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Synthesis of Piperidones from Benzyl Azides and Acetone

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A new method for the synthesis of 2,2-dimethyl-6-substituted 4-piperidone was developed; two equivalents of acetone were annulated with *N*-unsubstituted imines in-situ generated from benzyl azides using a ruthenium catalyst in the presence of L-proline.

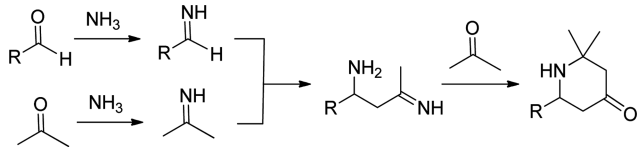
Key Words : 4-Piperidone, *N*-Unsubstituted imine, Benzyl azide, Synthetic method

Introduction

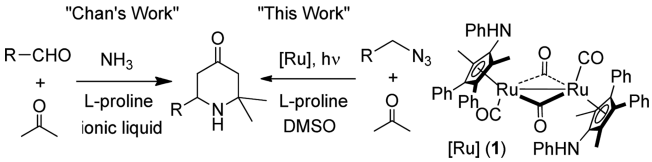
Although there are many methods for the synthesis of 4-piperidones,[1] those for 2,2,6-trisubstituted ones are rare. Noticeably, Chan and co-workers found a unprecedented tandem Mannich reaction to afford 2,2-dimethyl-6-substituted 4-piperidones when they tried the direct aldol reaction of aldehydes with acetone in ammonia solution.[2] They suggested imines as the key intermediates for the formation of 4-piperidones (Scheme 1).

Curiously, the 4-piperidones are formed as the major products in the reaction of acetone with hydroxybenzaldehydes, pyrrole-2-carbaldehyde, and indol-3-carbaldehyde in a solution of ammonia in methanol. Later they could extend the substrate scope by employing ionic liquid as the solvent and L-proline as an organocatalyst.[3] However, excess NH_3 is needed also for this protocol, which is added by bubbling ammonia gas into the ionic liquid. The preferential occurrence of Mannich reaction over aldol reaction was explained by the role of ionic liquid enhancing the formation of imine intermediates.

Recently, we reported a novel Ru-catalyzed transformation of alkyl azides into *N*-unsubstituted imines,[4] which had been known as unstable intermediates in general.[5] During our investigation about synthetic utility of *N*-unsubstituted imines,[6] we envisioned that the synthesis of 2,2-dimethyl-6-substituted 4-piperidones would be possible by employing N-H aldimines generated by our catalytic reaction. This alternative synthetic method will avoid the use of ammonia gas, enable the use of organic azides instead of aldehydes, and extend the scope of 4-piperidone products. Here we report a simple and one-pot protocol for the synthesis of 2,2-dimethyl-6-substituted 4-piperidones under mild conditions, in which N-H imines are directly generated from benzyl azides by a Ru-catalyzed reaction (Scheme 2).



Scheme 1. A suggested pathway involving imine intermediates for the formation of 2,2-dimethyl-6-substituted 4-piperidones.



Scheme 2. Synthetic methods for 2,2-dimethyl-6-substituted 4-piperidones.

Experimental

General Information. Air-sensitive manipulations were carried out with standard Schlenk techniques under argon atmosphere. Commercial chemicals were used without further purification. Flash column chromatography was carried out on silica gel (230-400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded with Bruker (300 MHz) spectrometer. ^{1}H NMR spectra were referenced to residual $CDCl_3$ (7.26 ppm) and reported as follows; chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet). Chemical shift of ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.23) ppm. Infrared spectra were recorded on a Shimadzu IR-470 spectrometer with KBr pellets. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer.

General Procedure for the Synthesis of 2,2-Dimethyl 6-Substituted 4-Piperidones from Benzyl Azide and Acetone. A solution of an azide (0.25 mmol), **1** (2.0 mol %), and L-proline (100 mol %) in acetone (0.50 mL) and DMSO (2.0 mL) was stirred at room temperature with illumination of 30 W fluorescent light for 12 h under argon atmosphere. The resulting mixture was extracted with dichloromethane (10 mL × 3). Combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated by a rotary evaporator, and the residue was purified by flash column chromatography using silica gel.

