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Convenient synthesis of furan-3-carboxylic acid and derivatives

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Abstract—A convenient synthesis of furan-3-carboxylic acid and derivatives from aromatization of 4-trichloroacetyl-2,3-dihydrofuran followed by nucleophilic displacement of the trichloromethyl group by hydroxide, alcohols, and amines, is presented.

Furans have attracted much attention due to their presence in commercially important pharmaceuticals, agrochemical bioregulators, dyes and photosensitizers, essential oils and cosmetics, fungicides, and their occurrence in natural compounds.[1] More specifically, the 2-methyl-furan-3-carboxylic acid phenylamine, commercially known as Fenfuram, is used as fungicidal seed dressing for the control of bunts and smuts.[2]

Derivatization of the 2-position of furan is usually achieved from a simple electrophilic aromatic substitution,[3] however, the introduction of a substituent in the position 3 (or 4) of furans requires special strategies. Many methodologies to functionalize the position 3 of furans have been reported but most of them involve multi-step synthesis,[4–6] modification of butyrolactone derivatives,[7] or the synthesis is accomplished with the use of expensive reagents.[8] More specifically, the introduction of carboxylic acid derivatives in position 3 of furans has been resumed in few cases. All these procedures involve a cyclization of acyclic compounds, which bears a carboxyl group in the appropriate position.[9–11]

In this work, a simple and convenient method to prepare furan-3-carboxylic acid and derivatives from the readily available 4-trichloroacetyl-2,3-dihydrofuran **1**, is presented. The synthetic potential of **1** for the synthesis of isoxazoles,[12] pyrazoles,[13] pyrimidines,[14–16] 3-aminomethylene-dihydro-furan-2-ones,[17] and analogues of cyclophosphamide,[18] has been reported.

The synthesis of 3-carbonylfuran derivatives was carried out in two steps (Scheme 1). In the first, the 4-trichloroacetyl-2,3-dihydrofuran[12] **1** was expected to react with N-bromosuccinimide in carbon tetrachloride in the presence of a catalytic amount of a peroxide to give the 3-bromo-2,3-dihydrofuran derivative, which was not isolated. Instead, the 3-trichloroacetylfuran **2** (see Scheme 1) was obtained after 2 h under reflux. Compound **2** was purified by vacuum distillation and obtained in 60% yield.

Treatment of compound **2** with sodium hydroxide solution gave the furan-3-carboxylic acid in 70% yield. The carboxylic acid derivative was isolated by acidifying the reaction mixture to pH ~2. At this pH, compound **3a** precipitated and was isolated by filtration and dried in desiccator under phosphorus pentoxide.

Reaction of **2** with alcohols in the presence of triethylamine, in sealed tube, led to furan-3-carboxylic esters, in good yields (see Table 1). Esters **3b** and **3c** were obtained from the reaction of **2** with an excess of methanol and ethanol, respectively, and the sealed tube was maintained in a water bath at 65 °C for 16 h. Esters **3d–f** were obtained from the reaction of **2** with an equivalent of allyl-, propargyl-, and benzyl-alcohols, respectively. The reactions were carried out in triethylamine, toluene as solvent, and the sealed tubes were maintained in a sand bath at temperatures indicated in Table 1. Esters **3b–f**

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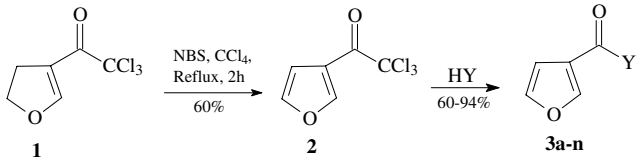

Compound	3a	3b	3c	3d	3e	3f	3g	3h
Y	-OH	$-OCH_3$	$-OCH_2CH_3$	$-OCH_2CH{=}CH_2$	$-OCH_2C{\equiv}CH$	$-OCH_2Ph$	$-NH_2$	$-NHCH_3$

Compound	3i	3j	3k	3l	3m	3n
Y	$-NHCH_2CH{=}CH_2$	$-NHNH_2$	-N	-N O	-NHPh	$-NHCH_2Ph$

Scheme 1.

