ORGANIC LETTERS

2008
Vol. 10, No. 21
4819−4822

Overcoming the Limitations of the Morita−Baylis−Hillman Reaction: A Rapid and General Synthesis of α-Alkenyl-β′-hydroxy Thioesters

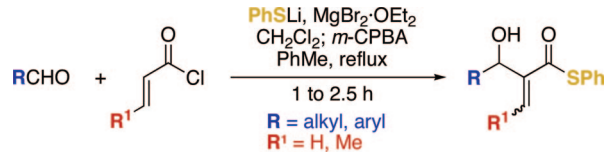
Emily Tarsis, Anna Gromova, Daniel Lim, Guoqiang Zhou, and Don M. Coltart*

Department of Chemistry, Duke University, Durham, North Carolina 27708

don.coltart@duke.edu

Received August 13, 2008

ABSTRACT



Acryloyl chlorides, aldehydes, and PhSLi undergo a direct aldol cascade sequence in the presence of $MgBr_2$·OEt_2 via in situ derived thioester enolates, which is followed by oxidative elimination to give α-alkenyl-β′-hydroxy thioesters. Overall, the procedure is rapid, efficient, and generally applicable, even to β-substituted acryloyl chlorides, thus providing an alternative to the Morita−Baylis−Hillman reaction with substantially greater synthetic scope and utility.

The Morita−Baylis−Hillman (MBH) reaction enables straightforward access to α-alkenyl-β′-hydroxy carbonyl compounds from aldehydes and α,β-unsaturated carbonyls.[1,2] These products are useful synthetic intermediates due to their multifunctional composition and, consequently, have been elaborated into a variety of natural products and related compounds.[2,3] The MBH reaction has been the subject of extensive methodological studies. Despite this, it remains for the most part remarkably slow, requiring up to days or even weeks for completion, depending on the nature of the substrates used.[2] Furthermore, reaction yields are often quite low, and it is by no means a general process, as it has scarcely been reported in the context of β-substituted α,β-unsaturated carbonyl species.[2] Several modifications to this reaction have been investigated in an effort to overcome these shortcomings, including the use of Lewis acids,[2] microwave irradiation,[4] high pressure,[5,6] high temperature and ultrasound,[7] and aqueous media.[8] While some progress has been made toward an improved MBH reaction, no general solution exists and reaction rates and yields remain highly variable and often low. Herein, we report an alternative approach to the preparation of MBH adducts that is rapid, efficient, and generally applicable, even to β-substituted α,β-unsaturated compounds.

We recently reported an operationally simple $MgBr_2$·OEt_2-promoted four-component, direct aldol addition between aldehydes and a thioester enolate, obtained by conjugate addition of lithium thiophenolate to an in situ-formed α,β-

(1) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972. Baylis, A. B.; Hillman, M. E. D. *Chem. Abstr.* **1972**, *77*, 3417q.

(2) Basavaiah, D.; Anumolu, J. R.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.

(3) See, for example: Krishna, P. R.; Narsingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 4773–4775. Mergott, D. J.; Frank, S. A.; Roush, W. R. *P. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955–11959. Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616–11617. Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318. Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *Tetrahedron* **1997**, *53*, 16423–16434.

(4) Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444.

(5) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007–5010.

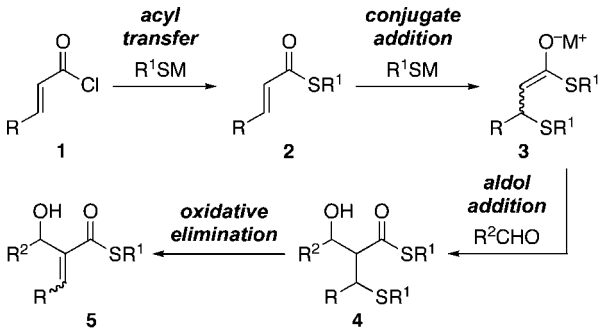
(6) Schuurman, R. J. W.; v. d. Linden, A.; Grimbergen, R. P. R.; Nolte, R. J. M; Scheeren, H. W. *Tetrahedron* **1996**, *52*, 8307–8314.

(7) Roos, G. H. P.; Rampersadh, P. *Synth. Commun.* **1993**, *23*, 1261–1266.

(8) Augé, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* **1994**, *35*, 7947–7948.

