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An improved method for the synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines via palladium-catalyzed heteroannulation using microwave heating

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Abstract—We herein report an improved synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines utilizing microwave heating. The reaction is a palladium-catalyzed heteroannulation process followed by deprotection to yield the desired substrates in good yield.

Microwave-assisted organic synthesis has received a vast amount of attention over the last several years.[1] The breadth of reactions that have been performed under these conditions is an ever increasing entity. One such reaction that has been used successfully under microwave conditions is transition metal-catalyzed couplings using a variety of substrates and conditions. The Sonogashira coupling,[2] Stille reaction,[3] Suzuki reaction,[4] aryl amination,[5] allylic alkylations,[6] and Heck reactions[7] have all been investigated and have been shown to perform well in the microwave. One distinct advantage of using microwave conditions is that it can increase the rate of reaction, sometimes very drastically.

We have previously reported[8] a novel synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines via a palladium-catalyzed heteroannulation process (Fig. 1). This process was shown to work well with a variety of substrates; however, when alkyl alkynes were used the reaction times were dramatically increased over the aromatic alkynes. The reaction yields ranged from 36% to 63% for a one-pot, three-step reaction.[9] In this communication, we report improved reaction conditions to synthesize these compounds utilizing microwave conditions to increase the reaction rates (especially with alkyl alkynes).

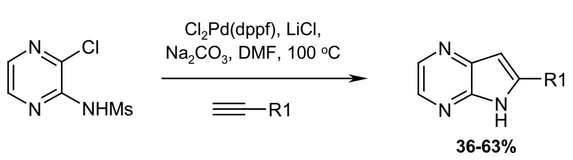

Figure 1. Synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines via conventional heating.

In the previously described study, we were unable to affect the coupling and subsequent cyclization with an unsubstituted aniline derivative. Using the microwave reaction conditions, we felt that the increased reactivity might allow this transformation to occur. However, as shown in Scheme 1,[10] the Sonogashira coupling did take place (under the appropriate conditions), but the aniline did not participate in the cyclization. As in the previous examples, the cyclization could be accomplished with a second, base-induced step. However, in the absence of CuI, neither the Sonogashira coupling,[11] nor the cyclization, took place, even under extended reaction times ($Cl_2Pd(dppf)$, LiCl, Na_2CO_3, DMF, MW, 100 W, 150 °C, 4 h).

Next, we turned our attention to the sulfonamide **5**, which was successful in the previous examples. The reaction proceeds with this starting material to yield the desired 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines, **4a–j**, in good overall yield (Table 1).[12] There were a number of reaction conditions that were evaluated and most of them investigated gave acceptable results. The lone

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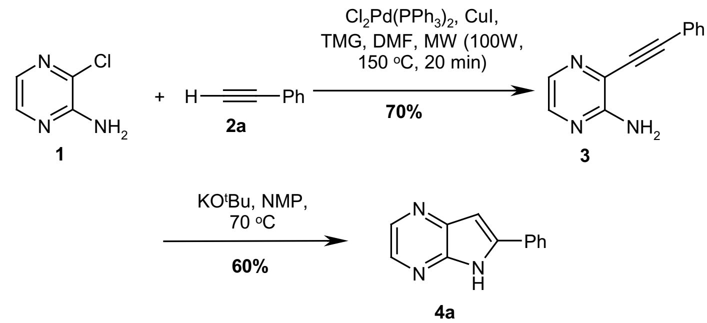
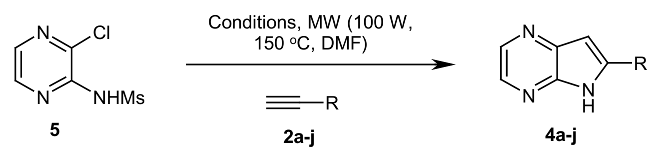


Scheme 1. Synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazine via two-step protocol of Sonogashira coupling under microwave conditions followed by base-induced cyclization.

