Synthetic Studies of Naphtho[2,3-b]furan Moiety Present in Diverse Bioactive Natural Products

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Abstract

The preparation of several functionalized furan derivatives and attempts to transform them into a derivative containing 6H-furo[3,4-b]furanone skeleton towards the construction of naphtho[2,3-b]furan are described. Attempted Pummerer reaction of a furan sulfoxide derivative produced four interesting furan derivatives. Base promoted annulation between methyl 2-(phenylsulfinylmethyl)-3-furoate and 2-cyclohexenone proceeded to give dihydro naphtho[2,3-b]furanone derivative in a regiospecific manner.

Keywords

6H-Furo[3,4-b]furanone, Naphtho[2,3-b]furan, Intramolecular Pummerer Reaction, Desulfanylation, Lactonization

1. Introduction

Functionally embellished naphtho[2,3-b]furan moiety has been widely encountered as a unique sub-structure among a diverse range of bioactive synthetic molecules and natural products. Particularly, the condensed quinone derivatives of naphtho[2,3-b]furans such as furonaphthoquinones have been proved to possess broad anticancer activities [1]. Recently, M. Koketsu and co-workers reported that the synthetic furonaphthoquinones showed moderate cytotoxicity against human leukemia U937 and HL-60 cells [2]. During the past decades, a wide range of furanoid natural products have been isolated from plant sources. Among these, furonaphthoqui...
nones (e.g. 1 - 9) are prominent due to their wide biological activities and structural significance (Figure 1). Although some strategies have been used for the construction of furanophthoquinone skeletons, most of the reported methods employ multistep to secure the target skeletons from readily available precursors [3]. Hence intense research in this area has been carried out in recent years leading to the development of simple and straightforward regiospecific route for the preparation of functionalized furanophthoquinone compounds [4].

Our continued interest in the application of anionic [4 + 2] cycloaddition [5] of isobenzofuranones prompted us to study the preparation of 6H-furo[3,4-b]furanes (10) towards the construction of naphtho[2,3-b]furan skeleton embedded in various biologically important molecules.

2. Results and Discussion

Our study began with the preparation of furanosulfoxide derivative 14, following the literature procedure [6]. Bromination of methyl 2-methyl-furan-3-carboxylate (11) with N-bromosuccinimide (NBS) under standard condition gave bromo derivative 12 was prepared in 75% yield. Reaction of compound 12 with sodium methoxide and thiophenol gave compound 13 in 88% yield followed by oxidation with sodium periodate in methanol and water medium provided methyl 2-(phenylsulfinylmethyl)-3-furoate (14a) in 75% yield (Scheme 1). Attempted intramolecular Pummerer reaction [7] of sulfoxide 14a with trimethylsilyl chloride (TMSCl) in dichloromethane for overnight, no reaction took place. But when this was refluxed with acetic anhydride, a polymeric product generated. When compound 14a was refluxed with trifluoro acetic anhydride or p-toluenesulfonic acid (PTSA), complex mixtures of products were obtained. Examination of the 1H NMR spectrum of the crude products did not indicate formation of desired 10a. The same result was obtained when the above reactions were performed on acid derivative 14b, prepared by hydrolysis of sulfoxide ester 14a with aqueous NaOH and ethanol.

For Scheme 1. Reagents and conditions: (i) NBS, CCl₄, (PhCO)₂O₂ (cat.), hv, 75%; (ii) PhSH, NaI, MeOH, reflux, 88%; (iii) NaIO₄, MeOH/H₂O, rt, 40 h, 75%; (iv) NaOH, ethanol, 85%; (v) TMSCl, CH₂Cl₂, overnight or (vi) Ac₂O, reflux, 10 h or (vii) (CF₃CO)₂O, reflux or PTSA, reflux.

Interestingly, treatment of sulfoxide 14a with acetic anhydride and a catalytic amount of sodium acetate under reflux produced four different products instead of 10a. All these products 15, 16, 17 and 18 were separated by column chromatography and characterized by NMR, IR studies. Under the same conditions the acid derivative 14b produced an oily polymeric product, 1H NMR spectrum of which revealed the absence of 10a.
For **Scheme 3. Reagents and conditions:** (viii) Ac₂O, NaOAc, reflux, 3 h, 28% (for 15), 8% (for 16), 6% (for 17) and 15% (for 18).

Except 18, all these products were expectedly generated through a common Pummerer intermediate 19. Nucleophilic addition of water to the Pummerer intermediate 19 and subsequent expulsion of thiophenol gave aldehydic ester derivative 15 as the major product (28%). Compound 15 could further be added to acetic anhydride to produce furan diacetate derivative 16 in 8% yield (Scheme 2).

Formation of compound 17 (6%) could be explained by addition of one equivalent of thiophenol to the common intermediate 19. On the other hand, the acetate derivative 18 (15%) could be formed by direct nucleophilic displacement of sulfoxide group of 14a by acetate anion.

