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Full Paper

A Facile Synthesis of *N*-Aryl Substituted Piperidones

GENG, Qian[a](耿谦) ZHANG, Hui*,[a](张慧)
CAO, Weiguo[a,b,c](曹卫国) CHEN, Yali[a](陈雅丽)

[a] *Department of Chemistry, Shanghai University, 99 Shangda Lu, Shanghai 200444, China.*
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai 200032, China*
[c] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai 200032, China*

A general and efficient procedure for the synthesis of *N*-aryl-substituted 4-piperidones was developed. The two step syntheses proceeded with an overall yield of 60%—83% using *L*-proline as the ligand for the Cu(I)-catalyzed Ullmann amination followed by subsequent hydrolysis of resulting ketals.

Keywords *N*-aryl 4-piperidone, Ullmann amination, ligand, copper(I) iodide

Introduction

Piperidones are attractive synthetic targets due to their interesting pharmacological properties.[1] They are also used as precursors to the piperidine ring, which is a frequently encountered heterocyclic unit in natural compounds and drug candidates.[1a,2,3] As a consequence, considerable interest is centered on the synthesis of piperidones in general, and *N*-substituted 4-piperidones[3f,4,5] in particular. The latter are most notably prevalent in many central nervous system, antiallergic, and cardiovascular agents.

For *N*-aryl substituted 4-piperidones, the general method for their synthesis is a classical three-step sequence, involving a bis-Michael addition of substituted anilines to ethyl acrylate, with the generated suitable amino diesters followed by Dieckman cyclization and base-catalyzed decarboxylation.[5a] But these reactions often result in very poor yields, requiring long reaction time and strong bases such as sodium alkoxide.

In 1999, an alternative approach to *N*-aryl substituted 4-piperidones was reported by Tortolani and Poss.[5b] The construction of the *N*-aryl 4-piperidones was conveniently achieved by the exchange reaction between *N*-methyl-*N*-benzyl-4-oxopiperidinium iodide and the desired aniline. In their process the troublesome bis-Michael addition is avoided, however, the major shortcoming of this approach is that exchange reactions frequently do not go to completion due to unfavorable equilibria.[5c]

The imino Diels-Alder reaction is also one of the most powerful and useful tools used to prepare heterocycles containing the piperidine nucleus, however, this reaction of 2-siloxydienes or 3-unsubstituted 2-aminodienes with *N*-arylated aldimines provides the corresponding 4-piperidones only with limited substrates or in low yields.[5d,5e]

Recent advance in Ullmann-type reactions provided the opportunity for the development of new methodologies to prepare *N*-aryl substituted heterocycles.[5f,5g,6,7] Taking advantage of the mild conditions applied to amino acid-promoted Ullmann-type reactions, our group has recently established some processes for *N*-arylation of nitrogen nucleophiles.[8] Continuing our efforts in this area, we became interested in the coupling reaction of aryl bromides with 4-piperidone or the corresponding 4-piperidone ethylene ketal to find a new protocol for the facile synthesis of *N*-aryl substituted 4-piperidones. Here, we described our result on the synthesis of this class of compounds by copper-catalyzed amination of different aryl bromides using *L*-proline as the ligand and K_2CO_3 as the base.

Experimental

General considerations

All reactions were carried out in Schlenk tubes and run under an atmosphere of argon. DMSO, DMF, THF, and dioxane were freshly distilled from CaH_2. Aryl bromides, amino acids, Cs_2CO_3, K_2CO_3 and K_3PO_4 were purchased from commercial sources and used without further purification. Copper(I) iodide was used after being washed with THF. Flash column chromatography was performed using silica gel H (10—40 μ). Melting points were recorded on a WRS-1 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz instrument and a DPX-400 MHz instrument respectively, with chemical shifts reported relative to TMS using residual deuterated

* E-mail: yehao7171@shu.edu.cn; Tel.: 0086-021-66134861
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solvent signals or TMS as an internal standard. LRMS (low resolution mass spectrum) (EI) was recorded on a HP5989A mass spectrometer and HRMS (high resolution mass spectrum) (EI) on a Waters Micromass GCT mass spectrometer. Unknown compounds were determined by their ^{1}H NMR, ^{13}C NMR, MS and HRMS data. Compounds previously described in the literature were characterized by comparing their ^{1}H NMR spectra to published data. All yields reported in this publication refer to isolated ones (average of at least two independent runs) of compounds and their purity was determined by ^{1}H NMR.

