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2-Pyridone Synthesis Using 2-(Phenylsulfinyl)acetamide

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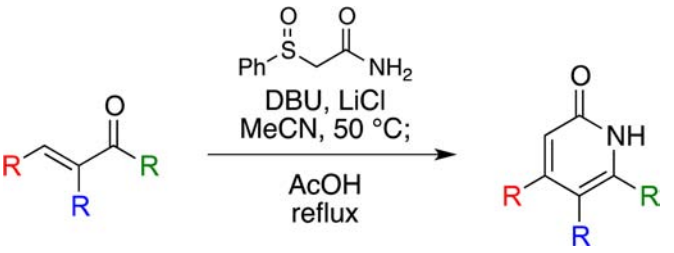
ABSTRACT



2-Pyridones were prepared by means of an efficient protocol including the 1,4-addition of 2-(phenylsulfinyl)acetamide to α,β-unsaturated ketones followed by cyclization and sulfoxide elimination.

2-Pyridones are found in a wide range of compounds, including biologically active natural products and medicines (Figure 1).[1] Due to the dual properties of an aromatic ring and an amide, 2-pyridones appear to have many effective interactions with biological molecules.

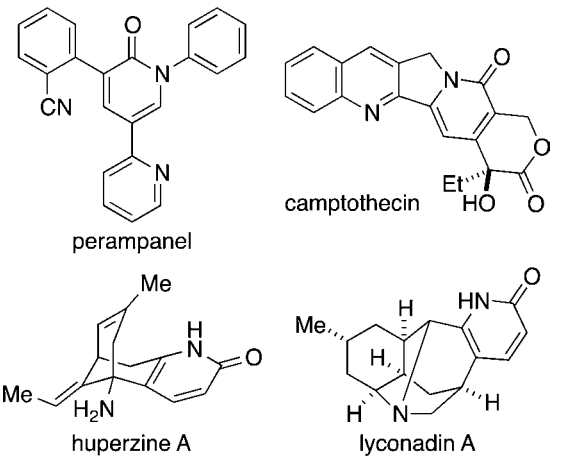


Figure 1. Biologically active natural products and medicines containing 2-pyridone rings.

To date, various methods have been developed to construct 2-pyridone rings.[2,3] Among them, the methods employing α,β-unsaturated ketones and 2-substituted acetamides as substrates proved to be effective in the preparation of a variety of 2-pyridones. These transformations

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(1) (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; Mcphail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888. (b) Liu, J. S.; Zhu, Y. L.; Yu, C. M.; Zhou, Y. Z.; Han, Y. Y.; Wu, F. W.; Qi, B. F. *Can. J. Chem.* **1986**, *64*, 837. (c) Fischer, U.; M Hler, H.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1990**, *73*, 763. (d) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901. (e) Parreira, R. L. T.; Abrahão, O.; Galembeck, S. E. *Tetrahedron* **2001**, *57*, 3243. (f) Hanada, T.; Hashizume, Y.; Tokuhara, N.; Takenaka, O.; Kohmura, N.; Ogasawara, A.; Hatakeyama, S.; Ohgoh, M.; Ueno, M.; Nishizawa, Y. *Epilepsia* **2011**, *52*, 1331.

(2) For a review of the 2-pyridone synthesis, see: Keller, P. A. In *Science of Synthesis*; Black, D. StC., Ed.; Georg Thieme Verlag: Stuttgart · New York, 2005; Vol. 15, pp 285−387.

(3) For selected recent examples of the 2-pyridone synthesis, see: (a) Boisse, T.; Rigo, B.; Millet, R.; Hénichart, J. P. *Tetrahedron* **2007**, *63*, 10511. (b) Chen, L.; Zhao, Y.-L.; Liu, Q.; Cheng, C.; Piao, C.-R. *J. Org. Chem.* **2007**, *72*, 9259. (c) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421. (d) Tsai, T. H.; Chung, W. H.; Chang, J. K.; Hsu, R. T.; Chang, N. C. *Tetrahedron* **2007**, *63*, 9825. (e) Imase, H.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 3563. (f) Liu, J.; Liang, D.; Wang, M.; Liu, Q. *Synthesis* **2008**, 3633. (g) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. *Org. Lett.* **2008**, *10*, 345. (h) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504. (i) Smith, A. B., III.; Atasoylu, O.; Beshore, D. C. *Synlett* **2009**, 2643. (j) Wang, X. W.; Cui, H. F.; Wang, H. F.; Yang, Y. Q.; Zhao, G.; Zhu, S. Z. *Tetrahedron* **2011**, *67*, 2468.

