ORGANIC LETTERS

2010
Vol. 12, No. 10
2418−2421

Morita−Baylis−Hillman Reaction of Lactams and Lactones with Alkyl Halides and Epoxides Catalyzed by Hydroxysulfides

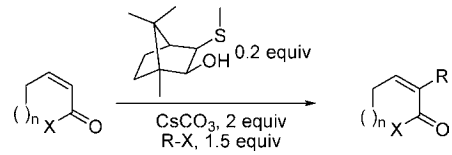
Irene Suarez del Villar, Ana Gradillas, Gema Domínguez, and Javier Pérez-Castells*

Facultad de Farmacia, Dpto. Química, Universidad San Pablo CEU, Urb. Montepríncipe, ctra. Boadilla km 5, 300 Boadilla del Monte, 28668 Madrid, Spain

jpercas@ceu.es

Received April 6, 2010

ABSTRACT



A new Morita−Baylis−Hillman reaction methodology in which alkyl halides and epoxides act as electrophiles in their reaction with lactones and lactams is shown. Catalysis is efficiently performed by hydroxy sulfides under basic conditions. The procedure works efficiently with many alkyl halides but fails with aldehydes with which a conventional acid-catalyzed procedure is used.

The Morita−Baylis−Hillman reaction (MBH) can be defined as a reaction between the α position of an activated alkene and an electrophile that generally contains an sp^2 electron-deficient carbon atom, catalyzed most times by a tertiary amine. The generally accepted mechanism consists of a Michael addition and subsequent elimination of the amine.[1]

Typical substrates for the MBH reaction are activated alkenes like alkyl vinyl ketones, alkyl acrylates, acrylonitrile, vinyl sulfones, acrylamides, allenic esters, vinyl sulfonates, vinyl phosphonates, and acrolein. As electrophiles, aldehydes have been exhaustively studied in the MBH reaction. In addition, α-keto esters, diketones, activated alkenes, and amidines give MBH adducts. In particular, imines also can take part in the reaction if they are activated adequately. In this case, the process is called aza-Morita−Baylis−Hillman.[2] DABCO is the most widely used catalyst, but other tertiary amines such as DBU or quinuclidine and phosphines can also catalyze the reaction.[3] The asymmetric version is carried out mostly using chiral amines.[4]

Sulfur-containing catalysts are able to mediate in MBH reactions, although they have been scarcely used. The first studies of MBH reactions with sulfur catalysts were realized in 1998 by Kataoka.[5] This group described the reaction of catalytic sulfides and stoichiometric quantities of Lewis acid $TiCl_4$ to carry out MBH reactions between a Michael acceptor and an aldehyde. The asymmetric version of the MBH reaction catalyzed by sulfur compounds has been used

(1) Reviews: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (b) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574. (c) Basavaiah, D.; Rao, K.; Venkateswara, R.; Raju, J. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588. (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062.

(2) Reviews on aza-MBH: (a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48. (b) Shi, Y. S.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905–2916.

(3) For recent appications of phosphine-catalyzed MBH-type reactions, see: (a) Webber, P.; Krische, M. J. *J. Org. Chem.* **2008**, *73*, 9379–9387. (b) Koech, P. K.; Krische, M. J. *Tetrahedron* **2006**, *62*, 10594–10602. (c) Koech, P. K.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 5350–5351. (d) Jellerich, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758–7759.

(4) (a) Krishna, P. R.; Sachwani, R.; Reddy, P. *Synlett* **2008**, *289*, 7–2912. (b) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628.

(5) (a) Kataoka, T.; Iwama, T.; Tsujiyama, S.-I. *Chem. Commun.* **1998**, 197–198. (b) Kataoka, T.; Iwama, T.; Tsujiyama, S.-I.; Iwamura, T.; Watanabe, S.-I. *Tetrahedron* **1998**, *54*, 11813–11824.

10.1021/ol100788g
Published on Web 04/23/2010

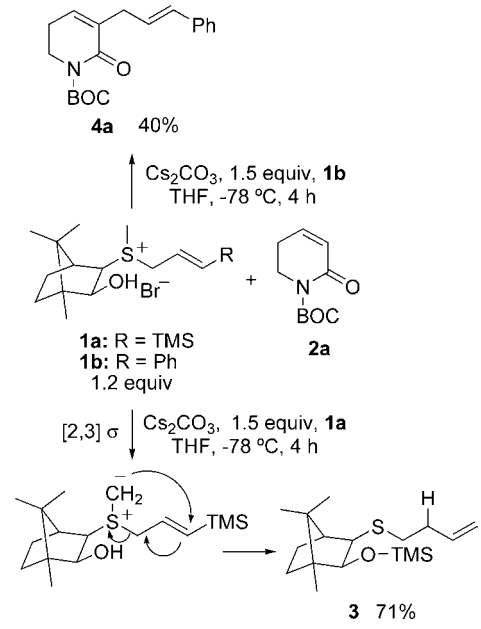
for the synthesis of allylic chiral alcohols.[6] Kataoka used several chiral sulfides and selenides that contained a hydroxy group or an ether. They achieved low enantiomeric excesses, and in some cases, the yields were low. The authors attributed the low yields to the formation of titanium alkoxides that disabled the MBH.[7] Miller recently reported the use of sulfur-based nucleophiles in asymmetric Rauhut−Currier reactions[8] also developed by Krische wherein tethered enones serve as electrophiles.[9]

