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The Development of a Short Route to the API Ropinirole hydrochloride.

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A four-step, three-stage synthesis of the API ropinirole hydrochloride has been developed from a commercially available naphthalene derivative. The new route has half the step-count and twice the overall yield of the current manufacturing process. Key features of the synthesis are a regioselective Birch reduction and an ozonolysis with concomitant ring closure to induce the required ring contraction.

Introduction

Ropinirole hydrochloride (2) was introduced by Smith, Kline and French as a non-ergoline, dopaminergic drug to alleviate symptoms related to Parkinson’s disease by activating postsynaptic D2 CNS receptors. In 2005 the FDA also approved it as a treatment for restless leg syndrome and a further repurposing has seen it used to treat selective serotonin reuptake inhibitor-induced sexual dysfunction, which is purported to result from the D3 agonistic activity of the drug. Worldwide sales of ropinirole-based medicines peaked at around $500 million per annum prior to its patent expiry in May 2008, which heralded the introduction of several generic medicines. It is currently marketed under various trade names, including Requip, Ronirol and Adartrel, and compliments other symptomatic drug therapies based on ergot alkaloids, anticholinergics, monoamine-oxidase (MOA-B) inhibitors and benzodiazepines.

Commercially, ropinirole hydrochloride (2) is prepared from isochroman in 12–25% overall yield using a nine step, five stage sequence (Scheme 1). Although alternative routes to the active pharmaceutical ingredient (API) have been developed, none has usurped the original manufacturing process. Key transformations include a Sommelet oxidation (step b) and a Royer cyclisation reaction (step e), which both proceed in modest yield and display a degree of variability from experiment to experiment. Additionally, the route produces a number of halogenated byproducts.

With current drives towards the clean manufacture of fine chemicals, it seemed timely to develop new strategies for the synthesis of ropinirole hydrochloride (2). Though the costs associated with registration of a new manufacturing route usually make it unviable commercially, there seemed sufficient scope for improvement to warrant investigation. Herein we report our preliminary findings, which have led to the development of new laboratory scale syntheses of the API. Importantly, the routes avoid the capricious Sommelet oxidation and Royer cyclisation reactions with the shortest proceeding in twice the yield and half the step-count of the manufacturing route.
reconnection strategy outlined in Scheme 2. Thus, we were confident that the API 2 could be prepared from aldehyde 4 by reductive amination. In turn we hoped that the required oxindole 4 might be prepared by an oxidative cleavage of dihydronaphthalene 5 with concomitant oxidation of the intermediate hemiaminal. As the dissolving metal reduction of 1-aminonaphthalene 6 → 5 was a known procedure, it became the start point of our investigation.

Results and Discussion

As expected, the Birch reduction of 1-aminonaphthalene 6 with sodium in liquid ammonia proceeded smoothly to give our key intermediate 5 in 90% yield contaminated with traces of 5-amino-tetralin and the starting material 6 (Scheme 3). Although this was a pleasing result, repeat experiments exposed a degree of variation in the outcome of the reaction. This was traced to a sensitivity of the product 5 to aerial oxidation, with CDCl₃ solutions of 5 becoming contaminated with 1-aminonaphthalene 6 on prolonged standing. Progress was slowed further when our planned oxidative cleavage of 5 with ozone gave rise to a complex product mixture under a wide range of conditions. Switching to a Lemieux-Johnson type oxidation (OsO₄; NaIO₃) proved equally intractable, leading us to question the compatibility of the aniline subunit under these cleavage conditions. A report by Pleininger et al. on the ozonolysis of related aromatic amides indicated that its protection might prove beneficial. This was borne out when ozonolysis of a methanolic solution of the Boc derivative 7 led to the formation of acid 8 in 20% yield following a reductive work-up.

As ozonolysis in methanol had given rise to a product at a higher oxidation level than we required, it seemed sensible to perform a solvent screen in the hope of attaining the desired aldehyde 10. Preliminary results offered encouragement, with the reaction in EtOAc producing the desired oxindole 10 in 20% yield together with its presumed precursor, hemiaminal 9, in 66% yield (Scheme 3). Alas, attempts to optimise the reaction for oxindole 10 went unrewarded. Notably, a Lemieux-Johnson type oxidation of 7 also gave hemiaminal 9 as the primary product, as did Motherwell and Gavrilidis’ protocol for conducting ozonolyses under continuous flow.

Indeed, the latter proved to be the method of choice for advancing our synthesis due to its ease of optimisation and its consistency in giving hemiaminal 9 in 75% yield following a PPh₃ quench.

