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New cyclic zwitterionic building blocks for the synthesis of piperidine-2,4-dione and pyridine-2-one compounds

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ABSTRACT

In this Letter we describe the synthesis of new chiral cyclic zwitterionic pyridin-2-one compounds **5a,b** via an intramolecular ring-closure reaction of a stabilize amide sulfur ylide **4a,b** derived from (*R*)-(−)-2-phenylglycinol and (*R*)-(+)-phenylethylamine in a high yield. In addition, we proved the utility of **5a,b** to produce piperidine-2,4-dione **6a,b** and pyridine-2-one **7a,b** depending on the reaction conditions.

1. Introduction

Stabilized sulfonium amide ylides are well-known reagents widely used in epoxydation[1] or cyclopropanation reactions.[2] Because of their relative stability, they generally react in a reversible manner with carbonyl electrophiles, unless the equilibrating transient betaine can evolve in a non-reversible manner to a stable species, such as an epoxide.[3] For this reason, stabilized sulfonium ylides are generally not considered as useful nucleophiles in intermolecular reactions. On the other hand, a special attention has been paid to the intramolecular cyclization of keto-stabilized sulfur ylides. This approach has been reported to be a good methodology to build nitrogen-containing heterocyclic systems such as indolizinoquinoline,[4] pyrrolizine- and indolizinediones,[5] from L-Proline, or α- and β-(*N*-phthaloyl)amino acids. In these cases, the formation of cyclic compound might prevent the reversibility of the ylide nucleophilic attack.

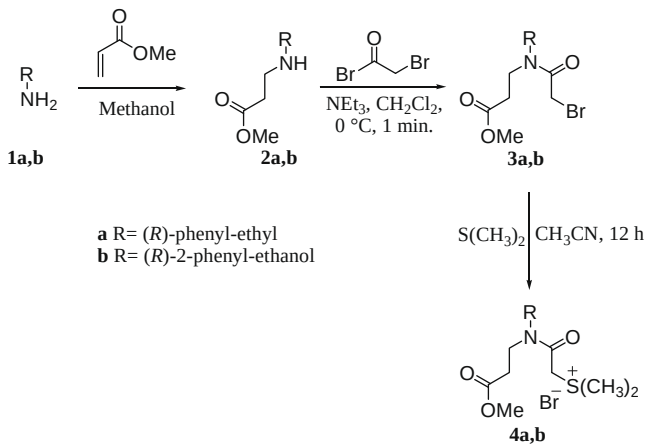
In this context, we present in this Letter a simple access to chiral non racemic zwitterionic 4-alcoxy-3-sulfonium ylide pyridin-2-ones **5a,b** from (*R*)-(−)-2-phenylglycinol and (*R*)-(+)-phenylethylamine using an intramolecular cyclization of sulfonium amide ylide intermediate. Beside the synthetic potential of such scaffolds, it is interesting to note that zwitterionic pyridin-2-one-type compounds have been little studied,[6,7] and might also exhibit interesting biological properties.[8]

2. Results and discussion

Sulfonium salts **4a,b** were prepared in three steps from **1a,b**. The secondary amines **2a,b** were first quantitatively obtained by Michael addition reaction between the primary amines **1a,b** and methyl acrylate. Acylation with bromoacetyl bromide in dichloromethane and triethylamine at 0 °C afforded compounds **3a,b** in 98% yield. Finally, compounds **3a,b** were treated with dimethylsulfur in CH_3CN at room temperature for 12 h, leading to the corresponding sulfonium salts **4a,b** (90% and 94% yields, respectively) (Scheme 1).

Reaction conditions for the key cyclization step were then investigated. As sulfur ylides are generally obtained by treatment of the corresponding sulfonium salt with KOH in CH_3CN,[9] salts **4a,b** were subject to these reaction conditions. To our delight, the corresponding zwitterionic dihydropyridin-2-ones **5a,b** could be obtained in 85% and 87% yields, respectively (Scheme 2). These relatively mild conditions ensured a chemoselective deprotonation, avoiding a possible base-catalyzed retro-Michael degradation of compounds **4a,b**.

