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Synthesis and functionalization of 2-hydroxypyrimido[4,5-*b*][1,4]oxazine

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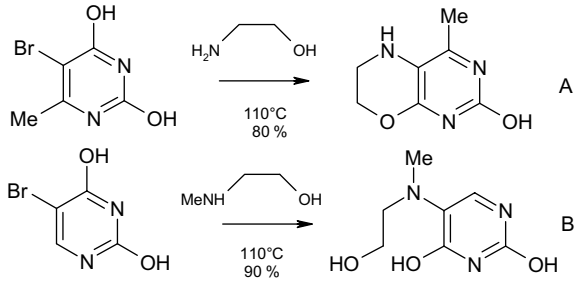
Abstract—An efficient synthesis of pyrimido[4,5-*b*][1,4]oxazines is realized using 5-bromouracil. Substitution in the 2-position was performed by palladium-mediated cross-coupling reactions (Suzuki, Stille and carbon–nitrogen bond forming process) and by S_NAr reactions. Microwave-heating is also used for high-speed synthesis.

1. Introduction

The 6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazines (DPO) constitute a class of biologically active compounds. Several molecules containing this moiety were reported in the areas of anticancer agents,[1,2] or antithrombotic drugs.[3] Two methods were described to obtain polysubstituted DPO. The first sequence started with a condensation of an α-hydroxyester on 5-amino-6-halopyrimidines protected in 5-position followed by deprotection and acidic cyclization.[3] The expected oxazinopyrimidine carbonylated in 7-position was then functionalized. The second way led, in a single step, to various 6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazines from 5-amino-6-hydroxypyrimidines and α-halocarbonylated compounds.[1,2,4–7]

Ehrenstein and co-workers[8] previously prepared the first DPO without any substituent on aliphatic ring (Scheme 1). Bicyclic system **A** was synthesized through cyclocondensation of 5-bromouracil with aminoethanol, and no further functionalization was reported. Reaction with *N*-methylaminoethanol only gave the monocondensation product **B** and cyclization did not occur.[8]

As far as we know, no route to generate monosubstituted DPO was explored. We therefore turned our attention to generate various 6,7-dihydro-5*H*-pyrimido[4,5-*b*]-[1,4] oxazines functionalized in 2-position via nucleophilic substitutions and microwave-assisted palladium-catalyzed cross-coupling reactions.



Scheme 1.

Most of the literature uses 2-chloropyrimidine[9] derivatives to perform substitution in 2-position, but in our case this proved to be difficult. The 2-hydroxy-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazine **2** was obtained by intramolecular Mitsunobu reaction of 5-[(2-hydroxyethyl)-methylamino] uracil **1** using a classical system: diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in DMF at room temperature (Scheme 2). The chlorination of this compound using $POCl_3$ to produce 2-chloro-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazine failed since only degradation was observed, probably due to destruction of oxazine ring in acidic conditions. On the contrary, generation of 2-triflyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazine **3** in quasi quantitative yield allowed us to have an efficient pathway leading to DPO.

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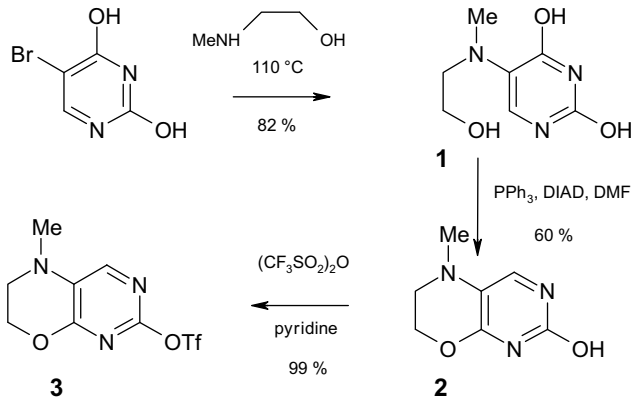


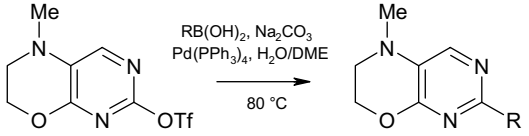
Scheme 2. Synthesis of 2-triflyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]-oxazine.