Table 1. Reaction conditions for the synthesis of furan-3-carboxylic acid and derivatives from compound **2**

HY, Reaction condition	Yield (%)[a]	Mp (°C)	Product
NaOH 1 M solution, benzene, reflux, 16 h	70	118–120[b]	**3a**
Methyl alcohol, Et_3N, sealed tube, 65 °C, 16 h	72	Oil	**3b**
Ethyl alcohol, Et_3N, sealed tube, 65 °C, 16 h	70	Oil	**3c**
Allyl alcohol, toluene, Et_3N, sealed tube, 98 °C, 24 h	60	Oil	**3d**
Propargyl alcohol, toluene, Et_3N, sealed tube, 114 °C, 24 h	85	Oil	**3e**
Benzyl alcohol, toluene, Et_3N, sealed tube, 200 °C, 24 h	80	Oil	**3f**
Ammonium hydroxide, sealed tube 80 °C, 20 h	72	169–171	**3g**
Methylamine (28% water sol.), sealed tube 80 °C, 20 h	80	98–101	**3h**
Allylamine, toluene, sealed tube, 80 °C, 24 h	91	Oil	**3i**
Hydrazine hydrate, toluene, sealed tube, 100 °C, 20 h	73	105–108	**3j**
Piperidine, toluene, sealed tube, 100 °C, 16 h	67	Oil	**3k**
Morpholine, toluene, sealed tube, 60 °C, 20 h	76	Oil	**3l**
Aniline, toluene, sealed tube, 180 °C, 72 h	91	Oil	**3m**
Benzylamine, toluene, sealed tube, 110 °C, 24 h	94	120–122	**3n**

[a] Yields of isolated compounds.
[b] Mp from literature 122–124 °C.[19]

were isolated by adjusting the reaction mixture to pH ~6 followed by extraction with ethyl acetate. All esters were obtained considerably pure by ^1H NMR, but they were further purified by column chromatography in silica gel (230–400 mesh) and eluted with a mixture of hexane/ethyl acetate (80:20).

Reaction of **2** with ammonium hydroxide, primary, and secondary amines, in sealed culture tubes, furnished a series of furan-3-carboxamides, in good yields. The reaction of **2** with ammonium hydroxide and methyl amine (water solution) were carried out in a sealed culture tube at 80 °C. The reaction of **2** with allylamine, morpholine, piperidine, aniline, benzylamine, and hydrazine were carried out in sealed tubes, in toluene, under temperature and reaction times indicated in Table 1. Amides **3g**–**n** were isolated by adjusting the pH of the reaction mixture to approximately 5 with 1 M hydrochloric acid solution followed by extraction with ethyl acetate. The solid products **3g**, **3h**, **3j**, and **3n** were further purified by recrystallization from a mixture of hexane/ethyl acetate and the oils **3i**, **3k**–**m** were purified by column chromatography in silica gel (230–400 mesh) and eluted with a mixture of hexane/ethyl acetate/dichloromethane (3:1:0.5). All products were analyzed by GC/MS and ^1H and ^{13}C NMR.[20]

In conclusion we have demonstrated a simple and convenient procedure to prepare a series of 3-tricloroacetyl furan, furan-3-carboxylic acid, esters, and amides derivatives, from the readily available 3-trichloroacetyl-4,5-dihydrofuran.