Product **3a**, **3b**, **3f**, **3g**, **3h**, **3o**, and **3q** are known compounds.[3]

6-(4-Methoxyphenyl)-2,2-dimethylpiperidin-4-one (3a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.32 (m, 2H), 6.90-6.87 (m, 2H), 4.16 (dd, *J* = 4.3, 10.5 Hz, 1H), 3.80 (s, 3H), 2.48-2.23 (m, 4H), 1.50 (br, 1H), 1.31 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.8, 159.2, 135.2, 127.8, 114.1, 55.5, 55.4, 54.3, 53.9, 50.0, 32.2, 25.5.

2,2-Dimethyl-6-phenylpiperidin-4-one (3b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.26 (m, 5H), 4.22 (dd, *J* = 3.9, 11.0 Hz, 1H), 2.54-2.25 (m, 4H), 1.50 (bs, 1H), 1.32 (s, 3H), 1.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.7, 143.0, 128.8, 127.9, 126.7, 56.1, 54.3, 54.1, 49.9, 32.3, 25.6.

2,2-Dimethyl-6-*o*-tolylpiperidin-4-one (3c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57-7.54 (m, 1H), 7.27-7.12 (m, 3H), 4.43 (dd, *J* = 6.5, 8.3 Hz, 1H), 2.46-2.41 (m, 3H), 2.37 (s, 3H), 2.32-2.28 (m, 1H), 1.37 (bs, 1H), 1.32 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.0, 140.7, 135.4, 130.7, 127.5, 126.7, 125.5, 54.5, 54.2, 51.6, 48.4, 32.3, 25.4, 19.2. IR (cm^{-1}): 3306, 2964, 1711, 1464, 1288, 1248, 751. HRMS (EI+) 217.1469 (calcd for $C_{14}H_{19}NO$ 217.1467).

2,2-Dimethyl-6-*m*-tolylpiperidin-4-one (3d). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.18 (m, 3H), 7.11-7.09 (m, 1H), 4.17 (dd, *J* = 4.2, 10.6 Hz, 1H), 2.48-2.40 (m, 3H), 2.36 (s, 3H), 2.30-2.26 (m, 1H), 1.53 (bs, 1H), 1.32 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.7, 142.9, 138.5, 128.7, 128.6, 127.3, 123.7, 56.1, 54.3, 54.0, 49.8, 32.3, 25.5, 21.5. IR (cm^{-1}): 3305, 2964, 1713, 1608, 1489, 1412, 1287, 1238, 813, 701. HRMS (EI+) 217.1465 (calcd for $C_{14}H_{19}NO$ 217.1467).

2,2-Dimethyl-6-*p*-tolylpiperidin-4-one (3e). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.28 (m, 2H), 7.17-7.15 (m, 2H), 4.18 (dd, *J* = 4.1, 10.7 Hz, 1H), 2.51-2.40 (m, 3H), 2.34 (s, 3H), 2.29-2.24 (m, 1H), 1.52 (bs, 1H), 1.31 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.8, 140.1, 137.5, 129.4, 126.6, 55.8, 54.3, 54.0, 49.9, 32.3, 25.5, 21.2. IR (cm^{-1}): 3308, 2964, 1710, 1474, 1288, 1247, 760. HRMS (EI+) 217.1466 (calcd for $C_{14}H_{19}NO$ 217.1467).

6-(4-Fluorophenyl)-2,2-dimethylpiperidin-4-one (3f). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41-7.37 (m, 2H), 7.06-7.01 (m, 2H), 4.20 (dd, *J* = 3.6, 11.2 Hz, 1H), 2.50-2.24 (m, 4H), 1.47 (bs, 1H), 1.32 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.4, 162.4 (d, *J* = 245 Hz), 139.0 (d, *J* = 3.2 Hz), 128.4 (d, *J* = 7.9 Hz), 115.7 (d, *J* = 21.2 Hz), 55.5, 54.3, 54.1, 50.1, 32.3, 25.6.

6-(4-Chlorophenyl)-2,2-dimethylpiperidin-4-one (3g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.35 (m, 2H), 7.33-7.30 (m, 2H), 4.19 (dd, *J* = 3.6, 11.2 Hz, 1H), 2.50-2.24 (m, 4H), 1.45 (bs, 1H), 1.32 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.1, 141.6, 133.5, 128.9, 128.1, 55.5, 54.2, 54.0, 49.8, 32.2, 25.5.

