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New synthesis of 3-arylpyrrolines

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Abstract—We present an easy and straightforward synthesis of 3-arylpyrrolines **4a**–**g** by repeated treatment of 4-aryl-1,2,5,6-tetrahydropyridines **2a**–**g** with *m*-chloroperoxybenzoic acid (MCPBA) and boron trifluoride etherate (BF_3-OEt_2). The transformation proceeds via epoxidation, ring contraction, Baeyer–Villiger oxidation and elimination reaction and affords 3-arylpyrrolines **4a**–**g** with 61–70% yield. This facile strategy was also used to synthesize racemic baclofen (**6**).

Synthesis of 3-pyrrolines and its analogs has been largely inspired by the structural relationship of this heterocycle to the ubiquitous pyrrolidine and pyrrole.[1,2] These substituted and functionalized 3-pyrrolines are often used as key intermediates for the synthesis of nitrogen containing heterocyclic natural products and potential biological activity compounds.[3] For example, 3-arylpyrrolines with different substitutents are reported to act as irreversible mechanism-based inactivators or inhibitors of various enzymes.[4]

Development of a general and novel procedure for 3-pyrrolines provides an expedient entry point. Basically, the adopted synthetic strategies of 3-pyrrolines and its related analogs can be summarized in transition metal-promoted, for example, palladium(0, II),[5] silver(I),[6] mercury(II),[7] gold(III),[8] organolanthanide[9] and phosphine-catalyzed[10] cyclization and cycloisomerization of a heteroatom onto an allene moiety, Suzuki coupling,[11] and ring-closing metathesis reaction[12] (Fig. 1). In this letter, we develop an easy and straightforward strategy to 3-arylpyrrolines by repeated treatment of 4-aryl-1,2,5,6-tetrahydropyridines with *m*-chloroperoxybenzoic acid (MCPBA) and boron trifluoride etherate (BF_3-OEt_2).

4-Hydroxypiperidine was chosen as the starting material in the synthesis of 3-arylpyrrolines as shown in Scheme 1. 4-Aryl-1,2,5,6-tetrahydropyridines **2a**–**f** were prepared by the four-step standard protocol and described as follows: (i) *N*-tosylation of 4-hydroxypiperidine with

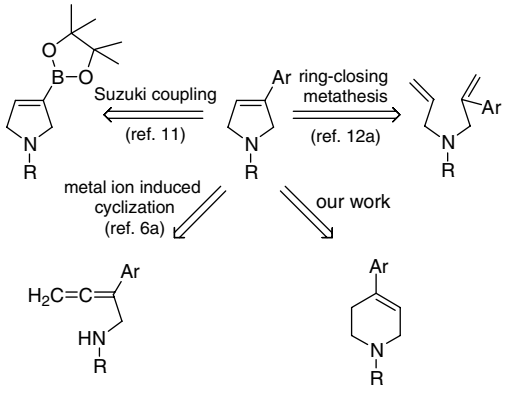
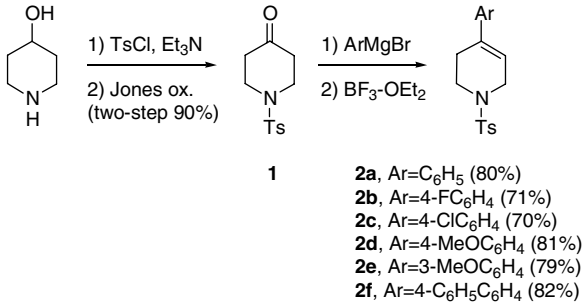


Figure 1.



1

2a, Ar=C_6H_5 (80%)
2b, Ar=4-FC_6H_4 (71%)
2c, Ar=4-ClC_6H_4 (70%)
2d, Ar=4-$MeOC_6H_4$ (81%)
2e, Ar=3-$MeOC_6H_4$ (79%)
2f, Ar=4-$C_6H_5C_6H_4$ (82%)

Scheme 1.

