A convenient synthesis of 4-(2-hydroxyethyl)indolin-2-one, a useful intermediate for the preparation of both dopamine receptor agonists and protein kinase inhibitors

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Abstract This paper describes a practical approach to preparation of 4-(2-hydroxyethyl)indolin-2-one, a key intermediate in the synthesis of dopaminergic agonists such as ropinirole, a drug used in the treatment of Parkinson's disease and in the restless legs syndrome, and of two sets of protein kinase inhibitors. The sequence starts from commercially available 2-(2-methyl-3-nitrophenyl)acetic acid, which was converted in five steps into the desired target compound. This procedure offers a convenient alternative route to existing methodologies in terms of the milder reaction conditions, the ease of the operations, and the overall yield (59%).

Keywords D_2/D_3 agonists ● Heterocycles ● Indolin-2-ones ● One-pot synthesis ● Ropinirole ● Synthetic improvement

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Introduction

Ropinirole (Requip®, Ropark®, Adartrel®, **1**), a $D_2/D_3/5\text{-}HT_{1A}$ receptor agonist (Fig. 1), is currently being used or tested for the treatment of a variety of disorders including Parkinson's disease [1], bipolar depression [2], and restless leg syndrome [3]. Recently, ropinirole has also been tested as a treatment for cocaine abuse and is reported to be effective in reducing the subjective "rush" of and craving for cocaine [4, 5]. A few among the known synthetic routes to this drug substance involve 4-(2-hydroxyethyl)indolin-2-one (**2**) as key intermediate (Fig. 1) [6-8]. Moreover, in the framework of a research project aimed at the pharmacological investigation of novel dopaminergic compounds, we designed a new series of ligands (**4**) incorporating the molecular skeleton of ropinirole (C. Matera et al., unpublished results). For such a purpose, we needed 4-[2-(propylamino)ethyl]indolin-2-one (**3**) as synthetic intermediate, which in turn can be easily derived from the primary alcohol **2** (Fig. 1). Compound **2** also represents an important building block in the synthesis of two sets of protein kinase inhibitors such as **5a** and **5b** (Fig. 1), potentially useful as anticancer agents [9-14].

< Fig. 1 >

Since we needed to prepare intermediate **2** of established importance to medicinal chemistry, we first thought to follow the synthetic procedures already reported in the literature, but, due to such disadvantages as long steps, low yields, and inconvenient operations, we came to develop a more convenient synthetic sequence.

Results and Discussion

Initially, we evaluated a known preparation of **2** [6, 7, 15], as depicted in Scheme 1. This six-step route makes use of cheap reagents and has been applied on a relatively large scale to the synthesis of ropinirole, though it is characterized by an overall yield of just 29%. In particular, in our hands the cyclisation step (**9**-**10**) was very low yielding (about 8%), thus discouraging the application of the whole synthetic sequence. Worth noting, a high yield procedure for the synthesis of **2** was recently claimed in the patent literature, based on slight modifications of the protocol illustrated in Scheme 1 [8]. Nevertheless, according to our evaluation, the overall yield of this variant was 10% only.

< Scheme 1 >

Thus, we aimed at synthesizing the target secondary amine **3** bypassing the primary alcohol **2**. We took as a model the original synthesis of ropinirole (**1**, Scheme 2) [16, 17] from commercially available 2-methyl-3-nitrophenylacetic acid (**12**), by replacing di-*n*-propylamine with benzyl-*n*-propylamine. However, this synthetic route resulted in many by-products and required complicated purification steps, affording the desired secondary amine **3** only in trace amounts (Scheme 2).

< Scheme 2 >

Therefore, we decided to modify the latter synthetic procedure as reported in Scheme 3, and prepared to this end 2-(2-methyl-3-nitrophenyl)ethanol (**17**) in 96% yield by reduction of **12** with borane tetrahydrofuran complex [18]. Subsequent protection of the hydroxyl group to the corresponding benzyl ether **18**, followed by homologation with diethyl oxalate and sodium hydride in DMF, provided the intermediate pyruvic acid ethyl ester **19** in a considerably higher overall yield (69%) in comparison to the preparation of **15b** in the previous synthetic route [19]. Treatment of **19** with hydroperoxide anion afforded the protected phenylacetic acid **20** (99% yield), which, upon palladium-catalyzed hydrogenation in ethanol, underwent an efficient one-pot

cyclisation/deprotection giving rise to the desired indolin-2-one **2** in 90% yield.

