Tetrahedron Letters 59 (2018) 2477–2484

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Recent application of acidic 1,3-azolium salts as promoters in the solution-phase synthesis of nucleosides and nucleotides

Masaki Tsukamoto [a,*], Kin-ichi Oyama [b]

[a] Graduate School of Informatics, Nagoya University, Chikusa, Nagoya 464-8601, Japan
[b] Chemical Instrumentation Facility, Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

ARTICLE INFO

Article history:
Received 15 February 2018
Revised 23 March 2018
Accepted 24 March 2018
Available online 26 March 2018

Keywords:
Acidic 1,3-azolium salt
Nucleoside
Nucleotide
Acidic imidazolium salt
Acidic oxazolium salt

ABSTRACT

Acidic 1,3-azolium salts are prepared from Brønsted acids and 1,3-azoles such as imidazole, thiazole, and oxazole. Acidic imidazolium salts are frequently employed as promoters for the synthesis of nucleotides using the phosphoramidite method in a solution phase. Recently, it was revealed that thiazolium and oxazolium salts catalyzed Vorbrüggen-type *N*-glycosylation reactions to give nucleosides. These reactivities are attributed to the stronger Brønsted acidities of the thiazolium and oxazolium salts relative to those of the imidazolium salts. This digest focuses on recent progress in the applicability of acidic 1,3-azolium salts as promoters in the solution-phase synthesis of nucleosides and nucleotides.

Contents

Introduction

Acidic 1,3-azolium salts are prepared from Brønsted acids and 1,3-azoles such as imidazole, thiazole, and oxazole (Fig. 1). These salts have been known for a long time and their physical characteristics have been well investigated by ^{1}H and ^{13}C NMR spectroscopies,[1,2] potentiometric titration,[3] and infrared spectroscopies.[4,5] The pK_a's of protonated imidazole, thiazole, and oxazole derivatives were determined by potentiometric titration, disclosing that the pK_a decreases in this order.[3] It is well known that the non-substituted acidic azolium salts have pK_a values of 7.0, 2.4, and 0.8, respectively (Fig. 1).[6]

In the first application of a protonated imidazole derivative as a coupling reagent, benzimidazolium triflate (BIT) was used to promote condensation of a nucleoside phosphoramidite and a nucleoside,[7–9] which is a key step for the synthesis of nucleotides and oligonucleotides.[10,11] As shown in Scheme 1, phosphoramidite **1** and nucleoside **2** were condensed with a stoichiometric amount of BIT to form the intermediary phosphite triester **3**, which was subsequently oxidized by *tert*-butyl hydroperoxide[12] to afford the dinucleoside phosphate **4** quantitatively. BIT is compatible with an acid-labile 4,4′-dimethoxytrityl (DMTr) protecting group and is more advantageous than a previously reported acidic pyridinium

* Corresponding author.
E-mail address: tsukamoto@is.nagoya-u.ac.jp (M. Tsukamoto).

https://doi.org/10.1016/j.tetlet.2018.03.074
0040-4039/

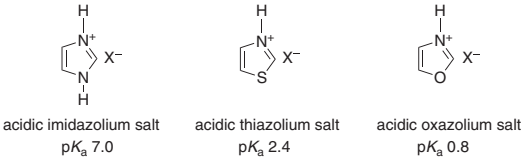
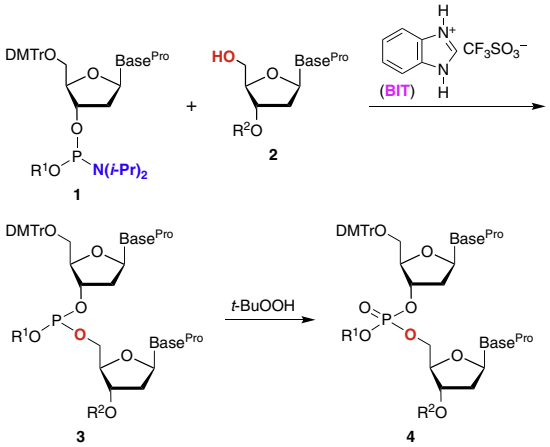


Fig. 1. pK_a values of representative acidic 1,3-azolium salts in water. X^- indicates a counter anion.



Scheme 1. Internucleotide bond formation reaction using benzimidazolium triflate (BIT) as a promoter. $Base^{Pro}$ indicates a protected nucleobase.

salt that partially cleaves the DMTr group.[13] Since this report, various combinations of imidazole derivatives and acids have been tested to identify more reactive promoters; several such promoters have already been found.[14,15] At present, acidic imidazolium salts such as BIT and imidazolium perchlorate (IMP) (Fig. 2)[16] are employed as promoters for the internucleotide bond formation. The mechanism of this reaction has been well described in comparison with those promoted by 1*H*-tetrazole and its analogs.[14]

The stronger acidity of acidic thiazolium and oxazolium salts compared to imidazolium salts enables the former to promote other types of reactions: thiazolium salts catalyze esterifications[17] and oxazolium salts catalyze Vorbrüggen-type *N*-glycosylation reactions.[18,19] The application of these salts as reagents has just begun.

