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Improved synthesis of functionalized 5,6-dihydro-pyrimido[4,5-*b*][1,4]oxazepines

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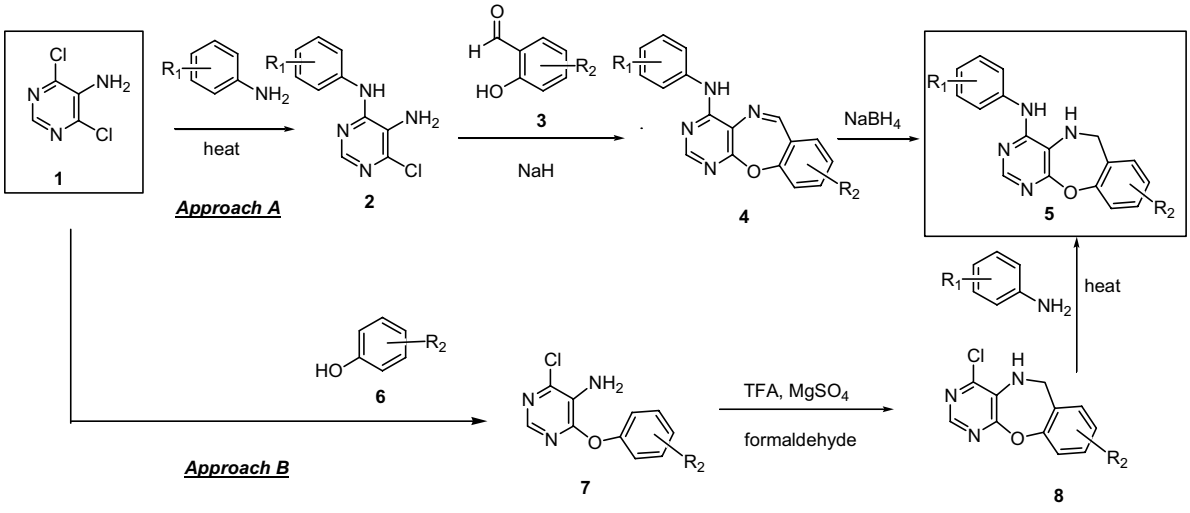
Abstract—Novel synthetic approaches toward 5,6-dihydro-pyrimido[4,5-*b*][1,4]oxazepines were reported that led to successful introduction of poorly reactive anilines and various 2-hydroxybenzaldehydes to this therapeutically relevant scaffold. More extensive SAR studies on this scaffold hence became possible.

Recently, the 5,6-dihydro-pyrimido[4,5-*b*][1,4]oxazepines **5** were described by us as potent EGFR inhibitors.[1] Additional attractive features of this scaffold also include its good PK profile. Prior to our work in this field, there was only one reported synthesis of the 5,6-dihydro-pyrimido[4,5-*b*][1,4]oxazepines,[2] and that route was adopted by us for the initial SAR work on the oxazepines (Scheme 1, approach A). Although it could be applied to a number of aldehydes (**3**), the synthesis was not convergent enough to allow facile variation of the anilines. This limitation was soon overcome by a Mannich cyclization approach developed by us (Scheme 1, approach B).[3] Nevertheless, this approach worked only with phenol **6** that bore electron donating groups, and certain restrictions on substitution pattern of **6** were also applied. Moreover, both approaches required reasonable nucleophilicity of the anilines to ensure the thermal or microwave assisted chloride



Scheme 1.

Keywords: Oxazepines; Reductive amination.
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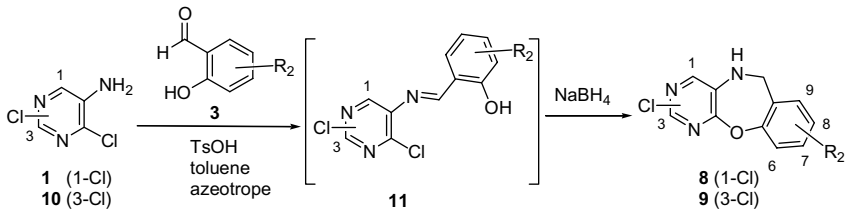
Table 1. Formation of **8/9** using reductive amination conditions



