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An efficient route to 4-(substituted benzyl)piperidines

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Abstract—A novel approach to 4-(substituted benzyl)piperidines has been developed. The key steps involve the cyclization of imines bearing an allylsilane in the side-chain followed by the palladium-catalyzed cross-coupling of the resulting 4-methylenepiperidine with organoboronic acids under an atmosphere of oxygen.

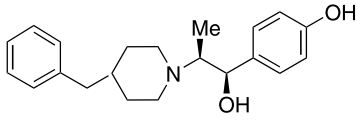
4-Benzylpiperidines possess a wide range of physiological and pharmacological activities. For example, ifenprodil **1** exhibits antihypertensive activity,[1] eliprodil **2** shows promise for the treatment of strokes,[2] whereas diphenylacetamides such as **3**, display activity as sodium channel blockers (Scheme 1).[3]

There are only a few synthetic methods suitable for the practical and efficient construction of 4-benzylpiperidines. Wick et al.[4] described a four-step procedure for the preparation of 4-benzylpiperidines. Recently, Zhou and Keana[5] reported a more general Wittig olefination/reduction sequence to generate 4-benzylpiperidines. Many different benzyl piperidines were prepared using Suzuki reactions as the key step.[6] However, the Suzuki protocol requires the use of expensive reagents (such as 9-BBN, Ph_3As, $PdCl_2dppf$) to provide efficient conversions.

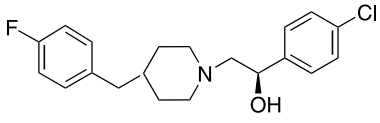
In this communication we present a simple and efficient synthesis of 4-benzylpiperidines. The proposed reaction sequence consists of cyclization of imines bearing a trimethylsilyl-allyl group followed by the palladium-catalyzed coupling of 4-methylenepiperidines with arylboronic acids (Scheme 2).

4-Amino-2-(trimethylsilylmethyl)but-1-ene **4**[7] was selected as a substrate for our studies. This was prepared efficiently in four steps starting from 3-methyl-3-buten-1-ol in 40% overall yield (Scheme 3).[7]

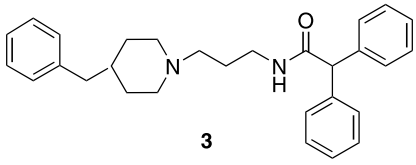
As outlined in Table 1, the aldimine **5** obtained from amine **4** and benzaldehyde (CH_2Cl_2, MS 4 Å, rt, 12 h, 95%) reacted successfully in the presence of a variety of Lewis acids to provide, after *N*-tosylation, the desired cycloadducts **6** in moderate to good yields. It should be noted that double-bond rearranged products were not detected.



Ifenprodil **1**



Eliprodil **2**



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Scheme 1.

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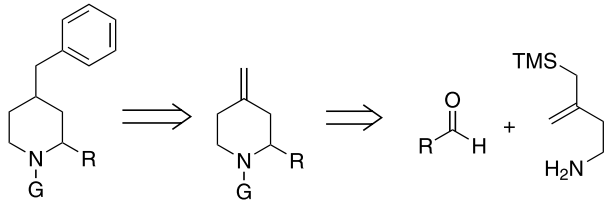
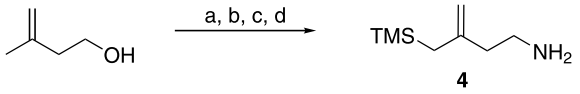


Scheme 2.



Scheme 3. *Reagents and conditions*: (a) 2.5 equiv. BuLi, 2.5 equiv. TMEDA, Et_2O/THF 2/1, 24 h, rt, then 5.0 equiv. TMSCl, then 1N H_2SO_4, THF, 70%; (b) TsCl, $(C_2H_5)_3N$, 0°C, 3 h, 90%; (c) NaN_3, DMF, rt, 10 h, 95%; (d) PPh_3, THF/H_2O, 20 h, rt, 65%.

