Novel, One-Pot Procedure for the Synthesis of 2-Arylethanol Derivatives

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Received 18 December 2007; revised 25 February 2008

Abstract: An efficient one-pot synthesis of 2-arylethanol derivatives using ethylene sulfate as a C₂ building block is described. High yields are obtained upon trapping of aryllithium intermediates generated by halogen–metal exchange or directed metalation with ethylene sulfate. The resulting heteroaryl or phenylethanol derivatives represent versatile building blocks for the synthesis of annulated pyran derivatives by oxa-Pictet–Spengler reaction.

Key words: alcohols, electrophilic aromatic substitutions, heterocycles, sulfates, lithiation

2-Arylethanol, as well as 2-arylethanamine, derivatives are of great interest as intermediates for the synthesis of pharmacologically active compounds. As an example 2-(2-thienyl)ethanamine is required as a starting material for the synthesis of the platelet aggregation inhibitor ticlopidine. In addition to the synthesis of pharmacologically active compounds, 2-arylethanol and 2-arylethanamine derivatives can be used in oxa-Pictet–Spengler reactions to prepare various aryl-annulated pyrans and pyridines, including isochromanes and isoquinolines.

There are several multistep syntheses of 2-arylethanol derivatives starting from aromatic compounds. For example, a four-step procedure comprises Blanc chloromethylation, followed by substitution with cyanide, saponification, and reduction to yield arylethanol derivatives. In another procedure an aromatic aldehyde is reacted with cyanide to afford an α-hydroxynitrile, which upon reductive hydrolysis and subsequent reduction leads to the desired arylethanol derivative.

However, only two methods are described in the literature for the direct, one-pot synthesis of arylethanol derivatives from aromatic compounds. In the first procedure a bromobenzene derivative was converted into a Grignard reagent, which was reacted with oxirane to provide an arylethanol derivative in 83% yield. Also thiophene derivatives metalated in position 2 or 3 react with oxirane to form 2-(2- or 3-thienyl)ethanol derivatives in good yields. A great drawback of these procedures is the handling of the gaseous, very toxic reagent oxirane. According to the second procedure, which was described in the patent literature very recently, 1-methylpyrazole was regioselectively α-metalated with n-butyllithium and the resulting aryllithium intermediate was reacted with an O-silyl-protected 2-bromoethanol derivative [2-bromo-1-(tert-butyl dimethylsiloxy)ethane] to afford the O-silyl-protected pyrazole ethanol derivative. After cleavage of the silyl protective group with sodium fluoride/hydrogen bromide in methanol–water the pyrazole arylethanol derivative was obtained in an overall yield of 13%. The low yield of this transformation clearly demonstrates the limitation of this procedure. In order to get easy access to a wide variety of aryl- and heteroarylethanol derivatives, which are of great interest for the preparation of annulated pyran derivatives by oxa-Pictet–Spengler reaction, an efficient and direct method for the synthesis of these derivatives is required. Herein we wish to report on a novel one-pot procedure for the direct synthesis of heteraryl and phenylethanol derivatives from aromatic systems using ethylene sulfate as a C₂ building block. In a short communication, ethylene sulfate is mentioned to form a 2-pyrylde ethanol derivative from a 2-bromopyridine in only 21% yield; an experimental procedure is not detailed. In contrast to oxirane, ethylene sulfate represents a stable solid, which is easy to handle and, moreover, is neither toxic nor volatile.

In the first attempt 2-bromoanisole (1a) was reacted with n-butyllithium at −78 °C to generate the aryllithium intermediate 2a by halogen–metal exchange. Subsequently, the aryllithium intermediate 2a was trapped with ethylene sulfate (3) at −78 °C. The cooling bath was removed and the mixture was stirred at room temperature to form the lithium sulfate 4a. After 16 hours dilute sulfuric acid was added and the reaction mixture was heated to reflux for 72 hours to hydrolyze the sulfuric acid ester 4a and produce the 2-phenylethanol derivative 5a in 73% yield (Scheme 1, Table 1). To the best of our knowledge this procedure represents the first one-pot, high-yielding synthesis of an arylethanol derivative starting from a benzene derivative.

