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Microwave-assisted three component one-pot synthesis of pyrimido-oxazepines

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Abstract—A synthetic approach toward pyrimido-oxazepine analogs was developed through the use of microwave heating. Certain analogs can be made in one step, which make this a valuable tool in the investigation of this therapeutically relevant scaffold.

It has become a widely accepted view that many classical reactions perform better under microwave irradiation than not.[1] In attempts to synthesize pyrimido[4,5-*b*]-[1,4]benzoxazepin-4-amines, it was discovered that such compounds could be accessed in a one-pot synthesis from 4,6-dichloropyrimidine, salicylaldehydes, and amines through the use of microwave heating. This finding is especially relevant given a series of recent publications that have revealed pyrimidio-oxazepines to be potent inhibitors of the epidermal growth factor receptor (EGFR),[2,3] which is the biological target of such cancer therapeutics as Iressa and Tarceva.[4,5] Our one-pot approach could be a valuable tool in studying the SAR of this chemotype.

Published synthetic routes to the pyrimido[4,5-*b*][1,4]-benzoxazepines proceeded through several pathways,[2,6–8] all of which had limitations (Scheme 1). In approach 1,[2] anilines were reacted with dichloropyrimidines to give intermediate **2**. Benzoxazepine ring **3** was formed in a condensation between the chloropyrimidine and the salicylaldehyde. Finally, the imine was reduced with sodium borohydride to give 4,5-dihydro compound **4**. A self-acknowledged shortcoming of this pathway was that only a narrow range of anilines performed well. In approach 2,[7] phenols were reacted with the dichloropyrimidine to provide ether **5**. Benzoxazepine **6** was formed via a Mannich cyclization with the ether. Then, the aniline displaced the chloride to give the final product. This pathway eliminated the need for the imine reduction. However, the substitution pattern of the phenols capable of being used in this pathway was limited due to regioselectivity issues in the Mannich reaction. In approach 3,[6] the formation of the benzoxazepine proceeded through imine intermediate **7**. In this approach, electron deficient aldehydes worked best. Substitution at the 6-position of the salicylaldehydes was not supported presumably due to the inhibition of imine formation.

In trying to access the pyrimido[4,5-*b*][1,4]benzoxazepin-4-amines, it was discovered that in the case of primary and secondary aliphatic amines, the product could be produced in one step by mixing amine, pyrimidine, aldehyde and heating using a SmithCreator microwave from Personal Chemistry (Scheme 2, approach A).[9] Upon synthesis of **9**, 2 equiv of $NaBH_4$ were added to the vial along with 1 mL of ethanol for solubility and the reaction was stirred overnight to afford product **10**. Similar to previously published reports,[2,6–8] a stepwise approach using acid catalysis was needed when anilines were coupled to the chloropyrimidine (approach B).[10] The reaction could still be performed in one pot, however. After the aniline was reacted with the pyrimidine, excess Cs_2CO_3 was added to quench the acid and make the reaction basic for the addition of the aldehyde. Imine **9** was reduced with $NaBH_4$ as it was in the case of approach A to the final amine **10**. No transfers of the reaction solution were necessary between the start and the completion of the synthesis and all the compounds discussed in this paper were made in less than

