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α-Hydroxy amides from carbamoylsilane and aldehydes

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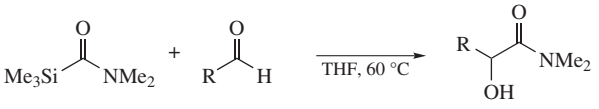
Reaction between *N*,*N*-dimethylcarbamoyl(trimethyl)silane and aldehydes affords α-hydroxy amides in good yields.

α-Hydroxy amides are important substances in organic synthesis and valuable agents in medicinal chemistry.[1,2] Commonly, they are accessed by addition of carbamoyllithium reagents onto carbonyl compounds. However, this approach can be complicated by thermal instability,[3–5] self-condensation[6] and potential problems arising from the high basicity of these reagents. Multi-component reactions using isonitriles and aldehydes such as the Passerini or Ugi reactions[7–9] generally require strong protic acids or Lewis acids to catalyze.[10–13] Previously, it was reported that *N*-methoxymethyl-*N*-methylcarbamoyl(trimethyl)silane adds at the C=O bond of carbonyl compounds to furnish the O-silylated α-hydroxy amides.[14] Carbamoylsilane can also react with α-keto amides,[15,16] aldehyde imines,[17] imidoyl chlorides,[18] alkenes[19] and acid chlorides[20] to give α-hydroxy-α-carbamoyl amides, α-imino amides, β-functionalized tertiary amides and α-keto amides.

Herein we report that reaction of *N*,*N*-dimethylcarbamoyl(trimethyl)silane **1** with aldehydes directly affords α-hydroxy amides **3** (Scheme 1).†

When 1.2 equiv. of carbamoylsilane **1**[21] was allowed to react with aldehydes **2** in THF solution under anhydrous conditions, good yields of α-hydroxy amides **3** were achieved, generally within 4.5–17 h at 25–60 °C (Table 1). Apparently, primarily formed silyl ethers undergo transformation into final α-hydroxy amides **3** by seizing the hydrogen from the medium. This occurred even in the case of products **3a**,**b**,**i** which were isolated by Kugelrohr distillation avoiding protic workup. Initial experiments were carried out using equimolar amounts of aldehydes and **1**. However, in the case of the enolizable aldehydes (see Table 1, entries 1 and 2), the higher yields were obtained on using an excess of carbamoylsilane. This may reflect competitive protonolysis of the latter. Similar phenomenon was previously observed when carbamoylsilane was completely destroyed if iminium salts with enolizable α-hydrogens were applied.[22] Substrate **2a** containing linear propyl substituent reacted essentially quicker than others with more bulky ones. To explore the scope of this reaction, we tested the representative series of benzaldehydes (entries 3–8). Electronic effect plays a significant role: the stronger electron-donating ability of the substituent, the slower the process and/or the lower the yield. No product was obtained from aldehyde **2c** even after 350 h at 60 °C. α,β-Unsaturated aldehydes **2i**,**j** were investigated to estimate whether 1,2- or 1,4-addition would occur in a conjugated system (entries 9 and 10). At 60 °C, acrolein **2i**



1 **2** **3**

Scheme 1

Table 1 Synthesis of α-hydroxy amides **3** from aldehydes **2** and carbamoylsilane **1**.

Entry	Aldehyde	Product	R	Time[a]/h	Yield[b,c] (%)
1	**2a**	**3a**	Pr	4.5[d]	78
2	**2b**	**3b**	Pr[i]	6.5[d]	75
3	**2c**	**3c**	4-$Me_2NC_6H_4$	350	0
4	**2d**	**3d**	4-$MeOC_6H_4$	16	76
5	**2e**	**3e**	4-MeC_6H_4	14	78
6	**2f**	**3f**	Ph	7.5	81
7	**2g**	**3g**	4-ClC_6H_4	7	85
8	**2h**	**3h**	4-$NO_2C_6H_4$	6	86
9	**2i**	**3i**	CH_2=CH	7[e]	71
10	**2j**	**3j**	PhCH=CH	10	73
11	**2k**	**3k**	2-Furyl	14.5	90
12	**2l**	**3l**	2-Thienyl	17	91

[a] To complete consumption of carbamoylsilane **1** at 60 °C in THF. [b] Isolated yield based on aldehyde. [c] 1:1.2 molar ratio of aldehyde and carbamoylsilane. [d] Reaction at 40 °C. [e] Reaction at ~20 °C.

† *α-Hydroxy amides* **3** *(general procedure)*. A Schlenk tube fitted with a Teflon vacuum stopcock and a micro stirbar was flame-heated *in vacuo* and refilled with argon. Aldehyde (1 mmol), THF (1 ml) and *N*,*N*-dimethylcarbamoyl(trimethyl)silane **1** (1.2 mmol) were then added. The tube was sealed and the mixture was stirred at 60 °C until carbamoylsilane was fully consumed (TLC). Volatiles were removed *in vacuo*, adducts **3** were isolated by Kugelrohr distillation, or recrystallization from anhydrous ethanol, or chromatography using 30–50% light petroleum–EtOAc as eluent.

For **3a**: colourless liquid, yield 78%. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.37 (t, 1H, *J* 4.2 Hz), 3.71 (br. s, 1H), 3.02 (s, 3H), 2.99 (s, 3H), 1.60 (m, 2H), 1.49 (m, 2H), 0.96 (t, 3H, *J* 7.2 Hz). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 174.4, 67.6, 36.7, 36.3, 35.8, 18.2, 13.7. IR (KBr, ν/cm^{-1}): 3409, 1645, 1520, 1430. Found (%): C, 57.65; H, 10.63; N, 9.45. Calc. for $C_7H_{15}NO_2$ (%): C, 57.90; H, 10.41; N, 9.65.

For **3f**: yellowish crystals, yield 81%, mp 105–107 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38–7.34 (m, 5H), 5.23 (s, 1H), 4.77 (br. s, 1H), 3.06 (s, 3H), 2.80 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 172.4, 139.2, 129.0, 128.5, 127.5, 71.6, 36.4, 36.3. IR (KBr, ν/cm^{-1}): 3387, 1636, 1397, 1278, 1135. Found (%): C, 67.00; H, 7.20; N, 7.79. Calc. for $C_{10}H_{13}NO_2$ (%): C, 67.02; H, 7.31; N, 7.82.

For **3k**: colourless crystals, yield 90%, mp 138–139 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.41 (m, 1H), 6.38–6.37 (m, 1H), 6.34 (d, 1H, *J* 3.6 Hz), 5.34 (s, 1H), 4.61 (br. s, 1H), 3.08 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 170.1, 152.1, 142.8, 110.6, 108.1, 64.7, 36.4, 36.2. IR (KBr, ν/cm^{-1}): 3377, 1647, 1492, 1241, 1186. Found (%): C, 56.75; H, 6.56; N, 8.31. Calc. for $C_8H_{11}NO_3$ (%): C, 56.80; H, 6.55; N, 8.28.

For characteristics of compounds **3b**,**d**,**e**,**g**–**j**,**l**, see Online Supplementary Materials.

polymerized only, however, the target product **3i** was obtained at room temperature (see entry 9). Compounds **3i**,**j** were exclusively 1,2-addition products. Aldehydes **2k**,**l** containing electron-rich heterocyclic rings gave excellent yields of the products **3k**,**l**.

The plausible mechanism of the process is very similar to the earlier published one.[15]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.04.018.

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