ORGANIC LETTERS

2002
Vol. 4, No. 1
111−113

2,2,2-Trifluoroethyl Formate: A Versatile and Selective Reagent for the Formylation of Alcohols, Amines, and *N*-Hydroxylamines

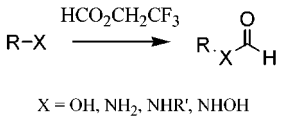
David R. Hill,* Chi-Nung Hsiao, Ravi Kurukulasuriya, and Steven J. Wittenberger

Abbott Laboratories, Global Pharmaceutical R&D, 1401 Sheridan Road, D-R450, Bldg. R8, North Chicago, Illinois 60064-4000

david.hill@abbott.com

Received October 30, 2001

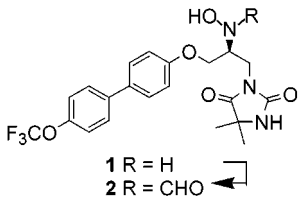
ABSTRACT



Treatment of a variety of alcohols, amines, and *N*-hydroxylamines with 2,2,2-trifluoroethyl formate gave the corresponding formylated adducts in high yields.

As part of an ongoing program directed at the synthesis of matrix metalloproteinase inhibitors, we required an efficient method for the formylation of the *N*-hydroxylamine **1** to give *N*-hydroxyformamide **2** (Scheme 1). The *N*-hydroxyformamide function is essential for the MMP inhibitory activity exhibited by this class of compounds.[1]

Scheme 1



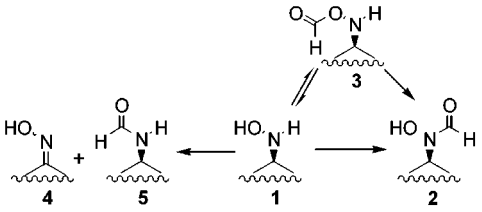
A variety of literature methods were examined but were found to give unsatisfactory results. In general, mixed anhydride methodologies (formic acid/EDAC,[2] formic acid/DCC,[3] acetic formic anhydride,[4] formyl-pivaloyl anhydride,[5] etc.) produced unacceptable amounts of *N*,*O*-bisformyl, *O*-formyl, and the associated acylated adducts. Cyanomethyl formate[6] gave selective *O*-formylation. Pentafluorophenyl,[7] 4-nitrophenyl,[8] phenyl,[9] and *N*-formyl imidazole[10] reacted similarly. Heating with ethyl formate[11] (or other simple alkyl formates) was more promising, but the reactions took several days at elevated temperatures to reach completion. These extended reaction times led to significant disproportionation[12] of the *N*-hydroxylamine to produce mixtures of *E*- and *Z*-oximes (**4**) and formamide (**5**), i.e., formylated primary amine (Scheme 2).

It was evident that a more reactive formylating reagent that would result in reduced reaction times was required. However, such a reagent (or reagents) should include a nucleophile to recycle any *O*-formylated adduct produced. 2,2,2-Trifluoroethyl formate (TFEF) was envisioned to be such a reagent. Surprisingly, a survey of the literature revealed that this compound has not been reported for the

(1) Michaelides, M. et al. *Curr. Pharm. Design* **1999**, *5*, 787−819.
(2) Chen, F. M. F.; Benoiton, N. L. *Synthesis* **1979**, 709.
(3) Waki, M.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 2019.
(4) Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081.
(5) Vlietstra, E. J.; Zwikker, J. W.; Nolte, R. J. M.; Drenth, W. *J. R. Neth. Chem. Soc*. **1982**, *101*, 460
(6) Deutsch, J.; Niclas, H.-J. *Synth. Commun*. **1993**, *23*(11), 1561−1568. Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H.-J. *Synthesis* **1996**, 37−38.
(7) Kisfaludy, L.; Otvos, L., Jr. *Synthesis* **1987**, 510.
(8) Yamamoto, K. *Bull. Chem. Soc. Jpn*. **1972**, *45*, 1253; Martinez, J.; Laur, J. *Synthesis* **1982**, 979.
(9) Yale, H. L. *J. Org. Chem*. **1971**, *36*, 3238.
(10) Kitagawa, T.; Ito, J.; Tsutsui, C. *Chem. Pharm. Bull.* **1994**, *42*, 1931.
(11) Schmidhammer, H.; Brossi, A. *Can. J. Chem.* **1982**, *60*, 3055.
(12) Yang, C. H.; Lin, Y. C. *J. Chin. Chem. Soc.* **1987**, *34*, 19.

