J. Braz. Chem. Soc., Vol. 20, No. 3, 564-568, 2009.
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0103 - 5053 $6.00+0.00

Short Report

A Highly Efficient and General Method for the Preparation of (*Z*)-Allylic Bromides Derived from Morita-Baylis-Hillman Adducts

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(*Z*)-2-(Bromometil)-2-alcenoatos são importantes intermediários sintéticos e foram preparados de forma simples e prática pelo tratamento de α-metileno-β-hidroxiésteres (produtos da reação de Morita-Baylis-Hillman) com LiBr/H_2SO_4 em acetonitrila à temperatura ambiente. Além de fornecer altos rendimentos e de tolerar a presença de diversos grupos funcionais, esta nova metodologia utiliza reagentes baratos e não faz uso de HBr.

Representative (*Z*)-2-(bromomethyl)-2-alkenoates were easily prepared in high yield by treating α-methylene-β-hydroxyesters (Morita-Baylis-Hillman adducts) with LiBr/H_2SO_4 in acetonitrile at room temperature. Besides the tolerance to many diverse functional groups, this new methodology employs inexpensive reagents and avoids the use of HBr.

Keywords: Morita-Baylis-Hillman reaction, α-methylene-β-hydroxyesters, (*Z*)-allylic bromides, *N*-allyl acetamides

Introduction

Allylic bromides **1** are versatile building blocks of many important substances including natural products, heterocycles and biologically-active molecules[1-13] (Scheme 1). These multifunctional compounds can be prepared from α-methylene-β-hydroxyesters **2**, which are easily obtained by the well-recognized Morita-Baylis-Hillman reaction.[14-17]

Scheme 1

Typically, the method of choice for the direct conversion of adduct **2** to the corresponding (*Z*)-allylic bromide **1** relies on the combination of 48% HBr and conc. H_2SO_4 in CH_2Cl_2 at low temperature.[18] In spite of the fairly good yields often achieved for this transformation, the required use of large quantities of noxious hydrobromic acid is a major disadvantage due to safety and environmental concerns. Alternative methods for converting alcohol **2** to bromide **1** include the use of NBS/Me_2S,[12] PBr_3,[19] $Br(Me_2)S^+Br^-$,[20] and also bromine salts immobilized in ionic liquids[21] or in the presence of solid catalysts such as montmorillonite KSF clay,[22] Amberlyst-15,[23] silica gel-supported $NaHSO_4$,[24] and silica gel alone under microwave irradiation.[25] Although all the above procedures have their own applications, many of them suffer from one or more drawbacks such as the use of harmful conditions, high temperatures, special equipment or commercially unavailable reagents or catalysts, eventually leading to long reaction times or low yields. Consequently, there is a great need to develop a simple and general method for the synthesis of allylic bromides **1**.

In a continuation of our work on the Morita-Baylis-Hilllman reaction,[26-29] herein we present a straightforward methodology for high-yield preparation of (*Z*)-allylic bromides **1** using LiBr/H_2SO_4 in acetonitrile at room temperature.

Results and Discussion

α-Methylene-β-hydroxyester **2a**[30] was submitted to a variety of reaction conditions in order to achieve optimal conversion to allylic bromide **1a**. Initially, treatment of alcohol **2a** with conc. HBr (48%, from a freshly-opened bottle) in acetonitrile or dichloromethane during 24 h led only to negligible yields (< 20%) of (*Z*)-allylic bromide **1a**. On the other hand, a combination of sulfuric acid and

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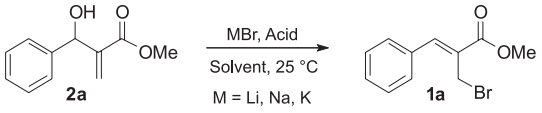
lithium bromide in acetonitrile as the solvent showed promising results even with nearly stoichiometrically amounts of reagents (Table 1, entry 1). Increasing the amount of either sulfuric acid or lithium bromide led to an improvement in the reaction rate (entries 2 and 3), but a two-fold excess of both the acid and the bromine salt caused a slight diminution in the conversion (entry 4). After some experimentation we found that an optimized ratio of 2.0 equiv. LiBr to 2.5 equiv. H_2SO_4 resulted in an excellent conversion to (*Z*)-allylic bromide **1a** after a short time (Table 1, entry 5).

