TFFH as an Excellent Reagent for Acylation of Alcohols, Thiols and Dithiocarbamates

Michael Pittelkow,[a] Fadhil S. Kamounah,[b] Ulrik Boas,[a] Brian Pedersen,[a] Jørn B. Christensen*[a]

[a] Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark
Fax +4535322012; E-mail: jbc@kiku.dk

[b] Department of Lifescience and Chemistry, Roskilde University, Universitetsvej 1, Postal Box 260, 4000 Roskilde, Denmark

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Abstract: A convenient and easy procedure to synthesize esters and thioesters from the corresponding carboxylic acid using TFFH as the coupling reagent is described. The preparation of *N*-acyl-dithiocarbamates from carboxylic acids and 1,3-thiazolidine-2-thione with TFFH as the coupling reagent is also described.

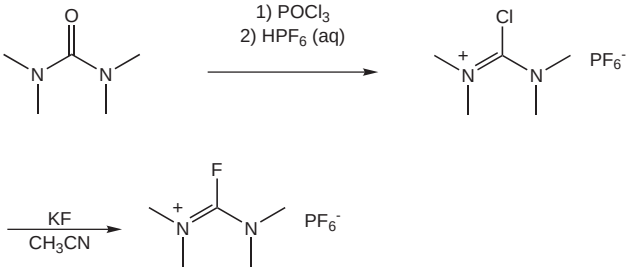
Key words: esterification, coupling reagents, acylations, esters, thioesters, thioacids, dithiocarbamates

Coupling of carboxylic acids with various nucleophiles to produce esters, amides, thioesters etc. belongs to the most important and most widely employed transformations in organic chemistry.[1] Many procedures have been developed to mediate these transformations since the classical Fischer esterification procedure using excess alcohol and strong Lewis or Brønsted acid catalysis.[2] Modern coupling reagents utilize an equimolar amount of acid and nucleophile. Besides being effective and easily handled, it is crucial that the conditions employed are mild and compatible with a wide variety of functional groups including the most common protecting groups.[1,3]

Dicyclohexylcarbodiimide (DCC) is one of the most widely used condensation agents in organic chemistry because it is inexpensive and can be used under mild reaction conditions.[4] DCC was introduced by Sheehan and coworkers[5] in 1955, and was crucial for the completion of the first total synthesis of penicillin V.[6] However, it has the disadvantage of low reactivity, formation of *N*-acylurea byproducts and high toxicity. The formation of *N*-acylurea byproducts lead to lowered yields and difficult purification, especially in polar aprotic solvents.[7]

The use of halo formamidinium salts such as the highly reactive 2-chloro-1,3-dimethylimidazolium chloride (DMC) and *N*,*N*,*N*,*N*-tetramethylchloroformamidinium chloride have only recently received attention as dehydration agents in the formation of carboxylic acid derivatives other than amides.[8] However, to the best of our knowledge fluoroformamidinium salts, generating in situ the acid fluoride as the active acylating agent, have only been described for amide and peptide synthesis.

Tetramethylfluoroformamidinium hexafluorophosphate, TFFH (**1**), was introduced by Carpino and co-workers and was shown to be an excellent peptide coupling reagent.[9] It is an easily handled crystalline compound, it has a long shelf-life and it reacts fast with carboxylic acids to give the corresponding acid fluorides or mixed anhydrides depending on the conditions. TFFH has been shown to be useful for coupling of highly hindered amino acids[10] and in the preparation of acid azides[11] and acid hydrazides.[12] TFFH has also been shown to be effective in the formation of isothiocyanates via the reaction between a primary amine, TFFH and carbondisulfide, both in solution[12] and on solid phase.[13]



1

Scheme 1 Convenient and low price synthesis of TFFH

Previously, we have described an inexpensive, convenient non-phosgene procedure for the large scale preparation of TFFH from tetramethylurea in two steps (Scheme 1).[12,14] TFFH has one of the lowest molecular weights of the tetraalkylhaloformamidinium salts, thus making it an attractive choice from an atom economical point of view.[15]

Herein we report our results demonstrating the use of TFFH in the synthesis of esters and thioesters via in situ acid fluoride formation (Scheme 2a). We also show that TFFH is effective in forming thioacids by reaction with a carboxylic acid and Na_2S, and the thioacids are easily reacted with bromides to produce thioesters (Scheme 2b). Chemoselective acylation of dithiocarbamates from in situ generated acid fluorides and thiazolidine-2-thione has been accomplished using TFFH (Scheme 3). These derivatives are useful for the preparation of aldehydes from the corresponding carboxylic acid by reduction with DIBAL, but the preparation of the acylated thiazolidine-2-thione usually proceeds via a Tl(I) salt making the synthetic procedure less attractive.[16]

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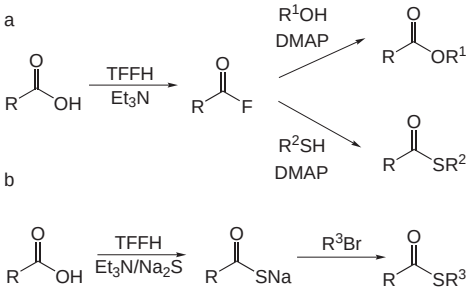
The acylation reactions proceed smoothly by addition of triethylamine to a concentrated solution of a carboxylic acid and one equivalent of TFFH in a variety of solvents such as dichloromethane, chloroform, THF and DMF. The reactions all proceed in high yields with little or no side reactions, and are catalyzed by addition of DMAP (typical 5–10 mol%). Inert atmosphere was only necessary when the reactants/products are air sensitive.

