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Ring-Opening Reactions of 2-Alkoxy-3, 4-dihydropyrans with Thiols or Thiophenols

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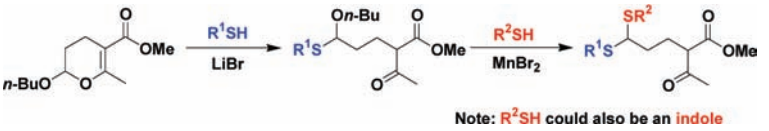
ABSTRACT



An electrophilic ring-opening reaction of 2-alkoxy-3,4-dihydropyran with a thiophenol or thiol is developed for the first time. The generated product contains not only a 1,3-dicarbonyl moiety but also a fragment of bis(alkylthio)methane. A possible mechanism is also proposed on the basis of postulating a ring-opening monotransthioacetalization product, which was prepared by using LiBr as catalyst as an intermediate.

Since organic sulfur compounds have become increasingly useful in organic synthesis and pharmaceutical chemistry, convenient preparations of appropriate sulfides, especially those which contain other functional groups, should be important.[1] Although a variety of the methods for their synthesis are available in the literature,[2] the most convenient method should involve not only transformation of a sulfur compound but also a simultaneous introduction of one or more organic functional groups into the final product. In this regard, a ring-opening reaction of epoxide with a thiol or thiophenol could be a typical example, in which both formation of C−S bond and generation of a hydroxyl group were realized at the same time.[3] Some other ring-opening reactions with thiol or thiophenol as nucleophile showed a similar performance on the creation of molecular complexity,[4] but unfortunately, these examples are still limited. To fit the current requirement of pharmaceutical chemistry on molecular diversity and

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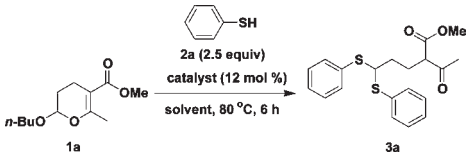
complexity, new and efficient reactions for the synthesis of organic sulfur compounds are appealingly needed.

Recently, the use of simple heterocycles as substrate in organic synthesis has gained much attention because heterocycles displayed in organic transformations a great productivity in creation of molecular complexicity and diversity.[5] We have reported a domino Knoevenagel/*oxo* Diels−Alder reaction of olefins, formaldehyde and β-dicarbonyl compounds, which generated a variety of 2,5,6-trisubstituted 3,4-dihydropyran derivatives in high yields under catalyst-free conditions.[6] Because the reaction procedure is quite simple, it not only allowed an easy scale-up of the reaction, but it also occurred to us how to use the reaction products. In literature, reactions of such substituted dihydropyrans have been rarely explored due perhaps to the difficulty of preparation.[7] We viewed that skeletons of the dihydropyrans involve either a semicyclic acetal or a benzyl ether fragment that is generally unstable in the presence of nucleophile under acidic condition.[8] Particularly, semicyclic acetals (**1**), such as *O*-glycosides, are known to react with various nucleophiles in the presence of a Lewis acid to give cyclic ether products (**2**) via cyclic oxocarbenium ion intermediates (eq 1).[9] On the basis of these results, we suspect that the substituted dihydropyran **1a** should be capable of reacting with a nucleophile in the presence of Lewis acid catalyst (eq 2). However, during our study, we found unexpectedly a highly selective ring-opening reaction of 2-alkoxy-3,4-dihydropyran with a thiol or thiophenol, which offers an efficient method to link a β-dicarbonyl fragment together with the core of the nucleophile. The optimal catalyst is manganese(II) bromide.

