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Reactions of a Carbamoylstannane with Acid Chlorides: Highly Efficient Synthesis of α-Oxo Amides

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Abstract: Treatment of acid chlorides with a carbamoylstannane under mild conditions (mostly rt for a few hours) affords α-oxo amides in high yields. Vicinal polycarbonyl compounds are also obtained, although spontaneous decarbonylation occasionally occurs.

α-Oxo amides are an important class of compounds, which have been exploited in organic syntheses mainly for pharmaceutical applications.[1] The synthetic methods of α-oxo amides have been rather well established as exemplified by the reaction of oxamates with Grignard reagents,[2] amidation of α-oxo acid derivatives with amine nucleophiles,[3] transition-metal-catalyzed double carbonylation reaction of organic halides in the presence of primary or secondary amines,[4] and oxidation of α-hydroxy amides.[5] However, exploration into more general and efficient methods that work under mild conditions still is a subject of research interest.[6]

TABLE 1. α-Oxo Amide Synthesis by the Reaction of Acid Chlorides with Carbamoylstannane 1[a]

entry	R	conditions	product, yield (%)[b]
1	CH_3	1 h, rt	**3a**, 96 (83)
2	$(CH_3)_2CH$	1 h, rt	**3b**, 95 (87)
3	$C_6H_5CH_2$	1 h, rt	**3c**, 91 (72)
4	$CH_2{=}C(CH_3)$	1 h, rt	**3d**, 90 (72)
5	*trans*-$C_6H_5CH{=}CH$	1 h, rt	**3e**, 92 (85)
6	$ClCH_2$	3 h, 80 °C	**3f**, 94 (81)
7	C_3F_7	1 h, 60 °C	**3g**, 95 (76)
8	C_6H_5	3 h, rt	**3h**, 97 (85)
9	*p*-$CH_3C_6H_4$	3 h, rt	**3i**, 95 (78)
10	*p*-BrC_6H_4	3 h, rt	**3j**, 92 (85)
11	2-furyl	8 h, rt	**3k**, 93 (76)
12	2-thienyl	10 h, rt	**3l**, 82 (70)
13	C_2H_5O	3 h, 80 °C	**3m**, 97 (78)
14	$(CH_3)_2N$	5 h, 120 °C[c]	**3n**, 31 (22)
15	C_2H_5OCO	5 h, −45 °C to rt	**3p**, 56 (39)

[a] Reactions were carried out in a 1.0-mmol scale with benzene (2.0 mL) as solvent. RCOCl/$Me_3SnCON^iPr_2$ = 1.0:1.1 (molar ratio). [b] GLC yield based on the amount of acid chloride charged. The figures in parentheses are isolated yields. [c] Run in a sealed glass tube.

During our study on the addition reaction of carbamoylstannane **1**[7] to alkynes catalyzed by transition metal complexes,[8] we came across the high reactivity of the Sn−$CONR_2$ bond. This finding prompted us to investigate the intrinsic reactivity of **1** in the absence of transition metal complexes. We wish to disclose in this paper that compound **1** indeed reacts very rapidly with acid chlorides affording α-oxo amides, some of which are not easy to synthesize by conventional methods (eq 1).

$$\underset{\mathbf{1}}{Me_3SnCON^iPr_2} + \underset{\mathbf{2}}{RCOCl} \xrightarrow[C_6H_6]{} \underset{\mathbf{3}}{RCOCON^iPr_2} + ClSnMe_3 \quad (1)$$

In a representative experiment, a benzene solution of acetyl chloride and carbamoylstannane **1** (1.1 equiv) was stirred at room temperature for 1 h. GLC analysis of the reaction mixture showed the formation of *N*,*N*-diisopropyl-2-oxo-propionamide **3a** in 96% yield (Table 1, entry 1).[9] Branched aliphatic and aralkyl acid chlorides such as isobutyryl chloride and phenylacetyl chloride react similarly to furnish high yields of the corresponding α-oxo amides (entries 2 and 3). The reactions of olefinic acid chlorides such as methacryloyl chloride and cinnamoyl chloride with **1** also proceed very cleanly to afford the products in more than 90% yields (entries 4 and 5). However, chloroacetyl chloride displays lower reactivity than the foregoing acid chlorides, which is peculiar from a view that the reaction proceeds via electrophilic substitution at the Sn−C bond.[10] Thus, the reaction of