Having been successful with the above **Scheme 3**, we focused our attempts to convert ethylsulfoxide 21a to furofuranone 10b via an intramolecular Pummerer reaction. It was presumed that the corresponding intermediate would have favorable geometry for an intramolecular Pummerer reaction [8]. Compound 12 was converted to 20 in 87% yield by the treatment with sodium methoxide and ethanethiol in refluxing methanol. Oxidation of 20 with sodium periodate gave two products which were separated using column chromatography (1:4 mixture of ethyl acetate/petroleum ether). After column chromatography, the desired ethylsulfoxide 21a as isolated in 56% yield and the more oxidized ethylsulfone 21b was isolated in 33% yield as shown in **Scheme 4**. Both the compounds 21a and 21b were fully characterized on the basis of spectroscopic (IR, NMR and mass spectral data) analysis. The 1H NMR spectrum exhibited two doublets, one at δ 7.40 (1H) and other at δ 6.73 (1H) for furan ring. It also showed an ABq signal at δ 4.44 (2H) corresponding to two α-hydrogen atoms of ethylsulfoxide group.

But, all attempts to effect intramolecular Pummerer reaction of 21a with various reagents such as PTSA in C₆H₆, Ac₂O in toluene, (CF₃CO)₂O in CH₂Cl₂, CF₃CO₂H, pyridinium PTSA in refluxing condition and phenyliodine...
These compounds were separated using column chromatography methods (1:4 mixture of CHCl₃/petroleum ether). The sequence is depicted in Scheme 4. Reagents and conditions: (i) EtSH, CHCl₃, Et₃N, rt, overnight, 87%; (ii) NaO₄, MeOH, 0°C, 2 h, 56%; (iii) PTSA in C₆H₆, reflux, 10 h or Ac₂O in toluene, reflux, 10 h or (CF₃CO)₂O in CH₂Cl₂, reflux, 12 h or CF₃CO₂H, pyridinium PTSA, reflux, 12 h or PIDA in CH₂Cl₂, reflux, 12 h.

Following the above failures, we turned to preparing furan sulfoxide derivative 26 starting from 3-furoic acid and chloromethylsulfanylbenzene (24) and examining its intramolecular cyclisation via Pummerer reaction to obtain 10a. Methylation of thiophenol with sodium hydroxide and dimethylsulfate in acetone under reflux condition gave 23 in 87% yield. Treatment of 23 with N-chlorosuccinimide in CH₂Cl₂ produced 24 in 82% yield. Then compound 24 was reacted with 3-furoic acid (25) in the presence of DBU to give 26 (70% yield). This was then transformed to sulfoxide 27 (76% yield) by sodium periodate (NaO₄) oxidation. Both the compounds 26 and 27 gave satisfactory IR, ¹H NMR and ¹³C NMR spectroscopic data. The ¹H NMR spectrum showed an ABq signal at δ 5.14 (2H) corresponding to two α-hydrogen atoms of phenylsulfoxide group. Several Pummerer reagents (vide reagents of Scheme 5) were employed for the intramolecular cyclization of 27, but none were effective to give 10a as shown in Scheme 5.

As we failed to achieve the preparation of fururofuranone 10a by Pummerer procedures, we modified our approach to synthesizing 10a through the desulfanylation of 17, in view of the success of this type of cyclization in benzene system reported by Hauser et al. [8]. Treatment of compound 15 with thiophenol and catalytic amounts of TMSCl in chloroform solvent produced 17 in 85% yield (Scheme 6). Attempted cyclization of 17 in trifluoroacetic acid under reflux condition failed to give expected compound 10a. ¹H NMR spectrum of the crude product revealed that starting material decomposed during the course of reaction.

As we could not carry out the above cyclization of 17, we thought that compound 32 might suit for this desulfanylation reaction due to lesser effect of nuclear oxygen atom. It was prepared in good yield starting from commercially available methyl 3-methyl-furan-2-carboxylate (28). The sequence is depicted in Scheme 7. NBS bromination of 28 produced dibromo derivative 29 (60%) along with monobromo derivative 30 in 25% yield. These compounds were separated using column chromatography methods (1:4 mixture of CHCl₃/petroleum ether). Hydrolysis of dibromo derivative 29 with silver nitrate in THF/H₂O produced furan-3-carboxaldehyde 31 in 42% yield. Finally, treatment of 31 with thiophenol and a catalytic amount of TMSCl provided compound 32. Attempted desulfanylation of 32 with trifluoroacetic acid and water in reflux condition failed to give expected product 10c, starting material was recovered exclusively meaning that no reaction took place.

