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Regioselective C5-alkylation and C5-methylcarbamate formation of 2,3-dihydro-4-pyridones and C3-alkylation and C3-methylcarbamate formation of 4-(pyrrolidin-1-yl)furan-2(5*H*)-one

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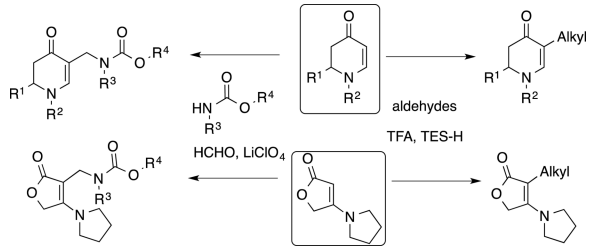
Abstract

Reactions of *N*-alkyl-2,3-dihydro-4-pyridones and 4-(pyrrolidin-1-yl)furan-2(5*H*)-one with aldehydes and triethylsilane in a one-flask procedure provided C5 and C3 alkylated derivatives, respectively. Mannich-type reactions with formaldehyde and carbamates in the presence of lithium perchlorate furnished C5/C3 methylcarbamates.

Graphical Abstract



Keywords

2,3-dihydro-4-pyridones; 4-(pyrrolidin-1-yl)furan-2(5*H*)-one; regioselective alkylation; Mannich reaction

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Supplementary data. Synthetic procedures and compound characterization for all new compounds (**5a-5d**, **8a-8m**, **10**, **11** and **12a-12f** and **12i-12k**) and their ^{1}H and ^{13}C NMR spectra can be found in the online version, at http://

Introduction

The 2,3-dihydro-4-pyridone scaffold **1** (Figure 1) is a useful building block for the synthesis of natural products,[1,2] including the potent anticancer agents tylocrebrine and boehmeriasin A.[3,4] In the context of this research, we have investigated the Pd^{+2}-catalyzed C5 arylation (Suzuki and Hiyama cross coupling reactions) and C5 alkenylation (Fujiwara-Moritani) of 2,3-dihydro-4-pyridones as an effective strategy for the preparation of diverse structural motifs and complex molecules.[5-8] However, attempts to perform Pd^{+2}-catalyzed introduction of an sp^3-hybridized group at C5 did not succeed,[5] presumably due to β-hydride elimination taking place after palladation but prior to the desired sequence of transmetalation and reductive elimination.[9] Therefore, other methods need to be discovered to affect these types of transformation, such as the direct, transition metal free C5 trifluoromethylation that was recently reported by us.[10]

Comins, *et al.* have reported a three-step procedure for the synthesis of C5-alkylated 2,3-dihydro-4-pyridones **4**, involving the iodination of 2,3-dihydro-4-pyridone **1a**, followed by a Nozaki–Hiyama–Kishi reaction of iodide **2** with aldehydes to furnish 5-(1-hydroxyalkyl)-2,3-dihydro-4-pyridones **3**, which were subsequently subjected to reactions with trifluoroacetic acid and triethylsilane to yield C5 alkylated pyridones **4** (Scheme 1).[11] We hypothesized that replacement of the *N*-carbonate moiety of the 2,3-dihydro-4-pyridone **1a**, used by Comins, with an *N*-alkyl group would greatly enhance the nucleophilicity at C5 and facilitate a direct C-C bond formation with aldehydes at C5.

Results and Discussion

No reaction was observed when 1-benzyl-2,3-dihydropyridin-4(1*H*)-one (**1b**) was subjected to butyraldehyde until TMSCl was added to the reaction. Surprisingly the reaction did not yield the expected hydroxyalkyl product but rather bis-addition product **5a** (Scheme 2). Reaction with other aldehydes furnished the bis-addition products **5b-5d** shown in Table 1. Attempts to trap the intermediate, by lowering the reaction temperature or by adding trapping reagents such as acetic anhydride or triethylsilylchloride to the reaction were unsuccessful. It is of note, that this bis-addition chemistry is analogous to the well-known acid–catalyzed reaction of indoles with aldehydes to form bisindolylmethanes.[12]

Since we were unable to isolate the hydroxyl intermediate **6** (Scheme 3), we introduced reducing agents into the reaction mixture, with the goal of preventing the undesired double addition and to obtain 5-alkyl-dihydropyridones directly. This should be possible if the reduction is faster than the second addition or if the second addition is a reversible process. While mild reducing agents, such as Palladium/ammonium formate and zirconocene hydrochloride (Schwartz's reagent) were ineffective, the combination of triethylsilane (TES-H) and trifluoroacetic acid (TFA), utilized by Comins *et al.* in the reduction of the *N*-acylhydroxyalkyl-dihydropyridones **3**,[11] reduced the postulated vinylogous iminium species **7** and yielded the desired C5-alkylated product **8a** in 81% yield (Scheme 3).