General procedure for the synthesis of 8-aryl-1,4-dioxo-8-azaspiro[4.5]decane (3)

An oven-dried Schlenk tube was charged with 10 mol% CuI, 20 mol% *L*-proline, 2 equiv. K_2CO_3, 4 mmol aryl bromide (if solid) and 1.5 equiv. 1,4-dioxa-8-azaspiro[4.5]decane, evacuated and backfilled with argon (3 cycles). 4 mmol aryl bromide (if liquid) and 5 mL DMSO were added by syringe at room temperature under argon. The capped tube was put into the oil bath that was preheated to 90 ℃ and the reaction mixture was stirred for the time specified. The cooled mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic layer was separated, and the aqueous layer was extracted with 10 mL EtOAc each time until TLC showed no trace of product left in the aqueous layer. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo.* Purification of the residue by flash chromatography on silica gel (2×20 cm, petroleum ether (30—60 ℃)/ethyl acetate) gave the desired product.

8-Phenyl-1,4-dioxo-8-azaspiro[4.5]decane (3a) Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24—7.27 (m, 2H), 6.96—7.22 (m, 2H), 6.83—6.94 (m, 1H), 3.98 (s, 4H), 3.32 (t, J=5.7 Hz, 4H), 1.84 (t, J=5.7 Hz, 4H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.2, 129.4 (2C), 119.7, 116.9 (2C), 107.4, 64.6 (2C), 48.0 (2C), 34.8 (2C); MS (EI) *m/z*: 219 $(M)^+$, 189, 174, 158, 132, 105, 91, 77; HRMS (EI) calcd for $C_{13}H_{17}NO_2$ 219.1259 $(M)^+$, found 219.1257.

8-*p*-Tolyl-1,4-dioxo-8-azaspiro[4.5]decane (3b) White solid, m.p. 64.6—65.6 ℃ (Lit.[9] 64.8—65.6 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.06 (d, J=8.7 Hz, 2H), 6.86—6.89 (m, 2H), 3.99 (s, 4H), 3.27 (t, J=5.2 Hz, 4H), 2.27 (s, 3H), 1.85 (t, J=5.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 129.9 (2C), 117.3 (2C), 103.7, 64.5 (2C), 48.6 (2C), 34.8 (2C), 20.7; MS (EI) *m/z*: 233 $(M)^+$, 234 $(M+1)^+$, 203, 188, 172, 146, 119, 118; HRMS (EI) calcd for $C_{14}H_{19}NO_2$ 233.1416 $(M)^+$, found 233.1413.

8-*m*-Tolyl-1,4-dioxo-8-azaspiro[4.5]decane (3c) Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11—7.17 (m, 1H), 6.66—6.78 (m, 3H), 3.99 (s, 4H), 3.31 (t, J=5.6 Hz, 4H), 2.31 (s, 3H), 1.84 (t, J=5.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.3, 139.0, 129.2, 120.6, 117.8, 114,0, 107.5, 64.6 (2C), 48.1 (2C), 34.9 (2C), 22.1; MS (EI) *m/z*: 233 $(M)^+$, 219, 188, 172, 159, 146, 119, 91; HRMS (EI) calcd for $C_{14}H_{19}NO_2$ 233.1416 $(M)^+$, found 233.1420.

8-(4-Nitrophenyl)-1,4-dioxo-8-azaspiro[4.5]decane (3e) Yellow solid, m.p. 156—157 ℃ (Lit.[10] 155—156 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, J=9.5 Hz, 2H), 6.84 (d, J=9.5 Hz, 2H), 4.01 (s, 4H), 3.58 (t, J=5.7 Hz, 4H), 1.81 (t, J=5.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.1, 137.9, 126.0 (2C), 112.6 (2C), 106.7, 64.4 (2C), 45.6 (2C), 34.3 (2C); MS (EI) *m/z*: 264 $(M)^+$, 248, 234, 219, 203, 177, 150, 120; HRMS (EI) calcd for $C_{13}H_{16}N_2O_4$ 264.1110 $(M)^+$, found 264.1112.

