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Preparation of 2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] via an *N*-sulfonyl Pictet–Spengler reaction

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Abstract—A high yielding synthesis of variously substituted 2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] is reported. *N*-(2-nitrophenyl)sulfonyl was successfully used as both an activating and protecting group for the key Pictet–Spengler reaction.

The privileged structure 1-(methylsulfonyl)-spiro[indoline-3,4′-piperidine] (**1**) has proved to be a versatile building block. Research at Merck & Co. led to the discovery of **MK-0677** containing a spiro[indoline-3,4′-piperidine] substructure. The compound is one of the most potent peptidomimetic growth hormone secretagogues and entered Phase III clinical trials.[1] The SAR study about structure **1** directed our interest to the (2-methylsulfonyl)-2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] (**2**) containing an expanded six member ring. Given its potential for biological activity, an efficient method for its preparation was required (Fig. 1).

A modestly yielding preparation of the dimethoxy substituted 2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] has been reported.[2] The synthesis uses a Schmidt reaction of spiro[indane-3,4′-piperidine]-1-one followed by reduction of the formed lactam. Pictet–Spengler cyclization[3] has been commonly used for the preparation of 1,2,3,4-tetrahydroisoquinoline derivatives from phenyl ethylamine. The reaction tolerates some electron-withdrawing substitutions on the phenyl ring when the amine is activated by acyl or sulfonyl groups.[4] Here we report the preparation of 2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] utilizing an *N*-sulfonyl Pictet–Spengler reaction to construct the isoquinoline ring.

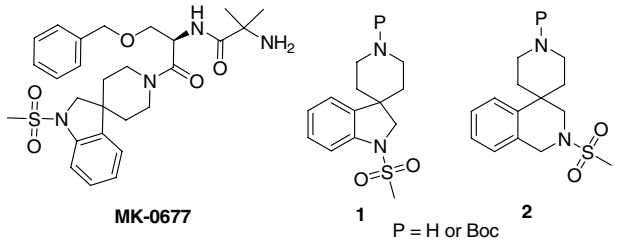
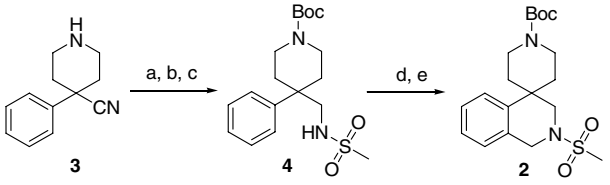


Figure 1.

As outlined in Scheme 1, the commercially available 4-cyano-4-phenyl piperidine (**3**) was used as the starting material for the synthesis. The piperidine nitrogen was initially protected as the Boc derivative, the nitrile was then reduced to the primary amine with the borane–THF complex and activation was achieved by forming the methanesulfonamide. Pictet–Spengler cyclization of the phenylethyl sulfonamide (**4**) with formaldehyde in a mixture of acetic acid and sulfuric acid (4:1) provided an excellent yield of 1′-Boc-(2-methylsulfonyl)-2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] (**2**) after the Boc reprotection.[5] The phenylethyl acetamide underwent the Pictet–Spengler reaction very slowly at elevated



Scheme 1. Synthesis of **2**. Reagents and conditions: (a) Boc_2O, NaOH (5 N), THF, 95%; (b) BH_3–THF, 40 °C; (c) $MeSO_2Cl$, TEA, CH_2Cl_2, 90% (two steps); (d) $(CH_2O)_n$, AcOH–H_2SO_4 (4:1); (e) Boc_2O, NaOH (5 N), EtOAc, 99% (two steps).

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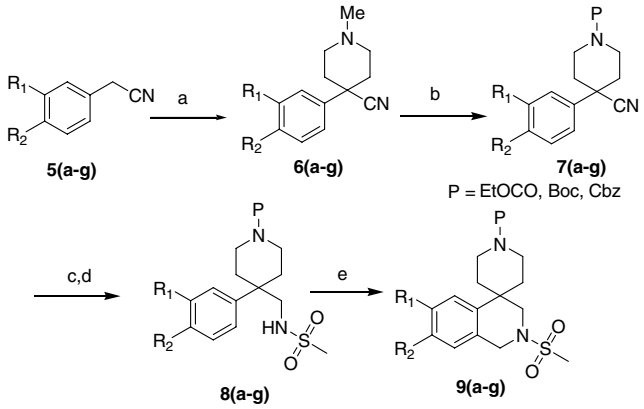