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20. Following are ^{1}H NMR and ^{13}C NMR, and GCMS spectral data of compounds: **2**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.96 (dd, 1H, $^3J_{H4-H5} = 1.4$ Hz, $^4J_{H4-H2} <$ 1.0 Hz, H-4), 7.50 (dd, 1H, $^3J_{H5-H4} = 1.4$ Hz, $^4J_{H5-H2} <$ 1.0 Hz, H-5), 8.36 (dd, 1H, $^3J_{H2-H4} =$, 1.0 Hz, $^4J_{H2-H5} <$ 1.0 Hz, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 95.4 (CCl_3), 110.9 (C-4), 118.3 (C-3), 143.7 (C-5), 150.6 (C-2), 176.4 (C=O). GCMS (EI, 70 eV) *m/z* (%): 213 (M^+, 3), 149 (10), 95 (100). Anal. Calcd for $C_6H_3Cl_3O_2$ (213.44): C, 33.76; H, 1.42. Found: C, 33.58; H, 1.63.
3a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.78 (d, 1H, $^3J_{H4-H5} = 1.3$ Hz, H-4), 7.45 (d, 1H, $^3J_{H5-H4} = 1.3$ Hz, H-5), 8.12 (d, 1H, $^3J_{H2-H4} < 1.0$ Hz, H-2), 11.03 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 110.1 (C-4), 119.0 (C-3), 144.3 (C-5), 149.4 (C-2), 169.16 (C=O). GCMS (EI, 70 eV) *m/z* (%): 112 (M^+, 100), 95 (92).
3b: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.83 (s, 3H, OCH_3), 6.74 (d, 1H, $^3J_{H4-H5} = 1.3$ Hz H-4), 7.43 (d, 1H, $^3J_{H5-H4} =$ 1.3 Hz, H-5), 8.02 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.4 (OCH_3), 109.6 (C-4), 119.1 (C-3), 143.6 (C-5), 147.6 (C-2), 163.4 (C=O).
3c: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, $^3J = 7.1$ Hz, CH_3), 4.21 (q, 2H, $^3J = 7.1$ Hz, OCH_2), 6.65 (dd, 1H, $^3J_{H4-H5} = 1.3$ Hz, $^4J_{H4-H2} < 1.0$ Hz, H-4), 7.34 (d, 1H, $^3J_{H5-H4} = 1.3$ Hz, H-5), 7.93 (dd, 1H, $^3J_{H2-H4} < 1.0$ Hz, $^4J_{H2-H5} < 1.0$ Hz, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (CH_3), 60.2 (OCH_2), 109.6 (C-4), 119.4 (C-3), 143.5 (C-5), 147.4 (C-2), 162.9 (C=O).
3d: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.75 (d, 2H, $J = 5.6$ Hz, –CH_2–), 5.25–5.42 (m, 2H, =CH_2), 5.89–6.07 (m, 1H, =CH), 6.76 (s, 1H, H-4), 7.43 (s, 1H, H-5), 8.04 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 64.9 (OCH_2), 109.7 (C-4), 118.0 (C-3), 119.1 (=CH_2), 132.0 (CH=), 143.6 (C-5), 147.5 (C-2), 162.6 (C=O). GCMS (EI, 70 e V) *m/z* (%): 152 (M^+, 6), 95 (100).
3e: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.46 (t, 1H, $^4J = 2.4$ Hz, ≡CH), 4.76 (d, 2H, $^4J = 2.4$ Hz, –CH_2–), 6.67 (dd, 1H, $^3J_{H4-H5} = 1.3$, $^3J_{H4-H2} < 1.0$ Hz, H-4), 7.35 (dd, 1H, $^3J_{H5-H4} = 1.3$, $^3J_{H5-H2} < 1.0$ Hz, H-5), 7.97 (dd, 1H, $^3J_{H2-H4} < 1.0$, $^3J_{H2-H5} < 1.0$ Hz, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.3 (–CH_2–), 73.0 (≡CH), 77.1 (–C≡), 109.1 (C-4), 117.9 (C-3), 143.3 (C-5), 147.6 (C-2), 166.8 (C=O). GCMS (EI, 70 e V) *m/z* (%): 150 (M^+, 100), 95 (92).
3f: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.28 (s, 2H, –CH_2–), 6.75 (d, 1H, $^3J_{H4-H5} = 2$ Hz, H-4), 7.33–7.39 (m, 6H, H-5, Ph), 8.02 (d, 1H, $J < 1.0$ Hz, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 66.1 (–CH_2–), 109.8 (C-4), 128.0, 128.1, 128.4, 135.9 (Ph), 143.7 (C-5), 147.8 (C-2), 162.8 (C=O). GCMS (EI, 70 e V) *m/z* (%): 202 (M^+, 24), 184 (14), 95 (100).