Reaction rates were also strongly influenced by the nature of the solvent (or solvent combination) used, with acetonitrile being highly superior to acetone, THF and aqueous combinations (Table 1, entries 6-9). The strength of the acid required to mediate the transformation was evaluated in control reactions by replacement of sulfuric acid with phosphoric acid or *para*-toluenesulfonic acid (TsOH). In spite of the moderate conversion observed for TsOH after a reasonable period (Table 1, entry 10), the result with H_3PO_4 was unsatisfactory (entry 11).

Finally, a competitive reaction took place when NaBr and KBr were tested as the source of bromide (Table 1, entries 12 and 13). Besides the lower conversions to **1a**, the starting alcohol **2a** was totally consumed to generate an inseparable mixture of isomeric *N*-allyl acetamides **3/4** in a 1.5:1 ratio (Scheme 2). The competitive formation of allylic acetamides **3/4** was confirmed by running the reaction in the absence of any bromine salt, which resulted in the expected 1.5:1 mixture of acetamides **3/4** (Table 1, entry 14). Participation of adduct **2** in this Ritter-type reaction has been recently described using either sulfonic acid or Amberlist-15 under reflux for hours,[31,32] but in our case the acetamide **3** was obtained at ambient temperature after a few minutes as a mixture with the unexpected isomer **4**. Unfortunately, attempts to separate the isomers by chromatography were unsuccessful.

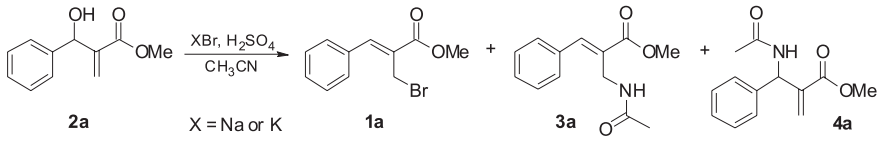
The best condition found for converting α-methylene-β-hydroxyester **2a** into (*Z*)-allylic bromide **1a** (Table 2, entry 1) was further extended to other representative Morita-Baylis-Hillman adducts **2**. As can be seen from data in Table 2, good to excellent yields were obtained in all cases regardless the substitution pattern on the starting α-methylene-β-hydroxyester **2**. However, a distinct difference in reactivity was clearly detected. Substrates containing electron-donating groups were the most reactive under Condition A (2.0 equiv. LiBr, 2.5 equiv. H_2SO_4) and gave the corresponding bromides **1b-e** quantitatively after a few minutes (Table 2, entries 2-5). This high reactivity allowed a reduction in the amount of LiBr to nearly 1 equiv. without compromising the reaction rate or yield (results not shown).

Table 1. Conversion of α-methylene-β-hydroxyester **2a** to (*Z*)-allylic bromide **1a** under different conditions



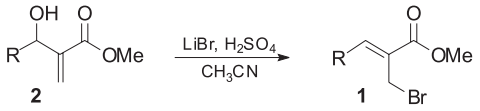
Entry	Salt (equiv.)	Acid (equiv.)	Solvent system	time / h	Conversion to **1a** / (%)[a]
1	LiBr (1.1)	H_2SO_4 (1.0)	CH_3CN	1	66
2	LiBr (2.0)	H_2SO_4 (1.0)	CH_3CN	1	78
3	LiBr (1.1)	H_2SO_4 (2.0)	CH_3CN	1	90
4	LiBr (2.0)	H_2SO_4 (2.0)	CH_3CN	1	85
5	LiBr (2.0)	H_2SO_4 (2.5)	CH_3CN	1	100
6	LiBr (2.0)	H_2SO_4 (2.5)	Acetone	1.5	50
7	LiBr (2.0)	H_2SO_4 (2.5)	THF	1.5	5
8	LiBr (2.0)	H_2SO_4 (2.5)	CH_3CN/H_2O (3:1)	1.5	0
9	LiBr (2.0)	H_2SO_4 (2.5)	Acetone/H_2O (3:1)	1.5	0
10	LiBr (2.0)	TsOH (2.0)	CH_3CN	7	70
11	LiBr (2.0)	H_3PO_4 (2.5)	CH_3CN	24	10
12	NaBr (2.0)	H_2SO_4 (2.5)	CH_3CN	1	75 [25][b]
13	KBr (2.0)	H_2SO_4 (2.5)	CH_3CN	5	38 [62][b]
14	-	H_2SO_4 (2.5)	CH_3CN	0.2	0 [100][b]