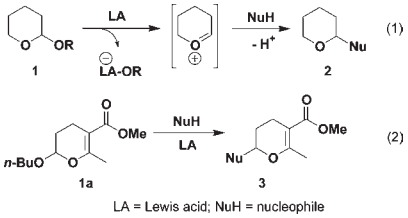
Table 1. Ring-Opening Reaction of **1a** with **2a** under Different Conditions[a]



entry	catalyst	solvent	yield (%)
1[b]		CH_3NO_2	0
2	H_3BO_3	CH_3NO_2	trace
3	$MnCl_2$	CH_3NO_2	10
4	$NiCl_2$	CH_3NO_2	12
5	$Bi(OTf)_3$	CH_3NO_2	trace
6	$FeCl_3$	CH_3NO_2	trace
7	$InCl_3$	CH_3NO_2	85
8	$ZnCl_2$	CH_3NO_2	80
9	$Sc(OTf)_3$	CH_3NO_2	75
10	$Y(OTf)_3$	CH_3NO_2	82
11	TsOH	CH_3NO_2	78
12	Amberlyst-15	CH_3NO_2	50
13	$MnBr_2$	CH_3NO_2	88
14	$MnBr_2$	toluene	10
15	$MnBr_2$	CH_3CN	trace
16	$MnBr_2$	DCE	5
17	$MnBr_2$	1,4-dioxane	trace
18	$MnBr_2$	EtOH	trace
19[c]	$MnBr_2$	CH_3NO_2	54
20[d]	$MnBr_2$	CH_3NO_2	62
21[e]	$MnBr_2$	CH_3NO_2	96
22[f]	$MnBr_2$	CH_3NO_2	94

[a] **1a**: 0.25 mmol; solvent: 1 mL. [b] No catalyst was used. [c] 5 mol % of catalyst was used. [d] Reaction was conducted at 60 °C. [e] 11 h. [f] Reaction was conducted in 10 mmol scale, 11 h.

To the best of our knowledge, only a few examples of ring-opening reactions of dihydropyrans have been performed so far,[10] and this type of ring-opening reaction has not been reported yet.



Initially, a reaction of an 2-alkoxy-3,4-dihydropyran, **1a**, with thiophenol, **2a**, was investigated, and the results are listed in Table 1.[11] In the absence of catalyst, no reaction occurred (entry 1). When some weak acids, such

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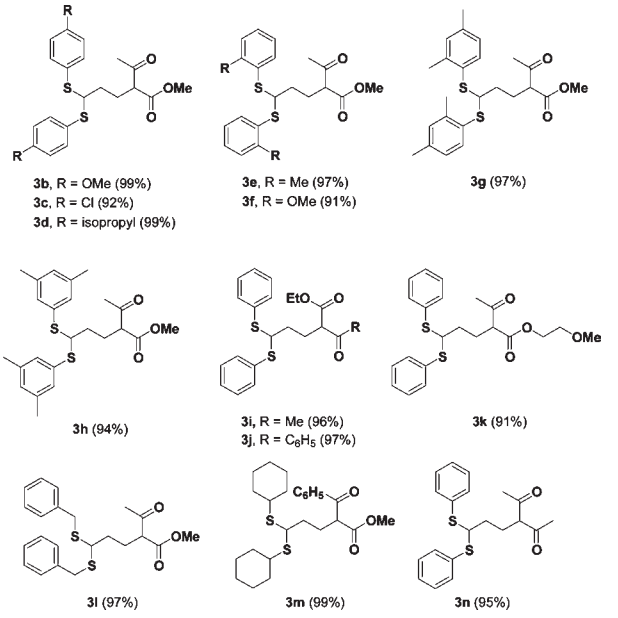
(11) All reactions were conducted in a 10 mL V-type flask equipped with triangle magnetic stirring. In a typical reaction, nitromethane (1.0 mL) was mixed with **1a** (60.5 mg, 0.25 mmol), **2a** (68.8 mg, 0.63 mmol), and $MnBr_2$ (6.4 mg, 12 mol %) under air. The mixture was stirred for 6 h at 80 °C. After reaction, the mixture was cooled to room temperature and the desired product, **3a**, was obtained by preparative TLC, using a mixed solution of ethyl acetate and petroleum ether as eluting solvent (the ratio of ethyl acetate/petroleum ether is 1/7). Tests for substrate scope and experiments concerning the mechanism were all performed according to an analogous procedure with the above mentioned.

