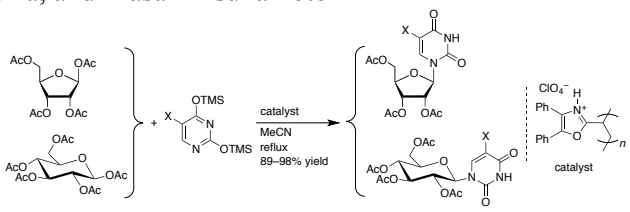
Graphical Abstract

A solid-supported acidic oxazolium perchlorate as an easy-handling catalyst for the synthesis of modified pyrimidine nucleosides via Vorbrüggen-type *N*-glycosylation

Nabamita Basu, Kin-ichi Oyama, and Masaki Tsukamoto*



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A solid-supported acidic oxazolium perchlorate as an easy-handling catalyst for the synthesis of modified pyrimidine nucleosides via Vorbrüggen-type *N*-glycosylation

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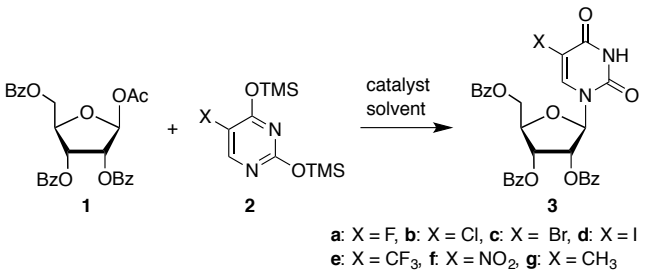
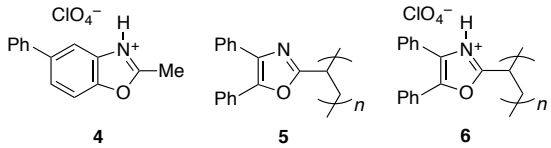
ABSTRACT

A solid-supported acidic oxazolium perchlorate was investigated as a heterogeneous catalyst in *N*-glycosylation reactions using silylated modified pyrimidines and an acylated ribose or glucose to afford the corresponding pyrimidine nucleosides. This salt is a nonhygroscopic and stable powder whose activity is comparable to that of 2-methyl-5-phenylbenzoxazolium perchlorate. A reaction with this polymer catalyst can be conducted on a gram scale. Reusability of the solid-supported catalyst was also investigated.

N-Glycosylation promoted by trimethylsilyl triflate (TMSOTf) utilizing sugar acetates such as **1** and silylated pyrimidines **2** is a standard method of synthesizing modified pyrimidine nucleosides that are utilized for antiviral and anticancer agents as well as for various applications in the life sciences (cf. Scheme 1).[1–4] To complete the reaction, a stoichiometric amount of TMSOTf is generally used due to its low reactivity. In addition, this reagent's hygroscopic nature requires extreme caution in handling.[1,2] To solve this problem, Jamison et al. proposed acidic pyridinium salts as the first Brønsted acid catalysts.[5] We invented 2-methyl-5-phenylbenzoxazolium perchlorate (**4**) as a nonhygroscopic and stable catalyst, which showed higher reactivity than those of TMSOTf and 2,6-di-*tert*-butyl-4-methylpyridinium triflate.[6] The only drawback of this method is the tedious purification procedure necessitated by the remaining oxazole compound after workup. If the acidic oxazolium salt derived from a polyoxazole were employed as a catalyst, it would be easier to remove it from the reaction mixture. Although various kinds of polymer-supported reagents have been developed,[7–9] they have not been applied to the synthesis of pyrimidine nucleosides. Because polyoxazoles such as poly(4,5-diphenyl-2-vinyloxazole) (**5**) have been synthesized,[10,11] we prepared a solid-supported acidic oxazolium salt **6** from **5** and investigated its potential as a catalyst for *N*-glycosylation.



Scheme 1. Standard *N*-glycosylation reactions using 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) and silylated 5-substituted uracils **2**.



