Synthesis of Structurally Diverse 2,3-Fused Indoles via Microwave-Assisted AgSbF₆-Catalysed Intramolecular Difunctionalization of o-Alkynylanilines

Yuanqiong Huang*, Yan Yang*, Hongjian Song, Yuxiu Liu & Qingmin Wang

2,3-Fused indoles are found in numerous natural products and drug molecules. Although several elegant methods for the synthesis of this structural motif have been reported, long reaction times and harsh conditions are sometimes required, and the yields tend to be low. Herein, we report a microwave method for straightforward access to various types of 2,3-fused indoles via AgSbF₆-catalysed intramolecular difunctionalization of o-alkynylanilines. AgSbF₆ played a role in both the hydroamination step and the imine-formation step. This method, which exhibited excellent chemoselectivity (no ring-fused 1,2-dihydroquinolines were formed), was used for formal syntheses of the natural products conolidine and ervaticine and the antihistamine drug latrepirdine.

Ring-fused indoles in general, and 2,3-fused indoles in particular, are found in numerous natural products and drug molecules (Fig. 1). Hexahydro-1H-azocino[4,3-b]indole is the core motif of numerous natural products, such as (+)-condylocarpine, (+)-uleine, conolidine and ervaticine, (−)-actinophyllic acid, and (−)-strychnine. In addition, the clinical antihistamine drug latrepirdine contains a tetrahydro-1H-pyrrolo[4,3-b]indole skeleton (also known as γ-carboline). 2,3-Fused indoles have synthetically challenging structures and interesting biological activities, and much attention has been paid to the development of new approaches to the synthesis of this structural motif. However, a practical method for the efficient synthesis of 2,3-fused indoles in a single operation is lacking.

Intramolecular difunctionalization of o-alkynylanilines is widely used to construct ring-fused indoles, but this method, and other conventional synthetic methods, suffer from long reaction times, harsh conditions, and low yields. Microwave-assisted organic synthesis, which was first reported by Gedye et al. and Giguere et al. in 1986, can be used to increase product yields and dramatically reduce reaction times compared to those of conventional synthetic methods. Therefore, we wondered whether microwave-assisted intramolecular difunctionalization could be used to construct 2,3-fused indoles efficiently.

Results
To evaluate this possibility, we initially carried out the reaction of o-alkynylaniline 1a and benzaldehyde (2 equiv) with 10 mol% Sc(OTf)₃ as a catalyst in 1,2-dichloroethane for 1.5 h at 80 °C at a microwave power of 100 W. These reaction conditions yielded indole 3aa′ as the sole product in 10% yield (Table 1, entry 1), and bicyclization product 3aa was still not obtained when In(OTf)₃ or Cu(OAc)₂ was used.
instead of Sc(OTf)₃ (entries 2 and 3). However, 3aa was obtained in 94% yield when AgSbF₆ was used as the catalyst (entry 4). The nature of the solvent greatly influenced the outcome of the reaction. No 3aa formed when the solvent was 1,4-dioxane or acetonitrile, and the yield was only 54% in toluene (entries 5–7, respectively). Neither lowering the reaction temperature (entry 8) nor shortening the reaction time (entry 9) provided any benefit. Other silver(I) catalysts gave no better results than AgSbF₆ (entries 10–12), and in the absence of microwaves, more than 30 h was required to give 3aa in 86% yield (entry 13). These preliminary results indicated that the optimal reaction conditions were as follows: 10 mol% AgSbF₆ in 1,2-dichloroethane at 80 °C (entry 4). This reaction exhibited excellent chemoselectivity: no ring-fused 1,2-dihydroquinoline 3aa′ was obtained.

We then used the optimal conditions to investigate the substrate scope of the reaction (Fig. 2). First, we carried out reactions of 1a with various substituted benzaldehydes (2a–2i). The corresponding
difunctionalization products (3aa–3ai) were obtained in more than 80% yield, indicating that neither
the position nor the electronic properties of the substituents had a marked effect on the reaction out-
come. We evaluated the electronic effects of substituents (R) on the benzene ring of 1 by carrying out