6-(4-Bromophenyl)-2,2-dimethylpiperidin-4-one (3h). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.46 (m, 2H), 7.32-7.27 (m, 2H), 4.18 (dd, *J* = 3.5, 11.3 Hz, 1H), 2.49-2.24 (m, 4H), 1.49 (bs, 1H), 1.32 (s, 3H), 1.19 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.1, 142.1, 131.9, 128.4, 121.5, 55.5, 54.1, 54.0, 49.8, 32.2, 25.5.

4-(6,6-Dimethyl-4-oxopiperidin-2-yl)benzonitrile (3i). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.64 (m, 2H), 7.58-7.55 (m, 2H), 4.28 (dd, *J* = 3.4, 11.5 Hz, 1H), 2.52-2.26 (m, 4H), 1.54 (bs, 1H), 1.34 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.4, 148.5, 132.7, 127.6, 118.8, 111.7, 55.8, 54.2, 54.1, 49.5, 32.3, 25.6. IR (cm^{-1}): 3309, 2965, 2227, 1710, 1479, 1295, 1242, 845. HRMS (EI+) 228.1263 (calcd for $C_{14}H_{16}N_2O$ 228.1263).

2,2-Dimethyl-6-(4-nitrophenyl)piperidin-4-one (3j). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22-8.20 (m, 2H), 7.64-7.61 (m, 2H), 4.34 (dd, *J* = 3.4, 11.5 Hz, 1H), 2.54-2.28 (m, 4H), 1.54 (bs, 1H), 1.36 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.3, 150.5, 147.7, 127.7, 124.2, 55.7, 54.3, 54.2, 49.6, 32.3, 25.6. IR (cm^{-1}): 3319, 2965, 1708, 1597, 1488, 1442, 1408, 1383, 1369, 1346, 1323, 814, 698 HRMS (EI+) 248.1162 (calcd for $C_{13}H_{16}N_2O_3$ 248.1161).

6-(4-Acetylphenyl)-2,2-dimethylpiperidin-4-one (3k). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97-7.94 (m, 2H), 7.54-7.52 (m, 2H), 4.28 (dd, *J* = 3.5, 11.3 Hz, 1H), 2.60 (s, 3H), 2.53-2.27 (m, 4H), 1.56 (bs, 1H), 1.35 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.9, 197.7, 148.3, 136.7, 128.9, 126.9, 55.8, 54.2, 54.1, 49.6, 32.2, 26.7, 25.5. IR (cm^{-1}) 3308, 2965, 1709, 1682, 1573, 1293, 1269, 1248, 839. HRMS (EI+) 245.1416 (calcd for $C_{15}H_{19}NO_2$ 245.1416).

Methyl 4-(6,6-Dimethyl-4-oxopiperidin-2-yl)benzoate (3l). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04-8.01 (m, 2H), 7.51-7.49 (m, 2H), 4.27 (dd, *J* = 3.5, 11.3 Hz, 1H), 3.92 (s, 3H), 2.53-2.26 (m, 4H), 1.55 (bs, 1H), 1.34 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.9, 166.8, 148.1, 130.1, 129.7, 126.7, 55.8, 54.2, 54.1, 52.2, 49.6, 32.2, 25.5. IR (cm^{-1}): 3312, 2962, 1719, 1612, 1577, 1282, 1248, 965. HRMS (EI+) 261.1363 (calcd for $C_{15}H_{19}NO_3$ 261.1365).

Ethyl 6,6-Dimethyl-4-oxopiperidine-2-carboxylate (3m). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.22 (q, *J* = 7.2 Hz, 2H), 3.86 (dd, *J* = 3.7, 11.7 Hz, 1H), 2.66-2.29 (m, 4H), 1.92 (bs, 1H), 1.33 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.8, 172.3, 61.7, 54.7, 54.4, 54.0, 44.3, 31.8, 25.2, 14.3. IR (cm^{-1}): 3317, 2967, 1738, 1720, 1292, 1209. HRMS (EI+) 199.1208 (calcd for $C_{10}H_{17}NO_3$ 199.1208).

