Synthesis of *O*-Ethyl Thioformate: A Useful Reagent for the Thioformylation of Amines

Christopher J. Borths,* Johann Chan,* Brenda J. Burke, Robert D. Larsen

Chemical Process R&D, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, USA
Fax +1(805)3754532; E-mail: cborths@amgen.com

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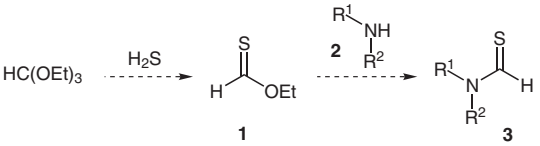
Abstract: *O*-Ethyl thioformate has been synthesized from triethylorthoformate and hydrogen sulfide gas using a Brønstead acid catalyst. The product can be isolated as a neat liquid in 83% overall yield. Both the crude and purified thiolate can be used to thioformylate a variety of amines in good to excellent yields.

Key words: hydrogen sulfide, thioformate, sulfur, amines, condensation

Thioformamides are synthetically useful intermediates in the construction of complex organic molecules. Thioformamides can be further elaborated into various heterocycles,[1] thioamides,[2] iminyl sulfides,[3] enamines,[4] and α-substituted amines.[5] Various methods have been reported for their synthesis, including the condensation of amines with thioformates,[2,6] thioamidation of secondary amines or Vilsmeier reagents with dimethylthioformamide,[7] condensation of tertiary ethyl amines with carbon disulfide,[8] condensation of secondary amines with hydrogen cyanide and hydrogen sulfide,[9] addition of dichlorocarbene and hydrogen sulfide to amines,[10] reduction of isothiocyanates,[11] conversion of formamides by phosphorus pentasulfide[1] or Lawesson's reagent,[12] and direct thionation of formamides by elemental sulfur.[13]

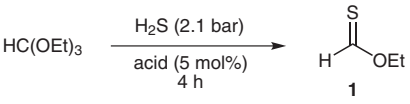
After considering the methods available to generate thioformamides, the thioamidation of amines with *O*-ethyl thioformate (**1**) was chosen for further examination (Scheme 1). The acid-catalyzed synthesis of *O*-ethyl thioformate was first reported in 1963[14] where the reagent was synthesized, albeit in only 33% yield, from hydrogen sulfide and triethylorthoformate using catalytic sulfuric acid in acetic acid. This methodology was later reported as a preparative procedure, generating the desired reagent in 30–38% isolated yield.[15] Perchloric acid was subsequently identified by Stowell and coworkers as a more efficient catalyst for the condensation of hydrogen sulfide with triethylorthoformate.[6] This allowed direct utilization of the crude reagent for the thioformylation of various amines.

Synthesis of *O*-ethyl thioformate via the perchloric acid catalyzed addition of hydrogen sulfide to triethylorthoformate requires superstoichiometric amounts of hydrogen sulfide gas and produces less than quantitative yields.[16] The use of excess hydrogen sulfide gas should be minimized due to its significant toxicity and flammability.[17] Additionally, the use of perchloric acid is contraindicated due to this reagent's toxicity and ability to form explosive salts.[18] Because of these concerns, we were interested in developing a method for the synthesis of *O*-ethyl thioformate that requires as little excess hydrogen sulfide as possible, utilizes a Brønsted acid catalyst other than perchloric acid, and is amenable to large-scale synthesis. Herein, we wish to report a safe and high-yielding procedure that meets these criteria for preparing *O*-ethyl thioformate. Furthermore, this reagent can be used to prepare a variety of thioamides.



Scheme 1 Thioformylation process

Table 1 Generation of *O*-Ethyl Thioformate Using Various Brønstead Acid Catalysts



Entry	Acid	pK_a	Orthoformate remaining (%)[a]	Assay yield (%)[b]
1	HCl	–8	0	91
2	H_2SO_4	–3.0	0	93
3	$MeSO_3H$	–2.6	0	90
4	H_3PO_4	2.1	50	31
5	AcOH	4.8	93	5

[a] As determined by ^{1}H NMR analysis of triethylorthoformate consumption.
[b] As determined by ^{1}H NMR.