At this point, we investigated the coupling reaction between diazo derivative of tetronic acid (36) and vinyl acetate for synthesizing 37 from which desired furo[3,4-b]furanone system could be obtained. Compound 36 was prepared from tosyl azide (34) and tetronic acid (35) in the presence of triethylamine according to the literature procedure in 40% yield [9]. ¹H NMR of 36 showed only one singlet at δ 4.70 (2H, s) corresponding to -CH₂ group. Then we examined its coupling with vinyl acetate under various conditions (Scheme 8) [10]. But
unfortunately, all the attempts failed to give 37. Examination of $^1$H NMR spectrum of the crude product indicated the exclusive presence of starting material in first two cases (with rhodium diacetate or ceric ammonium nitrate) and unidentifiable product mixture of products with PIDA treatment.

For Scheme 8. Reagents and conditions: (i) NaN₃, aq. Acetone, rt, 85%; (ii) Et₃N, CH₃CN, 40%; (iii) Rh₂(OAc)₆ or CAN, CH₃CN, 0°C or PhI(OAc)₂. Again we modified our route for the synthesis of furolactone 10d, from which desired compound 10a may be prepared. The hydroxy ester derivative 38 was prepared from 12 by heating it at 80°C in dimethyl sulfoxide and water. The NMR data of 38 matched with literature value [11]. Then compound 38 was transformed to 2-hydroxymethyl-furan-3-carboxylic acid (39) in 90% yield by the treatment of 40% aqueous solution of KOH solution in methanol (Scheme 9).

For Scheme 9. Reagents and conditions: (i) DMSO, 80°C, 4 h, 92%; (ii) KOH, H₂O, MeOH, 90%; (iii) attempted lactonization with SOCl₂ in CH₂Cl₂, DCC in DMF or in CH₂Cl₂, Ac₂O in toluene under refluxing condition and BF₃-ether in C₆H₆.

We then investigated lactonization of compound 39 with various well established literature methods. But, all
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Attempts for lactonization of 39 failed to give the expected furolactone 10d as shown in Scheme 9. In all the cases except with SOCl₂, ¹H NMR spectrum of the crude products showed exclusive presence of the starting material 39, meaning no reaction took place. Reaction with SOCl₂ produced intractable mixture of products which could not be identified by NMR studies. The above failure of the lactonization may be attributed due to the unfavorable distance between carbonyl “C” and hydroxyl “O” atoms in 39 compared to that in its benzene analog 40 (Figure 2) where lactonization is very facile. Geometries of molecules 39 and 40 were minimized by using density functional theory (DFT) calculations based on the BLYP level of theory with the DND basis set using DMol³ package program [12].

Then we thought that sulfoxide 14a itself may serve the purpose of furan annulating agents (i.e. 10a or 10b) for the synthesis of naphtho[2,3-b]furan skeleton. For that purpose, when the sulfoxide 14a was treated with lithium tert-butoxide (t-BuOLi), a light yellow color developed, indicating the generation of carbanion α to -SOPh group, and subsequently the color of the reaction mixture changed to light brown upon addition of 2-cyclohexenone. Work up of the reaction mixture led to formation of tricyclic compound 42 as white solid in 7% yield (Scheme 10). Further transformation of compound 42 to desired naphtho[2,3-b]furan derivative was postponed due to poor yield. We were able to taken only ¹H NMR and IR spectrum of this compound. The ¹H NMR spectrum exhibited three multiplets of six protons at the region of δ 2.18 - 2.97, corresponding to the cyclohexane ring and two doublets, one at δ 7.49 (1H) and other at δ 6.94 (1H) for furan ring. It also showed a ¹H sharp singlet at δ 13.51 corresponding to hydrogen bonded ‘OH’ group. We repeated the above annulation three times without any improvement in the yield. We also performed this cycloaddition reaction in presence of lithium diisopropyl amide (LDA). But, ¹H NMR spectrum of the crude indicated the formation of a polymeric material.

3. Conclusion

With the aim of preparing novel naphtho[2,3-b]furan derivatives, an investigation was carried out to synthesize, characterize and study furan[3,4-b]furanones by several approaches. The results showed that the intramolecular Pummerer reaction of furan sulfoxide derivative produced four interesting furan derivatives. The anionic cycloaddition between furan sulfoxide and 2-cyclohexenone produced dihydro naphtho[2,3-b]furanone derivative in

![Figure 2. Comparison of distances between carbonyl “C” and hydroxyl “O” atoms in 39 and 40.](image)

![Scheme 9. Attempted lactonization of 2-hydroxymethyl-furan-3-carboxylic acid (39).](image)

![Scheme 10. Synthesis of dihydro naphtho[2,3-b]furanone moiety 42.](image)
poor yield. This study reveals that synthesis of simple looking furan derivatives (like 10a-d) was elusive and they deserve further study.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes and are uncorrected. Among the spectra, ¹H NMR spectra and ¹³C-NMR spectra were recorded on 200 MHz and 300 MHz spectrometer (Brücker) as solution in ²H-Chloroform with TMS as the internal standard. Chemical shifts are expressed in δ unit and ¹H-¹H coupling constant in Hz. IR spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR spectrophotometers using KBr pellet. EI MS (70 eV) spectra were taken using a VG Autospec M mass spectrometer. Elemental analyses were carried out by using an elemental analyzer VARIO EL instrument. Dry solvents used for reactions were purified, before use, according to the standard protocols. All solvents for chromatography (column and preparative layer chromatography) were distilled prior to use.

