TOTAL SYNTHESIS OF AN EXPERIMENTAL ANTITUBERCULAR DRUG CDRI-830

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GRAPHICAL ABSTRACT

Abstract The triarylmethane antituberculosis drug CDRI-830 is synthesized. The triarylmethane derivative 4 is prepared from ether 6 by a rearrangement process. The total synthesis of the drug CDRI-830 is achieved in a good overall yield of 35% from a simple thiophene derivative 8.

Keywords CDRI-830; ether rearrangement; Friedel–Crafts reaction

INTRODUCTION

Tuberculosis (TB), an infectious disease, is caused by Mycobacterium tuberculosis.[1,2] The emergence of multi-drug-resistant (MDR) strains and its synergy with human immunodeficiency virus (HIV)[3] is a major concern of the World Health Organization. The CDRI (Central Drug Research Institute, Lucknow, India) identified compound CDRI-830 in their anti-TB program. CDRI-830 is triarylmethane (TRAM) derivative.[4]

RESULTS AND DISCUSSION

A novel method of building CDRI-830 was envisaged via an ether rearrangement method. Retrosynthetic analysis of CDRI-830 leads to phenol 4,
which can be synthesized from ether 6 via a known rearrangement method. Ether 6 can be made from diary methanol 3, which can be synthesized from readily available anisole 1 and thiophene-2-carbonyl chloride 8, as shown in Scheme 1.

Friedel–Crafts reaction of anisole (7) with thiophene-2-acid chloride (8) in the presence of Lewis acid (AlCl₃) gave (4-methoxy phenyl)-thiophen-2-yl-methanone (9) in 85% yield. The ketone on reduction with NaBH₄ gave quantitative yield of (4-methoxy-phenyl)-thiophen-2-yl-methanol (3). The diaryl methanol 3 on reaction with fluorobenzene and NaH in dimethylsulfoxide (DMSO) gave ether 2-[(4-methoxy-phenyl)-phenoxy-methyl]-thiophene (6). The obtained ether 6 is characterized completely. Ether 6 on rearrangement with BF₃OEt₂ gave both 4 and 5. Compound 4 prepared by this method was identical with the reported one.[4f] Compound 4 on reaction with di-isopropyl chloroacetamide (10) gave compound 11, N,N-diisopropyl-2-{4-[4-(4-methoxy-phenyl)-thiophen-2-yl-methyl]-phenoxy}–acetamide. Compound 11 on reduction with lithium

[Figure 1. Structure of CDRI-830.]

[Scheme 1. Retrosynthesis of CDRI-830.]
aluminium hydride (LAH)/tetrahydrofuran (THF) gave CDRI-830, which is identical (by spectra) with the reported one.

The synthetic scheme is depicted in Scheme 2.

As we observed, the yields in etherification 3 to 6 are not satisfactory (35%); we tried the synthesis of 4 as reported[4f] but in toluene solvent (not in dry benzene). We found that 4 and 5 are formed in 60% and 10% yields, respectively. The overall yield of CDRI-830 from thiophene-2-carbonylchloride is 35%.

In conclusion, we report a practical synthesis of CDRI-830, an experimental anti-TB compound.

Scheme 2. Synthesis of CDRI-830. (a) AlCl₃, DCM, 0–5 °C, 30 min, 87%; (b) NaBH₄, MeOH, rt, 95%; (c) NaH, DMSO, F-benzene, 85–90 °C, 4 h, 35%; (d) BF₃·OEt₂, EtOAc, rt, 2 h, 4: 60%, 5: 10%; (e) NaH, DMF, 45–50 °C, 30 min, 85%; (f) LAH, THF, rt, 45 min, 80%; (g) con. H₂SO₄, toluene, 4 h, 60 °C, 4: 60%, 5: 10%.
EXPERIMENTAL

Most of the reagents used in this work were obtained from commercial suppliers and were of laboratory reagent or analytical reagent grade. Solvents were purified before use by standard procedures. Melting points were determined using open capillary tubes on a Polmon melting-point apparatus (model 96) and are uncorrected. $^1$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were recorded using a Bruker 400 Spectrometer with tetramethylsilane (TMS) as internal standard. Infra-red (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 LC/MS/MS Applied Bio Systems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240CHN 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 ultraviolet (UV) light or in an iodine chamber. High-performance liquid chromatography (HPLC) was performed by using a Shimadzu 2010 instrument.

