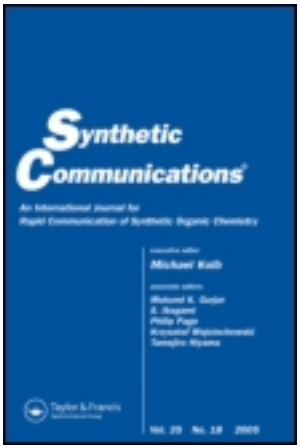


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Facile One-Pot Synthesis of N ^{4}-Alkyloxycarbonyl Cytosine Nucleosides

Yue-Lei Chen [a] & Jun-Da Cen [a]
[a] Department of Chemistry, Shanghai Institute of Pharmaceutical Industry, Shanghai, 200437, P.R. China
Published online: 10 Jan 2011.

To cite this article: YueLei Chen & JunDa Cen (2004) A Facile One-Pot Synthesis of N ^{4}-Alkyloxycarbonyl Cytosine Nucleosides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:18, 3273-3279, DOI: 10.1081/SCC-200030544

To link to this article: http://dx.doi.org/10.1081/SCC-200030544

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 18, pp. 3273–3279, 2004

A Facile One-Pot Synthesis of N^4-Alkyloxycarbonyl Cytosine Nucleosides

Yue-Lei Chen* and Jun-Da Cen

Department of Chemistry, Shanghai Institute of Pharmaceutical Industry, Shanghai, P.R. China

ABSTRACT

N^4-Alkyloxycarbonyl cytosine nucleosides can be easily prepared by reacting cytosine nucleosides with triphosgene and alcohols.

Key Words: N^4-Alkyloxycarbonyl cytosine nucleoside; Triphosgene; Cytosine nucleoside; Isocyanate.

In the medicinal chemistry of nucleosides, using alkyloxycarbonyl group to mask the 4-amino group of cytosine nucleoside has been proved to be an important tactic in the design of nucleoside prodrugs.[1] The desired active

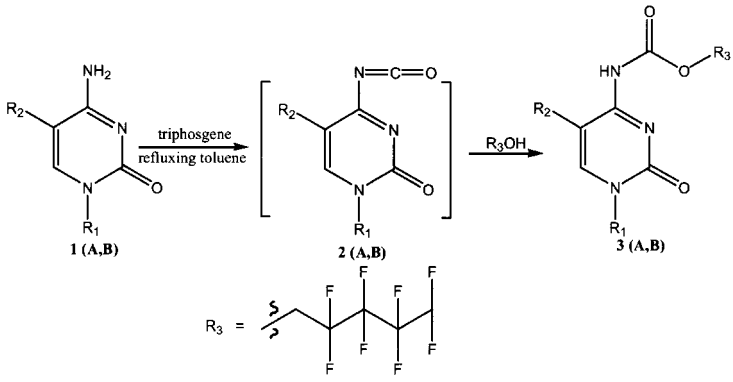
*Correspondence: Yue-Lei Chen, Department of Chemistry, Shanghai Institute of Pharmaceutical Industry, Shanghai, 200437, P.R. China; E-mail: yuelei_chen@yahoo.com.

DOI: 10.1081/SCC-200030544 0039-7911 (Print); 1532-2432 (Online)

nucleoside species will be released after cleavage of the inert carbamate structure by enzymes in vivo. The reported synthetic methods toward N^4-alkyloxycarbonyl cytosine nucleosides mainly focused on the reaction between the cytosine nucleosides and alkyl chloroformates.[1,2] But to our knowledge, most alkyl chloroformates are not commercially available and have to be prepared prior to use. In screening of a large number of bio-active compounds, the preparation of various of chloroformates, especially the complex ones, will be a tedious work. Hattori has reported on an improved method,[3] in which cytosine nucleoside derivatives were reacted with triphosgene and alcohols in the presence of *N*,*N*-diisopropyl ethylamine at room temperature. But this patent method is only suitable for mg-scale preparation. Herein we report a convenient method for preparing them in gram-scale from cytosine nucleoside derivatives and the corresponding alcohols without a base via unseparated cytosine nucleoside isocyanate intermediates to meet the requirement for in vivo screening of N^4-alkyloxycarbonyl cytosine nucleosides.

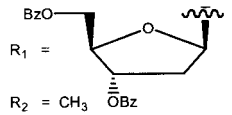
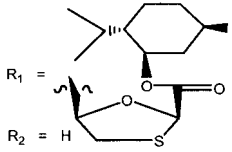
In our work, it was found that the classical reaction condition for aryl isocyanate from aryl amine is suitable to cytosine nucleosides. Reacting the nucleosides **1** with triphosgene in refluxing toluene gives the unprecedentedly reported cytosine nucleoside isocyanates **2**, which are sensitive to moisture and cannot be purified by chromatography on silica gel. We confirmed the existence of this intermediate by crystallization and mass spectroscopy. Fortunately, the separation of these isocyanates is not necessary for the synthesis of target compounds. The carbamates **3** will be produced easily in one pot by adding the corresponding alcohols to the reacting vessel directly.

In scaling up this reaction, we found the main essentials were that the yield and the purity of the product are variable to the concentration of the reactants



Scheme 1.

Table 1. Physical properties and spectral data of compounds **3A** and **3B**.

