HETEROCYCLES, Vol. 75, No. 1, 2008, pp. 183 - 188. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd August, 2007, Accepted, 27th September, 2007, Published online, 28th September, 2007. COM-07-11206

A CONVENIENT ONE-POT PREPARATION OF *N*-SUBSTITUTED 4-PHENYLPIPERIDINES

Shigehiro Asano and Hitoshi Ban*

Dainippon Sumitomo Pharma Co., Ltd. Enoki 33-94, Suita, Osaka, 564-0053, Japan. e-mail: hitoshi-ban@ds-pharma.co.jp

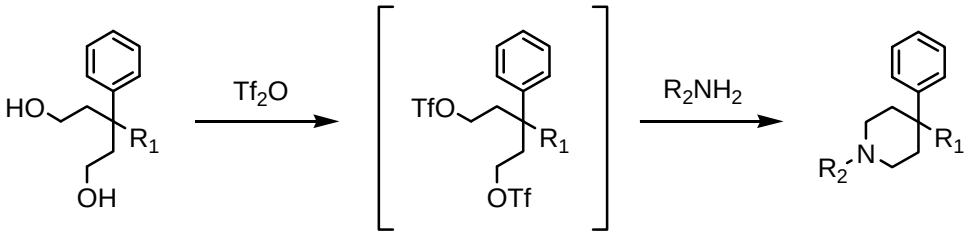
Abstract – *N*-Substituted 4-phenylpiperidines were readily synthesized by one-pot cyclization of diols with amines via bis-triflate intermediates. The new synthesis under mild conditions gave various *N*-substituted 4-phenylpiperidines in moderate to good yields.

INTRODUCTION

N-Substituted 4-phenylpiperidines are very important motifs in the range of medicines, particularly those used for central nervous system disorders, such as pethidine[1] and difenoxin.[2] Two typical synthetic routes for *N*-Substituted 4-phenylpiperidines are reported. One is cyclization of appropriate phenylacetonitriles with *N*-substituted bis(2-haloethyl)amines.[1,3,4] The other is cyclization of primary amines with α,α-bis(2-haloethyl)phenylacetonitrile[5,6] or α,α-bis(formylmethyl)phenylacetonitrile.[7] However, the use of these methods is limited to the preparation of some *N*-substituted piperidine derivatives. In addition, the former method requires the preparation of *N*-substituted bis(2-haloethyl)amine derivatives through multi-reaction steps, while the later method is not useful for the synthesis of piperidines substituted with *N*-aryl or *N*-sterically hindered alkyl groups.

In order to prepare various piperidine derivatives easily, new useful synthetic methods are desired. In this report, we present a convenient method for the synthesis of *N*-substituted 4-phenylpiperidines using bis-triflate as a key intermediate (Scheme 1).

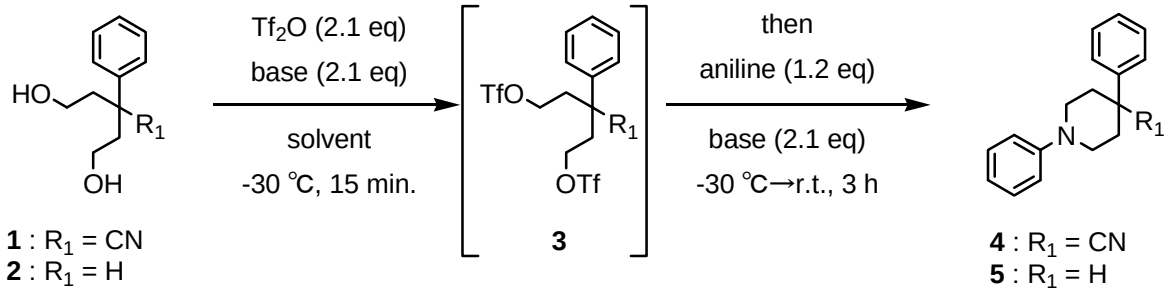
Scheme 1. Piperidine Formation via Bis-triflate



RESULTS AND DISCUSSION

Initially, a stepwise cyclization using bis-mesylate or bis-bromide precursor with aniline was attempted. The diol **1** was readily synthesized from commercially available phenylacetonitrile and 2-(2-bromoethoxy)tetrahydro-2*H*-pyran by alkylation[5] and methanolysis.[8] The diol **2** was obtained by the reduction of 3-phenylgurutalic acid according to the reported method.[9] The precursors were prepared from diols **1** and **2** by mesylation[10] or bromination using CBr_4/PPh_3. Despite screening various bases and solvents, the ensuing cyclization with aniline did not give sufficient yields (3 - 28%) of the corresponding piperidines. Therefore, we turned our attention to bis-triflate precursors possessing more reactive leaving groups. The cyclization was conducted without isolating bis-triflate **3** because of its instability at room temperature.

