JOC Note
pubs.acs.org/joc

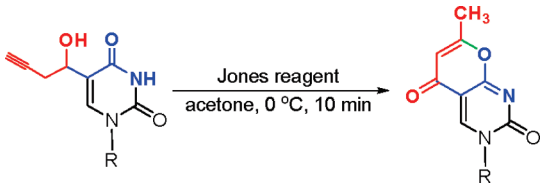
Tandem Reactions Leading to Bicyclic Pyrimidine Nucleosides and Benzopyran-4-ones

Xuesen Fan,* Yangyang Wang, Yingying Qu, Haiyun Xu, Yan He, Xinying Zhang,* and Jianji Wang

School of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, People's Republic of China

xuesen.fan@henannu.edu.cn; xinyingzhang@henannu.edu.cn

Received October 31, 2010



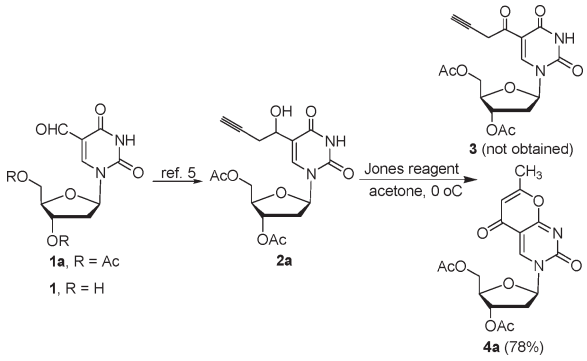
A novel, rapid, and efficient synthesis of bicyclic pyrimidine nucleosides and benzopyran-4-ones through oxidation of homopropargyl alcohols and subsequent isomerization, *intramolecular* addition of enol to allenic ketone has been developed. This methodology provides an efficient and promising approach to the structurally and pharmaceutically interesting pyrano[2,3-*d*]pyrimidine-2,5-dione nucleoside and benzopyran-4-one derivatives.

Although the modification of pyrimidine nucleosides and nucleotides has resulted in a plethora of therapeutic agents for a variety of diseases,[1] the hunt for novel nucleoside analogues as new drug candidates is still intense. It is not only because there are still many diseases without an effective remedy, but also due to the fact that many of the current agents have been found to show such limitations as adverse effects, insufficient selectivity for drug targets, and high propensity for drug resistance.[2]

In recent years, we have conducted an ongoing study on the design and synthesis of novel nucleoside analogues as potential antiviral and antimicrobial agents by exploiting the versatile aldehyde synthon 5-formyl-2′-deoxyuridine (**1**).[3] As a continuation of our efforts, we were interested in pyrimidine nucleoside with a propargyl ketone moiety on the 5-position of the pyrimidine unit (**3**). The rationale behind this strategy is that many pyrimidine nucleosides substituted at the 5-position are known to have potent biological activities and SAR studies indicate that the type of C-5 substituents likely to confer activity are electron-withdrawing groups conjugated to the pyrimidine ring.[1] Moreover, considering the diverse reactivity shown by propargyl ketones, the proposed hybrid compound combining a pyrimidine nucleoside and a propargyl ketone moiety is a good point of departure for further structural elaborations.

Our envisioned route to the proposed propargyl ketone **3** is based on a known oxidation of homopropargyl alcohol with Jones reagent.[4] Thus, **2a** was prepared from 5-formyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**1a**)[5] and then treated with Jones reagent at 0 °C in acetone (Scheme 1). It turned out that **2a** was consumed completely in 10 min to give a product whose ^{1}H NMR spectra did not support the formation of **3**. Upon analysis of its ^{1}H, ^{13}C NMR, COSY, NOESY, and mass spectra, the product was identified as a pyrano[2,3-*d*]pyrimidine-2,5-dione nucleoside (**4a**). To confirm this structure, single crystals of **4a** suitable for X-ray diffraction characterization were obtained by recrystallization from CH_2Cl_2/MeOH (2:1), and the molecular structure clearly shows the six-membered pyran-4-one ring.