Several dihydropyridone substrates were subsequently subjected to these conditions and provided C5 alkylated products **8a-8f** in excellent yields. The results are shown in Table 2.

Under the standard conditions, the reactions yielded C5 alkylated products exclusively, and none of the bis-addition side products were observed. Bicyclic dihydropyridones were also suitable substrates, affording reaction products **8g** and **8h** in good yields. This one flask C5 alkylation procedure provides reaction products in better yields than the three step procedure reported by Comins.[11] We subsequently explored the structurally related 4-(pyrrolidin-1-yl)furan-2(5*H*)-one (**9**), an exocyclic enaminone, and found that this substrate could also be alkylated to provide C3 alkylated products **8i-8m** in excellent yields (Table 2).). It is worth noting that iodination does not take place with *exocyclic* amino-furanones,[13] therefore the C3 alkylated products **8i-8m** are not accessible using the method developed by Comins.

Encouraged by the success with the alkylation reaction, we investigated the possibility of replacing the hydride with other nucleophiles in the alkylation reaction. Aliphatic primary amines such as butylamine and isopropylamine were reacted with paraformaldehyde and **1c** and **9** under mild acidic conditions and yielded Mannich reaction products **10** and **11**. However, the reaction products were very difficult to separate from the undesired bis-addition products that also formed (Scheme 4). A clean separation was only possible when preparative TLC was utilized for isolation. A related aminomethylation reaction has been reported by Todorov et al. that involved the reaction of quinolin-4(1*H*)-ones with paraformaldehyde and secondary amines piperidine and di-(2-picolyl)amine.[14] In that case, acid catalysis was not needed. On the contrary, the presence of acid was found to be detrimental to product yield.

An alternate method to obtain Mannich products of **9** and related analogs has been reported that involved an aminomethylation reaction with the Eschenmoser-Böhme salt (*N*-methyl-*N*-methylenemethanaminium iodide) to form 2-((dimethylamino)methyl)-3-(pyrrolidin-1-yl)cyclopent-2-enone.[15] Aminium salts are not readily available and quite hygroscopic and are therefore difficult to manage. Therefore we investigated carbamates instead, which are readily available and convenient to handle. It is rather unusual for carbamates to participate a Mannich-type reaction; in fact, we were only able to identify one example in the literature.[16] Since $LiClO_4$ has been introduced as a useful reagent to facilitate Mannich-type reactions,[17-20] we evaluated this Lewis acid as an additive for the reaction.

4-(Pyrrolidin-1-yl)furan-2(5H)-one (**9**), *t*-butyl carbamate and formaldehyde were selected as substrates for the test reaction (Scheme 5). In the presence of 0.5 equiv of $LiClO_4$, we obtained a 34% yield for the desired product **12a**. The yield improved after additional amounts of the Lewis acid were added. When 1.2 equivalents of $LiClO_4$ were added the reaction yielded 74% of product, without forming any bis-addition side product as had been observed in the Mannich reaction with amines. Addition of more $LiClO_4$ (up to 3 equiv) did not further improve the yield for **12a**. Other lithium salts or metal chelating reagents (eg. LiCl, LiI, Ti(O*i*Pr)$_4$) were also tested, but no desired product was detected. Formaldehyde was the only viable aldehyde for a successful reaction under the current conditions.

With the standard conditions established, several other carbamates were tested in the reaction with furanone **9** and provided derivatives **12a-12f**, listed in Table 3. As also shown in Table 3, dihydropyridinone **1b** furnished methylcarbamates **12i-12k**. Typically, high yields were achieved with furanone **9** as the reactant, whereas reaction with **1b** resulted in

lower yields when utilizing the same reaction conditions. When sterically hindered carbamates were employed, some reactions did not work well or did not take place. Reaction of benzyl (cyclohexylmethyl)carbamate and benzyl isopropylcarbamate with furanone **9** provided less than 10% of products **12g** and **12h**, respectively. The dihydropyridinone substrate **1b** did not react with *t*-butyl carbamate to form **12l**.