In Table 1 a number of esters are depicted that were prepared from the acid and the corresponding alcohol via the acid fluoride using TFFH as the fluorinating agent. The examples in Table 1 indicate that a wide range of functionalities are compatible with the mild esterification conditions.



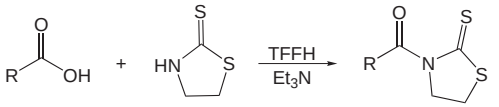
Scheme 2 Synthesis of esters and thioesters with TFFH

Entries 1–3 demonstrate that both linear and highly hindered alcohols can be used. Entry 4 shows that even the extremely acid-sensitive DMT group can be present, which makes the esterification procedure useful in the preparation of protected nucleotides for automated synthesis of nucleosides. Entry 5 shows that a bromoalcohol reacts selectively to give an ester. This compound has been prepared conveniently on a 30 gram scale, demonstrating that up-scaling was feasible. Entry 6 shows the preparation of a useful orthoester precursor of picolinic acid. Entries 7 and 8 utilize acrylic acid in the preparation of esters containing either an aza or a biphenyl moiety. The acrylic acid does not complicate the esterification procedure and the procedure was superior to the coupling between acrylic acid chloride and the corresponding alcohol in our hands. Entry 9 shows that the procedure works well on the difficult ferrocene carboxylic acid, again with a bromoalcohol as the coupling partner.

A variety of *O*-aryl esters were also prepared using TFFH as the dehydrating agent as shown in Table 2. Again, a wide range of functionalities are compatible with the esterification procedure. Entry 10 shows that the procedure works well on the difficult ferrocene carboxylic acid. We are interested in aromatic building blocks for application in liquid crystal displays and other disciplines within materials science. Our main focus is on biphenyl compounds and aza compounds, and esterification using substrates containing these functional groups worked without complications. It is noteworthy that sensitive functional groups such as the cinnamic acid and acrylate moiety do not interfere with the esterification procedure (entries 11 and 12). Entries 13 and 14 show that it is possible to mono-esterify 4,4′-dihydroxy biphenyl with TFFH in moderate yields.

Thioesters are useful compounds in materials science, and their preparation was demonstrated in two different ways. The first route proceeded via coupling between the acid fluoride, prepared from the corresponding carboxylic acid, and the thiol as shown in Scheme 2a. Entries 15 and 16 in Table 2 are examples of thioesters prepared in this way. Reactions between a carboxylic acid, TFFH and Na_2S gave the sodium salt of the corresponding thioacid as outlined in Scheme 2b. This can be reacted easily with alkyl halides to produce the thioesters shown in entries 17 and 18 in Table 3.

Thiazolidine-2-thione can be chemoselectively N-acylated in high yields with acid fluorides, prepared from carboxylic acids and TFFH (Scheme 3). This was demonstrated by the synthesis of two substrates as shown by entries 19 and 20 in Table 3.



Scheme 3 Chemoselective synthesis of *N*-acyl dithiocarbamates from thiazolidine-2-thione and the corresponding carboxylic acid

