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Synthesis of O- and N-alkylated products of 1,2,3,4-tetrahydrobenzo[c][2,7]naphthyrin-5(6H)-one

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Abstract

Efficient syntheses of O- and N-alkylated products of 1,2,3,4-tetrahydrobenzo[c][2,7]naphthyrin-5(6H)-one are presented. The O-alkylated analogues were synthesized through a reduction-cyclization cascade and a selective O-alkylation reaction; whereas the N-alkylated analogues were obtained through a key Buchwald coupling.

Graphical abstract

Keywords

Muscarinic acetylcholine receptors; 1,2,3,4-tetrahydrobenzo[c][2,7]naphthyrin-5(6H)-one; Suzuki coupling; Reduction-cyclization cascade; Buchwald coupling

Tetrahedron

Muscarinic acetylcholine receptors (mAChRs), consisting of five distinct subtypes (denoted M₁ to M₅), are important drug targets with various potential clinical applications.¹⁻³ These G-protein coupled receptors are involved in many critical physiological functions, with each subtype having distinct physiological roles.^{4,5} Thus, developing subtype-selective ligands for these receptors has been a major focus in drug discovery.¹ Specifically, the M₅ mAChR

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has been suggested to be a potential therapeutic target for a number of diseases,¹⁻³ including cerebrovascular insufficiency,^{6,7} Alzheimer's disease and cognitive impairment,⁷ schizophrenia,⁸ and drug dependence.⁹ Recent studies from our laboratory, employing a scaffold of 4-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid, have led to the discovery of a series of M₅-preferring orthosteric antagonists, e.g. **1** and **2** (Figure 1).¹⁰ One important strategy of lead optimization is to reduce conformational flexibility. Compounds **3** and **4** were designed to mimic the *cis*- and *trans*-rotamers, respectively, of 4-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylates in which the rotatable bond between the carboxylate moiety and C3 of tetrahydropyridine ring is locked by forming a ring structure (Figure 2). In the present study, we investigate the synthesis of **3** and **4**.

For the synthesis of **3** and **4** with variations on the O- or N-alkyl group, an efficient route would incorporate the alkyl groups on a common intermediate 1,2,3,4-tetrahydrobenzo[*c*] [2,7]naphthyrin-5(6*H*)-one (**5**) at the last step (Figure 3). This strategy is based on the assumption that selective alkylation of either the O or N atom of **5** can be achieved. We planned to synthesize intermediate **6** through the triflate intermediate (**7**), using a well-established Suzuki coupling reaction employed in our previous work.¹⁰ Conversion of **6** to **5** could be achieved via a reduction-cyclization cascade (Figure 3).

The preparation of **5** (R = Me) was relatively straightforward. Compound **7** was prepared from **8** (Figure 3) as reported.¹⁰ Suzuki coupling of **7** with 2-nitrophenylboronic acid in refluxing THF in the presence of Pd(PPh₃)₄ afforded compound **6** in 90% yield. Treatment of **6** with TFA in DCM at room temperature, followed by N-methylation using formalin and NaCNBH₃ in ethanol at 0 °C afforded compound **9** in 66% yield. Finally, a reduction-cyclization cascade was achieved by treating **9** with Na₂S₂O₆ and K₂CO₃ in ethanol and water (1:1 ratio) at room temperature to afford **5** in 69% yield. Alternatively, the same reduction-cyclization conditions were applied to compound **6** to form the tricyclic compound **10** in 74% yield. However, attempts to remove the Boc group from **10** resulted in complex mixtures (Scheme 1).

We then carried out a limited study to determine if regioselective N- versus O-alkylation of **5** could be achieved. Alkylation of 2-pyridones¹¹ and 2(1*H*)-quinolinones¹² usually results in formation of both N- and O- alkylated products. It was reported that alkylation of alkali salt of 2-pyridone in DMF occurred predominately at N atom whereas using the silver salt in benzene afforded exclusively the O-alkylated product.¹³ However, treatment of **5** with various bases, including NaH in THF or DMF, CaH₂¹⁴ in THF or DMF, LiHMDS in THF, nBuLi in THF, and K₂CO₃ in DMF, followed by reacting with 3,4-dimethoxyphenethyl bromide, afforded exclusively the O-alkylated product **3a** (Scheme 2). Among the reaction conditions studied, K₂CO₃ in DMF at 80 °C gave the best yields (75-82%, Scheme 2).

The selectivity between N- and O-alkylation can be affected by a number of factors.^{13,15} Under the same reaction conditions, selectivity is mainly affected by the structure features in the ambident nucleophiles and the alkylating agents. While the high regioselective alkylation of **5** is unexpected, a combination of the steric effect from the relatively large phenylalkylbromide and the electronic effect from the basic amino group in **5** that favors the phenolic formation could result in the observed exclusive O-alkylation.

