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A One-Pot Synthesis of Pyrido[2,3-*b*][1,4]oxazin-2-ones

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Abstract: Pyrido[2,3-*b*][1,4]oxazin-2-ones are conveniently prepared in excellent yields by a one-pot annulation of *N*-substituted-2-chloroacetamides with 2-halo-3-hydroxypyridines with use of cesium carbonate in refluxing acetonitrile. The key transformation features a Smiles rearrangement of the initial *O*-alkylation product and subsequent cyclization.

The wide occurrence of benzo-fused and heterocycle-fused [1,4]oxazines in bioactive natural products and pharmaceuticals has made them important synthetic targets.[1] For the most part, synthetic routes to benzo-[1,4]oxazines,[2] pyrido[3,2-*b*][1,4]oxazines,[3] and pyrimido-[5,4-*b*][1,4]oxazines[4] are well established.[5,6] In contrast, pyrido[2,3-*b*][1,4]oxazines have received scant attention.[7] As part of our continuing interest in the development of economic syntheses of heterocyclic systems, we investigated the utility of the Smiles rearrangement[8] and report herein its application to the synthesis of pyrido[2,3-*b*]-[1,4]oxazin-2-ones using readily available, stable precursors.

Typically, benzo[1,4]oxazines and pyrido[3,2-*b*][1,4]-oxazines are made by the direct cyclization of 2-haloacetyl halides or alkyl 2-halopropionates with 2-aminophenol or 2-amino-3-hydroxypyridine. A similar approach, however, is not directly applicable to the pyrido[2,3-*b*][1,4]-oxazine ring system. On the other hand, it was felt that the Smiles rearrangement could be exploited to circumvent this limitation. Since the Smiles rearrangement necessitates an electron-deficient center to proceed at a reasonable rate, we selected 2-haloacetamide and 2-halo-3-hydroxypyridine as the reaction partners.

In exploratory experiments, reaction of 2-bromo-3-hydroxypyridine (**2a**) with *N*-benzyl-2-chloroacetamide (**1a**) in the presence of potassium carbonate furnished *N*-benzyl-2-(2-bromopyridin-3-yloxy)acetamide (**3a**) as the major product and bicyclic adduct **4a** as only a minor product (Scheme 1). Subsequent exposure of **3a** to cesium carbonate induced cyclization and gave **4a** quantitatively. Spectral and physical comparisons (IR, 1D/2D-NMR, NOE, mp) of **4a** cogently demonstrated it was different from 4-benzyl-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (**5**), prepared from commercial 2*H*-pyrido[3,2-*b*][1.4]oxazin-3-one and benzyl chloride with potassium carbonate. X-ray analysis unambiguously confirmed the structure of **4a** as 1-benzyl-1*H*-pyrido[2,3-*b*][1,4]oxazin-2-one.

The overall annulation is best explained by a three-step process (Scheme 2). Alkylation of **1** by **2** generates adduct **3**, which can be observed by TLC monitoring. Rate

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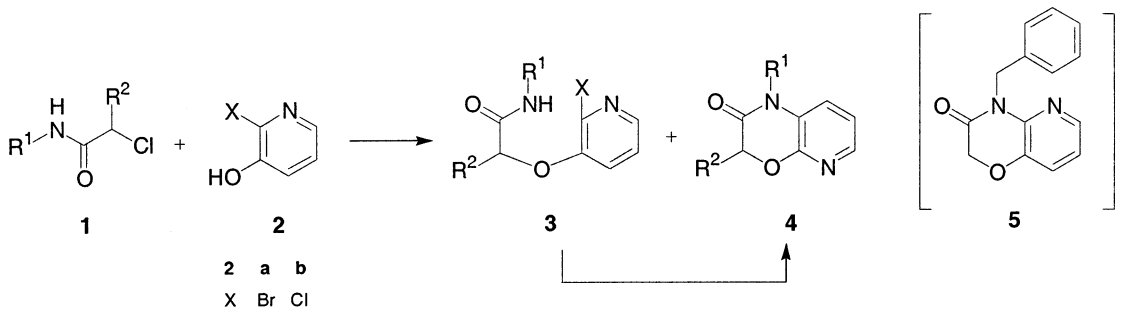
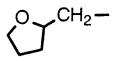
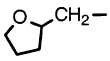
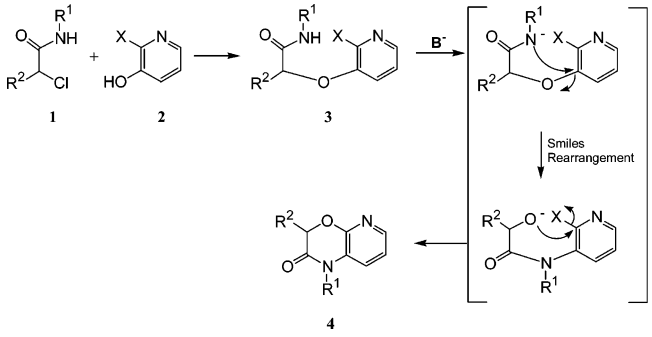
SCHEME 1