10.1021/ol801896q CCC: $40.75
Published on Web 10/10/2008

Scheme 1. Proposed Four-Component Direct Aldol Addition/ Oxidative Elimination Sequence



unsaturated thioester (cf. Scheme 1, **1** → **4**).[9] The effectiveness of this process stems from the highly nucleophilic nature of thiolates in forming the requisite magnesium enolates, coupled with the rapid addition of these species to aldehydes.[10] Given the pronounced nucleophilicity of thiolates, we reasoned that the scope of the coupling could be extended to α,β-unsaturated carbonyl species having β-substituents. If this were indeed the case, then we could potentially connect this feature with the straightforward and rapid oxidative elimination of thioethers (**4** → **5**),[11] thereby developing a two-step procedure that is formally equivalent to the MBH reaction, yet potentially consistently high-yielding, rapid, and most notably, general in scope.[12] While overall this approach would introduce the requirement of an oxidation step, the resulting decrease in the duration of the reaction and increase in scope would more than compensate for the additional step.

The aldol intermediates in this transformation (cf. **4**) contain a free alcohol and possess divalent sulfur in the form of both a thioester and thioether. Consequently, chemoselective oxidation would be required during regeneration of the α,β-unsaturation, and this would need to be managed in such a way that the retro-aldol reaction would be suppressed. Selective oxidation was not expected to be overly problematic since the sulfur atom in the thioester is considerably less nucleophilic than in the thioether. Furthermore, provided that the oxidation conditions used were suitably mild, the retro-aldol reaction should be avoidable.

We began our exploration of the thiolate-promoted oxidative MBH reaction by determining if the thioether function could indeed be oxidized without competing side reactions.

Scheme 2. Studies on the Stepwise Aldol Addition, Oxidation, and Elimination Sequence

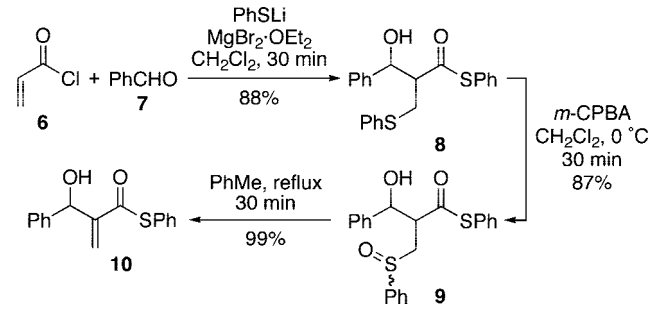
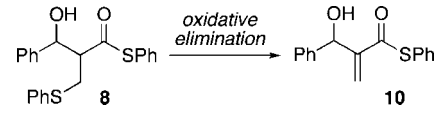
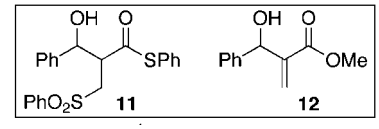


Table 1. Studies on the Oxidative Elimination of **8** to **10**



entry	conditions	time (h)	product(s) formed	ratio[a]	isolated yield of **10** (%)
1	$NaIO_4$ (1.5 equiv), MeOH-H_2O (4:1), reflux	12	**10** + **12**	2:1	46
2	$NaIO_4$ (1.5 equiv), THF-H_2O (4:1), reflux	12	**10** + **8**	1:4.5	16
3	$NaIO_4$ (1.5 equiv), MeCN-H_2O (4:1), reflux	12	**10** + **8**	9:1	39
4	Oxone (0.56 equiv), DMF-H_2O (1:1)	18	**9**	n.a.	74
5	Oxone (0.56 equiv), DMF-H_2O (1:1), reflux	0.5	**10**	n.a.	78
6	*m*-CPBA (1.0 equiv), CH_2CH_2; then PhMe, reflux[b]	0.5	**10**	n.a.	93
7	*m*-CPBA (1.0 equiv), PhMe, 0 °C to reflux	0.5	**10**	n.a.	96



[a] Determined by ^1H NMR. [b] Compound **8** was treated with *m*-CPBA in CH_2Cl_2 for 30 min, the solvent was evaporated, PhMe was added, and the mixture was refluxed for 30 min. n.a. = not applicable.

