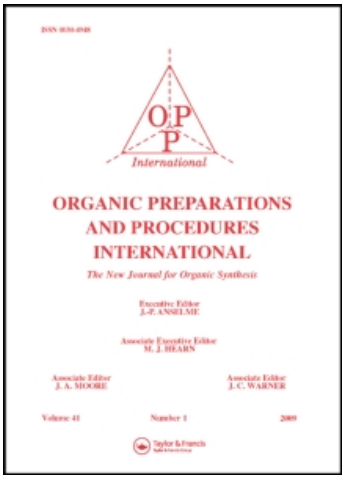

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TFFH AS A USEFUL REAGENT FOR THE CONVERSION OF CARBOXYLIC ACIDS TO ANILIDES, HYDRAZIDES AND AZIDES†

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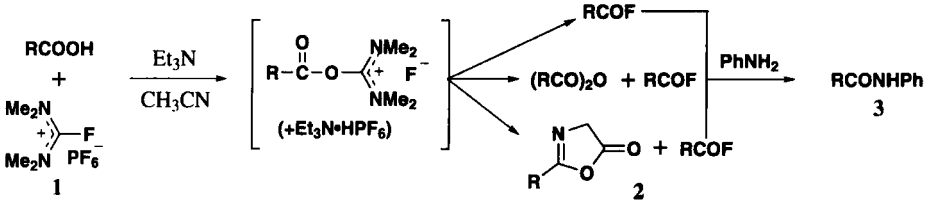
N-Protected amino acid fluorides are stable and powerful acylating reagents for peptide formation for both solution and solid phase peptide synthesis.[1] Such acid fluorides are more stable than the corresponding chlorides towards neutral oxygen nucleophiles such as water and methanol and yet appear to be of equal reactivity towards anionic nucleophiles and amines.[2] Recently, tetramethylfluoroformamidinium hexafluorophosphate (TFFH, **1**) was introduced by Carpino and El-Faham[3] and shown to be an excellent reagent for the *in situ* formation of acyl fluorides from the corresponding carboxylic acids. Moreover, TFFH is also a very convenient reagent for the preparation of isothiocyanates from the corresponding primary amines in the presence of carbon disulfide.[4] The present work describes the utility of TFFH for conversion of carboxylic acid to anilides, dihydrazides and acyl azides.

In preliminary studies, several anilides were prepared by activation of an equimolar solution of a carboxylic acid with TFFH in acetonitrile in the presence of triethylamine at 0°C. The mixture was stirred for 5-10 min and then aniline (1 equiv.) was added to the reaction mixture, followed by addition of one equivalent of triethylamine. The solution was stirred for 2 h at room temperature and then worked up to give the desired product (*Table 1*).



a) R = CH_3 b) R = $PhCH_2$- c) R = PhCH=CH- d) R = Z-Aib- f) R = Bz-Gly-

Scheme 1

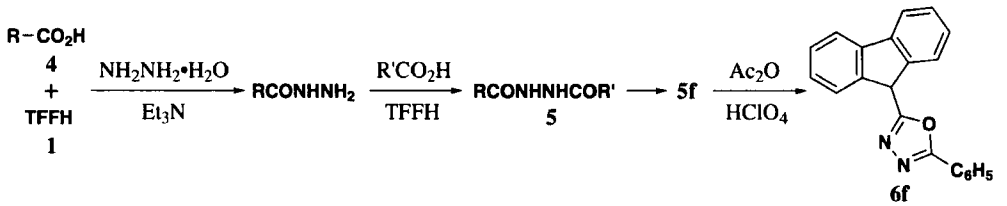
Table 1. Mps and Physical Data of Anilides [a]