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(1) For representative publications, see: (a) Andersen, K.; Liljefors, T.; Hytted, J.; Perregaard, J. *J. Med. Chem.* **1996**, *39*, 3723. (b) Ogawa, H.; Aoyama, T.; Shioiri, T. *Heterocycles* **1996**, *42*, 75. (c) Axten, M.; Krim, L.; Kung, H. F.; Winkler, D. *J. Org. Chem.* **1998**, *63*, 9628. (d) Singh, R. P.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2579. (e) Toda, F.; Miyamoto, H.; Inoue, M.; Yasaka, S.; Matijasic, I. *J. Org. Chem.* **2000**, *65*, 2728. (f) Meng, C. Q.; Rakhit, S.; Lee, D. K. H.; Kamboj, R.; McCallum, K. L.; Mazzocco, L.; Dyne, K.; Slassi, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 903. (g) Heaney, F.; Fenlon, J.; McArdle, P.; Cunningham, D. *Org. Biomol. Chem.* **2003**, *1*, 1122.

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(6) (a) Parlow, J. J.; Dice, T. A.; South, M. S. In *High-Throughput Synthesis*; Sucholeiki, I., Ed.; Marcel Dekker: New York, 2001, p 143. (b) Kobayashi, N.; Koji, T.; Fujita, T.; Nishimura, T.; Hosoda, A. PCT Int. Appl. WO 2002002546 A1, 2002. (c) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063.

(7) For the preparation of **1** and palladium-catalyzed cross-coupling reactions of **1** with organic halides, see: Lindsay, C. M.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 569.

(8) Hua, R.; Onozawa, S-y.; Tanaka, M. *Organometallics* **2000**, *9*, 3269. See also: Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221.

(9) In a preliminary experiment, treatment of (*N*,*N*-diisopropylcarbamoyl)tributylstannane with acetyl chloride over 1 h at room temperature without a solvent afforded 95% GC yield of **3a**.

(10) For the mechanism of substitution reactions of organostannanes, see: (a) Wardell, J. L. In *Chemistry of Tin*; Smith, P. J., Ed.; Blackie Academic & Professional: London, UK, 1998; p 121. (b) Davies, A. G. *Organotin Chemistry*; VCH: Weinheim, Germany, 1997; p 51.

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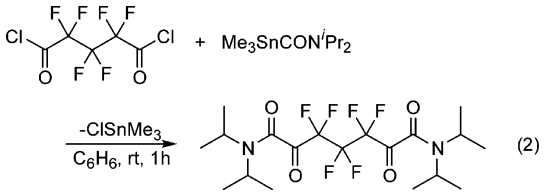
chloroacetyl chloride with **1** run at room temperature for 2 h gave the corresponding α-oxo amide only in 44% yield. To obtain a satisfactory yield (94%), heating at 80 °C for 3 h was needed (entry 6).[11] On the other hand, perfluoro acid chlorides, highly substituted by the electronegative fluorine substituent, react normally, i.e., more readily than chloroacetyl chloride; when a mixture of **1** and heptafluoro-*n*-butyryl chloride in benzene was heated at 60 °C for 1 h, the corresponding heptafluoro α-oxo amide **3g** was obtained in 95% yield (entry 7). In addition, the reaction of bifunctional hexafluoropentanedioyl dichloride with 2 equiv of **1** at room temperature for 1 h gave the corresponding product **4** in 79% GC yield (60% isolated yield; eq 2). Fluorine-containing α-oxo amides have



4 79% GC (60% isolated) yield

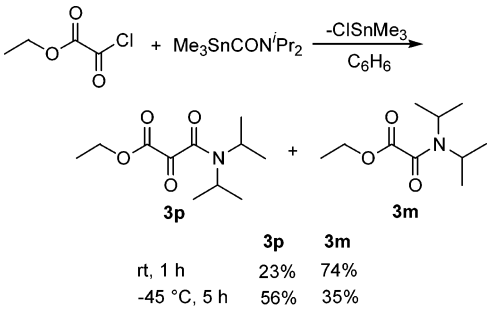
proved to be the useful intermediates for the syntheses of agrochemicals and pharmaceuticals, but there are only a few publications disclosing the preparation of these compounds.[12]

The reactions of aromatic and heteroaromatic acid chlorides with **1** proceed somewhat slowly as compared with aliphatic acid chlorides and prolonged reaction times are required at room temperature to achieve acceptable yields in excess of 90% (entries 8−12). Unlike aliphatic ones, however, benzoyl chloride, 4-bromobenzoyl chloride, and *p*-toluoyl chloride display similar reactivity despite the difference in the electronic nature of the para substituent.