Keywords: 3-Arylpyrrolines; 4-Aryl-1,2,3,6-tetrahydropyridines; *m*-Chloroperoxybenzoic acid; Boron trifluoride etherate.
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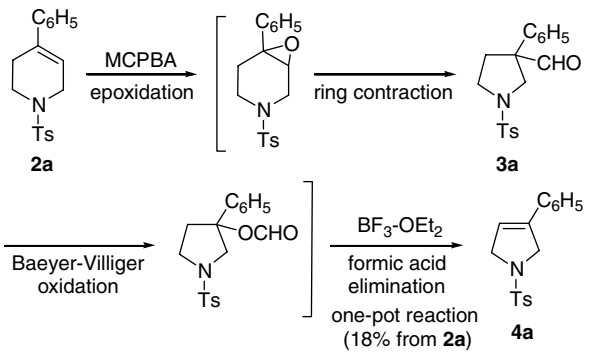
triethylamine and *p*-toluenesulfonyl chloride in dichloromethane at 0 °C for 1 h, (ii) oxidation of the resulting alcohol with excess Jones reagent in acetone at 0 °C for 15 min, (iii) Grignard addition of 1-tosylpiperidin-4-one (**1**) with different arylmagnesium bromide reagent (a, Ar = C_6H_5; b, Ar = 4-FC_6H_4; c, Ar = 4-ClC_6H_4; d, Ar = 4-$MeOC_6H_4$; e, Ar = 3-$MeOC_6H_4$; f, Ar = 4-$C_6H_5C_6H_4$) in tetrahydrofuran at −78 °C for 2 h, (iv) dehydration of the resulting tertiary alcohols with BF_3-OEt_2 in dichloromethane at 0 °C for 15 min. Thus, compounds **2a–f** were provided from compound **1** after two recrystallizations in 70–82% overall yield.[13]

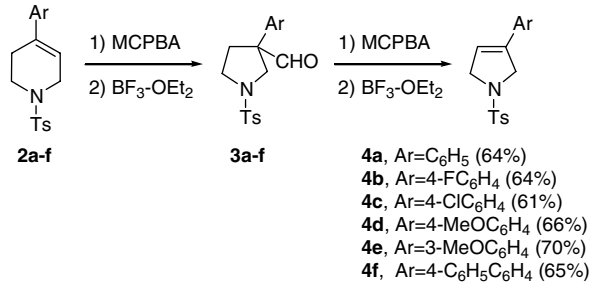
To initiate our work, reaction of compound **2a** was treated with excess MCPBA at rt for ca. 170 h in dichloromethane followed by treatment of BF_3-OEt_2 at 0 °C for 15 min. 3-Phenylpyrroline was separated in only 18% yield via the one-pot reaction with a series of functional group transformations. This is an interesting result. The possible reaction mechanism has been proposed as shown in Scheme 2. Presumably, epoxide of olefin **2a** was first generated. After MCPBA-mediated conversion of pinacol to pinacolone and following Baeyer–Villiger oxidation of the resulting aldehyde **3a**, formyl acid was then eliminated by the addition of BF_3-OEt_2 in dichloromethane, providing compound **4a**. During the one-pot process, 2-pyrroline framework was not observed under this combination of MCPBA and BF_3-OEt_2 conditions.

With the above results and enough amounts of compounds **2a–f**, we examined and investigated the integrity of ring contraction reaction sequence in the synthesis of 3-arylpyrrolines as shown in Scheme 3. This repeated combination of MCPBA and BF_3-OEt_2 could provide an easy and straightforward standard operation protocol with better yields from compounds **2a–f** to compounds **4a–f**.

The related overall procedure for synthesizing compounds **4a–f** is described as follows. First, aldehydes **3a–f** were first provided by epoxidation of compounds **2a–f** with MCPBA at rt for 3 h and followed by rearrangement reaction of the resulting epoxides with BF_3-OEt_2 at 0 °C for 15 min.[14,15] Next, Baeyer–Villiger reaction of aldehydes **3a–f** was further treated with MCPBA at rt for 3 h and followed by the elimination



Scheme 2.



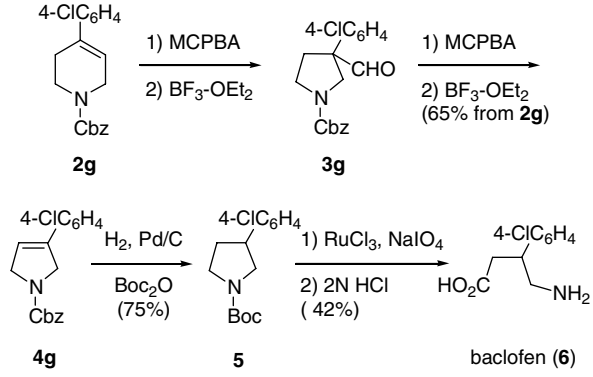
Scheme 3.

reaction of the resulting formyl group with BF_3-OEt_2 at 0 °C for 15 min. The continuous reaction showed shorter overall reaction time and higher reaction efficiency. For the transformation, 3-arylpyrrolines **4a–f** were obtained in 61–70% yield by only column chromatography purification on silica gel.[16] The total synthetic procedure must be monitored by TLC until the reaction was complete within a working day.

We had tried to study the synthesis of 3-methylpyrroline by repeated treatment of 4-methyl-1,2,5,6-tetrahydropyridine with MCPBA and BF_3-OEt_2, but 3-methylpyrroline was provided in trace yield. Especially, many products were produced by the treatment of 4-methyl-3,4-epoxypiperidine with BF_3-OEt_2. Although the synthetic application has been decreased, the present work is complementary to existing methodology.

