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A Facile and Efficient Direct Aldol Addition of Simple Thioesters

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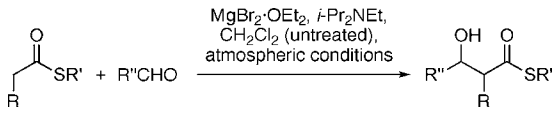
ABSTRACT



Simple thioesters undergo direct aldol addition to aldehydes in the presence of $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt using untreated, reagent-grade CH_2Cl_2 under atmospheric conditions. The reactions proceed extremely rapidly and in excellent yield.

The aldol reaction is among the most important chemical reactions. Substantial effort has gone into its development using preformed enolates, resulting in a remarkable level of regio- and stereochemical control.[1] However, the desire to develop milder and operationally simplified chemical methods has spawned a renewed interest in the direct aldol reaction,[1a] without reliance on preformed enolates. While only a limited number of reports have appeared,[1a,2] initial investigations into these in situ enolization approaches clearly establish their potential.

The majority of this research, for both metal-assisted and organocatalytic processes, focuses on the use of ketone- and, to a lesser extent, aldehyde-based nucleophiles.[1a] However, owing to the inherent advantages of carboxylate-derived nucleophiles in aldol addition reactions, such as obviating the issue of regioselectivity of deprotonation and the iterative potential of the process, it is extremely desirable to develop related procedures based on these systems.

Recently, a small number of examples along these lines have appeared. Evans and co-workers have begun to explore magnesium halide catalyzed aldol reactions of chiral *N*-acyloxazolidinones and *N*-acylthiazolidinethiones,[2a,b] as well as those of achiral *N*-acylthiazolidinethiones with a chiral Ni(II) bis(oxazoline) catalyst.[2c] In addition, copper-catalyzed decarboxylative enolization of malonic acid half thioesters has been demonstrated by Shair and co-workers, in both an asymmetric and nonasymmetric sense.[2d,e]

We were intrigued by the possibility of using readily accessible, simple thioesters in the direct aldol addition reaction. Our inspiration for this derives from Nature's use of thioesters, typically in the form of acetyl coenzyme A, in carbon−carbon bond-forming processes. Here, Nature's choice of thioesters over oxoesters is undoubtedly a deliberate one and may well be connected to the increased acidity of the thioester α-proton,[3] compared to that of the corresponding oxoester. The sophistication of Nature's aldol processes overcomes the need for prior enolate formation, lending simplicity and elegance to this important carbon−carbon bond-forming reaction. Of course, mimicking the direct nature of this reaction in the laboratory in a synthetic context would be advantageous in terms of procedural simplification and, potentially, reduced cost and environmental impact. From a practical point of view, the use of simple thioesters for such a direct aldol addition is desirable for a number of reasons. For instance, they are readily accessible from inexpensive, commercially available thiols, or are themselves

(1) (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; 2 Vols. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, pp 997−1065.

(2) (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393. (b) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127−1130. (c) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706−8707. (d) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852−2853. (e) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284−7285.

(3) The pK_a of the thioester α-proton has been reported to be 2 units less than that of a corresponding oxoester. See: Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218−4223.

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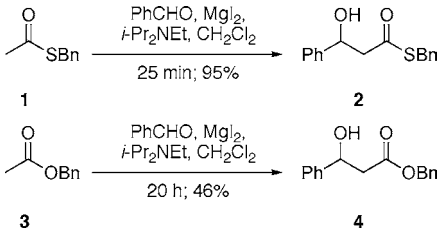
commercially available. They are also stable and easily handled, yet they undergo a number of important transformations under very mild conditions including reduction, hydrolysis, and direct amidation.

