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Chemoselective addition of organometallics to oxime ethers

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Abstract

In this paper, an efficient method for preparation of various substituted hydroxylamines from aldehydes is reported. We first prepare *O*-trimethylsilyl oxime ether in 5 M solution of lithiumperchlorate in diethyl ether (LPDE 5M) from condensation reaction between aldehyde and *O*-trimethylsilyl hydroxylamine, then add organosilane or organotin nucleophile in the same vessel to preparing the corresponding α-substituted hydroxylamines in one-pot synthesis.

Keywords: Oximes; Organosilane; Chemoselective reactions; Lithiumperchlorate; Multicomponent reaction; Organotin

1. Introduction

In recent years, there has been an increasing interest in multicomponent reactions (MCRs) [1–3]. These reactions are special types in synthetic organic chemistry, in which three or more starting materials react in one vessel to give one product. One of the most important MCRs is mannich-type reactions [4–7]. These three component reactions are interesting and important, not only because of forming two bonds in one reaction, but also because this methodology would be useful for making a broad variety of nitrogen-containing compounds [8,9]. Although the original mannich reaction was carried out with amines, these reactions can be performed with other N-heterosubstituted amines such as hydrazones and oximes [10–14].

In other words, nucleophilic addition to oximes in mannich-type reactions is one of the namely devised methods for preparation of substituted hydroxylamines (such as similar addition to imines, hydrazones, and iminium salts) [15]. If in these reactions the C–C bond is formed, the reaction has a new synthetic importance. Therefore, this procedure can be used for addition of organometallic compounds to oximes and oxime ethers. But the versatility of these reactions is often limited by poor electrophilicity of oximes [16] (vs. carbonyl or imines), tutomeric conversion of substrate that contains α-Hydrogen to enamine-type product, existence of geometric isomerisation (*syn* and *anti*), liability of N–O bond, possibility of addition to both carbon and nitrogen in C=N double bond, and formation of byproducts such as aziridine, nitrile, and Beckmann rearrangement products [17].

Thus, it is very important that one procedure can produce only one of these products in high yield without major formation of other byproducts.

2. Results and discussion

We first *in situ* prepared *O*-trimethylsilyl oxime ether from condensation reaction between aldehyde and *O*-trimethylsilyl hydroxylamine [18] in 5 M solution of lithiumperchlorate in diethyl ether (that we named it LPDE 5M) in 10 min [19], then in the same vessel, added ketene acetal (1-methoxy-1-trimethylsilyloxy-2-methyl propene, **3**) as a nucleophile with trimethylsilyl chloride (TMSCl) for activating oxime ethers [20]. The reaction was completed within 4 h. After this, we purified the product by column chromatography and obtained 3-hydroxyamino esters in

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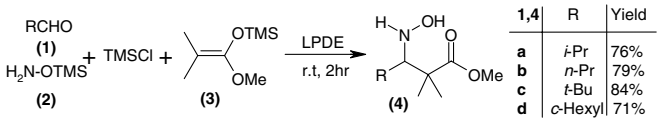
good yield (Scheme 1). These products are very important because of their synthetic utility especially in β-lactam synthesis.

Unfortunately, the reaction was only succeeded with aliphatic aldehydes and with aromatic aldehydes, only oxime ethers produced from this and nucleophilic attack to aromatic oxime ethers can not be observed; because the carbon of C=N double bond in these compounds is less electrophilic than the same carbon in aliphatic oxime ethers. This problem can be arised from aromatic rings, that show a good electron donor property in most case and this property can lower the electrophilicity of C=N double bond of oxime ethers. Therefore, we only succeed at preparation of aliphatic 3-hyroxyamino esters via these reactions.

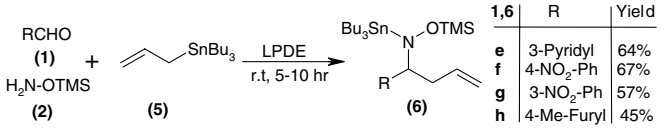
After this, in order to evaluate the scope of this nucleophilic addition to oxime ethers, we decided to add allyltributyltin to oxime ethers with this methodology for synthesis of homoallylic hydroxylamines. In this reaction, after preparing *O*-trimethylsilyl oxime ethers from aldehydes and *O*-trimethylsilyl hydroxylamine, we added equimolar amount of allyltributyltin for *in situ* preparation of homoallylic hydroxylamines in 5–10 h with good yield (Scheme 2).