Table 1. Cyclization with 2-chloro-3-(*N*-methansulfonamide) pyrazine utilizing a microwave reaction protocol



Entry	R	Method[a]	Time (min)	Product	Yield (%)
1	Phenyl	A	15	**4a**	39
2	3-Pyridyl	A	15	**4b**	48
3	4-Fluorophenyl	A	15	**4c**	49
4	Phenyl	B	20	**4a**	46
5	2-Methylphenyl	B	20	**4d**	24
6	2-Trifluoromethylphenyl	B	20	**4e**	65
7	4-Methoxyphenyl	B	20	**4f**	64
8	Phenyl	C	20	**4a**	19
9	Phenyl	D	20	**4a**	57
10	4-Fluorophenyl	D	20	**4c**	54
11	4-Cyanophenyl	D	20	**4g**	45
12	4-Acetonitrilephenyl	D	20	**4h**	43
13	Butyl	D	20	**4i**	55
14	$-(CH_2)_4$OTBDPS	D	20	**4j**	60

[a] Method A: $Cl_2Pd(PPh_3)_2$, CuI, 1,1,3,3-tetramethylguanidine; method B: $Cl_2Pd(dppf)$, CuI, 1,1,3,3-tetramethylquanidine; method C: $Pd(OAc)_2$, LiCl, K_2CO_3, PPh_3; method D: $Cl_2Pd(dppf)$, LiCl, Na_2CO_3.

exception was method C, which gave only 19% of the desired compound. This set of conditions also performed poorly under the conventional heating. From the table it can be determined that the reaction proceeds smoothly[13] giving the desired compounds in good yields for the overall three-step protocol. The cyclization sequence performs equally well with (methods A and B) and without (method D) the addition of CuI. The microwave conditions also tolerate much functional diversity (both electron-donating and electron-withdrawing functionalities). Halogens as well as cyano groups are well tolerated, along with silyl protected alcohols.

The direct comparison of the conventional and microwave heating conditions can be seen in Table 2. As can be seen from the table, all the substrates investigated perform well with much decreased reaction times in the microwave as compared to the conventional heating. The most drastic decrease in reaction times were observed for the alkyl alkynes (**4i** and **4j**). Also of note, when compound **4i** was synthesized under the conventional heating method a mixture of the sulfonylated and desulfonylated cyclized materials was isolated. In contrast, when the microwave conditions were used only the desulfonylated material was isolated.

Table 2. Comparison of reactions performed under conventional heating with those performed under microwave conditions

Compd	Conventional heating (time, yield)	Microwave heating (time, yield)
4a	3 h, 63%	20 min, 57%
4d	1.5 h, 57%	20 min, 24%
4e	1 h, 57%	20 min, 65%
4i	15 h, 52%	20 min, 55%
4j	20 h, 63%	20 min, 60%

In conclusion, we are reporting an improved synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines utilizing microwave reaction conditions. This methodology improves upon our earlier results using conventional heating to affect the same transformation. The reaction conditions are operationally simple and dramatic increases in the reaction rates can be observed. Further extension of this methodology to include more elaborate substrates are currently on-going in our laboratory and will be reported in due course.

Acknowledgements

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12. Representative example: *N*-(3-chloropyrazin-2-yl)-methansulfonamide **5** (163 mg; 0.785 mmol), 4-*tert*-butylphenylacetylene (128 mg; 0.806 mmol), $Cl_2Pd(PPh_3)_2$ (17.2 mg; 0.0245 mmol), CuI (9.80 mg; 0.0510 mmol), and 1,1,3,3-tetramethylguanidine (295 μL; 2.35 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, 20 min). The 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:Hept eluent) to yield 115 mg (0.458 mmol; 58%) of 6-(4-*tert*-butylphenyl)-5*H*-pyrrolo[2,3-*b*]pyrazine **4a** as a tan solid. HPLC (SYNERGI 2U HYDRO-RP 20X4.0MM COL, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 10/90 → 90/10): R_f = 3.22 min. $C_{16}H_{17}N_3$ (251.33) MS (ESI) 252 (M+H). ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 12.4 (s, 1H), 8.34 (d, 1H, J = 2.6 Hz), 8.18 (d, 1H, J = 2.6 Hz), 7.94 (d, 2H, J = 8.5 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.08 (d, 1H, J = 2.0 Hz), 1.33 (s, 9H).
13. The reaction was monitored at times: 5, 10, 15 and 20 min and the reaction was deemed complete at 20 min due to full consumption of the SM.