In order to contain the hydrogen sulfide during the generation of *O*-ethyl thioformate the reaction was performed in a pressure vessel. Initial experiments at 2.1 bar demonstrated that the consumption of hydrogen sulfide could be easily monitored and controlled.[19] To avoid the use of perchloric acid, alternative Brønsted acids were examined as catalysts (Table 1). The performance of the catalyst corre-

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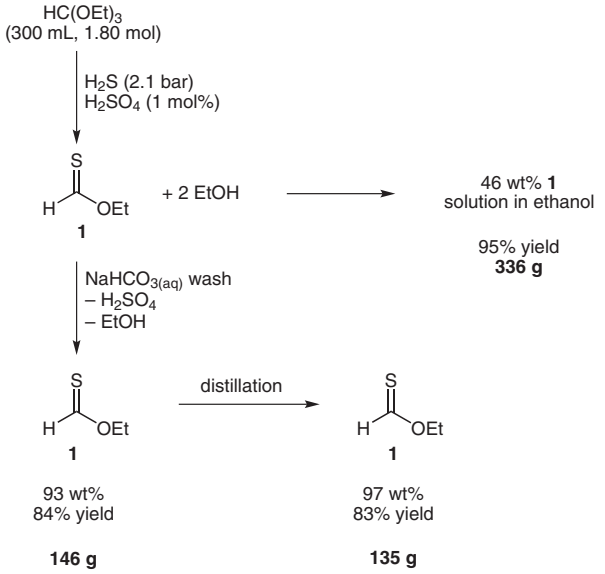
lated well with the pK_a of the acid. While hydrochloric, sulfuric, and methanesulfonic acids were competent catalysts, sulfuric acid was chosen for this transformation. Further development reduced the sulfuric acid charge to 1 mol%. Initially, small-scale preparations of *O*-ethyl thioformate required more than one equivalent of hydrogen sulfide, but as the scale of the reaction increased, the amount of H_2S consumed approached unity. When the synthesis of *O*-ethyl thioformate was performed on a preparative scale (1.80 mol) in a pressure vessel, only 1.26 equivalents of H_2S were required to fully consume triethylorthoformate.[20] A yellow solution of *O*-ethyl thioformate in ethanol (40–46 wt%) was reproducibly synthesized in 90% assay yield.



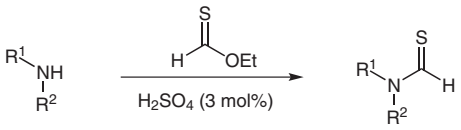
Scheme 2 Synthesis and isolation of *O*-ethyl thioformate

The ethanolic *O*-ethyl thioformate solution thus generated could be further purified. Basic aqueous washes removed the sulfuric acid and ethanol producing 93 wt% *O*-ethyl thioformate in 84% yield from the initial triethylorthoformate charge. Distillation at atmospheric pressure further purified *O*-ethyl thioformate, primarily by rejecting residual ethanol, yielding 97 wt% material in 83% overall yield from triethylorthoformate.[21] This procedure was demonstrated on a preparative scale (1.80 mol, Scheme 2). The isolated material is bench stable and can be easily stored for later use.[22]

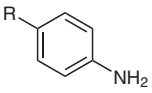
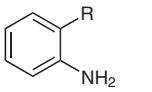
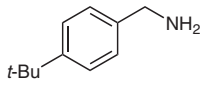
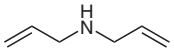
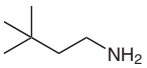
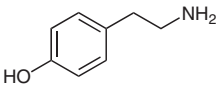
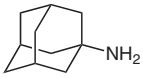
Having developed an efficient synthesis of *O*-ethyl thioformate, the thioformylation of amines was explored by using either the crude reagent as an ethanol solution or the purified thiolate in a variety of solvents. Thus, aniline was thioformylated in 95% and 99% yield with either crude or purified reagent, respectively (Table 2, entries 1 and 2).[23] Electron-rich anilines (entries 3, 6–8) were thioformylated with high efficiency. Electron-poor aromatic amines also performed well (83–94% yield, entries 4, 5, 9, 10). The condensation reaction tolerated aliphatic amines (entries 11–16), including benzylic, allylic, and sterically demanding systems, providing the thioamides in excellent yields. Secondary amines were also thioformylated with good efficiency, as demonstrated with diallylamine, morpholine, and diphenylamine (entries 12, 16, 17).

