Pergamon

Tetrahedron Letters 43 (2002) 8219–8222

TETRAHEDRON LETTERS

Sulfide–BF_3·OEt_2 mediated Baylis–Hillman reactions

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Received 2 August 2002; revised 10 September 2002; accepted 19 September 2002

Abstract—A sulfide–BF_3·OEt_2 mediated Baylis–Hillman reaction has been developed in which the sulfide acts via attack onto the activated alkene. The use of a chiral sulfide gives rise to Baylis–Hillman adducts with up to 53% ee.

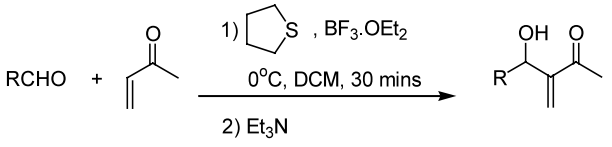
The coupling of an activated alkene and an aldehyde, the Baylis–Hillman reaction, has been the focus of much research interest.[1–3] Kataoka et al. recently developed the sulfide/Lewis acid mediated Baylis–Hillman reaction.[4,5] The Lewis acid must be present for these reactions to proceed, in contrast to amine promoted reactions where a Lewis acid is not always required. The most commonly used Lewis acid for the sulfide mediated reactions is $TiCl_4$ but more recently BBr_3·DMS and BCl_3·DMS have also been successfully employed.[6] Although it seems clear that the Lewis acid is required in these reactions, it is less clear whether the sulfide itself is necessary. The reaction of *p*-nitrobenzaldehyde and cyclohexenone is effected by the addition of $TiCl_4$ at room temperature.[7] However, Shi has reported that the reaction of methyl vinyl ketone and *p*-nitrobenzaldehyde in the presence of $TiCl_4$ at −78°C does not proceed unless an additional Lewis base is present.[2b,d,e] This poses the question: what is the role of the sulfide in the sulfide/Lewis acid mediated Baylis–Hillman reaction?

It was originally thought that the sulfide/$TiCl_4$ mediated Baylis–Hillman reactions proceeded via Michael attack of the sulfide onto the activated alkene but it is now believed that these reactions proceed via attack of a halide ion, released from the Lewis acid by the sulfide.[8] Supporting evidence for this was that the use of BF_3·OEt_2, where the release of a halide ion from the Lewis acid is far less likely, had thus far been unsuccessful.[4]

The literature suggests that a sulfide is not needed for $TiCl_4$ Baylis–Hillman reactions at room temperature (cyclohexenone)[7] but is needed at −78°C (MVK).[2b,d,e] We decided to clarify at which point the sulfide is required. We found, in contrast to results reported by Shi et al., that the reaction of methyl vinyl ketone and *p*-nitrobenzaldehyde in the presence of $TiCl_4$ was facile in the absence of a Lewis base, even at −90°C. Since our aim was to use chiral sulfides to lead to an asymmetric reaction, we decided that $TiCl_4$ was an unsuitable Lewis acid for our needs. We set out to develop a sulfide/Lewis acid mediated Baylis–Hillman reaction in which the sulfide was unambiguously required and ideally acting via attack on to the activated alkene.

We chose to use Lewis acids which did not bear chloride, bromide or iodide ligands as we anticipated that, in these cases, the halide ion could easily be liberated, perhaps even in the absence of a sulfide, and subsequently bring about the Baylis–Hillman reaction.

Table 1. Tetrahydrothiophene–BF_3·OEt_2 mediated Baylis–Hillman reaction of methyl vinyl ketone with various aldehydes[10]



Entry	R	Yield (%)
1	*p*-$NO_2C_6H_4$	50
2	*p*-ClC_6H_4	48
3	Ph	52
4	*p*-$MeOC_6H_4$	45
5	Et	45
6	$PhCH_2CH_2$	43

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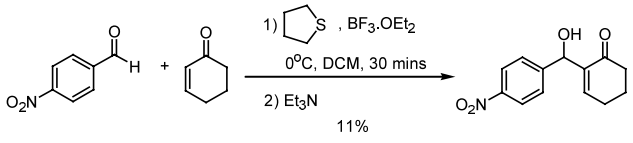
0040-4039/02/$ - see front matter
PII: S0040-4039(02)02053-1

Indeed, the reaction of cyclohexenone and various aliphatic aldehydes in the presence of Et_2AlI and no additional Lewis base at 0°C is complete in only 20 minutes.[9]