To do this, compound **8** was prepared from acryloyl chloride, benzaldehyde, and lithium thiophenolate using our previously established method.[9] Gratifyingly, when this compound was treated with *m*-CPBA, the desired mono-oxidation product (**9**) was obtained as a mixture of diastereomers, with neither overoxidation of the thioester nor the retro-aldol reaction detected (Scheme 2).[13] On heating, the desired elimination product was readily obtained in excellent yield (**9** → **10**). In total, the process required 1.5 h of reaction time and gave a

(9) Zhou, G.; Yost, J. M.; Sauer, S.; Coltart, D. M. *Org. Lett.* **2007**, *22*, 4663–4665.

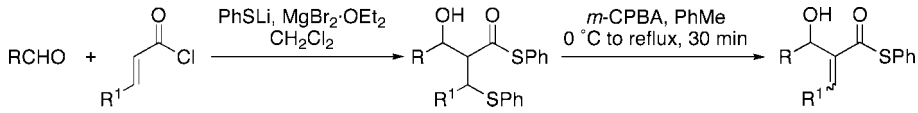
(10) Yost, J. M.; Zhou, G.; Coltart, D. M. *Org. Lett,* **2006**, *8*, 1503–1506. Zhou, G.; Yost, J. M.; Coltart, D. M. *Synthesis* **2007**, 478–482.

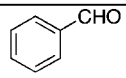
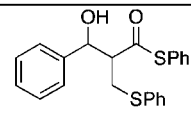
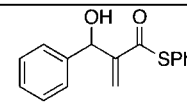
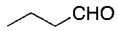
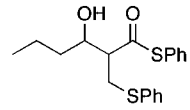
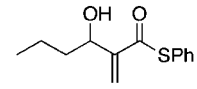
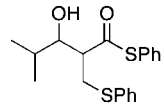
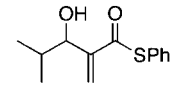
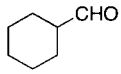
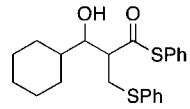
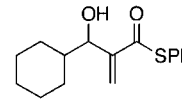
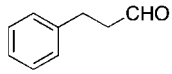
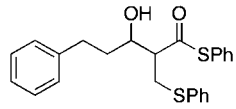
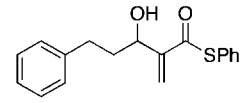
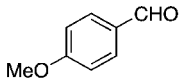
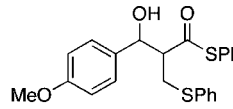
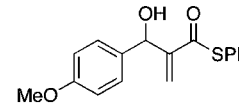
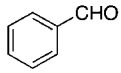
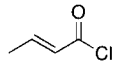
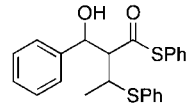
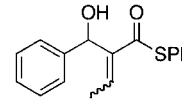
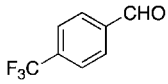
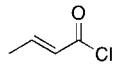
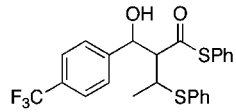
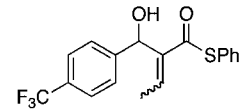
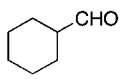
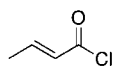
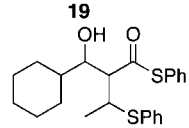
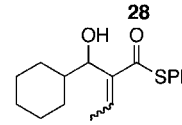
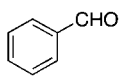
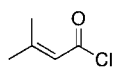
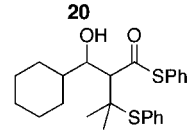
(11) For related applications of this strategy, see: Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117–8119. Danishefsky, S. J.; Armistead, D. M. *Tetrahedron Lett.* **1987**, *28*, 4959–4962. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274–278. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361–364.

(12) For applications of α,β-unsaturated thioesters in MBH-like processes, see, for example: Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 1856–1857. Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsujiyama, S.-i.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.-i. *Synlett* **1999**, 197–198.

(13) The corresponding sulfone (**11**) was obtained from this reaction in 7% yield due to the presence of a slight excess of *m*-CPBA.