Scheme 2. Synthesis of **9** with different substitutions on the phenyl ring. Reagents and conditions: (a) MeN $(CH_2CH_2Cl)_2$·HCl, $Bu_4N^+HSO_4^-$, NaOH (50%), 20–70%; (b) ethylchloroformate, $ClCH_2CH_2Cl$, 85 °C, or 1-chloroethylchloro formate, $ClCH_2CH_2Cl$, 85 °C, then MeOH, Boc_2O or CbzCl, NaOH (5 N) 70–85%; (c) BH_3–THF, 40 °C; (d) $MeSO_2Cl$, TEA, CH_2Cl_2, rt, 90% (two steps); (e) $(CH_2O)_n$, AcOH–H_2SO_4 (4:1), then NaOH (5 N), Boc_2O when P = Boc.

reaction temperature and provided a very low yield (<20%) of the spiro structure.

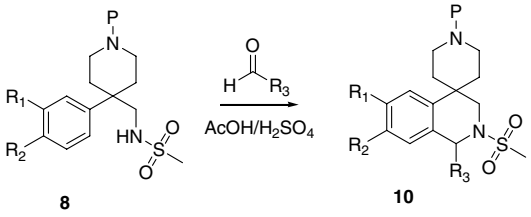
We then investigated the effect of different aryl substitutions on the Pictet–Spengler reaction (Scheme 2). Commercially available or readily prepared 4- or 3,4-substituted phenylacetonitriles (**5a**–**g**) were converted to *N*-methyl-4-cyano-4-phenyl piperidines (**6a**–**g**) by double alkylation with *N*-methyl-bis(2-chloroethyl) amine under basic, phase-transfer conditions.[6] Electron-donating substitutions on the phenyl ring slowed down the reaction and gave much lower yields [e.g. 4-methoxyphenyl acetonitrile (20% yield) and 3,4-dimethoxyphenyl acetonitrile (no product obtained)]. The *N*-methyl on the piperidine was removed and transformed to ethoxy, *t*-butoxy (Boc) or benzyloxy (Cbz) carbonyl group (**7a**–**g**). Subsequent reduction of the nitriles with borane–THF complex followed by conversion of the resultant amines to their methanesulfonamides (**8a**–**g**) generated the key cyclization precursors. The methanesulfonamides were subjected to the Pictet–Spengler reaction to provide moderate to excellent yields of spiro[isoquinoline-4,4′-piperidine] structures. The 3,4-disubstituted phenyl substrates provided mostly regioselective products on the sterically less hindered position (>12:1 selectivity as monitored by ^1H NMR of the crude product). The yields for these reactions are listed in Table 1. The cyclization is accelerated with electron-donating groups. The Boc group was removed under acidic reaction conditions and needed to be reattached. The loss of small portion of Cbz protection was observed, consequently leading to low yield when no reprotection was applied. The ethoxy carbonyl was untouched.

Different aldehydes were also used in the Pictet–Spengler reaction in order to investigate their activity (Scheme 3). The reactivity sequence is formaldehyde > acetaldehyde > benzaldehyde > propionaldehyde. Acid catalyzed polymerization of acetaldehyde complicated the transformation and low reaction temperature was required.

Table 1. Product substitutions and yields for Pictet–Spengler reaction

Products	R_1	R_2	P	Yield (%)[a]
9a	H	Me	EtOCO	97
9b	H	F	Boc[b]	65
9c	H	Cl	Cbz	52
9d	H	MeO	EtOCO	61
9e	F	F	Boc[b]	96
9f	Me	Me	Cbz	36
9g	Me	Cl	Boc[b]	82

[a] Separated yield.
[b] Boc was reattached after Pictet–Spengler reaction.



Scheme 3. Pictet–Spengler reaction with different aldehydes.

Table 2. Summary for the Pictet–Spengler reaction with different aldehydes

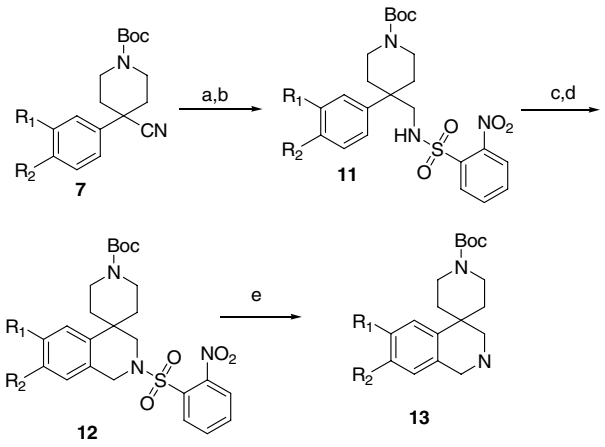
Products	R_1	R_2	R_3	T (°C)	Yield (%)[a]
10a	H	Me	Me	0	98[b]
10b	H	Me	Et	40	15[b]
10c	H	Me	Ph	80	61[b]
10d	Me	Me	Me	0	44[c]
10e	Me	Me	Et	40	63[c]
10f	Me	Cl	Me	rt	56[b]