At this juncture we examine various methods to effect the oxidation of hemiaminal 9 to oxindole 10 and found that a propensity for elimination to the corresponding indole consistently thwarted such efforts. By contrast, we were able to realise the reductive amination of 9 to 11 in quantitative yield. Again, direct oxidation of hemiaminal 11 to ropinirole was examined with an array of oxidants (including ozone, Dess–Martin periodinane, IBX, TEMPO/I₃ and MnO₂) but in all cases formation of ropinirole 13 was compromised by competitive elimination and deprotection to indole 12. As indole 12 was a known precursor of ropinirole, and could be prepared from hemiaminal 11 in excellent yield by the action of TFA, we decided to incorporate it as an intermediate in our synthesis. Thus, oxidation of indole 12 to ropinirole 13 was effected using NBS in tBuOH, giving us an overall yield of 37% for the sequence as a whole.

Development a Shorter and More Efficient Synthesis

The difficulties encountered with the control of oxidation level at key carbon centres had proven a major bugbear of our synthesis. On reflection, it seemed likely that its step-count would be reduced if the oxidation level at C-7 in our starting naphthalene were raised, as this would render the final two-step oxidation sequence redundant. A search of available chemicals revealed that 8-amino-2-naphthol 16 was a product of commerce. It therefore seemed sensible to examine its potential as a precursor to ropinirole hydrochloride 2 (Scheme 4).

Our initial plan was to employ a single protecting group for the aniline and phenol residues in 8-amino-2-naphthol 16 (R = R’, Scheme 4). To that end, diacylation was effected in quantitative yield. Unfortunately, dissolving metal reductions of the resulting naphthalene 17 failed to generate dihydronaphthalene 19 due to the sensitivity of the aryl/vinyl acetate functions under the reaction conditions (Scheme 5). Consequently, it was found necessary to proceed via the more
robust methyl vinyl ether 22. Its formation by Birch reduction of naphthalene 20 also proved capricious due to the propensity for aeral oxidation of the product back to the starting material. Nonetheless, performing the work-up with haste provided vinyl ether 22 in an acceptable 50% yield. Ozonolysis of vinyl ether 22 to aldehyde 21 also proceeded modestly and it was found necessary to use polymer-supported PPh₃ in the work-up phase in order to attain the product in a good state of purity. Reductive amination of 21 with concomitant cyclisation, completed the synthesis of ropinirole 13, albeit slow and in low yield. Although we were confident that the yields attained in the latter stages of this synthesis could be improved significantly, success with an alternative strategy had removed any incentive to do so.

Conclusions

In conclusion, we have developed a short and practicable synthesis of the API ropinirole hydrochloride 2 from commercial naphthalene 24. In the laboratory it proceeds in 45% overall yield and has a step-count half that of the current manufacturing process. Attractive features include i) the ability to run the first two steps concurrently in a single pot reducing the stage count to three; ii) a greatly reduced waste stream that is devoid of organic halides and iii) the option to run the oxidative cleavage step, 26 → 27, under continuous flow. As there remains scope for further optimisation through up-scaling, the case for further development of the aforementioned synthesis towards the bulk scale manufacture of ropinirole hydrochloride 2 could soon be a compelling one.

Experimental Section

1-Amino-5,8-dihydronaphthalene (5). Following the procedure of Rogers et al. 20 To a solution of aminonaphthalene 6 (50.0 g, 0.35 mol) in Et₂O (250 mL) were added BuOH (35 mL) and NaH (200 mL). Na (22.0 g, 0.94 g-atom) was added portionwise to the refluxing solution over 3 h, followed by additional BuOH (35 mL) and EtOH (70 mL) in two equal portions over 1 h. The solution warmed to RT over 20 h allowing NaH to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L). The organic phases were combined, dried (MgSO₄), concentrated in vacuo to afford the title compound as a yellow solid (98 g, 396 mmol). 1H NMR (500 MHz, CDCl₃): δ = 7.50 (app t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 6.11–5.90 (m, 2H), 3.64 (s, 2H), 3.51 (br s, 1H), 3.46–3.42 (m, 2H), 1.35–1.30 (m, 2H), 1.32–1.28 (m, 2H), 1.21–1.14 (m, 2H), 1.16–1.12 (m, 2H), 0.90–0.85 (m, 2H), 0.84–0.80 (m, 2H). The mixture was then placed in a sonication bath for 2 h then with extracted with Et₂O (3 × 150 mL). The organic phases were combined, dried (MgSO₄), warmed to RT and after 16 h was concentrated in vacuo to afford the title compound as a yellow solid (98 g, 396 mmol). 1H NMR (500 MHz, CDCl₃): δ = 7.50 (app t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 7.9 Hz, 1H), 6.11–5.90 (m, 2H), 3.64 (s, 2H), 3.51 (br s, 1H), 3.46–3.42 (m, 2H), 1.35–1.30 (m, 2H), 1.32–1.28 (m, 2H), 1.21–1.14 (m, 2H), 1.16–1.12 (m, 2H), 0.90–0.85 (m, 2H), 0.84–0.80 (m, 2H), 0.84–0.80 (m, 2H).

