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Regioselectivity of Pictet–Spengler cyclization: synthesis of halotetrahydroisoquinolines

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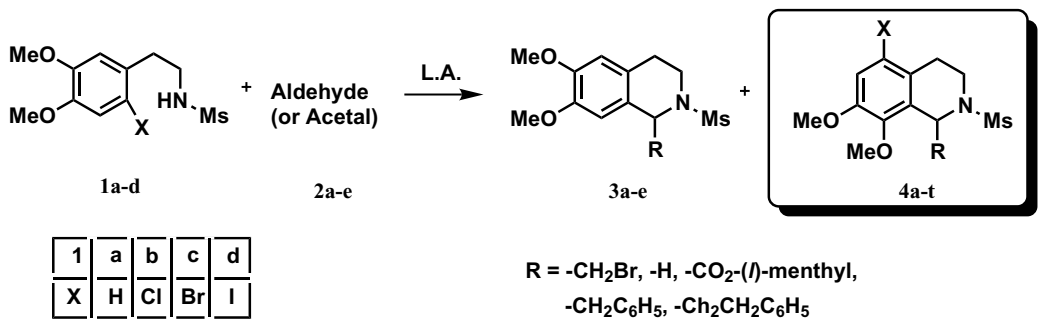
Abstract—The regioselectivity of the Pictet–Spengler cyclization for the synthesis of isoquinolines depends on the aryl substituent at C-2. The ratio of halotetrahydroisoquinoline **4** to isoquinoline **3** increases with increasing electrophilicity of the aromatic ring (H≪I<Br<Cl).

The Pictet–Spengler condensation of *N*-protected phenethylamines with aldehydes is a well known synthetic method for the construction of isoquinolines. This condensation proceeds most smoothly when the phenethyl aromatic ring is activated by electron donating substituents. However, α-phenethylamines bearing an electron withdrawing aryl substituent like acyl[1a–d] or sulfonyl[2a–d] are still amenable to Pictet–Spengler cyclization, although yields are variable. Generally, the least sterically hindered *ortho* position is the predominant site of cyclization unless blocked by a substituent at C-2 (Scheme 1). The latter is often a halogen that is subsequently removed in order to obtain a 7,8-disubstitution pattern.

Orazi et al.[2a] was one of the first to exploit a sulfonyl group as the *N*-substituent for a Pictet–Spengler condensation. Also, Kohno et al.[3a–b] reported the reaction of *N*-benzenesulfonyl-α-phenethylamines with ethyl chloro(methylthio)acetate in the presence of $SnCl_4$ affords isoquinolines. Silveira et al.[4] carried out similar cyclizations using β-halo-α-phenylselenyl esters. Notably, few examples of asymmetric Pictet–Spengler condensations have been published. For instance, Piper et al.[5] reported the addition of dopamine hydrochloride with D-glucose in aqueous solution gave a chiral tetrahydroisoquinoline in excellent yield. Similarly, Czarnocki et al.[6] observed that the treatment of *N*-glyoxyoly-(2*R*)-bornane-10,2-sultam with dopamine hydrochloride furnished a chiral isoquinoline.



Scheme 1.

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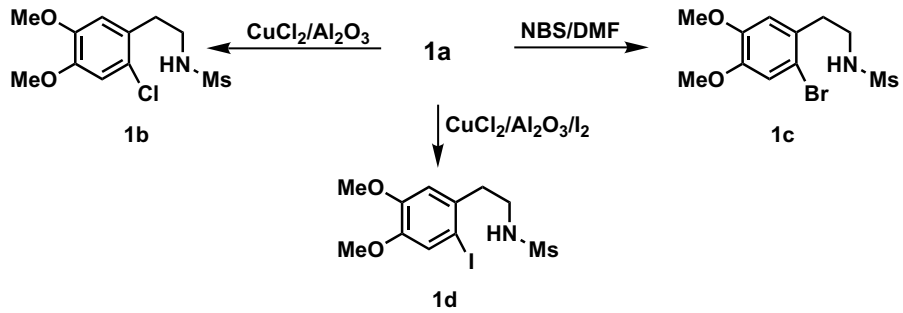
During the course of our studies directed at the synthesis of substituted 5-halotetrahydroisoquinolines **4**, we turned our attention to the regioselectivity of 2-halophenethylamines **1a–d** in Pictet–Spengler condensations with acetals or aldehydes under Lewis acidic conditions (Scheme 1).

