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# β-Ketothioester as a reactive Knoevenagel donor

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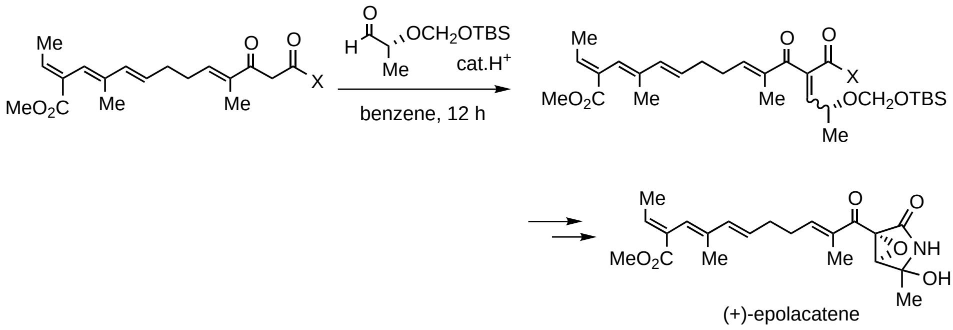
**Abstract**—The Knoevenagel condensation of β-ketothioesters with various aldehydes proceeds efficiently, affording the condensation products in moderate to good yield even in cases where the reactions of the corresponding β-ketoesters give the adducts in only low to moderate yield. © 2002 Published by Elsevier Science Ltd.

In the course of our synthetic studies on (+)-epolactaene, a neuritogenic compound, we encountered a problem with low reactivity of a β-keto amide,[1] and a β-ketoester,[2] towards an aldehyde in the Knoevenagel reaction (Table 1, entries 1 and 2). The Knoevenagel reaction is an important, classical carbon–carbon double bond forming reaction,[3] and many variations have been published, which however, cannot be applied to the synthesis of epolacatene owing to the labile triene moiety.[4] Searching for a suitable synthetic equivalent of the amide moiety, we found that a β-ketothioester reacts with this aldehyde efficiently under mild reaction conditions, affording the Knoevenagel condensation product in good yield, but with undesired *E*-stereochemistry (Table 1, entry 3). Although for this reason the Knoevenagel reaction of the β-ketothioester cannot be used in the total synthesis of epolactaene, the high reactivity of β-ketothioesters compared to β-ketoesters and β-ketoamides should prove important in terms of a useful synthetic modification of the Knoevenagel reac-

**Table 1.** Knoevenagel reaction in epolactaene synthesis



| Entry | X | Yield (%)[a] | |
|---|---|---|---|
| | | *Z* | *E* |
| 1 | $NH_2$ | 28[b] | 9[b] |
| 2 | $OCH_2CH_2SiMe_3$ | 0 | 0 |
| 3 | SEt | 0 | 78 |

[a] Isolated yield.

[b] Starting material was recovered in 58% yield.

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*Keywords*: Knoevenagel reaction; β-ketothioester; β-ketoester.

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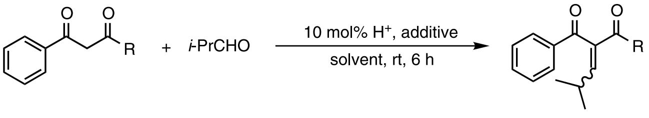
tion. We have compared the reactivities of these classes of compounds as Knoevenagel donors.[5]

We chose *S*-ethyl 3-oxo-3-phenylbutanethioate and isobutyraldehyde as model substrates and screened reaction conditions in detail. First of all, the catalyst was examined, and the traditional ammonium ion-based reagents such as ethylenediammonium diacetate[6] were found to be more effective than Lewis acid catalysts.[7] Next, the dehydrating reagent and solvent were investigated. The results are summarized in Table 2. For molecular sieves the pave size affected the yield considerably, and MS 5A was found to be the most effective. Dichloromethane was the solvent of choice. Thus, when the reaction was performed in the presence of MS 5A and 10 mol% of ethylenediammonium diacetate in $CH_2Cl_2$ at rt for 6 h, the Knoevenagel adduct was obtained in good yield (92%) with high *E*-selectivity (*E*:*Z* = 91:9, entry 9).[8] Under the same reaction conditions, however, the reaction of the corresponding β-ketoester, ethyl 3-oxo-3-phenylbutanoate, was slow, affording the condensation product in moderate yield (68%) with the same *E*/*Z* selectivity (*E*:*Z* = 90:10, entry 10). Since the superiority of the β-ketothioester as a Knoevanagel donor over the β-ketoester was confirmed in this model reaction, the generality of this finding was examined using several β-ketothioesters and β-ketoesters with various aldehydes, and these results are summarized in Table 3.[9]