SCHEME 1. Unexpected Formation of 4a



Further studies showed that with CrO_3 alone (1.2 equiv) as the oxidant, the reaction was reluctant to proceed. Over as long as 3 h, **4a** was only obtained in 15% yield. Increasing the amount of CrO_3 to 2.4 equiv did not improve the reaction. With sulfuric acid alone, however, the reaction gave a blackish mixture beyond identification over stirring for 3 h. As

(1) (a) Agrofoglio, L. A. *Curr. Org. Chem.* **2006**, *10*, 333. (b) De Clercq, E. *Antiviral Res.* **2005**, *67*, 56. (c) Mathe, C.; Gosselin, G. *Antiviral Res.* **2006**, *71*, 276. (d) Kumar, R. *Curr. Med. Chem.* **2004**, *11*, 2749. (e) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (f) Simons, C.; Wu, Q. P.; Htar, T. T. *Curr. Top. Med. Chem.* **2005**, *5*, 1191.

(2) (a) Mieczkowski, A.; Roy, V.; Agrofoglio, L. A. *Chem. Rev.* **2010**, *110*, 1828 and references cited therein. (b) Ii, K.; Ichikawa, S.; Al-Dabbagh, B.; Bouhss, A.; Matsuda, A. *J. Med. Chem.* **2010**, *53*, 3793. (c) Gazivoda, T.; Makuc, D.; Plavec, J.; Naesens, L.; Andrei, G.; Snoeck, R.; Balzarini, J.; Mintas, M. *Bioorg. Med. Chem.* **2008**, *16*, 5624. (d) Gazivoda, T.; Kralj, M.; Balzarini, J.; De Clercq, E.; Mintas, M. *Bioorg. Med. Chem.* **2007**, *15*, 749. (e) Lee, Y.-S.; Park, S. M.; Kim, B. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1126.

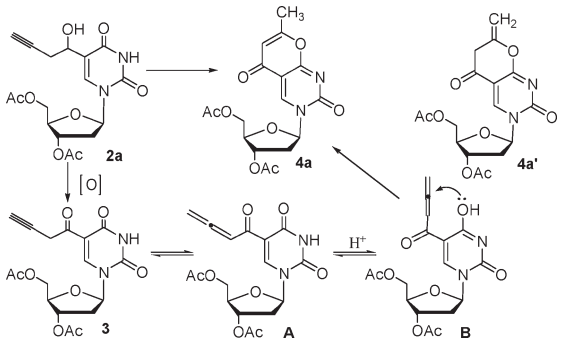
(3) (a) Fan, X. S.; Zhang, X. Y.; Zhou, L. H.; Keith, K. A.; Prichard, M. N.; Kern, E. R.; Torrence, P. F. *J. Med. Chem.* **2006**, *49*, 4052. (b) Fan, X. S.; Zhang, X. Y.; Zhou, L. H.; Keith, K. A.; Prichard, M. N.; Kern, E. R.; Torrence, P. F. *J. Med. Chem.* **2006**, *49*, 3377. (c) Fan, X. S.; Feng, D.; Qu, Y. Y.; Zhang, X. Y.; Wang, J. J.; Loiseau, P. M.; Andrei, G.; Snoeck, R.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 809. (d) Zhang, X. Y.; Li, X. Y.; Li, D. F.; Qu, Q. R.; Wang, J. J.; Loiseau, P. M.; Fan, X. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6280.

(4) Sniady, A.; Morreale, M. S.; Dembinski, R. *Org. Synth.* **2007**, *84*, 199.

(5) Wu, W. L.; Yao, Z. J.; Li, Y. L.; Li, J. C.; Xia, Y.; Wu, Y. L. *J. Org. Chem.* **1995**, *60*, 3257.

Published on Web 01/07/2011 DOI: 10.1021/jo102131y

SCHEME 2. Plausible Pathway for the Formation of 4a



a further aspect, Dess−Martin periodinane, a frequently used oxidant for the preparation of allenic ketones from homopropargyl alcohols,[6] was tried. It followed that upon treating with periodinane (1.2 equiv) for 3 h, **2a** was consumed and **4a** was obtained in a yield of 65%.

