 37%) of 7-methyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine and 6-methyl-7-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine (mixture of regioisomers, 4:1, respectively), **3a** as a tan solid. HPLC (SYNGERI 2U HYDRO-RP 20X4.0MM COL, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 10/90→90/10): R_f = 3.06 min. $C_{13}H_{11}N_3$ (209.25) MS (ESI) 210 (M+H). ^{1}H NMR (300 MHz, DMSO-d_6) Major δ 12.1 (s, 1H), 8.35 (d, 1H, J = 2.6 Hz), 8.20 (d, 1H, J = 2.6 Hz), 7.78–7.71 (m, 2H), 7.54 (t, 2H, J = 7.8 Hz), 7.46–7.41 (m, 1H), 2.45 (s, 3H). Minor δ 8.33 (d, 0.2H, J = 2.6 Hz), 8.16 (d, 0.2H, J = 2.6 Hz), 7.28–7.24 (m, 0.2H), 2.61 (s, 0.6H).

In conclusion, the palladium-catalyzed heteroannulation that was previously reported for the synthesis of monosubstituted pyrrolopyrazines has been extended to include disubstituted variants. The reaction proceeds under microwave irradiation conditions to yield the desired products in modest overall yields. This methodology offers an extension of the previously known reaction sequence and allows for a variety of substrates to be synthesized that were not available via the previous methods. Efforts are underway to extend this methodology to include more elaborate compounds and results will be reported in due course.

Acknowledgements

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References and notes

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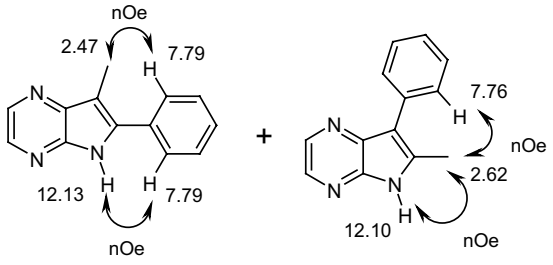
7. As with the previous examples, the 2-amino-3-chloropyrazine did not participate in this reaction (Ref. 5).
8. Increasing the temperature (even up to 175 °C) did not improve the reaction yields or times.
9. Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129–4132.
10. Both ^{1}H and NOESY NMR spectra were acquired for **3a** to determine the correct regiochemistry with respect to the major and minor species present. The ^{1}H and NOESY NMR data are consistent with the structures below for the major and minor species. The key NOESY correlations that distinguish the major isomer's regiochemistry are those between the pyrrolo[2,3-*b*]pyrazine methyl protons at 2.47 ppm and the phenyl *ortho* protons at 7.79 ppm and between the pyrrolo[2,3-*b*]pyrazine amine proton at 12.13 ppm and the same phenyl*ortho* protons at 7.79 ppm. The key NOESY correlations that distinguish the minor isomer's regiochemistry are those between the pyrrolo[2,3-*b*]pyrazine methyl protons at 2.62 ppm and the phenyl *ortho* protons at 7.76 ppm and the pyrrolo[2,3-*b*]pyrazine amine proton at 12.10 ppm and the same

methyl protons at 2.62 ppm. All of these NMR spectra were obtained in DMSO-d_6 at 25 °C using a Varian Unity Inova 500 MHz spectrometer.



Major Isomer Minor Isomer

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11. All new compounds were characterized by high resolution LC–MS and ^{1}H NMR and found to be in agreement with their structures.