2. Suzuki cross-coupling

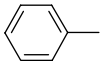
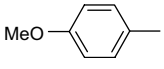
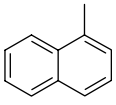
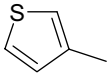
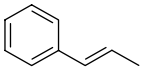
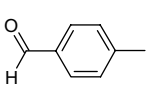
In order to introduce aryl, heteroaryl or alkynyl groups in 2-position of 5-methyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazine **3**, we initially investigated the Suzuki cross-coupling. The results are shown in Table 1.

The best conditions, with various boronic acids, were found to be the use of sodium bicarbonate and tetrakistriphenylphosphine palladium(0) as catalyst in a mixture of DME/H_2O.[10] Under these conditions, the expected compounds **4**–**9** were isolated in good yield (65–92%).

Table 1. Suzuki cross-coupling



3 **4-9**

Entry	R	Time	Product	Yield (%)
1		40 min	**4**	82
2		1 h	**5**	91
3		6 h	**6**	69
4		1 h	**7**	92
5		3 h	**8**	65
6		3 h	**9**	78

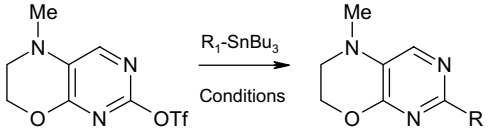
3. Stille cross-coupling

We also investigated the reactivity of **3** toward Stille cross-coupling reactions to produce a small library of compounds. The coupling of 2-(tributylstannyl)thiophene and **3** was performed in dioxane in the presence of triphenylarsine and tris(dibenzylideneacetone) dipalladium(0) at 50 °C (method A).[11] Unfortunately, only 50% of the starting material was consumed and no significant improvement was obtained using an excess of 2-(tributylstannyl)thiophene.

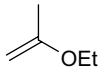
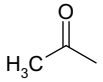
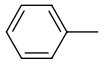
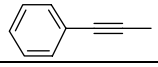
We decided to apply a method developed in our laboratory[12] using $Pd(PPh_3)_4$, copper(I) bromide-dimethylsulfide ($Me_2S{\cdot}CuBr$) in DME (method B) or $Pd(PPh_3)_4$, lithium chloride (LiCl) in THF (methods C_1 and C_2)[13] without success. The results are summarized in Table 2 and the conversions were calculated from ^1H NMR of crude product. Despite the recent advances in microwave instrumentation increasing the accessibility of this technique for organic synthesis,[14] very few microwave-assisted Stille cross-coupling reactions have been reported.[15]

Nevertheless, microwave-heating technology allowed us to obtain a full conversion for all the experiments. The

Table 2. Stille cross-coupling



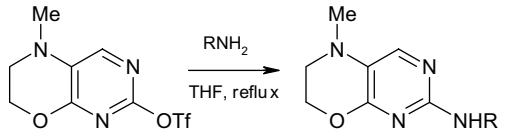
3 **4, 10-13**

Entry	R	Condition	Product	Conversion (%)	Yield (%)
1		A	**10**	50	35
		B		30	—
		C_1		17	—
		C_2		54	—
		D		100	85
2		A	**11**	0	0
		D		100	65
3		E	**12**	100	70
4		A	**4**	0	0
		D		100	70
5		D	**13**	100	76

Stille coupling conditions

A: $RSnBu_3$ (2 equiv), $Pd_2(dba)_3$, Ph_3As in dioxane, 50 °C, 24 h; B: $RSnBu_3$ (2 equiv), $Pd(PPh_3)_4$, $Me_2S{\cdot}CuBr$, in DME, reflux, 24 h; C_1: $RSnBu_3$ (1.1 equiv), $Pd(PPh_3)_4$, LiCl in THF, reflux. 24 h; C_2: $RSnBu_3$ (2 equiv), $Pd(PPh_3)_4$, LiCl in THF, reflux, 24 h; D: $RSnBu_3$ (1.1 equiv), $Pd(PPh_3)_4$, LiCl in THF at 160 °C under microwave irradiations, 15 min; E: Tributyl(1-ethoxyvinyl)tin (1.1 equiv), $Pd(PPh_3)_4$, LiCl in THF at 160 °C under microwaves irradiations, 15 min, then acid hydrolysis, HCl 10%.