Scheme 1. Substrate Scope of the Ring-Opening Reactions of 2-Butoxy-3,4-dihydropyrans with Thiophenols or Thiols[a]

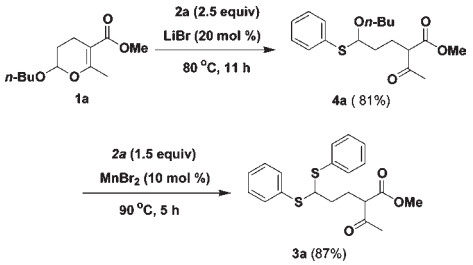


[a] All reactions were conducted under the optimized condition of Table 1.

as boric acid, $MnCl_2$, and $NiCl_2$, were used, a product, **3a**, was formed, but the yields obtained are rather poor (entries 2−4). Therefore, some strong acids, such as $Bi(OTf)_3$ and $FeCl_3$, were then examined in this reaction, and it was found that substrate **1a** was almost completely consumed; however, **3a** were obtained only in trace amount (entries 5 and 6). In these cases, many byproducts that are difficult to isolate were observed by TLC detection. Interestingly, when other acids, such as $Sc(OTf)_3$, $InCl_3$, $ZnCl_2$, TsOH, and $Y(OTf)_3$, were used as catalysts, the yield of **3a** reached 75−85% (entries 7−11). A solid acid, Amberlyst-15, was also used, and in this case, a 50% yield was obtained (entry 12). To further improve the reaction yield, an inexpensive catalyst, $MnBr_2$, was used in this reaction. To our great delight, the model reaction proceeded smoothly in this case, and **3a** was finally obtained in 88% yield (entry 13). Further investigation revealed that the solvent also played a key role in controlling the catalytic activity of $MnBr_2$, and nitromethane was proved to be an appropriate solvent for this system (entries 14−18). In later study, the reaction condition was optimized by using $MnBr_2$ as catalyst. And it was found that the best condition should be 80 °C and 12 mol % of catalyst (entries 19 and 20). Increase of reaction time can improve the reaction yield, and finally, a maximum yield, 96%, was obtained with 11 h of reaction. It should be noted that the reaction can be uneventfully scaled up to 10 mmol, and the yield obtained is still very high (94%, entry 22), indicating the effectiveness of this method for practical synthesis.

With the optimized conditions in hand, we probed the scope of the reaction with respect to both the dihydropyran and thiophenol. As shown in Scheme 1, a variety of

Scheme 2. Ring-Opening Monotransthioacetalization of **1a** with **2a** and the Following Reaction of the Generated Product with **2a**



3,4-dihydropyrans and thiophenols could be applied in the ring-opening reaction, and the corresponding products were obtained in good to excellent yields. Thiols could also be used instead of thiophenol, and the corresponding products were obtained in excellent yields. It should be noted that the skeleton of the ring-opening product has never been reported before, and it contains not only a moiety of 1,3-dicarbonyl compound, but also a fragment of bis(alkylthio)methane. In view of the extensive use of the both functional groups in various organic transformations, it would not be unreasonable to expect the formed products might be valuable for pharmaceutical synthesis. Our method thus offers the first path for accessing this novel class of complex molecules.

The mechanism of the ring-opening reaction of the dihydropyran, **1a**, most likely involves a manganese-assisted cleavage of a C−O bond of **1a**. However, there are two C−O bonds in the skeleton of **1a**, so in order to shed light on which C−O is more reactive, we then treated **1a** with LiBr, which has been reported to be a highly effective catalyst for monothioacetalization of acetals,[12] at 80 °C. In this case, the reaction proceeded sluggishly, and after 11 h of reaction, a product, **4a**, was isolated in 81% yield without detectable formation of any byproduct (Scheme 2). Following treatment of **4a** with **2a** in the presence of $MnBr_2$ in nitromethane resulted in an exclusive formation of **3a**.

