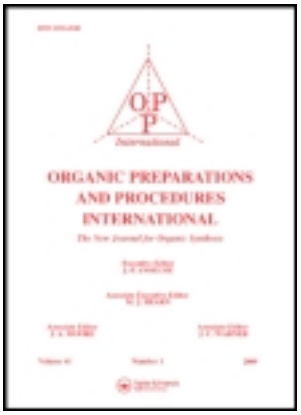

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An Improved Procedure for the Preparation of Ribavirin

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In recent decades, there has been considerable interest in *ribavirin* (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, **4**), as a broad-spectrum antiviral agent.[1–3] Because of its activity against both RNA and DNA viruses, it is extensively used for the treatment of influenzas, hepatitis B and C virus,[4] SARS,[5] syncytial virus,[6] and its value has been enhanced since oral ribavirin was approved by the FDA in 1998, and became part of a combination therapy for the treatment of hepatitis.[7]

There are two types of methods for the preparation of *ribavirin*, a chemical method[8–11] and an enzymatic synthesis.[12–15] A typical chemical protocol involves a three-step manufacturing process.[11] Condensation of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2**), prepared by the *p*-toluenesulfonic acid catalyzed acetylation of inosine (**1a**), with methyl 1,2,4-triazole-3-carboxylate gave methyl 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1H-1,2,4-triazole-3-carboxylate (**3**) which is subsequently converted to *ribavirin* (**4**) by deacetylation and ammonolysis (*Scheme 1*).

The process for the preparation of **2** from **1** suffer from drawbacks such as high cost, low yields, need for large amounts of catalyst and work-ups unsuitable for industrial production.[10] A major factor affecting this reaction is the acidity of the catalyst; if the catalyst is too acidic, the product decomposes while a catalyst of low acidity leads to long reaction times or incomplete cleavage of the nucleoside bond. Herein we report a practical, convenient and efficient process for the synthesis of **4** from inosine (**1a**, $R^1 = OH$, $R^2 = H$), adenosine (**1b**, $R^1 = NH_2$, $R^2 = H$), or guanosine (**1c**, $R^1 = OH$, $R^2 = NH_2$) in three steps.

Table 1 shows the results of acetylation and cleavage of purine nucleosides promoted by various catalysts. According to published results, inosine, adenosine and guanosine can be converted into **2** and to the corresponding acetyl purines with excess of acetic acid used both as a catalyst and a solvent (*Table 1, Entries 2–4*). Better results were obtained by the

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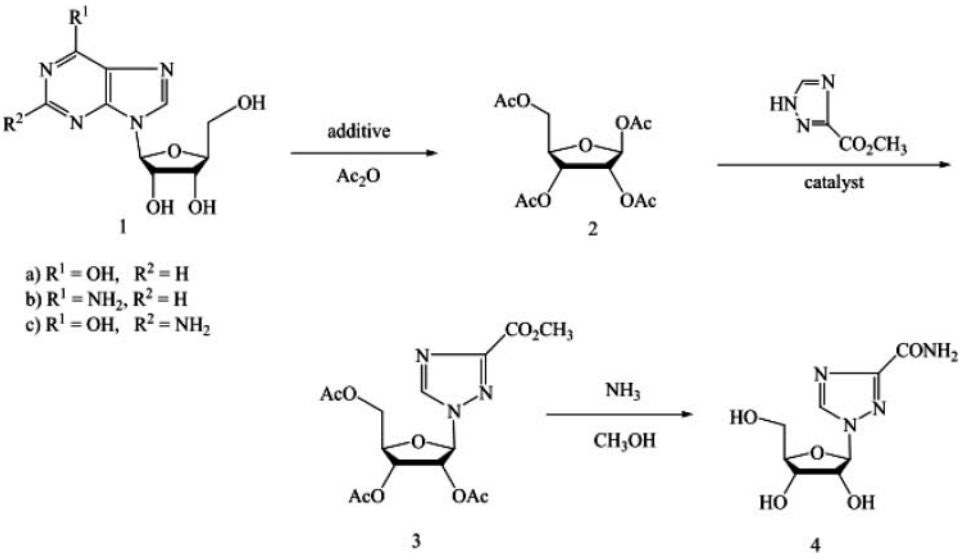

Scheme 1

use of *p*-Toluenesulfonic acid (*Table 1, Entry 1*). The acetylation and cleavage of purine nucleosides required less catalyst and gave better yields. Our results show that 0.45% of TFA was sufficient to accomplish this reaction (*Table 1, Entries 5–7*). Compared to other reported catalysts, the amount of catalyst used was greatly reduced, the yields were improved and reaction temperatures were milder.