4.2. Methyl 2-(Phenylsulfinylmethyl)-3-furoate (14a)

To a solution of compound ⁹ (5 g, 20 mmol) in MeOH (70 mL) containing water (15 mL) was added solid NaIO₄ (4.6 g, 21.5 mmol) in portions. The resultant mixture was stirred for 36 h at rt and the solvent was removed under reduced pressure. The resulting thick liquid was purified by column chromatography (3:7 ethyl acetate/petroleum ether, Rf 0.48) over silica gel to furnish the sulfoxide ¹⁴a (3.99 g, 75%) as pale yellow solid. mp 84˚C - 85˚C (lit. [6] mp. 85˚C - 86˚C); FT-IR (KBr) cm⁻¹ 12935, 1714 (s), 1616, 1440 (m), 1387 (m), 1053, 756; ¹H NMR (200 MHz, CDCl₃): δ 7.46 - 7.30 (m, 5H), 7.32 (d, 1H, J = 2 Hz), 6.65 (d, 1H, J = 2 Hz), 4.60 (d, 1H, J = 12 Hz), 4.51 (d, 1H, J = 12 Hz), 3.70 (s, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 163.1, 150.4, 142.9, 131.3, 128.9, 123.9, 117.5, 111.0, 55.6, 51.5; MS m/z (EI): 264 (M⁺), 233, 186, 139 (100%), 125, 109, 97, 77.

4.3. 2-Phenylsulfinylmethyl-furan-3-carboxylic Acid (14b)

A mixture of methyl 2-(phenylsulfinylmethyl)-3-furoate ¹⁴a (1 g, 3.78 mmol), 15 mL of 40% aqueous NaOH solution, 20 mL of MeOH and 15 mL of H₂O were stirred for 5 h at ambient temperature. On completion of the reaction, the whole mixture was diluted with water (40 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with water and 5% of HCl (20 mL), brine (20 mL), dried (Na₂SO₄) and concentrated. Purification of the crude residue by chromatography on SiO₂ (1:1 ethyl acetate/petroleum ether, Rf 0.32) gave compound ¹⁴b (0.8 g, 85%) as white solid. mp 110˚C - 112˚C; FT-IR (KBr) cm⁻¹ 3412, 2362, 1709 (s), 1601 (m), 1444, 1260, 1060, 746; ¹H NMR (200 MHz, CDCl₃): δ 7.30 (d, 1H, J = 2 Hz), 6.70 (d, 1H, J = 2 Hz), 4.62 (d, 1H, J = 12 Hz), 4.53 (d, 1H, J = 14 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 166.8, 150.6, 143.3, 141.9, 131.7, 129.2, 124.2, 117.9, 111.5, 55.2; HRMS: calcd. for C₁₂H₁₀O₄S [M + Na]⁺ 251.0380; found 251.0388.

4.4. Methyl 2-Formyl-furan-3-carboxylate (15)

To a stirred solution of ¹⁴a (1.0 g, 3.78 mmol) Ac₂O (10 mL) was added NaOAc (0.31 g, 3.78 mmol) and heated at 110˚C for 3 h. After completion of the reaction, the resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with water and 5% of HCl (20 mL), brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The resulting thick liquid was purified by column chromatography (3:7 ethyl acetate/petroleum ether, Rf 0.48) over silica gel to furnish the sulfoxide ¹⁴a (3.99 g, 75%) as pale yellow solid. mp 84˚C - 85˚C (lit. [6] mp. 85˚C - 86˚C); FT-IR (KBr) cm⁻¹ 2935, 1714 (s), 1616, 1440 (m), 1387 (m), 1053, 756; ¹H NMR (200 MHz, CDCl₃): δ 7.46 - 7.30 (m, 5H), 7.32 (d, 1H, J = 2 Hz), 6.65 (d, 1H, J = 2 Hz), 4.60 (d, 1H, J = 12 Hz), 4.51 (d, 1H, J = 12 Hz), 3.70 (s, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 163.1, 150.4, 142.9, 131.3, 128.9, 123.9, 117.5, 111.0, 55.6, 51.5; MS m/z (EI): 264 (M⁺), 233, 186, 139 (100%), 125, 109, 97, 77.