Ropinirole, NHBoc, R = Me, 90%

A short and practicable synthesis of the API ropinirole hydrochloride.

That alternative approach is summarised in Scheme 6 and began with the methylation of 8-amino-2-naphthalenol 16 to aryl methyl ether 23, itself a product of commerce. 19 A Birch reduction followed, leading to methyl vinyl ether 24 in near quantitative yield. Although the product proved susceptible to isomerisation to dihydronaphthalene 25 on standing, this was attenuated by Boc protection to carbamate 26. Pleasingly, ozonolysis of 26 proved facile in EtOAc, yielding aldehyde 27 in 71% yield. A reductive amination with acidic work-up then gave ropinirole 13 which, on treatment with HCl and recrystallization from CH₃CN, delivered the API 2 in a high state of purity.

2-(2-((tert-Butoxycarbonyl)amino)-6-(2-methoxy-2-oxoethyl)phenyl)acetic acid (8). Through a solution of carbamate 7 (368 mg, 1.50 mmol) in MeOH (15 mL) at −78 °C was bubbled a stream of O₃ (1–5% in O₂). When the solution turned blue, it was purged with O₂ for 10 min then NaBH₃ (153 mg, 4.04 mmol) was added. The solution was warmed to RT and after 16 h was concentrated in vacuo. Purification by column chromatography (1:1 Et₂O/MeOH) afforded the title compound as a yellow solid (87 mg, 0.30 mmol, 20%) MP 129–130 °C (aq. EtOH).

4-(6-(2-Amino-2-hydroxyethyl)phenyl)butanoyl chloride (9). Following the procedure of Rogers et al. 20 A solution of aminophenol 6 (50.0 g, 0.35 mol) in Et₂O (250 mL) was added BuOH (35 mL) and NaH (200 mL). Na (22.0 g, 0.94 g-atom) was added portionwise to the refluxing solution over 3 h, followed by additional BuOH (35 mL) and EtOH (70 mL) in two equal portions over 1 h. The solution warmed to RT over 20 h allowing NaH to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L). The organic phases were combined, dried (MgSO₄), warmed to RT over 20 h allowing NH₄H to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L). The organic phases were combined, dried (MgSO₄), warmed to RT over 20 h allowing NH₄H to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L). The organic phases were combined, dried (MgSO₄), warmed to RT over 20 h allowing NH₄H to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L). The organic phases were combined, dried (MgSO₄), warmed to RT over 20 h allowing NH₄H to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L). The organic phases were combined, dried (MgSO₄), warmed to RT over 20 h allowing NH₄H to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L). The organic phases were combined, dried (MgSO₄), warmed to RT over 20 h allowing NH₄H to evaporate. Sat. NH₄Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et₂O (3 × 1 L).
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**aldehyde**

**solution of aldehyde**

**343** (\([M+CH_3]^+\))

**NMR (100 MHz, CDCl_3)**: \(\delta = 9.69 \text{ (J, 2.0 Hz, 1H)}\), 7.38 (br s, 1H), 7.21 (app t, \(J = 7.8 \text{ Hz, 1H}\)), 6.84 (d, \(J = 7.6 \text{ Hz, 1H}\)), 6.01 (br s, 1H), 5.65 (d, \(J = 1.5 \text{ Hz, 2H}\)), 4.32 (dd, \(J = 17.2, 7.6 \text{ Hz, 1H}\)), 2.88 (s, \(J = 17.2 \text{ Hz, 2H}\)), 1.62 (s, 9H) ppm with some broadening of resonances due to rotamers;

**13C NMR (100 MHz, CDCl_3)**: \(\delta = 198.1 \text{ (C)}\), 153.2 (C), 140.8 (C), 128.7 (C), 128.0 (3CH), 121.7 (C), 113.7 (CH), 83.1 (CH), 82.7 (Cl), 40.8 (CH3), 34.4 (CH2), 28.4 (3 CH3) ppm with one C not observed; IR (neat): \(\nu = 3194, 2970, 2830, 1701, 1618, 1505, 1457, 1377, 1310, 758\); MS (ESI) \(+m/z\): 245 [M]+, 100%

**HRMS (ESI)**: \(+m/z\) calcd for C_{29}H_{28}N_{10}O_{3} [M+Na]+: 430.1999; found: 430.1996; these data being in accord with literature values.