Similarly, previous methods[8,11,17,18] for the conversion of **2** to **3** suffers from the need to use higher temperatures (−), longer reaction times (*Table 2, Entries*

Table 1
Comparison of Present Method with Previous Procedures for the Synthesis of **2**[a]

Entry	Nucleoside	Catalyst	Amount of catalyst% (mol)	Temp. (°C)	Yield (%)[b]
1	inosine	TsOH	3.10	90	84[10]
2	guanosine	acetic acid[c]	307	138	81[16]
3	adenosine	acetic acid[c]	296	138	73[16]
4	inosine	acetic acid[c]	296	138	83[16]
5	inosine	TFA	0.45	100	90
6	adenosine	TFA	0.45	100	84
7	guanosine	TFA	0.45	100	86

[a]Reaction mixtures containing 0.15 mol inosine or adenosine or guanosine and 1.5 mol acetic anhydride.
[b]Yield of **2** based on starting nucleosides.
[c]Used as the catalyst and the solvent.

Table 2
Comparison of Present Catalysis with Other Procedures for the Synthesis of **3**

Entry	Ribofuranose (mol)	Methyl 1,2,4-triazole-3-3-carboxylate/(mol)	Catalyst	Time (hrs)	Temp. (°C)	Yield (%)[a]
1	0.10	0.1	$(p\text{-}O_2NPh)_2PO_2H$	0.25–0.30	160–165	78[8]
2	1.26	1.46	$SnCl_4$	2	5–40	80[17]
3	0.19	0.21	*p*-TosOH	6	80–90	79[18]
4	0.01	0.01	$PhSO_3H$	5	90–100	80[18]
5	0.01	0.01	$MeSO_3H$	5	90–100	79[18]
6	0.15	0.17	CF_3SO_3H	2	130–135	88

[a]Isolated yield based on 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose.

3–5) and give lower yields (*Table 2, Entries 1–5*). Of several agents studied [*bis*-(*p*-nitrophenyl)phosphinic acid, stannic chloride, *p*-toluenesulfonic, benzenesulfonic and methanesulfonic acids), trifluoromethanesulfonic acid (TfOH)] (*Table 2, Entry 6*) was found to be the best catalyst for the conversion of **2** to **3** (88%) in high purity at 135° in 2 hrs.

In conclusion, we have developed an improved method for the preparation of ribavirin by using TFA as the catalyst for the conversion **1** to **2** and TfOH for the conversion **2** to **3**. The advantages of our procedure include short reaction times, easy work-up, low amount of catalyst, good yields and purity of the products. A further advantage in using **1b** and **1c** is that the by-products, adenine and guanine obtained in the first step maybe useful in the synthesis of *adefovir* and *acyclovir* respectively. The overall yields of **4** from **1a**, **1b** and **1c** were 75%, 70%, 71% respectively compared to 48%, 47%, 52% by the precious method.[11,15,18]

Experimental Section

All the starting materials were purchased from commercial sources and used without further purification. The IR spectra were obtained as KBr pellets on an AVATAR 370 FI-IR Thermon Nicolet spectrometer. ^{1}H NMR spectra were recorded on an AVANCE III (500 MHz) with TMS as an internal standard. Mps were determined on a Yanagimoto micromelting point apparatus and are uncorrected.

Typical Procedure for the Preparation of 1,2,3,5-Tetra-O-Acetyl-β-D-ribofuranose (2) from 1c. A suspension of guanosine 1c (42.5 g, 0.15 mol) and acetic anhydride (153.0 g, 1.5 mol) was stirred in a three-neck 250 mL flask at 136°C for 1 h. The temperature was reduced to 60°C and TFA (0.077 g, 0.68 mmol) was then added and heating at 100°C was continued for 20–30 hrs. The progress of the reaction was monitored by TLC (1:1 ethyl acetate-acetone). Upon cooling, the precipitate formed was collected and dried to give 33.75 g (96%) of N^2,N^9-diacetylguanine. The filtrate was evaporated under reduced pressure and the residue was recrystallized from methanol to give 41.1 g (86%) of the 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**2**) as a white solid, mp. 82–83°C, lit.[8] mp. 80–82°C.

Typical Procedure for the Preparation of 3. A mixture of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (47.1 g, 0.15 mol) and methyl 1,2,4-triazole-3-carboxylate (21.6 g, 0.17 mol) and TfOH (0.11 g, 0.75 mmol) was heated with vigorous stirring at 135°C for 2 h under vacuum (about 55 mmHg). The solid obtained was then recrystallized from methanol, collected and dried to give 53.1 g (92%) of **3** as a white solid, mp. 106–108°C, lit.[8] mp. 107–109°.

Typical Procedure for the Preparation of Ribavirin (4). A mixture of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (47.1 g, 0.15 mol) and methyl 1,2,4-triazole-3-carboxylate (21.6 g, 0.17 mol), TfOH (0.11 g, 0.75 mmol) was heated under vigorous stirring at 135° for 2 h under vacuum(about 55 mmHg). Methanol (100 mL) was added and NH_3 gas was introduced into the reaction mixture for 40 hrs at 20°. The solvent was removed by distillation, and the residual solid was recrystallized from EtOH and dried under vacuum at 60° for 10 h to give 31.1 g (83%) of **4** as a white soild, mp. 169–170°C, lit.[8] mp. 166–168°C. The overall yield from the former procedure was 71% based on guanosine.

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