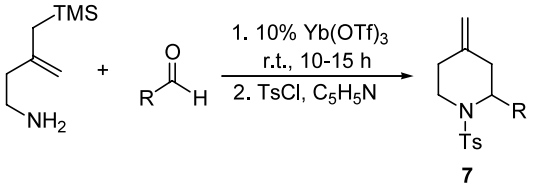
Table 1. Lewis acid mediated synthesis of 4-methylenepiperidines

Entry	Lewis acid	Conditions	Yield of **6** (%)
1	$TiCl_4$	1.0 equiv., CH_2Cl_2, −78°C	82
2	$SnCl_4$	1.0 equiv., CH_2Cl_2, −78°C	76
3	$BF_3{\cdot}Et_2O$	1.0 equiv., CH_2Cl_2, −78°C	80
4	TMSOTf	0.5 equiv., CH_2Cl_2, −78°C	66
5	$Yb(OTf)_3$	0.1 equiv., CH_3CN, rt	89

Since imines derived from aliphatic aldehydes, are usually not stable, it is synthetically useful if such aldimines are generated in situ and allowed to react further under one-pot reaction conditions. Most Lewis acids cannot be used in this fashion, however, because they decompose in the presence of the water which is formed during imine formation. Recently, Kobayashi et al.[8] reported that a catalytic amount of lanthanide triflate mediates effectively intermolecular allylation of in situ generated aldimines with allyltributylstannane, even in the presence of water.

Following this report,[8] we studied the direct synthesis of 4-methylenepiperidines as a one-pot reaction. All the condensation products obtained were characterized as *N*-tosyl derivatives **7**. As shown in Table 2, the modified procedure afforded the corresponding adducts in a good yields.[9]

Table 2. Direct synthesis of 4-methylenepiperidines



Entry	R	Solvent	Yield of **7** (%)
1	H	CH_3CN/H_2O	90
2	$(CH_3O)_2CH$	CH_3CN/H_2O	85
3	$CO_2CH_2CH_3$	CH_3CN	80
4	$CH_3CH_2CH_2$	CH_3CN	89
5	$(CH_3)_2CH$	CH_3CN	82
6	$(CH_3)_3C$	CH_3CN	86
7	C_6H_5	CH_3CN	96
8	4-$MeOC_6H_4$	CH_3CN	79
9	4-ClC_6H_4	CH_3CN	73
10	PhCH=CH	CH_3CN	76
11	2-Pyridyl	CH_3CN	83

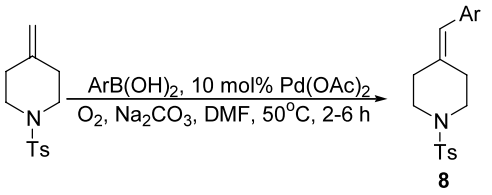
For all entries of Table 2, the yields of the 4-methylenepiperidines were comparable to those obtained by reaction of the pre-formed and isolated aldimines. The one-pot reaction can be carried out with various aldehydes, including formaldehyde, aliphatic and aromatic compounds.

Having 4-methylenepiperidines in hand, arylation of the exocyclic double bond was investigated. To the best of our knowlege, only a few examples of the Heck-type arylation of 1,1-disubstituted olefins have appeared in the literature.[10,11] As a model compound for these investigations, we used 4-methylenepiperidine (Table 2, entry 1), because only the simple 4-benzylpiperidine subunit appears to be of interest in clinical and preclinical development.[1–3] After a few, unsuccessful attempts, we found that the use of a catalytic amount of $Pd(OAc)_2$ (10 mol%) under an oxygen atmosphere[11] led to the formation of C–C bonds between organoboronic acids and 4-methylenepiperidine (Table 3).[12]

Table 3 shows that the selected arylboronic acids were coupled with 4-methylenepiperidine smoothly affording the respective styryl derivatives. The electron density in the arylboronic acids appears not to have a significant influence on the cross-coupling results: both the 4-methoxyphenylboronic acid (entry 3) and 4-acetylphenylboronic acid (entry 6) led to the arylated products in 78 and 72% yields, respectively. For all reactions, small amounts of the corresponding biphenyls (homocoupled products) were observed (5–7%).[13]

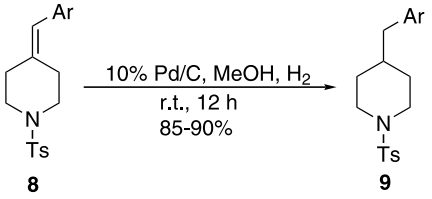
Reduction of the double bond in **8** using typical conditions (10% Pd/C, MeOH, H_2, rt, 12 h) led to the corresponding 4-benzylpiperidines **9** in a good yields (Scheme 4).[14]

Table 3. Palladium catalyzed cross-coupling of arylboronic acids and 4-methylenepiperidine



Entry	Ar	Yield of **8** (%)
1	C_6H_5	86
2	4-*t*-BuC_6H_4	80[a]
3	4-$MeOC_6H_4$	78
4	4-FC_6H_4	88
5	4-$Me_2NC_6H_4$	62
6	4-$MeCOC_6H_4$	72

[a] Yield calculated using ^{1}H NMR.