In Scheme 2, we see an interesting fact; these reactions are only succeeded with aromatic aldehydes (contrary to the reaction of Scheme 1). As a result, although these two reactions are limited to aromatic or aliphatic aldehydes, but these limitations show the chemoselectivity of these reactions. For proving this claim, we perform this reaction with both aliphatic and aromatic oxime ethers (that *in situ* prepared at one vessel), then both nucleophiles; allyltributyltin and ketene acetal/TMSCl were added. After completing the reaction and purification of products, we obtain two major products: aliphatic 3-hyroxyamino esters with aromatic homoallylic hydroxylamine and the amount of aromatic 3-hyroxyamino esters and aliphatic homoallylic hydroxylamine is about zero. So that, we deduced that allyltributyltin only react with aromatic oxime ethers and ketene acetal/TMSCl only react with aliphatic oxime ethers. This chemoselective double reaction is shown in Scheme 3.



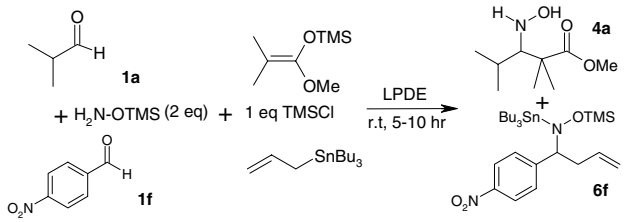
1,4	R	Yield
a	*i*-Pr	76%
b	*n*-Pr	79%
c	*t*-Bu	84%
d	*c*-Hexyl	71%

Scheme 1.



1,6	R	Yield
e	3-Pyridyl	64%
f	4-NO_2-Ph	67%
g	3-NO_2-Ph	57%
h	4-Me-Furyl	45%

Scheme 2.



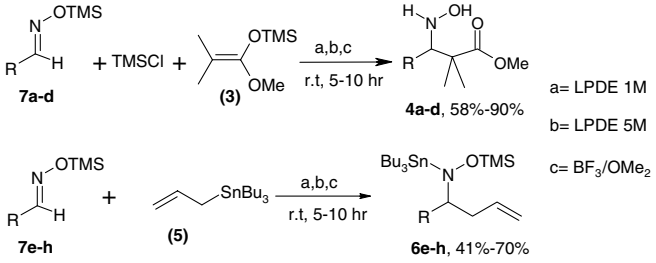
Scheme 3.

When we get these results, we decide to doing additional experiments for examining this chemoselectivity.

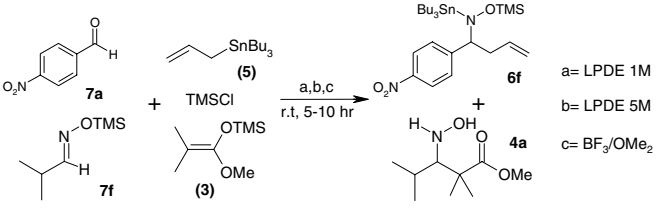
First, we prepared and isolated oxime ethers **7a**–**h** (both aliphatic and aromatic) and react them separately with both allyltributyltin and ketene acetal in some conventional organic media with lewis acid such as LPDE 1M, LPDE 5M and borontrifloride in dimethyl ether. The brief results of these experiments are shown in Scheme 4.

As you see, results of Scheme 4 are perfectly consistent with the results shown in Schemes 1 and 2. This means that even we use pure oxime ether as an initial compound and use various organic solvent and lewis acid, only aliphatic oxime ethers react with ketene acetal and only aromatic oxime ethers react with allyltributyltin to give corresponding products. This results confirm our idea about this chemoselectivity.

For completing our experiments, we make an experiment with one aliphatic **7a** and one aromatic **7f** oxime ether and both nucleophiles in some organic media (the same with Scheme 4). This new experiment (Scheme 5) is the same as experiment shown in Scheme 3 but we used pure oxime ethers as an initial compound versus in situ synthesis of them.



Scheme 4.



Scheme 5.

The results of Scheme 5 confirm our belief about the chemoselectivity of these reactions again, completely consistent with Schemes 1–4, so that we named these reactions: ''chemoselective'' [21].

