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Efficient synthesis of nucleoside 5′-triphosphates and their β,γ-bridging oxygen-modified analogs from nucleoside 5′-phosphates

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ABSTRACT

Thirteen nucleoside 5′-triphosphates (NTPs) and their β,γ-bridging oxygen-modified analogs (β,γ-CX_2-NTPs, X = H, F, Cl, and Br) have been efficiently synthesized from nucleoside 5′-phosphoropiperidates with 4,5-dicyanoimidazole as the activator. A high-yielding and chromatography-free protocol for the preparation of both natural and base-modified nucleoside 5′-phosphoropiperidates from the corresponding nucleoside 5′-phosphates was also developed.

Nucleoside 5′-triphosphates (NTPs) are a unique group of biomolecules that play key roles in a vast array of pivotal biological processes, such as energy metabolism, polymerization of DNA and RNA, signal transduction, and regulation of protein functions.[1] Due to the existence of the high-energy phosphoanhydride bonds, NTPs are highly susceptible to hydrolysis.[2] Replacement of the labile P–O–P linkage with an isosteric P–CXY–P (X, Y = H, F, Cl, Br, and OH) unit at β,γ-bridging position (Fig. 1) enhances the metabolic stability of the modified NTP analogs.[3] These hydrolysis-resistant NTP analogs have been extensively utilized to probe the catalytic mechanism of phosphoryl tranfer processes,[4] and investigated as enzyme inhibitors[5] and receptor agonists[6] in numerous medicinal studies.

Due to their important roles in biological research and potential pharmaceutical applications, various synthetic methods for NTPs have been adopted for the preparation of β,γ-bridging oxygen-modified NTP analogs (β,γ-CX_2-NTPs, X = H, F, Cl, and Br). The conventional 'one-pot, three-step',[6b–d] salicyl chlorophosphite,[5b] and phosphoromorpholidate[3d,4a,6e] methods have been employed to synthesize β,γ-CX_2-NTPs in moderate yields. These compounds have also been obtained from the coupling of nucleoside 5′-phosphates (NMPs) with diphosphonates in the presence of condensing reagents, such as diphenylphosphoryl chloride,[4e] CDI,[4d,7] $(CF_3CO)_2$-O/*N*-methylimidazole,[8] and sulfonyl imidazolium salts.[9] Moreover, a solid-phase method has been reported for the synthesis of β,γ-CH_2-NTPs.[5a] However, the preparation of special β,γ-CH_2-triphosphitylating reagent greatly limits its practical application.

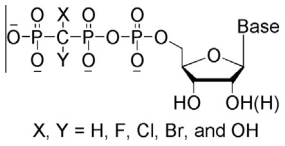

Figure 1. The structures of β,γ-bridging oxygen-modified NTP analogs.

More recently, we established a novel P(V)–N activation approach for the synthesis of nucleoside diphosphates (NDPs), triphosphates (NTPs),[10] and nucleoside diphosphate sugars (NDP-sugars)[11] from the fully protected phosphoropiperidates. Though the Bn and Cbz protecting groups of the phosphoropiperidate precursors could be quantitatively removed by catalytic hydrogenation, reducible functional groups, such as —N_3 and —C≡C— on ribose moiety and halogen atoms (e.g., F, Cl, Br, and I) on nucleobases could not be tolerated. Therefore, a direct and efficient access to the unprotected phosphoropiperidates may significantly simplify the original method and extend the applications of the P(V)–N activation strategy to more diversified nucleoside substrates. We report herein a high-yielding and chromatography-free method for the preparation of nucleoside 5′-phosphoropiperidates

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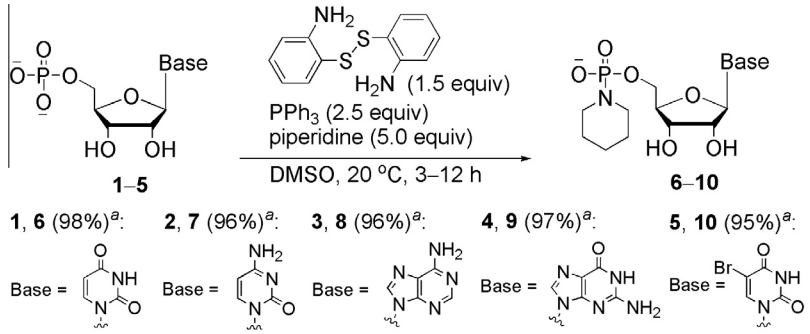

Scheme 1. A general and optimized method for the synthesis of nucleoside 5′-phosphoropiperidates (**6**–**10**) from nucleoside 5′-phosphates. [a]Isolated yield.

from the corresponding NMPs. The obtained nucleoside 5′-phosphoropiperidates exhibited excellent reactivity toward pyrophosphate and diphosphonate reagents in the presence of 4,5-dicyanoimidazole (DCI) and afforded NTP and β,γ-CX_2-NTP products in high isolated yields.