Compound	Cl	R_2	Conditions	% Yield[a]
9a	3-Cl	8-NO_2	A[b]	40
8a	1-Cl	8-NO_2	A	80
8b	1-Cl	H	B[c]	33
8c	1-Cl	6-OH	B	34
8d	1-Cl	6-OMe	B	36
8e	1-Cl	7-OH	A	0
8e	1-Cl	7-OH	B	8
8f	1-Cl	7-OMe	B	25
8g	1-Cl	8-OMe	B	55
8h	1-Cl	8-F	B	56
8i	1-Cl	9-OMe	B	0

[a] Isolated yield.
[b] Conditions A, detailed procedure in Ref. 5.
[c] Conditions B, detailed procedure in Ref. 6.

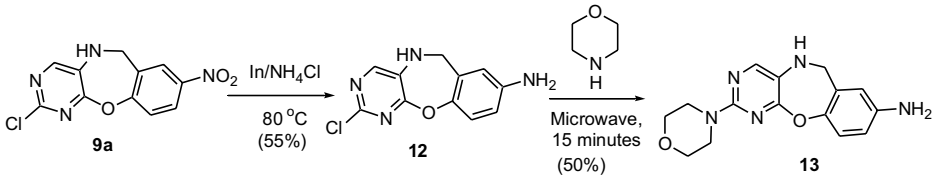
displacement in either **1** or **8**, and synthesis of **5** with heteroaryl amines remained unexplored.

Our interests in developing the benzoxazepines as kinase inhibitors necessitated a more general preparation of intermediate **8** and its 3-Cl regioisomer **9** (Table 1).[4] Previous attempts to make the oxazepine **8/9** via approach A (Scheme 1) all failed. Furthermore, the overall substitution patterns of R_2, for example, hydroxy or nitro, excluded the possibilities of using the Mannich type approach (Scheme 1, approach B) due to either regioselectivity issue during the addition step (**1** to **7**, Scheme 1), or the nitro's deactivating effect on the cyclization (e.g., **7** to **8**, Scheme 1). We hence envisioned a new synthetic route to those compounds via reductive amination reactions between amines **1/10**, and aldehydes **3**.

In the present study, imine **11** was first formed under acid catalyzed condition in toluene with azeotropic removal of water and a brief survey of the acids showed no difference among *p*-toluene sulfonic acid (*p*-TsOH), 10-camphor sulfonic acid, and oxalic acid. The formed imines were then reduced with sodium borohydride followed by cyclization to afford **8/9** after standard workup. The yield of the reaction was mainly determined by the extent of the imine formation, which in turn was largely affected by the electronic and steric property of the aldehyde functionality on **3**. As expected, for electron deficient aldehydes such as 2-hydroxy-5-nitro-benzaldehyde, **8a** was obtained in a 80% yield when the imine formation was carried out in toluene under normal azeotropic conditions (conditions A).[5] On the other hand, aldehydes with methoxy or hydroxyl substitutes required several rounds of azeotropic processes to maximize the imine formation (conditions B).[6] It is noteworthy to point out that **8e**, which arose from the reaction of a highly electron enriched *ortho*- and *para*-dihydroxy substituted benzaldehyde, was obtained in a 8% yield using conditions B. However, **8e** was previously not obtainable by using conditions A. Neither conditions A nor B produced **8i**. We assumed that the steric hindrance of the aldehyde moiety prevented the imine formation completely.

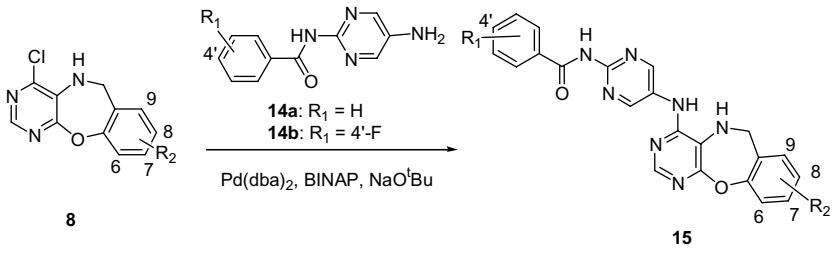
As an example of further chemical elaboration, the nitro in **9a** was reduced with indium in the presence of ammonium chloride to afford aniline **12** (Scheme 2).[7] The chloride in **12** was then displaced by a morpholine under microwave conditions to provide **13**, that served as a useful template for the preparation of therapeutically relevant molecules.