4.5. Methyl 2-Diacetoxymethyl-furan-3-carboxylate (16)

This compound was obtained as white solid in 8% yield from ¹⁴a on treatment with Ac₂O and NaOAc, following the procedure adopted for the preparation of compound ¹⁵ from ¹⁴a. mp 96˚C; FT-IR (KBr) cm⁻¹ 2937, 2388, 1769 (s), 1728 (s), 1623, 1378, 1236, 1200, 1044, 894, 755; ¹H NMR (200 MHz, CDCl₃): δ 8.18 (s, 1H), 7.42 (d, 1H, J = 2 Hz), 6.74 (d, 1H, J = 2 Hz), 3.85 (s, 3H), 2.12 (s, 6H); ¹³C NMR (50 MHz, CDCl₃): δ 178.7, 161.9, 152.4, 146.7, 126.2, 112.8, 52.5.
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4.6. Methyl 2-(Bis-phenylsulfanylmethyl)-furan-3-carboxylate (17)

Method 1: This compound was obtained as white solid in 15% yield from 14a on treatment with Ac₂O and NaOAc, following the procedure adopted for the preparation of compound 15 from 14a.

Method 2: To a well stirred solution of 15 (200 mg, 1.19 mmol) and thiophenol (132 mg, 1.2 mmol) in dry CHCl₃ (10 mL) at rt was added TMSCl (30 mg, 0.28 mmol) and stirring was continued for 5 h. After completion of the reaction, this was washed with 5% NaHCO₃ solution (20 mL), diluted with water (50 mL), extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (25 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the crude residue by chromatography on silica gel (1:2 ethyl acetate/petroleum ether, 0.68) gave 17 (360 mg, 85%) as a thick oil.

FT-IR (KBr) cm⁻¹ 13140, 1720 (s), 1591, 1475 (m), 1441, 1312 (m), 1162, 1042, 747; ¹H NMR (200 MHz, CDCl₃): δ 7.35 - 7.43 (m, 5H), 7.24 - 7.30 (m, 5H), 7.33 (d, 1H, J = 2 Hz), 6.35 (s, 1H), 3.66 (s, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 163.0, 156.9, 142.2, 133.3, 128.9, 128.3, 114.2, 110.4, 51.4, 50.8; HRMS: calcd. for C₁₉H₁₆O₃S₂ [M + H]+ 357.0629; found 357.0636.

4.7. Methyl 2-Acetoxymethyl-furan-3-carboxylate (18)

This compound was obtained as white solid in 15% yield from 14a on treatment with Ac₂O and NaOAc, following the procedure adopted for the preparation of compound 15 from 14a.

mp. 47°C; FT-IR (KBr) cm⁻¹ 1723 (s), 1633 (s), 1387 (s), 1108 (m), 1041, 754; ¹H NMR (200 MHz, CDCl₃): δ 7.37 (d, 1H, J = 2 Hz), 6.70 (d, 1H, J = 2 Hz), 5.36 (s, 2H), 3.84 (s, 3H), 2.08 (s, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 170.1, 163.1, 154.3, 142.6, 116.9, 111.0, 56.8, 51.6, 20.6; HRMS: calcd. for C₉H₁₀O₅ [M + H]+ 199.0608; found 199.0615.

4.8. Methyl 2-Ethylsulfanylmethylfuran-3-carboxylate (20)

To a stirred solution of ethanethiol (0.16 mL, 2.15 mmol) in dry CHCl₃ (5 mL) and triethylamine (217 mg, 2.15 mmol) at rt was added compound 12 (470 mg, 2.15 mmol). After overnight stirring, the resulting mixture was diluted with water (130 mL) and then extracted with chloroform (3 × 40 mL), washed with 5% of HCl (20 mL), brine (30 mL) and dried (Na₂SO₄). The combined organic layer was concentrated under reduced pressure and purified by column chromatography on silica gel (1:10 chloroform/petroleum ether, Rf 0.42) to give 20 (375 mg, 87%) as an oil.

FT-IR (KBr) cm⁻¹ 3434, 2953, 1722 (s), 1599, 1441, 1308 (m), 1210, 1063, 772; ¹H NMR (200 MHz, CDCl₃): δ 7.30 (d, 1H, J = 2 Hz), 6.64 (d, 1H, J = 2.4 Hz), 4.07 (s, 2H), 3.82 (s, 3H), 2.55 (q, 2H, J = 8 Hz), 1.32 (t, 3H, J = 8 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 163.8, 158.8, 141.3, 113.9, 110.6, 51.6, 26.5, 25.9, 14.4; HRMS: calcd. for C₉H₁₂O₃S [M + H]+ 201.0587; found 201.0575.

4.9. Methyl 2-Ethanesulfinylmethylfuran-3-carboxylate (21a)

To a solution of compound 20 (2 g, 10 mmol) in MeOH (50 mL) containing water (5 mL) was added solid NaIO₄ (2.30 g, 10.7 mmol) in portions. The resultant mixture was stirred for 2 h at 0°C and the solvent was removed under reduced pressure. The resulting crude liquid was purified by column chromatography over silica gel (1:1 chloroform/petroleum ether, Rf 0.68) to give 21a (1.20 g, 56%, oily liquid) as the major product along with sulfone derivative 21b (33%). FT-IR (KBr) cm⁻¹ 3434, 2953, 1722 (s), 1634, 1559, 1508, 769; ¹H NMR (200 MHz, CDCl₃): δ 7.40 (d, 1H, J = 2 Hz), 6.73 (d, 1H, J = 2 Hz), 4.44 (ABq, 2H, J = 12 Hz), 3.85 (s, 3H), 2.72 (q, 2H, J = 8 Hz), 1.35 (t, 3H, J = 8 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 163.3, 150.6, 143.0, 117.1, 110.9, 51.5, 49.1, 45.2, 6.2; HRMS: calcd. for C₉H₁₂O₃S [M + H]+ 217.0536; found 217.0542.