First, we optimized the conditions for the preparation of 4,5-diphenyl-2-vinyloxazole (**9**), which is the building block for poly(4,5-diphenyl-2-vinyloxazole) (**5**). Kurusu et al. prepared this monomer unit in 43% yield by reaction of benzoin (**7**) and acrylonitrile (**8**) (1.1 equiv) in the presence of sulfuric acid (Table 1, entry 1).[10] On the basis of their method, we conducted an experiment on a 1-gram scale to afford **9** in only 23% yield, with unidentified by-products. Therefore, we modified this

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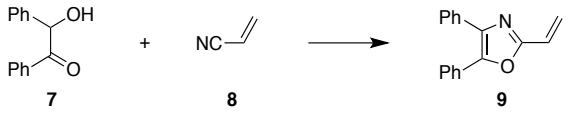
Table 1. Preparation of 4,5-diphenyl-2-vinyloxazole (**9**).



7 **8** **9**

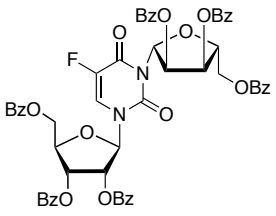
Entry	**7**, mmol	**8**, equiv	H_2SO_4, equiv	Tf_2O, equiv	Temperature and time	Yield, %
1[a]	40	1.1	14	0	0 °C for 2 h	43
2	5	10	8	0	0 °C for 10 min, then rt for 1 h	68
3	5	10	5	0.5	0 °C for 10 min, then rt for 1 h	81
4	14	10	5	0.5	0 °C for 10 min, then rt for 1 h	38

[a]Data from Ref 10.

procedure by using an excess amount of **8** as a solvent as well as by decreasing the amount of sulfuric acid. With 10 equiv of **8** and 8 equiv of sulfuric acid, the desired product was obtained in 68% yield (entry 2). The amount of sulfuric acid was reduced to 5 equiv in the presence of trifluoromethanesulfonic anhydride (0.5 equiv)[12,13] to afford **9** in 81% yield (entry 3). Unfortunately, scaling up to ca. 14 mmol of **7** decreased the yield to 38%. Nevertheless, a sufficient amount of pure **9** for the subsequent reaction was obtained by repeating the small-scale reaction.

The polymerization of **9** was conducted as reported by Kurusu et al. by using 2,2'-azodiisobutyronitrile (AIBN) as an initiator to give poly(4,5-diphenyl-2-vinyloxazole) (**5**),[10] whose number average molecular weight (M_n) and weight average molecular weight (M_w) were estimated to be 1.19 x 10^4 and 12.5 x 10^4, respectively, by gel permeation chromatography (GPC) measurement. **5** was then converted to nonhygroscopic poly(4,5-diphenyl-2-vinyloxazolium perchlorate) (**6**) by treatment with perchloric acid. The loading amount of acid on **6** was determined to be 2.6–2.8 mmol/g. The elemental analysis of **6** indicated that ca. 90% of the oxazole nitrogen was protonated.

The catalytic activity of poly(oxazolium perchlorate) **6** was evaluated in the reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) and silylated 5-fluorouracil **2a** on a 0.1 mmol scale as previously described (cf. Scheme 1).[6] The catalyst loading was set at 5 mol%. After refluxation for 2 h using a stirring bar, the yield of the *N*-glycosylated product **3a** was determined by ^{1}H NMR. The use of **6** in acetonitrile afforded a 77% yield of **3a**, which was comparable to that obtained by our conventional catalyst **4** (80% yield) and was superior to that with TMSOTf (50% yield).[6] In contrast to the reaction with **4**, N^1,N^3-bis-*N*-glycoside **10** was not detected. The polymer catalyst **6** also showed similar activity in acetone to afford a 74% yield. Therefore, we applied these conditions in acetonitrile for the synthesis of various modified pyrimidine nucleosides.