2-[(4-Methoxy-phenyl)-phenoxy-methyl]-thiophene (6)

A mineral oil suspension of 60% NaH (36.3 g, 0.90 mol) was taken in a round-bottomed flask, and dimethylsulfoxide (DMSO; 200 mL) was added in 10 min at rt under a nitrogen atmosphere and stirred for 5 min. The temperature was raised to 60–65 °C, maintained for 30 min, and cooled to rt, and a solution of 3 (100 g, 0.454 mol in 300 mL DMSO) was added over 15 min, followed by fluoro benzene (87.2 g, 0.90 mol) over 10 min at rt. The temperature was raised to 80–85 °C and stirred for 4 h; after completion of the reaction (monitored by TLC) the reaction mass was cooled to rt and 10 mL of methanol was added. The reaction mixture was quenched into demineralized water (1000 mL) and extracted with ethyl acetate (2 x 500 mL), and the aqueous layer was again extracted with ethyl acetate (500 mL). Both organic extracts were combined and washed with brine solution (500 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by silica-gel chromatography to get pure 6, 47 g (35%); IR (neat, cm$^{-1}$) 2940, 2771, 1597, 1236; mass for C$_{18}$H$_{16}$O$_2$S [M + 1] 297.3; NMR (400 MHz, CDCl$_3$) (δ ppm): 3.79 (3H, s, OCH$_3$), 6.73 (1H, s, Ar-CH-Ar), 6.86–7.0 (4H, m), 7.23 (2H, t, J = 7.56 Hz), 7.23–7.45 (4H, m), 7.47–7.60 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) (δ ppm): 55.13, 85.13, 113.6, 114.19, 120.28, 124.28, 125.97, 126.48, 129.66, 129.68, 136.16, 136.38, 145.98, 160.63, 162.63.

4-[(4-Methoxy-phenyl)-thiophene-2-yl-methyl]-phenol (4) and 2-[(4-Methoxy-phenyl)-thiophene-2-yl-methyl]-phenol (5) from 6

BF$_3$OEt$_2$ (30 mL) was added to a solution of 9 (15 g, 0.050 mol) and ethyl acetate (150 mL) over 10 min at 10–15 °C and the reaction mass allowed reach rt and stirred for 3 h. After completion of the reaction (monitored by TLC), the reaction mass was quenched in demineralized water (150 mL) and the organic layer was separated. The aqueous layer was again extracted with ethyl acetate (100 mL), and
the combined organic layers were washed with brine solution (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to get the crude product. Crude product was purified with silica-gel column chromatography, eluting the solvent system 20% ethyl acetate in hexane to obtain 4 (60%) and 5 (10%).

4-[(4-Methoxy-phenyl)-thiophene-2-yl-methyl]-phenol (4) and 2-[(4-Methoxy-phenyl)-thiophen-2-yl-methyl]-phenol (5) from 3

To a solution of 3 (30 g, 0.13 mol) and toluene (300 mL) were added charged phenol (19.2 g, 0.204 mol) and charged catalytic H₂SO₄ (2.0 mL) at rt. The temperature was raised to 60–65°C and stirred for 4 h. After completion of the reaction (monitored by TLC) reaction mass was cooled to rt, quenched in to DM water (500 mL), and extracted with toluene (2 × 500 mL). The combined organic extracts were washed with brine solution (500 mL), dried over sodium sulfate, and concentrated under reduced pressure to get the crude product. Crude product was purified using silica-gel column chromatography with eluting solvent system of 20% ethyl acetate in hexane to obtain 4 (60%) and 5 (9%).