Racemic baclofen[17] (Lioresal®; Baclon®) [4-amino-3-(4-chlorophenyl)butanoic acid] is a lipophilic analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). During the last decade, a number of specific agonists or antagonists for the $GABA_B$ receptor site have been developed. However, baclofen is the only selective and therapeutically useful $GABA_B$ agonist. Baclofen is used in the treatment of spasticity caused by disease of the spinal cord, particularly traumatic lesions. Due to its biological and pharmacological importance, there have been several reports on the total synthesis of baclofen.[18]

Here, we report a new approach for the synthesis of racemic baclofen from compound **2g** as shown in Scheme 4. Under the repeated combination of MCPBA



Scheme 4.

and BF_3-OEt_2 condition, compound **4g** was provided in 65% yield from compound **2g**. In view of the experimental simplicity, the preparation of compound **4g** was also conducted in a multigram scale (10 mmol) with 51% overall yield. Compound **5** was yielded by the treatment of compound **4g** with hydrogen and di-*tert*-butyl dicarbonate in the presence of a catalytic amount of 10% palladium on activated carbon.[19] Selective oxidation of compound **5** with ruthenium oxide and subsequent hydrolysis with aqueous hydrochloric acid yielded baclofen (**6**) in 42% yield.[20]

In summary, we present an easy and straightforward synthesis of 3-arylpyrrolines **4a**–**g** by repeated treatment of 4-aryl-1,2,5,6-tetrahydropyridines **2a**–**g** with MCPBA and BF_3-OEt_2. The transformation proceeds via epoxidation, ring contraction, Baeyer–Villiger oxidation and elimination reaction and affords 3-arylpyrrolines **4a**–**g** with 61–70% yield. This facile strategy was also used to synthesize racemic baclofen (**6**). We are currently studying the scope of this process as well as additional applications of the methodology to the synthesis of piperidines, indolizidines, quinolizidines and indoles.

Acknowledgements

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Supplementary data

Photocopies of ^{1}H NMR ($CDCl_3$ or D_2O) spectral data for compounds **2a**–**g**, **3g**, **4a**–**g** and **5**–**6** were supported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.008.

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13. A representative procedure of **2a**–**g** is as follows: A solution of arylmagnesium bromide (2.6 mmol) in tetrahydrofuran (10 mL) was added to a stirred solution of piperidin-4-one (2.23 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred at rt for 2 h. Water (5 mL) was added to the reaction mixture and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, a solution of boron trifluoride etherate (1 mL) in dichloromethane (5 mL) was added to a stirred solution of the crude product in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Recrystallizations from hexane and ethyl acetate (ca. 2:1) yielded **2a**–**f**. Purification on silica gel (hexane/ethyl acetate = 4:1–2:1) afforded **2g**. Representative data for **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.72 (d, $J = 8.5$ Hz, 2H), 7.35–7.26 (m, 7H), 5.97–5.95 (m, 1H), 3.77 (dd, $J = 2.5$, 6.0 Hz, 2H), 3.33 (t, $J = 6.0$ Hz, 2H), 2.63–2.61 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.63, 140.11, 135.39, 133.14, 129.67 (2×), 128.44 (2×), 127.77 (2×), 127.52, 124.97 (2×), 118.98, 45.24, 43.01, 27.55, 21.53; HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_2S$ (M^++1) 314.1215, found 314.1213. For **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.69 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.28–7.22 (m, 2H), 7.03–6.96 (m, 2H), 5.89 (td, $J = 1.8$, 3.6 Hz, 1H), 3.74 (dd, $J = 3.0$, 6.0 Hz, 2H), 3.33–3.29 (m, 2H), 2.59–2.55 (m, 2H), 2.43 (s, 3H); HRMS (ESI) m/z calcd for $C_{18}H_{19}FNO_2S$ (M^++1) 332.1121, found 332.1122. For **2g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 9H), 5.99 (br s, 1H), 5.18 (s, 2H), 4.16 (d, $J = 2.0$ Hz, 2H), 3.72 (t, $J = 5.5$ Hz, 2H), 2.52 (br s, 2H); HRMS (ESI) m/z calcd for $C_{19}H_{19}ClNO_2$ (M^++1) 328.1104, found 328.1106.