This digest focuses on the recent examples of solution-phase synthesis of nucleosides and nucleotides up to trinucleotides employing condensation reactions promoted by acidic imidazolium, thiazolium, and oxazolium salts. For applications of acidic imidazolium salts to the synthesis of oligonucleotides, please see the relevant reviews.[20,21] Nucleobases with and without protecting groups that appear in this digest are summarized in Fig. 3.

The general structure of an acidic 1,3-azolium salt is shown in Fig. 4. A heteroatom or heteroatom group Y (NH, *N*-alkyl, S, and O) strongly influences the Brønsted acidity,[3,6] while a counter anion X^- functions not only as a nucleophile[18,22] but also as a key factor for the hygroscopicity.[14,18] Substituents R^1, R^2, and R^3 enable control of the hygroscopicity and Brønsted acidity. Reagents

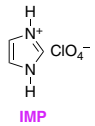


Fig. 2. Imidazolium perchlorate (IMP).

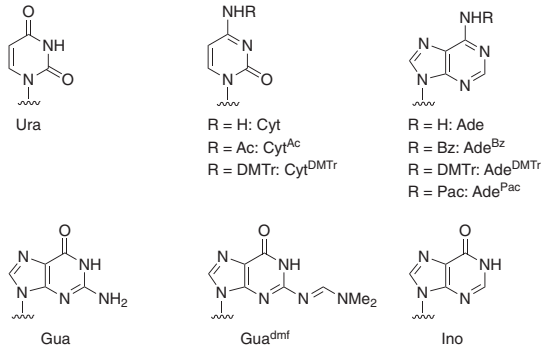


Fig. 3. Nucleobases with or without protecting groups. Pac = phenoxyacetyl.

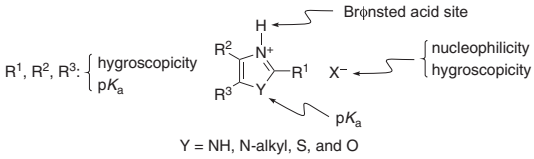


Fig. 4. General structure of an acidic 1,3-azolium salt.

with less hygroscopicity are obviously more favorable. In the following examples, the non-hygroscopic salts discovered by screening were employed as promoters or catalysts.[14,18]

Acidic imidazolium salts

Synthesis of mononucleotides

Diethyl guanosine 5′-monophosphate (**7**) was synthesized by using imidazolium triflate (IMT) for the conformational analysis in the gas phase (Scheme 2).[23] 2′,3′-*O*-Isopropylideneguanosine (**5**) was converted to 5′-*O*-monophosphate **6** by treatment with diethyl diisopropylaminophosphoramidite and IMT followed by oxidation with *tert*-butyl hydroperoxide.[12] Removal of the isopropylidene protector of **6** afforded the target phosphotriester **7**, which was vaporized by pulsed laser desorption and was analyzed by UV and IR spectroscopy. The result suggested the existence of an internal hydrogen-bonding structure between the oxygen atom of the P = O and one of the hydrogen atoms of the amino group in the guanine base.

IMT was uniquely employed for phosphitylations of three secondary hydroxy groups of the adenine-unprotected intermediate **8** derived from adenosine and glucose (Scheme 3).[24] Subsequent oxidation with *m*-CPBA followed by hydrogenolysis of the benzyl groups afforded adenophostin A, a potent D-*myo*-inositol 1,4,5-triphosphate receptor-agonist discovered from a culture broth of *Penicillium brevicompactum*.[25,26] An advantage of IMT is that base-unprotected adenine derivatives can be used as substrates. This tri-phosphitylation procedure has been applied to the synthesis of various adenophostin A analogs.[26–28] As a phosphitylation reagent, *o*-xylene *N,N*-diethylphosphoramidite[29] has also been employed.[26,27]

The Raines group developed a hydrophilic cancer prodrug, uridine 3′-(4-hydroxytamoxifen phosphate) (**12**), by using the phosphoramidite method with *N*-methylbenzimidazolium triflate (*N*-MeBIT) (Scheme 4).[30] First, uridine phosphoramidite **9** and 4-hydroxytamoxifen (**10**) were coupled with *N*-MeBIT to afford the corresponding phosphite triester, which was subsequently oxidized to the phosphate **11**. The protecting groups of **11** were cleaved in three steps to afford **12**. The cancer prodrug **12** was acti-