Compound 4 (60%). Brown color solid; mp 98.2–101.3 °C; IR (KBr, cm⁻¹) 3400, 2933, 1505, 1173; mass for C₁₈H₁₇O₂S [M + 1] 298.2; NMR (400 MHz, CDCl₃) (δ ppm): 3.81 (3H, s, OCH₃) 4.69 (1H, s, OH), 5.59 (1H, s, Ar-CH-Ar), 6.69 (1H, d, J = 3.13 Hz), 6.79 (2H, d, J = 8.43 Hz), 6.87 (2H, d, J = 8.58 Hz), 6.96 (1H, t, J = 4.25 Hz), 7.10 (2H, d, J = 8.35 Hz), 7.15 (2H, d, J = 8.53 Hz), 7.22 (1H, d, J = 4.91 Hz);¹³C NMR (100 MHz, CDCl₃) (δ ppm): 49.97, 55.30, 113.99, 115.41, 125.0, 126.0, 126.93, 129.68, 129.71, 134.86, 136.82, 149.37, 156.27, 158.10.

Compound 5 (10%). Light color thick mass; IR (neat, cm⁻¹) 3401, 2907, 1508, 1245; mass for C₁₈H₁₇O₂S [M + 1] 298.3; NMR (400 MHz, CDCl₃) (δ ppm): 3.82 (3H, s), 5.35 (1H, s), 5.97 (1H, s, Ar-CH-Ar), 6.82 (2H, d, J = 7.8 Hz), 6.92–6.88 (3H, m), 6.99 (2H, d, J = 5.8 Hz) 7.26–7.17 (4H, m);¹³C NMR (100 MHz, CDCl₃) (δ ppm): 44.94, 55.22, 113.9, 116.0, 120.75, 124.69, 124.69, 126.32, 126.67, 128.0, 129.60, 129.78, 131.78, 134.85, 147.34, 153.13, 158.33.

Diisopropyl-(2-[4-[(4-methoxy-phenyl)-thiophen-2-yl-methyl]-phenoxy]-ethyl)-amine (CDRI-830)

Lithium aluminum hydride (0.86 g, 0.022 mol) was taken in a round-bottomed flask under nitrogen atmosphere, and THF (15 mL) was added slowly for 5 min at rt (little exothermic). To this reaction mass 11 (5.0 g, 0.011 mol, dissolved in 10 mL THF) was added at rt for 5 min. It was exothermic, and the temperature slowly went up to reflux. It was refluxed for 30 min, and after completion of the reaction (monitored by TLC), the reaction mass was cooled to 5–10°C and quenched by adding chilled water (25 mL). The product was extracted with ethyl acetate (2 × 50 mL), and the organic layer was washed with brine solution (50 mL) and dried over sodium sulfate. It was concentrated under reduced pressure to get product (CDRI-830), a light green viscous liquid. IR (neat, cm⁻¹) 2965, 1507, 1247; mass for C₂₆H₃₁NO₃S [M + 1] 424.6; NMR (400 MHz, CDCl₃) (δ ppm): 1.06 (12H, d, J = 5.88 Hz), 2.84 (2H, t, J = 7.58 Hz), 3.08–3.02 (2H, m), 3.79 (3H s), 3.91 (2H, t, J = 7.55 Hz), 5.58
(1H, s), 6.68 (2H, d, J = 3.19 Hz), 6.85 (4H, d, J = 8.46 Hz), 6.94 (1H, t, J = 4.26 Hz), 7.10–7.14 (4H, m), 7.20 (1H, d, J = 5.0 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) (δ ppm): 20.81, 44.45, 49.64, 50.50, 55.13, 69.18, 113.66, 114.19, 124.28, 125.97, 126.46, 129.66, 129.68, 136.10, 136.38, 148.98, 157.63, 158.21. Anal. calcd. for C$_{26}$H$_{33}$NO$_2$S: C, 73.72; H, 7.85; N, 3.31; S, 7.52. Found: C, 72.79; H, 5.61; N, 3.08; S, 7.69.

ACKNOWLEDGMENT

We thank Suven Life Sciences for providing excellent facilities and allowing us to publish this work.

SUPPORTING INFORMATION

Full experimental details and $^1$H and $^{13}$C NMR spectra for this article can be accessed on the publisher’s website.

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