4-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)benzonitrile (3f) White solid, m.p. 135.5—135.9 ℃ (Lit.[10] 132—133 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 4.00 (s, 4H), 3.48 (t, J=5.8 Hz, 4H), 1.80 (t, J=5.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5, 133.4 (2C), 120.0, 114.2 (2C), 106.7, 99.5, 64.4 (2C), 45.6 (2C), 34.1 (2C); MS (EI) *m/z*: 244 $(M)^+$, 199, 183, 171, 157, 130, 116, 102; HRMS (EI) calcd for $C_{14}H_{16}N_2O_2$ 244.1212 $(M)^+$, found 244.1204.

8-(3-(Trifluoromethyl)phenyl)-1,4-dioxo-8-azaspiro[4.5]decane (3g) White solid, m.p. 76.1—77.2 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30—7.36 (m, 1H), 7.04—7.14 (m, 3H), 4.00 (s, 4H), 3.78 (t, J=5.7 Hz, 4H), 1.84 (t, J=5.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.2, 131.6 (q, J=31.3 Hz), 129.8, 124.6 (q, J=271 Hz), 119.5, 115.6 (d, J=3.7 Hz), 112.7 (d, J=3.7 Hz), 107.1, 64.6 (2C), 47.5 (2C), 34.6 (2C); MS (EI) *m/z*: 287 $(M)^+$, 268, 242, 226, 200, 173, 145, 99, 86; HRMS (EI) calcd for $C_{14}H_{16}NO_2F_3$ 287.1133 $(M)^+$, found 287.1126.

8-(4-Methoxyphenyl)-1,4-dioxo-8-azaspiro[4.5]-decane (3h) White solid, m.p. 60.2—61.1 ℃ (Lit.[5g] 60—61 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.81—6.96 (m, 4H), 3.99 (s, 4H), 3.77 (s, 3H), 3.19 (t, J=5.4 Hz, 4H), 1.87 (t, J=5.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.8, 119.0 (2C), 114.3 (2C), 107.0, 64.3 (2C), 55.3, 49.4 (2C), 34.8 (2C); MS (EI) *m/z*: 249 $(M)^+$, 234, 219, 204, 188, 162, 135, 120; HRMS (EI) calcd for $C_{14}H_{19}NO_3$ 249.1365 $(M)^+$, found 249.1366.

3-(1,4-Dioxo-8-azaspiro[4.5]decan-8-yl)aniline (3i) White solid, m.p. 84.2—85.5 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.01—7.06 (m, 1H), 6.20—6.42 (m, 3H), 3.99 (s, 4H), 3.80—3.95 (brs, 2H), 3.30 (t, J=5.7 Hz, 4H), 1.84 (t, J=5.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 147.4, 129.9, 107.3, 106.8, 103.4, 64.3 (2C), 47.6 (2C), 34.5 (2C); MS (EI) *m/z*: 234 $(M)^+$, 206, 189, 173, 161, 147, 120, 99; HRMS (EI) calcd for $C_{13}H_{18}N_2O_2$ 234.1368 $(M)^+$, found 234.1373.

8-(2,4-Dimethoxyphenyl)-1,4-dioxo-8-azaspiro-[4.5]decane (3j) White solid, m.p. 69.8—70.2 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.89—6.91 (m, 1H), 6.40—6.48 (m, 2H), 3.99 (s, 4H), 3.85 (s, 3H), 3.78 (s, 3H), 3.06 (t, J=5.4 Hz, 4H), 1.91 (t, J=5.4 Hz, 4H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 156.1, 153.3, 135.4, 118.9, 107.1, 103.3, 99.7, 64.2 (2C), 55.5, 55.4, 49.6 (2C), 35.3 (2C); MS (EI) *m/z*: 279 $(M)^+$, 264, 249, 234, 192, 178, 165, 150; HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1471 $(M)^+$, found 279.1470.