With **8** in hand, we then shifted our attention to the displacement of the chloride in **8** with amine **14** to give **15** (Table 2). Since initial attempts to generate **15** by direct substitution under thermal or microwave conditions all



Scheme 2.

Table 2. Formation of **15** via palladium catalyzed coupling



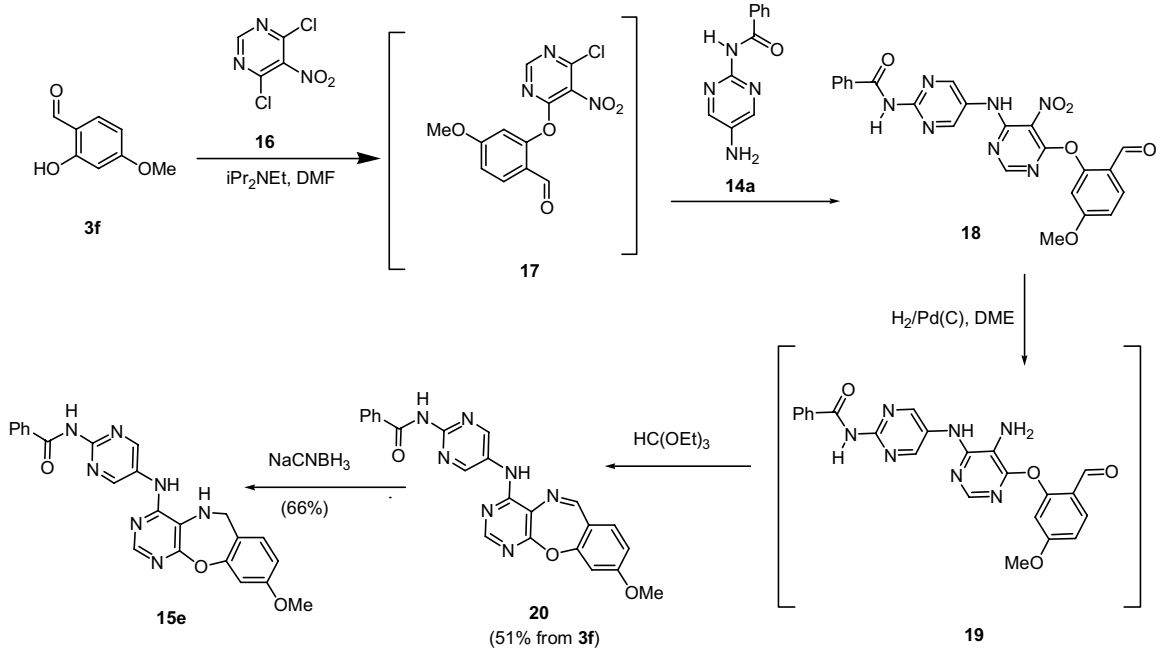
Compound	R_1	R_2	% Yield[a]
15a	H	H	36
15b	4′-F	H	32
15c	H	6-OH	7
15d	H	6-OMe	27
15e	H	7-OMe	53
15f	4′-F	7-OMe	14
15g	H	8-OMe	35
15h	4′-F	8-OMe	22
15i	H	8-F	14

[a] Isolated yield.

failed, the palladium catalyzed coupling conditions[8] became the method of choice. The optimized conditions utilized a catalyst/ligand combination of $Pd(dba)_2$ and *rac*-BINAP, and sodium *tert*-butoxide as the base.[9] The isolated yields of **15**, though modest and variable, were partially due to chromatographic purification followed by recrystallization to ensure purity for biological testing.

