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Selective synthesis of methyl dithienyl-glycolates

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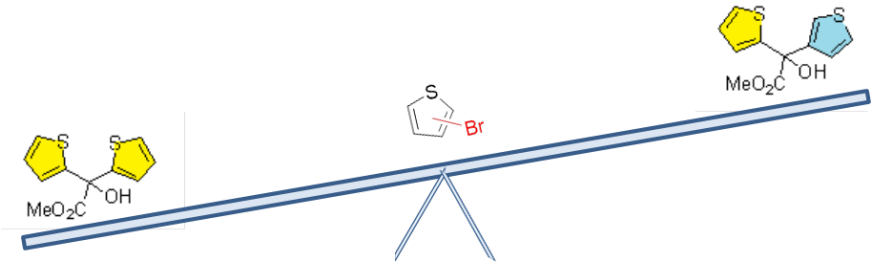
Abstract

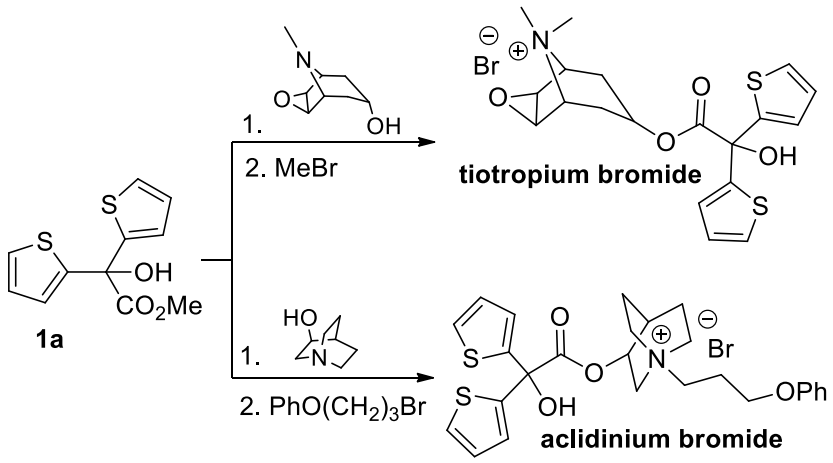
An efficient selective synthesis of methyl dithienyl-glycolates has been developed. The interest of this two steps protocol resides in the possibility of synthesized either methyl 2,2-dithienyl glycolate – the target intermediate for the preparation of anticholinergic agents – or its regio-isomer methyl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



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

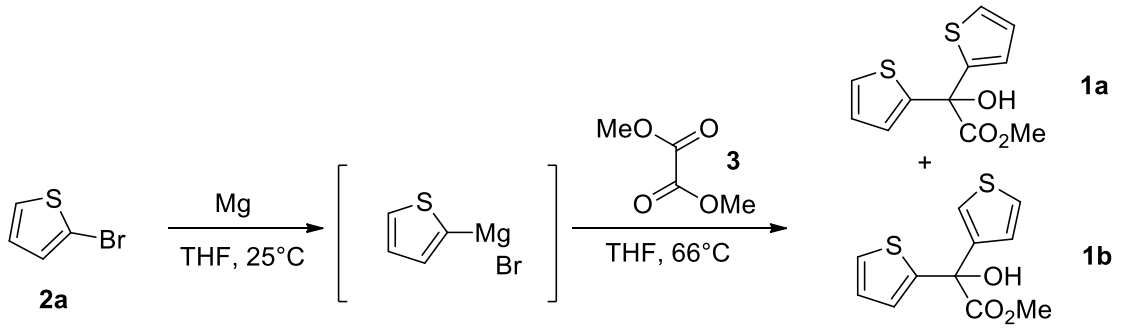
Introduction

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.



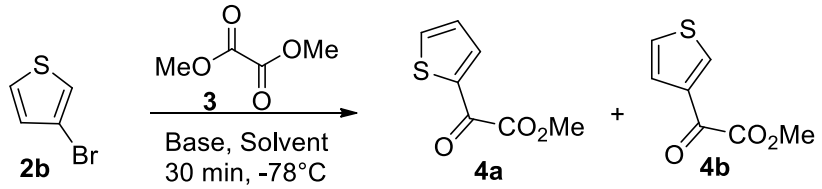
Reaction conditions: **2a** (2.0 mmol), **3** (1.0 mmol), Mg (2.1 mmol), solvent (10 mL).