4.10. Methyl 2-Ethanesulfonylmethylfuran-3-carboxylate (21b)

This compound was obtained in the above experiment (for the preparation of 21a) as white solid in 33% yield. mp. 90°C; FT-IR (KBr) cm⁻¹ 2940, 1711 (s), 1600, 1508, 1445, 1307, 1042, 827; ¹H NMR (200 MHz, CDCl₃): δ 7.46 (d, 1H, J = 2 Hz), 6.75 (d, 1H, J = 2 Hz), 4.74 (s, 2H), 3.86 (s, 3H), 3.02 (q, 2H, J = 8 Hz), 1.38 (t, 3H, J = 8 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 163.2, 148.3, 143.7, 118.1, 111.1, 51.8, 50.8, 47.2, 6.10. Anal. Calcd
4.11. Methylsulfanylbenzene (23)

A mixture of thiophenol 22 (5 g, 45.5 mmol) and 20% of aqueous solution NaOH (50 mL) was stirred for 30 min at rt. Then dimethyl sulfate (4.28 mL, 45.5 mmol) was added to the reaction mixture and stirring was continued for 1 h. Afterward, reaction mixture was heated at reflux for 7 h, cooled to rt, extracted with CH₂Cl₂ (3 × 40 mL). The combined extracts were washed with 10% aq. NaOH solution (30 mL), dried (Na₂SO₄) and distilled to give compound 23 [14] (4.9 g, 87%) as colorless oil. ¹H NMR (200 MHz, CDCl₃): δ 7.32 - 7.28 (m, 3H), 7.22 - 7.16 (m, 2H), 2.50 (s, 3H).

4.12. Chloromethylsulfanylbenzene (24)

To a stirred solution of compound 23 (2 g, 6.10 mmol) in CCl₄ (20 mL) was added N-chlorosuccinimide (2.36 g, 6.71 mmol) at room temperature and stirring was continued for 11 h. The reaction mixture then cooled (0 °C) and filtered off. The filtrate was then concentrated under reduced pressure and the residue distilled to give a brownish semisolid of 24 [15] (0.78 g, 82%). ¹H NMR (200 MHz, CDCl₃): δ 7.58 - 7.48 (m, 2H), 7.40 - 7.14 (m, 3H), 4.97 (s, 2H).

4.13. Phenylsulfanylmethyl Furan-3-carboxylate (26)

To a stirred solution of 3-furoic acid (25) (1.0 g, 9.0 mmol) and DBU (1.36 g, 9.0 mmol) in dry acetonitrile (10 mL) under inert atmosphere, was added compound 24 (1.42 g, 9.0 mmol). The resulting mixture was further stirred for 4 h at rt and extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate extracts were washed with saturated solution of NaHCO₃ (20 mL), brine (20 mL) and dried (Na₂SO₄). Concentration of the organic layer gave a light yellow residue. This was purified by column chromatography (1:10 chloroform/petroleum ether, Rf 0.60) to give 26 (1.02 g, 70%) as an oily liquid. FT-IR (KBr) cm⁻¹ 2930, 1730 (s), 1431, 1329, 1292, 1150 (s), 1126 (m) 1078, 973, 749; ¹H NMR (200 MHz, CDCl₃): δ 8.04 (d, 1H, J = 2 Hz), 7.42 - 7.55 (m, 3H), 7.28 - 7.38 (m, 3H), 6.76 (d, 1H, J = 2 Hz), 5.58 (s, 2H); HRMS: calcd. for C₁₂H₁₀O₃S [M + H]⁺ 235.0431; found 235.0439.


To a stirred solution of compound 26 (120 mg, 0.74 mmol) in MeOH (10 mL) containing water (2 mL) was added solid NaIO₄ (170 mg, 0.79 mmol) in portions. The resultant mixture was stirred for 5 h at rt and the solvent was removed under reduced pressure. The resulting crude liquid was extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate extracts was washed with brine (20 mL) and dried (Na₂SO₄). Concentration of the organic layer gave a solid residue which was purified by column chromatography (1:5 chloroform/petroleum ether, Rf 0.52) to give 27 (140 mg, 76%) as a white solid. mp. 84°C - 85°C; FT-IR (KBr) cm⁻¹ 3142, 1732 (s), 1608, 1420, 1382, 1252, 1065 (m), 875, 758; ¹H NMR (200 MHz, CDCl₃): δ 8.07 (d, 1H, J = 2 Hz), 7.66 - 7.75 (m, 2H), 7.52 - 7.58 (m, 3H), 7.41 - 7.47 (m, 1H), 5.14 (ABq, 2H, J = 12 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 161.4, 148.8, 144.1, 140.3, 131.8, 129.4, 124.5, 117.5, 109.7, 81.9; HRMS: calcd. for C₁₃H₁₀O₄S [M + H]⁺ 251.0380; found 251.0388.

