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Synthesis of Tricyclic 4-Chloro-pyrimido[4,5-*b*][1,4]benzodiazepines

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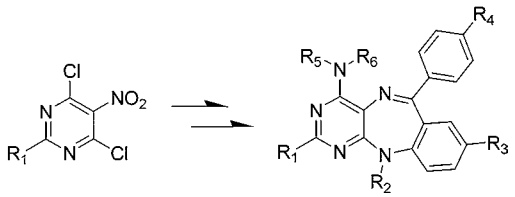
ABSTRACT



A novel methodology was developed for the efficient synthesis of 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepines. The key is the intramolecular Friedel–Crafts cyclization of 5-amino-4-(N-substituted)anilino-6-chloropyrimidine with either a carboxylic acid or its derivatives to construct the 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepine core. Subsequent nucleophilic substitution allows the introduction of one more diversity point in the target molecules. This strategy provides an efficient method to access a library of compounds based on privileged substructures that are of great interest in drug discovery.

The construction of privileged structures is an important strategy in medicinal chemistry. Benzodiazepines were first coined as the archetypal privileged substructure by Evans et al. in 1988.[1,2] These compounds have shown a variety of biological effects predominately ascribed to their actions in the central nervous system. For example, Clozapine, Olanzapine and Quetiapine are used to treat schizophrenia; Clonazepam, Diazepam, Lorazepam, Nitrazepam, and Oxazepam are used as antianxiety drugs. In addition, they are the basis of cholecystokinin receptor (CCK) A and B antagonists,[3] oxytocin antagonists,[4] and inhibitors of protein−DNA interactions.[5] There are four points of diversity in 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepines. For instance, the 4-chloro group can be easily converted to other groups by either a substitution reaction with a nucleophile (such as an amine, alcohol, and phenol) or by Suzuki−Miyaura cross-coupling reactions with boronic acids.[6] Several reports have been devoted to the synthesis of various tricyclic 1,4-benzodiazepines,[7−9] but there is no report describing the preparation of 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepines.[10]

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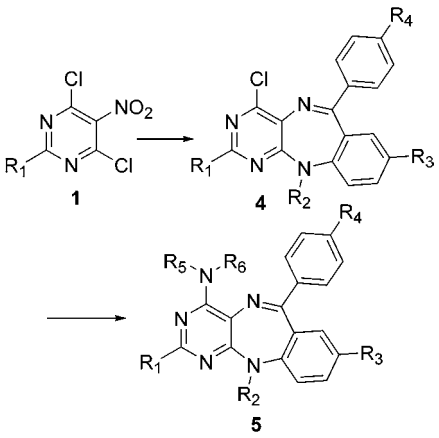
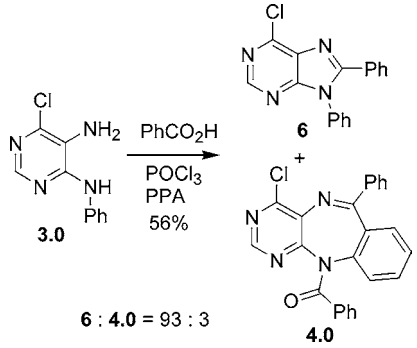
Herein, we report an efficient method for the synthesis of 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepines from commercial 4,6-dichloro-5-nitropyrimidine, which can be readily converted to 4-amino-pyrimido[4,5-*b*][1,4]benzodiazepines as depicted in Scheme 1.

Scheme 1



This synthesis was inspired by an unexpected observation during the preparation of various purine libraries.[11] As shown in Scheme 2, when 5-amino-4 anilino-6-chloro-pyrimidine

Scheme 2



(**3.0**) was treated with benzoic acid and $POCl_3$/PPA to prepare 6-chloropurine (**6**), the desired product was accompanied by a small contaminant that was isolated and characterized as 4-chloro-11-benzoyl-6-phenyl-pyrimido[4,5-*b*][1,4]benzodiazepine (**4.0**).