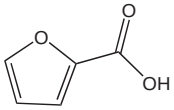
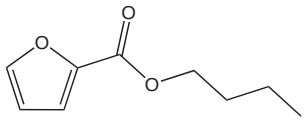
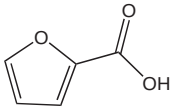
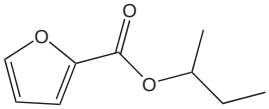
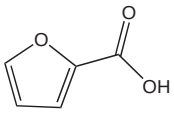
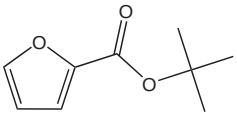
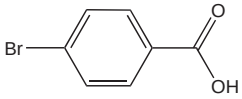
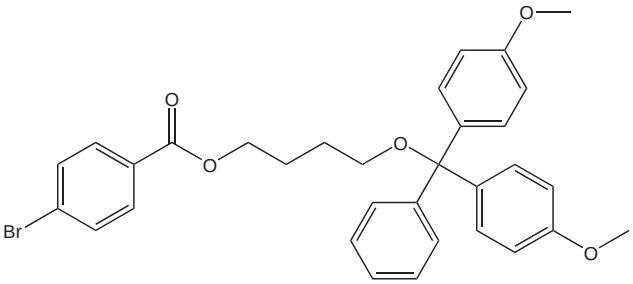
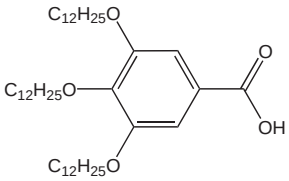
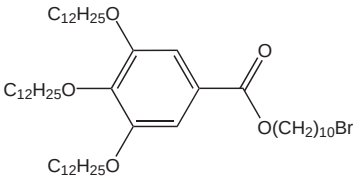
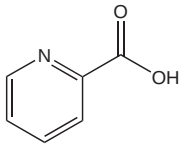
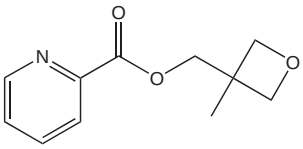
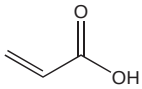
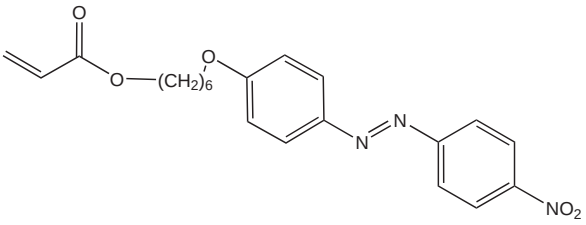
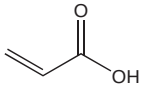
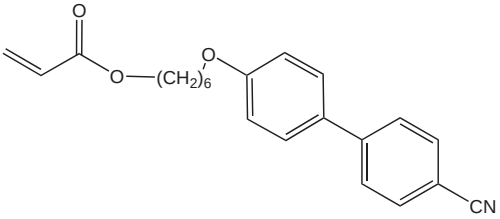
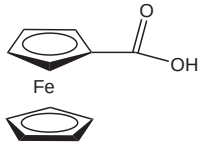
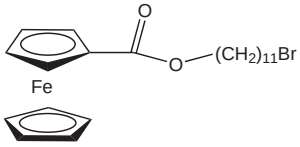
In conclusion, we have shown that TFFH is an easily handled and effective reagent for the preparation of esters, thioesters, thioacids and acylated thiazolidine-2-thione.

Unless otherwise stated, all starting materials were obtained from commercial suppliers and used as received. Solvents were HPLC grade and were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz NMR (Varian) apparatus (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) or on a 400 MHz NMR (Bruker) apparatus (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Proton chemical shifts are reported in ppm downfield from TMS and carbon chemical shifts in ppm downfield of TMS using the resonance of the deuterated solvent as internal standard. Melting points were measured on a Büchi B-140 apparatus and are uncorrected. Elemental analyses were performed by Mrs Karin Linthoe. Fast-atom bombardment (FAB) mass spectra were recorded on a Jeol JMS-HX 110A Tandem mass spectrometer in the positive ion mode using m-NBA as the matrix. HRMS were recorded on a Micromass Q-TOF apparatus using electrospray ionization (ESI) technique.

Esterification of Carboxylic Acids; General Procedure for Entries 1–14

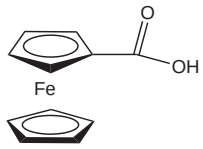
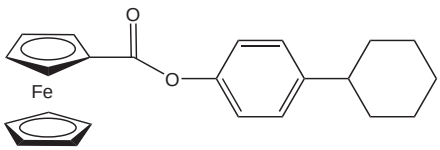
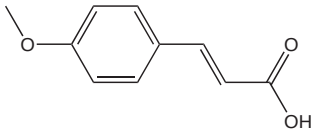
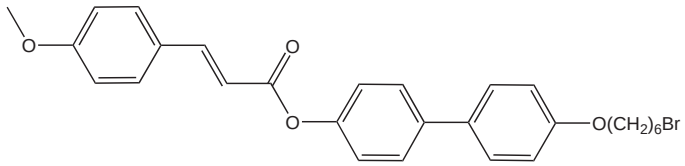
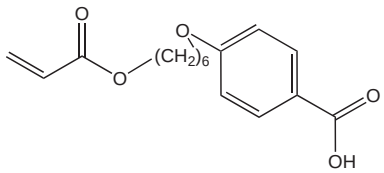
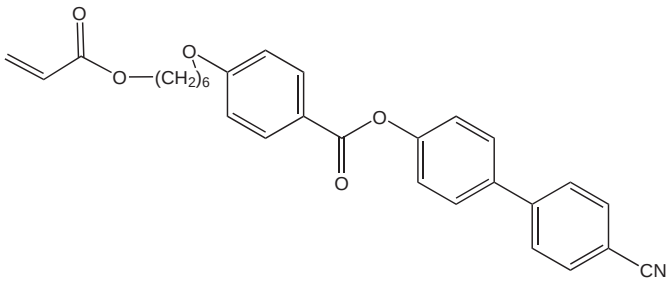
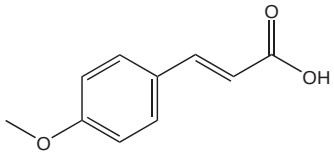
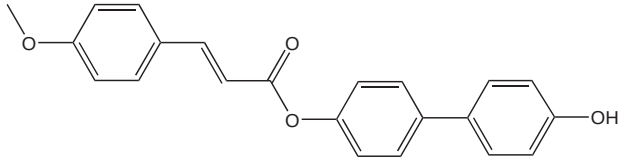
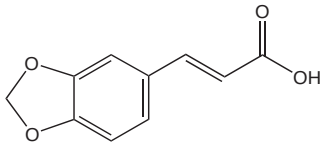
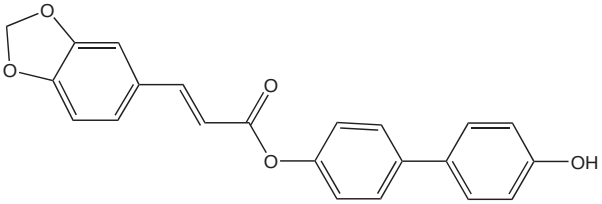
To an ice cooled suspension of the carboxylic acid (2.5 mmol) and TFFH (2.5 mmol, 0.66 g) in a minimum of solvent (ca. 10–20 mL) was added Et_3N (12.5 mmol, 1.26 g, 1.74 mL) resulting in a clear solution and some heat evolution. After stirring for 30 min at r.t. the alcohol (2.5 mmol) and a catalytic amount of DMAP (10 mol%, 30 mg) were added and the reaction mixture was stirred at r.t. over night. H_2O (30 mL) was added and the mixture extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting crude residue was purified by column chromatography (EtOAc–heptane) or recrystallization to yield the desired esters.

