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Synthesis of Benzo[b]furan and Benzo[b]thiophene-3-acetic Acids

Pailla Umareddy, Veera Reddy Arava*

R and D Center Suven Life Sciences Ltd, Plot No #18, Phase-III, Jeedimetla-500055, Hyderabad, India

ABSTRACT

Benzo[b]furan and Benzo[b]thiophene-3-acetic acids are prepared from the corresponding phenol or thiophenol by reacting with ethyl 4-chloro acetoacetate. The isolated acetoacetic ester derivatives were cyclized to give the respective ester of 3-acetic acids in good yields. Final hydrolysis resulted in 3-acetic acids in high yields.

Keywords: Benzo[b]furan, Benzo[b]thiophene-3-acetic acids, Ethyl 4-chloroacetoacetate, Aluminium chloride

INTRODUCTION

Benzofuran and benzothiophene derivatives are important class of heterocycles with a wide range of biological activities. Such as anti-inflammatory, antitumor, cytotoxic, antimicrobial, antitubercular, antioxidant, Hepatitis C Virus (HCV) inhibitory and HIV inhibitory activities have been reviewed [1-5]. Benzo furans have been the subject of more extensive studies for the development of efficient routes for the synthesis [6,7]. Benzothiophenes are biologically prominent heterocycles [8,9]. Both benzo[b]furan-3-acetic acid (1a) and benzo[b]thiophene-3-acetic acid (1b) are plant growth stimulants (Figure 1a) [10], and sertaconazole (Figure 1b) is an antifungal drug.

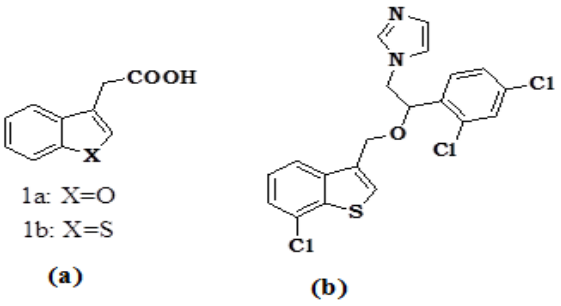
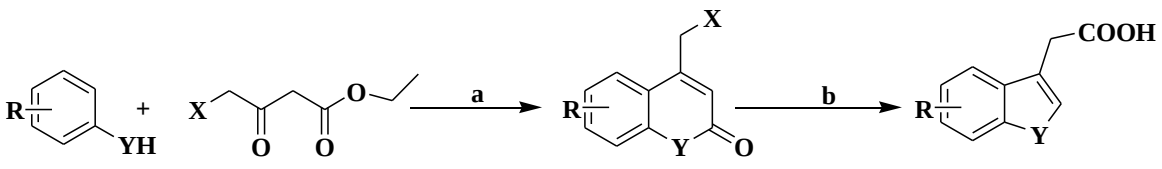


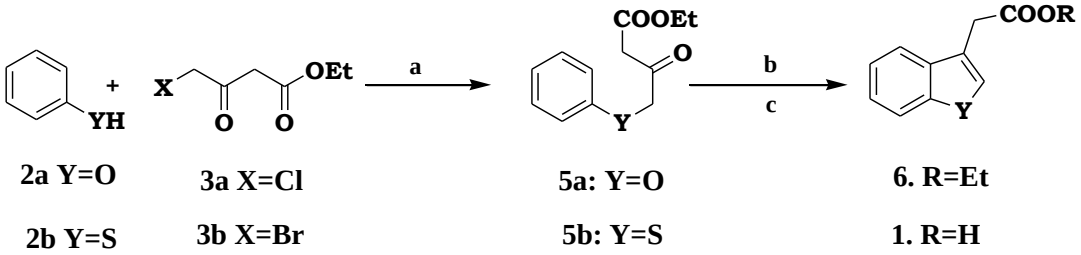
Figure 1: (a) Plant growth stimulants, (b) sertaconazole

The earlier reports of the synthesis of compounds of the type 1 are reported in two ways. The first synthesis is based on Von Pechmann cyclisation of substituted phenols 2 with 3 to give coumarins 4, which on Perkin rearrangement [11] gave 1 as shown in Scheme 1.