On the basis of the above observations, a tentative pathway for the formation of **4a** is depicted in Scheme 2. First, **2a** was oxidized by Jones reagent to give a propargyl ketone (**3**), which then isomerized into the corresponding 1,2-allenic ketone (**A**). The allenic group conjugated to the carbonyl then underwent an *intramolecular* nucleophilic addition with the in situ formed enol unit (**B**) to form a pyran-4-one scaffold. The fact that CrO_3 alone is not as effective as Jones reagent or Dess−Martin periodinane in the formation of **4a** suggests that acids (sulfuric acid in Jones reagent and acetic acid formed in the oxidation process with Dess−Martin periodinane) play an important role, which is most likely attributed to their capability as an acid in facilitating the keto−enol tautomerism. The acid may also play a catalytic role in generating and activating the allene and facilitating olefin isomerization. Moreover, it is possible to give either α,β-unsaturated adduct (**4a**) or β,γ-unsaturated adduct (**4a′**) from **B**. According to literature results, the regio-selectivity might be affected by the stability of products, the nature of the nucleophile, and the reaction conditions.[7] In our hands, only the more stable α,β-unsaturated ketone (**4a**) was obtained.

This unexpected result turned out to be very interesting and promising since bicyclic pyrimidine nucleosides have long been of remarkable interest in both medicinal and synthetic chemistry. To date, various bicyclic pyrimidine nucleosides, such as furano-,[8] pyrrolo-,[9] imidazo-,[10] thiazolo-,[11] thieno-,[12] oxazolo-,[13] or pyridopyrimidine[14] nucleoside analogues, have been achieved and many of them have demonstrated highly potent biological activities. To our knowledge, however, there is still no report on the synthesis and biological study of pyrano[2,3-*d*]pyrimidine-2,5-dione nucleoside. This prompted us to investigate the scope and generality of this procedure and to prepare more pyrano[2,3-*d*]pyrimidine-2,5-dione nucleoside derivatives for biological studies.

Thus, a series of homopropargyl alcohols (**2b**−**h**) were prepared and treated with Jones reagent (Table 1). This showed that not only susbstrates in the 2′-deoxyuridine series underwent this procedure efficiently to give the bicyclic nucleosides in high yields (entries 1 and 2), the 2′,3′-dideoxyuridine (entry 3), ribonucleoside (entry 4), and acyclic pyrimidine nucleoside substrates (entries 5−8) all afforded the desired products in good yields. It was also shown that several functional groups, such as acetyl, benzyl, homopropargyl, and azido groups, were well tolerated under the reaction conditions, thus resulting in a very efficient and general methodology for the preparation of pyranopyrimidine-2,5-dione nucleosides.

It is then noted that for substrates **2a**−**d**, the 2′-, 3′-, or 5′-hydroxyl group(s) are protected with acetyl to avoid possible side reactions and to facilitate purification in subsequent reactions. Since the biological activity of nucleosides is often correlated to their ability to be phosphorylated in vivo, and nucleoside drugs are usually administered with free hydroxyl group(s), efforts were then made to deprotect **4a**−**d**. We were able to find that the acetyls of **4a**−**d** could be conveniently removed with saturated ammonia in MeOH at room temperature (Table 2).[15]

In a further aspect, based on the above results and taking into account the proposed mechanism for the formation of **4**, we envisioned that 2-(1-hydroxybut-3-ynyl)phenol (**6a**), derived from 2-hydroxybenzaldehyde and propargyl bromide, if treated with Jones reagent, might follow the oxidation/*intramolecular* cyclization cascade process to give benzopyran-4-one (**7a**). Indeed, subsequent studies revealed that upon treating with Jones reagent in acetone, **6a** reacted rapidly to give **7a** in a yield of 88% in 5 min (Scheme 3).

It is well-known that the benzopyran-4-one moiety is a key component for a number of natural products and clinically used drugs by acting as one of the most powerful pharmacophores. Compounds with this framework have shown various pharmacological and biological activities.[16−22] On the other hand, benzopyran-4-ones are also important synthons in

(6) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) Ma, S. M.; Yu, S. C.; Yin, S. H. *J. Org. Chem.* **2003**, *68*, 8996.