The structures of compounds **5a,b** were confirmed by ^1H and ^{13}C NMR analysis. Both compounds showed two singlet picks



Scheme 1.

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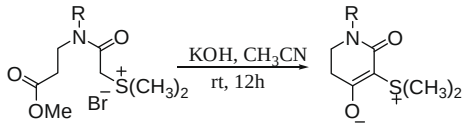
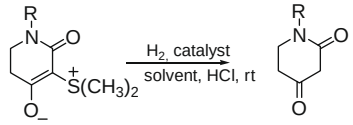


a R= (*R*)-phenyl-ethyl
b R= (*R*)-2-phenyl-ethanol

Scheme 2.

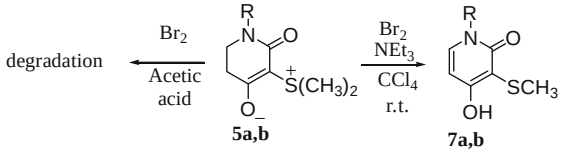
Table 1
Reduction of compounds **5a,b**



Entry	Compound	Catalyst (10 mol %)	Conditions	Product	Yield (%)
1	**5a,b**	Ni(Raney)	EtOH, 48 h	**6a,b**	Traces
2	**5a,b**	Zn	EtOH, 48 h	**6a,b**	0
3	**5a**	PtO_2	EtOH, 120 h	**6a**	35
4	**5b**	PtO_2	EtOH, 120 h	**6b**	40
5	**5a**	Pd–C[b]	EtOH, 25 h	**6a**	46
6	**5b**	Pd–C[b]	EtOH, 17 h	**6b**	65
7[a]	**5a**	Pd–C[b]	THF, 26 h	**6a**	42
8[a]	**5b**	Pd–C[b]	THF, 22 h	**6b**	60

[a] 20 mol % of catalyst was used.
[b] Conducted under ultrasound activation.

Table 2
Oxidation of compounds **5a,b**



Entry	Compound	Br_2 (equiv)	Conditions	Product	Yield (%)
1	**5a,b**	1.2	AcOH, 12 h	—	—
2	**5a,b**	1.2	MeOH, 17 h	**7a,b**	—
3	**5a,b**	1.2	CCl_4, 16 h	**7a,b**	20
4	**5a,b**	5.0	CCl_4, 16 h	**7a,b**	20
5[a]	**5a**	1.5	CCl_4, 6 h	**7a**	49
6[a]	**5b**	1.5	CCl_4, 6 h	**7b**	52

[a] Et_3N (1.5 equiv) was added.

around δ 2.9–3.0 ppm assigned to $S(CH_3)_2$, proving that demethylation did not occur during the cyclization step. Compounds **5a,b** displayed a benzylic proton around δ 5.7–5.9 ppm, typical for a cyclic structure. Finally, ^{13}C NMR signals at δ 187, 166 and 74 ppm revealed the presence of enol and amide functions. All spectroscopic details are described in the experimental part and are in accordance with the proposed zwitterionic structure.

Some preliminary chemical reactivity studies were conducted on these remarkable compounds. Catalytic hydrogenation of the sulfonium moiety was first attempted under various heterogeneous hydrogenation conditions (Table 1). Best results were obtained when the hydrogenation was carried out using Pd–C as a catalyst in acidic (HCl) EtOH under ultrasonic activation (Table 1, entry 5 and 6), leading to 2,4-diketo piperidines **6a,b**.

Later, reactivity of the zwitterions pyridin-2-one **5a,b** with bromine was investigated. Oxidation in acetic acid was unsuccessful, but we were pleased to see the formation of 4-hydroxy-3-thiomethyl pyridin-2-ones **7a,b** in CCl_4, in a moderate yield. A major improvement was obtained by addition of NEt_3, giving the best results (Table 2, entries 5 and 6).