2,2-Dimethyl-6-(4-vinylphenyl)piperidin-4-one (3n). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.35 (m, 4H), 6.75-7.66 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.74 (d, *J* = 17.5 Hz, 1H), 5.24 (d, *J* = 10.9 Hz, 1H), 4.21 (dd, *J* = 3.8, 11.0 Hz, 1H), 2.52-2.24 (m, 4H), 1.47 (bs, 1H), 1.32 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.6, 142.6, 137.3, 136.4, 126.9, 126.6, 114.1, 55.8, 54.3, 54.0, 49.8, 32.3, 25.5. IR (cm^{-1}): 3307, 3006, 1711, 1652, 1293, 1276, 750. HRMS (EI+) 229.1470 (calcd for $C_{15}H_{19}NO$ 229.1467).

2,2-Dimethyl-6-(pyridin-2-yl)piperidin-4-one (3o). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60-8.59 (m, 1H), 7.71-7.65 (m, 1H), 7.29-7.20 (m, 2H), 4.32 (dd, *J* = 5.4, 9.4 Hz, 1H), 2.57-2.39 (m, 4H), 1.37 (s, 3H), 1.20 (s, 3H), 0.86 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.9, 160.4, 149.8, 137.2, 123.0, 122.0, 57.7, 55.0, 54.9, 48.6, 32.1, 25.6.

2,2-Dimethyl-6-(thiophen-2-yl)piperidin-4-one (3p). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.35 (m, 2H), 7.31-7.27 (m, 1H), 4.19 (dd, *J* = 3.6, 11.2 Hz, 1H), 2.50-2.24 (m, 4H), 1.51 (bs, 1H), 1.32 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75

MHz) δ 209.1, 141.6, 133.5, 128.9, 128.1, 55.5, 54.2, 54.0, 49.8, 32.2, 25.5. IR (cm^{-1}): 3306, 3101, 2963, 1712, 1475, 1413, 1294, 1267, 829. HRMS (EI+) 209.0874 (calcd for $C_{11}H_{15}NOS$ 209.0874).

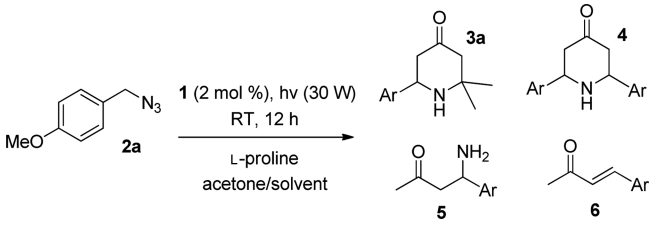
2,2-Dimethyl-6-(naphthalen-2-yl)piperidin-4-one (3q). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.81 (m, 4H), 7.56-7.45 (m, 3H), 4.37 (dd, *J* = 4.0, 10.8 Hz, 1H), 2.61-2.28 (m, 4H), 1.55 (bs, 1H), 1.35 (s, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.6, 140.4, 133.5, 133.1, 128.6, 127.9, 127.7, 126.3, 126.0, 125.2, 125.0, 56.2, 54.3, 54.1, 49.8, 32.3, 25.6.

6-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-dimethylpiperidin-4-one (3r). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.25 (m, 1H), 6.96-6.86 (m, 1H), 6.78-6.75 (m, 1H), 5.94 (s, 2H), 4.12 (dd, *J* = 3.8, 10.9 Hz, 1H), 2.46-2.23 (m, 4H), 1.52 (bs, 1H), 1.31 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.7, 148.1, 147.2, 137.2, 120.0, 108.4, 107.2, 101.2, 56.0, 54.3, 54.0, 50.1, 32.3, 25.6. IR (cm^{-1}): 3309, 2964, 2901, 1711, 1559, 1504, 1297, 1273, 1039, 932. HRMS (EI+) 247.1209 (calcd for $C_{14}H_{17}NO_3$ 247.1208).