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To investigate the applicability of our polymer catalyst **6**, we conducted reactions of **1** with silylated pyrimidines **2** having halogens, trifluoromethyl, and nitro groups on a 0.3 mmol scale in acetonitrile (Scheme 1). As shown in Table 2, reactions with the silylated pyrimidines **2a**–**2e** were finished within 6 h, giving the corresponding nucleosides **3a**–**3e** in 87–97% yields without the formation of a significant amount of unwanted N^1,N^3-bis-*N*-glycosides. After the reaction was over, the polymer residue derived from catalyst **6** was stuck to the wall of a reaction vessel and was not soluble in acetonitrile. Therefore, it was easy to remove the polymer from the reaction mixture.[14] In the reaction with silylated 5-nitrouracil **2f**, the desired nucleoside **3f** was not obtained (entry 6) along with the recovered starting materials (i.e., sugar acetate **1** and 5-nitrouracil). The reaction with silylated thymine **2g** was quite slow and could not be completed within 6 h. Thus, the reaction temperature was increased. As a result, the reaction at 140 °C for 14 h afforded **3g** in 95% yield (entry 7). This may have been due to the electron-donating property of **2g**, which deactivates the catalytic activity. The same approach was applied to the reaction of **1** (0.3 mmol) and silylated N^6-benzoyladenine to produce N^6,2',3',5'-tetra-*O*-benzoyladenosine (**11**) in 88% yield.[15,16]

Table 2. Synthesis of pyrimidine ribosides **3** from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) and silylated 5-substituted uracils **2** by using solid-supported oxazolium perchlorate **6**[a]

Entry	Silylated base	Nucleoside	Isolated yield, %
1	**2a**	**3a**	90
2	**2b**	**3b**	87
3	**2c**	**3c**	92
4	**2d**	**3d**	95
5[b]	**2e**	**3e**	97
6	**2f**	**3f**	0[c,d]
7	**2g**	**3g**	15[e] (95)[f]

[a]Unless otherwise stated, reactions were conducted on a 0.3 mmol scale under the following conditions: [**1**] = 100 mM, [**2**] = 130 mM, **6** (5 mol %), MeCN, reflux, 6 h.

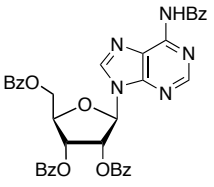
[b][**2e**] = 120 mM.

[c]The same result was obtained in acetone.

[d]**1** and 5-nitrouracil were recovered.

[e]The yield was determined by ^{1}H NMR analysis. **1** (85%) and thymine were also observed by TLC and ^{1}H NMR analyses.

[f]The reaction was conducted under the following conditions: [**1**] = 100 mM, [**2g**] = 110 mM , **6** (5 mol %), MeCN, 140 °C, 14 h.



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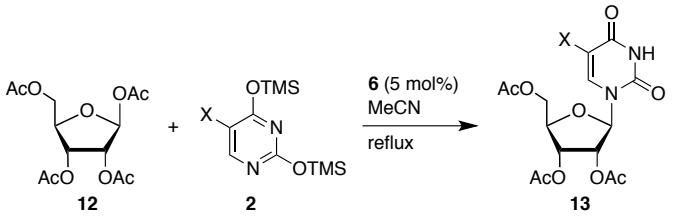
Subsequently, we employed tetra-*O*-acetyl-β-D-ribofuranose (**12**) as a glycosyl donor in acetonitrile. As shown in Table 3, the tri-acetylated pyrimidine ribosides **13** were obtained in 89–98% yields. For the synthesis of **13e**, the reaction was easily scaled up to the 1-gram level. The reaction was finished within 30 min, as in the case of that using catalyst **4**.[6] Triacetyl 5-nitrouridine (**13f**) was obtained in a reasonable yield (entry 6) in contrast to the reaction using the glycosyl donor **1** (Table 2, entry 6).

Table 3. Synthesis of pyrimidine ribosides **13** from 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**12**) and silylated 5-substituted uracils **2** by using solid-supported oxazolium perchlorate **6**[a]



12 **2** **13**

a: X = F, **b**: X = Cl, **c**: X = Br, **d**: X = I
e: X = CF_3, **f**: X = NO_2

Entry	Silylated base	Nucleoside	Time, h	Isolated yield, %
1	**2a**	**13a**	6	91
2	**2b**	**13b**	6	89
3	**2c**	**13c**	6	93
4	**2d**	**13d**	7	96
5[b]	**2e**	**13e**	0.5	98
6	**2f**	**13f**	6	90

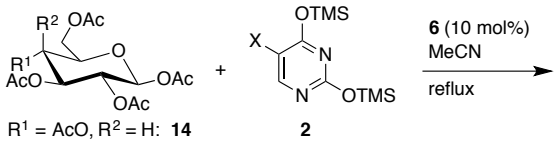
[a]Unless otherwise stated, reactions were conducted on a 0.3 mmol scale under the following conditions: [**12**] = 100 mM, [**2**] = 130 mM.