Cmpd	Yield (%)	mp (°C)	*lit.* (°C)	Elemental Analysis (Found)		
				C	H	N
3a	80	112-114	111-112	----	----	----
3b	81	116-118	116-117	----	----	----
3c	76	150-152	151-152	----	----	----
3d	88	142-144	----	67.61(67.42)	5.63(5.82)	9.86(9.72)
3e	78	163-165	----	69.23(68.99)	6.41(6.62)	8.97(8.69)
3f	75	124-125	----	70.87(70.71)	5.51(5.38)	11.02(10.97)

[a] All products were fully characterized by spectroscopic data and they were in accordance with the values cited in the literature.[5c]

Infrared examination of the reaction mixture during the activation step provides a picture of the reactive intermediates present (*Scheme 1*). Activation of the *N*-benzyloxycarbonyl amino acids (Z-amino acids) by means of TFFH gave initially acid fluorides (IR: 1842 cm^{-1}) as the only detectable species. With the *N*-benzoyl amino acid, a mixture of the acid fluoride (IR: 1840 cm^{-1}) and the corresponding oxazolone **2e** (IR: 1830 and 1685 cm^{-1}) was formed and on standing, **2e** was converted exclusively to the acid fluorides by attack of fluoride ion.[3,6] Activation of carboxylic acids such as phenylacetic acid or cinnamic acid by means of TFFH gave mixtures of the acid fluorides (IR: 1842 cm^{-1}) and acid anhydrides (IR: 1824 and 1780cm^{-1}) in 1:1 ratio. For some weak nucleophiles, *e. g.*, 4-nitroaniline, it was found that the use of TFFH gave results that were less satisfactory than those obtained with isolated acid flourides.[6b]

We also successfully employed TFFH for the direct conversion of acids to *N,N'*-diaroylhydrazines (*Scheme 2*), which are valuable intermediates for the synthesis of oxadiazole,[7] and



5a) R = R' = 2-pyridyl; **5b**) R = R' = 2-furyl; **5c**) R = R' = *o*-ClC_6H_4; **5d**) R = R' = *o*-HOC_6H_4; **5e**) R = R' = *p*-$NO_2C_6H_4$; **5f**) R = 9-fluorenyl, R' = Ph; **5g**) R = 9-fluorenyl, R' = *p*-BrC_6H_4; **5h**) R = 9-fluorenyl, R' = *p*-ClC_6H_4; **5i**) R = 9-fluorenyl, R' = *o*-HOC_6H_4; **5j**) R = 9-xanthenyl, R' = *o*-HOC_6H_4; **5k**) R = Z-Gly, R' = 9-xanthenyl; **5l**) R = Z-Gly, R' = *o*-HOC_6H_4

Scheme 2

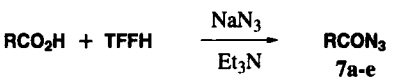
metal chelates.[8] Various carboxylic acids were activated in the presence of triethylamine and then condensed with hydrazine at ambient temperatures to give the corresponding symmetrical and unsymmetrical diaroylhydrazines (*Table 2*). Treatment of the diaroylhydrazine **(5f)** with acetic anhydride in the presence of perchloric acid at room temperature gave the corresponding 1,3,4-oxadiazole[9] **(6f)** (*Scheme 2*)

Table 2. Mps and Physical Data of *N,N'*-Diaroylhydrazines[a]

Entry	Yield (%)	mp. (°C)	*lit.*(°C)	Elemental Analysis (Found)		
				C	H	N
5a	83	225-226	224-226	----	----	----
5b	72	239-240	238-239	----	----	----
5c	71	220-222	221-222	----	----	----
5d	78	316-318	315-316	----	----	----
5e	85	298-300	297-298	----	----	----
5f	78	242-243	240-242	----	----	----
5g	78	286-289	285	----	----	----
5h	73	248-250	248	----	----	----
5i	74	263-264	----	73.26(73.00)	4.65(4.56)	8.14(7.95)
5j	76	246-248	----	70.00(69.75)	4.44(4.62)	7.78(7.53)
5k	75	293-295	----	66.82(66.95)	4.87(4.92)	9.74(9.58)
5l	73	237-239	----	59.48(59.23)	4.96(5.10)	12.24(12.10)