We studied the reaction of *p*-nitrobenzaldehyde and methyl vinyl ketone both with and without tetrahydrothiophene with various Lewis acids. Kataoka et al. have previously reported that $BF_3{\cdot}OEt_2$ is an ineffective Lewis acid for both the dimethylsulfide mediated Baylis–Hillman reaction of *p*-nitrobenzaldehyde and cyclohexenone[4b] and also for the 2,6-diphenyl-4*H*-thiopyran-4-one mediated reaction of *p*-nitrobenzaldehyde and methyl vinyl ketone.[4c] We found $BF_3.OEt_2$ and tetrahydrothiophene to be effective for this transformation and that this reaction is rapid. The reaction of 1 equiv. of *p*-nitrobenzaldehyde and 3 equiv. of methyl vinyl ketone in the presence of 1.2 equiv. of tetrahydrothiophene and 1.5 equiv. $BF_3{\cdot}OEt_2$ at 0°C for just 30 minutes followed by the addition of Et_3N gave a 50% yield of the Baylis–Hillman adduct (Table 1, entry 1). Moreover, there is no reaction in the absence of sulfide.

It is necessary to use 1.5 equiv. of $BF_3{\cdot}OEt_2$ to obtain optimum yields in this reaction. The use of just 1 equiv. of $BF_3{\cdot}OEt_2$ gives a 20% yield of the Baylis–Hillman adduct. Increasing the amount of Lewis acid to 2 equiv., however, does not improve on the 50% yield.

This sulfide–$BF_3{\cdot}OEt_2$ mediated Baylis–Hillman reaction is very versatile with respect to the aldehyde used: the use of both aromatic and aliphatic aldehydes leading to successful reactions (Table 1). Particularly noteworthy are the results with the aliphatic enolisable aldehydes (entries 5 and 6). No side products were obtained and the yields are similar to those observed with aromatic aldehydes. Baylis–Hillman reactions with simple aliphatic aldehydes such as propionaldehyde are often troublesome[11] and low yielding so this is a particularly pleasing result.



Scheme 1.

The analogous reaction of *p*-nitrobenzaldehyde and the less reactive enone, cyclohexenone, also yields the desired Baylis–Hillman adduct, albeit in a reduced yield of 11% (Scheme 1).

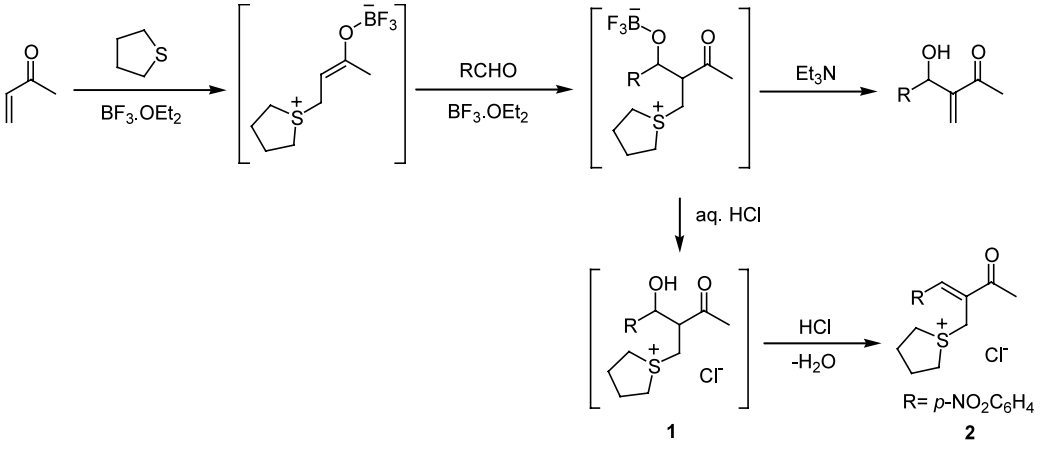
Scheme 2 illustrates the most likely mechanistic pathway for this reaction; the sulfide directly attacking the methyl vinyl ketone and the resultant species then attacking the aldehyde. Treatment with base leads to elimination of the sulfide to yield the Baylis–Hillman adduct.

Evidence to support this pathway was obtained by quenching the reaction with dilute HCl instead of base. Under these conditions elimination of the sulfide did not occur and **2** was recovered from the aqueous extracts, formed from the acid mediated dehydration of **1**. It seems likely, therefore, that the sulfide is acting in a similar fashion to the amine in an amine promoted Baylis–Hillman reaction.

Since we believed the sulfide to be attacking the methyl vinyl ketone we envisaged that the use of a chiral sulfide would result in an asymmetric version of this reaction.

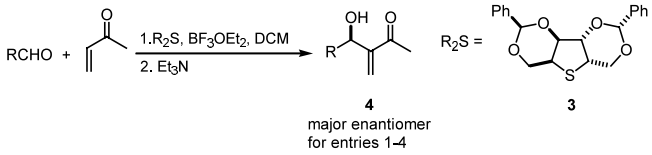
The C_2 symmetric tricyclic sulfide **3** has recently been synthesised in our group[12] and, used in the one-pot sulfur-ylide epoxidation reaction, gives epoxides in >94% ee.[13] We therefore decided to use this sulfide in the Baylis–Hillman reaction. We were pleased to find that the chiral sulfide successfully mediated the reaction giving enantioenhanced Baylis–Hillman adducts (Table 2). The sulfide could be recovered after each reaction.