4.15. Methyl 3-Dibromomethyl-furan-2-carboxylate (29)

A mixture of commercially available methyl 3-methyl-2-furoate (28) (2.0 g, 14.30 mmol), NBS (5.08 g, 28.60 mmol) and a pinch of benzoyl peroxide in CCl₄ (150 mL) was heated at reflux for 3.5 h under the exposure of a bulb (100 W). The reaction mixture was then cooled (0°C) and succinimide filtered. The filtrate was concentrated under reduced pressure to give a yellowish residue which was then subjected to column chromatography over silica gel (60 - 120 mesh) using chloroform/petroleum ether mixture (3:7, v/v, Rf 0.58 ) as eluent to furnish dibromo compound 29 (2.54 g, 60%, white solid) as a main product along with 30 (25%). mp. 80°C - 82°C; FT-IR (KBr) cm⁻¹ 3142, 1732 (s), 1608, 1420, 1382, 1252, 1065 (m), 875, 758; ¹H NMR (200 MHz, CDCl₃): δ 7.51 (d, 1H, J = 2 Hz), 7.36 (s, 1H), 6.92 (d, 1H, J = 2 Hz), 3.95 (s, 3H); HRMS: calcd. for C₁₃H₆Br₂O₃ [M + H]⁺ 295.8684; found 295.8678.
4.16. Methyl 3-Bromomethyl-2-carboxylate (30)

This compound was obtained as white solid in 25\% yield and co-product if 30. mp. 51\°C (lit. [16] 52\°C - 53\°C); \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \textit{\delta} 7.50 (d, 1H, \textit{\textit{J}} = 2 \text{ Hz}), 6.60 (d, 1H, \textit{\textit{J}} = 2 \text{ H}), 4.65 (s, 2H), 3.92 (s, 3H).

4.17. Methyl 3-Formyl-furan-2-carboxylate (31)

To a solution of compound 29 (1.28 g, 4.29 mmol) in THF (20 mL) was added aqueous solution of AgNO\textsubscript{3} (1.45 g, 8.58 mmol in 5 mL water) in portions and stirring was continued for overnight at room temperature. The resulting mixture was filtered and after usual work-up of the concentrated filtrate, the residue was purified by column chromatography (1:8 ethyl acetate/petroleum ether, \textit{Rf} 0.52) to give 31 (0.28 g, 42\% ) as white crystalline solid. mp. 72\°C - 74\°C; FT-IR (KBr) cm\textsuperscript{−1} 3264, 2890, 1732 (s), 1682 (s), 1612, 1412, 1320, 1246, 1085, 756; \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \textit{\delta} 10.51 (s, 1H), 7.54 (d, 1H, \textit{\textit{J}} = 1.8), 6.90 (d, 1H, \textit{\textit{J}} = 1.8), 4.0 (s, 1H).

4.18. Methyl 3-(1,1-Diphenylsulfanyl)-methylfuran-2-carboxylate (32)

This compound was prepared by reaction of 31 with thiophenol in 80\% yield as yellow liquid, according to the procedure described for 17 from 15 (Method 2). FT-IR (KBr) cm\textsuperscript{−1} 3160, 1728 (s), 1592, 1470 (m), 1438, 1310 (m), 1140, 1102, 1046, 746; \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \textit{\delta} 7.34 - 7.44 (m, 5H), 7.22 - 7.30 (m, 7H), 6.66 (d, 1H, \textit{\textit{J}} = 2 \text{ Hz}), 6.33 (s, 1H), 3.78 (s, 3H); \textsuperscript{13}C NMR (50 MHz, CDCl\textsubscript{3}): \textit{\delta} 158.9, 145.2, 138.9, 133.9, 133.5, 132.8, 128.8, 128.0, 112.5, 51.7, 49.6; MS \textit{m/z} (EI): [M + H\textsuperscript{+}] 357.0640.

4.19. 4-Methyl-benzenesulfonyl Azide (34)

This compound was prepared according to the procedure reported procedure [9]. A mixture of \textit{p}-toluenesulfonyl chloride (33) (1.35 g, 7 mmol), NaN\textsubscript{3} (0.55 g, 8.5 mmol) in aqueous solution of acetone (1:2 mixture of acetone and water) were stirred for 5 h and then acetone was removed under reduced pressure. After usual work-up, drying (Na\textsubscript{2}SO\textsubscript{4}), solvent was evaporated to furnish the desired product 34 [17] as light yellow liquid (1.17 g, 85\%), which was sufficiently pure for the next experiment. \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \textit{\delta} 7.82 (d, 2H, \textit{\textit{J}} = 8), 7.32 (d, \textit{2H}, \textit{\textit{J}} = 8), 2.45 (s, 3H).