Since direct alkylation of **5** is overwhelmingly favorable towards O-alkylation, an alternative synthetic route was designed to obtain N-alkylated analogues **4**. As depicted in Scheme 3, Suzuki coupling of triflate **7** with 2-bromophenylboronic acid yielded compound **12** in 80% yield. Compound **12** was subjected to ester hydrolysis in the presence of NaOH to give the carboxylic acid **13**. Compound **13** was subsequently coupled with various amines in the presence of EDCI to form the corresponding amide **14** in 65-75% yield. Intramolecular Buchwald coupling of **14** in the presence of Pd(OAc)₂, BINAP and Cs₂CO₃ in dry toluene at 90 °C for 12 h provided the cyclization product **15** in 78-95% yield.¹⁶ Removal of the Boc group in **15** by TFA afforded **16** (87-92% yield), which was then treated with formalin and NaCNBH₃ in ethanol at 0 °C for 1 h to generate the desired product **4** in 71-90% yield.

Structural assignments for O-alkylated and N-alkylated isomers were made by 1-D and 2-D NMR experiments.¹⁷ The most distinct NMR signals between **3a** and **4a**¹⁸ are the ¹³C chemical shifts of C11 and C5 (Figure 4). As observed in the HSQC data, in compound **3a**, the ¹H signal of H11 (triplet) at 4.45 ppm exhibited a cross peak to C11 at 75.8 ppm, such a significant downfield shift is typical for a carbon that connects to an oxygen atom. On the other hand, for compound **4a**, the ¹³C chemical shift of C11 appeared at 46.1 ppm, which is common for a nitrogen bearing carbon. Long-range carbon–hydrogen couplings observed in the HMBC experiments further supported these assignments. For example, the carbonyl carbon in **4a** exhibited a peak at 160.6 ppm, as indicated by the HMBC cross peak between H11 and C5, while the corresponding C5 in **3a** was found at 130.4 ppm.

In summary, we have developed efficient methods for the synthesis of O- and N-alkylated products of 1,2,3,4-tetrahydrobenzo[c][2,7]naphthyrin-5(6H)-one. These compounds represent conformational restricted analogues of 4-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylates. Biological evaluation of these novel analogues is currently underway.

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18. Spectra data of selective compounds: compound **3a**, ^1H NMR (CDCl_3 , 400 MHz): δ 7.64 (d, J = 8.4 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.21–7.26 (m, 2H), 6.83–6.92 (m, 3H), 4.46 (t, J = 6.8 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.58 (s, 2H), 3.17 (t, J = 6.8 Hz, 2H), 3.02 (br s, 2H), 2.78 (t, J = 5.6 Hz, 2H), 2.55 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 156.8, 149.2, 148.0, 139.8, 136.6, 130.4, 130.1, 123.7, 122.8, 121.3, 119.8, 112.5, 112.2, 111.5, 75.8, 56.2, 56.1, 53.1, 51.4, 45.9, 34.3, 26.2 ppm; EIMS m/z 378.2 (M^+); HRMS (ESI/APCI) m/z found 377.1488, calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$ (M-H) 377.1485; **4a**, ^1H NMR (CDCl_3 , 400 MHz): δ 7.71 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 7.2 Hz, 1H), 6.82–6.93 (m, 3H), 4.50 (t, J = 8.0 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.56 (s, 2H), 3.03 (br s, 2H), 2.96 (t, J = 8.0 Hz, 2H), 2.77 (t, J = 4.8 Hz, 2H), 2.54 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.4, 149.1, 147.8, 140.1, 137.4, 131.1, 129.5, 126.2, 124.1, 124.0, 122.0, 120.8, 120.7, 114.1, 112.11, 112.07, 111.4, 56.0, 55.9, 53.4, 51.4, 45.9, 44.0, 33.4, 26.2 ppm; EIMS m/z 378.2 (M^+); HRMS (ESI/APCI) m/z found 379.2020, calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$ (M+H) 379.2022.

Figure 1.
Structures of compounds **1** and **2**.

Figure 2.
General structures of the target analogues.

Figure 3.
Retrosynthetic plan.

Figure 4.
Characteristic carbon–hydrogen couplings (HSQC and HMBC) observed for **3a** and **4a**.

Scheme 1.
Synthesis of intermediate 5.

Scheme 2.
Synthesis of O-alkylated analogues **3a-3d**.

Scheme 3.
 Synthesis of N-alkylated analogues **4a-4e**.