Table 2. Four-Component Direct Aldol Addition Reaction and Oxidative-Elimination Sequence



entry	aldehyde	acid chloride	aldol product	time (h)	yield (%)	elimination product	*E*:*Z* [a]	yield (%)
1			 **8**	0.5	88	 **10**	n.a	96
2			 **13**	0.5	71	 **22**	n.a	77
3			 **14**	0.5	76	 **23**	n.a	84
4			 **15**	0.5	81	 **24**	n.a	81
5			 **16**	0.5	71	 **25**	n.a	88
6			 **17**	2.0	80	 **26**	n.a	99
7			 **18**	2.0	68	 **27**	1:2.3	96
8			 **19**	2.0	86	 **28**	1:2.3	94
9			 **20**	1.0	61	 **29**	1:2.2	88
10			 **21**	4.0	no reaction	n.a.	n.a	n.a

[a] n.a. = not applicable.

76% overall yield. By comparison, the Baylis−Hillman reaction between methyl acrylate and benzaldehyde conducted neat using DABCO as the catalyst has been reported to give 39% yield of **12** after 6 days.[14−16]

To simplify the oxidative-elimination process, we set out to develop a direct, one-pot protocol to circumvent isolation and purification of the sulfoxide intermediate. Thus, a variety of oxidizing conditions were surveyed using compound **8**

as a model substrate (Table 1). Use of $NaIO_4$ gave only modest yields of the desired elimination product in standard solvents (entries 1−3), and when MeOH was used a considerable amount of the *S*→*O* acyl transfer product was obtained (entry 1). Oxone proved to be an effective oxidant for the transformation, providing a very good yield of the desired product (entries 4 and 5), as did *m*-CPBA (entries 6 and 7), which gave even better yields.

Having developed effective conditions for the oxidative-elimination sequence, we examined the scope of the four-component aldol addition reaction further. This was done using a variety of aldehydes and α,β-unsaturated acid chlorides (Table 2), in addition to those that we had examined previously (entries 1−5).[9] The four-component direct aldol addition proved very general and provided the desired products in a reasonably short period of time (30 min to 2 h), with both electron-rich and electron-poor aldehydes. Hindered α-disubstituted aldehydes were also amenable to the cascade sequence and gave very good product yields (entries 3 and 4). Notably, as we had hoped, the thiolate-promoted aldol addition reaction proceeded effectively even in the case of the β-substituted α,β-unsaturated acid chloride, crotonoyl chloride (entries 7−9). An especially interesting example appears in entry 9 where a hindered α-disubstituted aldehyde and a β-substituted α,β-unsaturated acid chloride gave the desired aldol product in good yield. The success of the aldol addition in these hindered systems prompted us to examine the β-disubstituted system, 3-methylbutenoyl chloride (entry 10), but the reaction was not successful with this very hindered system.

Lastly, we undertook the conversion of the aldol addition products into the corresponding α-alkenyl-β′-hydroxy thioesters using the oxidative-elimination protocol developed above. We were pleased to find that this transformation also proved both general and reliable (Table 2). In all cases, the elimination product was produced in very good to excellent yield, within only 30 min. Entries 7−9 are especially noteworthy as the products obtained equate to MBH couplings that would be extremely difficult, if not impossible, to achieve under conventional conditions.

In conclusion, we have developed a reliable, practical, and general alternative to the MBH reaction that provides straightforward access to α-alkenyl-β′-hydroxy thioesters. Unlike the traditional MBH reaction, this procedure is consistently rapid and high yielding and is amenable to the use of both electron-rich and electron-poor aldehydes. Moreover, it can be applied in situations involving both sterically hindered aldehydes and β-substituted α,β-unsaturated acid chlorides, thus providing access to structures that would be difficult or impossible to generate using conventional MBH reaction conditions.

Acknowledgment. E.M.T. and G.Z. hold C. R. Hauser Fellowships (Department of Chemistry, Duke University); D.L. holds a Burroughs Wellcome Fellowship (Department of Chemistry, Duke University).

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.

OL801896Q

(14) Perlmutter, P.; Puniani, E.; Westman, G. *Tetrahedron Lett.* **1996**, *37*, 1715–1718.

(15) Recently, the same transformation has been reported to give 85% yield after 3 days, although details of the reaction conditions used were not given. See: Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2015–2017.

(16) The Baylis−Hillman reaction of *S*-phenyl thioacrylate has been reported to proceed extremely slowly and/or give numerous byproduct with various aldehydes. See: Shi, M.; Li, C.-Q.; Jiang, J.-K. *Helv. Chim. Acta* **2002**, *85*, 1051–1057.