C-C Bond Formation at C-5 Position of Dimethyluracil Derivatives Using SmI_2*

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Derivation of purine and pyrimidine nucleosides has attracted much attention because of potent antitumor or antiviral activity.[1] (Figure 1) Pyrimidine nucleosides substituted at the C-5 position constitute a class of biologically significant molecules.[2] The well-known cancer chemotherapeutic 5-fluorouracil and antiviral agents, such as 5-iodo-2'-deoxyuridine and 5-(trifluoromethyl)-2'-deoxyuridine, have been in clinical use for several years.[3] Meanwhile, in recent years, there have been significant interests in the potential usages of the C-5-substituted pyrimidine nucleosides in synthetic oligonucleotide probes as a tether site for linking reporter groups to nucleic acids.[4] When the modified nucleosides are incorporated into the duplex B-DNA, C-5-substituents are located in the major groove,[5] and so do not disrupt Watson-Crick base pairing. As a result, the methodologies for constructing suitable linker arms and generating bonds to C-5 are important for the synthesis of potential therapeutic agents and synthetic oligonucleotide probes. Therefore, the 5-position of pyrimidine nucleosides has been the target of extensive studies on modifications.[1]

Generally, C-C bond formation at C-5 of uracils has been achieved by the application of photolytic reaction[6a] and palladium-catalyzed coupling reactions.[6] Although the utilization of the lithiation methodology was developed for the introduction of a carbon functionality at the C-5 or C-6 position of uridine derivatives,[7] the ratio (C-5/C-6) of substitution is governed by the substituents on the pyrimidine base and the protecting groups on the sugar. On the other hand, $Mn(OAc)_3$ and $Ce(NH_4)_2(NO_3)_6$ gave regioselective C-C bond formation at the 5-position of pyrimidine derivatives.[8]

In the new attempts for the functionalization of pyrimidine bases and because of the biological interest of the related compounds, we became interested in the introduction of alkyl group at C-5 position of pyrimidines.

Kim *et al.* reported that the reaction of α-bromoacrylamides with carbonyl compounds in the presence of SmI_2 can provide Baylis-Hillman adducts through samarium Grignard type of anionic process, solving several problems of Baylis-Hillman reaction.[9] (Scheme 1) It has been described that the α-carbon of the acrylamide with a phenyl group is rather electron-deficient than other moieties devoid of the phenyl group due to resonance effect. Therefore, the vinyl radical can undergo further reduction to vinylsamarium reagent by SmI_2. This mechanism was supported by the fact that ethyl α-bromoacrylate and 2-bromo-2-cyclohexen-1-one as well as dimethyl α-bromoacrylamide did not give the corresponding desired products. We set out to address the question of whether this samarium chemistry would be applicable to the pyrimidine case. Similar to the resonance effect of the phenyl group, it was considered that the pyrimidine structure having another amide group might be able to react with electrophiles through a vinylsamarium intermediate.

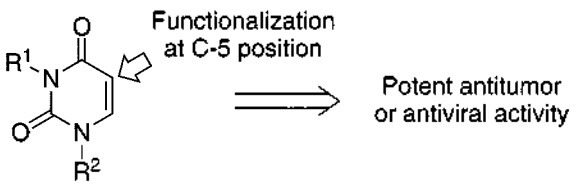
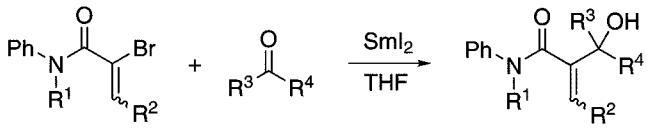


Figure 1



Scheme 1

We focused our initial efforts on the coupling of 5-iododimethyluracil with propionaldehyde under the same condition as the previously reported one.[9] Unfortunately, when 1 equivalent of aldehyde was used, only trace amount of coupling product (**2a**) was observed by TLC and ^1H NMR, while the reduction product (**3**) was obtained as a major product (Table 1, entry 1). However, this result encouraged us to keep finding the appropriate condition for pyrimidine substrates. Finally, it was found that the more loading of aldehyde led to both the more desired product (**2a**) and the less reduced one (**3**) (Table 1, entries 1-3). In contrast, 5-bromodimethyluracil showed less reactivity than iodo-substrate under the same condition, it can be considered as a general trend that the reactivity of α-iodoenones is higher, especially in transition metal mediated reactions, than the corresponding bromo or chloro derivatives (Table 1, entry 4). On the other hand, the use of additive such as HMPA was not successful (Table 1, entry 6). Sterically hindered aldehydes afforded the alkylated pyrimidines in only moderate chemical yields (Table 2, entry 5-6) and