A plausible mechanism for the formation of compound **4.0** is proposed as shown in Scheme 3. It was rationalized that under the purine formation conditions of refluxing $POCl_3$/PPA, a small amount of diamine **3.0** was converted to diacylated product **7**. Compound **7** could not undergo cyclization to a purine ring; however, it was able to undergo an intramolecular Friedel−Crafts reaction in acidic condition

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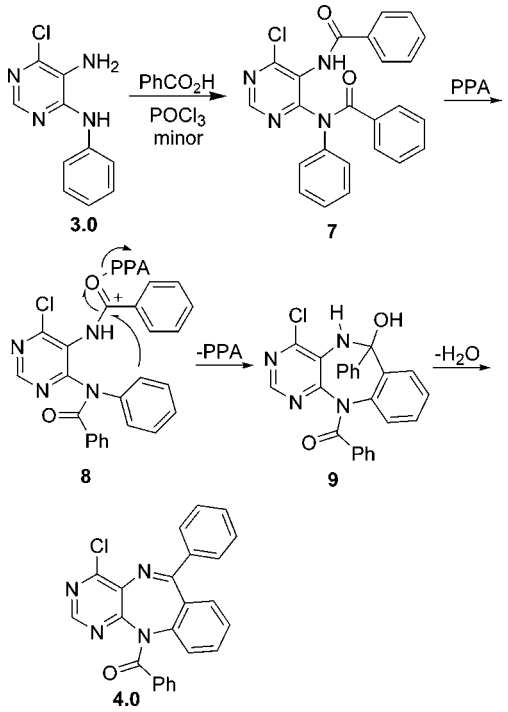
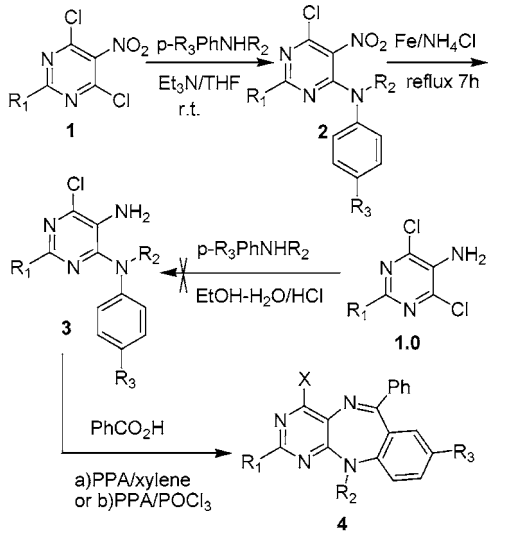
Scheme 3



to form compound **9**, which is subsequently dehydrated to produce compound **4.0**.

On the basis of the above analysis, a facile synthesis of 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepine (**4**) was envisaged as shown in Scheme 4. While reaction of 5-amino-4,6-

Scheme 4



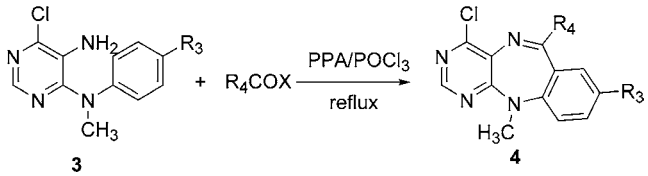
dichloro-pyrimidine (**1.0**) with *N*-methyl-aniline failed to give

the desired aminated product,[12] utilization of a known two-step process provided 6-chloro-4,5-diamino pyrimidines (**3**) ($R_2 = CH_3$).[13,14]

Commercial 4,6-dichloro-5-nitro-pyrimidine **1** was treated with *N*-methylbenzenamines to give pyrimidines **2** in high yields, and the nitro group was easily reduced by Fe/NH_4Cl in good chemical yield. Two cyclization conditions were studied for the formation of tricyclic 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepines. When pyrimidine **3.1** and benzoic acid were treated with PPA in refluxing xylene for 5 h, 4-hydroxy-11-methyl-6-phenyl-pyrimido[4,5-*b*][1,4]-benzodiazepine (**4.19**) resulted in 61% isolated yield. Compound **4.19** could be readily converted to 4-chloro-11-methyl-6-phenyl-pyrimido[4,5-*b*][1,4] benzodiazepine (**4.3**) by treatment with $POCl_3$. Alternatively, the two-step transformation could be achieved using PPA/$POCl_3$ in a one-pot procedure to give **4.3** in 74% yield. This observation was consistent with what was observed during the preparation of a purine library.[11]

Under the $POCl_3$/PPA conditions, 6-chloro-4,5-diamino pyrimidines **3** ($R_2 = CH_3$) reacted with various acids or its derivatives to yield the desired 4-chloro-pyrimido[4,5-*b*][1,4] benzodiazepine ring system (Table 1).