[a]Conversion determined by ^{1}H NMR (400 MHz, $CDCl_3$); [b]Numbers in brackets refer to the relative amount of isomeric allyl acetamides **3/4** formed as an inseparable mixture (1.5:1 ratio).



Scheme 2

Table 2. Synthesis of (*Z*)-allylic bromides **1** from alcohols **2** using LiBr/H_2SO_4 in acetonitrile



Entry	Allylic bromide	R	Condition[a]	time / h	Yield / (%)[b]
1	**1a**	C_6H_5	A	1	90
2	**1b**	2-$C_{10}H_7$	A	0.5	95
3	**1c**	4-$CH_3OC_6H_4$	A	0.5	91
4	**1d**	3,4-$(CH_3O)_2C_6H_3$	A	0.5	95
5	**1e**	3,4-$(OCH_2O)C_6H_3$	A	0.5	87
6	**1f**	4-ClC_6H_4	A	2	91
7	**1g**	2-ClC_6H_4	A	4	80
8	**1g**		B	3	89
9	**1h**	2,4-ClC_6H_3	A	24	88
10	**1h**		B	3	91
11	**1i**	4-$NO_2C_6H_4$	A	24	82
12	**1i**		B	5	87
13	**1j**	3-$NO_2C_6H_4$	B	5	75
14	**1k**	CH_3	A	1	85
15	**1l**	CH_3CH_2	A	1	76

[a]Condition A: 2.0 equiv. LiBr, 2.5 equiv. H_2SO_4, acetonitrile, 25 °C. Condition B: 4.0 equiv. LiBr, 5.0 equiv. H_2SO_4, acetonitrile, 25 °C; [b]Isolated yields after purification by column chromatography.

On the other hand, chloro-substituted derivatives were less reactive and acceptable yields were only obtained after a prolonged time at room temperature (Table 2, entries 7 and 9). In an effort to improve the conversion rate by using higher amounts of reagents, **2g** and **2h** were treated with 4.0 equiv. LiBr and 5.0 equiv. H_2SO_4 (Condition B). Indeed, this more extreme condition led to the corresponding bromides **1g** and **1h** in better yields after shorter periods (entries 8 and 10). As expected, nitro-substituted adducts **2i**,**j** were the most unreactive substrates under Condition A (entry 11), but good yields in reasonable time were achieved with Condition B (entries 12 and 13). Finally, alkyl-substituted substrates **2k**,**l** were also successful transformed in the corresponding bromides **1k**,**l** by employing Condition A (entries 14 and 15), thus demonstrating the generality of the method.

The anticipated *Z*-stereochemistry assigned to all allylic bromides **1** was based on the characteristic NMR shift of the highly deshielded β-olefinic hydrogen cis to the carboxyl group[15,18,22-24] and also on the previous X-ray crystallography analysis of **1e**.[33] Products were obtained nearly pure and no signals for an elusive formation of *E*-isomer was ever detected.

Conclusions

An efficient methodology to access representative (*Z*)-2-(bromomethyl)-2-alkenoates **1** based on readily available reagents and simple experimental conditions has been developed. The high yields and excellent *Z*-stereoselectivity observed in all cases, even for substrates carrying electron-withdrawing groups, makes this method very attractive and expands the potential applicability of allylic bromides in synthesis. Mechanistic studies dealing with the formation of **1** and their use in synthetic transformations are currently under investigation.

