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Synthesis of α-Ketoamides from a Carbamoylsilane and Acid Chlorides

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Received April 2, 2004

Abstract: Treatment of acid chlorides with a carbamoylsilane affords α-ketoamides. In some instances, in situ reaction of additional carbamoylsilane with these products yielded α-organyl-α-siloxymalonamides.

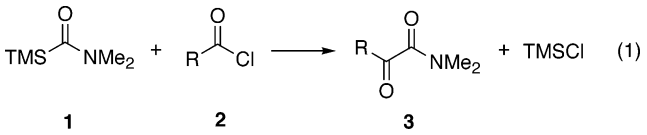
α-Ketoamides are known to have important roles as protease inhibitors[1] and serve as precursors to pharmacologically important structures such as oxazolidinones,[2] β-lactams,[2,3] and chiral α-hydroxyamides.[4] Due to such interests, numerous methods for the synthesis of α-ketoamides have been reported. Earlier approaches have been summarized,[5] and new methodologies have continued to appear,[6] with the palladium-catalyzed amino (double) carbonylation of organic halides arguably representing the most commercially useful approach.[7] The latter, however, is attendant with drawbacks associated with the use of toxic carbon monoxide, usually employed under elevated temperatures and high pressures.[8] Most recently, the reaction of acid chlorides with a carbamoylstannane has been reported to afford good yields of α-ketoamides, for the most part under ambient conditions.[9] Unfortunately, this approach does not remove carbon monoxide from the synthetic stream, as it is required for the preparation of the carbamoylstannane.[10] In addition, the toxicity of organotin compounds,[11] and the possibility of trace organotin contamination in pharmaceutical applications, limit the appeal of this method. Herein, we present an alternative entry to α-ketoamides which avoids these problems.

TABLE 1. Reaction of Acid Chlorides [2, RC(Cl)=O] with Carbamoylsilane 1

entry	R of **2**	conditions[a]	product (% yield)[b]
1	Me	11 h	**3a** (72)
2	Me	6 h, THF	**3a** (68)
3	Me	12 h[c]	**3a** (81)
4	Me	11 h[d]	**3a** (35) + **4a** (64)
5	tBu	1 week	**3b** (91)
6	*n*-C_3F_7	7 h	**3c** (52) + **4c** (24)
7	*n*-C_3F_7	7 h, THF, −78 °C	**3c** (66)
8	*n*-C_3F_7	11 h[d]	**4c** (89)
9	Ph	22 h	**3d** (87)
10	Ph	69 h[d], 60 °C	**3d** (20) + **4d** (70)
11	*E*-PhCH=CH	21 h	**3e** (70) + **4d** (13)
12	*E*-PhCH=CH	19 h, THF	**3e** (61) + **4d** (0)
13	*E*-PhCH=CH	40 h[d]	**3e** (9) + **4e** (88)
14	PhC≡C	10 h	**3f** (42) + **4f** (26)
15	PhC≡C	8 h, THF, −78 °C	**3f** (39) + **4f** (33)
16	PhC≡C	23 h[d]	**4f** (94)
17	$ClCH_2$	10 h, 0 °C	**3g** (56)
18	$MeO_2CCH_2CH_2$	10 h	**3h** (77)
19	MeO_2C	5 h, 0 °C	**3i** (65)
20	*o*-AcetoxyPh	36 h	**3j** (75)
21	*o*-AcetoxyPh	28 h, THF	**3j** (88)
22	^{i}PrO	40 h	**3k** (82)
23	MeO_2CCH_2	3 h	**3l** (0)
24	Et_2NC=O	3 days, 60 °C	No reaction
25	ClC=O	6 h, 0 °C	**5** (50)
26	ClC=O	6 h, THF, −78 °C	**5** (47)

[a] Ratio of **1**:**2** was 1.1:1, benzene solvent, rt, unless otherwise indicated. [b] Isolated yield based on acid chloride. [c] 1.4:1 ratio. [d] 2.1:1 ratio.

When 1.1 equiv of a carbamoylsilane (**1**)[12] was allowed to react with acid chlorides (**2**) in benzene or THF solution under anhydrous conditions at ambient conditions or below, good yields of α-ketoamides (**3**) were obtained, generally within a matter of hours (eq 1). Results are



displayed in Table 1. Entries 1−4 are indicative of the behavior encountered. The reaction was typically allowed to proceed in benzene solvent until all of **1** was consumed, affording a mixture of unreacted **2** (if present), product **3**, small amounts of DMF, and TMSCl. Purification was then carried out by distillation or chromatography. The appearance of DMF is due to protonolysis of **1** by either adventitious protonic sources and/or enolizable C−H

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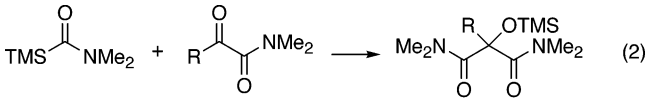
10.1021/jo040164o CCC: $27.50
Published on Web 07/10/2004

moieties in the acid chloride (see later). Use of THF instead of benzene (entry 2) accelerated the reaction, but had little effect on yield. In entry 3, the **1** to **2** ratio was increased to 1.4:1 in an attempt to compensate for DMF formation and this did increase the yield of **3** to some extent. However, small absorptions were noted in the NMR of the crude reaction mixture suggesting the presence of a second, minor, amide product. Entry 4 outlines the result of increasing the **1**:**2** ratio to 2.1:1. Under these conditions, some of the initially formed α-ketoamide undergoes addition of a second molecule of **1** (eq 2) to give the α-methyl-α-siloxymalonamide (**4a**).