[b][**2e**] = 120 mM.

We also conducted reactions of pentaacetyl-β-D-glucose (**14**) and silylated 5-substituted uracils **2** in the presence of polymer catalyst **6** as shown in Table 4.[2,17,18] Because the glycosyl donor **14** had lower reactivity than ribofuranoses **1** and **12**, catalyst loading was set at 10 mol% in order to complete the reactions within 24 h.[6] The pyrimidine glucosides **16** were obtained in 91–98% yields. In the case of **2e**, the reaction was completed in 2 h (entry 5). A mixture of penta-*O*-acetyl-β-D-galactopyranose (**15**), **2a**, and **6** (10 mol%) led to the formation of **17a**[17] in 98% yield (entry 7).

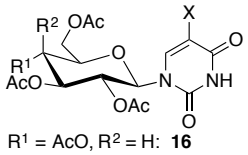
Finally, catalyst reusability was investigated in the reaction of 1,2,3-tri-*O*-acetyl-5-deoxy-β-D-ribofuranose (**18**) and silylated 5-(trifluoromethyl)uracil **2e** (Table 5).[19] With 5 mol% of **6**, 2′,3′-di-*O*-acetyl-5-(trifluoromethyl)-5′-deoxyuridine (**19**) was obtained in 98% yield (Run 1). The recovered polymer, however, did not show any catalytic activity with the recovery of the

Table 4. Synthesis of pyrimidine glucosides **16** and galactoside **17** by using solid-supported oxazolium perchlorate **6**[a]



R^1 = AcO, R^2 = H: **14**
R^1 = H, R^2 = AcO: **15**

2



a: X = F, **b**: X = Cl, **c**: X = Br
d: X = I, **e**: X = CF_3, **f**: X = NO_2

R^1 = AcO, R^2 = H: **16**
R^1 = H, R^2 = AcO: **17**

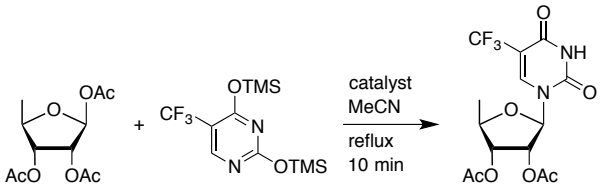
Entry	Glycosyl donor	Silylated base	Nucleoside	Time, h	Isolated yield, %
1	**14**	**2a**	**16a**	24	93
2	**14**	**2b**	**16b**	24	92
3	**14**	**2c**	**16c**	24	91
4	**14**	**2d**	**16d**	24	98
5[b]	**14**	**2e**	**16e**	2	98
6	**14**	**2f**	**16f**	24	98
7[c]	**15**	**2a**	**17a**	24	98

[a]Unless otherwise stated, reactions were conducted on a 0.3 mmol scale under the following conditions: [**14**] or [**15**] = 100 mM, [**2**] = 130 mM.

[b][**2e**] = 120 mM.

[c]Polyoxazole **5** was recovered in a ratio of 94%.

Table 5. Investigation of catalyst reusability in the reaction of 1,2,3-tri-*O*-acetyl-5-deoxy-β-D-ribofuranose (**18**) and silylated 5-(trifluoromethyl)uracil **2e** by using solid-supported oxazolium perchlorate **6**[a]



18 **2e** **19**

Run	Catalyst	Isolated yield, %
1	**6** (5 mol%)	98
2	Polymer recovered after Run 1	0[b]
3[c]	Polymer recovered after Run 2 was acidified and used as catalyst	97

[a]Reactions were conducted on a 1 mmol scale under the following conditions: [**18**] = 100 mM, [**2e**] = 110 mM.

[b]Determined by TLC and ^{1}H NMR analyses.

[c]After Run 3 was conducted, polyoxazole **5** was recovered in a ratio of 82% based on the amount of **6** used in Run 1, indicating that 93–94% of the polymer was recovered for each Run.

starting materials (Run 2). We assumed that **6** was converted to the polyoxazole **5**. Therefore, the recovered polymer after Run 2 was acidified with perchloric acid and then used for the *N*-glycosylation (Run 3). The catalytic activity of the acidified polymer was returned to the original level, supporting the above assumption.