Results and Discussion

To find conditions suitable for the selective formation of 4-piperidones, solvent and the amount of L-proline were varied in the reaction of 1-(azidomethyl)-4-methoxybenzene (Table 1). In dioxane or THF the coupling reaction with acetone did not occur, although the N-H alimine was generated (entries 1 and 2). The desired piperidone **3a** was formed only in 5% yield along with the aldol condensation product **6** in 9% yield when acetone was used as solvent (entry 3). Polar solvents such as DMF and DMSO were effective for the selective formation of **3a** (entries 4 and 5). Increasing the amount of L-proline increased the yield and the selectivity for **3a** (entries 5-7). Decreasing the amount of the ruthenium catalyst **1** decreased the yield of **3a** (entry 8).

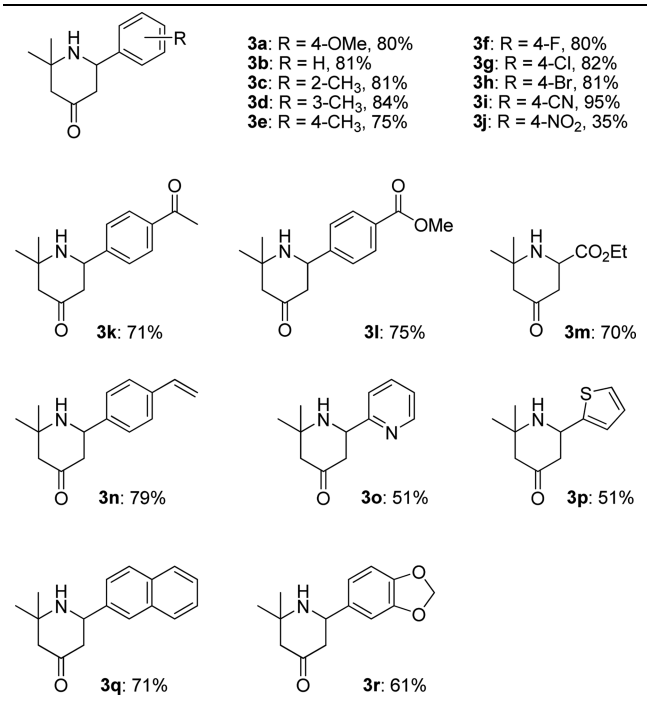
Table 1. Synthesis of 2,2-dimethyl-6-substituted 4-piperidones[a]



Entry[a]	Solvent	L-proline	**3a** : **4** : **5** : **6** (%)[b]
1	THF	35 mol %	<1 : <1 : <1 : <1
2	Dioxane	35 mol %	<1 : <1 : <1 : <1
3	Acetone	35 mol %	5 : <1 : <1 : 9
4	DMF	35 mol %	47 : 20 : <1 : 9
5	DMSO	35 mol %	56 : 23 : <1 : 11
6	DMSO	50 mol %	70 : 19 : <1 : 9
7	DMSO	100 mol %	80 : 14 : <1 : 6
8[c]	DMSO	100 mol %	67 : 12 : <1 : 16

[a]The reaction was performed with **1** (2 mol %), **2a** (0.25 mmol), L-proline, acetone (0.50 mL), and solvent (2.0 mL) at room temperature for 12 h under argon atmosphere with illumination of 30 W fluorescent light. [b]Determined by ^{1}H NMR with cyclohexene as an internal standard. [c]1 mol % of **1** was used.

Table 2. Substrate Scope of benzyl azides[a,b]



[a]The reaction was performed with azide (0.25 mmol), **1** (2.0 mol %), L-proline (100 mol %), acetone (0.50 mL), and DMSO (2.0 mL) at room temperature for 12 h under argon atmosphere with illumination of 30 W fluorescent light. [b]Isolated yield