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solution over 5 min then sat. NH₄Cl (1 mL) was added after a further 30 min. The NH₄Cl was allowed to evaporate and H₂O (5 mL) was added. The aqueous phase was extracted with EtOAc (3 × 50 mL) then the organic phases were combined, dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (10% MeOH in CH₂Cl₂) afforded the title compound as a beige solid (44 mg, 0.20 mmol, 50%) MP 204-205 °C (EtOAc) (lit. 191-192 °C). 1H NMR (400 MHz, d₆-DMSO): δ = 9.25 (br s, 1H), 7.22 (d, J = 7.7 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 4.85 (m, 1H), 3.55 (s, 3H), 3.34–3.44 (m, 2H), 3.24–3.24 (m, 2H), 2.05 (s, 3H) ppm; 13C NMR (100 MHz, d₆-DMSO): δ = 168.2 (C), 152.4 (C), 135.7 (C), 134.5 (C), 127.8 (C), 125.7 (CH), 124.8 (CH). 1H, 90.3 (s), 53.9 (CH), 29.1 (CH), 28.1 (CH) ppm; IR (neat): ν : 3263, 3037, 2836, 1687, 1658, 1538, 1218, 793; MS (ESI): m/z (%) : 281 ([M+CH₃CN+Na]+, 100%); HMRS (ESI): m/z calculated for C₃₇H₃₂N₂O₃Na [M+Na]+ : 529.0995; found: 529.0995; these data being in accord with literature values.18

Methyl 2-(2-acetamido-6-oxo-phenyl)acetate (21). Through a solution of methyl vinyl ether (22) [100 mg, 0.46 mmol] in EtOAc (100 mL) at −78 °C was bubbled a stream of O₂ (1%–5% in O₂). On disappearance of the pale yellow colour, the solution was purged with O₂ then polymer-bound PPh₃ (3 mmol/g, 385 mg, 1.15 mmol) was added. The solution was warmed to RT and after 16 h was concentrated in vacuo. Purification by column chromatography (60%–100% EtOAc in petrolio) afforded the title compound as a yellow oil (67 mg, 0.27 mmol, 58%) 1H NMR (400 MHz, CDCl₃): δ = 9.71 (t, J = 1.8 Hz, 1H), 8.57 (br s, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 3.84 (d, J = 1.8 Hz, 2H), 3.72 (s, 3H), 3.63 (s, 2H), 2.23 (s, 3H) ppm; 13C NMR (100 MHz, CDCl₃): δ = 198.5 (CH₂), 172.5 (168.8 Hz, 137.6 (C), 131.7 (C), 128.4 (CH₂), 128.0 (C), 125.8 (C), 124.9 (CH₂), 48.8 (CH₃), 34.2 (CH₃), 24.3 (CH₃) ppm; IR (neat): ν : 3259, 3017, 2954, 2843, 1720, 1664, 1526, 1283, 1161 (Ms (ESI): m/z (%) : 172 (M, 100%); HMRS (ESI): m/z calculated for C₂₄H₂₃NO₃Na : 272.0893; found: 272.0896.

Ropinirole (13). To a solution of aldehyde 21 (130 mg, 0.52 mmol) in CH₂Cl₂ (5 mL) was added 1H NMR (100 MHz, d₆-DMSO): δ = 7.74 (d, J = 9.1 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.21–7.24 (m, 2H), 7.08 (d, J = 2.2 Hz, 1H), 6.81 (d, J = 6.7 Hz, 1H), 4.02 (br s, 2H), 3.95 (s, 3H) ppm; 13C NMR (75 MHz, CDCl₃): δ = 157.2 (C), 140.9 (C), 130.2 (C), 129.8 (C), 124.7 (C), 123.9 (CH), 119.2 (CH), 118.2 (CH), 110.2 (CH), 99.8 (CH), 55.3 (CH) ppm; IR (neat): ν : 3389, 3327, 3242, 3028, 2881, 2825, 1693, 1647, 1627, 1277, 789; MS (ESI): m/z (%) : 215 ([M+CH₃CN]⁺, 100%); these data being in accord with literature values.18

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Notes and references

Please do not adjust margins
19 1-Aminonaphthalene 6 is widely available as a bulk chemical. At the time of publication it could be sourced for less than €4/kg. Similarly, 7-methoxynaphthalen-1-amine 24 was available from Far Top Ltd, China for €800/kg.