Scheme 1: Synthesis of compound 1 *via* Von Pechmann reaction
(a) H_2SO_4, RT; (b) NaOH, 80°C

The second method is the alkylation of phenol 2 to give 5, which were cyclized with poly phosphoric acid [12-14] to give 1, as shown in Scheme 2.



2a Y=O **3a X=Cl** **5a: Y=O** **6. R=Et**

2b Y=S **3b X=Br** **5b: Y=S** **1. R=H**

Scheme 2: Synthesis of compounds 1 and 6 with PPA
(a) KOH (X=O)/TEA (X=S), RT; (b) PPA, 120°C; (c) NaOH, RT

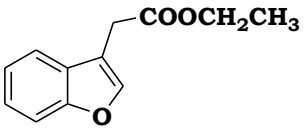
MATERIALS AND METHODS

Most of the reagents used in this work were obtained from commercial suppliers and were of LR/AR grade. Solvents were purified before use by standard procedures. Melting points were determined using open capillary tubes on Polmon melting points apparatus (Model-96) and are uncorrected. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded by using a Bruker 400 Spectrometer with Tetramethylsilane (TMS) as internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR Spectrophotometer as KBr pellets or with the neat products. Mass spectra were recorded on an API 2000 LCMS/MS Applied Bio Systems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240C, H, N elemental analyzer. Analytical Thin Layer Chromatography (TLC) was conducted on E-Merck 60F254 aluminium-packed plates of silica gel (0.2 mm). Developed plates were visualized by using UV light or in an iodine chamber. High Performance Liquid Chromatography (HPLC) was performed by using a Shimadzu 2010 instrument.

General procedure for the syntheses of benzo[b]furan and benzo[b]thiophene-3-acetic acid ethyl esters (6a-i)

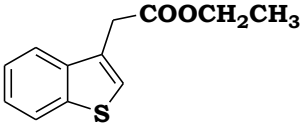
To a stirred solution of aluminum chloride (0.06 mol) in 80 ml of ethylene dichloride was added a solution 4-(phenoxy)-3-oxo-butyric acid ethyl ester (0.042 mol) in (20 ml) ethylene chloride at 10-15°C. The mixture was maintained at 10-15°C for 10 min and the temperature was raised to room temperature. After completion of the reaction (monitored by TLC) water (200 ml) was added and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with 100 ml of ethylene dichloride. The combined organic layer was washed with 100 ml of water and the solvent was evaporated to yield 6a-6i, which was purified on silica gel column.

Benzofuran-3-yl-acetic acid ethyl ester (6a)



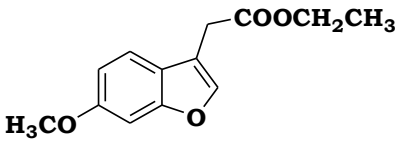
Reaction time 2 h; Yeild-78%; IR (Neat in cm^{-1}): 2982, 1736, 1453, 1169, 746; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 7.66 (s, 1H), 7.60 (d, *J*=8.2 Hz, 1H), 7.51 (d, *J*=7.65 Hz, 1H), 7.34 -7.28 (m, 2H), 4.24 (q, 2H), 3.71 (s, 2H), 1.29 (t, *J*=8.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 170.68, 155.25, 142.89, 129.59, 127.70, 124.48, 122.64, 119.76, 114.70, 113.25, 111.53, 61.09, 29.83, 14.21.

Benzo[b]thiophen-3-yl-acetic acid ethyl ester (6b)



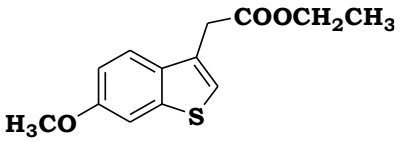
Reaction time-1.5 h; Yeild-72%; IR (Neat in cm^{-1}): 2980, 1731, 1158, 760; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm):7.86 (d, *J*=7.76 Hz, 1H), 7.78 (d, *J*=7.78, 1H), 7.42-7.34 (m, 2H), 4.20 (q, 2H), 3.86 (s, 2H), 1.26 (t, *J*=7.11 Hz, 3H); ^{13}C0NMR (100 MHz, $CDCl_3$) (δ ppm): 17.71, 140.22, 138.65, 128.44, 124.55, 124.44, 124.20, 122.88, 121.81, 61.10, 34.59, 14.25.