General procedure for the synthesis of 4-phenylcyclo-hexanone (4)[5f]

A solution of **1a** (219 mg, 1 mmol) in anhydrous acetone (5 mL) was magnetically stirred at room temperature in the presence of a catalytic amount of *p*-toluenesulfonic acid for 36 h, quenched by the addition of a few drops of triethylamine and concentrated. The residue was purified by silica gel chromatography (elution with 5∶1 hexanes-ether) to give the desired product.

1-Phenylpiperidin-4-one (4a) White solid, m.p. 36.5—37.2 ℃ (Lit.[11] 37—38 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26—7.33 (m, 2H), 7.00—7.01 (m, 2H), 6.87—6.92 (m, 1H), 3.61 (t, J=5.9 Hz, 4H), 2.56 (t, J=5.9 Hz, 4H); MS (EI) *m/z*: 175 $(M)^+$, 176, 174, 132,105, 104, 77, 51.

1-*p*-Tolylpiperidin-4-one (4b) Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (d, J=8.4 Hz, 2H), 6.91 (d, J=8.4 Hz, 2H), 3.55 (t, J=6.0 Hz, 4H), 2.55 (t, J=6.0 Hz, 4H), 2.29 (s, 3H); MS (EI) *m/z*: 189 $(M)^+$, 188, 146, 119, 118, 91, 77, 65.

1-*m*-Tolylpiperidin-4-one (4c) Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18—7.23 (m, 1H), 6.70—6.85 (m, 3H), 3.59 (t, J=6.0 Hz, 4H), 2.55 (t, J=6.0 Hz, 4H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.2, 139.2, 129.3, 120.8, 116.7, 113.0, 48.9 (2C), 40.8 (2C), 21.8; MS (EI) *m/z*: 189 $(M)^+$, 188, 146, 119, 118, 91, 65; HRMS (EI) calcd for $C_{12}H_{15}NO$ 189.1154 $(M)^+$, found 189.1157.

1-(4-Nitrophenyl)piperidin-4-one (4e) Yellow solid, m.p. 167.0—167.5 ℃ (Lit.[12] 167—169 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=9.0 Hz, 2H), 6.86 (d, J=9.0 Hz, 2H), 3.83 (t, J=6.2 Hz, 4H), 3.64 (t, J=6.2 Hz, 4H); MS (EI) *m/z*: 220 $(M)^+$, 219, 204, 190, 177, 150, 132,120.

4-(4-Oxopiperidin-1-yl)benzonitrile (4f) White solid, m.p. 97.5—98.3 ℃ (Lit.[13] 98—100 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 (d, J=9.0 Hz, 2H), 6.91 (d, J=9.0 Hz, 2H), 3.75 (t, J=6.0 Hz, 4H), 2.59 (t, J=6.0 Hz, 4H); MS (EI) *m/z*: 200 $(M)^+$, 199, 157, 130, 129, 116, 102, 89, 75.

1-[3-(Trifluoromethyl)phenyl]piperidin-4-one (4g) White solid, m.p. 49.5—50.7 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36—7.39 (m, 1H), 7.10—7.15 (m, 3H), 3.65 (t, J=6.0 Hz, 4H), 2.56 (t, J=6.0 Hz, 4H); MS (EI) *m/z*: 243 $(M)^+$, 226, 200, 173, 149, 145, 86, 43.

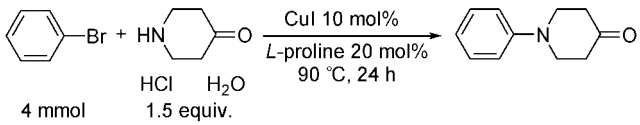
1-(4-Methoxyphenyl)piperidin-4-one (4h) White solid, m.p. 64.3—65.1 ℃ (Lit.[13] 64—65 ℃); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.97 (d, J=9.0 Hz, 2H), 6.87 (d, J=9.0 Hz, 2H), 3.78 (s, 3H), 3.46 (t, J=5.8 Hz, 4H), 2.57 (t, J=5.8 Hz, 4H); MS (EI) *m/z*: 205 $(M)^+$, 190, 162, 135, 120, 107, 92, 77.