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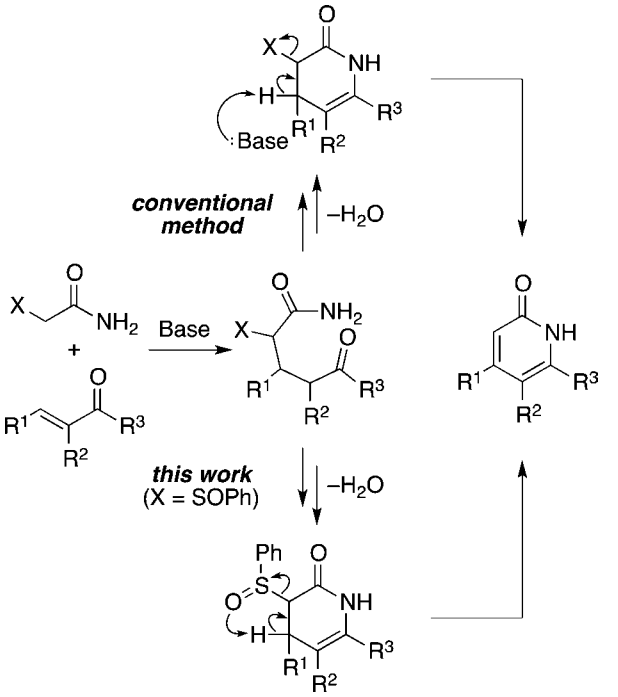
involve 1,4-addition of the acetamides to α,β-unsaturated ketones followed by cyclization and elimination (Scheme 1).[4,5] Since the elimination step usually proceeds via the E2 mechanism or deprotonation of the less acidic position, relatively harsh conditions are required.

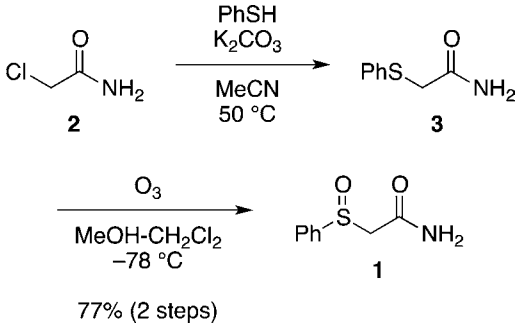
Scheme 1. Synthesis of 2-Pyridone



During the course of our synthetic studies on *Lycopodium* alkaloids,[6] we encountered difficulties in forming 2-pyridone rings from α,β-unsaturated ketones by means of conventional procedures. Hence, we developed a novel method to construct 2-pyridone rings using 2-(phenylsulfinyl)acetamide (X = SOPh, Scheme 1) and successfully applied it to the total synthesis of the natural products. Our method is characterized by the enhanced acidity of the α-position of the acetamide by the phenylsulfinyl group as well as its facile elimination from the Michael adduct through sulfoxide elimination. Extensive efforts have been made to improve our method so that it could be regarded as the method of choice for certain 2-pyridones. Herein we disclose the scope and limitations of our 2-pyridone synthesis.

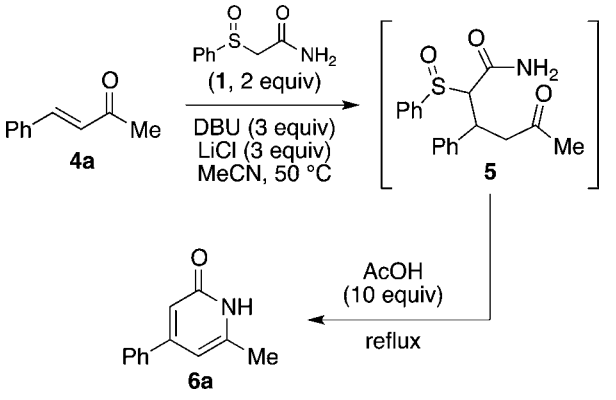
The key reagent, 2-(phenylsulfinyl)acetamide (**1**),[7] was prepared from commercially available 2-chloroacetamide (**2**) in two steps (Scheme 2). A substitution reaction of **2** with benzenethiol in the presence of potassium carbonate afforded 2-(phenylthio)acetamide (**3**). The crude product **3** was oxidized with ozone to give, after recrystallization from methanol, **1** in 77% yield.