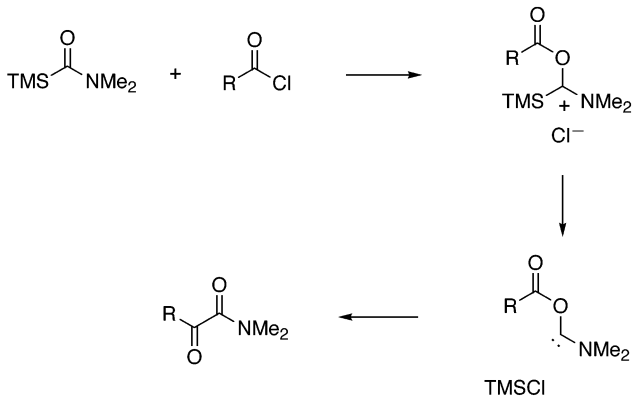
(2)

1 **3** **4**

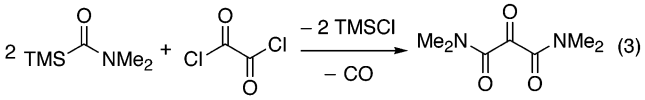
This was not unexpected behavior, as we have previously shown that **1** will add in this fashion to isolated carbonyl groups in aldehydes and ketones, albeit under more elevated temperatures.[13] It seems reasonable to assume that those keto functions in **3** which would be considered to be more reactive on steric and/or electronic grounds would exhibit this reactivity under less forcing conditions. The antithesis of this possibility is represented by entry 5, where only **3b** is formed slowly, but in high yield, because of steric inhibition to carbonyl attack. In contrast, entry 6, in which **2c** contains the electron-withdrawing perfluoropropyl group, affords a 2:1 mixture of **3c** and **4c** with the standard 1.1 equiv of **1** at room temperature. Keto addition could be suppressed, however, by carrying out the reaction at −78 °C (entry 7), or alternatively, completely favored by using 2.1 equiv of **1** (entry 8). Only α-ketoamide **3d** was obtained under standard conditions from benzoyl chloride, but with the use of excess **1**, a higher temperature, and longer reaction time, the diadduct could be made the major product (entry 10). Other conjugated systems were found to be more prone to diaddition. The less sterically demanding cinnamoyl chloride afforded a good yield of **3e**, but accompanied by small amounts of diadduct under standard conditions (entry 11). The latter could be completely eliminated by the use of THF as solvent (entry 12) or made the major product in good yield using excess **1** (entry 13). The ketoamide obtained from phenylpropiolyl chloride (entry 14) proved more reactive toward further addition of **1**, giving a 2:1 ratio of **3f** to **4f**. Surprisingly, an attempt to suppress diaddition by employing the previously successful techniques of THF solvent and low-temperature failed to eliminate this competition.

Other functionalized acid chlorides could also be converted to the corresponding α-ketoamides. Substrates containing chloro (entry 17) and ester functionalities such as entries 18−21 behaved normally,[14] but methyl 3-chloro-3-oxopropionate quickly converted **1** into DMF, presumably due to its readily enolizable α-protons (entry 23).

SCHEME 1



N,*N*-Dimethylcarbamoyl chloride, containing an electron-rich carbonyl group, proved to be totally inert even at 60 °C for 3 days (entry 24). The double carbamoylation of oxalyl chloride was only partially successful (entries 25 and 26), in that it was accompanied by decarbonylation to only give **5** (eq 3).[15]



(3)

5

We suggest a mechanism for α-ketoamide formation as shown in Scheme 1.

O-Acylation of the carbamoylsilane by the acid chloride is believed to form an isoimidium salt as a transient intermediate. Although rare, such salts have actually been isolated as stable species in cyclic systems.[16] The facility of acylation is thus seen to be correlated with the steric availability and electrophilicity of the carbonyl group of the acid chloride. Subsequent attack of chloride ion at the silicon of the TMS group may expel a resonance-stabilized acyloxy(amino)carbene.[17] Similar species bearing both acyloxy and carbon substituents on the carbenic carbon are known to rearrange efficiently to α-diketones,[18] and parallel behavior in the present case would afford α-ketoamides.

Although the current results specifically address the formation of (tertiary) *N*,*N*-dimethyl α-keto amides, our ability to synthesize carbamoylsilanes bearing other N-substituents,[12] including the easily hydrolyzable methoxymethyl moiety, suggests that primary and secondary α-ketoamides may also be accessible by this methodology. In addition, a one-pot entry into certain representatives

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(14) The yield of **3g** was presumably reduced due to competition from protonolysis. If crude **3i** was chromatographed instead of distilled, a solid was obtained having ^{1}H NMR (C_6D_6) absorptions at δ 5.59 (2H), 3.29 (3H), 2.57 (3H), and 2.48 (3H). This material may have been a hydrate, but was not investigated further.

(15) Gas evolution could be seen upon adding **1** to oxalyl chloride at 0 °C. We note that it has been reported that the reaction of oxalyl chloride with a carbamoylstannane does not lead to decarbonylation of the tetracarbonyl product.[9]

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of α-substituted tartronic acid (α-hydroxymalonic acid) amides has been demonstrated.

Acknowledgment. This work was supported by NIH Grant No. R15 GM065864.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040164O