(7) (a) Sugita, T.; Eida, M.; Ito, H.; Komatsu, N.; Abe, K.; Suame, M. *J. Org. Chem.* **1987**, *52*, 3789. (b) Ma, S. M. *Chem. Rev.* **2005**, *105*, 2829.

(8) (a) McGuigan, C.; Yarnold, C. J.; Jones, C.; Velázquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 4479. (b) Balzarini, J.; McGuigan, C. *J. Antimicrob. Chemother.* **2002**, *50*, 5. (c) Amblard, F.; Aucagne, V.; Guenot, P.; Schinazi, R. F.; Agrofoglio, L. A. *Bioorg. Med. Chem.* **2005**, *13*, 1239.

(9) Ivanov, M. A.; Ivanov, A. V.; Krasnitskaya, I. A.; Smirnova, O. A.; Karpenko, I. L.; Belanov, E. F.; Prasolov, V. S.; Tunitskaya, V. L.; Alexandrova, L. A. *Russ. J. Bioorg. Chem.* **2008**, *34*, 593.

(10) (a) Mansour, T. S.; Evans, C. A.; Charron, M.; Korba, B. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 303. (b) Kifli, N.; De Clercq, E.; Balzarini, J.; Simons, C. *Bioorg. Med. Chem.* **2004**, *12*, 4245.

(11) Schmidt, C. L.; Townsend, L. B. *J. Org. Chem.* **1975**, *40*, 2476.

(12) (a) Brancale, A.; McGuigan, C.; Algain, B.; Savy, P.; Benhida, A.; Fourrey, J.-L.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2501. (b) Patil, V. D.; Wise, D. S.; Wotring, L. L.; Bloomer, L. C.; Townsend, L. B. *J. Med. Chem.* **1985**, *28*, 423.

(13) Patil, V. D.; Wise, D. S.; Townsend, L. B. *J. Med. Chem.* **1974**, *17*, 1282.

(14) Girardet, J.-L.; Gunic, E.; Esler, C.; Cieslak, D.; Pietrzkowski, Z.; Wang, G. Y. *J. Med. Chem.* **2000**, *43*, 3704.

(15) Jin, X. Y.; Ding, H. X.; Yang, R. C.; Xiao, Q.; Ju, Y. *Synthesis* **2008**, 865.

(16) (a) Costantino, L.; Corso, A. D.; Rastelli, G.; Petrash, J. M.; Mura, U. *Eur. J. Med. Chem.* **2001**, *36*, 697. (b) Rastelli, G.; Costantino, L.; Gamberini, M. C.; Corso, D. A.; Mura, U.; Petrash, J. M.; Ferrari, A. M.; Pacchioni, S. *Bioorg. Med. Chem.* **2002**, *10*, 1427.

(17) (a) Amin, R.; Krammer, B.; Abdel-Kader, N.; Verwanger, T.; El-Ansary, A. *Eur. J. Med. Chem.* **2010**, *45*, 372. (b) Göker, H.; Boykin, D. W.; Yidiz, S. *Bioorg. Med. Chem.* **2005**, *13*, 1707.

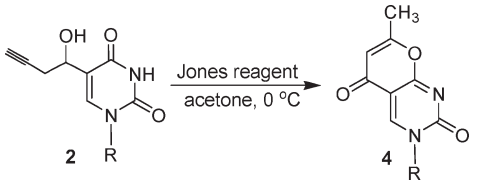
(18) Kuroda, M.; Uchida, S.; Watanabe, K.; Mimaki, Y. *Phytochemistry* **2009**, *70*, 288.