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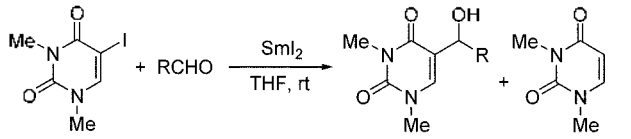
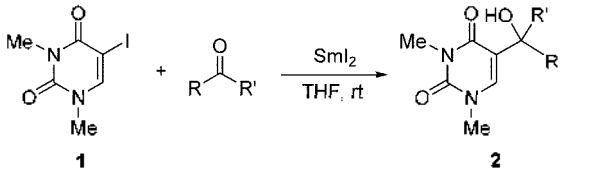
Table 1. Optimizations of Reaction Conditions



Entry	RCHO (eq.)	Product	R	Yield (%)[c]
1	CH_3CH_2CHO (1)	**2a**	CH_3CH_2	trace (93)
2	CH_3CH_2CHO (3)	**2a**	CH_3CH_2	45 (9)
3	CH_3CH_2CHO (5)	**2a**	CH_3CH_2	88 (3)
4	CH_3CH_2CHO (5)[d]	**2a**	CH_3CH_2	13 (8)
5	$PhCH_2CH_2CHO$ (5)	**2b**	$PhCH_2CH_2$	25 (10)
6	$PhCH_2CH_2CHO$ (5)[b]	**2b**	$PhCH_2CH_2$	– (91)
7	$PhCH_2CH_2CHO$ (10)	**2b**	$PhCH_2CH_2$	63 (6)

All reactions were performed with 3 eq. of SmI_2 (0.1 M) in THF at room temperature for 10 minutes. [a]5-Bromodimethyluracil was employed as substrate instead of **1**. [b]6 eq. of HMPA were used as additive. [c]Isolated yields of **2**. The yields in parentheses are those of 1,3-dimethyluracil (**3**).

Table 2. Functionalization at 5-Position of Pyrimidines



Entry	RC(=O)R'	Product	R	R'	Yield (%)[c]
1	CH_3CH_2CHO	**2a**	CH_3CH_2	H	88
2	$PhCH_2CH_2CHO$	**2b**	$PhCH_2CH_2$	H	63
3	$CH_3(CH_2)_4CHO$	**2c**	$CH_3(CH_2)_4$	H	92
4	$CH_3(CH_2)_8CHO$	**2d**	$CH_3(CH_2)_8$	H	81
5	*c*-HexCHO	**2e**	*c*-Hex	H	42
6	Ph_2CHCHO	**2f**	Ph_2CH	H	30
7	CH_3COCH_3	**2g**	CH_3	CH_3	27

All reactions were performed with 3 eq. of SmI_2 (0.1 M) and carbonyl compounds (5-10 eq.) in THF at room temperature for 10 minutes. [c]Isolated yields.

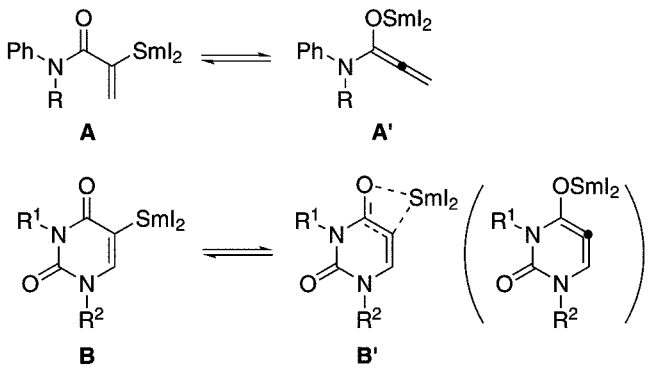


Figure 2

ketone as substrates was not so successful (Table 2, entry 7).

It is likely that this reaction proceeds via an allenoate intermediate (**A'**)[9-10] (Figure 2). However, since the corresponding intermediate of pyrimidine derivatives (**B'**) seems not to be constructed favorably due to their inflexible ring structures and the resonance effect of another amide group might not be so efficient as phenyl group, alkylations of pyrimidine derivatives (in comparison to the reduction) were not achieved so well as those of simple amides.[9] Nevertheless, a carbon functionalization at the C-5 position of pyrimidine derivatives was performed successfully using SmI_2.

In summary, it has been demonstrated that the reaction of 5-iododimethyluracil with carbonyl compounds in the presence of SmI_2 can provide the C-5-substituted pyrimidines in moderate to good yields. This methodology will facilitate the development of pyrimidine nucleosides substituted at the 5-position, biologically important molecules, by the introduction of the α-hydroxyalkyl group at C-5 position, whose hydroxy moiety can be transformed to a variety of other functional groups.

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