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Synthesis of 2-hydroxymalonamides from carbamoylsilane and α-keto carboxamides

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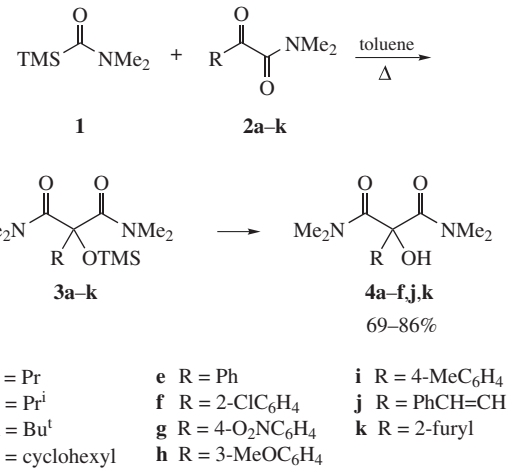
Reaction between *N*,*N*-dimethylcarbamoylsilane and *N*,*N*-dimethyl-α-keto carboxamides affords 2-hydroxy-*N*,*N*,*N*′,*N*′-tetramethyl-2-R-malonamides in good yields.

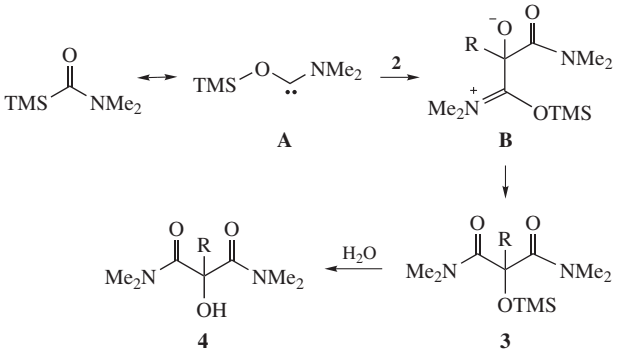
Carbamoylsilanes have proved to be useful synthetic reagents in the past few years.[1–3] Aldehydes may be directly converted to *O*-silyl-2-hydroxyalkanamides by reaction with (*N*-methoxymethyl-*N*-methylcarbamoyl)(trimethyl)silane.[4] The thus accessed 2-hydroxyalkanamides find wide applications in biomedical fields.[5,6] In an attempt to extend this chemistry, we found that (*N*-methoxymethyl-*N*-methylcarbamoyl)(trimethyl)silane reacted poorly with ketones and did not react with α-keto carboxamides. However, in some instances, we observed formation of 2-silyloxymalonamide derivatives in the reaction of acid chlorides with *N*,*N*-dimethylcarbamoylsilane **1**.[7] So we started testing activity within the variety of carbonyl compounds towards *N*,*N*-dimethylcarbamoylsilane. Herein, we report our results on the reaction between *N*,*N*-dimethyl-α-keto carboxamides **2** as the C=O substrate with the reagent **1** (Scheme 1) leading to 2-hydroxy-*N*,*N*,*N*′,*N*′-tetramethyl-2-R-malonamides **4**.†

Initial experiments were carried out with equimolar amounts of the reactants. However, when the starting α-keto carboxamides contained enolizable β-hydrogen atoms (**2a**,**b**,**d**), higher yields were achieved on using excess of carbamoylsilane. This may reflect competitive protonolysis of the carbamoylsilane. Similar phenomenon was previously[8] observed when iminium salts with enolizable α-hydrogens were used as substrates and when carbamoylsilane was completely destroyed. A comparison of the results obtained from **2a**–**d** indicates that the steric envoronment is an important factor since longer reaction time was needed both in case of **2b** (144 h) and **2d** (95 h) than in case of **2a** (76 h), whereas no product was obtained from substrate **2c**. The reaction of **2g**–**i** affords the O-silylated adducts **3g**–**i** while others directly give hydroxy derivatives **4a**–**f**,**j**,**k**. Olefinic substrate **2j** was investigated to determine whether 1,2- or 1,4-addition would occur in a conjugated system. Although the yield of the product **4j** was somewhat lower, it was good, while the structure of **4j** corresponded to 1,2-addition product. α-Keto amide **2k** containing an electron-rich heterocyclic ring reacted with carbamoylsilane **1** giving a good yield of **4k**, although it needed longer time for its completion. Further investigations of this carbamoylation are in progress.



Scheme 1

A plausible mechanism of the process is presented in Scheme 2. Carbamoylsilane **1** can rearrange to its nucleophilic carbene form



Scheme 2

† *General procedure for the synthesis of malonamides* **3** or **4**. A Schlenk tube fitted with a Teflon vacuum stopcock and a micro stirbar was flame-heated *in vacuo* and refilled with argon. α-Keto carboxamide (1.0 mmol), 1.6 ml of anhydrous toluene and 1.2 equiv. of (*N*,*N*-dimethylcarbamoyl)-trimethylsilane **1** were then added. The sealed reaction mixture was stirred at 105 °C until no carbamoylsilane could be detected by TLC. Volatiles were removed *in vacuo*, and the residue was chromatographed using 30–50% acetone–hexane as eluent to yield products **3** or **4**.

For **3g**: yield 85%, mp 139–140 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.23–7.57 (q, 4H, C_6H_4), 3.06 (s, 6H, 2NMe), 2.98 (s, 6H, 2NMe), 0.05 (s, 9H, Me_3Si). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.1, 147.5, 146.6, 129.6, 122.7, 85.3, 37.9, 37.4, 2.0. IR (KBr, ν/cm^{-1}): 1630, 1503, 1150, 623. Found (%): C, 52.33; H, 6.82; N, 11.29. Calc. for $C_{16}H_{25}N_3O_5Si$ (%): C, 52.30; H, 6.86; N, 11.43.

For **4a**: yield 76%, mp 82–84 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.02 (s, 1H, OH), 3.03 (s, 6H, 2NMe), 2.97 (s, 6H, 2NMe), 1.99 (t, 2H, CH_2, J 8.4 Hz), 1.25 (m, 2H, CH_2, J 8.4 Hz, J 7.2 Hz), 0.94 (t, 3H, CMe, J 7.2 Hz). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 170.9, 77.6, 38.4, 37.4, 37.1, 16.2, 14.3. IR (KBr, ν/cm^{-1}): 3480, 1720, 850. Found (%): C, 55.69; H, 9.48; N, 12.73. Calc. for $C_{10}H_{20}N_2O_3$ (%): C, 55.53; H, 9.32; N, 12.95.

For characteristics of compounds **3h**,**i** and **4b**,**d**–**f**,**j**,**k**, see Online Supplementary Materials.

A,[9] which attacked the carbonyl group of α-keto carboxamides to produce an unstable intermediate **B**, followed by silyl group migration to give the O-silylated adducts **3**. The latter can be hydrolyzed to form the ultimate 2-hydroxymalonamides **4**.

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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.2013.03.019.

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