(6-Methoxy-benzofuran-3-yl)-acetic acid ethyl ester (6c)



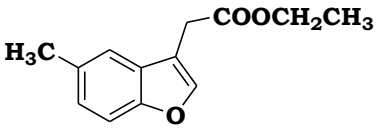
Reaction time 3 h; Yeild-75%; m.p: 37-40°C; IR (in KBr, cm^{-1}): 2982, 1737, 1144, 808; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 7.53 (s, 1H), 7.43 (d, *J*=8.5 Hz, 1H), 7.0 (s, 1H), 6.90-6.87 (m, 1H), 4.26 (q, 2H), 3.84 (s, 3H, OCH_3), 3.66 (s, 2H), 1.26 (t, *J*=7.13 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 170.73, 158.20, 156.24, 141.88, 121.03, 119.89, 113.10, 111.75, 95.98, 61.05, 55.67, 29.90, 14.19.

(6-Methoxy-benzo[b]thiophen-3-yl)-acetic acid ethyl ester (6d)



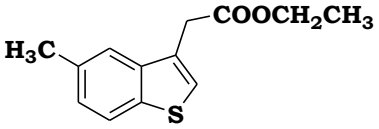
Reaction time 0.5 h; Yeild-80%; IR ((Neat in cm^{-1}): 2979, 1735, 1177, 812; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 7.64 (d, *J*=8.81 Hz, 1H), 7.32 (s, 1H), 7.16 (s, 1H), 7.03 (dd, *J*1=2.14, *J*2=2.14 Hz, 1H), 4.19 (q, 2H), 3.89 (s, 3H, OCH_3), 3.80 (s, 2H), 1.25 (t, *J*=7.16 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 170.31, 157.25, 141.32, 132.43, 127.78, 122.09, 121.46, 113.92, 104.90, 60.65, 55.16, 34.29, 13.88.

(5-Methyl-benzofuran-3-yl)-acetic acid ethyl ester (6e)



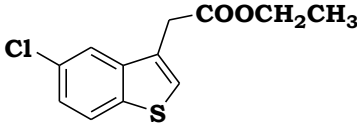
Reaction time 2 h; Yeild-68%; IR ((Neat in cm^{-1}): 2980, 1736, 1474, 1156, 799; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 7.60 (s, 1H), 7.38-7.36 (m, 2H), 7.12 (d, *J*=8.46 Hz, 1H), 4.24 (q, 2H), 3.68 (s, 2H), 2.47 (s, 3H), 1.29 (t, *J*=7.12 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm):170.64, 153.55, 142.85, 131.94, 127.61, 125.60, 119.38, 112.78, 110.88, 60.93, 29.70, 21.24, 14.07.

(5-Methyl-benzo[b]thiophen-3-yl)-acetic acid ethyl ester (6f)



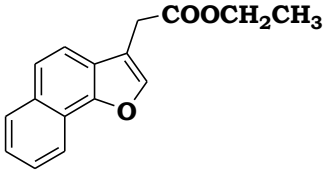
Reaction time-3 h; Yeild-65%; IR ((Neat in cm^{-1}): 2979, 1735, 1442, 1158; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 7.75 (d, *J*=8.21 Hz, 1H), 7.59 (s, 1H), 7.38-7.34 (m, 1H), 7.22-7.18 (m, 1H), 4.24 (q, 2H), 3.81 (s, 2H), 2.52 (s, 3H), 1.29 (t, *J*=3.4, 3h); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 170.18, 133.92, 129.15, 128.05, 124.67, 124.65, 122.49, 121.76, 61.05, 34.65, 21.60, 140.24.

(5-Chloro-benzo[b]thiophen-3-yl)-acetic acid ethyl ester (6g)



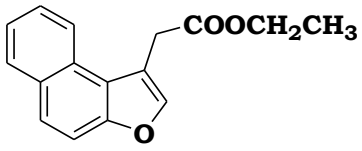
Reaction time 8 h; Yeild-60%; m.p: 38-40°C; IR (in KBr, cm^{-1}): 2973, 1719, 1193, 874; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 7.74-7.71 (m, 2H), 7.39 (s, 1H), 7.30-7.28 (m, 1H), 4.21 (q, 2H), 3.79 (s, 2H), 1.25 (t, *J*=3.7 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 17.31, 139.86, 138.32, 130.62, 127.93, 126.52, 124.86, 123.80, 121.59, 61.20, 34.36, 14.20.