Table 1 Synthesis of *O*-Alkyl Esters from the Corresponding Carboxylic Acid Using TFFH

Entry	Carboxylic acid	Product[a]	Yield [%][b]
1			97
2			92
3			90
4			94
5			92
6			95
7			76(<90)[c]
8			60(<90)[c]
9			70(<90)[c]

[a] *O*-Alkyl ester via the acid fluoride.
[b] Isolated yields based on the carboxylic acid.
[c] Yields based on the acid and recovered alcohol.

Table 2 Synthesis of *O*-Aryl Esters from the Corresponding Carboxylic Acid Using TFFH

Entry	Carboxylic acid	Product[a]	Yield [%][b]
10			72(<90)[c]
11			76(<90)[c]
12			64(<90)[c]
13			42[c]
14			38[c]

[a] *O*-Aryl ester via the acid fluoride.
[b] Isolated yields based on the carboxylic acid.
[c] Yields based on the carboxylic acid and phenolic species.

Butyl-2-furoate (Entry 1)[17]
This compound was prepared from 2-furoic acid and 1-butanol using CH_2Cl_2 as the solvent.

Yield: 0.406 g, 97%; colorless oil.

^{1}H NMR ($CDCl_3$): δ = 0.96 (t, 3 H, *J* = 7.4 Hz), 1.39–1.45 (m, 2 H), 1.67–1.78 (m, 2 H), 4.30 (t, 2 H, *J* = 6.6 Hz), 6.48–6.51 (m, 1 H), 7.20 (d, 1 H, *J* = 1.2 Hz), 7.57 (d, 1 H, *J* = 6.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 13.6, 19.0, 30.6, 64.7, 111.6, 117.5, 144.8, 146.0, 158.6.

GC-MS: *m*/*z* = 168.

***sec*-Butyl 2-Furoate (Entry 2)[18]**
This compound was prepared from 2-furoic acid and 2-butanol using CH_2Cl_2 as the solvent.

Yield: 0.386 g, 92%; colorless oil.

^{1}H NMR ($CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.5 Hz), 1.32 (d, 3 H, *J* = 6.2 Hz), 1.54–1.68 (m, 2 H), 5.00–5.08 (m, 1 H), 6.44–6.47 (m, 1 H), 7.11 (d, 1 H, *J* = 5.8 Hz), 7.52–7.54 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 9.5, 19.4, 28.7, 72.9, 111.5, 117.2, 145.0, 145.8, 158.3.

GC-MS: *m*/*z* = 168.

***tert*-Butyl 2-Furoate (Entry 3)[19]**
This compound was prepared from 2-furoic acid and *tert*-butanol using CH_2Cl_2 as the solvent.

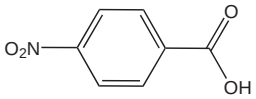
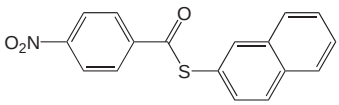
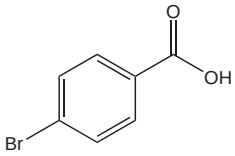
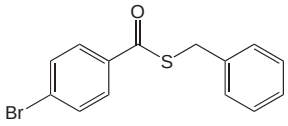
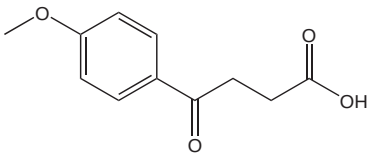
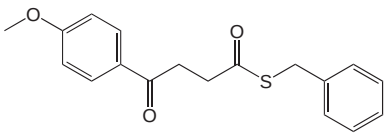
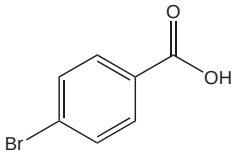
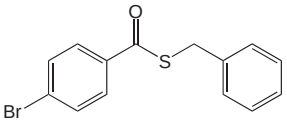
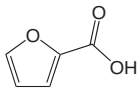
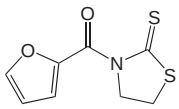
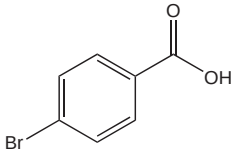
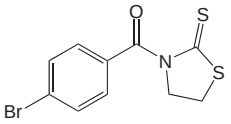
Yield: 0.380 g, 90%; colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 9 H), 6.38–6.39 (m, 1 H), 6.98 (d, 1 H), 7.45–7.46 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 28.1, 81.7, 111.4, 116.8, 145.5, 145.8, 157.9.