10.1021/ol016976d CCC: $22.00
Published on Web 12/14/2001

Scheme 2

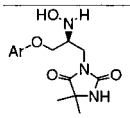
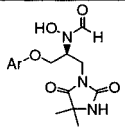
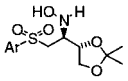
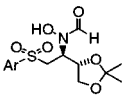
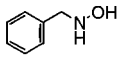
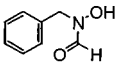
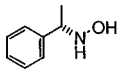
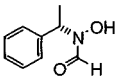


selective *N*-formylation of *N*-hydroxylamines, nor has the formylation of alcohols, amines and *N*-hydroxylamines been described. A report of the formylation of enolates has recently appeared.[13] We describe here our findings on the utility of TFEF as a versatile and selective reagent for the formylation of alcohols, amines, and hydroxylamines.

In contrast to many of the formylating reagents mentioned earlier, TFEF was simple to prepare from formic acid and 2,2,2-trifluoroethanol using a straightforward literature procedure.[14] TFEF was distilled from the reaction.[15] This procedure has been scaled up to prepare multi-kilogram quantities of the reagent. TFEF is stable at ambient temperature and can be stored on the bench for more than 2 years with no significant degradation.

Trifluoroethyl formate can be used in a variety of reaction manifolds depending on the presence of other additives. Initially we thought that the 2,2,2-trifluoroethanol produced in the reaction might act as a nucleophile and recycle the *O*-formyl adduct. However, it was quickly apparent that 2,2,2-trifluorethanol was too poor a nucleophile to deformylate this side product. For *N*-hydroxylamines (e.g., **1**), formic acid was typically employed. The presence of some formic acid in the reaction mixture appears to facilitate the conversion of the *O*-formyl isomer to the *N*-formyl product, either by *O*-to-*N* formyl transfer or by nucleophilic *O*-deformylation to regenerate starting material. A systematic study of formic acid concentration revealed that up to 20 wt % formic acid was tolerated in the reaction without significant degradation of the *N*-hydroxyformamide product. The optimum rate enhancement was seen when 10 wt % formic acid was used. Thus, for the formylation of *N*-hydroxylamine **1**, 10 equiv of TFEF reagent containing 10 wt % formic acid was employed. The resulting mixture was then heated at reflux until the substrate was consumed.[16] Early in the formylation reaction, the amount of *O*-formyl-*N*-hydroxylamine **3** relative to *N*-hydroxyformamide **2** was much greater than later on in the reaction, indicating that *O*-formylation was kinetically competitive with *N*-formylation. However, the *N*-formyl isomer is thermodynamically more stable than the *O*-formyl isomer and by the end of the reaction dominates the mixture (Scheme 2).

Table 1. *N*-Formylation of *N*-Hydroxylamines with 2,2,2-Trifluoroethyl Formate (TFEF)

substrate	reaction conditions	product	yield[a]
	10eq TFEF 10wt% HCO_2H THF/MTBE 4h, reflux		92%
	10eq TFEF 10wt% HCO_2H 1eq HCO_2Na IPAc 5h, 60°C		88%
	5eq TFEF 5h, 55°C MTBE		95%
	5eq TFEF 5h, 65°C THF		90%

[a] Yields determined after purification.

As illustrated in (Table 1) various *N*-hydroxylamines gave high yields of the corresponding *N*-formyl derivatives upon treatment with the TFEF reagent. It was typically necessary to heat these reactions in order to rapidly obtain the

(13) Zayia, G. H. *Org. Lett.* **1999**, *1*, 989.

(14) Blackburn, G. M.; Dodds, H. L. H. *J. Chem. Soc. B* **1971**, 826.