Naphtho[1,2-b]furan-3-yl-acetic acid ethyl ester (6h)



Reaction time 1 h; Yeild-72%; mp: 37-42°C; IR (in KBr, cm^{-1}): 2984, 1737, 1187, 804; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 8.34(d, *J*=8.18 Hz, 1H), 7.95 (d, *J*=8.12, 1H), 7.79 (s, 1H), 7.71-7.59 (m, 3H), 7.53-7.50 (m, 1H), 4.26 (q, 2H), 3.79 (s, 2H), 1.30 (t, *J*=8.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 170.80, 150.9, 142.0, 131.52, 128.32, 126.41, 125.25, 123.38, 123.11, 121.52, 120.05, 118.26, 114.36, 61.16, 30.01, 14.25.

Naphtho[2,1-b]furan-1-yl-acetic acid ethyl ester (6i)



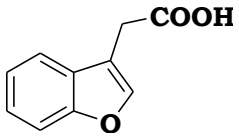
Reaction time 1.5 h; Yeild-68%; IR (Neat in cm^{-1}): 2994, 1741, 1192; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 8.36(d, *J*=7.93 Hz, 1H), 7.88 (d, *J*=8.10, 1H), 7.82 (s, 1H), 7.71-7.59 (m, 3H), 7.53-7.50 (m, 1H), 4.22 (q, 2H), 3.81 (s, 2H), 1.28 (t, *J*=8.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$)

(δ ppm): 171.68, 150.9, 142.0, 131.52, 128.32, 126.41, 125.25, 123.38, 123.11, 121.48, 120.21, 118.31, 114.41, 61.22, 30.22, 14.28.

General procedure for the syntheses of benzo[b]furan and benzo[b]thiophene-3-acetic acids (1a-i)

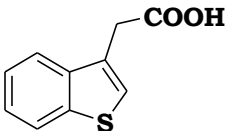
To a stirred solution of benzofuran-3-acetic acid ethyl ester (6) (0.022 mol) in (30 ml) ethanol was added 10% sodium hydroxide solution 30 ml at 5-10°C for 10 min. The reaction mixture was maintained at room temperature. After completion of the reaction (monitored by TLC) the reaction mixture was concentrated completely. To the crude charged water 100 ml and ethyl acetate 50 ml and stirred for 15 min, separate the organic layer. Then aqueous acidified with HCl (6N) and extracted with ethyl acetate (2 × 50 ml). The combined organic layer was washed with 100 ml of water and the solvent was evaporated to yield 1a-i. It was crystallized from appropriate solvents.

Benzofuran-3-yl-acetic acid (1a)



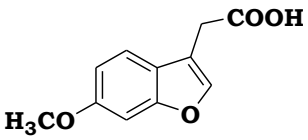
Hydrolysis time 1 h; Yield-90%; m.p: 85-88°C (It was crystallized from methanol) (Lit 88-89°C); IR (in KBr, cm^{-1}): 2835, 1867, 1725, 1428; ^{1}H-NMR (400 MHz, DMSO) (δ ppm): 12.56 (s, 1H, COOH), 7.87 (s, 1H), 7.60-7.53 (m, 2H), 7.31-7.22 (m, 2H) 3.68 (s, 2H); ^{13}C-NMR (100 MHz, DMSO) (δ ppm): 172.4, 154.9, 143.8, 128.21, 124.78, 122.98, 120.61, 114.46, 111.69, 29.44. HPLC purity 98.60%.

Benzo[b]thiophen-3-yl-acetic acid (1b)



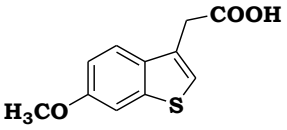
Hydrolysis time 0.5 h; Yield-82%; m.p: 85-88°C (It was crystallized from methanol) m.p: 109-111°C (Lit 108-109°C); IR (in KBr, cm^{-1}): 2919, 1819, 1700, 1229, 759; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 10.25 (s, 1H, COOH), 7.88 (d, *J*=7.67 Hz, 1H), 7.75 (d, *J*=7.46 Hz, 1H), 7.43-7.36 (m, 3H), 3.90 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 177.15, 140.19, 138.41, 127.40, 125.10, 124.54, 124.32, 122.29, 121.70, 34.17; HPLC purity 99.43%.