Conclusions

In summary, a one-flask procedure was developed to prepare C5 alkyl-substituted analogues of *N*-benzyl-2,3-dihydro-4-pyridones. This method was extended to the C3 alkylation of 4-(pyrrolidin-1-yl)furan-2(5*H*)-one, an enaminone containing an exocyclic nitrogen. In addition, a Mannich-type reaction was discovered that provides C5 and C3 methylcarbamates of 4-(pyrrolidin-1-yl)furan-2(5*H*)-one and 1-benzyl-2,3-dihydropyridin-4(1*H*)-one, respectively, when reacted with formaldehyde, carbamates, and the additive lithium perchlorate,

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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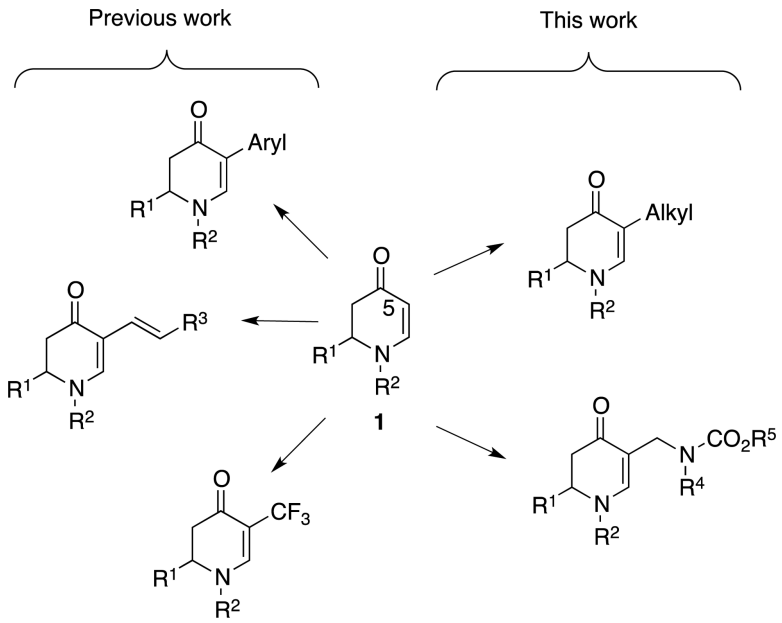
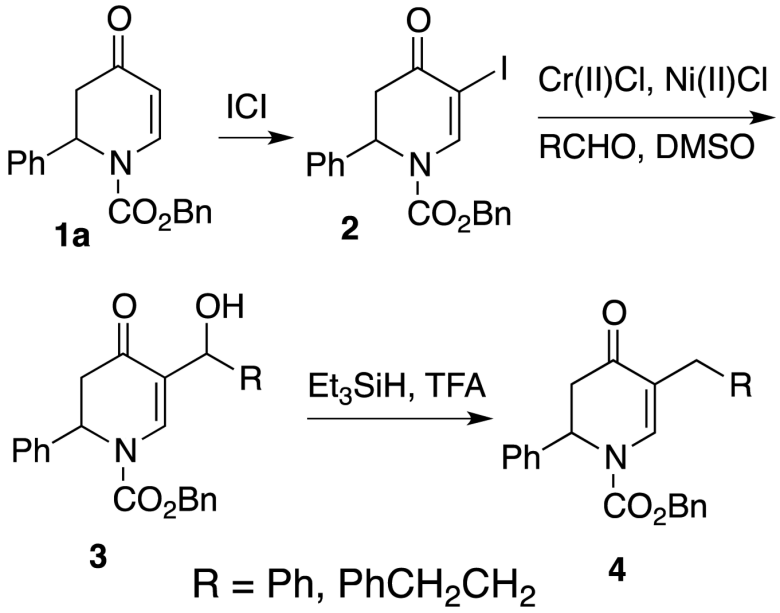
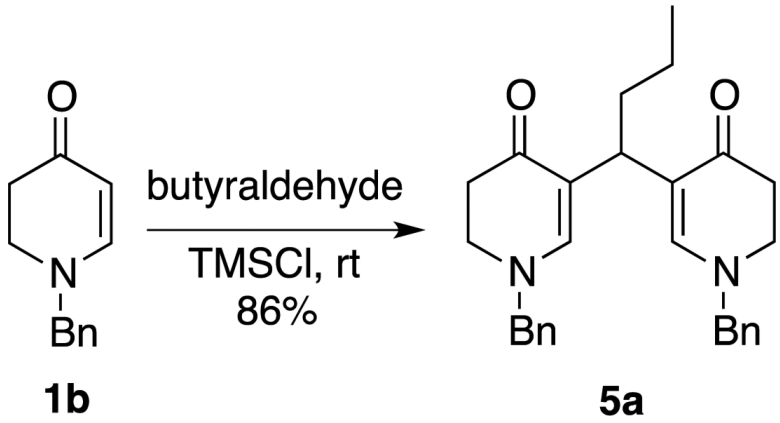