Table 3. S_NAr under conventional and microwaves heating conditions



3 **14-17**

Conventional heating				
Entry	R	Time (h)	Product	Yield (%)
1	*n*-Butyl	24	**14**	80
2	Benzyl	48	**15**	88
3	Cyclohexyl	92	**16**	85

Microwaves heating					
Entry	R	Time (min)	*T* (°C)	Product	Yield (%)
1	*n*-Butyl	5	160	**14**	88
2	Benzyl	5	160	**15**	92
3	Cyclohexyl	15	160	**16**	85
4	*n*-Propyl	12	140	**17**	86
5	4-$MeC_6H_4(CH_2)_2$	5 min	180	**18**	80

reactions were performed in THF at 160 °C using LiCl and $Pd(PPh_3)_4$ (methods D and E), leading to compounds (**4** and **10–13)** in good yields between 65% and 85%. In addition, the reaction times could be shortened to 15 min (Table 2).

4. S_NAr

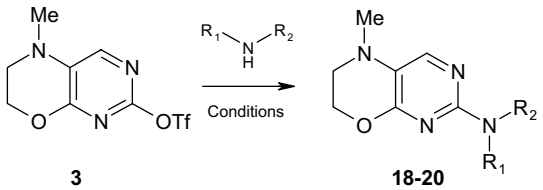
In order to generate C–N bond by nucleophilic aromatic substitution (S_NAr), displacement of OTf group was carried out with various primary amines in refluxing THF. We obtained the expected S_NAr compounds but with very long reaction times (conventional heating, Table 3). Once more, the use of microwave-irradiation in similar S_NAr conditions (amines in THF) at 140–180 °C, afforded the desired compounds **14–18** in only 5–15 min (80–92% yield). The results are summarized in Table 3.

5. Palladium catalyzed N-arylation

Unfortunately, no reaction with compound **3** was observed when we used aromatic or secondary amines in S_NAr reaction conditions. Consequently, we applied the palladium cross-coupling reaction recently developed in our laboratory.[16] Thus, the N-arylation reactions were carried out using xantphos, $Pd(OAc)_2$ and K_2CO_3 in the presence of various amines (aniline, *N*-methylbenzylamine or 4-nitroaniline) in dioxane at reflux temperature. This method gave corresponding products (Table 4, entries 1–3) in very good yields (81–88%).

In conclusion, we have developed a new method for 6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazines synthesis using 'Suzuki' and 'Stille' palladium-mediated cross-coupling

Table 4. S_NAr using palladium cross-coupling method



3 **18-20**

Entry	R_1	R_2	Time	Conditions	Pdt	Yield (%)
			24 h	A	**19**	0
1	H	Ph	15 min	B		0
			4 h	C		81
2	Me	$C_6H_5CH_2$	1 h	C	**20**	85
			15 min	B		0
3	H	4-$NO_2C_6H_4$	2 h	C	**21**	88

S_NAr reaction conditions
A: R_1R_2NH, THF, reflux; B: R_1R_2NH, THF at 160 °C under microwaves irradiations; C: R_1R_2NH, xantphos, $Pd(OAc)_2$, K_2CO_3, dioxane, reflux.

and N-arylation reactions. Microwave irradiations as heating source allowed complete conversion. On the other hand, the Pd-catalyzed N-arylation using palladium acetate as catalyst and xantphos as ligand efficiently proceeded to introduce secondary and aromatic amines in the 2-position of DPO.

Acknowledgments

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A.; Guillaumet, G. *Tetrahedron Lett.* **2002**, *43*, 3193; (c) Wenderborn, S.; Berteina, S.; Brill, W. K.-D.; De Mesmaeker, A. *Synlett* **1998**, 671; (d) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215.
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