[a] Isolated yield.
[b] The N-protection was ethoxy carbonyl.
[c] The N-protection was Cbz.

Reactions with benzaldehyde and propionaldehyde needed elevated reaction temperature. No reaction was detected with isobutyraldehyde presumably because of serious steric hindrance. With an electron-withdrawing group on the aromatic ring, such as in **8b** (F) and **8c** (Cl), the Pictet–Spengler reaction only occurred with formaldehyde. Table 2 summarizes these data.

For ease of further derivatization we also explored alternative protecting/activating groups that would allow selective deprotection of the piperidine and isoquinoline nitrogens. Given its ease of removal under mild conditions, we investigated the cyclization of compound **11** containing Fukuyama's 2-nitrophenyl sulfonamide[7] (Scheme 4). We discovered that the reaction took place with high yield of **12**. The 2-nitrophenyl sulfonyl group could be selectively removed with lithium hydroxide and mercaptoacetic acid without affecting the Boc protecting group. On the other hand, treatment with HCl in dioxane, effected the Boc protection leaving the sulfonyl group intact.

In summary, we have demonstrated that the biologically interesting (2-methylsulfonyl)-2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] can be prepared via an *N*-sul-



Scheme 4. Pictet–Spengler reaction with 2-nitrophenyl sulfonamide. R_1, R_2 = H, H; H, Me; Me, Cl. Reagents and conditions: (a) BH_3–THF, 40 °C; (b) 2-nitrophenyl sulfonyl chloride, TEA, CH_2Cl_2 (80–90% two steps) (c) $(CH_2O)_n$, AcOH–H_2SO_4 (4:1); (d) Boc_2O, NaOH, EtOAc (>90%, two steps); (e) $HSCH_2COOH$, LiOH, DMF.

fonyl Pictet–Spengler reaction. This methodology allows for a variety of different substitutions on the phenyl ring and works with various aldehydes. The *N*-2-nitrophenyl sulfonamide can be used in place of methane sulfonamide and allows for easy, selective deprotection of either nitrogen for further derivatization.

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5. Procedure for the preparation of **2** (Pictet–Spengler reaction): A 25 mL one neck round bottom flask was charged with **4** (341 mg, 0.925 mmol), paraformaldehyde (83 mg, 2.78 mmol) and acetic acid (1.6 mL). The mixture was stirred for 10 min and then cooled to 0 °C in an ice-water bath. Concentrated sulfuric acid (0.4 mL) was added dropwise over 5 min. The resulting reaction mixture was stirred at 0 °C for 20 min and at room temperature for a further 1 h. The mixture was then cooled to 0 °C in ice-water bath, diluted with ethyl acetate (20 mL) and quenched with NaOH (5 N) until pH ~ 9. Boc_2O (303 mg, 1.39 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. After the organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed by water, brine, dried over $MgSO_4$, filtered and concentrated. The crude material was then purified by MPLC (12 M, 0–40% ethyl acetate in hexanes) to afford 0.350 g product **2** (99%, rf = 0.3 by ethyl acetate:hexanes = 2:3): Formula: $C_{19}H_{28}N_2O_4S$ (380.18); LC–MS: $(M+H)^+$: 381.2; ^1H NMR (500 MHz, $CDCl_3$, ppm, $t = 25$ °C): δ 7.37 (d, $J = 7.5$ Hz, 1H), 7.27 (t, $J = 8$ Hz, 1H), 7.20 (t, $J = 7.3$ Hz, 1H), 7.08 (d, $J = 7.5$ Hz, 1H), 4.45 (br, 2H), 4.09 (br, 2H), 3.70 (br, 1H), 3.31 (br, 1H), 3.00 (br, 2H), 2.91 (s, 3H), 2.10 (br, 1H), 1.86 (br, 1H), 1.75 (br, 2H), 1.48 (s, 9H).
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