Scheme 2. Reported synthesis of dithienylglycolate **1a-b** [a].

Results and Discussion

The difficult separation of **1a** and **1b** leads to pollute drugs, due to the formation of pharmacological regio-isomer impurities.[31] 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 dithienyl-glycolate **1a** and **1b** production. Preliminary runs (entries 1–2, Table 1), evidenced that a mixture of regio-isomers **4a** and **4b** could be obtained when oxalate **3** was added to 3-thienyl lithium: in according to the anion equilibration, the longer the metalation time of **2b,** the higher the yield of **4a**.

Table 1. Reactivity of bromothiophene **2b** [a]

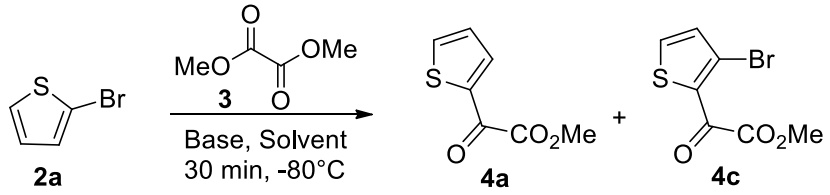


Entry	Base	solvent	Base addition	**4a%**[b]	**4b%**[b]
1	BuLi	THF	**A**	35	24
2	BuLi	THF	**B**	61	--
3	BuLi	THF	**C**	--	48
4	BuLi	THF	**D**	--	66
5	BuLi	Et_2O	**D**	--	35
6	BuLi	Toluene	**D**	--	22
7	LDA	THF	**D**	<5	--

[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.[32-36] 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).

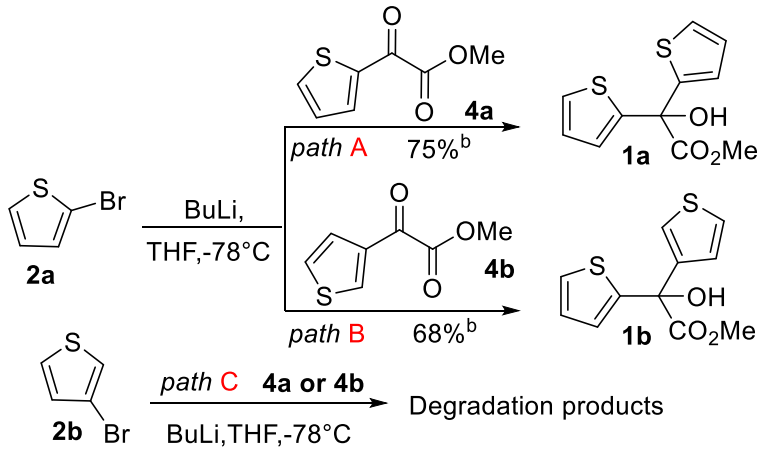
Table 2. Reactivity of bromothiophene **2a**.[a]



Entry	Base	solvent	Base addition	**4a%**[b]	**4c%**[b]
1	LDA	THF	**A**	--	36
2	BuLi	THF	**A**	67	--
3	BuLi	THF	**B**	73	--

[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.



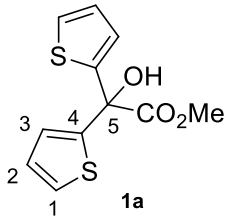
[a] Reaction conditions: **2** (1.0 mmol), **4** (1.0 mmol), Base (0.95 mmol), solvent (10 mL), reaction time: 30 min. [b] Isolated yields.
***path* A** and **B**: BuLi was dropped in 5 min to **2a** and the mixture was stirred for 30 min before addition of **4**; ***path* C:** Base was added to the mixture of **2b** and **4**.

Scheme 3. Synthesis of **1a** and **1b**.[a]

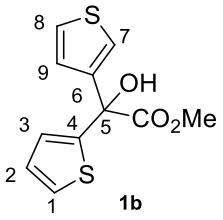
On the contrary, our attempts to isolate **1b** or its regio-isomer methyl 3,3-dithienylglycolate by 3-bromothiophene **2b** lithium halogen exchange in the presence of either oxo-acetate **4b** or **4a**, gave a mixture of degradation compounds (path c.). Comparison between ^{1}H NMR spectra of compounds **1a** and **1b** (Table 3), exhibited a slightly highfield chemical shifts for almost all **1a** signals (only **1a** and **1b** H_3 protons resonate together at ~7.19 ppm); furthermore, **1b** ^{1}H NMR showed two additional signals at 7.39 ppm (H_7) and 7.10

ppm (H_9). Even for ^{13}C 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 (C_6) and 123.2 ppm (C_7).

