Selective synthesis of methyl dithienyl-glycolates

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Abstract

An efficient selective synthesis of methyl dithienyl-glycolates has been developed. The interest of this two steps protocol resides in the possibility of synthesized either methyl 2,2-dithienyl glycolate – the target intermediate for the preparation of anticholinergic agents – or its regio-isomer methyl 2,3-dithienyl glycolate – the most critical precursor of anticholinergic drug impurity.

Keywords: Bromothiophene lithiation, dithienyl glycolate, muscarinic antagonist, COPD
Introduction

Methyl 2,2-DiThienylGlycolate (1a, Figure 1) is a key intermediate for the preparation of a wide range of anticholinergic agents, as muscarinic receptor antagonists, used in the treatment of ‘Chronic Obstructive Pulmonary Disease’ (COPD). In particular, condensation of 1a with scopine or 3-quinuclidinol derivatives under basic conditions, followed by quaternization of the tertiary amino moiety to increase their lipophilicity, is a classical pharmaceutical process to obtain tiotropium bromide (Scheme 1; marketed as SPIRIVA® HANDIHALER®),¹-⁷ aclidinium bromide (trade name: TUDORZA® PRESSAIR®),⁸ and their analogues.⁹-¹⁸

Scheme 1. Synthesis of tiotropium bromide and aclidinium bromide starting from 1a.

In general, synthesis of 1a is carried out via either Friedel—Crafts acylation of thiophene,¹⁹-²⁹ or Grignard reactions.³⁰ In our hands, reaction of the Grignard reagent derived from 2a with dimethyl oxalate 3 in diethyl ether at reflux afforded 1a in 54% yield, but in inseparable mixture with an impurity identified as the regio-isomer 1b (12% yield, Scheme 2); 1b probably derived by equilibration of the initial 2-thienylmagnesium bromide.

Reaction conditions: 2a (2.0 mmol), 3 (1.0 mmol), Mg (2.1 mmol), solvent (10 mL).

Scheme 2. Reported synthesis of dithienylglycolate 1a-b.³⁰
Results and Discussion

The difficult separation of 1a and 1b leads to pollute drugs, due to the formation of pharmacological regioisomer impurities. Thus, to find an alternative method to selectively obtain either 1a or 1b, we decided to modulate the reactivity of the thienyl anion species by changing the nature of the counter cation. To that aim 2-thienyl lithium and 3-thienyl lithium (derived, respectively, from lithiation of 2-bromothiophene 2a and 3-bromothiophene 2b), were reacted with oxalate 3 to obtain methyl 2-oxo-2-(thiophen-2-yl)acetate 4a and methyl 2-oxo-2-(thiophen-3-yl)acetate 4b. The latter compounds are intermediates for methyl dithienylglycolate 1a and 1b production. Preliminary runs (entries 1–2, Table 1), evidenced that a mixture of regioisomers 4a and 4b could be obtained when oxalate 3 was added to 3-thienyl lithium: in agreement to the anion equilibration, the longer the metalation time of 2b, the higher the yield of 4a.

Table 1. Reactivity of bromothiophene 2b

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a Reaction conditions: 3 (1.5 mmol), 2b (1 mmol), Base (0.95 mmol), solvent (10 mL). b Isolated yields.

A: Base was dropped in 5 min to a solution of 2b and stirred for 15 min before addition of a solution of 3; B: Base was dropped in 5 min to a solution of 2b and stirred for 30 min before addition of a solution of 3; C: 2b was added to a solution of BuLi and 3 in THF; D: Base was added to a solution of 2b and 3.

In fact, a complete regio-selectivity in favor of 4b was reached by adding 2b to a cold mixture of base (n-BuLi) and 3 (entry 4). Furthermore, the best yield of 4b (66%, entry 4) was achieved by adding the strong, non-hindered base n-BuLi at –78 °C, to a mixture of 2b and a slightly excess of 3 in THF as the solvent. Other solvents (entries 5–6), gave worst results while, the use of non-nucleophilic base LDA, resulted in the formation of a series of by-products (entry 7). Similarly, LDA induced on 2a a base catalyzed halogen-dance reaction, forming, as the main reactive intermediate, the 2-thienyl anion specie bearing the bromine atom in the C-3 position. This latter, in turn, evolves in the 4c product in presence of 3 (entry 1, Table 2). Furthermore, 1a reacted under the best reaction conditions found for 1b, giving 4a in good yield (entry 2); we were able to increase the yield of 4a by generating the stable lithium anion at the thiophene C-2 position and then adding oxalate 3 to the reaction mixture (entry 3).
Table 2. Reactivity of bromothiophene 2a.\(^a\)

<table>
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\(^a\)Reaction conditions: 3 (1.5 mmol), 2b (1 mmol), Base (0.95 mmol), solvent (10 mL). \(^b\)Isolated yields. A: Base was added to the mixture of 2a and 3; B: Base was dropped in 5 min to a solution of 2a and stirred for 30 min before addition of a solution of 3.