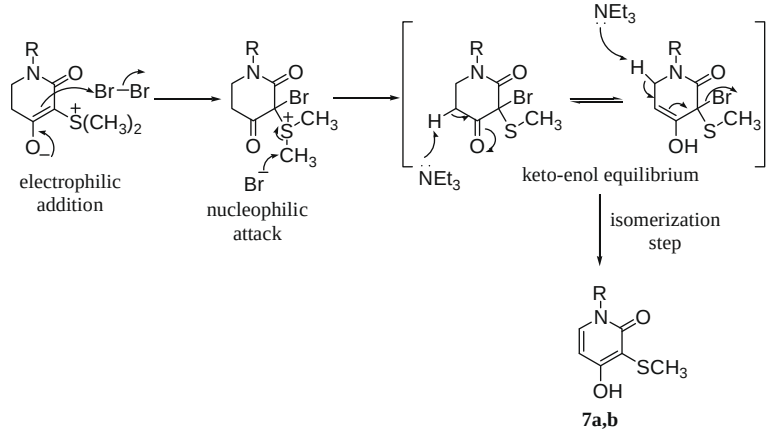
This transformation can be explained by the following mechanism (Scheme 3). First, bromine reacts with the C–C double bond by an electrophilic addition reaction, assisted by the electron lone pair of oxygen giving a sulfonium salt which through nucleophilic attack from bromide at methyl group gave the corresponding α-bromo ketone intermediate. This intermediate began to establish the keto–enol equilibrium. Finally, a base-catalyzed double bond isomerization of the enol intermediates affording compounds **7a,b**.

3. Conclusion

In conclusion, we have reported in this Letter the first synthesis of zwitterionic dihydropyridones based on an original ring-closure step involving a stabilized sulfonium ylide. The overall yield of this simple synthetic route enables a large-scale access to these interesting building blocks. Some preliminary reactivity studies have been presented, showing the good synthetic potential of these compounds, for instance for the preparation of 2,4-diketo piperidines of 4-hydroxy-3-thiomethyl pyridin-2-ones. Finally, the presence of a chiral appendage enables further asymmetric transformations of the piperidine skeleton, a reactivity which is under investigation in our laboratory.

4. Experimental

^1H NMR spectra were measured with a Varian VX400 (400 MHz) and ^{13}C NMR spectra at 100 MHz (tetramethylsilane



Scheme 3.

as internal reference). IR spectra were obtained with a Nicolet FT-IR Magna 750 spectrometer. Optical rotations were determined at room temperature with a Perkin–Elmer 341 polarimeter, using a 1 dm cell with a total volume of 1 mL and are referenced to the D-line of sodium. Mass spectra were recorded with a JEOL JEM-AX505HA instrument at a voltage of 70 eV.

4.1. General procedure for the synthesis of sulfonium salts, 4a,b

To a solution of compounds **3a,b** (1.60 mmol) in CH_3CN (3 mL) was added dimethyl sulfur (0.23 mL). The mixture reaction was stirred for 20 h at room temperature. The excess of dimethyl sulfur and the solvent was eliminated under reduced pressure. Finally the crude reaction was washed with pentane affording the corresponding sulfonium salts **4a,b**.

4.1.1. (*R*)-(+)-{[(2-Methoxycarbonyl-ethyl)-(1-phenyl-ethyl) carbamoyl]-methyl}-dimethyl-sulfonium bromide, 4a

Yield 90%, $[\alpha]_D$ = +142.03 (*c* 2.0, EtOH). IR (KBr) 1736, 1634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 1.70 (d, *J* = 6.9, 3H, Me), 2.37 (m, 2H), 3.30 (s, 3H, SMe), 3.34 (s, 3H, SMe), 3.41 (m, 2H), 3.55 (s, 3H, OMe), 5.19 (q, *J* = 6.9, 1H), 5.66 (d, *J* = 10.8, 1H), 5.94 (d, *J* = 10.8,1H), 7.27–7.40 (m,5H). ^{13}C NMR ($CDCl_3$) δ(ppm) 17.2, 24.7, 26.8, 32.1, 38.2, 49.2, 51.3, 55.9, 126.4–138.7, 163.6, 171.2. HRMS (FAB): Calcd for $C_{16}H_{24}BrNO_3S$: 390.31. Found: 391.0256, 389.1237.