As shown in Scheme 1, the phosphoropiperidates of four natural nucleosides (**6**–**9**) and a base-modified nucleoside (5-bromouridine, **10**) were prepared from the corresponding NMP starting materials (**1**–**5**). In contrast to the DCC condensation method,[4a,12] the redox condensation approach based on 2,2′-dipyridyldisulfide/PPh_3 is amenable to amine nucleophiles with a wide range of pK_a values.[13] In precedent reports, 2.0–5.0 equiv of 2,2′-dipyridyldisulfide/PPh_3 in 1:1 molar ratio were used to give the phosphoromorpholidates and phosphoropiperidates of adenosine and guanosine in good yields (~70–80%).[14] In the present work, 2,2′-dithiodianiline, a less expensive disulfide reagent, was used

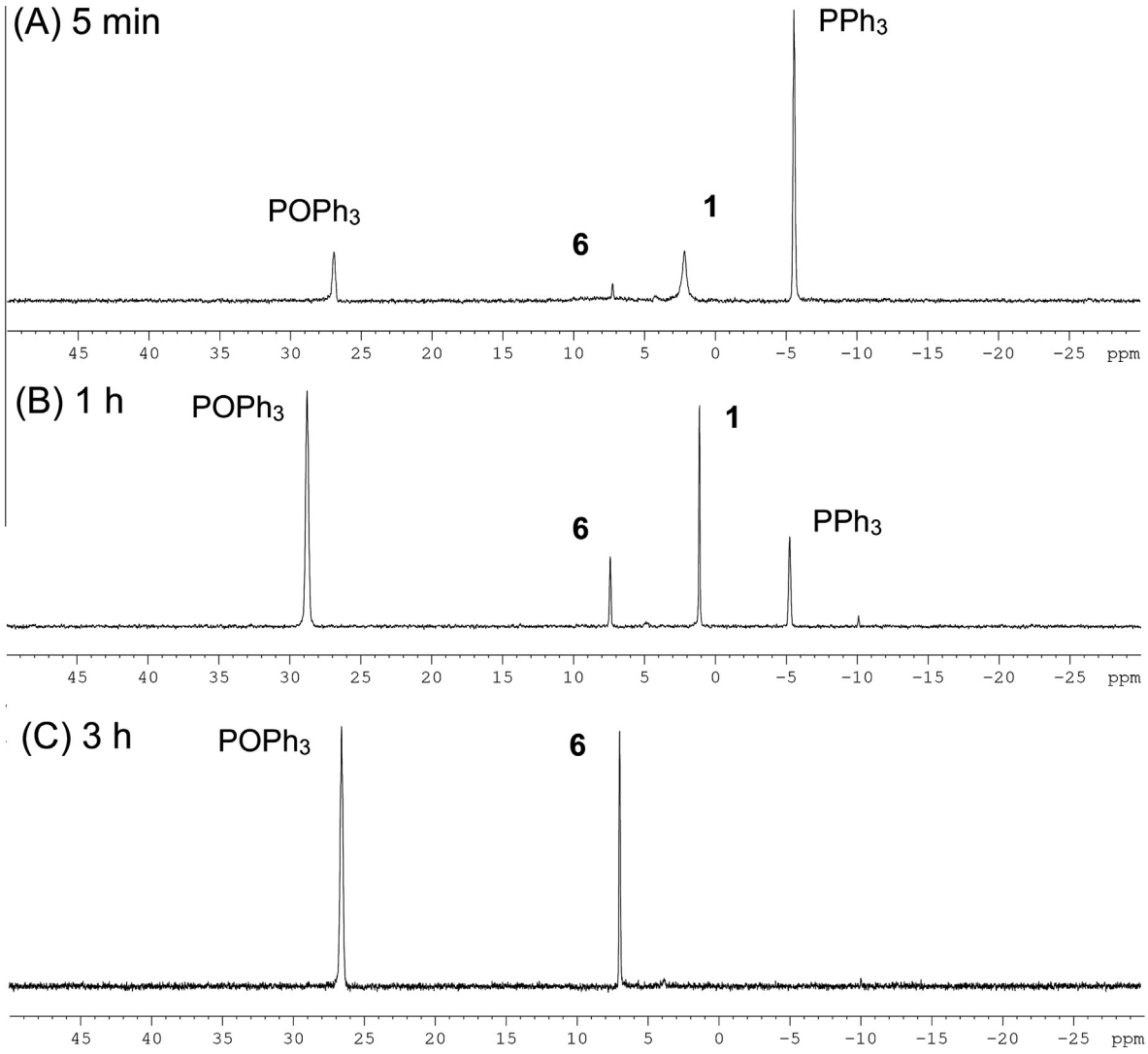

Figure 2. ^{31}P NMR tracing of the redox condensation reaction mixture for the synthesis of uridine 5′-phosphoropiperidate (**6**).