In order to get access to such imines as **20**, a further modified synthesis of the oxazepines was developed that exploited the high reactivity of 4,6-dichloro-5-nitropyrimidine **16** (Scheme 3).[10] Its synthetic utility was demonstrated by using 2-hydroxy-4-methoxy-benzaldehyde **3f** as a standard substrate. As expected, a sequential displacement of the chlorides on **16** by hydroxyl aldehyde **3f**, followed by **14a**, afforded crude **18**. A one-pot reduction of the nitro group on **18**, followed by triethyl orthoformate promoted cyclization, gave imine **20** in a 51% overall yield. Standard reduction of **20** with $NaCNBH_3$ gave **15e**, with its spectroscopic properties identical to those obtained previously.

In conclusion, the synthetic methods reported herein led to the successful introduction of poorly reactive anilines and various 2-hydroxybenzaldehydes to the 5,6-dihydropyrimido[4,5-*b*][1,4]oxazepines scaffold, whereby allowing a more extensive SAR study on this scaffold. The biological results for some of the compounds prepared in this study will be reported in due course.



Scheme 3.

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5. Compound **8a** (conditions A): In a 200 mL round-bottomed flask equipped with a Dean–Stark trap and a condenser were placed 5-amino-2,4-dichloropyrimidine (20 mmol, 3.26 g), 2-hydroxy-5-nitrobenzylaldehyde (20.5 mmol, 3.50 g) and *p*-toluenesulfonic acid (40 mg) in 100 mL anhydrous toluene. The mixture was refluxed till no water was brought to Dean–Stark trap (ca. 100 min). The toluene was removed and the solid obtained was collected and dried in vacuum oven.Reduction of the crude imine (0.77 g, 2.5 mmol) similarly to that described in condition B[6] gave **8a** as yellowish solid (0.55 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.71 (d, $J = 4.0$ Hz, 2H), 6.12 (br s, 1H), 7.52 (m, 1H), 8.19 (s, 1H), 8.29 (m, 2H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 42.4, 116.8, 120.3, 121.0, 126.8, 139.9, 143.8, 142.2, 148.3, 152.0, 159.1. LC–MS (M+1): 279. Anal. Calcd for $C_{11}H_7ClN_4O_3$: C, 47.41; H, 2.53; N, 20.11. Found: C, 47.22; H, 2.33; N, 20.38.
6. Compound **8g** (conditions B): In a 100 mL round-bottomed flask equipped with a Dean–Stark trap and a condenser were placed 5-amino-4,6-dichloropyrimidine (10 mmol, 1.63 g), 2-hydroxy-5-methoxylbenzylaldehyde (10 mmol, 1.52 g) and 10-camphorsulfonic acid (20 mg) in 30 mL anhydrous toluene. The mixture was refluxed under argon for 30 min, then the toluene collected in the Dean–Stark trap was released. The toluene collecting and releasing process was repeated until about a total of 20 mL of toluene was removed from the reaction mixture. Then, another 20 mL of anhydrous toluene was added to the reaction mixture and the azeotrope continued. The removal-addition procedure was repeated three more times. Then, the toluene was removed under vacuum to give the crude imine, which was dissolved in 1,4-dioxane (40 mL). To that solution was added sodium borohydride (10 mmol, 0.40 g), and the mixture was stirred at 44 °C overnight under argon. The reaction was then cooled down, and ethyl acetate (40 mL) and brine (40 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give the crude product. The residue was washed with ether (2×15 mL) to give the product **8g** as a yellowish solid (1.43 g, 55%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H), 4.47 (d, $J = 4.2$ Hz, 2H), 6.37 (t, $J = 4.2$ Hz, 1H), 6.87–6.96 (m, 2H), 7.18 (d, $J = 8.7$ Hz, 1H), 7.97 (s, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 43.7, 51.2, 113.0, 113.2, 126.7, 133.4, 135.2, 140.2, 142.3, 148.2, 151.7, 159.8. LC–MS (M+1): 264. Anal. Calcd for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94. Found: C, 54.36; H, 4.02; N, 15.64.