Figure 2. Synthesis of tetrahydro-1H-pyrido[4,3-b]indole and tetrahydropyrano[4,3-b]indole by
intramolecular difunctionalization[^a].[^b] The yields given are isolated yields. DCE = 1,2-dichloroethane,
Ts = 4-methylphenylsulfonyl, Ms = methanesulfonyl, MW = microwave. The reaction was conducted with
1a (1 equiv) in the presence of AgSbF₆ (10 mol%) in DCE at a MW power of 100 W for 1 h at 80°C. Then 2k
(2 equiv) and CF₃COOH (1.5 equiv) were added, and the mixture was reacted under the same conditions for
3 h.
reactions of 1a–1k with 2j. Substrates with no substituents, a weak electron-donating substituent (1a–1e), or an electron-withdrawing substituent (1f–1g) afforded desired compounds 3aj–3gj in more than 80% yield. Substrates with a strongly electron-donating group, such as a cyano, trifluoromethyl, nitro, or methoxycarbonyl group, could also be converted to the desired products (3hj–3kj), albeit in slightly lower yields. Disfunctionalization products 3ak–3ao were obtained in moderate to good yields when 1a was allowed to react with aliphatic aldehydes 2k–2o, and the structures of 3aa and 3ak were confirmed by X-ray diffraction analysis25. Substrate 1a reacted with aromatic aldehydes 2-naphthaldehyde (3ap, 81%), thiophene-2-carbaldehyde (3aq, 64%), and piperonaldehyde (3as, 87%).

We also evaluated various nucleophile moieties. The reaction worked well when the methylphenylsulfonyl group (XH = NHTs) was changed to a methanesulfonyl group (3lj, 72%), and tetrahydropyran-4,3-b-indole (3mj) was obtained in 64% when XH was OH rather than NHTs. However, when YH was OH, intramolecular disfunctionalization product 3nj was not obtained, owing to the poor nucleophilicity of the phenolic hydroxyl group; instead, 5-endo-trig product 3nj‘ resulting from a reaction in which water acted as a nucleophile was the sole product.

We also investigated ring-closure reactions to form ring systems of various sizes (Fig. 3). Substrate 3o (n = 1) reacted both with aromatic aldehydes (2a, 2d, 2e, and 2g) and with aliphatic aldehydes (2j, 2l, and 2n) to afford the corresponding hexahydro-1H-azocino[4,3-b]indoles. We investigated both a one-pot method (Method A) and a stepwise method (Method B) and found that the latter gave higher yields. When CF3COOH was added to the reaction mixture (Method C), indoles fused to nine-membered rings (3ok, 3pk, and 3qk) were obtained; 3pk (hexahydro-1H-azocino[4,3-b]indole) is the core skeleton of many natural products (Fig. 1). The structures of 3pk and 3qo were confirmed by X-ray diffraction analysis26.

Plausible pathways for the disfunctionalization reactions between n-butanal and 1a (YH = NHTs) and 1n (YH = OH) are depicted in Fig. 4a. Pathway 1 involves initial closure of the B ring to form 3aa‘ via an AgSbF6-catalysed hydrosilation reaction. Subsequently, AgSbF6 promotes the formation of imine A29, which is further transformed to target compound 3aj via a 6-endo-trig cyclization. In this pathway, AgSbF6 catalyses both the hydroamination step and the formation of imine A. In pathway 2, an initial AgSbF6-catalysed imination reaction results in the formation of imine B, which can undergo two possible cyclizations: (1) 6-endo-trig leading to intermediate C, which can then be transformed to 3aj or (2) 5-endo-trig cyclization (when YH = OH) leading to intermediate D, which can afford pyrrolidine 3nj‘ by means of the addition of water. A third reaction pathway, leading to ring-fused 1,2-dihydroquinoline 3aa‘“ via 5-endo-dig cyclization, is also possible; however, no 3aa‘“ was obtained from the reaction.

To determine which of these pathways occurred under our reaction conditions, we monitored the formation of 3aj over time by means of 1H NMR spectroscopy (Fig. 4b). The 1H NMR spectrum of 1a exhibited a triplet at δ = 2.61 ppm and a quartet at δ = 3.17 ppm. After 10 min of reaction under the optimal conditions (Table 1, entry 4), a new singlet (δ = 6.38 ppm), attributable to the hydrogen at the 3-position of indole 3aa‘ (Fig. 2a), was observed, along with a new triplet (δ = 3.22 ppm) and a new quartet (δ = 3.38 ppm), which are attributable to the two CH3 protons of 3aa‘. Note also that at this stage, the triplet and quartet attributable to 1a shifted from 2.61 and 3.17 ppm to 2.80 and 3.10 ppm, respectively, owing to the formation of a complex between 1a and AgSbF6. At 30 min, all of the complex had been transformed to 3aa‘. As the reaction progressed, the signals for 3aa‘ disappeared gradually, and signals due to 3aj appeared and increased in intensity. The reaction was almost complete after 60 min. These 1H NMR spectroscopy results suggest that the intramolecular disfunctionalization reaction of 1a occurred via pathway 1 in Fig. 4a.