The Baylis–Hillman adduct obtained from the reaction of *p*-nitrobenzaldehyde and methyl vinyl ketone using the chiral sulfide **3** at 0°C was found to have an enantiomeric excess of 21% (Table 2, entry 1). By



Scheme 2.

Table 2. Asymmetric Baylis–Hillman reaction of methyl vinyl ketone with various aldehydes



Entry	R	Temp. (°C)	Time (min)	Yield (%)	Ee (%)[a,b]
1	p-$NO_2C_6H_4$	0	30	37	21
2	p-$NO_2C_6H_4$	−78	1	8	53
3	p-$NO_2C_6H_4$	−78	5	38	49
4	p-$NO_2C_6H_4$	−78	30	48	46
5	Et	−78	30	18	28
6	Et	−78	120	60	23
7	$PhCH_2CH_2$	−78	120	41	14

[a] Determined by HPLC analysis using a Chiralcel™ OD column eluting with hexane/propan-2-ol (R = p-$NO_2C_6H_4$, 9:1; R = Et, 49:1; R = $PhCH_2CH_2$, 19:1).

[b] All $[\alpha]_D$ values are negative. When R = p-$NO_2C_6H_4$ the absolute configuration is known by comparison with the literature value ($[\alpha]_D = -12.1$, $c = 0.53$).[14]

lowering the temperature of the reaction to −78°C, the ee could be increased. A reaction time of 1 minute led to an ee of 53% but in only 8% yield (Table 2, entry 2). Increasing the reaction time results in an increase in yield with a slight decrease in ee; a reaction time of 30 minutes at −78°C gave a 48% yield of the Baylis–Hillman adduct with 46% ee.

By comparison of the sign of the specific rotation of Baylis–Hillman adduct **4** (R = p-$NO_2C_6H_5$) with the literature value[14] the selectivity of the reaction was found to be in favour of the *R* enantiomer. In order to rationalise this selectivity, MacroModel MM2* calculations[15,16] were undertaken on the sulfonium species **5**. RHF/6-31G** calculations verified that the *Z* enol is preferred over the *E* enol. The calculations revealed a lowest energy conformation in which the reactive enolate chain attached to the sulfur points away from the bulky sulfide substituent. This in turn leads to one face of the enolate being shielded by the other side of the tricyclic sulfide. Attack onto the aldehyde can therefore only occur from one side of this intermediate. Reaction with the aldehyde via an extended transition state **6**[17] gives rise to the *R* enantiomer as shown in Fig. 1. This serves as a qualitative model to explain the selectivity and could help design other chiral sulfides for further studies.

In summary, we have developed a Baylis–Hillman reaction in which the sulfide directly participates via Michael addition to the α,β-unsaturated ketone. The reaction is rapid and a number of aldehydes can be used with methyl vinyl ketone to give the Baylis–Hillman adducts in moderate yields. The use of a chiral sulfide gives Baylis–Hillman adducts with ee's of up to 53%.

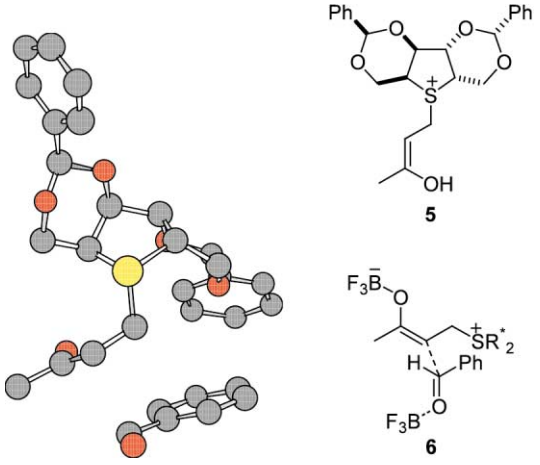


Figure 1. Lowest energy conformation of **5** and its approach to benzaldehyde via an extended transition state **6**.

Acknowledgements

We would like to thank the EPSRC for financial support.

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10. Typical procedure: To a solution of aldehyde (1 mmol), methyl vinyl ketone (3 mmol) and tetrahydrothiophene (1.2 mmol) in DCM (5 ml) at 0°C was added $BF_3{\cdot}OEt_2$ (1.5 mmol). After stirring the reaction for 30 min at this temperature Et_3N (1 mmol) was added and the mixture stirred for a further 10 min whilst warming to room temperature. The solution was washed with dilute HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo to give the crude product which was purified by column chromatography.
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