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Convenient synthesis of 1,1′-*H*-spiro[indoline-3,3′-piperidine]

Jeffrey A. Pfefferkorn *, Chulho Choi

Pfizer Global Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States

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ABSTRACT

The spirocyclic indoline ring system represents an important scaffold for the discovery of novel therapeutics. Herein, we describe the synthesis of 1,1′-*H*-spiro[indoline-3,3′-piperidine] using an intramolecular palladium-catalyzed α-arylation reaction.

Spirocyclic indolines **1**–**3** (Fig. 1) represent important scaffolds for drug discovery. These heterocycles offer well-defined substituent vectors and their conformational rigidity, small size, and polarity confer favorable physical properties for oral bioavailability; hence, they have found application in a variety of therapeutic areas. For example, the spiro[indoline-3,3′-pyrrolidine] system has been utilized in glycine receptor antagonists (**4**, Fig. 2).[1] The spiro[indoline-3,4′-piperidine] system has found numerous applications, including nonpeptidyl growth-hormone secretagogues (**5**),[2] muscarinic receptor modulators (**6**),[3] and histone deacetylase inhibitors (**7**);[4] furthermore, it has been identified as a privileged scaffold for the discovery of ligands for G-protein coupled receptors.[5]

While synthesis of 1,1′-*H*-spiro[indoline-3,3′-pyrrolidine] (**1**)[1] and 1,1′-*H*-spiro[indoline-3,4′-piperidine] (**2**)[2,6] have been previously reported, there is less precedent for the synthesis of the corresponding 1,1′-*H*-spiro[indoline-3,3′-piperidine] system (**3**). Grigg et al. have described the synthesis of various derivatized spiro[indoline-3,3′-piperidine] systems[7]; however, as part of a medicinal chemistry program, we required convenient access to the unsubstituted 1,1′-*H*-spiro[indoline-3,3′-piperidine] core (**3**) for further elaboration.[8]

Examining the spiro[indoline-3,3′-piperidine] ring system, we envisioned its construction via an intramolecular palladium-catalyzed α-arylation reaction of a suitable functionalized amide enolate. While the intermolecular palladium-mediated α-arylation of amide enolates is generally less facile than that of enolates generated from esters or ketones,[9,10] this approach has been successfully applied to the intramolecular synthesis of lactams and oxindoles.[11]

As shown in Scheme 1, construction of a suitably functionalized cyclization precursor (i.e., **8**) commenced with treatment of ethyl nipecotate (**4**) with Boc_2O in the presence of Et_3N to provide intermediate carbamate **5**. Reaction of the ethyl ester of **5** with 2-bromoaniline (**6**) in the presence of $AlMe_3$ at elevated temperature generated amide **7**, which was subsequently reacted with NaH

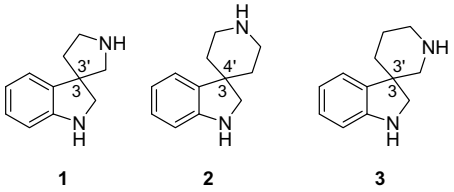

Figure 1. Spirocyclic indolines **1**–**3**.

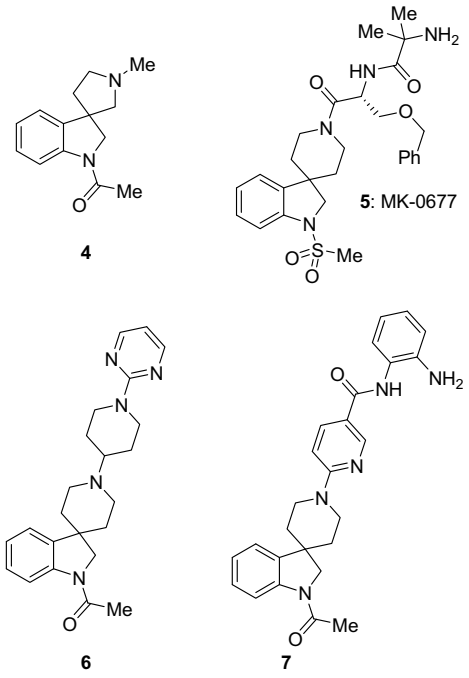

Figure 2. Representative therapeutic applications of spirocyclic indolines.