Experimental

General procedures

All chemicals were of reagent grade (Aldrich, CarloErba, JTBaker, Nuclear, Riedel, Strem) and were used as received. Melting points were determined using a Microquímica MQPF301 apparatus and are uncorrected. Infrared spectra were acquired with a Perkin-Elmer FTIR 1600 spectrometer using KBr for solids and film for liquid samples (range 4000-400 cm^{-1}). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz, fully decoupled) spectra were recorded with a Varian AS-400 spectrometer. Samples were prepared in $CDCl_3$ solution containing 1-2% tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in parts *per* million (δ) relative to TMS. Elemental analyses were conducted in Carlo Erba CHNS EA-1110 equipment by UFSC-Central Analítica, Departamento de Química, Florianópolis, SC, Brazil. Purifications by column chromatography were performed with silica gel (Aldrich, 100-200 mesh particle size). Compounds **2a**,**b**,**c**,**e**,**f**,**h**,**i**,**j**,**k**,**l** were prepared according to the known methods and showed physical and spectral data in accordance with their expected structure and by comparison with data in literature.[11,29,30,33-36]

*Methyl 3-hydroxy-2-methylene-3-(3,4-dimethoxyphenyl) propanoate (**2d**)*

Clear yellow oil; IR (neat) ν_{max}/cm^{-1}: 3496, 3000, 2949, 2839, 1719, 1631, 1512, 1444, 1262, 1145, 1032; ^1H NMR: δ 3.65 (s, 3H), 3.80 (s, 6H), 5.45 (s, 1H), 5.81 (s, 1H), 6.26 (s, 1H), 6.76 (d, *J* 8.0 Hz, 1H), 6.82 (d, *J* 8.0 Hz, 1H), 6.86 (s, 1H); ^{13}C NMR: δ 52.1 (CH_3), 56.0 (2 x CH_3), 72.9 (CH), 110.1 (CH), 111.1 (CH), 119.2 (CH), 125.8 (=CH_2), 134.2 (C), 142.4 (C), 148.8 (C), 149.1 (C), 167.1 (C=O).

*Methyl 3-hydroxy-2-methylene-3-(2-chlorophenyl) propanoate (**2g**)*

Colorless oil; IR (neat) ν_{max}/cm^{-1}: 3437, 3067, 3000, 2953, 1720, 1632, 1440, 1270, 1149, 1032; ^1H NMR: δ 3.74 (s, 3H), 5.58 (s, 1H), 5.95 (s, 1H), 6.31 (s, 1H), 7.19-7.34 (m, 3H), 7.53 (dd, *J* 1.5, 6.0 Hz, 1H), ^{13}C NMR: δ 52.4 (CH_3), 69.4 (CH), 127.2 (=CH_2), 127.3 (CH), 128.4 (CH), 129.2 (CH), 129.7 (CH), 133.0 (C), 138.6 (C), 140.9 (C), 167.2 (C=O).

*Typical procedure for the synthesis of (Z)-2-(bromomethyl)-2-alkenoates (**1**)*

To a stirred solution of a Morita-Baylis-Hillman adduct **2** (5.0 mmol) in 15.0 mL of acetonitrile at 0-5 ºC were added LiBr (Condition A: 10.0 mmol; Condition B: 20.0 mmol) and 96% H_2SO_4 (Condition A: 12.5 mmol; Condition B: 25.0 mmol). The reaction was allowed to warm up and stirring was continued at 25 ºC for the time presented in Table 2. The final mixture was diluted with CH_2Cl_2, and the organic extract was washed with H_2O, sat. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/ethyl acetate 9:1) to give the corresponding allylic bromides **1**. Compounds **1a**,**b**,**e**,**f**,**g**,**i**,**k**,**l** showed physical and spectral data in accordance with their expected structure and by comparison with data in literature.[8,11,18,20-25]

*Methyl (Z)-2-(bromomethyl)-3-(4-methoxyphenyl)-2-propenoate (**1c**)*

White solid; mp 59.6-60.1 ºC; IR (KBr) ν_{max}/cm^{-1}: 3451, 2936, 2836, 1705, 1596, 1507, 1439, 1171, 767; ^1H NMR: δ 3.86 (s, 3H), 3.87 (s, 3H), 4.45 (s, 2H), 6.99 (d, *J* 8.5 Hz, 2H), 7.58 (d, *J* 8.5 Hz, 2H), 7.78 (s, 1H); ^{13}C NMR: δ 27.9 (CH_2), 52.7 (CH_3), 55.7 (CH_3), 114.8 (2 x CH), 126.5 (C), 127.1 (C), 132.3 (2 x CH), 143.3 (=CH), 161.2 (C), 167.3 (C=O). Anal. Calc. for $C_{12}H_{13}BrO_3$ (%): C, 50.55; H, 4.60. Found: C, 50.80; H, 4.60.