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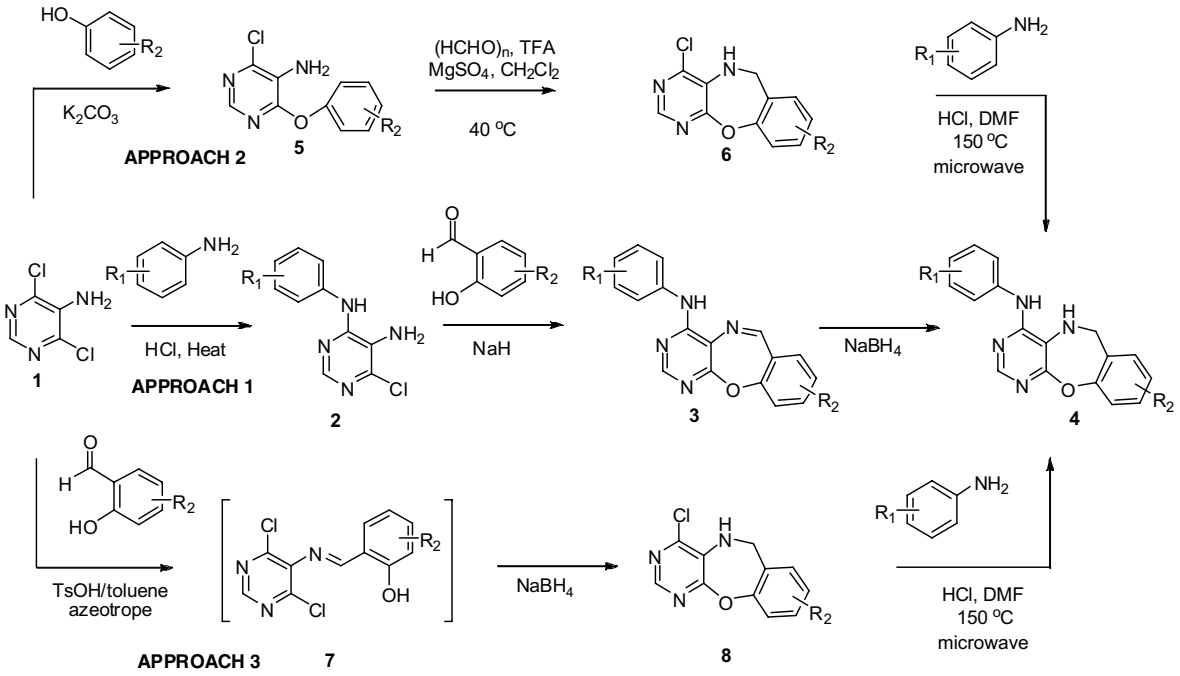
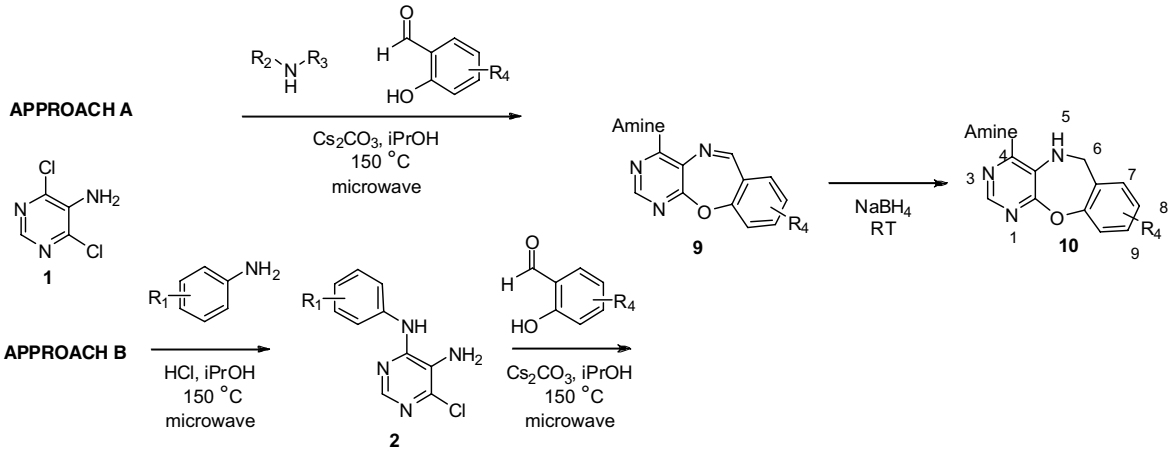


Scheme 1. Previous approaches.



Scheme 2. One-pot approaches.

24 h. All reactions were purified using HPLC–MS purification.[11]

The one-pot approach is fairly robust in both the variety of amines and salicylaldehydes capable of being incorporated and the availability of both imines **9** and amines **10** as the final products. The examples of the products made are shown below (Table 1). The products are available in as little as 10 min for the imines and in less than 24 h for the amines. This could be very valuable especially with the iterative synthesis necessary during the development of structurally related therapeutics. Typical reaction times in the literature take 3–4 days and three chromatographies. The yields shown in Table 1 are of purified compounds and they compare very favorably to those obtained in the prior art.[2,6–8] For example, the literature reports the overall yield of **10f** to be 8%.[2] Using our method, **10f** was obtained in a 35% yield. A separate publication[6] indicates yields for molecules of the type **10e–i** were made in overall yields ranging between 8% and 18%. We were able to make the compounds in the yields of 30–41%. Additionally, this approach allows access to analogs not accessible from the current methods. Notable among these is the ability to introduce substitution(s) at the 7-position. Some of the existing methods have been unable to produce analogs with substitution at this position.[6] The authors suggested that steric hindrance may prevent imine formation. However, the analogs with substitution at this position have appeared in a subsequent publication,[3] although no yields were given.

It is interesting to note that the yields obtained for the reduced products **10** were lower when aryl amines were

Table 1. Examples of products made from one-pot method

Compound	Amine	Salicylaldehyde	Approach	Yield[11]
9a	Aniline	$R_4 = H$	B	38
9b	Benzylamine	$R_4 = H$	A	71
9c	Piperidine	$R_4 = H$	A	63
10a	Aniline	$R_4 = H$	B	42
10b	Benzylamine	$R_4 = H$	A	98
10c	Piperidine	$R_4 = H$	A	74
10d	Aniline	$R_4 = 5$-OMe	B	41
10e	3-F–aniline	$R_4 = 5$-OMe	B	30
10f	3-CN–aniline	$R_4 = 5$-OMe	B	35
10g	4-Cl–aniline	$R_4 = 5$-OMe	B	31
10h	Aniline	$R_4 = 5$-F	B	31
10i	Aniline	$R_4 = 6$-OMe	B	41

used in the syntheses. With these less reactive amines, it was difficult to find conditions that drove the reactions to completion without resulting in side products or decomposition. Isopropanol was used as the reaction solvent and produced much cleaner reaction mixtures than the other solvents explored (DMF, DMSO, and ACN). Since isopropanol is a modest microwave absorber, it was difficult to push the temperature higher than 150 °C. Side products varied according to the reagents used but included di-addition of the amine in the first step and reaction of the amine with the salicylaldehyde. Optimization of the method is ongoing. Also, yields of some of imines **9** were lower than amines **10** that would result from their reduction. Certain compounds exhibited a small amount of instability under the purification conditions and methods are currently being optimized to minimize decomposition.

