

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

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Received October 27, 2003

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.

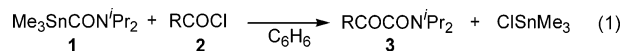
α -Oxo amides are an important class of compounds, which have been exploited in organic syntheses mainly for pharmaceutical applications.¹ The synthetic methods of α -oxo amides have been rather well established as exemplified by the reaction of oxamates with Grignard reagents,² amidation of α -oxo acid 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) ₂ CH	1 h, rt	3b , 95 (87)
3	C ₆ H ₅ CH ₂	1 h, rt	3c , 91 (72)
4	CH ₂ =C(CH ₃)	1 h, rt	3d , 90 (72)
5	<i>trans</i> -C ₆ H ₅ CH=CH	1 h, rt	3e , 92 (85)
6	ClCH ₂	3 h, 80 °C	3f , 94 (81)
7	C ₃ F ₇	1 h, 60 °C	3g , 95 (76)
8	C ₆ H ₅	3 h, rt	3h , 97 (85)
9	<i>p</i> -CH ₃ C ₆ H ₄	3 h, rt	3i , 95 (78)
10	<i>p</i> -BrC ₆ H 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 ₂ H ₅ O	3 h, 80 °C	3m , 97 (78)
14	(CH ₃) ₂ N	5 h, 120 °C ^c	3n , 31 (22)
15	C ₂ H ₅ OCO	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/Me₃SnCONⁱPr₂ = 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** to alkynes catalyzed by transition metal complexes,⁸ we came across the high reactivity of the Sn–CONR₂ 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).



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

(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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(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.

(2) Barre, R. *Ann. Chim. Phys.* **1928**, *9*, 237; *Chem. Abstr.* **1928**, *22*, 2268.

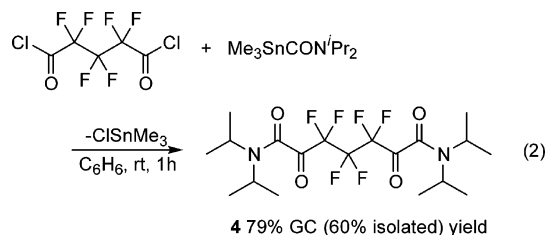
(3) Li, Z.; Patil, G. S.; Chu, D.-L.; Foreman, J. E.; Eveleth, D. D.; Powers, J. C. *J. Med. Chem.* **1996**, *39*, 4089.

(4) (a) Review: des Abbayes, H.; Salaün, J.-Y. *Dalton Trans.* **2003**, 1041. (b) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *23*, C64. (c) Ozawa, F.; Soyama, T.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1982**, *23*, 3383.

(5) Harbeson, S. L.; Abelleira, S. M.; Akiyama, A.; Barrett, R.; Straub, J. A.; Tkacz, J. N.; Wu, C.; Musso, G. F. *J. Med. Chem.* **1994**, *37*, 2918.

(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.

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



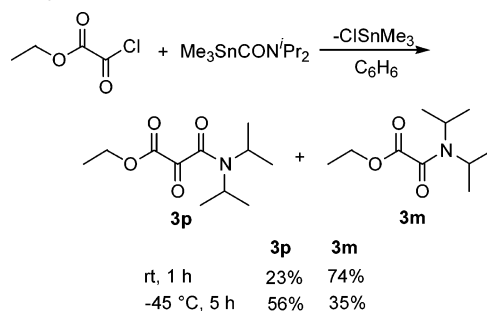
proved to be the useful intermediates for the syntheses of agrochemicals and pharmaceuticals, but there are only a few publications disclosing the preparation of these compounds.¹²

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

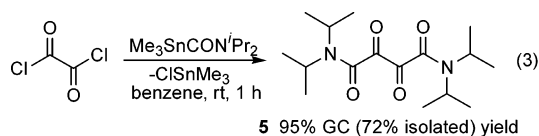
Synthesis and reactivity of vicinal polycarbonyl compounds $[R-(CO)_n-R, n \geq 3]$ continue to be a vital area of research since the first review article appeared in 1975.¹⁴ In view of the foregoing high reactivity of the carbamoylstannane species, it appeared promising to synthesize the polycarbonyl 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*-diisopropylami-

SCHEME 1. Reaction of Ethoxalyl Chloride with Carbamoylstannane 1



no)propionate **3p** and ethyl *N,N*-diisopropylcarbamate **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 CDCl₃ 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).

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.



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 Me₃SnCl, 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 CH₂Cl₂ 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. ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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 C₉H₁₁NO₂: 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). ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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 C₁₁H₂₀NO₄ (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). ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) δ 181.6 (t, ²*J*_{CF} = 32.0 Hz), 161.5, 110.1 (tquint, ¹*J*_{CF} = 267.0 Hz; ²*J*_{CF} = 34.0 Hz), 109.6 (tt, ¹*J*_{CF} = 270.0 Hz; ²*J*_{CF} = 34.0 Hz), 50.4, 46.6, 20.5, 19.8. ¹⁹F NMR (CDCl₃) 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 C₁₉H₂₈F₆N₂O₄ 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). ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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 C₁₅H₂₈N₂O₃ (M⁺ – CO) 284.2098, found 284.2099.

Acknowledgment. We thank the Japan Science and Technology Corporation (JST) for financial support through the CREST program.

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>.

JO035572R