Scheme 4.

In conclusion we have reported a simple and efficient procedure for the synthesis of 4-(substituted benzyl)piperidines. The protocol is general in scope and does not require anhydrous reaction conditions.

Acknowledgements

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9. A typical experimental procedure: To a suspension of $Yb(OTf)_3$ (0.01 mmol, 10 mol%) in CH_3CN (5 mL) were added an aldehyde (0.1 mmol) and an amine **4** (0.1 mmol) at room temperature. The mixture was stirred for 10–15 h, water was added and the product was extracted with CH_2Cl_2 (3×5 mL). After the organic layer was dried and evaporated, the crude product was dissolved in CH_2Cl_2 (5 mL) and pyridine (0.1 mL), cooled to 0°C and TsCl (0.1 mmol) was added in one portion. The mixture was stirred at rt for 5 h. A solution of aqueous $NaHCO_3$ (10 mL) was added and the product was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the crude product chromatographed on silica gel (10% ethyl acetate/hexanes for elution). Representative data for 4-methylene-1-(toluene-4-sulfonyl)piperidine (Table 2, entry 1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.29 (m, 4H), 4.69 (s, 2H), 3.05 (t, 4H, $J=5.7$ Hz), 2.42 (s, 3H), 2.30 (t, 4H, $J=5.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 143.5, 133.4, 129.6, 127.6, 109.9, 47.6, 33.8, 21.5; HRMS (EI) calcd for $C_{13}H_{17}NO_2S$ 251.09800, found 251.09776.
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12. A typical experimental procedure: 4-Methylenepiperidine (Table 2, entry 1) (0.1 mmol) was dissolved in DMF, to the solution were added phenylboronic acid (0.13 mmol), Na_2CO_3 (0.3 mmol) and $Pd(OAc)_2$ (0.01 mmol) in one portion. The flask was fitted with an oxygen balloon and heated to 50°C for 2 h. After that time the mixture was diluted with ethyl acetate, washed with brine and dried over ($MgSO_4$). Evaporation of the solvent followed by silica-gel column chromatography gave the corresponding product. Representative data for 4-benzylidene-1-(toluene-4-sulfonyl)piperidine (Table 3, entry 1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.64 (m, 9H), 6.29 (s, 1H), 3.12 (m, 2H), 2.99 (m, 2H), 2.57 (m, 2H), 2.45 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 136.9, 136.4, 133.2, 129.6, 128.7, 128.2, 127.7, 126.5, 125.2, 47.7, 41.1, 35.6, 28.4, 21.5; HRMS (EI) calcd for $C_{19}H_{21}NO_2S$ 327.12930, found 327.12919.
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14. A typical experimental procedure: To a solution of 4-benzylidene-1-(toluene-4-sulfonyl)piperidine (Table 3, entry 1) in 10 mL of methanol was added 20 mg of 10% Pd/C.

The reaction mixture was fitted with a hydrogen balloon and stirred for 12 h. After that time the catalyst was removed by filtration through a short pad of Celite. Evaporation of the solvent followed by silica-gel column chromatography gave the corresponding product. Representative data for 4-benzyl-1-(toluene-4-sulfonyl)piperidine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.05 (m, 9H), 3.75 (d, 2H, $J=12.0$ Hz), 2.51 (d, 2H, $J=6.7$ Hz), 2.42 (s, 3H), 2.16 (dt, 2H, $J=2.5, 12.0$ Hz), 1.67 (m, 2H), 1.47–1.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 143.3, 139.8, 133.1, 129.5, 128.9, 128.3, 127.7, 126.0, 46.4, 42.6, 37.3, 31.3, 21.5; HRMS (EI) calcd for $C_{19}H_{23}NO_2S$ 329.14495, found 329.14479.