Figure 1.
C5 Functionalization of 2,3-dihydro-4-pyridones.



Scheme 1.

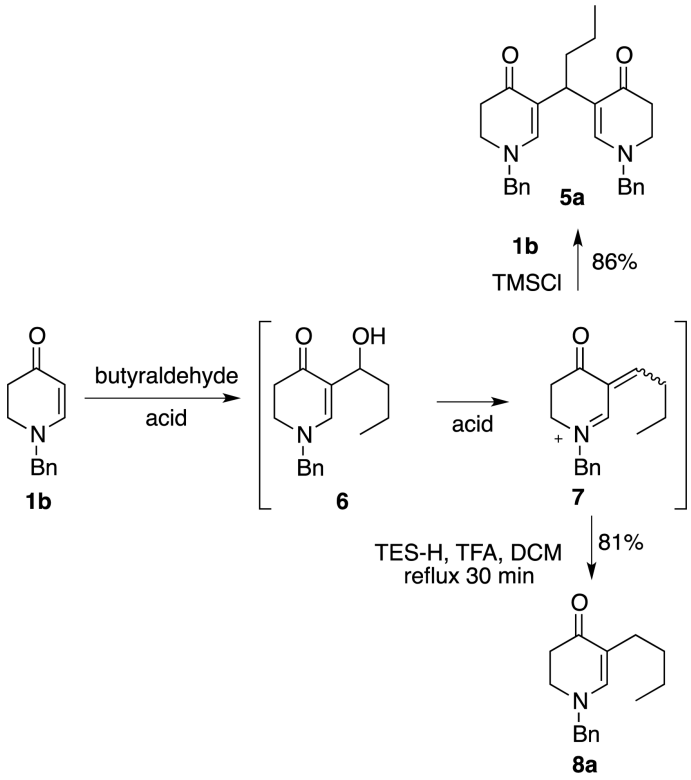
Literature method for the preparation of 5-alkyl-*N*-acyl-2,3-dihydro-4-pyridones **4** in three steps[11]



1b **5a**

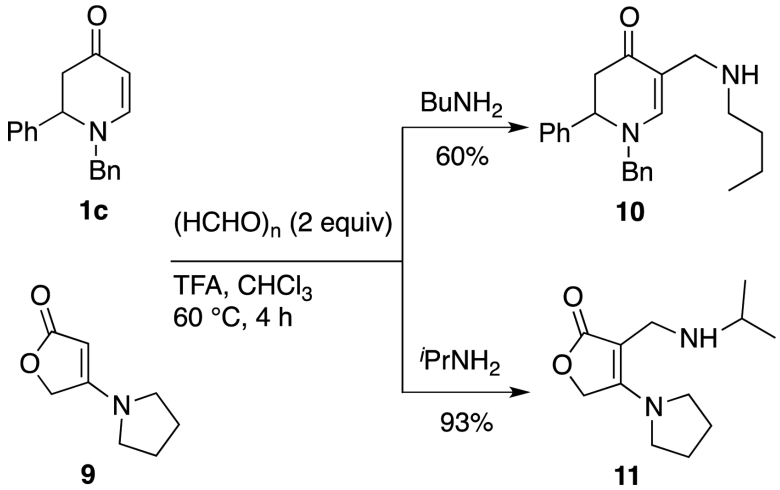
Scheme 2.