In summary, poly(4,5-diphenyl-2-vinyloxazolium perchlorate), prepared by the reaction of poly(4,5-diphenyl-2-vinyloxazole) and perchloric acid, was found to be effective as an easy-handling catalyst for the synthesis of modified pyrimidine nucleosides via *N*-glycosylation reaction. The catalytic activity was comparable to that of 2-methyl-5-phenylbenzoxazolium perchlorate. The reaction can be scaled up to the gram level. Because the polymer residue derived from the catalyst can be removed from the reaction mixture, the purification procedure is simpler than that of 2-methyl-5-phenylbenzoxazolium perchlorate. The recovered polymer lost the catalytic activity; however, treatment with perchloric acid activated the polymer residue so that it could be used as a catalyst.

Acknowledgments

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References and notes

1. Vorbrüggen, H. *Acc. Chem. Res*. **1995**, *28*, 509–520.
2. Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*; Wiley: New York, NY, 2001.
3. *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum: New York, NY, 1993.
4. Ahmadian, M.; Bergstrom, D. E. In *Modified Nucleosides: in Biochemistry, Biotechnology and Medicine*; Herdewijn, P., Ed.; Wiley-VCH, Weinheim, Germany, 2008, Chap. 10, pp. 251–276.
5. Sniady, A.; Bedore, M. W.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 2155–2158.
6. Shirouzu, H.; Morita, H.; Tsukamoto, M. *Tetrahedron* **2014**, *70*, 3635–3639.
7. Manecke, G.; Storck, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 657–670.
8. Lu, J.; Toy, P. H. *Chem. Rev*. **2009**, *109*, 815–838.
9. Bradley, M.; Galaffu, N. In *Encyclopedia of Polymer Science and Technology, 4th edn.*; Mark, H. F., Eds.; Wiley: Hoboken, NJ, 2014, Vol. 11, pp. 17–47.
10. Kurusu, Y.; Nishiyama, H.; Okawara, M. *Kogyo Kagaku Zasshi* **1968**, *71*, 1741–1744.
11. Hilborn, J. G.; Labadie, J. W.; Hedrick, J. L. *Macromolecules* **1990**, *23*, 2854–2861.
12. Martínez, A. G.; Alvarez, R. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett*. **1989**, *30*, 581–582.
13. Lai, P.-S.; Taylor, M. S. *Synthesis* **2010**, 1449–1452.
14. The polymer residue after the *N*-glycosylation can be recovered by an aqueous workup or by simply removing the reaction mixture from the vessel. Quantitative analyses were made in the syntheses of **17a** (Table 4) and **19** (Table 5). The polymer can be included in the crude material, but due to its high polarity, it is easily removed by column chromatography.
15. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber*. **1981**, *114*, 1251–1255.
16. Under the refluxing conditions in either acetonitrile or acetone, the reaction of sugar acetate **1** (0.1 mmol) and silylated N^6-benzoyladenine ended with the recovery of **1** and N^6-benzoyladenine, as in the case of catalyst **4**.[6]
17. Haeckel, R.; Weber, K.; Germann, C.; Haberkorn, U.; Zeisler, S.; Eisenbarth, J.; Wiessler, M.; Oberdorfer, F. *J. Label. Compds. Radiopharm*. **1996**, *38*, 1061–1070.
18. Kantsadi, A. L.; Hayes, J. M.; Manta, S.; Skamnaki, V. T.; Kiritsis, C.; Psarra, A.-M. G.; Koutsogiannis, Z.; Dimopoulou, A.; Theofanous, S.; Nikoleousakos, N.; Zoumpoulakis, P.; Kontou, M.; Papadopoulos, G.; Zographos, S. E.; Komiotis, D.; Leonidas, D. D. *ChemMedChem* **2012**, *7*, 722–732.
19. Shen, B.; Jamison, T. F. *Org. Lett*. **2012**, *14*, 3348–3351.

Supplementary Material

Supplementary material including the detailed experimental procedures and spectral data related to this article can be found at the journal's homepage.