To explore the possibility of using simple thioesters to develop a direct aldol addition reaction, we investigated the reaction of *S*-benzyl thioacetate[4] (**1**) with benzaldehyde under a variety of conditions using several different metal salts based on Zn, Cu, and Ni. In no case was there any indication of a reaction between the thioester and aldehyde. However, we eventually found that the aldol addition could be promoted by MgI_2, and after screening a variety of solvents and amine bases, we settled on the use of *i*-Pr_2NEt in CH_2Cl_2. Coincidentally, these conditions had previously been reported to provide moderate to high yields for the direct aldol reaction between ketones and aromatic aldehydes, and modest yields with certain oxoesters and benzaldehyde.[5]

In the presence of MgI_2 and *i*-Pr_2NEt, **1** reacted with benzaldehyde in CH_2Cl_2 to give the corresponding β-hydroxy thioester (**2**) in 95% isolated yield in only 25 min (see Scheme 1).[6] In comparison to oxoester substrates, the yield

Scheme 1. MgI_2-Promoted Direct Aldol Reaction of Thioester **1** and Oxoester **3** with Benzaldehyde[a]



[a] Conducted under Ar by combining 1 molar equiv of thioester, 1.2 molar equiv of benzaldehyde, and 1.2 molar equiv of MgI_2 in CH_2Cl_2 (concn 0.2 M), followed by addition of 1.3 molar equiv of *i*-Pr_2NEt.

of addition product from **1** was significantly higher (cf. 60 to 72% for the oxoesters[5]), with a somewhat shorter reaction time. The superior reactivity of the thioester was confirmed via a competition experiment between **1** and *O*-benzyl acetate (**3**) with benzaldehyde, in which 92% conversion to **2** was observed after 30 min, with no corresponding β-hydroxy oxoester (**4**) detected. Reaction of **3** with benzaldehyde in the presence of MgI_2 and *i*-Pr_2NEt gave 46% yield of **4** after 20 h (see Scheme 1).

We next investigated the effect of the thiol component of the thioester on its reactivity. Thus, thioesters **5**−**9** (see Table 1) were subjected to the conditions described above. Remarkably, thioesters **5**−**7** provided the aldol product nearly quantitatively within only 20 min. Given the extremely rapid

Table 1. Investigation of the Effect of the Thiol on Thioester Reactivity in the MgI_2-Promoted Direct Aldol Reaction[a]

Entry	Thioester	β-Hydroxythioester	Time (min)	Isolated Yield (%)
1	AcSBn **1**	OH O Ph SBn **2**	25	95
2	AcSPh **5**	OH O Ph SPh **10**	20	94
3	AcS OMe **6**	OH O Ph S OMe **11**	20	98
4	AcS **7** OMe	OH O Ph S **12** OMe	20	96
5	AcS NO_2 **8**	OH O Ph S NO_2 **13**	60	92
6	AcS O **9**	OH O Ph S O **14**	30	96

[a] Conducted under Ar by combining 1 molar equiv of thioester, 1.2 molar equiv of benzaldehyde, and 1.2 molar equiv of MgI_2 in CH_2Cl_2 (concn, 0.2 M), followed by addition of 1.3 molar equiv of *i*-Pr_2NEt.

nature of the reaction in the cases of **5**−**7**, we were unable to establish a clear preference for either thioester in the aldol addition. However, competition experiments involving **5**−**7** with benzaldehyde showed a slight preference for the formation of **10** over **11** and **12**. On this basis, and the fact that it is commercially available, **5** was chosen for subsequent studies. Significantly, a competition experiment between **5** and acetophenone gave a 3:1 mixture of the corresponding β-hydroxy ketone to **10**, demonstrating that the reactivity of a simple thioester in the direct aldol reaction is comparable to that of a highly reactive ketone.

While the direct aldol demonstrated above is rapid and highly efficient, our attempts to conduct it catalytically using **5**, **7**, or **9** were unsuccessful. This was as expected in the case of **5**, given the presumed thermodynamic preference of MgI_2 for interaction with the β-hydroxy thioester product over either **5** or benzaldehyde. For **7** and **9**, however, there is a somewhat greater possibility that the MgI_2/β-hydroxy thioester complex would be able to exchange with the starting thioester, given the availability of additional oxygen atoms in the thiol component for coordination, albeit through a seven-membered ring. Efforts to facilitate this exchange via in situ silylation of the product through addition of TMSCl[2a−c] showed no indication of catalysis.