GC-MS: *m*/*z* = 168.

Table 3 Thioesters and Dithiocarbamates from the Corresponding Carboxylic Acid Using TFFH

Entry	Carboxylic acid	Product	Yield [%][d]
15[a]			90
16[a]			94
17[b]			60
18[b]			76
19[c]			94
20[c]			96

[a] Thioester via acid fluoride.
[b] Thioester via thioacid.
[c] Dithiocarbamate from 1,3-thiazolidine-2-thione.
[d] Isolated yields based on the carboxylic acid.

4-[Bis(4-methoxyphenyl)(phenyl)methoxy]butyl 4-Bromobenzoate (Entry 4)
This compound was prepared from 4-bromobenzoic acid and 4-[bis(4-methoxyphenyl)(phenyl)methoxy]butan-1-ol using CH_2Cl_2 as the solvent.

Yield: 94%; colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.70–1.79 (m, 2 H), 1.81–1.87 (m, 2 H), 3.12 (t, 2 H, *J* = 6.3 Hz), 3.77 (s, 6 H), 4.28 (t, 2 H, *J* = 6.5 Hz), 6.81 (d, 4 H, *J* = 8.9 Hz), 7.25–7.34 (m, 7 H), 7.43 (d, 2 H, *J* = 8.6 Hz), 7.56 (d, 2 H, *J* = 8.6 Hz), 7.87 (d, 2 H, *J* = 8.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 25.7, 26.6, 55.1, 62.7, 65.2, 85.7, 112.9, 113.1, 126.5, 127.0, 127.6, 128.0, 129.0, 131.0, 131.6, 136.4, 139.4, 145.1, 158.3.

HRMS (FAB): *m*/*z* (M^+) calcd for $C_{32}H_{31}BrO_5$: 574.1355; found: 574.1356.

10-Bromodecyl 3,4,5-Tris(dodecyloxy)benzoate (Entry 5)
This compound was prepared from 3,4,5-tris(dodecyloxy)benzoic acid (40 mmol, 27.0 g) and 10-bromodecan-1-ol (40 mmol, 9.49 g) using CH_2Cl_2 as the solvent.

Yield: 32.2 g, 90%; white solid; mp 34–34 °C.

^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 9 H), 1.26–1.30 (m, 56 H), 1.45–1.50 (m, 10 H), 1.70–1.90 (m, 10 H), 3.40 (t, 2 H), 4.01 (t, 6 H), 4.28 (t, 2 H), 7.24 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.0, 22.6, 25.9, 26.0, 28.0, 28.6, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 30.2, 31.8, 32.7, 33.9, 65.0, 69.1, 73.4, 107.9, 125.0, 142.3, 152.7, 166.4.

MS (DI): *m*/*z* = 893.5.

Anal. Calcd for $C_{53}H_{97}BrO_5$: C, 71.19; H, 10.93. Found: C, 70.88; H, 11.03.

(3-Methyloxetan-3-yl)methyl Pyridine-2-carboxylate (Entry 6)
This compound was prepared from pyridine-2-carboxylic acid and (3-methyloxetan-3-yl)methanol using CH_2Cl_2 as the solvent.

Yield: 0.492 g, 95%; colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 3 H), 4.30 (d, 2 H, *J* = 5.9 Hz), 4.42 (s, 2 H), 4.49 (d, 2 H, *J* = 5.9 Hz), 7.63–7.69 (m, 1 H), 7.98–8.10 (m, 2 H), 8.72–8.76 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 20.9, 45.9, 69.4, 78.5, 125.1, 127.5, 137.6, 147.5, 150.0, 164.8.

HRMS (FAB): *m*/*z* (MH^+) calcd for $C_{11}H_{14}NO_3$: 208.0974; found: 208.0975.

6-{4-[(4-Nitrophenyl)diazenyl]phenoxy}hexyl Acrylate (Entry 7)

This compound was prepared from acrylic acid and 6-{4-[(4-nitrophenyl)diazenyl]phenoxy}hexan-1-ol using CH_2Cl_2 as the solvent.

Yield: 76% (<90 based on recovered alcohol component); colorless solid; mp 101–103 °C.