1,3,4	**a**	**b**	**c**	**d**	**e**	**f**
R^1	$C_6H_5CH_2$-	$C_6H_5CH_2$-			*c*-C_6H_{11}-	*c*-C_6H_{11}-
R^2	H	CH_3	H	CH_3	H	CH_3
1,3,4	**g**	**h**	**i**	**j**	**k**	**l**
R^1	*c*-$C_6H_{11}CH_2$-	*c*-$C_6H_{11}CH_2$-	3,4-$(MeO)_2$-$C_6H_3(CH_2)_2$-	3,4-$(MeO)_2$-$C_6H_3(CH_2)_2$-	$C_6H_5(CH_2)_2$-	$C_6H_5(CH_2)_2$-
R^2	H	CH_3	H	CH_3	H	CH_3
1,3,4	**m**	**n**	**o**	**p**	**q**	**r**
R^1	(*S*)-C_6H_5-$CH(CH_3)$-	(*S*)-C_6H_5-$CH(CH_3)$-	4-$PhOC_6H_4$-	4-$PhOC_6H_4$-	C_6H_5-	C_6H_5-
R^2	H	CH_3	H	CH_3	H	CH_3

SCHEME 2



determining Smiles rearrangement then sets the stage for a rapid ring closure giving rise to 1-substituted-pyrido[2,3-*b*][1,4]oxazin-2-one **4**.

To study this reaction in more detail, we systematically investigated the reaction parameters using **1a** and **2** (Table 1). The common alkali carbonates Li_2CO_3, Na_2CO_3, and K_2CO_3 (entries 1−3, respectively) generated a trace or very little of **4a** even after prolonged heating in refluxing acetonitrile; strontium and silver carbonate (entries 6 and 7) proved disappointing as well. In sharp contrast, cesium and rubidium carbonate afforded **4a** in excellent yields (entries 4 and 5) after just 3 h in refluxing acetonitrile.

Polar, aprotic solvents such as *N*,*N*-dimethylformamide and acetonitrile were quite effective (Table 2: entries 1 and 4), whereas a protic solvent, ethanol (Entry 2), and the nonpolar solvents toluene and dichloromethane were ineffective (entries 5 and 6). THF (entry 3) fell between the two extremes. Consequently, all following Smiles

TABLE 1. Effect of Base on the Yield of 4a from 1a and 2 in Refluxing Acetonitrile

entry	base	time	**4a** yield (%)[a]
1	Li_2CO_3	7 days	trace
2	Na_2CO_3	7 days	40
3	K_2CO_3	7 days	48
4	Rb_2CO_3	3 h	93
5	Cs_2CO_3	3 h	97
6	$SrCO_3$	7 days	0
7	Ag_2CO_3	48 h	0

[a] Isolated yield.

TABLE 2. Effect of Solvent on the Yield of 4a from 1a and 2, Using Cesium Carbonate

entry	reaction conditions	time (h)	**4a** yield (%)[a]
1	CH_3CN, reflux	3	97
2	CH_3CH_2OH, reflux	3	0
3	THF, reflux	3	60
4	DMF, 90−100 °C	1	96
5	toluene, reflux	3	5
6	CH_2Cl_2, reflux	3	0

[a] Isolated yield.