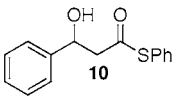
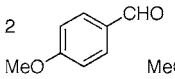
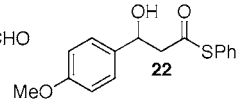
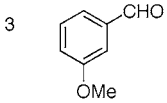
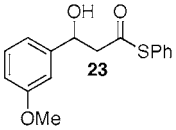
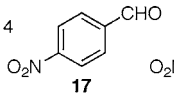
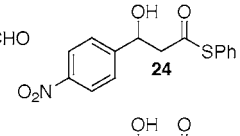
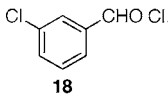
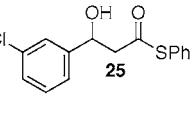
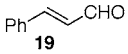
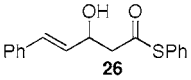
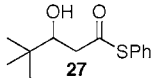
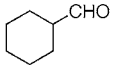
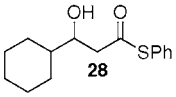
The majority of methods for effecting the direct aldol addition reported recently employ catalytic amounts of the activating component, be it a metal or organic molecule.[1a,2] When organic molecules are used to promote a reaction, it is generally desirable that they be used catalytically, given the time, effort, and cost often associated with their prepara-

(4) All thioesters used in this work, with the exception of commercially available **5**, **8**, **9**, and **29**, were prepared via acylation of the corresponding commercially available thiols. See the Supporting Information.

(5) Wei, H.-X.; Li, K.; Zhang, Q.; Jasoni, R. L.; Hu, J.; Paré, P. W. *Helv. Chim. Acta* **2004**, *87*, 2354−2358.

(6) A control experiment in which MgI_2 was omitted gave only starting material after 2 days. Likewise, omission of base gave no product.

Table 2. $MgBr_2 \cdot OEt_2$-Promoted Direct Aldol Addition between **5** and Various Aldehydes Using Untreated Solvent under Atmospheric Conditions[a]

Entry	Aldehyde	β-Hydroxythioester	Time (min)	Isolated Yield (%)
1	PhCHO	 **10**	30	96
2	 **15**	 **22**	30	97
3	 **16**	 **23**	30	96
4	 **17**	 **24**	60	94
5	 **18**	 **25**	60	95
6	 **19**	 **26**	60	92
7	 **20**	 **27**	60	94
8	 **21**	 **28**	60	82

[a] Conducted under atmospheric conditions by combining 1 molar equiv of **5**, 1.2 molar equiv of aldehyde, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in untreated, reagent-grade CH_2Cl_2 (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-Pr_2NEt.

tion. For a transition-metal-mediated process, a catalytic mode of action is also generally desirable for reasons typically associated with cost and toxicity of the metal, along with downstream purification requirements of the products, especially in pharmaceutical applications.

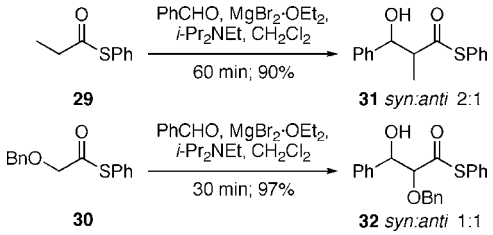
The catalytic requirement of a process is diminished when one uses promoters that are themselves readily accessible, very inexpensive, and environmentally benign. Along these lines, given the extremely rapid nature of the reaction with thioester **5**, we wondered about the possibility of substituting $MgBr_2 \cdot OEt_2$ for MgI_2. This compound is commercially available and very inexpensive and, like MgI_2, generates no toxic byproducts on aqueous workup. While the reaction with $MgBr_2 \cdot OEt_2$ would be expected to be slower, we hoped that this would be more than compensated for, not only by the low cost of the reagent, but also by allowing us to conduct the reactions open to the atmosphere using untreated, reagent grade solvent.