3. Conclusion

In summary, we wish to report, two chemoselective, one-pot and three or four component reaction between organometallic nucleophiles and oxime ethers for preparing aliphatic 3-hyroxyamino esters and aromatic homoallylic hydroxylamines. These reactions are very clean and the procedures are very easy and consist of simple mixing of the equimolar amounts of an aldehydes, *O*-trimethylsilyl hydroxylamine, and organometallic nucleophiles.

4. Experimental

Starting materials were obtained from Fluka and Merck and were used without further purification. IR spectra were determined as KBr pellets on a shimadzu model 470 spectrophotometer. ^{1}NMR and ^{13}C NMR spectra were recorded using a JEOL FT-90 MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. All yields refer to isolated products after purification.

4.1. General procedure for preparation of 4a–d

To a mixture of aldehydes (2 mmol) in 5.0 M LPDE (3 ml) was added or *O*-trimethylsilyl hydroxylamine (2 mmol) at room temperature. After the mixture stirred for 10 min, keteneacetal (2.2 mmol) and trimethylsilyl chloride (2.5 mmol) was added. After this, the mixture stirring at room temperature for 2 h. The reaction monitored by TLC (1:1 hexane:ethyl acetate). Then the reaction was quenched with saturated sodium bicarbonate (until the pH of aqueous layer reach to 9) and then extracted with dichloromethane. The organic extracts were combined, dried over magnesium sulphate, and concentrated. The crude product was purred by column chromatography with silica gel using a hexane: ethyl acetate gradient from 3:2 to 1:1. ^{1}H NMR, ^{13}C NMR, and IR spectra were entirely consistent with the assigned structures. The physical and spectra data of compounds **4a–d** are as follows.

4.2. Methyl 3-(hydroxyamino)-2,2,4-trimethylpentanoate (4a)

Yellow oil, yield 0.287 g (76%); IR (KBr), ν/cm^{-1}: 3395, 3185 (NH, OH), 2900 (CH), 1710 (C=O), 1450 (C–N), 1379 (N–O). ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.11 (d, $J = 9$ Hz, 6H, H_5), 1.42 (s, 6H, 2Me), 2.89 (m, 1H, H_4), 3.73 (s, 3H, OMe), 4.24 (d, $J = 8$ Hz, 1H, H_3), 4.42–5.09 (bs, 2H, NH, OH). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 20.2, 21.8, 22.9, 23.0 (2Me, C_5), 29.6 (C_4), 36.7 (C_2), 52.2 (OMe), 55.9 (C_3), 158 (C=O). Anal. Calc. for $C_9H_{19}NO_3$ (189): C, 57.14; H, 10.05; N, 7.41; O, 25.40. Found: C, 57.27; H, 10.02; N, 7.35; O, 25.36%.

4.3. Methyl 3-(hydroxyamino)-2,2-dimethylhexanoate (4b)

Colorless oil, yield 0.298 g (79%); IR (KBr), ν/cm^{-1}: 3270, 3195 (NH, OH), 2910 (CH), 1714 (C=O), 1447 (C–N), 1380 (N–O). ^{1}NMR (90 MHz, $CDCl_3$) δ: 1.03 (t, $J = 7$ Hz, 3H, Me), 1.31 (s, 6H, 2Me), 1.21–1.63 (m, 2H, H_5), 2.03–2.41 (m, 2H, H_4), 3.57 (t, $J = 4$ Hz, 1H, H_3), 3.65 (s, 3H, OMe), 7.01–7.58 (bs, 2H, NH, OH). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 13.3 (C_6), 18.9 (C_5), 21.8 (Me), 21.9 (Me), 31.2 (C_4), 36.7 (C_2), 52.0 (OMe), 55.3 (C_3), 153.5 (C=O). Anal. Calc. for $C_9H_{19}NO_3$ (189): C, 57.14; H, 10.05; N, 7.41; O, 25.40. Found: C, 57.29; H, 9.94; N, 7.42; O, 25.35%.