1-(2,4-Dimethoxyphenyl)piperidin-4-one (4j) Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.88—6.91 (m, 1H), 6.51—6.52 (m, 1H), 6.42—6.45 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.28 (t, J=6.0 Hz, 4H), 2.63 (t, J=6.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.0, 156.5, 153.4, 134.1, 119.3, 103.4, 99.9, 55.5, 55.4, 51.4 (2C), 41.9 (2C); MS (EI) *m/z*: 235 $(M)^+$, 236 $(M+1)^+$, 220, 192, 178, 164, 151, 150; HRMS (EI) calcd for $C_{13}H_{17}NO_3$ 235.1208 $(M)^+$, found 235.1203.

Results and discussion

At first, we attempted the reaction of bromobenzene with 4-piperidone monohydrochloride monohydrate under the reaction conditions of CuI/*L*-proline as the catalytic system, K_2CO_3 as the base and DMSO as the solvent at 90 ℃. The desired *N*-aryl substituted 4-piperidone was isolated in 33% yield (Table 1, Entry 1). Increasing the amount of 4-piperidone monohydrochloride monohydrate gave the better result (Entry 2). But under other various conditions, the yields were lower and even no desired product was observed due to the self-condensation of the 4-piperidone monohydrate (Entries 4—8). So, we carried out the synthesis by an alternate approach using 1,4-dioxo-8-azaspiro[4,5]-decane (4-piperidone ethylene ketal) followed by hydrolysis of the resulting *N*-aryl-4-piperidone ethylene ketal which gave *N*-aryl-4-piperidone.

Table 1 Conditions screened for the coupling of 4-piperidone monohydrochloride monohydrate with bromobenzene

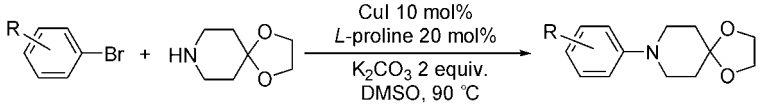


Entry	Base	Ligand	Solvent	Yield[a]/%
1	K_2CO_3	*L*-proline	DMSO	33
2	K_2CO_3	*L*-proline	DMSO	54[b]
3	K_2CO_3	*N*,*N*-dimethylglycine	DMSO	No reaction
4	K_2CO_3	*L*-proline	DMF	17
5	K_2CO_3	*L*-proline	THF	Trace
6	K_2CO_3	*L*-proline	dioxane	Trace
7	K_3PO_4	*L*-proline	DMSO	No reaction
8	Cs_2CO_3	*L*-proline	DMSO	No reaction

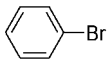
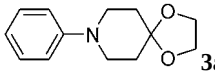
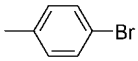
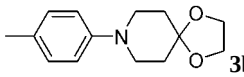
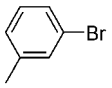
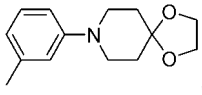
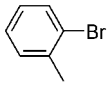
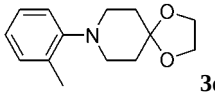
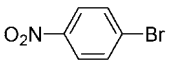
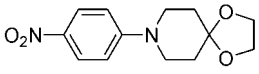
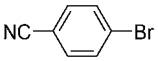
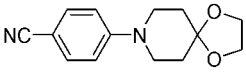
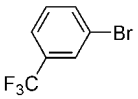
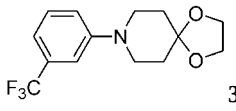
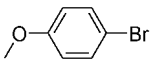
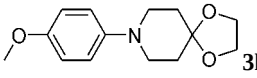
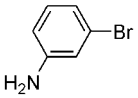
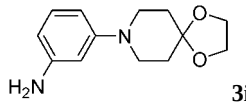
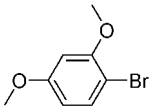
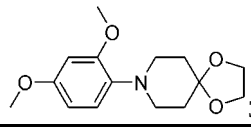
[a] Isolated yield. [b] 4-Piperidone monohydrochloride monohydrate 3.0 equiv.