* Corresponding author. Tel.: +1 860 686 3421; fax: +1 860 715 4068.
E-mail address: jeffrey.a.pfefferkorn@pfizer.com (J. A. Pfefferkorn).

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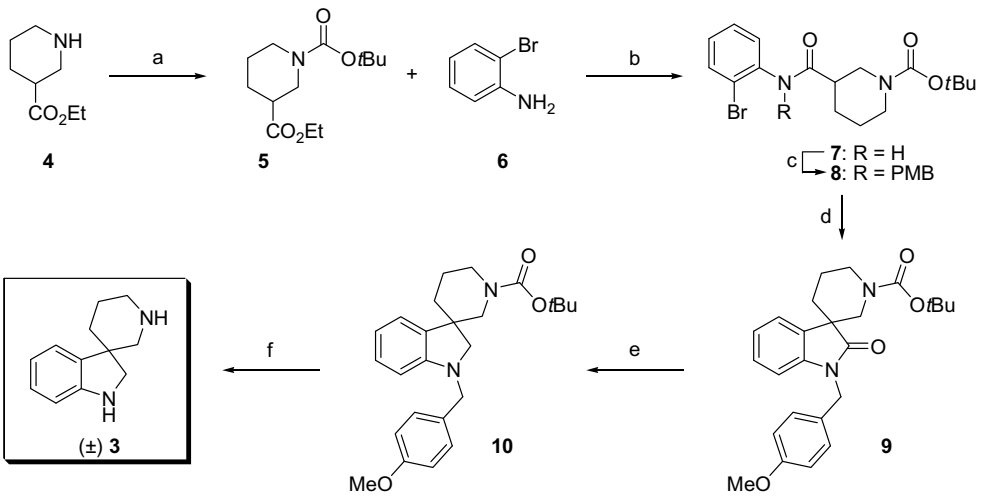

Scheme 1. Synthesis of (±) spiro[indoline-3,3′-piperidine] **3**. Reagents and conditions: (a) Boc_2O, Et_3N, CH_2Cl_2, 25 °C, 18 h, 38%; (b) $AlMe_3$, CH_2Cl_2, 40 °C, 16 h, 68%; (c) PMB–Cl, NaH, DMF, 0 → 25 °C, 4 h, 100%; (d) $Pd(OAc)_2$, $(C_6H_{11})_3P$; KO*t*Bu, Dioxane/THF (10:1), 85 °C, 54%; (e) $BH_3{\cdot}SMe_2$, THF, 60 °C, 4 h, 90%; (f) (i) 1-chloroethyl chloroformate, CH_2Cl_2, 0 °C, 1 h; (ii) MeOH, 60 °C, 1 h, 49% (2 steps).

and PMB–Cl to afford tertiary amide **8** as the desired cyclization precursor. In the palladium-catalyzed cyclization event, **8** was treated with $Pd(OAc)_2$, $(C_6H_{11})_3P$ and KO*t*Bu at elevated temperature to provide oxindole **9** in 54% yield. Separate attempts to cyclize precursor **7** directly (without PMB protection) were not successful and resulted only in debromination. The synthesis was then completed by reduction of oxindole **9** to indoline **10** with $BH_3{\cdot}SMe_2$ followed by exhaustive deprotection with 1-chloroethyl chloroformate to provide racemic 1,1′-*H*-spiro[indoline-3,3′-piperidine] (**3**) in 49% yield.[12]

In conclusion, we have described a convenient synthesis of the spiro[indoline-3,3′-piperidine] ring system utilizing an intramolecular palladium-catalyzed α-arylation reaction.

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12. *Analytical data for 1,1′-H-spiro[indoline-3,3′-piperidine]* (**3**): ^{1}H NMR ($CDCl_3$) δ 7.03 (dd, J = 7.6, 1.2 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.70 (dd, J = 7.2, 1.2 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 4.05 (d, J = 9.6 Hz, 1H), 3.43–3.37 (m, 4H), 2.91–2.83 (m, 2H), 1.97–1.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 151.0, 131.8, 129.3, 122.8, 119.0, 110.3, 56.3, 50.0, 44.6, 43.4, 32.6, 20.0; MS(APCI$^+$): m/z 189.1 (M+H). These data were consistent with previously reported derivatives of the 1,1′-*H*-spiro[indoline-3,3′-piperidine] ring system, see Ref. 8.