^{1}H NMR ($CDCl_3$): δ = 1.38–1.47 (m, 4 H), 1.66 (quint, 2 H, *J* = 6.9 Hz), 1.78 (quint, 2 H, *J* = 5.7 Hz), 4.00 (t, 2 H, *J* = 5.6 Hz), 4.11 (t, 2 H, *J* = 6.5 Hz), 5.76 (dd, 1 H), 6.05 (dd, 1 H), 6.34 (dd, 1 H), 6.94 (d, 2 H, *J* = 9.0 Hz), 7.85–7.93 (m, 4 H), 8.26 (d, 2 H, *J* = 9.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 25.6, 28.4, 28.9, 64.3, 68.2, 114.8, 123.0, 124.6, 125.5, 128.4, 130.4, 146.7, 148.1, 155.9, 162.7, 166.2.

MS (FAB): *m*/*z* = 398.31 ($M + H^+$).

Anal. Calcd for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.29; H, 5.76; N, 10.58.

6-[(4′-Cyanobiphenyl-4-yl)oxy]hexyl Acrylate (Entry 8)

This compound was prepared from acrylic acid and 4′-[(6-hydroxyhexyl)oxy]biphenyl-4-carbonitrile using CH_2Cl_2 as the solvent.

Yield: 72% (<90 based on recovered alcohol component); white solid; mp 70–71 °C.

^{1}H NMR ($CDCl_3$): δ = 1.38–1.45 (m, 4 H), 1.60–1.80 (m, 4 H), 3.94 (t, 2 H, *J* = 6.4 Hz), 4.10 (t, 2 H, *J* = 6.6 Hz), 5.75 (dd, 1 H), 6.04 (dd, 1 H), 6.33 (dd, 1 H), 6.91 (d, 2 H, *J* = 6.8 Hz), 7.45 (d, 2 H, *J* = 8.8 Hz), 7.53–7.63 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 25.6, 28.4, 29.0, 64.3, 67.8, 109.9, 114.9, 119.0, 126.9, 128.2, 128.4, 130.4, 131.2, 132.4, 145.1, 159.6, 166.2.

MS (FAB): *m*/*z* = 349.14 (M^+).

Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.38; H, 6.62; N, 4.01.

Ferrocene Carboxylic Acid 11-Bromoundecyl Ester (Entry 9)

This compound was prepared from ferrocene carboxylic acid and 11-bromoundecan-1-ol using CH_2Cl_2 as the solvent.

Yield: 70%; orange solid; mp 51–52 °C (petroleum ether).

^{1}H NMR ($CDCl_3$): δ = 1.10–1.45 (m, 18 H), 1.55–1.85 (m, 4 H), 3.28–3.41 (m, 2 H), 4.10–4.40 (m, 5 H), 4.75–4.85 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 26.0, 26.8, 28.1, 28.6, 28.8, 29.2, 29.3, 32.7, 33.9, 45.1, 64.2, 69.9, 70.3, 71.5, 71.8, 171.7.

MS (FAB): *m*/*z* = 463.9 ($M + H^+$).

Anal. Calcd for $C_{22}H_{31}BrFeO_2$: C, 57.04; H, 6.75. Found: C, 57.40; H, 6.89.

Ferrocene Carboxylic Acid 4-Cyclohexylphenyl Ester (Entry 10)

This compound was prepared from ferrocene carboxylic acid and 4-cyclohexylphenol using CH_2Cl_2 as the solvent.

Yield: 78% (<90 based on recovered alcohol component); orange solid; mp 120–121 °C (petroleum ether).

^{1}H NMR ($CDCl_3$): δ = 1.30–1.40 (m, 5 H), 1.81–2.02 (m, 5 H), 2.45–2.54 (m, 1 H), 4.32–4.40 (m, 5 H), 4.40–4.52 (m, 2 H), 4.90–5.10 (m, 2 H), 7.10–7.20 (m, 2 H), 7.30–7.40 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 26.0, 26.8, 34.4, 43.9, 70.0, 70.3, 70.7, 71.9, 121.2, 127.6, 145.2, 148.7, 170.3.

GC-MS: *m*/*z* = 388.

Anal. Calcd for $C_{23}H_{24}FeO_2$: C, 71.15; H, 6.23. Found: C, 71.13; H, 6.23.

4′-[(6-Bromohexyl)oxy]biphenyl-4-yl 3-(4-Methoxyphenyl)acrylate (Entry 11)

This compound was prepared from 3-(4-methoxyphenyl)acrylic acid and 4′-[(6-bromohexyl)oxy]biphenyl-4-ol using a THF–CH_2Cl_2 mixture as the solvent.

Yield: 76% (<90 based on recovered alcohol component); colorless solid; mp 146–148 °C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 1.43–1.46 (m, 4 H), 1.73–1.76 (m, 2 H) 1.81–1.85 (m, 2 H), 3.35 (t, 2 H), 3.78 (s, 3 H), 3.92 (t, 2 H), 6.44 (dd, 1 H), 6.85–6.89 (m, 4 H), 7.12 (m, 2 H), 7.47–7.49 (m, 6 H), 7.76 (dd, 1 H).

^{13}C NMR ($CDCl_3$): δ = 25.3, 27.9, 29.0, 32.6, 33.7, 55.3, 67.7, 114.4, 114.6, 114.7, 121.8, 126.8, 127.6, 128.0, 129.9, 132.8, 138.4, 146.2, 149.7, 158.5, 161.6, 165.7.