Then we tested the reaction of bromobenzene with 1,4-dioxo-8-azaspiro[4,5]decane under the same reactions as Table 1, Entry 1. Fortunately, the coupling product was isolated in 92% yield this time, and the reaction scope with different aryl bromides was further investigated. The results are summarized in Table 2. To our delight, aryl bromides with either electron-withdrawing or electron-donating substituents at various

Table 2 Synthesis of *N*-aryl-4-piperidone ethylene ketals



1 (4 mmol) **2** (1.5 equiv.) **3**

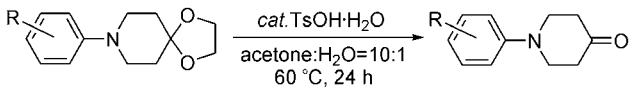
Entry	Aryl bromide	Product **3**	Time/h	Yield of **3**[a]/%
1		 **3a**	48	92
2		 **3b**	48	71
3		 **3c**	48	85
4		 **3d**	48	Trace
5		 **3e**	36	93
6		 **3f**	36	86
7		 **3g**	36	84
8		 **3h**	48	89
9		 **3i**	48	88
10		 **3j**	100	74[b]

[a] Isolated yield. [b] 17% 1-bromo-2,4-dimethoxybenzene was recovered.

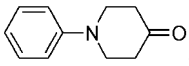
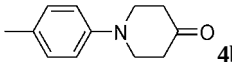
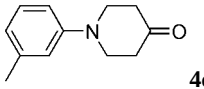
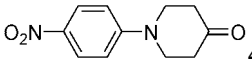
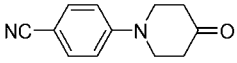
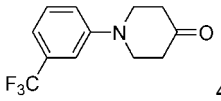
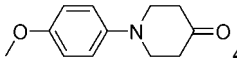
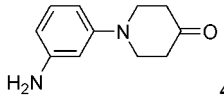
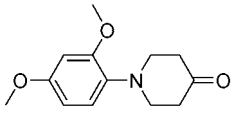
positions on the benzene rings could give the corresponding piperidone ketals **3** in good to excellent yields. For the sterically hindered aryl bromide 1-bromo-2-methylbenzene, a higher temperature and a prolonged time did not give **3d** in satisfactory yield (Entry 4), but **3j** was obtained in the yield of 74% when extending the reaction time from 48 h to 100 h (Entry 10). Furthermore, aryl substituted 4-piperidone ketals upon hydrolysis catalyzed by TsOH•H_2O in acetone/H_2O (V∶V=10∶1) at 60 ℃ for 24 h gave the corresponding aryl substituted 4-piperidones in good yields too (Table 3). However, 1-(3-aminophenyl)-piperidin-4-one (**4i**) was not observed due to the condensation of free amino group of the aryl moiety with the deprotected keto group of the piperidine ring (Table 3, Entry 8).[14]

In summary, we have developed an efficient, mild and economic two-step procedure for the synthesis of *N*-aryl substituted piperid-4-ones from aryl bromides and 4-piperidone ethylene ketals. In most cases, the key amination step proceeded well with a variety of aryl bromides, including those with electron-withdrawing and electron-donating groups. Given these attributes, it should find applications to many other derivatives.

Table 3 Synthesis of substituted *N*-aryl piperidones



3 **4**

Entry	Ketal **3**	Product **4**	Yield of **4**[a]/%	Overall yield of two steps[a]/%
1	**3a**	 **4a**	90	83
2	**3b**	 **4b**	93	66
3	**3c**	 **4c**	92	78
4	**3e**	 **4e**	86	80
5	**3f**	 **4f**	90	77
6	**3g**	 **4g**	87	73
7	**3h**	 **4h**	91	81
8	**3i**	 **4i**	No product	
9	**3j**	 **4j**	85	63

[a] Isolated yield.

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