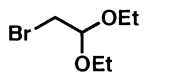
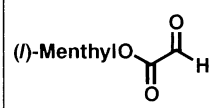
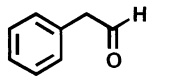
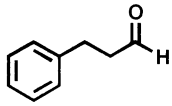
The starting material, sulfonamide[7] **1a** (X = H), was easily prepared from the corresponding phenethylamine by addition of methanesulfonyl chloride. Halogenation of **1a** according to literature procedures gave rise to 2-halosulfonamides **1b–d** in good yields (Scheme 2). Specifically, chlorosulfonamide **1b** (X = Cl) was readily prepared via reaction of **1a** with $CuCl_2/Al_2O_3$/chlorobenzene[8] (91%), bromosulfonamide **1c** (X = Br) using NBS/DMF[9] (93%), and iodosulfoamide **1d** (X = I) (88%) utilizing $CuCl_2/Al_2O_3/I_2$.[10]

As anticipated, condensation of sulfonamide **1a** with bromoacetaldehyde diethyl acetal (**2a**) in CH_2Cl_2 and cyclization of the adduct using boron trifluoride diethyl etherate complex or conc. H_2SO_4 at room temperature for 1 hour afforded **3a** as the sole product in excellent yield (Table 1). Following literature precedent, introduction of a chloride at C-2 as in **1b**, completely altered the regiochemical selectivity to give **4b** in 90% yield accompanied by a trace of **3a** (0.2%). On the other hand, Pictet–Spengler cyclization of **1c** with **2a** resulted in a mixture of **3a** and **4c**, although the latter cyclization mode still predominates. In contrast, iodo derivative **1d** was the least regioselective and produced a virtually equimolar mixture of **3a** and **4d**. Replacement of $BF_3{\cdot}Et_2O$ with mineral acids (H_2SO_4, HCl) and various other Lewis acids did not influence the cyclization yield.



Scheme 2.

Table 1. The yields and ratio of **3**/**4** by Pictet–Spengler condensation of **1** and **2**

Entry	1, X		Aldehyde(or Acetal), 2		3/4, R		Yield(%)[a] of 3/4	Ratio[b] of 3/4
1	a b c d	H Cl Br I	2a		3a/4a 3a/4b 3a/4c 3a/4d	-CH_2Br	95 90 92 89	100/0 0.2/99.8 5.0/95.0 41.1/58.9
2	a b c d	H Cl Br I	2b		3b/4e 3b/4f 3b/4g 3b/4h	-H	83 88 91 89	100/0 0.1/99.9 6.8/93.2 23.9/76.1
3	a b c d	H Cl Br I	2c	 [c]	3c/4i 3c/4j 3c/4k 3c/4l	-CO_2-(*l*)-Menthyl	89 81 76 83	100/0 0/100 12.8/87.2 61.4/38.6
4	a b c d	H Cl Br I	2d		3d/4m 3d/4n 3d/4o 3d/4p	-$CH_2C_6H_5$	67 58 65 75	100/0 0.2/99.8 28.2/71.8 51.2/48.8
5	a b c d	H Cl Br I	2e		3e/4q 3e/4r 3e/4s 3e/4t	-$CH_2CH_2C_6H_5$	58 55 70 62	100/0 0.1/99.9 41.5/58.5 96.7/3.3

[a] Isolated yield after flash chromatography.

[b] Determined via the analysis of the GC-MS spectra.

[c] L-Menthyl 2,2-dihydroxyacetate was synthesized in Kg scale in our lab.

Inspection of Table 1 reveals a similar reactivity pattern for dimethylacetal **2b**. Total yields for aldehydes **2c–e** are somewhat reduced, but they still reflect the same regioselectivity pattern. In general, the ratio of isoquinoline **3** to halotetrahydroisoquinoline **4** depends on the identity of the halo-substituent at C-2 on the aromatic moiety, regardless of the reaction conditions and condensation partner. The percentage of halotetrahydroisoquinoline **4** increased in the order H≪I<Br< Cl, i.e. with increasing electrophilicity.

In conclusion, we have described a Pictet–Spengler cyclization strategy to prepare halotetrahydroisoquinolines **4** based upon the C-2 halogen substituent. Applications of this strategy to the syntheses of biologically active compounds are under investigation and will be reported in due course.

Typical procedure: $BF_3{\cdot}OEt_2$ (3.2 mL, 25.6 mmol, 3.5 equiv.) was slowly added to a solution of bromosulfonamide **1c** (2.47 g, 7.3 mmol, 1.0 equiv.) and **2a** (R = $-CH_2Br$) (1.03 mL, 8.7 mmol, 1.2 equiv.) in dichloromethane 20 mL and stirred at room temperature under N_2 atmosphere for 1 hour. The reaction mixture was poured into cold water and extracted twice with dichloromethane (30 mL). The combined organic extracts were washed water and dried over $MgSO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane:ethyl acetate (1/1) as eluent to afford **3a**/**4c** (92% yield) as white solid. **3a**: mp 143–144°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.61 (s, 1H), 5.05–5.10 (q, 1H), 3.85–3.92 (m, 1H), 3.87 (s, OCH_3), 3.86 (s, OCH_3), 3.60–3.72 (m, 2H), 3.42–3.52 (m, 1H), 3.00–3.08 (m, 1H), 2.99 (s, 3H), 2.67–2.74 (m, 1H); MS (*m*/*z*) 364.

4c: mp 156–157°C; ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 1H), 5.12–5.22 (s, 1H), 3.91–3.94 (m, 1H), 3.85 (s, OCH_3), 3.80 (s, OCH_3), 3.63–3.78 (m, 2H), 3.40–3.49 (m, 1H), 3.24–3.26 (m, 1H), 3.07 (s, 3H), 2.72–2.90 (m, 1H); MS (*m*/*z*) 443.

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