3g: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.91 (s, 1H, H-4), 7.23 (br s, 2H, NH_2), 7.70 (s, 1H, H-5), 8.18 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.3 (C-4), 122.9 (C-3), 144.0 (C-5), 145.3 (C-2), 163.4 (C=O). GCMS (EI, 70 eV) *m/z* (%): 111 (M^+, 60), 95 (100).
3h: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.89 (d, 3H, $J = 4.4$ Hz, NMe) 6.91 (s, 1H, H-4), 7.23 (br s, 1H, NH), 7.70 (s, 1H, H-5), 8.18 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.8 (NMe) 109.3 (C-4), 122.9 (C-3), 144.0 (C-5), 145.3 (C-2), 163.4 (C=O). GCMS (EI, 70 eV) *m/z* (%): 111 (M^+, 60), 95 (100).
3i: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.88–3.93 (m; 2H, CH_2), 5.01–5.16 (m, 2H, =CH_2), 5.70–5.88 (m, 1H, =CH), 6.63 (d, 1H, $^3J_{H4-H5} = 1.7$ Hz, H-4), 6.70 (br s, 1H, NH), 7.33 (d, 1H, $^3J_{H5-H4} = 1.7$ Hz, H-5), 7.91 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.8 (CH_2), 108.4 (C-4), 116.3 (=CH_2), 122.4 (C-3), 134.0 (=CH), 143.6 (C-5), 144.8 (C-2), 162.7 (C=O). MF (MW): $C_8H_9NO_2$ (151.16). GCMS (EI, 70 eV) *m/z* (%): 151 (M^+, 6), 122 (10), 95 (100).
3j: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.44 (s, 2H, –NH_2), 6.89–6.90 (dd, 1H, $^3J_{H4-H5} = 1.7$ Hz, $^4J_{H4-H2} < 1.0$ Hz H-4), 7.76–7.75 (dd, 1H, $^3J_{H5-H4} = 1.7$ Hz, $^4J_{H2-H5} < 1.0$ Hz, H-5), 8.19–8.20 (t, 1H, $J < 1.0$ Hz, H-2), 9.60 (br s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 108.6 (C-4), 121.3 (C-3), 142.8 (C5), 144.7 (C-2), 161.5 (C=O).
3k: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.59 (m, 6H, –CH_2–), 3.40 (m, 4H, –N–CH_2–), 6.45 (d, 1H, $^3J_{H4-H5} = 1.2$ Hz, H-4), 7.34 (d, 1H, $^3J_{H5-H4} = 1.2$ Hz, H-5), 7.60 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.3 (–CH_2–), 48,1 (–N–CH_2–), 108.9 (C-4), 121.1 (C-3), 142.5 (C-5), 142.8 (C-2), 163.4 (C=O).
3l: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (m, 8H, O–CH_2–CH_2-N), 6.47 (d, 1H, $^3J_{H4-H5} = 1.3$ Hz, H-4), 7.36 (d, 1H, $^3J_{H5-H4} = 1.3$ Hz, H-5), 7.64 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 66.7 (O–CH_2–CH_2–N), 109.9 (C-4), 120.5 (C-3), 143.0 (C-5), 143.5 (C-2), 163.8 (C=O).
3m: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.93 (s, 1H, H-4), 7.23–7.14 (m, 6H, –Ph, N–H), 7.45 (s, 1H, H-5), 8.33 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 110.5 (C-4), 119.5 (C-3), 124.9, 127.8, 128.6, 137.4 (Ph), 143.3 (C-5), 150.2 (C-2), 176.0 (C=O).
3n: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.57 (d, 2H, $J = 6.0$ Hz, –CH_2–), 6.62 (s, 1H, H-4), 7.27–7.39 (s, 6H, Ph, NH), 7.41 (s, 1H, H-5), 7.94 (s, 1H, H-2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 43.0 (–CH_2–), 108.0 (C-4), 122.0 (C-3), 127.0–128.2, 137.9 (–Ph), 143.2 (C-5), 144.6 (C-2), 162.3 (C=O). GCMS (EI, 70 e V) *m/z* (%): 201(M^+, 39), 172 (13), 95 (100).