Table 1. The one-pot cyclization of diol with aniline



1 : R_1 = CN
2 : R_1 = H

3

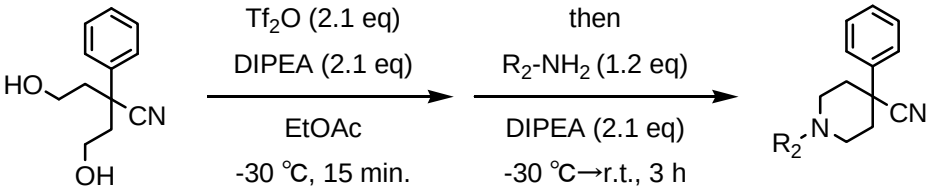
4 : R_1 = CN
5 : R_1 = H

Entry	Diol	Base	Solvent	Isolated yield (%)
1	**1**	TEA	MeCN	51
2	**1**	TEA	CH_2Cl_2	22
3	**1**	TEA	toluene	7
4	**1**	TEA	EtOAc	67
5	**1**	pyridine	EtOAc	18
6	**1**	DIPEA	EtOAc	81
7	**2**	DIPEA	MeCN	78
8	**2**	DIPEA	EtOAc	78

In the presence of triethylamine (TEA) (2.1 eq.), diol **1** (1.0 eq.) and trifluoromethanesulfonic anhydride (Tf_2O) (2.1 eq.) were reacted in acetonitrile (MeCN) at -30 ℃ for 15 min. Without isolating the bis-triflate precursor, aniline (1.2 eq.) and TEA (2.1 eq.) were then added. After one hour at the same

temperature, the reaction mixture was stirred at ambient temperature for 2 hours. The resulting piperidine **4** was obtained in 51% yield (Entry 1 in Table 1). As a result of extensive screening of various bases and solvents, the stability of the key intermediate **3** in the reaction turned out to be important, since **3** was gradually decomposed in the presence of pyridine (Entry 5 in Table 1). The use of dichloromethane or toluene as reaction solvents gave poor yields due to the low solubility of **1** (Entries 2 and 3 in Table 1). When Hünig's base (DIPEA) was used, the reaction proceeded to completion and the one-pot cyclization gave a satisfactory result (Entry 6). The reaction of 3-phenyl-1,5-pentanediol **2** with aniline under the same conditions gave the desired product **5** in good yields (Entries 7 and 8).

Table 2. The one-pot cyclization of **1** with various amines



1

Entry	R_2	Product	Isolated yield (%)
1	*o*-MeO-C_6H_4	**6**	66
2	*m*-MeO-C_6H_4	**7**	85
3	*p*-MeO-C_6H_4	**8** [3]	70
4	*p*-F-C_6H_4	**9**	78
5	*p*-MeO_2C-C_6H_4	**10**	73
6	*p*-NO_2-C_6H_4	**11**	39
7	Bn	**12** [1]	82
8	Ph_2CH	**13**	79
9	*n*-Bu	**14** [11]	78
10	*t*-Bu	**15** [4]	70

Based on the results above, one-pot cyclizations of **1** with various amine nucleophiles were conducted, and *N*-substituted 4-phenylpiperidines were obtained in moderate to high yields as shown in Table 2. The reaction with anisidines, possessing an electron-donating group gave good yields (Entries 1, 2 and 3), even if the methoxy group was located at the ortho-position. The presence of electron-withdrawing groups, such as a fluorine atom or a methoxy carbonyl group, did not affect the chemical yield (Entries 4

and 5). Furthermore, piperidines with *N*-aliphatic substituents could be obtained in good yields regardless of the amine's steric barrier (Entries 7, 8, 9 and 10). The *N*-benzyl groups in **12** and **13** were readily removed by the common method for preparing un-substituted piperidines (not shown).[1] Although a variety of amine nucleophiles possessing electron-donating, electron-withdrawing, or sterically hindered substituent underwent the cyclization reaction, reaction with the less nucleophilic 4-nitroaniline resulted in an exceptionally moderate yield (Entry 6).

CONCLUSION

In summary, we developed a convenient, one-pot synthetic method of *N*-substituted 4-phenylpiperidines via bis-triflate starting from 3-aryl-1,5-pentanediols. This method does not require individual multi-steps preparation of *N*-substituted bis(2-haloethyl)amine derivatives as cyclization precursors. Furthermore, we found that electron-poor and sterically hindered amines react readily under mild conditions.

EXPERIMENTAL

Melting points were determined on an Electrothermal apparatus without correction. ^{1}H NMR spectra were recorded on a JEOL JNM-LA300 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts (σ) are expressed in ppm. Mass spectra were recorded on a Bruker Daltonics esquire3000plus MS equipment. Elemental analysis was performed on a CE Instrument EA1110 and a Yokokawa analytical system IC7000.