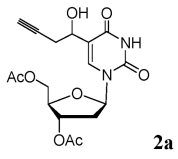
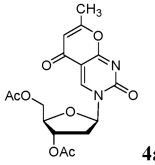
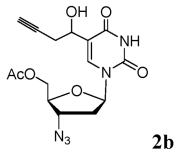
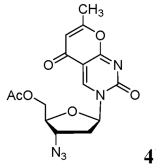
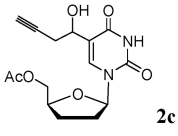
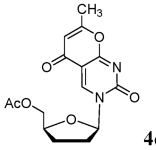
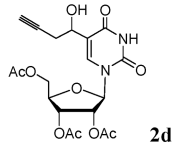
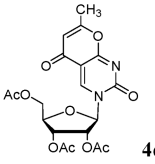
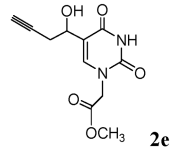
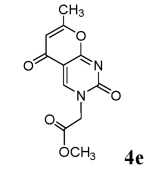
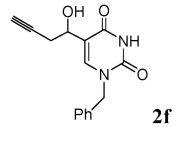
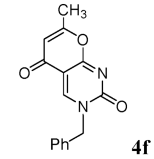
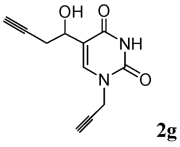
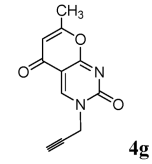
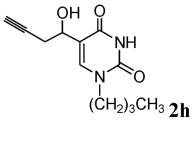
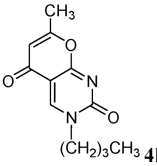
(19) (a) Chen, I. L.; Chen, J. Y.; Shieh, P. C.; Chen, J. J.; Lee, C. H.; Juang, S. H.; Wang, T. C. *Bioorg. Med. Chem.* **2008**, *16*, 7639. (b) Kristof, A. S.; Pacheco-Rodriguez, G.; Schremmer, B.; Moss, J. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1134.

(20) Matin, A.; Gavande, N.; Kim, M. S.; Yang, N. X.; Salam, N. K.; Hanrahan, J. R.; Roubin, R. H.; Hibbs, D. E. *J. Med. Chem.* **2009**, *52*, 6835.

(21) Ismail, K. A.; Aziem, T. A. E. *Eur. J. Med. Chem.* **2001**, *36*, 243.

TABLE 1. Synthesis of Bicyclic Pyrimidine Nucleosides 4[a]

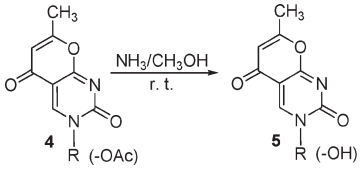


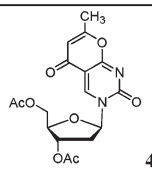
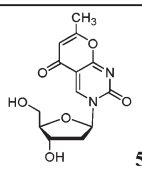
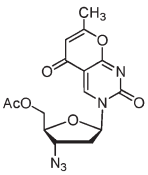
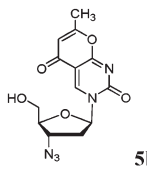
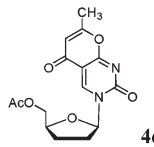
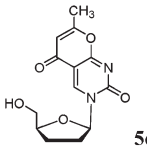
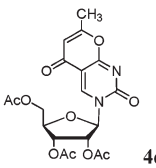
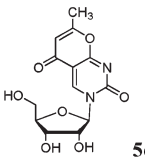
Entry	2	4	Yield (%)[b]
1	 **2a**	 **4a**	78
2	 **2b**	 **4b**	75
3	 **2c**	 **4c**	80
4	 **2d**	 **4d**	71
5	 **2e**	 **4e**	75
6	 **2f**	 **4f**	81
7	 **2g**	 **4g**	75
8	 **2h**	 **4h**	83

[a]Reaction conditions: **2** (1.0 mmol), Jones reagent (1.2 mmol), acetone (10 mL), 0 °C, 10 min. [b]Isolated yields.