4.20. 3-Diazotetrahydrofuran-2,4-dione (36)

To a stirred solution of tetrahydrofuran-2,4-dione 35 (2.0 g, 0.02 mol) and \textit{p}-tosyl azide 34 (3.7 g, 0.02 mol) in acetonitrile (50 mL) was added triethylamine (2 g, 0.02 mol) dropwise over 15 min resulting in a darkening of the solution. After one hour stirring at room temperature the reaction mixture was concentrated and extracted with ether (3 × 50 mL). The combined organic phases were washed with 5\% of HCl (20 mL), brine (25 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure. Purification of the crude residue by chromatography on silica gel (1:1 ethyl acetate/petroleum ether, \textit{Rf} 0.61) gave 36 [9] (1.0 g, 40\%) as a yellowish solid. mp. 90\°C; FT-IR (KBr) cm\textsuperscript{−1} 2166, 1760 (s), 1692 (s); \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \textit{\delta} 4.70 (2H, s).

4.21. Methyl 2-Hydroxymethylfuran-3-carboxylate (38)

To a solution of DMSO and water (100 mL, 90:10, v/v) at 80\°C temperature was added compound 12 (1.0 g, 4.58 mmol) and stirring was continued for 4 h. The resulting reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and the organic phase was evaporated under reduced pressure. The residue was subjected to column chromatography over silica gel (1:1 ethyl acetate/petroleum ether, \textit{Rf} 0.61) gave 38 (0.78 g, 5 mmol) as a white solid mp. 107\°C; FT-IR (KBr) cm\textsuperscript{−1} 3448, 2925, 1760 (s), 1438, 1260, 1024, 762; \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}): \textit{\delta} 7.82 (d, 2H, \textit{\textit{J}} = 8), 7.32 (d, \textit{2H}, \textit{\textit{J}} = 8), 2.45 (s, 3H).

4.22. 2-Hydroxymethylfuran-3-carboxylic acid (39)

Hydroxy ester compound 38 (0.78 g, 5 mmol) was treated with a mixture of 15\% solution of aqueous KOH (15 mL) and methanol (30 mL) for 2 h at rt. On completion of the reaction, 5\% of HCl solution (20 mL) was added dropwise till pH 6.5. A white solid separated out from the reaction mixture, which was filtered and washed tho-
roughly with water to furnish pure acid derivative 39 (640 mg, 90%) as white solid. mp. 76°C - 78°C FT-IR (KBr) cm⁻¹: 3455, 2924, 1686 (s), 1551 (m), 1269, 1166, 1375, 743; 1H NMR (200 MHz, d6-DMSO): δ 7.40 (d, 1H, J = 2 Hz), 6.75 (d, 1H, J = 2 Hz), 4.81 (s, 1H), 2.59 (d, 1H, J = 2 Hz); 13C NMR (50 MHz, d6-DMSO): δ 169.54, 165.18, 147.36, 119.82, 116.04, 59.50. HRMS: calcd. for C₁₃H₁₀O₄ [M + Na]⁺ 165.0156; found 165.0166.

4.23. 4-Hydroxy-7,8-dihydro-6H-naphtho[2,3-b]furan-5-one (42)

To a stirred solution of lithium tert-butoxide (2.42 mmol) in THF (10 mL) at −60°C (chloroform/liquid N₂ bath) under an inert atmosphere was added a solution of furansulfoxide (200 mg, 0.75 mmol) in THF (1.5 mL). The resulting yellowish solution was stirred at −60°C for 25 min, after which a solution of a 2-cyclohexenone (0.90 mmol) in THF (1.5 mL) was added to it. The cooling bath was removed after about 1 h at −60°C and the reaction mixture was brought to room temperature over a period of 1 h and further stirred for 5 h. The reaction was then quenched with 10% NH₄Cl (10 mL) and the resulting solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na₂SO₄) and concentrated to provide crude product. The crude solid product was purified by column chromatography on silica gel to give compound 42 (10mg, 7%) as white solid. mp. 118°C - 20°C; FT-IR (KBr) cm⁻¹: 3405, 2940, 2502, 2375, 1982, 1630 (s), 1450, 1450 (m), 1356, 1331, 1284, 1128; FT-IR (CDCI₃): δ 13.51 (s, 1H), 7.49 (d, 1H, J = 2 Hz), 6.94 (d, 1H, J = 0.8 Hz), 6.84 (s, 1H), 2.97 - 3.10 (m, 2H), 2.66 - 2.74 (m, 2H), 2.05 - 2.18 (m, 2H).

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References


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