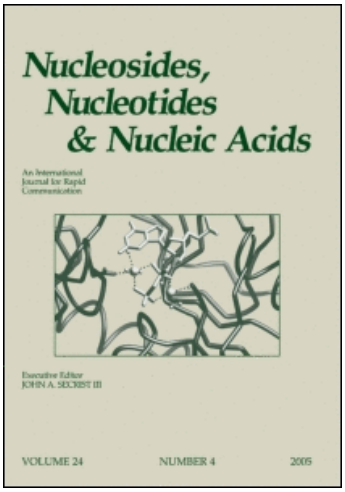

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Convenient Method for the Synthesis of ATP and Ap_4A

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To cite this Article Fukuoka, Koichiro , Suda, Fuminori , Ishikawa, Masahide and Hata, Tsujiaki(1995) 'A Convenient Method for the Synthesis of ATP and Ap_4A', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 693 — 694
To link to this Article: DOI: 10.1080/15257779508012451
URL: http://dx.doi.org/10.1080/15257779508012451

NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 693-694 (1995)

A CONVENIENT METHOD FOR THE SYNTHESIS OF ATP AND Ap_4A.

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Abstract: A bifunctional phosphorylating reagent, *O*-8-(5-chloroquinolyl) *S*-phenyl phosphorothioate (**1**) was employed for the synthesis of adenosine 5'-triphosphate(ATP) and diadenosine 5'-tetraphosphate(Ap_4A) from adenosine 5'-phosphate(AMP) on a large scale.

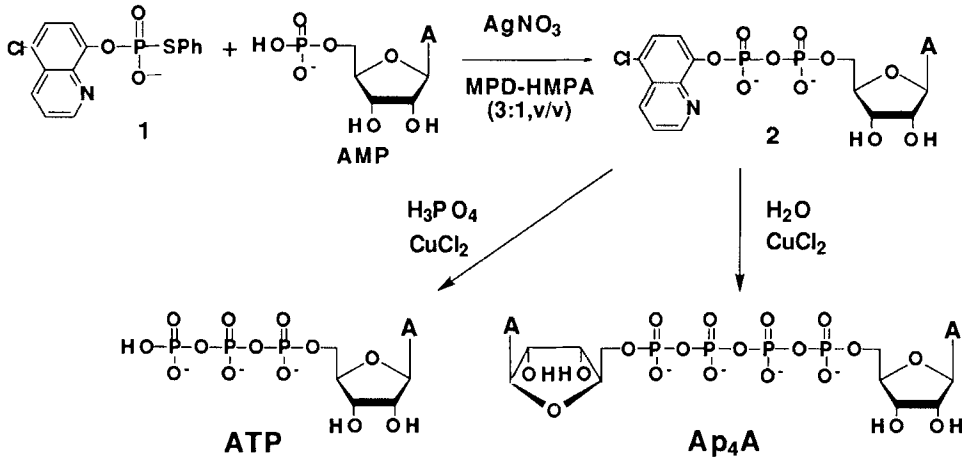
Nucleoside polyphosphates, such as ATP, Ap_4A and the cap structure, $m^7G^{5'}pppN$ (N=A or G) in eukaryotic mRNA, play important roles in various biological processes. These polyphosphates and their analogues have been synthesized in order to elucidate their biological functions. ATP and Ap_4A were synthesized enzymatically or chemically from activated AMP and pyrophosphate.[1] In the latter, it was difficult to separate ATP or Ap_4A from pyrophosphate by anion exchange column chromatography. Therefore, a convenient method for the synthesis of these polyphosphates is required.

Recently, we have reported the new bifunctional phosphorylating reagent **1** was available for the one-pot synthesis of the cap structure, $m^7G^{5'}pppN$ (N=A or G).[2] Compound **1** has two different leaving groups, which are activatable selectively. The phenylthio group can be activated by silver ion,[3] and the 5-chloro-8-quinolyloxy group can be activated by copper(II) ion.[4] Therefore, compound **1** would be widely applicable to the convenient synthesis of ATP and Ap_4A.

First, compound **1** was used for the synthesis of ATP. A 1:1 mixture of **1** and AMP was allowed to react with 1.2 equiv of silver nitrate in 1-methylpyrrolidone(MPD)-HMPA(3:1,v/v) at room temperature for 30 min. As a result, the diphosphate intermediate (**2**) was formed along with AgSPh. Without isolating **2**, the mixture was treated with 5 equiv of phosphoric acid and 5 equiv of anhydrous copper(II) chloride. The resulting mixture was stirred at room temperature for 24 h. Column chromatography using DEAE Sephadex A-25 gave ATP in 64% yield (92 mg).

Next, compound **1** was also used for the synthesis of Ap_4A. When 10 equiv of H_2O were employed in place of phosphoric acid in the above reactions, ADP was formed by partial hydrolysis from **2**. Subsequent reaction between ADP and **2** afforded Ap_4A. After purification by DEAE Sephadex A-25 column chromatography, Ap_4A was obtained in 54% yield (62 mg).

In conclusion, it is noteworthy that ATP and Ap_4A were prepared in high yields by use of **1** in a one-pot reaction without activating AMP. All the above reactions proceeded smoothly to give simple reaction mixtures at room temperature under neutral conditions. Therefore, isolation of ATP and Ap_4A can be facilitated compared with the known methods. The reagent **1** would be further applicable to the synthesis of other polyphosphate derivatives.



ACKNOWLEDGMENT: This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas No. 04226105 from the Ministry of Education, Science and Culture, Japan.

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