[a] All products were fully characterized by spectroscopic data and they were in accordance with the values cited in the literature.[9,10]

Activation of carboxylic acids with TFFH in the presence of sodium azide and triethylamine was carried out similarly (*Table 3*). Infrared examination of the reaction mixture after 5 min showed the presence of the acyl azide (IR: 2100 cm^{-1}) and traces of the acyl fluoride (IR: 1840 cm^{-1}). Eventually, the acyl fluoride disappeared (ca. 1 h). For all the systems described above, triethylamine is essential as no product is formed in its absence.



Scheme 3

Table 3. Preparation of Acyl Azides from Carboxylic Acid and NaN_3 Using TFFH

Entry	Product[a]	Yield (%)	mp. (°C)	*lit.* (°C)
7a	Benzoyl azide	78	25-27	29- 30
7b	*p*-Nitrobenzoyl azide	69	68-69	68-69
7c	*o*-Chlorobenzoyl azide	68	63-65	62-64
7d	3,5-Dinitrobenzoyl azide	60	102-105	100-102
7e	*p*-Toluoyl azide	80	89-91	88-90

[a]All products were fully characterized by spectroscopic data (IR; ^{1}HNMR; MS) and in accordance with literature.[11]

EXPERIMENTAL SECTION

Melting points were obtained in open capillary tubes using a melting heating apparatus and are uncorrected. NMR spectra were recorded using a Brucker 300 MHz instrument with TMS as internal standard. Infrared Spectra were recorded using a Shimadzu 8300 series Fourier Transform instrument. Elemental analyses were carried out at the University of Cairo, Microanalytical Laboratories. All solvents were HPLC grade or of equivalent purity and used without further purification.

General Procedure for Preparation of Anilides (3a-f).- The carboxylic acid (10 mmol) and TFFH (10 mmol) were suspended in DMF and the mixture was cooled in an ice bath and triethylamine (20 mmol) was added followed by aniline (10 mmol), while cooling in an ice bath. The reaction mixture was stirred at 0°C for 30 min and at room temperature for 2 h. The product was precipitated by adding 100 mL of cold water; it was then collected, washed with water, dried and recrystallized from an appropriate solvent.

Compound 3d, white solid from ethyl acetate/hexane. ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 6.85 (t, 1H, NH), 6.89-7.88 (m, 11H, Ar-H and N-H).

Compound 3e, white solid from ethyl acetate/hexane. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 6H, $2CH_3$), 6.8 (s, 1H, NH), 6.89-7.88 (m, 11H, Ar-H and N-H).

Compound 3f, white solid from ethyl acetate/hexane. ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 2H, CH_2), 9.30 (s, 2H, CH_2), 6.72(s, 1H, NH), 6.89-7.91 (m, 11H, Ar-H and N-H).

General Procedure for Preparation of Diaroylhydrazines (5a-l).- The carboxylic acid (10 mmol) and TFFH (10 mmol) was suspended in DMF. The mixture was cooled in an ice bath and triethylamine (20 mmol) was added followed by hydrazine hydrate (20 mmol). The reaction mixture was stirred at 0°C for 20 min and then at room temperature for 30 min. The monohydrazide was precipitated by addition of 100 mL of ice/water, collected, washed with water and then dried. The crude product (5 mmol) was added to another cold solution of the same or a different carboxylic acid (5 mmol), TFFH (5 mmol) and triethylamine (10 mmol) in DMF (10 mL). The reaction mixture was stirred at 0°C for 30 min and at room temperature for 2 h. The course of the reaction was followed by TLC, EtOAc/hexane; 70/30. The diaroylhydrazine was precipitated by adding ice cold water (100 mL), it was then collected, washed with water, dried and recrystallized from an appropriate solvent.