In conclusion, the one-pot approach provides a flexible and facile pathway to the pyrimido[4,5-*b*][1,4]benzoxazepin-4-amines. By taking advantage of the speed of microwave chemistry, the fact that no transfers of the reaction mixture need to take place, and no workups of the intermediates are necessary, the products discussed here were produced in less than 24 h. Such a rapid process should allow for an accelerated investigation of the SAR of this scaffold as a cancer therapeutic.

References and notes

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9. A typical procedure would be to add 400 μL of a 0.25 M (100 μmol, 1.0 equiv) solution of **1** in anhydrous isopropanol to a microwave vial with stirbar followed by 100 μL of a 1.0 M (100 μmol, 1.0 equiv) solution of benzyl amine in anhydrous isopropanol. The vial was vortexed. 200 μL of a 0.5 M (100 μmol, 1.0 equiv) solution of salicylaldehyde in anhydrous isopropanol was added followed by 100 mg (excess) of Cs_2CO_3. The vial was capped and then vortexed. The reaction was heated for 10 min at 150 °C using the normal setting on the microwave to produce a compound of type **9**. If the imine was the desired product, it proceeded to workup. If reduction of the imine to the amine was required, the vial was uncapped and 2 equiv of dry $NaBH_4$ was added to the vial followed by 1 mL of ethanol. The vial was capped and vortexed. The vial was heated to 50 °C overnight with stirring. The vial was uncapped. After concentration in vacuo and aqueous workup by portioning between water and DCM, the organic layer was concentrated in vacuo. The residue was suspended in 1 mL of DMSO and purified by HPLC. This yielded 23 mg (74%) of **10c**, a white solid. (M+H) = 321. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.33–7.10 (br m, 4H), 4.45 (d, $J = 3.2$ Hz, 2H), 4.09 (br s, 1H), 3.09 (br s, 4H), 1.64 (br m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160, 155.8, 154.8, 147.3, 130.8, 129.6, 128.7, 124.9, 123.3, 121.4, 49.6, 48, 26.3, 24.6.
10. A typical procedure would be to add 400 μL of a 0.25 M (100 μmol, 1.0 equiv) solution of **1** in anhydrous isopropanol to a microwave vial with stirbar followed by 100 μL of a 1.0 M (100 μmol, 1.0 equiv) solution of aniline in anhydrous isopropanol. The vial was vortexed. Concentrated HCl (5 μL) was added by pipette. The vial was capped and vortexed. The reaction was heated for 10 min at 150 °C using the normal setting on the microwave. The vial was uncapped and 200 μL of a 0.5 M (100 μmol, 1.0 equiv) solution of 5-OMe–salicylaldehyde in anhydrous isopropanol was added followed by 100 mg (excess) of Cs_2CO_3. The vial was capped and then vortexed. The reaction was heated for 10 min at 150 °C using the normal setting on the microwave to produce a compound of type **9**. If the imine was the desired product, the reaction proceeded to workup. If reduction of the imine to the amine was required, the vial was uncapped and 2 equiv of dry $NaBH_4$ was added to the vial followed by 1 mL of ethanol. The vial was capped and vortexed. The vial was heated to 50 °C overnight with stirring. The vial was uncapped. After concentration of the reaction in vacuo and aqueous workup by portioning between water and DCM, the organic layer was concentrated in vacuo. The residue was suspended in 1 mL of DMSO and purified by HPLC. This yielded 12 mg (41%) of **10d**, a yellow solid. (M+H) = 283. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79 (br s, 1H), 8.01 (s, 1H), 7.46 (m, 2H), 7.26 (m, 2H), 7.11 (d, J = 8.6 Hz, 2H), 6.71 (m, 2H) 4.37 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 157.2, 148.8, 145.1, 137.4, 132.2, 129.2, 125.7, 122.4, 121.8, 115.1, 114.1, 114, 55.9, 47.5.
11. All reactions were purified using HPLC–MS purification. *Equipment*: A Maccel semi-prep SH-C18 50 × 20 mm column was used. All compounds were purified using a Shimadzu HPLC system consisting of two LC-8A prep pumps, LC-10ADvp pump, 2 SPD-10A UV detectors, and an SCL-10A system controller. Two Gilson liquid

handlers were used for injection and collection and a Waters ZQ mass spectrometer was used for detection. The Masslynx version 4.0 platform controlled the injections and tracked all data outputs.

Experimental conditions: Purification was done by RP-HPLC with MS trigger using a gradient of water (solvent A) and acetonitrile (solvent B) with 0.1% TFA and a 2.5 min run time. Molecular weights were detected using positive electrospray ionization mode on the mass spectrometer with a cone voltage of 20 V. These conditions were optimized for individual compounds using varying acetonitrile/water gradients.