*Methyl (Z)-2-(bromomethyl)-3-(3,4-dimethoxyphenyl)-2-propenoate (**1d**)*

White solid; mp 79.1-79.4 ºC; IR (KBr) ν_{max}/cm^{-1}: 3455, 2957, 2832, 1708, 1604, 1509, 1431, 1263, 768; ^1H NMR: δ 3.85 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 4.44 (s, 2H), 6.92 (d, *J* 8.5 Hz, 1H), 7.16 (dd, *J* 2.0, 8.5 Hz, 1H), 7.23 (d, *J* 2.0 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR: δ 28.1 (CH_2), 52.7 (CH_3), 56.2 (CH_3), 56.3 (CH_3), 111.4 (CH), 112.7 (CH), 124.4 (CH), 126.4 (C), 127.2 (C), 143.6 (=CH), 149.2 (C), 150.6 (C), 167.1 (C=O). Anal. Calc. for $C_{13}H_{15}BrO_4$ (%): C, 49.54; H, 4.80. Found: C, 49.78; H, 5.12.

*Methyl (Z)-2-(bromomethyl)-3-(2,4-dichlorophenyl)-2-propenoate (**1h**)*

White solid; mp 75.4-75.7 ºC; IR (KBr) ν_{max}/cm^{-1}: 3416, 3081, 1712, 1616, 1572, 1436, 1280, 765; ^1H NMR: δ 3.91 (s, 3H), 4.24 (s, 2H), 7.37 (dd, *J* 2.2, 8.5 Hz, 1H), 7.47 (d, *J* 2.2 Hz, 1H), 7.66 (d, *J* 8.5 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR: δ 26.2 (CH_2), 53.0 (CH_3), 127.8 (CH), 130.1 (CH), 130.7 (CH), 131.3 (C), 131.7 (C), 135.7 (C), 136.3 (C), 138.6 (=CH), 166.2 (C=O). Anal. Calc. for $C_{11}H_9BrCl_2O_2$ (%): C, 40.78; H, 2.80. Found: C, 40.88; H, 2.84.

*Methyl (Z)-2-(bromomethyl)-3-(3-nitrophenyl)-2-propenoate (**1j**)*

Pale yellow solid; mp 80.5-82.0 ºC; IR (KBr) ν_{max}/cm^{-1}:

3394, 3077, 2952, 1709, 1624, 1532, 1432, 1355, 1299, 1259, 772; ^{1}H NMR: δ 3.92 (s, 3H), 4.33 (s, 2H), 7.68 (t, *J* 7.5 Hz, 1H), 7.84 (s, 1H), 7.92 (d, *J* 7.5 Hz, 1H), 8.27 (d, *J* 7.5 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR: δ 25.5 (CH_2), 53.1 (CH_3), 124.4 (CH), 124.6 (CH), 130.4 (CH), 131.8 (C), 135.2 (CH), 136.1 (C), 140.1 (=CH), 148.9 (C), 166.2 (C=O). Anal. Calc. for $C_{11}H_{10}BrNO_4$ (%): C, 44.02; H, 3.36; N, 4.67. Found: C, 44.06; H, 3.25; N, 4.37.

Acknowledgments

The authors wish to thank Central de Análises (Departamento de Química, UFSC, Florianópolis) for spectroscopic analysis. M.M.S. is grateful to CNPq for a research fellowship. M.F and L.F. are grateful to CAPES and CNPq for fellowships. Financial support by PRONEX-2003 (CNPq/FAPESC) and FAPESC (Santa Catarina State Research Council, Brazil, CON 16060/2007-1) is also gratefully acknowledged.

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Received: October 24, 2008
Web Release Date: February 20, 2009