TABLE 3. Preparation of 4 from 1 and 2

Entry		R^1	R^2	Method[a]	**4** Yield (%)[b]	Entry		R^1	R^2	Method[a]	**4** Yield (%)[b]
1	**a**	$C_6H_5CH_2$-	H	A	90	10	**k**	$C_6H_5(CH_2)_2$-	H	A	92
				B	93					B	96
2	**b**	$C_6H_5CH_2$-	CH_3	A	87	11	**l**	$C_6H_5(CH_2)_2$-	CH_3	A	90
				B	94					B	92
3	**c**		H	A	90	12	**m**	(*S*)-C_6H_5-$CH(CH_3)$-	H	A	92
				B	95					B	94
4	**d**		CH_3	A	88	13	**n**	(*S*)-C_6H_5-$CH(CH_3)$-	CH_3	A	92[c]
				B	92					B	94[c]
5	**e**	*c*-C_6H_{11}-	H	A	90	14	**o**	4-$PhOC_6H_4$-	H	A	90
				B	95					B	95
6	**f**	*c*-C_6H_{11}-	CH_3	A	93	15	**p**	4-$PhOC_6H_4$-	CH_3	A	91
				B	94					B	93
7	**g**	*c*-$C_6H_{11}CH_2$-	H	A	93	16	**q**	C_6H_5-	H	A	90
				B	95					B	93
8	**h**	*c*-$C_6H_{11}CH_2$-	CH_3	A	89	17	**r**	C_6H_5-	CH_3	A	91
				B	93					B	90
9	**i**	3,4-$(MeO)_2$-$C_6H_3(CH_2)_2$-	H	A	93						
				B	97						
10	**j**	3,4-$(MeO)_2$-$C_6H_3(CH_2)_2$-	CH_3	A	92						
				B	94						

[a] Method A: **1** + **2** → **4**. Method B: **1** + **2** → **3** → **4**. [b] Isolated yield. [c] Yield of diastereomers: (*S*,*S*)-isomer (47%) and (*S*,*R*)-isomer (45%).

rearrangements/annulations were conducted with cesium carbonate in refluxing acetonitrile.

A variety of pyrido[2,3-*b*][1,4]oxazin-2-ones **4** were synthesized with two related protocols (Table 3). Method A involved direct cyclization of **1** with **2** in the presence of cesium carbonate in refluxing acetonitrile without isolation of **3**. In Method B (Method A), intermediate **3** was preformed and then converted to **4** under the standard conditions. Yields were excellent, ranging from 87 to 97%, even for acetamides with bulky *N*-substituents (entries 5, 6, 15, 16, and 17). Cyclizations of **3d** and **3n** yielded **4d** and **4n** as mixtures of diastereomers since the precursor *N*-substituted α-methylacetamides were diastereomeric by virtue of two different chiral centers. The diastereomeric mixture **4n** could be separated into its (*S*,*S*)-isomer (**4n-a**, 47%) and (*S*,*R*)-isomer (**4n-b**, 45%) by column chromatography. The absolute configurations of **4n-a** and **4n-b** were established by using the proton coupling constants of C2−H and N4−Cα−H. The diastereoisomers of **4d** could not be separated by SiO_2 column chromatography.

Notably, cyclization of bromophenol instead of 3-hydroxy-2-chloropyridine with *N*-substituted chloroacetamides under the same conditions did not form the corresponding benzo[1,4]oxazin-3-ones.

In conclusion, we have developed an operationally simple and economic synthesis of pyrido[2,3-*b*][1.4]oxazin-2-ones based on the Smiles rearrangement. Its application in the synthesis of natural compounds is underway in our laboratory and will be reported in due course.

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Supporting Information Available: $^1H/^{13}C$ NMR and IR spectral data, CHN analyses, melting points for **3** and **4**; X-ray analytical data for **4a** and *N*-substituted-2-haloacetamides. This material is available free of charge via the Internet at http://pubs.acs.org.

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