Similar behavior (Scheme 3) was found when the 2-thienyl anion specie, generated by metalation of 2a at low temperature, was then trapped using as electrophiles 4a or 4b: under these reaction conditions, compounds 1a (derived from intermediate 4a, path a.) and 1b (derived from 4b, path b.) were isolated as pure isomers and fully characterized.

Scheme 3. Synthesis of 1a and 1b.\(^a\)

On the contrary, our attempts to isolate 1b or its regio-isomer methyl 3,3-dithienylglycolate by 3-bromothiophene 2b lithium halogen exchange in the presence of either oxo-acetate 4b or 4a, gave a mixture of degradation compounds (path c.). Comparison between \(^1\)H NMR spectra of compounds 1a and 1b (Table 3), exhibited a slightly highfield chemical shifts for almost all 1a signals (only 1a and 1b H3 protons resonate together at \(~7.19\) ppm); furthermore, 1b \(^1\)H NMR showed two additional signals at 7.39 ppm (H7) and 7.10
ppm (H₉). Even for ¹³C NMR spectra, all the peaks of 1a and b are quite good shifted; the major difference arise in the presence on substrate 1b of both the isolated signal at 142.5 ppm (C₆) and 123.2 ppm (C₇).

Table 3. ¹H and ¹³C assignment for 1a and 1b

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Conclusions

We have described a complete regio-selective protocol for methyl 2,2-dithienylglycolate 1a and methyl 2,3-dithienylglycolate 1b synthesis. Depending on both the nature of the bromothiophene derivative used and the condensation conditions, it was possible to obtain either 1a - the key starting material in the preparation of important anticholinergic agents - or 1b, precursor of pharmacological impurities. By this way 1b was fully characterized, giving the characteristic signals that permit its differentiation for the target compound.

Experimental Section

General. All available chemicals and solvents were purchased from commercial sources and were used without any further purification. Thin layer chromatography (TLC) was performed using 0.25 mm silica gel precoated plates Si 60-F254 (Merck) visualized by UV-254 light and CAM staining. Purification by flash column chromatography (FCC) was conducted by using silica gel Si 60, 230-400 mesh, 0.040-0.063 mm (Merck).
Melting points were determined on a Büchi B450 apparatus and are corrected. ¹H and ¹³C NMR spectra were recorded on a Bruker Fourier 300 (recorded at: 300.13 MHz for ¹H; 75.00 MHz for ¹³C) or Bruker Avance Spectrometer (recorded at: 400.13 MHz for ¹H; 100.62 MHz for ¹³C); chemical shifts are indicated in ppm downfield from TMS, using the residual proton (CHCl₃ 7.28 ppm; acetone 2.05 ppm) and carbon (CDCl₃ 77.0 ppm; acetone 207.1 and 30.9 ppm) solvent resonances as internal reference. Coupling constants values J are given in Hz.

**Preparation of methyl 2-oxo-2-(thiophen-3-yl)acetate (4b).** In a flame-dried round flask, BuLi [1.6] (0.60 mL, 0.95 mmol) was added by syringe under N₂ to a solution of dimethyl oxalate (177 mg, 1.5 mmol) and 3-bromothiophene (193 mg, 1.0 mmol) in anhydrous THF (25 mL) under N₂ at -80 °C. After 20 min, THF (5.0 mL) solution of oxalate 3 or oxo-acetate 4a–c was added. After the disappearance of the starting thiophene, the reaction was quenched with saturated aqueous NH₄Cl and extracted with AcOEt (2×20 mL); the collected organic phases were washed with brine (1×10 mL), dried over Na₂SO₄ and, after evaporation of the solvent in vacuum, the crude was purified by FCC - AcOEt/hexane (1:9) - on silica gel to afford the pure compound 4b (112 mg, 66%) as a slightly yellow waxy solid; ¹H NMR (400 MHz, Acetone-d₆) δ 8.67 (dd, 1H, J 2.7, 1.5 Hz), 7.67 – 7.65 (m, 2H), 3.96 (s, 3H); ¹³C NMR (75 MHz, Acetone-d₆) δ 179.3, 164.0, 138.7, 138.2, 128.3, 127.7, 52.9. Anal. Calcd. for C₁₇H₆O₃S: C, 49.40; H, 3.55. Found: C, 49.01; H, 3.48.