(6-Methoxy-benzofuran-3-yl)-acetic acid (1c)



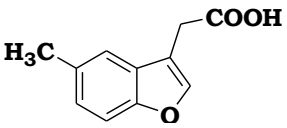
Hydrolysis time 1.5 h; Yield-88%; m.p: 85-88°C (It was crystallized from methanol) m.p: 124-126.7°C (Lit 124-126°C); IR (in KBr, cm^{-1}): 2835, 1860, 1707, 1440, 1233; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 12.80 (s, 1H, COOH), 7.53 (s, 1H), 7.41 (d, *J*=8.34 Hz, 1H), 7.01 (s, 1H), 6.9-6.88 (m, 1H), 3.84 (s, 3H, OCH_3), 3.71 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 177.0, 158.2, 156.25, 142.13, 120.7, 119.7, 112.25, 111.91, 96.11, 55.75, 29.57; HPLC purity-99.88%.

(6-Methoxy-benzo[b]thiophen-3-yl)-acetic acid (1d)



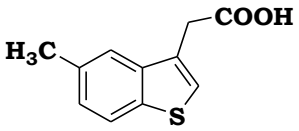
Hydrolysis time 2 h; Yield-85%; m.p: 85-88°C (It was crystallized from ethyl acetate) m.p: 140-142°C (Lit 141-142°C); IR (in KBr, cm^{-1}): 2841, 1858, 1710, 1440, 1224; ^{1}H-NMR (400 MHz, DMSO) (δ ppm): 12.44 (s, 1H), 7.66 (d, *J*=8.81 Hz, 1H), 7.54 (s, 1H), 7.36 (s, 1H), 7.04 (d, *J*=8.2 Hz, 1H), 3.81 (s, 5H, OCH_3, CH_2), 3.85 (s, 2H); ^{13}C-NMR (100 MHz, DMSO) (δ ppm): 172.44, 157.54, 141.43, 133.20, 129.48, 123.11, 122.53, 114.44, 105.87, 55.92, 34.42; HPLC purity 99.72%.

(5-Methyl-benzofuran-3-yl)-acetic acid (1e)



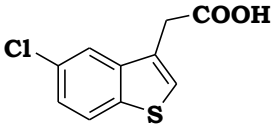
Hydrolysis time 1 h; yield-78%; m.p: 85-88°C (It was crystallized from methanol) m.p: 100-102°C (Lit 97-98°); IR (in KBr, cm^{-1}): 2925, 1721, 1224, 1089, 792; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 11.0 (s, 1H, COOH), 7.60 (s, 1H), 7.39-7.35 (m, 2H), 7.14 (s, 1H), 3.73 (s, 2H), 2.47 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 177.38, 153.66, 143.24, 132.29, 127.48, 125.93, 119.37, 112.6, 111.13, 29.52, 21.39; HPLC purity 99.34%.

(5-Methyl-benzo[b]thiophen-3-yl)-acetic acid (1f)



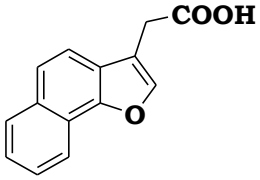
Hydrolysis time 0.5 h; Yield-83%; m.p: 85-88°C (It was crystallized from ethanol) mp: 155-158°C (Lit 155-157°C); IR (in KBr, cm^{-1}): 2925, 1868, 1721, 1224, 1089, 792; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 12.50 (s, 1H, COOH), 7.84 (d, *J*=8.16 Hz, 1H), 7.58 (s, 1H), 7.54 (s, 1H), 7.20 (d, *J*=8.08 Hz, 1H), 3.80 (s, 2H);); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 172.50, 139.51, 137.16, 133.77, 129.57, 126.40, 125.40, 122.95, 122.30, 34.27, 21.58; HPLC purity-99.66%.

(5-Chloro-benzo[b]thiophen-3-yl)-acetic acid (1g)



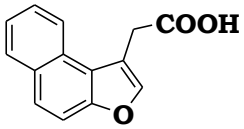
Hydrolysis time 2.5 h; Yield-80%; m.p: 85-88°C (It was crystallized from dichloromethane) m.p: 154-156°C (Lit 152-155°C); IR (in KBr, cm^{-1}): 2911, 1905, 1707, 1225, 1084, 752; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ ppm): 12.24 (s, 1H), 8.0 (d, *J*=8.55 Hz, 1H), 7.85 (s, 1H), 7.69 (s, 1H), 7.39 (d, *J*=4.7 Hz, 1H), 3.88 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ ppm): 172.31, 140.66, 138.47, 129.81, 129.62, 127.88, 124.95, 124.76, 122.15, 34.07; HPLC purity 99.55%.