organic synthesis.[23] Generally, they are prepared through (i) cyclodehydration of 1-(*o*-hydroxyaryl)-1,3-diketone or equivalent intermediates catalyzed by strong acids or strong bases,[24] (ii) cyclocondensation of salicylate with dimethyl allene-1,3-dicarboxylate in the presence of *t*-BuOK in *t*-BuOH,[25] and (iii) *intramolecular* Wittig reaction of acylphosphoranes.[26] More recently, Snieckus et al. reported that chromone derivatives could be obtained by anionic carbamoyl translocation reactions.[27] In spite of the success of the aforesaid methods,

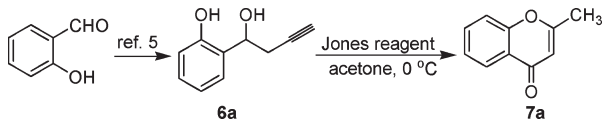
TABLE 2. Deprotection of Bicyclic Nucleosides 4[a]



Entry	4	5	Yield (%)[b]
1	 **4a**	 **5a**	66
2	 **4b**	 **5b**	68
3	 **4c**	 **5c**	72
4	 **4d**	 **5d**	62

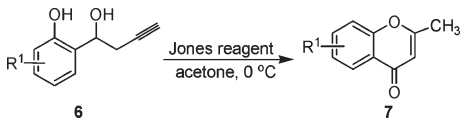
[a]Reaction conditions: **4** (0.5 mmol), sat. NH_3/MeOH (5 mL), rt, 6 h. [b]Isolated yields.

SCHEME 3. Synthesis of Benzopyran-4-one (7a)

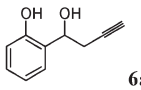
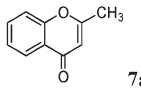
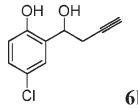
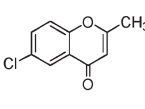
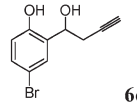
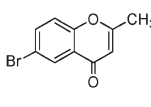
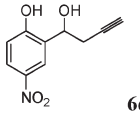
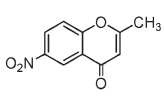
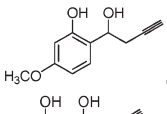
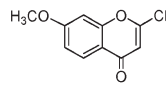
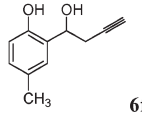
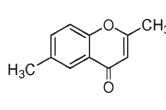
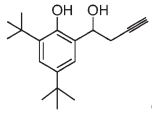
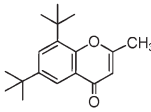
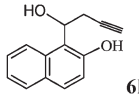
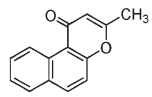


(22) Hasan, S. M.; Alam, M. M.; Husain, A.; Khanna, S.; Akhtar, M.; Zaman, M. S. *Eur. J. Med. Chem.* **2009**, *44*, 4896.
(23) (a) Ghosh, C. K. *J. Heterocycl. Chem.* **2006**, *43*, 813. (b) Ibrahim, M. A.; Ali, T. E.; Alnamer, Y. A.; Gabr, Y. A. *Arkivoc* **2010**, 98.
(24) (a) Baker, W. *J. Chem. Soc.* **1933**, 1381. (b) Hirao, I.; Yamaguchi, M.; Hamada, M. *Synthesis* **1984**, 1076.
(25) (a) Nixon, N. S.; Scheinmann, F.; Suschitzky, J. L. *Tetrahedron Lett.* **1983**, *24*, 597. (b) Nixon, N. S.; Scheinmann, F.; Suschitzky, J. L. *J. Chem. Res.* (*S*) **1984**, 380.
(26) (a) Hercouet, A.; Le Corre, M.; Le Floc'h, Y. *Synthesis* **1982**, 597. (b) Lee, K. J.; Kim, S.; Park, H. *Bull. Korean Chem. Soc.* **1991**, *12*, 120. (c) Bestmann, H. J.; Schade, G. *Chem. Lett.* **1983**, 997. (d) Kumar, P.; Bodas, M. S. *Org. Lett.* **2000**, *2*, 3821.
(27) Macklin, T. K.; Panteleev, J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 2097.