2-Aminopyridine was thioformylated in excellent yield under acid-catalyzed conditions (Table 2, entry 18), but the thioformylation of 3-aminopyridine failed, producing an intractable mixture using both thioformylation protocols (entry 19). However, by using the purified reagent under basic conditions, the thioformylation of 3-aminopyridine proceeded in 81% yield (Equation 1).

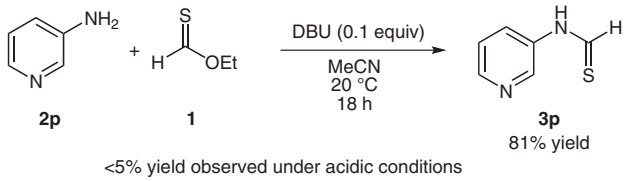
Table 2 Thioformylation of Amines with *O*-Ethyl Thioformate



2 **3**

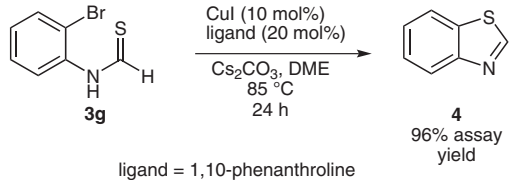
Entry	Amine			Yield (%)
1	R = H	**2a**		95[a]
2				99[b]
3	R = OMe	**2b**		99[a]
4	R = F	**2c**		94[a]
5	R = CN	**2d**		83[b]
6	R = Me	**2e**		95[a]
7	R = *i*-Pr	**2f**		69[a]
8				97[b]
9	R = Br	**2g**		84[a]
10				83[b]
11		**2h**		94[b]
12		**2i**		83[b]
13		**2j**		82[b]
14		**2k**		73[b]
15		**2l**		88[b]
16		**2m**		99[a]
17		**2n**	Ph_2NH	88[b]
18	R = 2-NH_2	**2o**		98[a]
19	R = 3-NH_2	**2p**		<5[a,b]

[a] Thioformylation performed using crude ethanolic reagent.
[b] Thioformylation performed using isolated thiolate.



Equation 1 Base-catalyzed thioformylation

This methodology was further expanded to the synthesis of thiazoles.[24] For example, the condensation of *ortho*-bromoaniline with *O*-ethyl thioformate produced the thioamide **3g** that was amenable to cyclization to benzothiazole (**4**) in 96% assay yield using copper-catalyzed conditions (Equation 2). By judicious application of this chemistry, a wide variety of benzothiazoles could be accessed quickly.



Equation 2 Copper-catalyzed benzothiazole formation

In summary, an efficient synthesis of *O*-ethyl thioformate has been developed. This process allows safe generation of the reagent on preparative scales (1.80 mol). The thiolate can be used directly as an ethanolic solution or further purified to a neat oil. This flexibility allows thioformylations to be performed under a variety of conditions, increasing the utility of this simple reagent and allowing access to a variety of substrates. We anticipate the applications of *O*-ethyl thioformate will increase as a result of this simple, safe procedure for its preparation. Other examples of its utility will be reported in due course.

Procedure for the Preparation of Ethanolic *O*-Ethyl Thioformate (1)

Triethylorthoformate (300 mL, 1.80 mol) and H_2SO_4 (98%, 0.96 mL, 0.018 mol) were charged to a pressure vessel and stirred under an atmosphere of N_2. The vessel was then pressurized to 2.1 bar with H_2S gas. Additional H_2S was charged to the vessel as needed to maintain the internal pressure at 1.7–2.1 bar. When no additional H_2S charges were required to maintain reaction pressure for 30 min (3 h from initial H_2S charge), the reactor was vented and purged with a nitrogen sweep. (Note: All gases were vented through an aqueous scrubber containing NaOH and NaOCl.) A yellow solution was isolated (336 g) that contained 46 wt% *O*-ethyl thioformate (95% yield).