4.4. Methyl 3-(hydroxyamino)-2,2,4,4-tetramethylpentanoate (4c)

Yellow oil, yield 0.341 g (84%); IR (KBr), ν/cm^{-1}: 3420, 3285 (NH, OH), 2900 (CH), 1732 (C=O), 1448 (C–N), 1378 (N–O). ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.22 (s, 9H, *t*-Bu), 1.45 (s, 6H, 2Me), 2.14–2.72 (bs, 2H, NH, OH), 3.8 (s, 3H, OMe), 3.85 (s, 1H, H_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 20.2 (Me), 21.7 (Me), 27.4 (*t*-Bu), 33.6 (C_4), 36.7 (C_2), 52.2 (OMe), 55.95 (C_3), 159.3 (C=O). Anal. Calc. for $C_{10}H_{21}NO_3$ (203): C, 59.11; H, 10.34; N, 6.90; O, 23.65. Found: C, 59.26; H, 10.27; N, 6.85; O, 23.62%.

4.5. Methyl 3-cyclohexyl-3-(hydroxyamino)-2,2-dimethylpropanoate (4d)

Colorless oil, yield 0.325 g (71%); IR (KBr), ν/cm^{-1}: 3260, 3160 (NH, OH), 2905 (CH), 1707 (C=O), 1440 (C–N), 1307 (N–O). ^{1}NMR (90 MHz, $CDCl_3$) δ: 0.92–1.53 (m, 6H, H_6, H_7), 1.34 (s, 6H, 2Me), 1.52–1.89 (m, 4H, H_5), 2.22 (m, 1H, H_4), 3.45 (d, $J = 9$ Hz, 1H, H_3), 3.73 (s, 3H, OMe), 8.11–8.87 (bs, 2H, NH, OH); ^{13}C NMR(22.5 MHz, $CDCl_3$) δ: 14.5 (C_7), 21.7 (C_6), 25.1 (Me), 25.3 (Me), 25.7 (C_5), 29.9 (C_4), 36.6 (C_2), 52.5 (OMe), 55.7 (C_3), 156 (C=O). Anal. Calc. for $C_{12}H_{23}NO_3$ (229): C, 62.88; H, 10.04; N, 6.11; O, 20.96. Found: C, 62.98; H, 10.00; N, 6.07; O, 20.95%.

4.6. General procedure for preparation of 6e–h

To a mixture of aldehyde (2 mmol) in 5.0 M LPDE (3 ml) was added *O*-trimethylsilyl hydroxylamine (2 mmol) at room temperature. After the mixture stirring for 10 min, allyltributyltin (2 mmol) was added. After this, the mixture was allowed to stir at room temperature for 4–5 h. The reaction monitored by TLC (2:1 hexane:ethyl acetate). Then the reaction was quenched with cooled brine and then extracted with dichloromethane. The organic extracts were combined, dried over magnesium sulphate, and concentrated. The crude product was purred by column chroma-

tography with silicagel using a hexane:ethyl acetate gradient from 2:1 to 3:1. ^{1}H NMR, ^{13}C NMR, and IR spectra were entirely consistent with the assigned structures. The physical and spectra data of compounds **6a–d** are as follows.

*4.7. N-tributyltin-N-trimethylsilyloxy-1-(3-pyridinyl)but-3-en-1-amine (**6e**)*

Yellow oil, yield 0.672 g (64%); IR (KBr) ν/cm^{-1}: 1648 (aromatic ring), 1434 (C–N), 1347 (N–O). ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.2 (s, 9H, $SiMe_3$), 0.71–1.83 (m, 27H, $SnBu_3$), 2.62 (2d, 2H, H_2), 4.89 (dd, $J = 9$ Hz, 6 Hz, 1H, H_1), 5.05–5.22 (m, 2H, H_4), 5.63–6.14 (m, 1H, H_3), 7.38–8.78 (m, 4H, aromatic ring); ^{3}C NMR (125.8 MHz, $CDCl_3$) δ: −1.0 ($SiMe_3$), 13.6, 17.6, 26.9, 27.9 ($SnBu_3$), 43.8 (C_2), 70.9 (C_1), 109.6 (C_4), 123.6 (C_3), 119.3, 123.7, 133.5, 146.7, 150.2 (aromatic ring). Anal. Calc. for $C_{24}H_{46}N_2OSiSn$ (525): C, 54.86; H, 8.76; N, 5.33; O, 3.05; Si, 5.33; Sn, 22.67. Found: C, 54.97; H, 8.84; N, 5.290; O, 2.97%.