To test this, **5** was combined with benzaldehyde, *i*-Pr_2NEt, and $MgBr_2 \cdot OEt_2$ in untreated, reagent-grade CH_2Cl_2[7] under atmospheric conditions. Significantly, not only was the reaction highly efficient, giving a 96% yield of product, but it remained extremely facile, taking only 30 min to go to completion. No increase in yield or decrease in reaction time was observed when the reaction was conducted using dry CH_2Cl_2 under an Ar atmosphere. When MgI_2 was used in this manner, reaction yields were lower than when anhydrous conditions were employed.

Using these conditions, we investigated the scope of the reaction with a variety of aldehydes (see Table 2). In all cases, reaction times were short and yields were excellent. Significantly, the reaction could be conducted using an aldehyde having a single α-proton (entry 8) with only a small amount (<4%) of the self-addition product produced. In this case, best results were obtained when the thioester was used in a 1.5-fold excess, relative to the aldehyde.

The effect of α-substitution on the thioester was examined via the direct aldol addition between benzaldehyde and each of *S*-phenyl thiopropionate (**29**) and *S*-phenyl-α-benzyloxy thiopropionate (**30**) (see Scheme 2). In both cases, the reaction gave an excellent yield of the respective diastereomeric products in a reasonably short time.

Scheme 2. $MgBr_2 \cdot OEt_2$-Promoted Direct Aldol Reaction of α-Substituted Thioesters with Benzaldehyde[a]



[a] Conducted under atmospheric conditions by combining 1 molar equiv of **5**, 1.2 molar equiv of aldehyde, and 1.4 molar equiv of $MgBr_2 \cdot OEt_2$ in untreated, reagent-grade CH_2Cl_2 (concn 0.2 M), followed by addition of 2.0 molar equiv of *i*-Pr_2NEt.

Last, we probed the issue of reversibility of the addition reaction. Thus, **10** was combined with $MgBr_2 \cdot OEt_2$ (1.4 molar equiv), *i*-Pr_2NEt (2.0 molar equiv), and **6** (1 molar equiv). A 1:1 mixture of **10** to **11** was obtained from this experiment, suggesting that the addition process is reversible under these conditions. The corresponding experiment in which **5** was added to a mixture containing **11**, $MgBr_2 \cdot OEt_2$, and *i*-Pr_2NEt was also conducted and gave a similar result. These results indicate that, to develop an asymmetric varient of this reaction, it will be necessary to trap the kinetic product in a manner similar to that reported by Evans.[2a−c] Investigations in this regard are ongoing.

In conclusion, we have developed a mild and efficient direct aldol reaction using simple thioesters. The reaction is conducted using inexpensive $MgBr_2 \cdot OEt_2$ in untreated,

(7) Aldrich. ACS reagent grade, ≥99.5%.

reagent grade solvent under atmospheric conditions and produces innocuous byproducts on workup. To our knowledge, this is the first report of a direct aldol addition involving simple thioesters. The superior reactivity of thioesters over oxoesters in this reaction was established via competition experiments and is fundamental to the facility of this procedure. Given the operational simplicity of the reaction and the accessibility of thioesters,[4] we expect that this method will meet with wide application. Work is currently ongoing to develop an asymmetric variant of the reaction through incorporation of a recoverable chiral auxiliary, and we are also exploring other modes of incorporating heteroatoms into the starting thioesters, in both the thiol region (cf. **7** and **9**) and at the α-position (cf. **30**), to investigate the development of a catalytic asymmetric process using a metal possessing chiral ligands. Additionally, we have begun to explore the use of thioesters in the context of several other reactions.

Acknowledgment. We thank Dr. Anna Gromova and Drew Schwartz for their assistance in conducting certain experiments.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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