SYNTHESIS 2008, No. 11, pp 1793–1797
Advanced online publication: 11.04.2008
DOI: 10.1055/s-2008-1067021; Art ID: T19607SS
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In order to demonstrate the scope and limitation of the new procedure several examples were studied (Table 1). At first the regioisomer 3-bromoanisole (1b) was reacted in the same way to form the regioisomeric arylethanol 5b in 62% yield.

As an example for a sulfur-containing heterocycle 2-(3-thienyl)ethanol (5c) was prepared in 53% yield by bromine–lithium exchange of 3-bromothiophene (1c), trapping of the 3-thienyllithium intermediate 2c with ethylene sulfate and hydrolysis of the resulting sulfuric acid ester 4c with diluted sulfuric acid. For the synthesis of the regioisomeric 2-(2-thienyl)ethanol (5d), thiophene (1d) without further substituents served as starting material. In this case the 2-thienyllithium intermediate 2d was generated by a-deprotonation of thiophene (1d) with n-butyllithium. However, the variation of the generation of the aryllithium intermediate 2d (deprotonation instead of halogen–metal exchange) did not influence the yield of the 2-(2-thienyl)ethanol (5d) (79%).

In addition to benzene and thiophene derivatives, nitrogen-containing heterocycles were also employed in this reaction sequence. 1-Phenyl-1H-pyrazole (1e) was a-lithiated with n-butyllithium at –78 °C to generate the pyrazol-5-yl lithium intermediate 2e.18 Trapping of 2e with ethylene sulfate and subsequent hydrolysis gave the pyrazolylethanol 5e in 75% yield. A comparable yield (54%) was obtained with 1-methyl-1H-pyrazole (1f) as the starting compound. However, a considerable decrease in the yield was observed when 1-phenyl-1H-pyrole (1g) was reacted with ethylene sulfate in the hydroxyethylation procedure. Though the pyrrolylethanol 5g was formed the yield was rather low (38%). This might be due to the low regioselectivity during the metalation of 1-phenyl-1H-pyrole (1g) with potassium tert-butoxide and n-butyllithium. Meta-

<table>
<thead>
<tr>
<th>Compound</th>
<th>Generation of ArLi</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>n-BuLi, –78 °C</td>
<td>5a</td>
<td>73</td>
</tr>
<tr>
<td>1b</td>
<td>n-BuLi, –78 °C</td>
<td>5b</td>
<td>62</td>
</tr>
<tr>
<td>1c</td>
<td>n-BuLi, –78 °C</td>
<td>5c</td>
<td>53</td>
</tr>
<tr>
<td>1d</td>
<td>n-BuLi, –78 °C</td>
<td>5d</td>
<td>79</td>
</tr>
<tr>
<td>1e</td>
<td>n-BuLi, –78 °C</td>
<td>5e</td>
<td>75</td>
</tr>
<tr>
<td>1f</td>
<td>n-BuLi, –78 °C</td>
<td>5f</td>
<td>54</td>
</tr>
<tr>
<td>1g</td>
<td>n-BuLi, t-BuOK, –78 °C</td>
<td>5g</td>
<td>38</td>
</tr>
</tbody>
</table>
component (Scheme 2). Whereas the thienylethanol 5d reacted with benzaldehyde and catalytic amounts of p-toluene sulfonic acid to afford the thiopyran 6d in 23% yield, the pyrazolylethanol derivatives 5e and 5f did not provide annulated pyran derivatives using p-toluene sulfonic acid as catalyst. We assume that this failure is due to the basicity of the pyrazole heterocycle leading upon treatment with strong acids to protonated intermediates, which are deactivated for the intramolecular electrophilic aromatic substitution in position 4. Therefore, pyridinium p-toluenesulfonate with reduced acidity was used instead of p-toluene sulfonic acid. In fact, with the weak acidic catalyst pyridinium p-toluenesulfonate the oxa-Pictet–Spengler reaction of the pyrazole derivatives 5e and 5f with benzaldehyde led to the pyranopyrazole derivatives 6e and 6f in 97% and 79% yield.