*4.8. N-tributyltin-N-trimethylsilyloxy-1-(4-nitrophenyl)but-3-en-1-amine (**6f**)*

Yellow oil, yield 0.762 g (67%); IR (KBr), ν/cm^{-1}: 1620 (aromatic ring), 1457 (C–N), 1342 (N–O), 740 (*para*-disubstituted benzene) ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.4 (s, 9H, $SiMe_3$), 0.71–1.78 (m, 27H, $SnBu_3$), 2.50 (2d, 2H, H_2), 4.60–5.31 (m, 3H, H_1, H_4), 5.60 –6.12 (m, 1H, H_3), 7.50 (d, $J = 10$ Hz, 2H, Ar), 8.1 (d, $J = 10$ Hz, 2H, Ar); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: −1.5 ($SiMe_3$), 13.6, 15.0, 27.1, 27.8 ($SnBu_3$), 43.9 (C_2), 72.2 (C_1), 116.9 (C_4), 123.2 (C_3), 123.5, 126.7, 135.2, 146.8 (Ar). Anal. Calc. for $C_{25}H_{46}N_2O_3$ SiSn (569): C, 52.72; H, 8.08; N, 4.92; O, 8.44; Si, 4.92; Sn, 20.91. Found: C, 52.81; H, 8.13; N, 4.86; O, 8.48%.

*4.9. N-tributyltin-N-trimethylsilyloxy-1-(3-nitrophenyl)but-3-en-1-amine (**6g**)*

Yellow oil, yield 0.648 g (57%); IR (KBr), ν/cm^{-1}: 1611 (aromatic ring), 1451(C–N), 1347 (N–O), 1071, 970, 871 (*meta*-disubstituted benzene); ^{1}H NMR (90 MHz, $CDCl_3$) δ: 0.3 (s, 9H, $SiMe_3$), 0.8–1.9 (m, 27H, $SnBu_3$), 2.5 (t, 2H, H_2), 4.5–5.2 (m, 3H, H_1, H_4), 5.5– 6.2 (m, 1H, H_3), 7.4–8.5 (m, 4H, Ar); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ: −1.3 ($SiMe_3$), 8.9, 13.5, 27.2, 28.8 ($SnBu_3$), 43.9 (C_2), 68.0 (C_1), 109.4 (C_4), 122.1 (C_3), 124.5, 130.0, 132.9, 138.5, 147.8, 151.7 (Ar). Anal. Calc. for $C_{25}H_{46}N_2O_3$ SiSn (569): C, 52.72; H, 8.08; N, 4.92; O, 8.44; Si, 4.92; Sn, 20.91. Found: C, 52.82; H, 8.11; N, 4.84; O, 8.47%.

*4.10. N-tributyltin-N-trimethylsilyloxy-1-(4-methyl-2-furyl)but-3-en-1-amine (**6h**)*

Yellow oil, yield 0.475 g (45%); IR (KBr), ν/cm^{-1}: 1613 (aromatic ring), 1448 (C–N), 1375 (N–O); **^{1}H NMR (90 MHz, $CDCl_3$)** δ: 0.4 (s, 9H, $SiMe_3$), 0.7–1.6 (m, 27H, $SnBu_3$), 2.3 (s, 3H, Me), 2.4 (t, 2H,H_2), 4.5–4.8 (m, 3H, H_1, H_4), 5.6– 6.1 (m, 1H,H_3), 5.9–6.5 (m, 2H, Ar); **^{13}C NMR (22.4 MHz, $CDCl_3$)** δ: −0.9 ($SiMe_3$), 10.2, 16.9, 29.1, 30.5 ($SnBu_3$), 18.7 (Me), 44.2 (C_2), 65.9 (C_1), 108.2, 109.6, 114.4, 138.6, 140.3, 146.3 (C_3, C_4, Ar). Anal. Calc. for C_{24} $H_{47}NO_2$ SiSn (528): C, 54.55; H, 8.90; N, 2.65; O, 6.06; Si, 5.30; Sn, 22.54. Found: C, 54.66; H, 8.83; N, 2.60; O, 6.15%.

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[19] We use *O*-trimethylsilyl hydroxylamine versus normal hydroxylamine salts because of good solubility of it in various organic solvent and fast syntheses of oxime ethers without needing to catalyst or pH control.
[20] If we carried out the reaction without TMSCl, formation of desired product was not being observed.
[21] We decide to complete these experiments by using allylsilane as a nucleophile. But, unfortunately we don't access to this compound for doing this.