MS (EI): *m*/*z* = 509.44.

Anal. Calcd for $C_{28}H_{29}BrO_4$: C, 66.01; H, 5.74. Found: C, 65.78; H, 5.68.

4′-Cyanobiphenyl-4-yl 4-{[6-(Acryloyloxy)hexyl]oxy}benzoate (Entry 12)

This compound was prepared from 4-{[6-(acryloyloxy)hexyl]oxy}benzoic acid and 4′-hydroxybiphenyl-4-carbonitrile using CH_2Cl_2 as the solvent.

Yield: 64% (<90 based on recovered alcohol component); colorless solid; mp 110–111 °C.

^{1}H NMR ($CDCl_3$): δ = 1.4–1.6 (m, 4 H), 1.69 (quint, 2 H, *J* = 7.5 Hz), 1.75 (quint, 2 H, *J* = 7.5 Hz), 3.99 (t, 2 H, *J* = 6.4 Hz), 4.11 (t, 2 H, *J* = 6.6 Hz), 5.74 (dd, 1 H), 6.07 (dd, 1 H), 6.33 (dd, 1 H), 6.90 (d, 2 H, *J* = 11.7 Hz), 7.25 (d, 2 H, *J* = 6.9 Hz), 7.53–7.68 (m, 6 H), 8.09 (d, 2 H, *J* = 11.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 25.6, 28.4, 28.9, 64.3, 68.0, 110.9, 114.2, 118.7, 121.2, 122.4, 127.6, 128.2, 128.4, 130.4, 132.2, 132.5, 136.6, 144.8, 151.5, 163.5, 164.7, 166.2.

MS (FAB): *m*/*z* = 470.21 ($M + H^+$).

Anal. Calcd for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.98. Found: C, 73.93; H, 5.75; N, 2.96.

4′-Hydroxybiphenyl-4-yl 3-(4-Methoxyphenyl)acrylate (Entry 13)

This compound was prepared from 3-(4-methoxyphenyl)acrylic acid and biphenyl-4,4′-diol using CH_2Cl_2 as the solvent.

Yield: 42%; colorless crystals; mp 220–222 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 3.82 (s, 3 H), 6.73 (dd, 1 H), 6.85 (m 2 H), 7.05 (m, 2 H), 7.24 (m, 2 H), 7.48 (m, 2 H), 7.60 (m, 2 H), 7.79 (m, 2 H), 7.85 (dd, 1 H), 9.56 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 55.5, 114.4, 114.6, 115.8, 122.2, 126.6, 127.0, 127.8, 130.2, 130.6, 137.9, 146.4, 149.4, 157.2, 161.6.

MS (EI): *m*/*z* = 346.38.

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.15; H, 5.17.

4′-Hydroxybiphenyl-4-yl 3-(1,3-Benzodioxol-5-yl)acrylate (Entry 14)

This compound was prepared from 3-(1,3-benzodioxol-5-yl)acrylic acid and biphenyl-4,4′-diol using THF as the solvent.

Yield: 38%; colorless crystals; mp 230–232 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 3.33 (s, 2 H), 6.75 (dd, 1 H), 6.86 (m, 1 H), 7.00 (m, 2 H), 7.25 (m, 2 H), 7.48 (m, 2 H), 7.58 (m, 2 H), 7.76 (m, 2 H), 7.81 (dd, 1 H), 9.55 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 101.8, 166.7, 108.6, 115.0, 115.8, 122.2, 125.6, 127.0, 127.8, 128.4, 130.2, 137.9, 146.4, 148.2, 149.3, 149.8, 157.2, 165.3.

MS (EI): *m*/*z* = 360.2.

Anal. Calcd for $C_{22}H_{16}O_5$: C, 73.33; H, 4.48. Found: C, 72.81; H, 4.48.

Thioesterification of Carboxylic Acids; General Procedure for Entries 15, 16

To an ice-cooled suspension of the carboxylic acid (2.5 mmol) and TFFH (2.5 mmol, 0.66 g) in a minimum of solvent (ca. 10–20 mL) was added Et_3N (12.5 mmol, 1.26 g, 1.74 mL) resulting in a clear solution and some heat evolution. After stirring for 30 min at r.t. the thiol (2.5 mmol) and a catalytic amount of DMAP (10 mol%, 30 mg) were added and the reaction mixture was stirred at r.t. over night. H_2O (30 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting crude residue was purified by column chromatography (EtOAc–heptane) or recrystallization to yield the desired thioesters.

***S*-2-Naphthyl 4-Nitrobenzenecarbothioate (Entry 15)[20]**

This compound was prepared from 4-nitrobenzoic acid and naphthalene-2-thiol using CH_2Cl_2 as the solvent.

Yield: 0.70 g, 90%; yellow solid; mp 180–182 °C.

^{1}H NMR ($CDCl_3$): δ = 7.45–7.52 (m, 3 H), 7.78–7.86 (m, 2 H), 7.89 (s, 1 H), 7.98–7.99 (m, 1 H), 8.13 (d, 2 H), 8.28 (d, 2 H).