Alkyl halides have only been used as electrophiles in the MBH reaction in a few works, in which it is said that they have a poor reactivity. The first example is due to Basavaiah's group and consisted of an intermolecular reaction of an allyl halide, 2-bromomethyl-2-propenoate, and various Michael acceptors.[10] On the other hand, in the second precedent, Krafft's group developed the synthesis of cyclic 5- and 6-membered ketones from chlorides derived from primary and secondary allylic alcohols through an intramolecular MBH reaction.[11] Therefore, the intermolecular sulfide catalyzed MBH reaction, using alkyl bromides as electrophiles and lactams or lactones as substrates, lacks precedent.

In the present study, we describe the behavior of lactams and lactones in their MBH reactions with alkyl halides and epoxides using sulfides as catalysts. Several studies have demonstrated that the formation of a hydrogen bond in the reaction intermediate can favor the reaction rate. A good example of this consisted of the introduction of a hydroxy group at the terminal position of alkyl acrylates in their reaction with benzaldehyde using DABCO as catalyst.[12] We envisioned the possibility of using sulfides bearing a suitable situated hydroxy group to promote the MBH reaction using alkyl halides as electrophiles. We used basic conditions to aid in the elimination of the sulfide avoiding the presence of Lewis acids. In principle, the main problem could be the competence with a cyclopropanation reaction that uses similar reaction conditions.[13]

The sulfonium salts **1a**,**b**, described by Tang, were selected as their synthesis was straightforward and their chirality could be used further to induce asymmetry in the reaction with aldehydes or imines.[10] We performed the reaction of lactam **2a** with an excess of these sulfonium salts, using cesium carbonate as the base to study the competition between the MBH and the cyclopropanation reactions. The reaction with **1a** led to the [2,3]-sigmatropic reorganization product **3** together with starting material (Scheme 1).[10] On the other hand, the reaction with **1b** provided the MBH adduct with a moderate yield, recovering 36% of **2a** not detecting any cyclopropanation products (Scheme 1, Table 1, entry 1).

Scheme 1. Reaction of Lactam **2a** with Sulfonium Salts

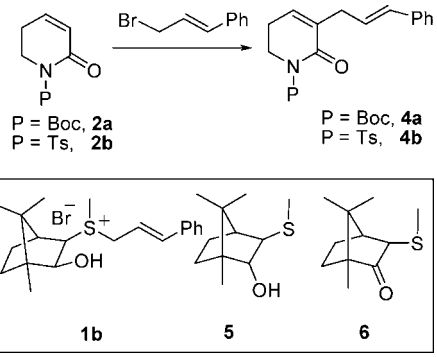


Although this preliminary result was not completely satisfactory, it encouraged us in searching for new conditions, if possible catalytic, that improved the yields. Thus, we carried out the reaction of **2a** with 0.2 equiv of sulfonium salt **1b** and 1.5 equiv of 3-phenylallyl bromide. The temperature was determinant in this reaction since at 0 °C only 15% of the final product was formed (Table 1, entry 2), whereas at 80 °C the yield raised to 56% (entry 3). With substrate **2b**, a low yield was observed at room temperature (entry 4, 38%) that increased to 65% at 80 °C (entry 5). The next step was verifying the behavior of sulfide **5** as the catalyst. The reaction of compound **2b** with 0.2 equiv of **5** provided the product **4b** with good yield (entry 6, 75%), which became excellent on prolonging the reaction time to 12 h (entry 7, 89%). Then, we verified the crucial role of the base. The reaction in the absence of cesium carbonate scarcely took place though the product was detected in the crude mixture (entry 8). An essential question in this development was to justify the need of the presence of the hydroxyl group on the catalyst. When we used ketone **6** as catalyst, only starting material was recovered (entries 9 and 10). In addition, THT proved to be unable to catalyze this reaction as no conversion was observed even with stoichiometric quantities of this reagent (entries 11 and 12). Finally, the conditions of entry 6, applied to compound **2a**, gave **4a** in high yield (entry 13, 85%).