Procedure for the Isolation of Neat *O*-Ethyl Thioformate (1)

The ethanolic solution of *O*-ethyl thioformate (336 g, 46 wt%), was washed with combined sat. aq $NaHCO_3$ (100 mL) and sat. NaCl (50 mL) three times. The organic solution was then washed with sat. aq NaCl (2 × 50 mL). The resulting yellow liquid (146 g) contained 93 wt% *O*-ethyl thioformate (84% yield from triethylorthoformate) and was distilled at atmospheric pressure (1 bar) to yield *O*-ethyl thioformate as a yellow oil (135 g, 97 wt%, 83% yield from triethylorthoformate; contains 3 wt% ethyl formate).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 4.59 (qd, *J* = 7.1, 1.1 Hz, 2 H), 1.44 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.7, 66.3, 13.4 ppm. IR (neat): 2983, 1381, 1294, 1218, 1151, 1105, 1009, 981, 906, 810, 626 cm^{-1}. HRMS (EI): *m/z* calcd for C_3H_6OS [M]: 90.0139; found: 90.0135. Bp 89–91 °C.

Representative Procedure for the Thioformylation of Amines Using Ethanolic *O*-Ethyl Thioformate: Synthesis of *N*-Phenylmethanethioamide (3a)

To a crude ethanolic solution of *O*-ethyl thioformate (19.49 g, 40 wt%, 86.5 mmol), was added aniline (2.62 mL, 28.8 mmol) via syringe under an atmosphere of N_2. The mixture was stirred at r.t. (20 °C) for 24 h, after which the reaction was concentrated to a residue. The resulting residue was recrystallized from EtOAc–heptane to yield *N*-phenylmethanethioamide (3.75 g, 95%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (d, *J* = 14.6 Hz, 1 H), 9.51 (br s, 1 H), 7.41 (t, *J* = 7.8 Hz, 2 H), 7.22–7.30 (m, 1 H), 7.16 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.4, 138.5, 130.0, 126.3, 118.9, 117.5 ppm. IR (neat): 1692, 1600, 1560, 1496, 1481, 1449, 1354, 1330, 1317, 1263, 1244, 1217, 1180, 1059, 1011, 943, 924, 891, 744, 683, 598, 573, 503, 432 cm^{-1}. ESI-HRMS: *m/z* calcd for C_7H_8NS [M + H]: 138.03720; found: 138.03666. Mp 136 °C.

Representative Procedure for the Thioformylation of Amines Using Neat *O*-Ethyl Thioformate: Synthesis of *N*-(1-Adamantyl)methanethioamide (3l)

H_2SO_4 (41 mg, 0.42 mmol, 96 wt%) was added to a mixture of 1-adamantylamine (2.19 g, 14.0 mmol) and *O*-ethyl thioformate (3.79 g, 42.0 mmol) in MeCN (11 mL) under an atmosphere of N_2. The mixture was stirred at r.t. (20 °C) for 22 h, after which the reaction was concentrated to a residue. The resulting residue was recrystallized from toluene–heptane to yield *N*-(1-adamantyl)methanethioamide as a white solid (2.40 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (d, *J* = 15.6 Hz, 1 H), 7.82 (br s, 1 H), 2.19 (br s, 3 H), 1.86 (d, *J* = 2.5 Hz, 6 H), 1.53–1.81 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.4, 56.2, 42.9, 35.6, 29.1 ppm. IR (neat): 3144, 3059, 3004, 2903, 2850, 1568, 1449, 1384, 1330, 1306, 1262, 1130, 1090, 1043, 972, 947, 934, 815, 619, 455, 422 cm^{-1}. ESI-HRMS: *m/z*: calcd for $C_{11}H_{18}NS$ [M + H]: 196.11545; found: 196.11450. Mp 246 °C.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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References and Notes

(1) (a) Hurd, R. N.; DeLaMater, G. *Chem. Rev.* **1961**, *61*, 45. (b) Zou, J. P.; Zeng, R. S.; Lu, Z. E.; Chen, K. Q. *Trends Heterocycl. Chem.* **2001**, *7*, 107.
(2) Seebach, D.; Lubosch, W.; Enders, D. *Chem. Ber.* **1976**, *109*, 1309.
(3) Scott, M. K.; Joacoby, H. I.; Mills, J. E.; Bonfilio, A. C.; Rasmussen, C. R. *J. Med. Chem.* **1983**, *26*, 535.