Scheme 2  Reagents and conditions: (a) benzaldehyde, PTSA, MeCN, reflux; (b) PhCHO, PPTS, MeCN, reflux.

Herein it is demonstrated that the nontoxic solid ethylene sulfate represents an attractive alternative C₂ building block for the synthesis of arylethanol derivatives. The hydroxyethylation can be applied on carbocyclic as well as heterocyclic aromatic systems. Irrespective of the formation of the required aryllithium intermediates (halogen–metal exchange or directed metatlation) high yields of arylethanol derivatives are obtained. Some of the heteroarylethanol derivatives are reacted in an oxa-Pictet–Spengler reaction to form heteroaryl-annulated pyran derivatives.

Unless otherwise mentioned, moisture sensitive reactions were conducted under dry N₂. THF was dried with Na/benzophenone and freshly distilled before use. The concentration of n-BuLi was determined by titration with 1,3-diphenylpropan-2-one p-toluene sulfonylethyldrazine in THF under N₂ atmosphere. TLC: Silica gel 60 F₂₅₄ Plates (Merck). Flash chromatography: Silica gel 60, 40–64 μm (Merck). Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan). HRMS: MicroToF (Bruker Daltonics, Bremen), calibration with sodium formate clusters before measurement. IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ¹H NMR (400 MHz), ¹³C NMR (100 MHz); Mercury-400BB spectrometer (Varian); δ relative to TMS; coupling constants are given with 0.5 Hz resolution. Elemental analysis: CHN-Rapid Analyser (Fons-Heraeus). HPLC: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher 60 RP-select B (5 μm); LiChroCART 250–4 mm cartridge; flow rate: 1.000 ml/min; injection volume: 5.0 μL; detection at λ = 210 nm; solvents (v/v): A: H₂O with 0.05% TFA; B: MeCN with 0.05% TFA; gradient elution: 0.0 min: 90.0% of A, 10.0% of B; 4.0 min: 90.0% of A, 10.0% of B; 29.0 min: 0.0% of A, 100.0% of B; 31.0 min: 0.0% of A, 100.0% of B; 31.5 min: 90.0% of A, 10.0% of B; 40.0 min: 90.0% of A, 10.0% of B. Preparative HPLC: Merck Hitachi Equipment; UV-Detector: L-7400; autosampler: L-7200; pump: L-7150; column: phenomenex Gemini 5 μm C18 110A, 250–21.2 mm; eluent: MeCN–H₂O–NH₃ (25%) 140:60:5; flow rate: 5.0 ml (0–0.5 min), 20.0 ml (0.5–14 min); injection volume: 400 μL; detection at 254 nm.

2-(2-Methoxyphenyl)ethanol (5a)
2-Bromoanisole (1a, 300 μL, 2.43 mmol) was dissolved in THF (35 mL), then 1.48 M n-BuLi in n-hexane (1.64 mL, 2.43 mmol) was added dropwise over 30 min at –78 °C; the mixture was stirred at –78 °C for 2 h. Then, ethylene sulfate (3, 361 mg, 2.92 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at r.t. for 16 h. H₂O (10 mL) and concd H₂SO₄ (1.8 mL) were added and the suspension was heated to reflux for 72 h. The soln was made alkaline with 5 M NaOH (20 mL) and extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo and the residue was purified by flash chromatography (4 cm diameter, n-hexane–EtOAc, 8:2, Rf = 0.24) to obtain 5a as a pale yellow oil; yield: 271 mg (73%).

HPLC: 97.9%, tᵣ = 15.4 min.

An alternative synthesis of compound 5a is available.

2-(3-Methoxyphenyl)ethanol (5b)
3-Bromoanisole (1b, 300 μL, 2.39 mmol) was dissolved in THF (35 mL), then 1.48 M n-BuLi in n-hexane (1.62 mL, 2.39 mmol) was added dropwise over 30 min at –78 °C; the mixture was stirred at –78 °C for 2 h. Then ethylene sulfate (3, 355 mg, 2.87 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at r.t. for 16 h. H₂O (10 mL) and concd H₂SO₄ (1.8 mL) were added and the suspension was heated to reflux for 47 h. The soln was made alkaline with 5 M NaOH (20 mL) and extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo and the residue was purified by flash chromatography (4 cm diameter, n-hexane–EtOAc, 8:2, Rf = 0.16) to give a colorless oil; yield: 225.1 mg (62%).