After this initial work, we studied the scope of the process so that we reacted compound **2b** with various alkyl

(6) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049–3052.
(7) (a) Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S.-I.; Iwamura, T.; Watanabe, S.-I.; Muraokab, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725–4731. (b) Iwama, T.; Tsujiyama, S.; Kinoshita, H.; Kanematsu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.-I.; Kataoka, T. *Chem. Pharm. Bull.* **1999**, *47*, 956–961. (c) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Kanematsu, K.; Iwamura, T.; Watanabe, S.-I. *Chem. Lett.* **1999**, 257–258.
(8) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256–257.
(9) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403.
(10) (a) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. *J. Org. Chem.* **2002**, *67*, 7135–7137. (b) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85–87.
(11) (a) Krafft, M. E.; Haxell, T. F. N. *J. Am. Chem. Soc.* **2005**, *127*, 10168–10169. (b) Krafft, M. E.; Seibert, K. A. *Synlett* **2006**, 3334–3336. (c) Krafft, M. E.; Seibert, K. A.; Haxell, T. F. N.; Hirosawa, C. *Chem. Commun.* **2005**, 5772–5774. (d) Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Abboud, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4174–4175.
(12) (a) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, 285–293. (b) Basavaiah, D.; Sarma, P. K. *Synth. Commun.* **1990**, *20*, 1611–1615.
(13) Ye, S.; Huang, Z. Z.; Xia, C.-A.; Tang, Y.; Dai, L.-X. *J. Am. Chem. Soc.* **2002**, *124*, 2432–2433.

Table 1. Reaction Conditions for the MBH Reaction of Lactams **2a**,**b**

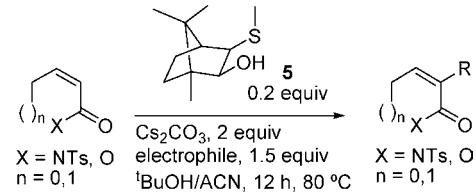


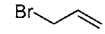
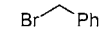
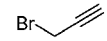
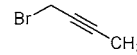
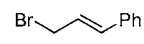
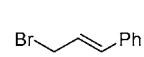
entry	P	cat. (equiv)	Cs_2CO_3 (equiv)	time (h)	temp (°C)	yield (%) 2a,b	yield (%) 4a,b
1	Boc	**1b** (1.2)[a]	2	96	rt	44	36
2	Boc	**1b** (0.2)	2	24	0	70	15
3	Boc	**1b** (0.2)	2	2	80	10	56
4	Ts	**1b** (0.2)	2	36	rt	50	38
5	Ts	**1b** (0.2)	2	2	80	5	65
6	Ts	**5** (0.2)	2	2	80		75
7	Ts	**5** (0.2)	2	12	80		89
8	Ts	**5** (0.2)		96	80	90	<5
9	Ts	**6** (0.2)		12	80	100	
10	Ts	**6** (0.2)	2	12	80	98	
11	Ts	**THT**[b] (0.2)	2	12	80	100	
12	Ts	**THT**[b] (1.2)	2	12	80	80	
13	Boc	**5** (0.2)	2	2	80		85

[a] Conditions: 1.5 equiv of 3-phenylallyl bromide (except for entry1, in which no halide was added), CH_3CN/^{t}BuOH (2.5:1) as solvent. [b] THT = tetrahydrothiophene.

halides under our best conditions (entry 7, Table 1).[14] The results are summarized in Table 2. The reaction with allyl bromide, benzyl bromide, and methyl iodide gave products **4c**, **4d**, and **4e** with good yields (entries 1−3). In the case of cyclopropyl bromide (entry 4), though we tried different conditions, changing the temperature and the reaction time, we were not able to obtain any positive results, always recovering the starting material. Propargyl bromide did not react, possibly due to interference of the hydrogen of

Table 2. MBH Reaction of Lactones and Lactams with Different Electrophiles



entry	substrate	electrophile	R	prod	yield (%) 2a-b	yield (%) 4a-b
1	**2b**		$CH_2CH{=}CH_2$	**4c**	10	82
2	**2b**		CH_2Ph	**4d**	-	90
3	**2b**	CH_3I	CH_3	**4e**	-	96
4	**2b**		n.r.		-	99	0
5	**2b**		n.r.		-	99	0
6	**2b**		$CH_2C{\equiv}CCH_3$	**4f**	29	67
7	**2b**		$CH_2CHOHCH_3$	**4g**	32	63
8	**2b**		n.r.		99	0
9			$CH_2CH{=}CH$-Ph	**4h**	--	48
10			$CH_2CH{=}CH$-Ph	**4i**	--	68