This observation led us to postulate **4a** as an intermediate of the reaction. And a plausible reaction mechanism is thus deduced as shown in Figure 1. In the beginning of the reaction, dihydropyran **1a** was activated with the aid of $MnBr_2$ catalyst to form an oxonium intermediate (**I**). This step was generally catalyzed by Lewis acid.[13] Once **I** was formed, it tended to react with **2a** to generate the intermediate **4a**. In the presence of $MnBr_2$, **4a** underwent a cleavage of the C−O bond to form an another intermediate (**II**) that tended to react with the next thiophenol to generate the final product **3a**.[14] It should be noted that, in the presence of a strong acid catalyst, cleavage of the C−O bond out of the ring is also possible, which will

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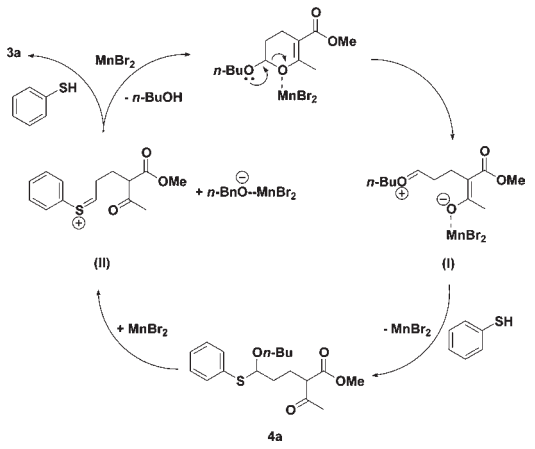
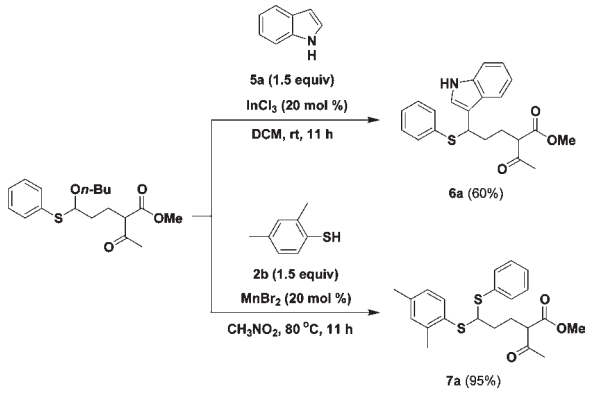


Figure 1. Plausible mechanism for the model reaction.

Scheme 3. Reactions of **4a** with Indole and 2,4-Dimethylthiophenol in the Presence of Catalyst



generate a cyclic oxonium intermediate that can also react with **2a**. Fortunately, two different mechanisms are both operative for the formation of **3a** because all the starting materials can finally flow the same way regardless of the mechanism.

It should be noted that the ring-opening monothioacetalization of **1a**-type dihydropyran has not been reported yet. LiBr-assisted selective formation of **4a** in this reaction encouraged us to further examine the reactivity of **4a** in the presence of other nucleophiles. As shown in Scheme 3, in the presence of an appropriate catalyst, **4a** can react smoothly with indole or 2,4-dimethylthiophenol to form unsymmetrical double-substituted product, **6a** or **7a**, in good to excellent yields. Because skeletons of the formed products contain not only a fragment of 1,3-dicarbonyl compound but also the core structure of two different nucleophiles, this type of reaction can thus be considered as an effective method for creation of molecular complexity and diversity.

In conclusion, an electrophilic ring-opening reaction of **1a**-type 2-alkoxy-3,4-dihydropyran with two molecules of thiophenol or thiol was described. The generated product contains not only a 1,3-dicarbonyl moiety but also a fragment of bis(alkylthio)methane. By using LiBr as catalyst, the dihydropyran can react selectively with thiophenol to form a ring-opening monotransthioacetalization product, which can be further converted to the final ring-opening product. Therefore, a possible mechanism for the ring-opening reaction of 2-alkoxy-3,4-dihydropyran with thiophenol was proposed on the basis of postulating the ring-opening monotransthioacetalization product as an intermediate. In addition, the ring-opening monotransthioacetalization product can further react with other nucleophiles, such as indole and 2,4-dimethylthiophenol, to form the corresponding unsymmetrical double-substituted product in high yields.

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Supporting Information Available. Experimental details, characterization data of the products, and ^{1}H NMR and ^{13}C NMR profiles of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.