HPLC: 99.6%, tᵣ = 14.8 min.

An alternative synthesis of compound 5b is available.

2-(3-Thienylethanol (5c)
To a soln of 3-bromothiophene (1c, 500 mg, 3.07 mmol) in THF (20 mL), 1.6 M n-BuLi in hexane (1.90 mL, 3.04 mmol) was added dropwise at –78 °C; the mixture was stirred for 15 min. Then a soln of ethylene sulfate (3, 450 mg, 3.63 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at –78 °C for 30 min and at r.t. for 90 min. H₂O (10 mL) and concd H₂SO₄ (3 mL) were added and the mixture was heated to reflux for 4 h with vigorous stirring. The mixture was made alkaline with 5 M NaOH (35 mL) and extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and filtered and the solvent was evaporated in vacuo. Purification of the residue by flash chromatography (3 cm diameter, cyclohexane–EtOAc, 7:3; Rf = 0.16) afforded a colorless liquid; yield: 210 mg (53%).

HPLC: 99.5%, tᵣ = 12.0 min.
IR (neat): 3237 (O–H), 1044 (C–O) cm⁻¹.

1H NMR (CDCl₃): δ = 1.46 (t, J = 6.4 Hz, 1 H, ArCH₂CH₂OH), 2.91 (t, J = 6.4 Hz, 2 H, ArCH₂CH₂OH), 3.85 (q, J = 6.4 Hz, 2 H, ArCH₂CH₂OH), 6.99 (dd, J = 5.2, 1.2 Hz, 1 H, H₂thiophene), 7.04–7.07 (m, 1 H, H₂thiophene), 7.30 (dd, J = 5.2, 3.2 Hz, 1 H, H₃thiophene).

IR (neat): 3328 (O–H), 3067 (C–Harom), 1598, 1501 (C=C) cm⁻¹.

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Anal. Calcd for C₁₂H₁₂O₂: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.81; H, 7.22; N, 7.34.

Compound 5g is mentioned in the literature; however, details of the synthesis and interpretation of the H NMR data are not given.

4-Phenyl-6,7-dihydropyrido[2,3-c]pyran (6d)

Thienylethanol 5d (0.06 g, 0.47 mmol) was dissolved in MeCN (5 mL). Then PhCHO (40.5 μL, 0.39 mmol), PPTS (334 mg, 1.33 mmol), and Na₂SO₄ (100 mg) were added and the mixture was heated to reflux for 2 h. After filtration, the solid was washed by addition of 2 M NaOH (15 mL), diluted with H₂O, and extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and the solvent was evaporated in vacuo. Purification of the residue by flash chromatography (3 cm diameter, cyclohexane–EtOAc 9:1, Rₖ = 0.55) afforded a colorless solid, mp 37 °C; yield: 71 mg (97%).

HPLC: 98.0%, tᵣ = 21.2 min.

IR (neat): 3126 (C–Harom), 1049 (C–O) cm⁻¹.

1H NMR (CDCl₃): δ = 2.67 (br d, J = 4.0 Hz, 1 H, ArCH₂O), 6.48 (d, J = 5.2 Hz, 1 H, PhCH), 7.04 (d, J = 5.9 Hz, 1 H, H₂ phenyl), 7.28–7.37 (m, 5 H, Hphenyl). 13C NMR (CDCl₃): 63.7 (ArCH₂), 78.4 (PhCH), 122.3 (C₃ thiophene), 125.6 (C₂ thiophene), 128.2 (C phenyl), 133.4 (C phenyl), 136.1 (C phenyl), 141.1 (C₂pyrazole), 144.1 (Ph). MS (EI): m/z (%) = 215 [M⁺, 35].


References