General Preparation of Piperidine. To a solution of the diol (0.487 mmol) in dry EtOAc (2.0 mL) at - 30 ℃ was slowly added trifluoromethanesulfonic anhydride (Tf_2O) (1.02 mmol) followed by addition of diisopropylethylamine (DIPEA) (1.02 mmol). The reaction mixture was maintained at an internal reaction temperature of - 30 ℃ for 15 min. The primary amine (0.585 mmol) was then added, followed by addition of DIPEA (1.02 mmol). The reaction mixture was kept at - 30 ℃ for 1h and then warmed to rt for 2 h. The reaction was quenched by adding water and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by silica gel column chromatography and recrystallized to give piperidine products in the yields indicated.

4-Cyano-1-(2-methoxyphenyl)-4-phenylpiperidine 6 (Entry 1 in Table 2)

This compound was obtained as white needle-like crystals (MeOH), mp 97 - 98 ℃; ^{1}H NMR ($CDCl_3$): δ 2.23 (2H, m), 2.37 (2H, m), 3.13 (2H, m), 3.59 (2H, m), 3.89 (3H, s), 6.88 (1H, m), 6.96 (1H, m), 7.05 (2H, m), 7.35 (1H, m), 7.45 (2H, m), 7.56 (2H, m); MS: m/z 293 (M^+). *Anal*. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.91; H, 6.90; N, 9.58.

4-Cyano-1-(3-methoxyphenyl)-4-phenylpiperidine 7 (Entry 2 in Table 2)

This compound was obtained as white needle-like crystals (Et_2O-hexane), mp 67 - 68 ℃; ^1H NMR ($CDCl_3$): δ 2.21 (4H, m), 3.25 (2H, m), 3.77 (2H, m), 3.81 (3H, s), 6.48 (1H, dd, *J* = 8.2, 2.1 Hz), 6.54 (1H, dd, *J* = 2.1, 2.1 Hz), 6.59 (1H, dd, *J* = 8.2, 2.1 Hz), 7.21 (1H, dd, *J* = 8.2, 8.2 Hz), 7.32-7.45 (3H, m), 7.51 (2H, m); MS: m/z 293 (M^+). *Anal*. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.93; H, 6.89; N, 9.61.

4-Cyano-1-(4-fluorophenyl)-4-phenylpiperidine 9 (Entry 4 in Table 2)

This compound was obtained as white needle-like crystals (Et_2O-hexane), mp 71 - 72 ℃; ^1H NMR ($CDCl_3$): δ 2.26 (4H, m), 3.20 (2H, m), 3.62 (2H, m), 6.93-7.03 (4H, m), 7.33-7.46 (3H, m), 7.53 (2H, m); MS: m/z 281 (M^+). *Anal*. Calcd for $C_{18}H_{17}FN_2$: C, 77.12; H, 6.11; F, 6.78; N, 9.99. Found: C, 77.06; H, 6.09; F, 6.51; N, 10.02.

4-Cyano-1-(4-methoxycarbonylphenyl)-4-phenylpiperidine 10 (Entry 5 in Table 2).

This compound was obtained as white needle-like crystals (MeOH), mp 115 - 117 ℃; ^1H NMR ($CDCl_3$): δ 2.14 (2H, m), 2.19 (2H, m), 3.37 (2H, m), 3.88 (3H, s), 3.97 (2H, m), 6.96 (2H, d, *J* = 9.0 Hz), 7.33-7.46 (3H, m), 7.49 (2H, m), 7.94 (2H, d, *J* = 9.0 Hz); MS: m/z 321 (M^+). *Anal*. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.68; H, 6.24; N, 8.69.

4-Cyano-1-(4-nitrophenyl)-4-phenylpiperidine 11 (Entry 6 in Table 2).

This compound was obtained as yellow crystals (*i*-PrOH), mp 180 - 182 ℃; ^1H NMR ($CDCl_3$): δ 2.16 (2H, m), 2.26 (2H, m), 3.47 (2H, m), 4.06 (2H, m), 6.94 (2H, d, *J* = 9.2 Hz), 7.37-7.51 (5H, m), 8.15 (2H, d, *J* = 9.2 Hz); MS: m/z 308 (M^+). *Anal*. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 69.62; H, 5.49; N, 13.55.

4-Cyano-1-diphenylmethyl-4-phenylpiperidine 13 (Entry 8 in Table 2)

This compound was obtained as white needle-like crystals (MeOH), mp 133 - 135 ℃; ^1H NMR ($CDCl_3$): δ 2.08 (2H, m), 2.16 (2H, m), 2.37 (2H, m), 2.99 (2H, m), 4.37 (1H, s), 7.19 (2H, m), 7.26-7.45 (11H, m), 7.51 (2H, m); MS: m/z 353 (M^+). *Anal*. Calcd for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95. Found: C, 84.71; H, 6.77; N, 8.02.

ACKNOWLEDGEMENTS

We are grateful to Ms. K. Bando for performing the elemental analysis, and Ms. K. Sakamoto for recording MS spectra.

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