Table 1. Formation of Tricyclic 4-Chloro-pyrimido[4,5-*b*][1,4]benzodiazepines

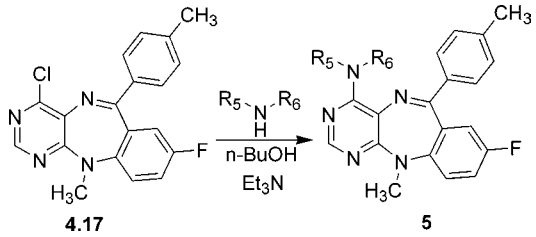


compd	R_3	R_4	X	yield (%)	time
4.1	H	$CH_3CH_2CH_2$	Cl	60	45 min
4.2	H	CH_3	OAc	52	30 min
4.3	H	Ph	OH	74	5 h
4.4	H	4′-F−C_6H_4	OH	79	5 h
4.5	H	4′-CH_3−C_6H_4	OH	90	5 h
4.6	H	4′-NO_2−C_6H_4	OH	38	12 h
4.7	CH_3	$CH_3CH_2CH_2$	Cl	65	30 min
4.8	CH_3	CH_3	OAc	57	30 min
4.9	CH_3	Ph	OH	85	5 h
4.10	CH_3	4′-F−C_6H_4	OH	88	5 h
4.11	CH_3	4′-CH_3−C_6H_4	OH	97	5 h
4.12	CH_3	4′-NO_2−C_6H_4	OH	49	12 h
4.13	F	$CH_3CH_2CH_2$	Cl	50	1 h
4.14	F	CH_3	OAc	45	30 min
4.15	F	Ph	OH	88	5 h
4.16	F	4′-F−C_6H_4	OH	81	5 h
4.17	F	4′-CH_3−C_6H_4	OH	90	5h
4.18	F	4′-NO_2−C_6H_4	OH	37	12h

Higher yields of the products (**4.7**−**4.12**) were observed when R_3 was an electron-donating group (CH_3) compared to those with either no substitution (compounds **4.1**−**4.6**, R_3 = H) or an electron-withdrawing group (compounds **4.13**−**4.18**, R_3 = F). These results are consistent with the proposed Friedel−Crafts reaction mechanism shown in Scheme 3, since electron-donating groups should activate the aromatic ring toward electrophilic substitution reactions. When R_4 was aliphatic (**4.1**, **4.2**, **4.7**, **4.8**, **4.13**, **4.14**), the reactions proceeded faster than when R_4 was aromatic (**4.3**−**4.6**, **4.9**−**4.12**, **4.15**−**4.18**). On the other hand, the yields of the aromatic acids (except *p*-nitrobenzoic acid) (**4.6**, **4.12**, **4.18**) were higher presumably due to the stablization effect caused by conjugation of the aromatic ring. When R_4 was an aromatic group substituted with electron-donating groups, the yields were highest (**4.5**, **4.11**, **4.17**). When R_4 was substituted with an electron-withdrawing group (NO_2) (**4.6**, **4.12**, **4.18**), the yields were lowest. These results are also consistent with a Friedel−Crafts-type mechanism since electron-donating group R_4 activates the benzene ring and stabilized the carbon cation intermediate **6** and the electron-withdrawing group R_4 destabilizes it.

To test the reactivity of the 4-Cl group in tricyclic 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepines, nuclephilic substitution reactions were conducted with amines as shown in Scheme 5. As expected, good chemical yields were

Scheme 5



obtained for compounds **5.1** and **5.2**.

In conclusion, a novel methodology for the preparation of 4-chloro-pyrimido[4,5-*b*][1,4]benzodiazepines was developed. This new method utilizes readily available 4,6-dichloro-5-nitropyrimidine, amines, and carboxylic acids (or its derivatives) and generates the desired heterocycles in good to high yields. The resulting 4-chloro-pyrimido[4,5-*b*][1,4]-benzodiazepines can be subjected to nucleophilic substitution to yield products with more diversity. This strategy provides an efficient way to access a library of compounds based on privileged substructures that are of great interest in drug discovery.

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Supporting Information Available: Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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