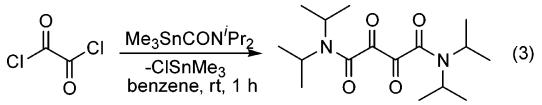
Ethyl chloroformate and *N*,*N*-dimethylcarbamoyl chloride are also reactive although their reactivity is much less than acid chlorides (entries 13 and 14). The reaction of the former needed heating at 80 °C for 3 h to furnish the corresponding product **3m** in 97% yield, whereas the latter gave only a trace of product **3n** under the same conditions, and heating at 120 °C for 5 h afforded **3n** in only 31%.[13]

Synthesis and reactivity of vicinal polycarbonyl compounds [R−(CO)$_n$−R, $n \geq 3$] continue to be a vital area of research since the first review article appeared in 1975.[14] In view of the foregoing high reactivity of the carbamoylstannane species, it appeared promising to synthesize the polycarbonyl compounds in one step. In practice, the reaction of ethoxalyl chloride with **1** indeed proceeded readily at room temperature to almost completion within 1 h. Ethyl 2,3-dioxo-3-(*N*,*N*-diisopropylamino)propionate **3p** and ethyl *N*,*N*-diisopropyloxamate **3m** were formed in 23% and 74% GC yield, respectively (Scheme 1). The latter product is envisioned to have arisen from decarbonylation of **3p**,[14c] which is substantiated by the change of the **3p**/**3m** ratio from 64/36 to 34/66, observed when the mixture was kept standing in $CDCl_3$ at room temperature for 2 days. Accordingly in another reaction of ethoxalyl chloride with **1** run at −45 °C to room temperature for 5 h, the yield of **3p** increased to 56% (GC) at the expense of **3m** (35%, entry 15).

SCHEME 1. Reaction of Ethoxalyl Chloride with Carbomoylstannane 1



The ease of the decarbonylation appears to be very much dependent on the structure. Rather unexpectedly, for instance, the reaction of oxalyl chloride with 2 equiv of **1** afforded the corresponding tetracarbonyl compound, *N*,*N*,*N*′,*N*′-tetraisopropyl-2,3-dioxosuccinamide **5**, as an exclusive amide product (95% GC and 72% isolated yield) (eq 3). The result suggests that the new methodology with **1** provides a very simple and efficient access to vicinal polycarbonyl compounds.



5 95% GC (72% isolated) yield

In all of the foregoing reactions, benzene was used as the solvent. However, the reaction of **1** with acetyl chloride in toluene (otherwise identical conditions) worked as well to result in 93% GC yield of **3a**, suggesting that toluene may be used for the reactions with other acid chlorides. In addition, when the starting acid chloride is liquid, the reaction can be effected without using a solvent, as exemplified by the reaction of **1** with acetyl chloride affording 98% GC yield of **3a** (room temperature, 1 h).

In conclusion, the reaction of the carbamoylstannane species with acid chlorides has proved to offer a general and efficient route to α-oxo amides, some of which are not easily prepared via other routes.

Experimental Section

A Typical Procedure for the Reaction of Carbamoylstannane with Acid Chlorides. At room temperature, to a solution of (*N*,*N*-diisopropylcarbamoyl)trimethylstannane (**1**,1.1 mmol) and docosane (0.37 mmol, as an internal standard for GLC analysis) in 2.0 mL of benzene was added 1.0 mmol of acetyl chloride by a macrosyringe over 10 min and the resulting solution was stirred at room temperature for 1 h. The GLC analysis of the reaction mixture revealed that acetyl chloride was almost completely consumed (>99%) and that the product

(11) The chloro substituent at the α-carbon remained intact.

(12) Urata, H.; Ishii, Y.; Fuchikami, T. *Tetrahedron Lett.*, **1989**, *30*, 4407 and references therein.

(13) The reaction was very clean; GLC and GC-MS analyses showed that, besides the corresponding α-oxo amide and Me_3SnCl, no other byproduct was formed and that both of the starting materials remained.

(14) For the synthesis and synthetic applications of vicinal polycarbonyl compounds, see: (a) Rubin, M. B. *Chem. Rev.* **1975**, *75*, 177. (b) Rubin, M. B.; Gleiter, R. *Chem. Rev.* **2000**, *100*, 1121. (c) Wasserman, H. H.; Lee, K.; Xia, M. *Tetrahedron Lett.* **2000**, *41*, 2511.

N,*N*-diisopropyl-2-oxo-propionamide **3a** was formed in 96% yield. After removal of the volatiles in vacuo, the residue was subjected to column chromatography on silica gel with hexane and then CH_2Cl_2 as the eluting solvent. **3a** was obtained as a colorless oil (142.0 mg, 0.83 mmol, 83% yield).