When the β-substituent of the thioester or ester is small (methyl), there is little difference in reactivity between the two derivatives and both afford the adducts in good yields, in short reaction time (3 h), as shown by the reactions of *S*-ethyl 3-oxobutanethioate and methyl 3-oxobutanoate (entries 1 and 2). When the substituent at the β-position is large, on the other hand, a marked difference in reactivity was observed between thioester and ester. Namely, when this substituent is *i*-propyl or cyclohexyl, the reaction of β-ketoesters with aldehydes affords the condensation products in only low to moderate yields (<5–67%), while moderate to good yields (56–89%) are obtained in the reaction of the corresponding β-ketothioesters. The same phenomenon was also observed in the reactions of γ,δ-unsaturated and β-aryl derivatives: good yields are obtained in the reactions of *S*-ethyl 4-methyl-3-oxo-4-hexenethioate and *S*-ethyl 3-oxo-3-phenylbutanethioate with aldehydes. Although a β-ketothioester does not react with a bulky aldehyde such as 2,2-dimethyl-2-propanal, a β-ketothioester reacts both aromatic and the other aliphatic aldehydes including a linear aldehyde like propanal (entries 8, 9, 18), an α-branched aldehyde like isobutylaldehyde (entries 6, 11, 20, 24), and an α-alkoxyaldehyde like 2-(*p*-methoxybenzyloxy)propanal (entry 16), affording the condensation products in good yield. As the reaction conditions are mild, no self-condensation products of aldehydes were observed even in the reaction of an enolizable α-alkoxyaldehyde (entry 16). The amount of an aldehyde can be reduced to 1.5 equiv. to a β-ketothioester without affecting the yield, although longer reaction time was necessary (entries 8 and 9). The reason to use excess amount (4–6 equiv.) of aldehydes in some cases is to obtain the condensation products in good yield in a reduced reaction time when the reaction is slow.

**Table 2.** Knoevenagel reaction of β-ketothioester and isobutyraldehyde[a]



| Entry | R | Solvent | Additive[b] | Yield (%)[c] | *E*:*Z*[d] |
|---|---|---|---|---|---|
| 1 | SEt | Benzene | – | 54 | 92:8 |
| 2 | SEt | Benzene | MS 3A | 55 | 92:8 |
| 3 | SEt | Benzene | MS 4A | 64 | 92:8 |
| 4 | SEt | Benzene | MS 5A | 78 | 91:9 |
| 5 | SEt | Benzene | MS 13X | 23 | 89:11 |
| 6 | SEt | Benzene | $CaSO_4$ | 58 | 92:8 |
| 7 | SEt | MeOH | MS 5A | 35 | 90:10 |
| 8 | SEt | THF | MS 5A | 47 | 91:9 |
| 9 | SEt | $CH_2Cl_2$ | MS 5A | 92 | 91:9 |
| 10 | OEt | $CH_2Cl_2$ | MS 5A | 68 | 90:10 |

[a] Ethylenediammonium diacetate (10 mol %) was used as an acid catalyst and 2 equiv. of the aldehyde was used.

[b] 0.2 g of additive was used per 1 mmol of the ester.

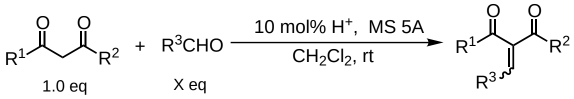
[c] Isolated yield.

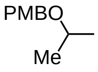
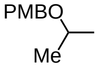
[d] The *E*:*Z* ratio was determined by $^1$H NMR.

*E*/*Z*-selectivity is mostly dependent on the substituent at the β-position, and differed little between β-ketothioester and β-ketoester. Low selectivity is observed in the reactions of both derivatives when the β-substituent is an alkyl group such as methyl, *i*-propyl and cyclohexyl, while high *E*-selectivity is obtained with γ,δ-unsaturated and β-aryl β-keto derivatives. The bulkiness of the substituent on sulfur has a little effect on selectivity; better *Z*-selectivity was observed in the reaction of the *S*-*tert*-butyl thioester compared with that of the *S*-ethyl thioester (entries 3 and 4).

The Knoevenagel reaction consists of two reactions: The first is the addition of an enolate of an active methylene compound to an aldehyde, and an elimination of water is the next reaction.[3] The high reactivity of β-ketothioesters in comparison to β-ketoesters could be explained as follows: (1) Because of the longer atomic radius of sulfur than oxygen, there is less steric repulsion in the reactions of a β-ketothioester, making it more reactive as a Knoevenagel donor. (2) As the HOMO level of a vinylsulfide is higher than that of a vinylether,[10] an enolate of a β-ketothioester is expected to be more reactive than that of a β-ketoester. This is why the first step becomes more feasible in the reaction of a β-ketothioester. (3) As the α-proton of a thioester is more acidic than that of an ester, the second reaction of an elimination of water becomes fast in the reaction of a β-ketothioester. At present we were not sure which effect is predominant in causing the higher reactivity of β-ketothioesters.