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9. Compound **15e**: In a sealed tube were placed sodium *t*-butoxide (0.28 mmol, 0.027 g), bis(dibenzylideneacetone) palladium (0.07 mmol, 0.041 g), and *rac*-(2,2′-bis(diphenylphosphino))-1,1′-binaphthyl (0.21 mmol, 0.131 g). The tube was then purged with argon. Then, **8f** (0.2 mmol, 0.053 g) in anhydrous 1,4-dioxane (1 mL) was added, followed by **14a** (0.2 mmol, 0.043 g) in 1,4-dioxane (1 mL). The tube was then sealed and the reaction was stirred at 75 °C for 10 h, then cooled down to rt. Dichloromethane (5 mL) was added and the mixture was stirred for another 20 min before filtration of the mixture. The insoluble was washed with methanol (5 mL) followed by acetone (4 mL), and the filtrate was concentrated to give a residue that was purified with TLC ($MeOH/CH_2Cl_2$: 5/100) to give a green solid, which upon recrystallization from dichloromethane gave **15e** as a white solid (0.046 g, 53%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (s, 3H), 4.40 (d, $J = 4.2$ Hz, 2H), 5.35 (t, $J = 4.2$ Hz, 1H), 6.73–6.80 (m, 2H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.48–7.62 (m, 3H), 7.92 (s, 1H), 7.95–7.98 (m, 2H), 8.72 (br s, 1H), 8.96 (s, 2H), 10.91 (br s, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 45.7, 53.2, 102.5, 104.8, 112.0, 126.3, 127.6, 129.8, 130.9, 131.3, 132.5, 133.2, 143.8, 144.3, 153.2, 156.1, 157.3, 158.1, 160.7, 163.2. LC–MS (M+1): 442. Anal. Calcd for $C_{23}H_{19}N_7O_3$: C, 62.58; H, 4.34; N, 22.21. Found: C, 62.33; H, 4.10; N, 22.29.
10. Compound **15e** (Scheme 3): In a 15 mL round bottomed flask were placed **3f** (152 mg, 1 mmol), and **16** (193 mg, 1 mmol) in DMF (2 mL). The solution was cooled to 0 °C, and diisopropylethylamine (0.35 mL, 2.0 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 h, warmed to rt for 14 h. The reaction was then cooled to 0 °C, **14a** (214 mg, 1 mmol) in 2 mL of DMF was added slowly, followed by diisopropylethylamine (0.35 mL, 2.0 mmol). The mixture was stirred at 0 °C for 1 h, at rt for additional 3 h, then quenched with water (5 mL). The precipitation formed was filtered, washed with ethyl ether (2×10 mL), and dried to afford 366 mg of crude **18**.
In a 100 mL round bottomed flask equipped with a hydrogen balloon were placed crude **18** (366 mg) and Pd/C (20 mg) in ethylene glycol dimethyl ether (DME, 10 mL). Hydrogen was then connected and the reaction was stirred at rt for 12 h. The hydrogen was disconnected, and triethyl orthoformate (5 mL) was added to the reaction. The mixture was stirred for 5 h and then filtered. The filtrate was concentrated under vacuum and the residue was purified by preparative TLC (5% $MeOH/CH_2Cl_2$) to afford **20** (226 mg, 51% from **3f**) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.96 (s, 1H), 9.82 (s, 1H), 9.11 (s, 2H), 8.73 (s, 1H), 8.36 (s, 1H), 8.10–7.96 (m, 3H), 7.62–7.50 (m, 4H), 6.97 (d, 1H, $J = 6.3$ Hz), 3.92 (s, 3H); LC–MS (M+1): 439.88. ^{13}C NMR (300 MHz, DMSO-d_6): δ 55.2, 101.6, 107.1, 115.1, 122.2, 126.3, 129.3, 130.8, 131.3, 132.9, 133.6, 142.6, 151.4, 152.8, 158.7, 160.7, 161.8, 163.2, 164.3, 166.0. Anal. Calcd for $C_{23}H_{17}N_7O_3$: C, 62.87; H, 3.90; N, 22.31. Found: C, 62.97; H, 4.12; N, 22.61.
In a round bottomed flask was placed **20** (70 mg, 0.16 mmol) in 4 mL of THF. Sodium cyanoborohydride (30 mg, 0.48 mmol) was added in one portion. The reaction was stirred at rt for 1 h, cooled to 0 °C, and quenched slowly with aq HCl (3 M, 3 mL). Standard workup followed by preparative TLC (5% MeOH/CH_2Cl_2) afforded **15e** (46 mg, 66%) as a white solid with spectroscopic properties identical to those obtained from the reductive amination procedure.