(15) **Preparation of Trifluoroethyl Formate (TFEF).** In a 3-L jacketed flask fitted with reflux condenser and temperature probe, 2,2,2-trifluoroethanol (500 g, 5.0 mol, 1.0 equiv) was combined with 95% formic acid (1000 g, 21.7 mol, 4.3 equiv). The mixture was then heated at an internal temperature of 80 °C for 18 h. NMR analysis of a sample taken after 18 h showed a 1.4:1 ratio of trifluoroethanol to trifluoroethyl formate. The mixture was then subjected to fractional distillation though a 10-in. vacuum jacketed fractionating column packed with Aldrich "Pro-pak" packing. The fraction boiling at <70 °C was collected; 448 g of distillate was obtained (70% yield adjusted for purity). The purity was assessed by NMR. Typically some 2,2,2-trifluoroethanol and formic acid codistill with the product if the distillation temperature is allowed to rise above 70 °C.

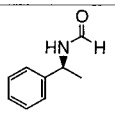
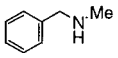
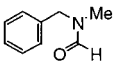
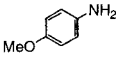
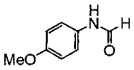
(16) **Typical Experiment.** The tosylate salt of *N*-hydroxylamine **1** (1.95 kg), was free based in tetrahydrofuran (5.07 kg) and methyl *tert*-butyl ether (4.12 kg) using 15% aqueous potassium bicarbonate solution (4.29 kg, 2.06 equiv vs tosylate salt of **1**). The mixture was stirred until all of the solids had dissolved. The separated organic portion assayed by HPLC for 1.346 kg (2.97 mol) *N*-hydroxylamine free base **1**. HPLC conditions: Zorbax SB-C8 (4.6 mm × 25 cm) column, gradient 40/60 to 43/57 0.1% phosphoric acid/acetonitrile over 5 min, then 43/57 isocratic to 15 min, then gradient 43/57 to 90/10 over 5 min, hold at 90/10 5 min; flow rate at 1.5 mL/min, UV detection at 260 nm. Peak identification: *N*-hydroxylamine **1** (7.1 min). The *N*-hydroxylamine free base solution was charged to a 100-L round-bottom flask. The solution was concentrated in vacuo to 20−30 wt % solution of *N*-hydroxylamine free base. The 2,2,2-trifluoroethyl formate reagent (5.27 kg at 71.9 wt % = 3.79 kg [29.6 mol, 10 equiv] containing 10 wt % formic acid) was charged to the *N*-hydroxylamine free base solution. The mixture was warmed to gentle reflux (internal temperature ca. 65 °C), and the reaction was monitored by HPLC for the disappearance of starting material. The reaction was continued until the peak area of the *N*-hydroxylamine **1** was less than 0.5% area (typically in ca. 4 h). The reaction mixture was cooled to less than 30 °C, water (5.33 kg) was added and mixed, and then the layers were separated. The organic portion was washed twice with 15 wt % aqueous potassium bicarbonate solution (ca. 5.3 kg portions). The organic portion was washed with water (4.76 kg). The organic layer was then solvent switched to ethyl acetate in vacuo. The concentration was measured by HPLC assay and adjusted by either solvent removal in vacuo or addition to within the range of 10−35% weight solution of product. To the stirred product solution was added heptanes (10.71 kg, 1.5 × wt of EtOAc in the solution) over 25 min. The suspension was stirred at ambient temperature for 2−4 h. The product was collected by filtration. The cake was rinsed with a solution of 1:2 (v/v) EtOAc/heptanes (5.63 kg). After the solvent was removed by suction, the solid was dried in vacuo (ca. 100 mmHg with a nitrogen sweep at 100 °C). The dried product, 2.685 kg (92% yield), had a potency of 100% and a chiral purity of ≥99% ee. Spectral data: ^{1}H NMR (300 MHz, d_6−DMSO) δ 9.95 (br s, 0.5H), 9.80 (br s, 0.5H), 8.41 (br s, 0.5H), 8.37 (br s, 0.5H), 8.35 (s, 0.5H), 7.95 (s, 0.5H), 7.76 (d, 2H, J = 8.9 Hz), 7.65 (d, 2H, J = 8.5 Hz), 7.43 (d, 2H, J = 8.5 Hz), 7.04 (d, 2H, J = 8.9 Hz), 4.92-4.80 (m, 0.5H), 4.50-4.38 (m, 0.5H), 4.28-4.06 (m, 2H), 3.82-3.68 (m, 1H), 3.66−3.54 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H).

N-hydroxyformamide as the exclusive product. Formic acid was again used as a catalyst in entry 2. In this case, it was beneficial to add 1 equiv of sodium formate to prevent the 1−2% acetonide cleavage that otherwise occurred.