^{13}C NMR ($CDCl_3$): δ = 123.3, 123.9, 126.7, 127.4, 127.8, 127.9, 128.4, 129.1, 130.8, 131.1, 133.5, 134.9, 141.2, 150.6, 188.9.

GC-MS: *m*/*z* = 309.

***S*-Benzyl 4-Bromobenzenecarbothioate (Entry 16)**

This compound was prepared from 4-bromobenzoic acid and phenylmethanethiol using CH_2Cl_2 as the solvent.

Yield: 94%; white solid; mp 67–68 °C.

^{1}H NMR ($CDCl_3$): δ = 4.32 (s, 2 H), 7.27–7.40 (m, 5 H), 7.58 (d, 2 H, *J* = 8.7 Hz), 7.83 (d, 2 H, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 33.7, 127.7, 128.7, 128.9, 129.0, 129.2, 132.1, 135.8, 137.4, 190.5.

GC-MS: *m*/*z* = 306.

Anal. Calcd for $C_{14}H_{11}BrOS$: C, 54.74; H, 3.61. Found: C, 55.31; H, 3.47.

Thioesterification of Carboxylic Acids via the Thioacid; General Procedure for Entries 16–18

To an ice-cooled suspension of the carboxylic acid (10 mmol) and TFFH (11 mmol, 2.91 g) in a minimum of dry DMF (ca. 5 mL) was added Et_3N (20 mmol, 2.02 g, 2.79 mL) resulting in a clear solution and some heat evolution. After stirring for 30 min at r.t. dry Na_2S (100 mmol, 7.81 g) was added and the reaction mixture was stirred at r.t. for 2 h. The reaction mixture was cooled to 0 °C and benzylbromide (100 mmol, 17.1 g) was added in one portion and stirring was continued over night. H_2O (50 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting crude residue was purified by recrystallization from MeOH to yield the desired thioesters. Alternatively the thioacids could be isolated using column chromatography on silica (heptane–EtOAc) resulting in comparable yields.

***S*-Benzyl 4-(4-Methoxyphenyl)-4-oxobutanethioate (Entry 17)**

This compound was prepared from 4-(4-methoxyphenyl)-4-oxobutanoic acid and benzylbromide.

Yield: 60%; pale yellow solid; mp 66–67 °C.

^{1}H NMR ($CDCl_3$): δ = 3.03 (t, 2 H, *J* = 7.1 Hz), 3.32 (t, 2 H, *J* = 6.7 Hz), 3.89 (s, 3 H), 4.15 (s, 2 H), 6.93 (d, 2 H, *J* = 9.0 Hz), 7.28–7.31 (m, 5 H), 7.95 (d, 2 H, *J* = 9.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 33.2, 37.6, 55.4, 113.7, 127.1, 128.5, 128.7, 129.4, 130.2, 137.4, 163.5, 195.9, 197.9.

MS (FAB): *m*/*z* = 314.97 ($M + H^+$)

Anal. Calcd for $C_{18}H_{18}O_3S$: C, 68.76; H, 5.77. Found: C, 68.74; H, 5.71.

***S*-Benzyl 4-Bromobenzenecarbothioate (Entry 18)**

This compound was prepared from 4-bromobenzoic acid and benzylbromide.

Yield: 76%; white solid.

For analytical data see compound **16**.

Acylation of Thiazolidine-2-thione; General Procedure for Entries 19, 20

To an ice-cooled suspension of the carboxylic acid (2.5 mmol) and TFFH (2.5 mmol, 0.66 g) in a minimum of solvent (ca. 20 mL) was added Et_3N (12.5 mmol, 1.26 g, 1.74 mL) resulting in a clear solution and some heat evolution. After stirring for 30 min at r.t. the thiazolidine-2-thione (2.5 mmol, 298 mg) was added and the reaction mixture was stirred at r.t. over night. H_2O (30 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting crude residue was purified by column chromatography (EtOAc–heptane) to yield the desired amides.

3-(2-Furoyl)-1,3-thiazolidine-2-thione (Entry 19)[8d]

This compound was prepared from 2-furoic acid and 1,3-thiazolidine-2-thione using CH_2Cl_2 as the solvent.

Yield: 0.501 g, 94%; yellow solid; mp 126–128 °C.

^{1}H NMR ($CDCl_3$): δ = 3.40 (t, 2 H, *J* = 7.2 Hz), 4.40 (t, 2 H, *J* = 7.2 Hz), 6.48–6.50 (m, 1 H), 7.20 (m, 1 H), 7.49–7.50 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 30.0, 56.0, 112.6, 120.1, 146.1, 146.7, 160.0, 201.1.

GC-MS: *m*/*z* = 213.

3-(4-Bromobenzoyl)-1,3-thiazolidine-2-thione (Entry 20)[16]

This compound was prepared from 4-bromobenzoic acid and 1,3-thiazolidine-2-thione using CH_2Cl_2 as the solvent.

Yield: 0.726 g, 96%; yellow solid; mp 119–120 °C.

For analytical data see reference.[16b]

Acknowledgment

The University of Copenhagen is acknowledged for a PhD fellowship for Michael Pittelkow.

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