



Alkyl 2-(2-benzothiazolylsulfinyl)acetates as useful synthetic reagents for alkyl 4-hydroxyalk-2-enoates by sulfinyl-Knoevenagel reaction

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ABSTRACT

Isopropyl, ethyl, and methyl 2-(2-benzothiazolylsulfinyl)acetates have been found to be useful synthetic reagents for sulfinyl-Knoevenagel reaction with various aldehydes to give directly the corresponding 4-hydroxyalk-2-enoates [R'CH(OH)CH=CHCO₂R], which are ubiquitous structures in biologically active natural products and useful building blocks for organic synthesis of chiral compounds. From the optically pure (*R*)-2-(2-benzothiazolylsulfinyl)acetates (>99% ee) prepared by the enzymatic kinetic resolution of (±)-2-(2-benzothiazolylsulfinyl)acetates, optically active 4-hydroxyalk-2-enoates (up to 91% ee) have been obtained in good yields.

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1. Introduction

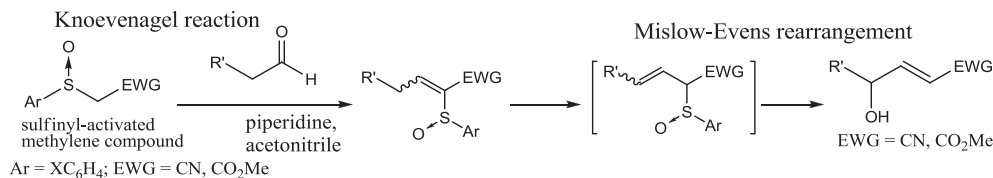
Alkyl 4-hydroxyalk-2-enoates [R'CH(OH)CH=CHCO₂R] are quite useful functional groups in organic synthesis, because there are many bioactive natural compounds such as macrolides bearing these functional groups in a side chain¹ or in a macrolide ring.² Although the structure–activity relationship of those compounds has not yet been clear, it seems to be plausible that these functional groups play an important role to show bioactivity by reacting with –SH moiety of a binding site in receptors of enzymes.

In the beginning of 1980s, we^{3a} and Tanikaga's group^{4b} independently discovered that Knoevenagel-type reactions⁵ of sulfinyl-activated methylene compounds such as 2-(phenylsulfinyl)acetonitrile [PhS(O)CH₂CN]³ and methyl 2-(*p*-chlorophenylsulfinyl)acetate [*p*-ClC₆H₄S(O)CH₂CO₂Me]⁴ with aldehyde (R'CH₂CHO) in the presence of a base directly gave a sulfur free highly functionalized product, 4-hydroxyalk-2-enenitrile [R'CH(OH)CH=CHCN] and methyl 4-hydroxyalk-2-enoate [R'CH(OH)CH=CHCO₂Me], respectively, in good yield. We may call this reaction 'sulfinyl-Knoevenagel reaction', because 4-hydroxyalk-2-enenitriles and alkyl 4-hydroxyalk-2-enoates were directly obtained conveniently by Knoevenagel reaction of aldehyde with sulfinyl-activated

methylene compounds where oxidation of α -carbon of the starting aldehyde occurred due to the characteristic sigmatropic reaction (Mislow–Evans rearrangement)⁶ of the sulfinyl group (Scheme 1).

Since then, these reactions have been applied not only for the synthesis of various 3-hydroxyalk-1-enyl ketones, sulfones, sulfoxides, and diethyl phosphonates [R'CH(OH)CH=CH–EWG; EWG=CO₂R,⁷ SO₂Ar,⁸ SOAr,⁹ PO(OEt)₂¹⁰], but also for that of the optically active compounds starting from the corresponding optically active sulfoxides.¹¹ For example, we carried out several asymmetric sulfinyl-Knoevenagel reactions of optically active sulfinyl-activated methylene compounds with aldehydes in the presence of piperidine in acetonitrile and discovered that (*R*)-2-(*p*-chlorophenylsulfinyl)acetonitrile gave the corresponding optically active 4-hydroxyalk-2-enenitrile in 77% yield with higher optical yield (75% ee) than that obtained using (*R*)-2-(*p*-tolylsulfinyl)acetonitrile in 64% yield with 54% ee.^{11a} Burgess and his co-workers reported that sulfinyl-Knoevenagel reaction of (*R*)-methyl 2-(aryl-sulfinyl)acetates (aryl=phenyl, *p*-chlorophenyl, and *p*-nitrophenyl) with pentanal gave the desired (*R*)-methyl 4-hydroxyhept-2-enoate in moderate yields with 61% ee, 72% ee, and 79% ee, respectively.^{11c,e} Thus, we thought that an electron-withdrawing substituent on sulfinyl group might give the desired products in good yields with higher optical yields. Actually, (*S*)-ethyl 2-(*p*-chlorophenylsulfinyl)acetate was successfully applied to the synthesis of biologically active natural compounds (+)-brefeldin A.²¹

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Although organosulfur chemistry is quite useful in organic synthesis, we have to be cautious of handling the starting sulfur compounds because of their unpleasant smell and expensive price for practical use. Thus, we thought that 2-mercaptobenzothiazole (2-BTSH), which is odorless and much cheaper than other arene-thiols, seems to be useful for the above described sulfanyl-Knoevenagel reaction.