4.1.2. (*R*)-(−)-{[(2-Hydroxy-1-phenyl-ethyl)-(2-methoxycar bonyl-ethyl)-carbamoyl]-methyl}-dimethyl-sulfonium bromide, 4b

Yield 94%, $[\alpha]_D$ = −49.29 (*c* 1.0, EtOH). IR (KBr) 1730, 1636 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 2.07 (ddd, *J* = 5.2, 10.2, 1H), 2.45 (ddd, *J* = 5.2, 10.2, 1H), 3.18 (s, 3H, SMe), 3.25 (s, 3H, SMe), 3.29 (m, 1H), 3.45 (m, 1H), 3.55 (s, 3H, OMe), 3.94 (dd, *J* = 4.4, 9.6, 1H), 4.15 (dd, *J* = 4.4, 9.6, 1H), 4.67 (br, 1H, OH), 5.08 (dd, *J* = 4.4, 9.6, 1H), 5.76 (d, *J* = 15.6, 1H), 5.92 (d, *J* = 15.6, 1H), 7.27–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) δ (ppm) 25.1, 27.3, 32.2, 38.8, 49.2, 51.5, 59.8, 62.3, 127.9–134.8, 164.4, 171.7. HRMS (FAB): Calcd for $C_{16}H_{24}BrNO_4S$: 406.03. Found: 407.0748, 405.0123.

4.2. General procedure of the synthesis of zwitterionic piperidine derivatives, 5a,b

To a stirred room temperature solution of the corresponding sulfonium salts **4a,b** (0.50 g, 1.23 mmol) in CH_3CN (20 mL), was added KOH (0.13 g). After 15 h, the resulting mixture was filtered and CH_3CN was removed under vacuum to give the corresponding zwitterionic compounds **5a,b**.

4.2.1. (*R*)-(+)-[4-Alcoxy-2-oxo-1-(1′-phenyl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-dimethyl-sulfonium, 5a

Yield 85%, white solid, Mp 139–140 °C. $[\alpha]_D$ = +70.5 (*c* 1.1, MeOH). IR (KBr) 1656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 1.51 (d, *J* = 7.2, 3H, Me), 2.32 (m, 2H), 2.90 (m, 1H), 2.98 (s, 3H, SMe), 3.00 (s, 3H, SMe), 3.16 (m, 1H), 5.94 (q, *J* = 7.2, 1H), 7.27–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ ppm 15.4, 26.0, 26.3, 36.3, 37.6, 48.9, 74.3, 126.5–141.0, 166.2, 187.5. HRMS (FAB): Calcd for $C_{15}H_{19}NO_2S$: 277.1124. Found: 277.1103.

4.2.2. (*R*)-(−)-[4-Alcoxy-1-(2′-hydroxy-1′-phenyl-ethyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-dimethyl-sulfonium, 5b

Yield 87%, white solid, Mp 141–142 °C. $[\alpha]_D$ = −24.7 (*c* 1.1, MeOH). IR (KBr)1655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 2.36 (m, 2H), 2.96 (s, 3H, SMe), 2.98 (s, 3H, SMe), 3.03 (m, 1H), 3.30 (m, 1H), 4.05 (AB, *J* = 5.0, 11.6, 1H), 4.15 (AB, *J* = 5.0, 11.6, 1H), 5.78 (dd, *J* = 5.0, 11.6, 1H), 7.27–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 26.3, 26.6, 36.8, 39.7, 57.7, 62.0, 74.6, 127.3–128.4, 137.9, 168.2, 188.1. HRMS (FAB): Calcd for $C_{15}H_{19}NO_3S$: 293.1115. Found: 293.1023.