To further explore the utility of the TFEF reagent, a variety of amine and alcohol substrates were formylated with the reagent. The results of this study are described below.

Table 2 illustrates that primary and secondary amines were rapidly converted into the corresponding formamides in near

Table 2. *N*-Formylation of Amines with 2,2,2-Trifluoroethyl Formate (TFEF)

substrate	reaction conditions	product	yield[a]
	1.1eq TFEF 1h, 0°C to r.t. MTBE		94%
	1.1eq TFEF 1h, 0°C to r.t. MTBE		99%
	1.1eq TFEF 18h, r.t. MTBE		99%
	5eq TFEF 10wt% HCO_2H 65°C 24h		83%

[a] Isolated yield after purification.

quantitative yield using 1.1 equiv of TFEF reagent. These reactions were mildly exothermic, requiring initial cooling (ice bath) while the TFEF reagent was added.

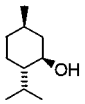
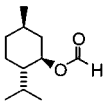
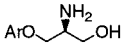
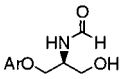
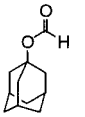
TFEF was also found to be effective in formylating both electron-rich and electron-poor anilines in high yields. The reaction of 2-nitroaniline is particularly noteworthy, requiring 24 h at 65 °C to produce the expected formamide in 83%. This compares favorably with the corresponding reaction using *N*-formylbenzotriazole,[17] which required 48 h at 138 °C to achieve a similar yield of 2-nitroformanilide

Secondary and tertiary alcohols were also efficiently transformed into the corresponding formates using TFEF. Thus, (1*R*,2*S*,5*R*)-(−)-menthol afforded the corresponding formate in 93% isolated yield after 18 h. As an example of a tertiary alcohol, 1-adamantanol yielded 53% of the corresponding formate after 72 h. In both cases, TFEF was used as the solvent. These results compare very favorably with corresponding formylations using other reagents. Moreover, this difference in reactivity between amines and alcohols toward the TFEF reagent is sufficient that a chemospecific formylation of a primary amine could be readily achieved in the presence of an unprotected primary alcohol.

The formylation of amino acid derivatives (Table 4) was readily achieved with TFEF. For example, serine benzyl ester was formylated starting with the hydrochloride salt in high

(17) Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503.

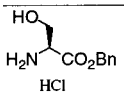
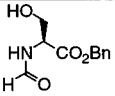
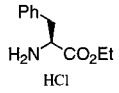
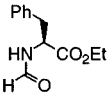
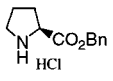
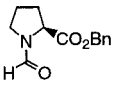
Table 3. *N*-Formylation of Alcohols and Amino Alcohols with 2,2,2-Trifluoroethyl Formate (TFEF)

substrate	reaction conditions	product	yield[a]
	5eq TFEF 10wt% HCO_2H 65°C, 18h		93%
	5eq TFEF THF r.t., 18h		97%
	10 eq TFEF 10% HCO_2H 65°C, 72h		51%

[a] Isolated yield after purification.

yield within 18 h. The reaction was initiated at 0 °C and subsequently warmed to ambient temperature. In the case

Table 4. *N*-Formylation of Amino Acid Derivatives with 2,2,2-Trifluoroethyl Formate (TFEF)

substrate	reaction conditions	product	yield[a]
	1.05eq TFEF 1eq HCO_2Na 18h, 0°C to r.t. THF		94%
	5eq TFEF 5eq HCO_2Na 18h, 65°C THF		95%
	2N K_2CO_3, then 10eq TFEF 18 h, 65°C THF		92%

[a] Isolated yield after purification.

of serine benzyl ester, formylation of the amine function occurred exclusively and no *O*-formylated product was observed. Phenylalanine ethyl ester and proline benzyl ester were somewhat more sluggish to react, requiring 18 h at reflux in THF for complete reaction. The hydrochloride salts could be neutralized either in situ with sodium formate or as a separate step using potassium carbonate for example.

In conclusion, 2,2,2-trifluoroethyl formate is easily prepared from inexpensive starting materials and can clearly be a powerful and versatile reagent for a variety of formylation reactions.

Supporting Information Available: Full experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016976D