Because our intramolecular disfunctionalization method efficiently gave hexahydro-1H-azocino[4,3-b] indole 3pk, we used the method for the rapid formal synthesis of the natural products ervatine and conolidine as follows (Fig. 5a). Reaction of 2-iodoaniline with Ts-protected hex-5-yn-1-amine gave the corresponding coupled product, which reacted with 4-methylbenzene-1-sulfonyl chloride to give 1p in 72% yield for the two steps27. Exposure of 1p to the optimal disfunctionalization reaction conditions afforded 3pk in 73% yield. Removal of the N-tosyl group with sodium and naphthalene30 followed by protection with Boc2O provided 5pk in 81% over two steps, and subsequent oxidation with SeO2 afforded 6pk (56% yield)31, which has been converted to ervatine and conolidine as described previously32.

We also used our method for a formal synthesis of latrepirdine as follows (Fig. 5b). Compound 1f was obtained by Sonogashira coupling and subsequent protection of the primary amine with 4-methylbenzene-1-sulfonyl chloride in 67% yield for the two steps. Reaction between 1f and formaldehyde by means of the method described for the synthesis of 3ak (Fig. 2) gave 3fk in 95% yield. Removal of the N-tosyl group30 and subsequent reductive amination33 afforded 5fk (81% yield over two steps), which could be converted to latrepirdine as reported in the literature34.

In summary, we developed a straightforward method for accessing various 2,3-fused indoles via microwave-assisted AgSbF6-catalysed intramolecular disfunctionalization of o-alkynylanilines. The reaction exhibited excellent chemoselectivity: no ring-fused 1,2-dihydroquinolines were formed. In addition to indoles fused to six-membered rings, indoles fused to saturated medium-sized N-containing rings could also be constructed. We used the method for efficient formal syntheses of the indole alkaloids ervatine and conolidine and the antihistamine drug latrepirdine.
Figure 3. Synthesis of indoles fused to saturated medium-sized N-containing rings by means of intramolecular difunctionalization[^a].[^b] The yields given are isolated yields. DCE = 1,2-dichloroethane, MW = microwave. ^[b] Method A: The reaction was conducted with 1 (1 equiv) and 2 (2 equiv) in the presence of AgSbF₆ (10 mol%) at a MW power of 100 W in DCE for 6 h at 80 °C. ^[c] Method B: The reaction was conducted with 1 (1 equiv) in the presence of AgSbF₆ (10 mol%) at a MW power of 100 W in DCE for 3 h at 80 °C. Then 2 (2 equiv) was added, and the mixture was allowed to react under the same conditions for another 3 h. ^[^d] Method C: Similar to method B, except that CF₃COOH (1.5 equiv) was added along with 2 (2 equiv) in the second step.

Methods

**One-pot synthesis of 3aa.** A microwave vessel was charged with o-alkynylaniline 1a (98.5 mg, 0.21 mmol, 1 equiv), AgSbF₆ (7.1 mg, 0.021 mmol, 0.1 equiv), aldehyde 2a (26.7 mg, 0.25 mmol, 1.2 equiv), and DCE (5.0 mL); and the mixture was heated at a microwave power of 100 W at 80 °C for 1.5 h. After the reaction mixture cooled to room temperature, CH₂Cl₂ (10 mL) and H₂O (10 mL) were added. The
organic layer was separated, dried over anhydrous Na₂SO₄, and filtered. The filtrate was evaporated, and the residue was purified by silica gel chromatography with 10:1 (v/v) petroleum ether/ethyl acetate as the eluent to afford 3oa (110.0 mg, 94%) as a white solid (see Supplementary Information).

Stepwise synthesis of 3pk. A microwave vessel was charged with 1p (100.0 mg, 0.20 mmol, 1 equiv), AgSbF₆ (6.8 mg, 0.02 mmol, 0.1 equiv), and DCE (5.0 mL) in that order; and the mixture was heated at a microwave power of 100 W at 80 °C for 3 h. Then 2k (40% formaldehyde, 30.0 mg, 0.40 mmol, 2.0 equiv) and CF₃COOH (34.2 mg, 0.30 mmol, 1.5 equiv) were added, and the mixture was allowed to react under the same conditions for another 1 h. CH₂Cl₂ (10 mL) and H₂O (10 mL) were added to the resulting mixture. The organic layer was separated, dried over anhydrous Na₂SO₄, and filtered. The filtrate was evaporated, and the residue was purified by silica gel chromatography with 10:1 (v/v) petroleum ether/ethyl acetate as the eluent to afford 3pk (74.2 mg, 73%) as a white solid.

Figure 4. (a) Plausible reaction pathways and (b) time course of ¹H NMR spectra measured during synthesis of 3aj.
Figure 5. Formal syntheses of (a) ervaticine and conolidine and (b) latrepirdine.

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