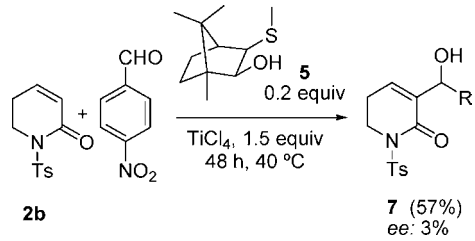
the triple bond. Moreover, 2-butyne bromide gave the desired adduct **4f** with good yield (entries 5 and 6). On the other hand, since the epoxides are excellent electrophiles, we studied the reaction of **2b** with propylene oxide, which provided product **4g** with 63% yield (entry 7), whereas we could not detect any products in the reaction with styrene oxide (entry 8).[15] Finally, we applied the reaction to lactones, in particular, 5,6-dihydro-2-pyranone and 2-(5*H*)-furanone (entries 9 and 10), obtaining the MBH aducts **4h**,**i** with acceptable yields. In these cases, no starting product was recovered.

Finally we explored the feasibility of our procedure for the synthesis of MBH adducts using aldehydes as electrophiles. As aromatic aldehydes bearing electron-withdrawing groups are those that react better in these reactions, we selected *p*-nitrobenzaldehyde which was reacted with **2b** (Scheme 2). Under our experimental conditions the MBH reaction did not take place, so we used a Lewis acid to activate the aldehyde instead of the base. Thus, in the

(14) **General Procedure for the MBH Reaction with Alkyl Halides.** To a solution of the catalyst **5** (0.2 equiv) and the α,β-unsaturated lactone or lactam (1 equiv) in CH_3CN/^{t}BuOH (2.5:1) were added Cs_2CO_3 (2 equiv) and the electrophile (1.5 equiv). The resulting mixture was heated to 40 °C and stirred until the reaction was complete (TLC). The solvent was then eliminated under vacuo, and the resulting crude oil was purified by column chromatography on silica gel. Synthesis of **1-[(4-methylphenyl)sulfonyl]-3-[(2*E*)-3-phenyl-2-propen-1-yl]-5,6-dihydro-(1*H*)-2-pyridinone, 4b.** Following the general procedure (Table 1, entry 7), from compound **2b** 50 mg (0.19 mmol), (*E*)-3-bromo-1-phenylpropene (56 mg, 0.3 mmol), and 8 mg of **5** (0.03 mmol), reaction time 12 h at 80 °C, 64 mg (89%) of **4b** was obtained as a colorless oil (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3); 2.50 (d, 2H, J = 4.9 Hz, CH_2); 3.06 (d, 2H, J = 7.3 Hz, CH_2); 4.43 (t, 2H, J = 6.3 Hz, CH_2); 6.06−6.14 (m, 1H, CH═); 6.33 (d, 1H, J = 16.1 Hz, CH═); 6.53−6.56 (m, 1H, CH═); 7.18−7.31 (m, 7H, ArH); 7.91 (d, 2H, J = 8.3 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 25.1, 32.9, 44.1, 126.0, 126.3, 127.2, 128.4, 128.5, 129.4, 132.4, 134.3, 136.0, 137.0, 139.3, 144.6, 163.8. IR (film) 3010, 2920, 1800, 1680, 1590, 1489, 1462, 1440, 1345, 1278, 1160, 1100 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_3S$ (367.46): C, 68.64; H, 5.76; N, 3.81. Found: C, 68.56; H, 5.57; N, 3.65.

(15) The only precedent in the use of epoxides in MBH reactions is an intramolecular phosphine-catalyzed reaction: Krafft, M. E.; Wright, J. A. *Chem. Commun.* **2006**, 2977–2979.

Scheme 2. MBH Reaction of **2b** with *p*-Nitrobenzaldehyde



presence of 1.5 equiv of $TiCl_4$ at 40 °C we obtained a 57% of the MBH adduct **7**, observing hardly no induction.[16]

(16) The ee was 3%, determined by HPLC using a CHIRAL-AGP column (100 × 4.0 mm); with 9% 2-propanol in 10 mM sodium phosphate buffer as mobile phase; pH = 7.0; flow rate = 0.9 mL/min.

In conclusion, a new MBH methodology where alkyl halides and epoxides act as electrophiles in their reaction with lactones and lactams is shown. Catalysis is efficiently performed by hydroxy sulfides. Extension of this procedure to other substrates is underway in our laboratories.

Acknowledgment. Funding of this project by the Spanish MEC (No. CTQ2009-007738/BQU) and FUSP-CEU (PC16/09) is acknowledged. I.S.-V. thanks the Fundación San Pablo-CEU for a predoctoral fellowship.

Supporting Information Available: Experimental procedures, spectroscopic data, and spectra for compounds **4a**,**c**−**i** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100788G