(4) Ireland, R. E.; Brown, F. R. *J. Org. Chem.* **1980**, *45*, 1868.
(5) (a) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780. (b) Murai, T.; Ui, K.; Narengerile *J. Org. Chem.* **2009**, *74*, 5703.
(6) Stowell, J. C.; Ham, B. M.; Esslinger, M. A.; Duplantier, A. J. *J. Org. Chem.* **1989**, *54*, 1212.
(7) (a) Helbert, M.; Renou, J. P.; Martin, M. L. *Tetrahedron* **1979**, *35*, 1087. (b) Mills, J. E. *Synthesis* **1986**, 482.
(8) Plieninger, H.; Petermann, J. *Tetrahedron* **1975**, *31*, 1209.
(9) De Benneville, P. L.; Strong, J. S.; Elkind, V. T. *J. Org. Chem.* **1956**, *21*, 772.
(10) Walter, W.; Maerten, G. *Justus Liebigs Ann. Chem.* **1963**, *669*, 66.
(11) (a) Babiano, M. A.; Garcia-Verdugo, C.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron Lett.* **1990**, *31*, 2467. (b) Park, H. S.; Lee, I. S.; Kim, Y. H. *Chem. Commun.* **1996**, *15*, 1805.
(12) Yde B, ; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* **1984**, *40*, 2047.
(13) Shibahara, F.; Sugiura, R.; Murai, T. *Org. Lett.* **2009**, *11*, 3064.
(14) Mayer, R.; Berthold, H. *Z. Chem.* **1963**, *3*, 310.
(15) Hartman, G. D.; Weinstock, L. M. *Org. Synth.* **1979**, *59*, 183.
(16) In our hands, the addition of H_2S to 7 g triethylorthoformate with 2 mol% $HClO_4$ (70 wt% aq solution) using a balloon (as described in ref. 6) yielded 75% *O*-ethyl thioformate with 25% ethyl formate. Using this procedure, the formation of *O*-ethyl thioformate decreased with an equal increase in the formation of ethyl formate as the scale of the reaction increased.
(17) (a) *Hydrogen Sulfide,* In *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck & Co., Inc.: Whitehouse Station NJ, **1996**, 823. (b) Truong, D. H.; Eghbal, M. A.; Hindmarsh, W.; Roth, S. H.; O'Brien, P. J. *Drug Metab. Rev.* **2006**, *38*, 733.
(18) (a) *Perchloric Acid,* In *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck & Co., Inc.: Whitehouse Station NJ, **1996**, 1231. (b) *Perchloric Acid,* In *CRC Handbook of Laboratory Safety*, 3rd ed.; Furr, A. K., Ed.; CRC Press, Inc.: Boca Raton FL, **1990**, 273–285.
(19) Hydrogen sulfide was charged to the reaction mixture at 2.1 bar. Consumption of H_2S was monitored as a decrease in pressure, and additional H_2S was added to maintain reaction pressure between 1.7 and 2.1 bar. The reaction was judged to be complete when the pressure change over 30 min was $<6.9 \cdot 10^{-2}$ bar.
(20) All excess H_2S was scrubbed by venting through a solution of aq NaOH and NaOCl.
(21) *O*-Ethyl thioformate purified by distillation typically contains 3 wt% ethyl formate as an impurity. The presence of ethyl formate does not affect the thioformylation chemistry described herein.
(22) When stored under nitrogen, **1** is stable for 1 month at r.t. and for 5 months at –20 °C. See Supporting Information.
(23) Details available in Supporting Information.
(24) (a) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (b) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446.