Naphtho[1,2-b]furan-3-yl-acetic acid (1h)



Hydrolysis time 2 h; Yield-88%; m.p: 85-88°C (It was crystallized from methanol) m.p: 163-165°C (Lit 158-159°C); IR (in KBr, cm^{-1}): 2911, 1691, 1231, 804; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 11.0 (s, 1H, COOH), 8.30 (d, *J*=8.18 Hz, 1H), 7.93 (d, *J*=4.14 Hz, 1H), 7.69 (s, 1H), 7.68 (d, *J*=8.78 Hz), 7.63-7.57 (m, 2H), 7.50 (t, *J*=7.42 Hz, 1H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 176.92, 150.94, 142.27, 131.55, 128.34, 126.46, 125.33, 123.53, 122.92, 121.48, 120.02, 118.0, 113.48, 29.61; HPLC purity-99.38%.

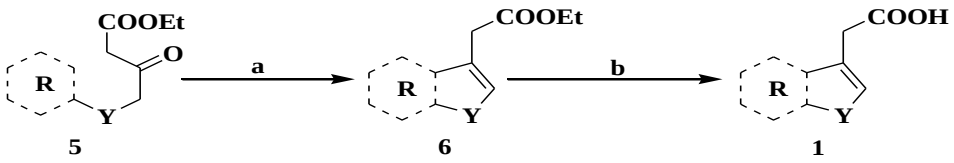
Naphtho[2,1-b]furan-1-yl-acetic acid (1i)



Hydrolysis time 1.5 h; Yield-75%; m.p: 85-88°C (It was crystallized from ethyl acetate) m.p: 175-177°C (Lit 171-172°C); IR (in KBr, cm^{-1}): 2918, 1818, 1705, 1396, 1201, 777; ^{1}H-NMR (400 MHz, DMSO) (δ ppm): 8.22 (d, *J*=8.2 Hz, 1H), 8.01-8.04 (m, 2H), 7.84-7.77 (m, 2H), 7.62 (t, *J*=7.87 Hz), 7.51 (t, *J*=8.22 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO) (δ ppm): 172.76, 153.12, 144.05, 130.78, 129.41, 128.37, 126.88, 126.08, 124.82, 123.51, 121.56, 116.22, 113.12, 31.38; HPLC purity 99.71%.

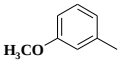
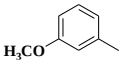
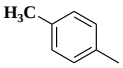
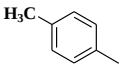
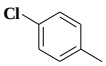
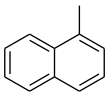
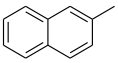
RESULTS AND DISCUSSION

In our efforts to synthesize compounds 1 *via* second method, we found that the yields are not satisfactory with PPA (~70%) and also the workup methodology found to be a tedious one. We developed a simple method of cyclisation with $AlCl_3$ in better yields. The compounds 5a and 5b were cyclized with ease in ethylene dichloride (EDC)/$AlCl_3$ at Room Temperature (RT). The isolated esters 5 were hydrolyzed with ease to give acids, and all the acids are compared with the known compounds (Table 1). The chemistry developed is given in Scheme 3.



Scheme 3: Synthesis of compound 1 with $AlCl_3$ cyclisation
(a) $AlCl_3$, EDC, RT; (b) NaOH, RT

Table 1: Preparation of compounds 1 from 6

Entry	Y	R	Cyclisation time for **6**	Yield of **6**	Yield of **1**
a	O		2 h	78	90
b	S		1.5 h	72	82
c	O		3 h	75	88
d	S		0. h	80	85
e	O		2 h	68	78
f	S		3 h	65	83
g	S		8 h	60	80
h	O		1 h	72	88
i	O		1.5 h	68	75

All cyclisation's are carried at RT. Compound 1g is commercially available (Aldrich)

CONCLUSION

We have developed a simple methodology for the preparation of benzo[b] furan and benzo[b] thiophene-3-acetic acids.

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