***N*-Fluorenyl-9-carbonyl-*N'*-salicylylhydrazine (5i)**, yellowish-white solid from benzene/methanol. ^{1}H NMR (DMSO-d_6): δ 4.99 (s, 1H), 6.91-6.98 (m, 2H), 7.33-7.44 (m, 8H), 7.6 (d, 1H). MS: m/z = 345.

***N*-Xanthenyl-9-carbonyl-*N'*-salicylylhydrazine (5j)**, yellowish white solid from ethyl acetate. ^{1}H NMR (DMSO-d_6): δ 5.1 (s, 1H), 6.90-7.15 (m, 2H), 7.31-7.82 (m, 10H), 7.85-7.87 (m, 2H), 10.65 (s, 1H), 10.95 (s, 1H), 11.82 (s, 1H). MS: m/z = 360.

***N*-(-Z-Gly)-*N'*-Xanthenyl-9-carbonylhydrazine (5k)**, white solid from ethyl acetate. ^{1}H NMR (DMSO-d_6): δ 3.91 (d, 2H), 5.02 (s, 1H), 7.08-7.20 (m, 5H), 7.30-7.82 (m, 8H), 8.77 (t, 1H), 10.18 (s, 1H), 10.58 (s, 1H). MS: m/z = 432.

***N*-(Z-Gly)-*N'*-salicylylhydrazine (5l)**, white solid from ethyl acetate. ^{1}H NMR (DMSO-d_6): δ 4.01 (d, 2H), 6.90-6.96 (m, 2H), 7.43-7.55 (m, 5H), 7.87-7.91 (m, 2H), 8.87 (t, 1H), 10.36 (s, 1H), 10.65 (s, 1H), 11.85 (s, 1H). MS: m/z = 344.

General Procedure for Preparation of Acyl Azides (7a-e).- To a stirred solution of carboxylic acid (5 mmol) and TFFH (5 mmol) in dry acetone (20 mL) was added triethylamine (1.30 mL, 10 mmol) at 0°C. The reaction mixture was stirred at this temperature for about 5 min and then sodium azide (0.65 g, 10 mmol) was added over a period of 2-3 min. The reaction mixture was slowly allowed to warm up to room temperature and then stirred for 24 h. The reaction mixture was filtered to remove insoluble salts and the filtrate was evaporated under vacuum, the product was purified by passage through a short silica gel column using a 50/50 mixture of acetone and petroleum ether as eluent. The solvent was removed under reduced pressure to give the pure acyl azides.

Synthesis of 2-Phenyl-5-(9-fluorenyl)-1,3,4-oxadiazole (6f).- Perchloric acid (0.4 mL, 80% v/v) was added dropwise to a cold solution of *N*-fluorenyl-9-carbonyl-*N'*-benzoylhydrazine (**5f**) (0.36 g, 1.1 mmol) in acetic anhydride (4 mL) at such a rate that the temperature did not rise above 40°C and the resulting clear solution was set aside at room temperature for 4-6 h. The reaction mixture was treated with ether (20 mL) to give an oily product, and then triturated with sodium carbonate solution (5%), collected, washed with ether (2 x 10 mL). The product obtained was recrystallized from ethanol to give 0.19 g (61%) white crystals, mp. 168-170°C. ^{1}H NMR (DMSO-d6): δ 5.4 (s, 1H), 7.53-7.84 (m, 13H). MS: m/z = 310.

Anal. Calcd for $C_{21}H_{14}N_2O$: C, 81.29; H, 4.52; N, 9.03. Found: C, 81.05; H, 4.76; N, 9.31

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†**Abbreviations used**: TFFH = Tetrafluoroformamidinium hexafluorophosphate; DMF = Dimethylformamide; Z-Gly- = *N*-Benzyloxycarbonyl glycine; Z-Aib: *N*-Benzyloxycarbonyl α-aminoisobutyric acid; Bz-Gly = *N*-Benzoylglycine. Amino acids are abbreviated and designated following the rules of the IUPAC-IUB Commission of Biochemical Nomenclature (J. Biol. Chem., 247 (1972) 977).

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