**Lithiation of 2-Bromothiophene: preparation of oxo-acetate (4a,c) and glycolates (1a,b).** In a flame-dried round flask, organolithium reagent (0.95 mmol) was added dropwise to a solution of 2-bromothiophene 1b (193 mg, 1.0 mmol) in anhydrous THF (15 mL) under N₂ at -80 °C. After 20 min, a THF (5.0 mL) solution of oxalate 3 was added. After evaporating of the solvent in vacuum, the crude was purified by FCC - AcOEt/hexane (1:9) - on silica gel. Yield, physical, spectroscopic and analytical data of products 4a,c, 1a,b are as follows.

**Methyl 2-oxo-2-(thiophen-3-yl)acetate 4a.** BuLi [1.6] (0.6 mL), dimethyl oxalate 3 (177 mg, 1.5 mmol). 4a (124 mg, 73%, 40 min); slightly yellow waxy solid. ¹H NMR (300 MHz, CDCl₃) δ 8.18 (dd, 1H, J 3.9, 1.1 Hz), 7.84 (dd, 1H, J 4.9, 1.1 Hz), 7.22 (dd, 1H, J 4.9, 3.9 Hz), 3.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.9, 162.0, 139.0, 137.6, 137.4, 128.7, 53.2. Anal. Calcd. for C₁₁H₆O₃S: C, 49.40; H, 3.55. Found: C, 49.01; H, 3.51.

**Methyl 2-[3-bromothiophen-2-yl]-2-oxoacetate (4c).** LDA [1.0] (0.95 mL), dimethyl oxalate 2 (177 mg, 1.5 mmol). 4c (90 mg, 36%, 30 min); yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 7.94 (d, 1H, J 4.2 Hz), 7.19 (d, 1H, J 4.2 Hz), 3.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.1, 161.4, 139.8, 137.6, 131.8, 127.4, 53.4. Anal. Calcd. for C₁₇H₆BrO₃S: C, 33.75; H, 2.02. Found: C, 33.39; H, 1.99.

**Methyl 2-hydroxy-2-(thiophen-2-yl)-2-(thiophen-2-yl)acetate (1a).** BuLi [1.6] (0.6 mL), oxo acetate 4a (187 mg, 1.1 mmol). 1a (191 mg, 75%, 30 min), whitish solid, mp 94 – 95 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.32 (d, 2H, J 4.9 Hz), 7.20 – 7.18 (m, 2H), 7.00 (dd, 2H, J 5.1, 3.6 Hz), 4.68 (s, 1H), 3.92 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.3, 145.7 (2C₆H), 126.8 (2CH₆H), 126.0 (2CH₆H), 125.9 (2CH₆H), 76.4, 54.3. HPLC analyses were carried out on a Zorbax Rx-C8 column (5 μm, 4.6 × 150 mm) by using as eluent a mixture of solvents [solvent A H₂O (with 1% trimethylamine and adjusting pH to 3.0 with perchloric acid) and solvent B CH₃CN]. Gradient: 0 – 20 min, % B 25 (isocratic); 20 – 36 min, % B 51 (gradient); 36 – 36.1 min, % B 25 (gradient). Flow rate 2 mL/min, T=25°C; UV detector λ 254 nm. Retention times: 1b, 13.20 min; 1a, 14.51 min. Anal. Calcd. for C₁₁H₁₀O₃S₂: C, 51.95; H, 3.96. Found: C, 51.71; H, 3.89.

**Methyl 2-hydroxy-2-(thiophen-2-yl)-2-(thiophen-3-yl)acetate (1b).** BuLi [1.6] (0.6 mL), oxo acetate 4b (187 mg, 1.1 mmol). 1b (173 mg, 68%, 30 min), greyish waxy solid, mp 90 – 92 °C. ¹H NMR (400 MHz, Acetone-d₆) δ
7.47 (s, 1H), 7.44 (dd, 1H, J 5.1, 3.2 Hz), 7.41 (dd, 1H, J 5.2, 1.2 Hz), 7.22 (dd, 1H, J 5.0, 1.4 Hz), 7.12 (dd, 1H, J 3.6, 1.2 Hz), 7.00 (dd, 1H, J 5.1, 3.6 Hz), 5.76 (bs, 1H), 3.83 (s, 3H); 13C NMR (101 MHz, Acetone-\textit{d}_6) δ 173.3, 147.9, 144.7, 127.6, 127.1, 126.2, 126.1, 126.0, 123.2, 77.5, 53.3.


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30. Each API’s impurity greater than 0.1% must be unambiguously identified for Analytical Method Development and Validation. Guidance for Industry - ANDAs: Impurities in Drug Substances; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); June 2009