Table 3. ^{1}H and ^{13}C assignment for **1a** and **1b**



1a



1b

^{1}H	^{13}C	position	^{1}H	^{13}C	^{1}H	^{13}C
$CDCl_3$			$CDCl_3$		*d*$_6$-Acetone	
7.32	126.0	**1**	7.28	125.8	7.41	126.1
7.00	126.1	**2**	6.97	126.7	7.00	127.1
7.19	126.8	**3**	7.18	125.9	7.12	126.2
– –	145.7	**4**	– –	146.0	– –	147.9
– –	76.6	**5**	– –	77.5	– –	77.5
4.68	– –	**OH**	4.47	– –	5.76	– –
– –	172.8	**CO**	– –	173.4	– –	173.3
3.92	54.2	**OCH_3**	3.87	53.9	3.83	53.3
		6	– –	142.5	– –	144.7
		7	7.39	123.2	7.47	123.2
		8	7.28	125.8	7.44	126.0
		9	7.10	126.8	7.22	127.6

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. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Fourier 300 (recorded at: 300.13 MHz for ^{1}H; 75.00 MHz for ^{13}C) or Bruker Avance Spectrometer (recorded at: 400.13 MHz for ^{1}H; 100.62 MHz for ^{13}C); chemical shifts are indicated in ppm downfield from TMS, using the residual proton ($CHCl_3$ 7.28 ppm; acetone 2.05 ppm) and carbon ($CDCl_3$ 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 N_2 to a solution of dimethyl oxalate (177 mg, 1.5 mmol) and 3-bromothiophene (193 mg, 1.0 mmol) in anhydrous THF (25 mL) at -80 °C. The reaction mixture was stirred at -80 °C until completion [30 min, TLC analysis - AcOEt/hexane (1:9)], then was quenched with saturated NH_4Cl solution (5 mL). After extraction with AcOEt (2×20 mL), the collected organic phases were washed with brine (1×10 mL), dried over Na_2SO_4 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; ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.67 (dd, 1H, *J* 2.7, 1.5 Hz), 7.67 – 7.65 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 179.3, 164.0, 138.7, 138.2, 128.3, 127.7, 52.9. Anal. Calcd. for $C_7H_6O_3S$: 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 N_2 at -80 °C. After 20 min, a THF (5.0 mL) solution of oxalate **3** or oxo-acetate **4a–c** was added. After the disappearing of the starting thiophene, the reaction was quenched by saturated aqueous NH_4Cl and extracted with AcOEt (2×20 mL); the collected organic phases were washed with brine (1×10 mL), dried over Na_2SO_4 and the solvent was evaporated under vacuum (RV). The resulting 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. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 162.0, 139.0, 137.6, 137.4, 128.7, 53.2. Anal. Calcd. for $C_7H_6O_3S$: 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 1H, *J* 4.2 Hz), 7.19 (d, 1H, *J* 4.2 Hz), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 161.4, 139.8, 137.6, 131.8, 127.4, 53.4. Anal. Calcd. for $C_7H_5BrO_3S$: 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. ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 145.7 ($2C_{Ar}$), 126.8 ($2CH_{Ar}$), 126.0 ($2CH_{Ar}$), 125.9 ($2CH_{Ar}$), 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 H_2O (with 1% trimethylamine and adjusting pH to 3.0 with perchloric acid) and solvent B CH_3CN]. 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 $C_{11}H_{10}O_3S_2$: 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. ^{1}H NMR (400 MHz, Acetone- d_6) 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); ^{13}C NMR (101 MHz, Acetone-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. Anal. Calcd. for $C_{11}H_{10}O_3S_2$: C, 51.95; H, 3.96. Found: C, 51.55; H, 3.90.

Supplementary Material

Supplementary material related to this article, including Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) figures for methyl dithienyl glycolates **1a,b** and oxo-acetate **4a–c** are available in the online version of the text.

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