***N,N*-Diisopropyl-2-oxopropionamide 3a:** Colorless oil, isolated yield 83%, bp 100 °C. ^{1}H NMR ($CDCl_3$) δ 3.72 (hept, 1H, J = 6.6 Hz), 3.51 (hept, 1H, J = 6.8 Hz), 2.35 (s, 3H), 1.42 (d, 6H, J = 6.8 Hz), 1.20 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 198.8, 167.4, 49.7, 45.9, 27.3, 20.8. IR (neat) 2976, 2942, 1715, 1686, 1450, 1375, 1199 cm^{-1}. GCMS *m*/*z* (% rel intensity) 171 (M^+, 0.5), 128 (31), 86 (100), 58 (11). Anal. Calcd for $C_9H_{11}NO_2$: C, 63.16; H, 9.94; N, 8.19. Found: C, 62.62; H, 10.0; N, 7.91.

Ethyl 3-(*N,N*-diisopropylamino)-2,3-dioxopropionate 3p: Colorless product, isolated yield 39%, mp 79.0−80.0 °C (recrystallization in hexane). ^{1}H NMR ($CDCl_3$) δ 4.28 (q, 2H, J = 7.1 Hz), 3.94 (hept, 1H, J = 6.6 Hz), 3.47 (hept, 1H, J = 6.8 Hz), 1.42 (d, 6H, J = 6.8 Hz), 1.32 (t, 3H, J = 7.1 Hz), 1.14 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 179.8, 170.3, 160.2, 63.1, 50.1, 46.3, 20.5, 19.9, 13.9. IR (neat) 2978, 2946, 1742, 1647, 1421, 1379, 1292, 1261, 1145, 1129, 1089, 1040, 592 cm^{-1}. GCMS *m*/*z* (% rel intensity) 229 (M^+, 0.1), 201 (0.1), 128 (38), 86 (100), 70 (6), 58 (4). HRMS calcd for $C_{11}H_{20}NO_4$ (MH^+) 230.1391, found 230.1393.

***N,N,N′,N′*-Tetraisopropyl-3,3,4,4,5,5-hexafluoro-2,6-dioxopimelamide 4:** Colorless oil, isolated yield 60%, bp 85 °C (0.15 Torr). ^{1}H NMR ($CDCl_3$) δ 3.67 (hept, 1H, J = 6.6 Hz), 3.56 (hept, 1H, J = 6.8 Hz), 1.46 (d, 6H, J = 6.8 Hz), 1.24 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 181.6 (t, $^2J_{CF}$ = 32.0 Hz), 161.5, 110.1 (tquint, $^1J_{CF}$ = 267.0 Hz; $^2J_{CF}$ = 34.0 Hz), 109.6 (tt, $^1J_{CF}$ = 270.0 Hz; $^2J_{CF}$ = 34.0 Hz), 50.4, 46.6, 20.5, 19.8. ^{19}F NMR ($CDCl_3$) δ 26.1 (s(br), 2F), 22.1 (s(br), 2F). IR (neat) 2982, 2944, 1750, 1657, 1475, 1452, 1377, 1348, 1209, 1183, 1139 cm^{-1}. GCMS *m*/*z* (% rel intensity) 424 (M^+ − 2F, 1), 334 (0.6), 264 (3), 216 (2), 128 (55), 86 (100), 70 (4), 58 (4). HRMS calcd for $C_{19}H_{28}F_6N_2O_4$ 462.1951, found 462.1958.

***N,N,N′,N′*-Tetraisopropyl-2,3-dioxosuccinamide 5:** Colorless product, isolated yield 72%, mp 88.0−89.5 °C (recrystallization in hexane). ^{1}H NMR ($CDCl_3$) δ 4.11 (hept, 1H, J = 6.6 Hz), 3.53 (hept, 1H, J = 6.8 Hz), 1.44 (d, 6H, J = 6.8 Hz), 1.26 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 181.6, 166.2, 50.4, 46.0, 20.6, 20.1. IR (neat) 2976, 2942, 1717, 1636, 1458, 1365, 735, 592 cm^{-1}. GCMS *m*/*z* (% rel intensity) 312 (M^+, 0.3), 213 (3), 128 (30), 100 (2), 86 (100), 70 (4), 58 (3). HRMS calcd for $C_{15}H_{28}N_2O_3$ (M^+ − CO) 284.2098, found 284.2099.

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Supporting Information Available: Detailed experimental procedure and characterization data of products **3a**−**p**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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