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16. A representative procedure of **4a**–**g** is as follows: A solution of *m*-chloroperoxybenzoic acid (510 mg, 75%, 2.2 mmol) in dichloromethane (10 mL) was added to a solution of **2a**–**g** (2.0 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at rt for 3 h. Saturated sodium carbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, a solution of boron trifluoride etherate (1 mL) in dichloromethane (5 mL) was added to a stirred solution of the resulting crude epoxide product in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude products **3a**–**g** under reduced pressure. Without further purification, a solution of *m*-chloroperoxybenzoic acid (510 mg, 75%, 2.2 mmol) in dichloromethane (10 mL) was added to a solution of resulting aldehyde **3a**–**g** and sodium bicarbonate (750 mg, 8.93 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at rt for 3 h. Saturated sodium carbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, a solution of boron trifluoride etherate (1 mL) in dichloromethane (5 mL) was added to a stirred solution of the resulting crude product in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 2:1–1:1) afforded **4a**–**g**. Representative data for **4a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, $J = 8.5$ Hz, 2H), 7.33–7.27 (m, 7H), 6.01 (t, $J = 2.0$ Hz, 1H), 4.49 (td, $J = 2.0$, 4.0 Hz, 2H), 4.31 (td, $J = 2.0$, 4.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.56, 137.34, 134.08, 132.48, 129.83 (2×), 128.68 (2×), 128.43, 127.47 (2×), 125.38 (2×), 118.86, 55.66, 54.90, 21.50; HRMS (ESI) m/z calcd for $C_{17}H_{18}NO_2S$ (M^++1) 300.1058, found 300.1058. For **4b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.27–7.24 (m, 2H), 7.02 (t, $J = 8.5$ Hz, 2H), 5.94 (t, $J = 2.0$ Hz, 1H), 4.46–4.44 (m, 2H), 4.31–4.28 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.59, 161.62, 143.62, 136.28, 133.99, 129.85 (2×), 127.45 (2×), 127.13, 127.06, 118.64, 115.77, 115.59, 55.60, 54.92, 21.50; HRMS (ESI) m/z calcd for $C_{17}H_{17}FNO_2S$ (M^++1) 318.0964, found 318.0963. For **4c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 8.5$ Hz, 2H), 6.00 (t, $J = 2.0$ Hz, 1H), 4.45 (td, $J = 2.0$, 4.5 Hz, 2H), 4.30 (td, $J = 2.0$, 5.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.66, 136.30, 134.22, 133.98, 130.94, 129.86 (2×), 128.87 (2×), 127.45 (2×), 126.63 (2×), 119.60, 55.62, 54.77, 21.52; HRMS (ESI) m/z calcd for $C_{17}H_{17}ClNO_2S$ (M^++1) 334.0669, found 334.0670.
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19. The synthetic procedure of **5** is as follows: 10% palladium on activated carbon (10 mg) was added to a solution of **4g** (100 mg, 0.32 mmol) and di-*tert*-butyl dicarbonate (110 mg, 0.5 mmol) in methanol (10 mL). Then, hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir at rt for 10 h. The catalyst was filtered through a short plug of Celite and washing with methanol (2 × 10 mL). The combined organic layers were evaporated under reduced pressure to yield the crude compound. Purification on silica gel (hexane/ethyl acetate = 3:1) afforded **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.15 (m, 4H), 3.85–3.72 (br s, 1H), 3.70–3.52 (br s, 1H), 3.42–3.20 (m, 3H), 2.32–2.18 (br s, 1H), 2.01–1.83 (m, 1H), 1.65 (s, 9H); HRMS (ESI) m/z calcd for $C_{15}H_{21}ClNO_2$ (M^++1) 282.1261, found 282.1263.
20. The synthetic procedure of baclofen-HCl (**6**) is as follows: Compound **5** (56 mg, 0.2 mmol) was dissolved in carbon tetrachloride (2 mL), acetonitrle (2 mL) and water (3 mL) with vigorous stirring. Then, sodium periodate (210 mg, 1.0 mmol) and ruthenium (III) chloride hydrate (5 mg) were added. The reaction was stopped after 6 h, diluting

with dichloromethane (20 mL) and the organic layer was separated. The aqueous layer was then extracted with dichloromethane (2×10 mL) and the organic layers were filtered on a Celite pad, collected and concentrated to yield lactam as the major product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (br s, 1H), 7.27–7.24 (m, 2H), 7.14–7.13 (m, 2H), 3.76–3.72 (m, 1H), 3.65–3.57 (m, 1H), 3.33 (dd, $J = 7.2$, 9.4 Hz, 1H), 2.68 (dd, $J = 9.0$, 16.9 Hz, 1H), 2.40 (dd, $J = 8.6$, 16.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.73, 140.64, 132.70, 128.85 (2×), 128.02 (2×), 49.42, 39.51, 37.98. A mixture of the resulting lactam product in aqueous hydrogen chloride solution (2 N, 10 mL) was refluxed for 12 h. The solvent was evaporated under reduced pressure and the residue was triturated in isopropanol yielding baclofen-HCl (**6**). ^{1}H NMR (400 MHz, D_2O) δ 7.49 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 2H), 3.42–3.24 (m, 3H), 2.67 (dd, $J = 6.4$, 14.6 Hz, 1H), 2.57 (dd, $J = 8.4$, 14.6 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 175.71, 138.62, 133.49, 129.88 (2×), 129.66 (2×), 44.55, 42.66, 41.22.