TABLE 3. Synthesis of Benzopyran-4-ones 7[a]



6 7

Entry	6	7	Yield (%)[b]
1	 6a	 7a	88
2	 6b	 7b	87
3	 6c	 7c	86
4	 6d	 7d	90
5	 6e	 7e	83
6	 6f	 7f	81
7	 6g	 7g	86
8	 6h	 7h	80

[a]Reaction conditions: **7** (1.0 mmol), Jones reagent (1.2 mmol), acetone (10 mL), 0 °C, 5 min. [b]Isolated yields.

some of them still suffer from harsh reaction conditions, tedious procedures, or low yields. This prompted us to investigate the possibility of developing the present procedure into a general and practical method for the synthesis of benzopyran-4-ones. Thus, a variety of propargyl alcohols (**6b**−**h**) were prepared and treated with Jones reagent. The results are summarized in Table 3.

From Table 3, it was concluded that for substrates with either electron-withdrawing or electron-donating groups, the reactions proceeded smoothly to give the desired products in good yields. Functional groups, such as nitro, methoxy, and halide, were well tolerated under these conditions. It is notable that **6g** with bulky *tert*-butyl groups on the phenyl ring could also react smoothly to give **7g** in 86% yield (entry 7). In addition, 1-(1-hydroxybut-3-ynyl)naphthalen-2-ol (**6h**) proved to be a suitable substrate for this reaction and afforded 3-methyl-1*H*-benzo[*f*]chromen-1-one (**7h**) in good yield (entry 8). These promising results allow the present procedure to be used as a rapid and general protocol for the preparation of benzopyran-4-ones.

In summary, a novel and efficient synthesis of bicyclic pyrimidine nucleosides and benzopyran-4-ones is developed. To the best of our knowledge, this is the first report of pyrano[2,3-*d*]pyrimidine-2,5-dione nucleosides and the first example in which benzopyran-4-one derivatives are prepared via oxidation of homopropargyl alcohol derived from 2-hydroxyaromatic aldehyde. The synthetic procedure itself has advantages such as high efficiency, readily obtainable starting material, very cheap reagents, and extremely mild reaction conditions. Current studies are in progress to extend the synthetic potential of this novel procedure and to study the biological activities of the bicyclic pyrimidine nucleosides obtained in this work.

Experimental Section

5-Formylpyrimidine nucleosides (**1a**−**h**) were prepared through oxidation of the corresponding 5-methylpyrimidine nucleosides. Homopropargyl alcohols **2a**−**h** were prepared through zinc promoted propargylation of 5-formylpyrimidine nucleosides (**1a**−**h**) with propargyl bromide based on literature procedure.[5] Homopropargyl alcohol substrates **6a**−**h** were prepared through zinc-promoted propargylation of 2-hydroxybenzaldehydes which are all commercially available.[5]

Typical Procedure for the Preparation of 4a. To a solution of **2a** (380 mg, 1 mmol) in acetone (10 mL) cooled to 0 °C was added Jones reagent (1.2 mmol) in a dropwise manner. Upon complete consumption of the starting material as monitored by TLC, the reaction mixture was quenched by addition of isopropanol. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel with CH_3OH/CH_2Cl_2 (0−2%) to give **4a** as colorless solids. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.17 (s, 3H), 2.23−2.30 (m, 1H), 2.35 (s, 3H), 2.86−2.92 (m, 1H), 4.37−4.45 (m, 3H), 5.20−5.23 (m, 1H), 5.98 (s, 1H), 6.28−6.31 (m, 1H), 9.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.6, 20.8, 39.5, 63.0, 73.2, 83.4, 88.5, 104.4, 110.3, 148.0, 153.3, 167.1, 168.3, 170.2, 170.4, 175.8. MS *m*/*z* 379 $(MH)^+$. HRMS (FAB) calcd for $C_{17}H_{19}N_2O_8$ 379.1142 [M + H], found 379.1148.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (Nos. 20772025 and 20972042), Innovation Scientists and Technicians Troop Construction Projects of Henan Province (No. 104100510019), and the program for Innovative Research Team in University of Henan Province (2008IRTSTHN002) for financial support.

Supporting Information Available: Experimental details, X-ray crystal structure of **4a**, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.