**Table 3.** Knoevenagel reaction of β-ketothioester and β-ketoester with various aldehydes[a]



| Entry | $R^1$ | $R^2$ | $R^3$ | X (equiv.) | Time (h) | Yield[b] (%) | *E*:*Z*[c] |
|---|---|---|---|---|---|---|---|
| 1 | Me | SEt | *i*-Pr | 2.0 | 3 | 77 | 66:34 |
| 2 | Me | OMe | *i*-Pr | 2.0 | 3 | 72 | 65:35 |
| 3 | *i*-Pr | S-*t*-Bu | Ph | 4.0 | 24 | 82 | 33:67 |
| 4 | *i*-Pr | SEt | Ph | 4.0 | 10 | 89 | 51:49 |
| 5 | *i*-Pr | OEt | Ph | 4.0 | 10 | 67 | 63:37 |
| 6 | *i*-Pr | SEt | *i*-Pr | 4.0 | 16 | 56 | 54:46 |
| 7 | *i*-Pr | OEt | *i*-Pr | 4.0 | 16 | 20 | 62:38 |
| 8 | Cyclohexyl | SEt | Et | 4.0 | 10 | 78 | 54:46 |
| 9 | Cyclohexyl | SEt | Et | 1.5 | 22 | 79 | 54:46 |
| 10 | Cyclohexyl | OMe | Et | 4.0 | 10 | 30 | 56:44 |
| 11 | Cyclohexyl | SEt | *i*-Pr | 4.0 | 10 | 89 | 66:34 |
| 12 | Cyclohexyl | OMe | *i*-Pr | 4.0 | 10 | 36 | 48:52 |
| 14 | Cyclohexyl | SEt | Ph | 4.0 | 10 | 86 | 58:42 |
| 15 | Cyclohexyl | OMe | Ph | 4.0 | 10 | 57 | 62:38 |
| 16 | Cyclohexyl | SEt |  | 1.5 | 5 | 76 | 58:42 |
| 17 | Cyclohexyl | OMe |  | 1.5 | 5 | <5 | – |
| 18 | 1-Methyl-1-propenyl | SEt | Et | 6.0 | 110 | 72 | 96:4 |
| 19 | 1-Methyl-1-propenyl | OMe | Et | 6.0 | 110 | 12 | 95:5 |
| 20 | 1-Methyl-1-propenyl | SEt | *i*-Pr | 6.0 | 110 | 84 | 96:4 |
| 21 | 1-Methyl-1-propenyl | OMe | *i*-Pr | 6.0 | 110 | 40 | 94:6 |
| 22 | 1-Methyl-1-propenyl | SEt | Ph | 4.0 | 18 | 94 | >95:5 |
| 23 | 1-Methyl-1-propenyl | OMe | Ph | 4.0 | 18 | 30 | 81:19 |
| 24 | Ph | SEt | *i*-Pr | 2.0 | 6 | 92 | 91:9 |
| 25 | Ph | OEt | *i*-Pr | 2.0 | 6 | 68 | 90:10 |

[a] Ethylenediammnonium diacetate was used as a catalyst.

[b] Isolated yield.

[c] The *E*:*Z* ratio was determined by $^1$H NMR.

In summary, we have shown that β-ketothioesters are reactive Knoevenagel donors which react with various aldehydes efficiently, affording the condensation products in good yield under mild reaction conditions. Since the β-ketothioester are easily prepared,[11] and the thioester moiety of the Knoevenagel adduct can be converted to several functional groups under mild reaction conditions,[12] the Knoevenagel reaction of β-ketothioesters should prove to be a synthetically useful carbon–carbon double bond forming reaction.

## Acknowledgements

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5. There is a report using β-ketothioester and β-ketoester as a Knoevenagel donor, but there is no description concerning the reactivity between these two esters. Moorhoff, C. M. *Synthesis* **1997**, 685.

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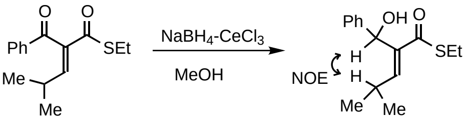
7. The reaction scarcely proceeded in the presence of 10 mol% of the following Lewis acid; $BF_3·OEt_2$, $AlCl_3$, $ZnI_2$, $SnCl_2$, $MgCl_2$, $ZrCl_4$, $Sn(OTf)_2$, $Lu(OTf)_3$, $Dy(OTf)_3$, and $Yb(OTf)_3$. The Knoevenagel product was obtained in 30% yield in the presence of $Sc(OTf)_3$ at 50°C for 16 h.
8. The stereochemistry was determined by observation of the following NOEs in the NOESY spectrum of the alcohol prepared by reduction of the condensation product with $NaBH_4$–$CeCl_3$.



9. A typical experimental procedure is as follows (Table 3, entry 22): To a $CH_2Cl_2$ solution (0.60 mL) of *S*-ethyl 4-methyl-3-oxo-4-hexenethiolate (45.0 mg, 0.242 mmol) and benzaldehyde (98 μL, 0.97 mmol) were added in succession ethylenediammonium diacetate (4.4 mg, 0.024 mmol) and molecular sieves 5 A (48.0 mg). After the reaction mixture had been stirred for 18 h at room temperature, the reaction was quenched by the addition of aq. $NaHCO_3$ (5 mL). After removal of molecular sieves by filtration, the organic materials were extracted with ethyl acetate and dried over anhydrous $Na_2SO_4$, and concentrated in vacuo after filtration. Purification by TLC ($Et_2O$:hexane = 1:3) gave 59.5 mg (94%) of *S*-ethyl 2-benzylidene-4-methyl-3-oxo-4-hexenethiolate.
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