4.3. General procedure of catalytic hydrogenation of zwitterionic compounds, 5a,b

To a solution of **5a,b** (1.70 mmol) in EtOH (5 mL) saturated with $HCl_{(g)}$, was added 10% Pd/C (0.05 g) and the mixture was place under hydrogen atmosphere. The mixture reaction was located in an ultrasonic activation apparatus and stirred at room temperature until the disappearance of starting material confirmed by thin layer chromatography. After, the reaction was filtered and the solvent was evaporated under reduced pressure to afford the corresponding piperidine-2,4-dione **6(a–b).**

4.3.1. (*R*)-(+)-1-(2-Phenyl-ethyl)-piperidine-2,4-dione, 6a

Yield 46%, Yellow oil. $[\alpha]_D$ = +7.1 (*c* 1.0, CH_2Cl_2). IR (KBr) 1726, 1647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 1.51 (d, *J* = 6.68, 3H), 2.32 (m, 2H), 3.14 (m, 2H), 3.5 (s, 2H), 6.08 (q, *J* = 6.68, 1H), 7.32–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 15.7, 37.5, 38.8, 49.6, 50.40, 126.8–139.5, 165.2, 203. HRMS (FAB): Calcd for $C_{13}H_{15}NO_2$: 217.14. Found: 217.0863.

4.3.2. (*R*)-(−)-1-(2-Hydroxy-1-phenyl-ethyl)-piperidine-2,4-dione, 6b

Yield 65%, yellow oil. $[\alpha]_D$ = −56.6 (*c* 1.0, CH_2Cl_2). IR (KBr) 1729, 1645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 2.34 (m, 2H), 2.55 (m, 2H), 3.30 (m, 1H), 3.47 (d, *J* = 16.2, 2H), 3.55 (m, 1H), 4.10 (dd, *J* = 6.68, 1H), 4.20 (dd, *J* = 6.68, 1H), 5.87 (dd, *J* = 6.68, 1H), 7.29–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 38.9, 49.5, 53.4, 57.9, 61.3, 127.5–138.5, 167.9, 203.9. HRMS (FAB): Calcd for $C_{13}H_{15}NO_3$: 233.1114. Found: 233.0984.

4.4. General procedure for the synthesis of pyridin-2-ones, 7a,b

To a stirred suspension of zwitterions **5a,b** (1.7 mmol) in CCl_4 (24 mL) was added a solution of Br_2 (1.5 equiv, of a 1 M solution in CCl_4) and NEt_3 (1.2 equiv) at room temperature. The resultant pale orange solution was stirred for 6 h. Finally, the reaction mixture was quenched with a saturate aqueous solution of sodium thiosulfate (3 mL). The reaction was filtered and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting mixture was purified through column chromatography (dichloromethane/petroleum ether, on SiO_2) afforded the corresponding pyridine-2-ones **7a,b**.

4.4.1. (*R*)-(+)-4-Hydroxy-1-(1′-phenyl-ethyl)-3-methylsulfanyl-1H-pyridin-2-one, 7a

Yield 49%. $[\alpha]_D$ = +21.6 (*c* 1.0, CH_2Cl_2). IR (KBr) 1656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 1.70 (d, *J* = 7.2, 3H), 2.31 (s, 3H), 6.05 (d, *J* = 8, 1H), 6.40 (q, *J* = 7.2, 1H), 7.05 (d, *J* = 7.6, 1H), 7.28–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 16.5, 18.9, 53.8, 98.7, 104.6, 127.1–139.8, 135.3, 162.0, 165.5. HRMS (FAB): Calcd for $C_{14}H_{15}NO_3S$: 277.10. Found: 277.0054.

4.4.2. (*R*)-(−)-4-Hydroxy-1-(2′-hydroxy-1′-phenyl-ethyl)-3-methylsulfanyl-1*H*-pyridin-2-one, 7b

Yield 52%, white liquid. $[\alpha]_D$ = −58.0 (*c* 1.1, CH_2Cl_2). IR (KBr) 3348, 1656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 2.29 (s, 3H), 4.27 (m, 2H), 6.06 (d, *J* = 7.6, 1H), 6.29 (dd, *J* = 4.8 and 6.8, 1H), 7.25 (d, *J* = 7.6, 1H), 7.31–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 16.6, 60.2, 63.4, 98.6, 104.9, 126.7–141.3, 137.0, 163.2, 166.0. HRMS (FAB): Calcd for $C_{14}H_{15}NO_3S$: 277.10. Found: 277.0054.

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