Bis-addition product **5a** from reaction of **1b** with butyraldehyde

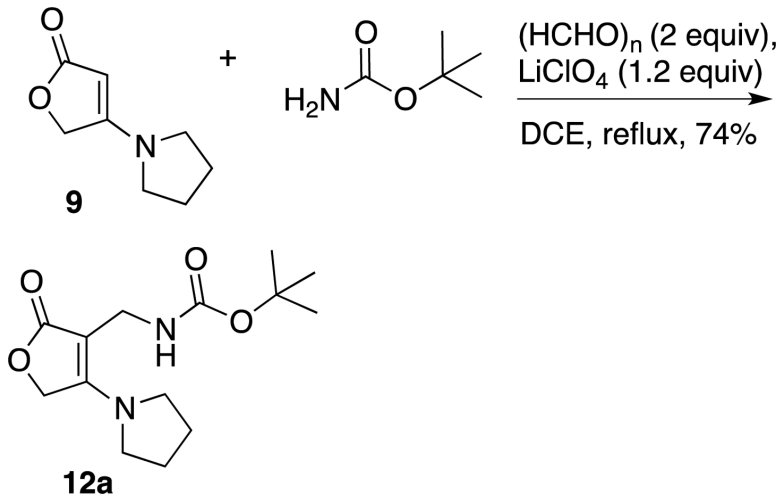


Scheme 3.

Preparation of bis-addition product **5a** and 5-butyl-2,3-dihydro-4-pyridone **8a**



Scheme 4.
Synthesis of Mannich products **10** and **11**



Scheme 5.

Mannich-type reaction of **9** with *tert*-butyl carbamate as the nucleophile

Table 1

Bis-addition products **5** from 2,3-dihydropyridin-4(1*H*)-ones and aldehydes

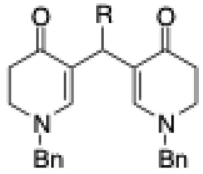
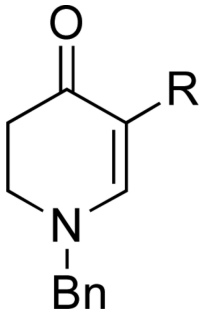
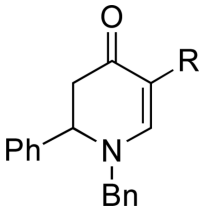
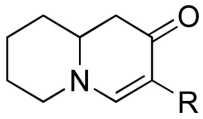
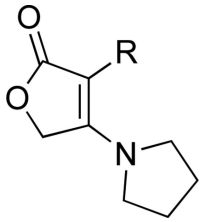
Product	Compound	R	Yield (%)
 **5**	**5a**	Pr	86
	5b	Ph	90
	5c	2-MeC_6H_4	83
	5d	4-NO_2,2-MeC_6H_3	75

Table 2

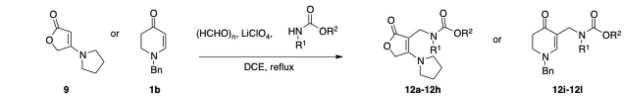
[a]Reaction scope for alkylation reaction

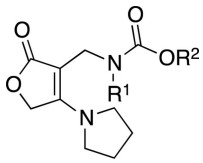
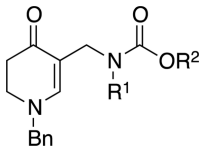
Product	Compound	R	Yield (%)
	**8a**	*n*Bu	81
	8b	Bn	85
	**8c**	*n*Bu	92
	8d	Bn	86
	8e	*n*Nonyl	77
	8f	*i*Bu	93
	**8g**	*n*Bu	88
	8h	Bn	93
	**8i**	*n*Bu	89
	8j	Bn	98
	8k	*i*Pr	88
	8l	2-Me$C_6H_4CH_2$	97
	8m	4-Cl$C_6H_4CH_2$	96

[a]Aldehydes (1.2 equiv), TES-H (4 equiv), TFA (4 equiv), DCM, reflux 30 min.

Table 3

Reaction scope for the synthesis of methylcarbamates **12**



Product	Compound	R^1	R^2	Yield (%)
	**12a**	H	*t*Bu	74
	12b	H	Ph	99
	12c	Bn	Bn	86
	12d	Bn	Allyl	99
	12e	Allyl	Bn	74
	12f	*n*Bu	Bn	51
	12g	$C_6H_{11}CH_2$	Bn	<10
	12h	*i*-Pr	Bn	<10
	**12i**	H	Ph	54
	12j	Bn	Bn	62
	12k	4-$MeOC_6H_4CH_2$	Bn	51
	12l	H	*t*Bu	0