Fortunately, we found that alkyl 2-(2-benzothiazolyl(2-BT)sulfanyl)acetates prepared by using 2-BTSH reacted with various aldehydes more smoothly to give the desired alkyl 4-hydroxyalk-2-enoates in better product and optical yields (up to 91% ee) than those prepared by so far reported reactions using methyl 2-(*p*-nitrophenylsulfanyl)acetate (79% ee).^{11b,e} Here, we report our detailed results of the improved sulfanyl-Knoevenagel reaction using 2-BT-sulfanyl compounds.

2. Results and discussion

2.1. Reactivity of alkyl 2-(2-benzothiazolyl(2-BT)sulfanyl)acetates **1**, **2**, and **3**

Isopropyl, ethyl, and methyl 2-(2-BT-sulfanyl)acetates (**1**, **2**, and **3**) were readily prepared via oxidation (by *m*-CPBA) of the corresponding sulfides¹² derived from the respective reactions of isopropyl, ethyl, and methyl 2-chloroacetates with 2-mercaptobenzothiazole (2-BTSH) in the presence of K₂CO₃ in acetone at 20 °C (Eq. 1).

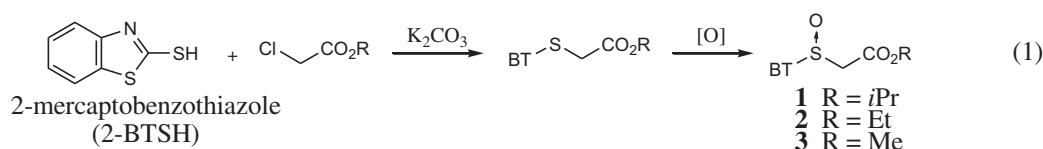
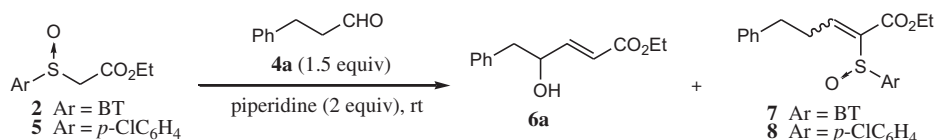


Table 1
Reactions of **2** and **5** with 3-phenylpropanal (**4a**) in various solvents



Entry	Ar	Solvent ^a	Reaction time (h)	Yield ^b (%)		
				6a	7 or 8 ^c	
1	2	MeCN	5	93	7	ND
2	2	Benzene	8	82	7	10
3	2	90% Aq EtOH	8	84	7	ND
4	5	<i>p</i> -ClC ₆ H ₄	5	75 ^d	8	5
5	5	<i>p</i> -ClC ₆ H ₄	10	91	8	ND
6	5	<i>p</i> -ClC ₆ H ₄	20	38 ^e	8	23
7	5	<i>p</i> -ClC ₆ H ₄	20	80	8	9

^a Commercially available solvents were used without further purification and drying.

^b ND means 'not detected' by TLC and ¹H NMR in crude products.

^c Though the geometry (*E* or *Z*) was not clear, single stereoisomer was detected in both **7** and **8** (see ¹H and ¹³C NMR).¹³

^d Compound **5** was recovered (12%).

^e Compound **5** was recovered (28%).

In order to investigate the reactivity of newly developed sulfanyl-activated methylene compounds bearing 2-BT-sulfanyl group, we treated ethyl 2-(2-BT-sulfanyl)acetate (**2**) with 3-phenylpropanal (**4a**) under Knoevenagel conditions (Table 1). It was revealed that **2** gave the desired ethyl 4-hydroxy-5-phenylpent-2-enoate (**6a**) in higher yields in shorter reaction time than those of similar reactions using ethyl 2-(*p*-chlorophenylsulfanyl)acetate (**5**) in various solvents. The result clearly shows the advantage of the 2-BT-sulfanyl compound in addition to cheaper price and odorless character of 2-mercaptobenzothiazole (2-BTSH).

2.2. Asymmetric sulfanyl-Knoevenagel reaction

2.2.1. Preparation of optically active isopropyl, ethyl, and methyl 2-(2-benzothiazolylsulfanyl)acetates (1**, **2**, and **3**, respectively).** To investigate further the effect of 2-benzothiazolyl(2-BT) group on the sulfanyl-Knoevenagel reaction including chirality transfer from chiral sulfanyl group to the hydroxy-carbon of the product, we tried to prepare optically active sulfoxides (*R* or *S*)-**1**, **2**, and **3** of high ee in good yield using available inexpensive reagents. First, we employed the enzymatic kinetic resolution of (±)-**1**, **2**, and **3**, according to Burgess and a co-worker's pioneering work, in which they obtained (*R*)-methyl 2-(arylsulfanyl)acetate [aryl=*p*-XC₆H₄ (X=H, NO₂, CH₃O, Cl)] in >98% ee and in good chemical yield using *Pseudomonas* sp. AK (Amano).^{11b} The reported method was, however, ineffective for our 2-benzothiazolyl derivatives such as **2**. Although, Burgess and co-workers reported very recently the improved method for

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