Compound	R_1 & R_2	Yield (%)	M.p. (°C)	H^1 Nuclear magnetic resonance (NMR)	Electro spray ionization mass spectroscopy (ESI-MS) (m/z)
3A		59.2	156–157	1.728(d, 3H), 2.333(m, 1H), 2.809(m, 1H), 4.587(m, 1H), 4.682(m, 2H), 4.812(m, 2H), 5.659(m, 1H), 5.939–6.200(tt, 1H), 6.410(q, 1H), 7.427–8.060(m, 11H)	708.31 (MH^+)
3B		63.9	217(dec.)	0.780(d, 3H), 0.913(t, 6H), 1.071(m, 2H), 1.428(m, 1H), 1.540(m, 2H), 1.724(d, 2H), 1.726(m, 1H), 2.070(d, 1H), 3.246(q, 1H), 3.673(d, 1H), 4.706(t, 2H), 4.807(m, 1H), 5.536(s, 1H), 5.927–6.187(tt, 1H), 6.422(t, 1H), 7.267(d, 1H), 8.760(d, 1H)	662.13 (MNa^+)

in toluene and the initial heating rate. After optimization, it was found that keeping the concentration of the nucleoside substrate in toluene less than 0.1*M* and heating the reaction mixture rapidly to reflux are crucial points to obtain high yield of pure product.

Application of 3′,5′-dibenzoyl-4-amino thymidine **1A** and a synthetic intermediate **1B** for Lamivudine (an antiviral agent) exemplified the use of the synthesis tactic (Sch. 1, Table 1).

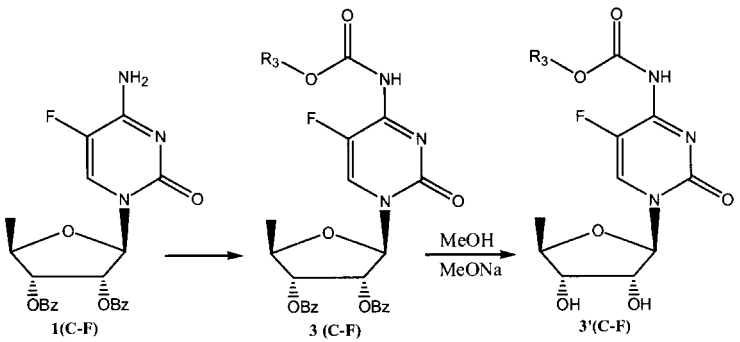
Further examples are demonstrated by the synthesis of several Capecitabine (an antitumor agent) analogues **3′(C–F)** (Sch. 2, Table 2) using this method. The carbamates **3(C–F)** obtained are very pure and the protection groups of the free hydroxyls on the sugar moiety of **3(C–F)** are finally removed to afford the desired compounds **3′(C–F)**. Some of the products have been subjected to bioactivity test.

EXPERIMENTAL

All melting points were uncorrected. H^1 NMR were recorded on INOVA-400 spectrometer in $CDCl_3$ or $(CD_3)SO$ using tetramethylsilane (TMS) as an internal standard. Mass spectra were performed on Micro Mass Q-Tof Micro high performance liquid chromatography (HPLC)-MS. Data of H^1 NMR shown in Tables 1 and 2 do not contain peaks of all protons exchangeable with D_2O.

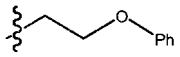
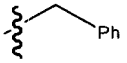
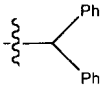
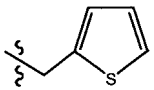
GENERAL PROCEDURE

Mix 2.2 mmol cytosine nucleoside derivative **1** and 0.75 g (2.5 mmol) triphosgene in 40 mL toluene. Rapidly heat the mixture to reflux and keep



Scheme 2.

Table 2. Physical properties and spectral data of compounds **3′(C–F)**.

Compound	R_3	Yield (%)	M.p. (°C)	H^1 NMR	ESI-MS (m/z)
3′C		66.7	Amorphous solid	1.341(d, 3H), 3.739(m, 1H), 3.938(m, 1H), 4.114(m, 1H), 4.259(t, 2H), 4.472(t, 2H), 5.712(q, 1H), 6.954 ~ 7.333(m, 5H), 7.974(d, 1H)	410.08 (MH^+)
3′D		67.7	162–164	1.343(d, 3H), 3.670(m, 1H), 3.902(m, 1H), 4.049(m, 1H), 5.162(s, 2H), 5.715(d, 1H), 7.309–7.411(m, 5H), 7.966(d, 1H)	380.17 (MH^+)
3′E		54.1	82–85	1.320(d, 3H), 3.651(m, 1H), 3.905(t, 1H), 4.044(m, 1H), 5.643(q, 1H), 6.747(s, 1H), 6.747–7.444(m, 10H), 7.951(d, 1H)	911.17 ($2MH^+$)
3′F		64.7	119–121	1.395(d, 3H), 3.871(t, 1H), 4.247(m, 2H), 5.355(s, 2H), 5.673(d, 1H), 6.967(m, 1H), 7.134(m, 1H), 7.313(m, 1H), 7.755(d, 1H)	386.07 (MH^+)

boiling for 1 hr (here the isocyanate intermediate **2** could be isolated by crystallization from proper solvents after removing toluene). To this clear boiling solution, add 5 mmol alcohol in one portion. The reaction completes in 10 min by thin layer chromotography (TLC) (silica gel, GF254). After evaporating the solvent in vacuo, the residue could be crystallized in suitable solvent to get **3**.

If the deprotected product is desired, taking the benzoyl protection as an example, the retained residue is dissolved in 50 mL methanol and cooled to 0°C. Two mL of 5*N* sodium methoxide in methanol is added and the mixture is stirred at room temperature for 1 hr. Then the mixture is neutralized with HCl-EtOH and the solvent is removed in vacuo. The residue could be crystallized in suitable solvent or purified by chromatography on silica gel column to get **3′**.

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Received in Japan April 22, 2004