Scheme 2. Preparation of 2-(Phenylsulfinyl)acetamide



Scheme 3 illustrates the typical procedure to synthesize 2-pyridones. Although a strong base such as sodium hydride was used initially for the Michael addition, we found that the reaction could be carried out under much milder conditions similar to the ones used for the Horner–Wadsworth–Emmons reactions by Roush and

Scheme 3. Typical Procedure for 2-Pyridone Synthesis



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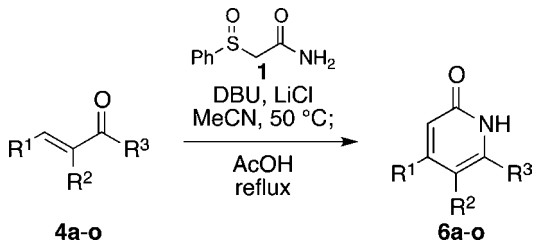
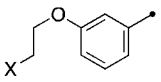
(5) Reactions of α,β-unsaturated ketones with 2-cyanoacetamide to synthesize 3-cyano-2-pyridones have been reported. These methods involve oxidation of the intermediates: (a) Al Hajjar, F. H.; Jarrar, A. A. *J. Heterocycl. Chem.* **1980**, *17*, 1521. (b) Jain, R.; Roschangar, F.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 3307. Related oxidative 2-pyridone syntheses have also been reported: (c) Wang, S.; Tan, T.; Li, J.; Hu, H. *Synlett* **2005**, 2658. (d) Li, S.; Wang, S. *J. Heterocycl. Chem.* **2008**, *45*, 1875.

(6) (a) Koshiba, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2009**, *11*, 5354. (b) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 418.

(7) 2-(Phenylsulfinyl)acetamide was first reported by Durst and coworkers in 1973: Durst, T.; Tin, K. C.; Marcil, M. *Can. J. Chem.* **1973**, *51*, 1704.

Table 1. Substrate Scope of the 2-Pyridone Synthesis[a]



entry	R^1	R^2	R^3	product	yield[b] (%)
1	Ph	H	Me	**6a**	83
2	*n*-Pr	H	Me	**6b**	68
3	*i*-Pr	H	Me	**6c**	39
4	*t*-Bu	H	*t*-Bu	**6d**	0
5	Ph	-$(CH_2)_4$-		**6e**	65
6	2-furyl	H	Me	**6f**	68
7	Ph	H	Ph	**6g**	53
8	Ph	H	4-$MeOC_6H_4$	**6h**	53
9	4-$MeOC_6H_4$-	H	Ph	**6i**	47
10	4-$O_2NC_6H_4$-	H	Ph	**6j**	69
					
11	X = OTBS	H	Me	**6k**	89
12	X= OMOM	H	Me	**6l**	82
13[c]	X = OBz	H	Me	**6m**	72
14	X = NHBoc	H	Me	**6n**	81
15	X = NHNs	H	Me	**6o**	79

[a] Reaction conditions: **1** (2 equiv), DBU (3 equiv), LiCl (3 equiv), MeCN, 50 °C; AcOH (10 equiv), reflux. [b] Isolated yield. [c] Deprotected alcohol (X = OH) was concomitantly obtained in 7% yield.

Masamune.[8] Thus, the 1,4-addition proceeded smoothly by treatment of a mixture of **4a** and **1** with DBU and lithium chloride in acetonitrile at 50 °C.[9,10] After the addition is complete, subsequent cyclization was facilitated by the addition of acid. Screening of a series of acids revealed that acetic acid was optimum for the cyclization. After addition of an excess of acetic acid, the reaction mixture was heated at reflux to promote cyclization and sulfoxide elimination, giving pyridone **6a** in good yield.

Table 1 summarizes the substrate scope of the 2-pyridone synthesis. α,β-Unsaturated ketones possessing substituents at the α- or β-position of the ketone could be converted into 2-pyridones (entries 1−3, 5, and 6). Bulky substituents tend to decrease the yield, perhaps due to the difficulties in the 1,4-addition (entries 3 and 4). In addition, chalcones could be employed as substrates (entries 7−10). The mild reaction conditions are compatible with a variety of functional groups, including TBS, MOM, Boc, and Ns groups (entries 11−15). Somewhat base-sensitive benzoate underwent partial hydrolysis to give 72% yield of **6m** along with 7% of debenzoylated product (entry 13).

In conclusion, we have demonstrated an efficient 2-pyridone synthesis using 2-(phenylsulfinyl)acetamide. A variety of functional groups survived the mild reaction conditions. Since 2-pyridone is ubiquitous in biologically active molecules, this method is likely to find widespread use in the synthesis of medicinally relevant compounds.

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Supporting Information Available. Experimental details and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charges via the Internet at http://pubs.acs.org.

(8) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(9) In the absence of LiCl, the reaction does not proceed at all. Employing other salts instead of LiCl resulted in low yields (LiBr, LiI, $MgCl_2$) or no production of the pyridone (NaCl, KCl, $ZnCl_2$). For details, see Supporting Information.

(10) Roush and Masamune reported that the acidity of phosphonoacetates seems to be enhanced by complexation with a lithium ion. 2-(Phenylsulfinyl)acetamide (**1**) can form the same type of complex with a lithium ion, generating the corresponding anion under milder conditions.

The authors declare no competing financial interest.