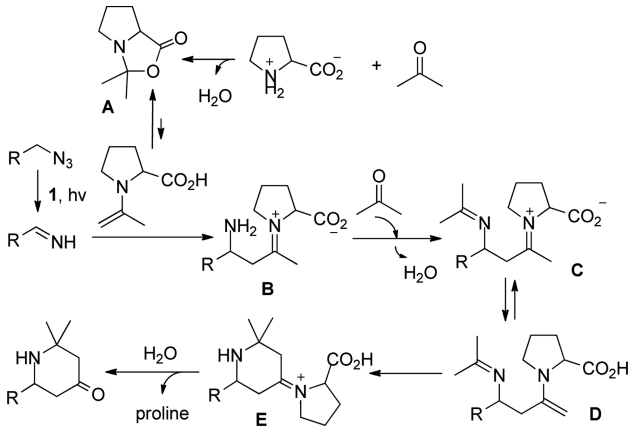
The substrate scope was explored (Table 2). A wide range of benzylic azides (**2a**-**2i**) were successfully transformed to the expected 4-piperidones (**3a**-**3i**) in good to high yields except 1-(azidomethyl)-4-nitrobenzene (**2j**). The results implicate that the transformation was not affected significantly by the substituents of benzene ring. The electron-withdrawing effect of nitro group would not be responsible for the poor result in the case of **3j**, because the piperidones containing fluoride (**3f**) or cyano group (**3i**) were obtained in good yield. Various functional groups are compatible with azido group to give potentially useful 4-piperidones. Particularly, those (**3k**-**3m**) containing carbonyl groups are distinct examples, which cannot be provided by the previous method using excess ammonia. Alkenyl (**3n**) group was also compatible. The piperidones containing pyridyl (**3o**), thiophenyl (**3p**) and naphthyl (**3q**) groups were obtained in 50-70% yield. Acetal group (**3r**) was also well tolerated in this transformation. However, in contrast to the previous method using aldehyde and ammonia, it was not successful to produce the derivatives containing aliphatic groups due to complex side reactions in our catalyst system. In fact, the poor results are consistent with the well-known instability of *N*-unsubstituted aliphatic aldimines.[7] The attempts employing other aldehydes or ketones such as 2-butanone, acetophenone and 1,3-dichloropropan-2-one instead of acetone were not successful either.

To our disappointment, the enantioselectivity for **3b** was only 20 % ee in the reaction under the conditions of Table 2.

Table 3. Enantioselectivity in the reaction of benzyl azide with acetone in the presence of L-proline[a,b]

Entry[a]	L-proline	H_2O	**3b**[b] (*ee*)[c] : **4**[b] : **5**[b]
1	100 mol %	None	81 (20) : 16 : 3
2	100 mol %	5 equiv	57 (38) : 15 : 5
3	100 mol %	10 equiv	58 (44) : 16 : 7
4	100 mol %	15 equiv	57 (34) : 16 : 7
5	50 mol %	None	72 (22) : 22 : 3
6	35 mol %	None	60 (22) : 20 : 3
7	35 mol %	10 equiv	52 (32) : 12 : 23

[a]The reaction was performed with **1** (2 mol %), **2b** (0.25 mmol), L-proline, acetone (0.50 mL), and DMSO (2.0 mL) at room temperature for 12 h under argon atmosphere with illumination of 30 W fluorescent light. [b]Determined by ^{1}H NMR with cyclohexene as an internal standard. [c]Determined by HPLC equipped with a chiral column (Chiral OD).



Scheme 3. A plausible pathway for the formation 2,2-dimethyl-6-substitued 4-piperidones.

We tried to improve the enantioselectivity with varying reaction conditions (Table 3). Addition of water increased the enantioselectivity with decreasing the yield of **3b** (entries 2-4); with using 10 equivalents of water **3b** was formed in 58% yield and 44% ee (entry 3).[8] The yield of **3b** decreased with decreasing the amount of L-proline without improving the enantioselectivity (entries 5-7).

According to the experimental outcomes and the previous report describing the formation of oxazolidinone A from proline and acetone,[9] a plausible pathway for the formation of 4-piperidones is proposed in Scheme 3. First, *N*-unsubstituted imines generated from the corresponding alkyl azides by **1** under fluorescent light react with the enamine formed from acetone and proline to give β-aminoiminium intermediate **B**. The intermediate **B** undergoes imine condensation reaction with acetone to give **C**, which would be tautomerized to another enamine **D**. Then 4-piperidones are produced by the cyclization of **D** and the subsequent hydrolysis of the cyclic intermediate **E**.

Conclusion

In summary, we developed a new method for the synthesis of 2,2-dimethyl-6-substituted 4-piperidones with benzyl azides and two equivalents of acetone under mild conditions. Our method extended the scope of accessible piperidones, including those having carbonyl groups which are not compatible with the synthetic conditions using ammonia.

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