< Scheme 3 >

Compound **2** was finally converted into the corresponding secondary amine **3** via nucleophilic substitution of the bromide **21a** or the tosylate **21b** (Scheme 3). In analogy to what known for similar cases [20], nucleophilic substitution leading to **3** was more efficient with tosylate rather than bromide. In fact, the reaction between bromide **21a** and *n*-propylamine produced similar amounts of substitution (**3**, 45% yield) vs. elimination (**22**, 35% yield) product. Conversely, the use of tosylate **21b** selectively promoted the substitution reaction and markedly improved the secondary amine **3** (87% yield) to styrene **22** (5% yield) ratio.

In conclusion, we developed an improved synthetic route to 4-(2-hydroxyethyl)indolin-2-one (**2**), characterized by a lower number of steps and a considerably higher overall yield (59% vs. 29%) with respect to the most convenient known protocol. Moreover, our synthesis makes use of readily available and cheap reagents, simple work-up procedures, and requires only one chromatographic purification in five steps. This synthetic route allowed us an easy access to a set of novel dopaminergic compounds,

whose results will be published in due course, as well as it could be used alternatively to the known procedures for the synthesis of the drug ropinirole (**1**) or for the synthesis of potential anticancer agents acting as protein kinase inhibitors (**5a** and **5b**).

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Mercury 300 (^{1}H: 300.063 MHz, ^{13}C: 75.451 MHz) spectrometer at 20 °C. Chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hz. TLC analyses were performed on commercial silica gel 60 F254 aluminum sheets; spots were further evidenced by spraying with a dilute alkaline potassium permanganate solution or a phosphomolybdic acid solution (20 wt.% in ethanol). Preparative separations were performed using flash column chromatography on silica gel (60-200 mesh). Melting points were determined on a model B540 Büchi apparatus. Electrospray ionization (ESI) mass spectra were obtained on a Varian 320 LC-MS/ MS instrument. Data are reported as mass-to-charge ratio (m/z) of the corresponding positively charged molecular ions. Microanalyses (C, H, N) of new compounds agreed with the theoretical value within ±0.4%. All reagents were purchased from Sigma-Aldrich and used directly as obtained commercially, unless otherwise noted.

2-(2-Methyl-3-nitrophenyl)ethanol (**17**)

2-Methyl-3-nitrophenylacetic acid (**12**, 2.00 g, 10.25 mmol) was placed in a flame-dried round-bottomed flask under argon atmosphere and dissolved in 20 cm^3 THF. To this solution, 20.5 cm^3 1 M BH_3-THF (2 equiv) was added dropwise via syringe at 0 °C and stirred at room temperature for 3 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$, diluted with water, and extracted with ethyl acetate. The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo to afford 1.78 g (96%) **17** as a pale yellow oil. R_f = 0.4 (cyclohexane/ethyl acetate 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.63 (bs, 1H), 2.92 (t, 2H, J = 6.9 Hz), 3.78 (t, 2H, J = 6.9 Hz), 7.21 (dd, 1H, J = 7.6, 8.0 Hz), 7.37 (d, 1H, J = 7.6 Hz), 7.55 (d, 1H, J = 8.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0, 36.7, 62.3, 122.4, 126.5, 130.7, 134.1, 140.1, 151.6 ppm; MS: *m*/*z* calcd. for $C_9H_{13}NO_4$ [M+H_2O] 199.08, found 199.1.

1-[(2-Methyl-3-nitrophenethyloxy)methyl]benzene (**18**, $C_{16}H_{17}NO_3$)

60% Sodium hydride (w/w) in mineral oil (0.41 g, 10.31 mmol) was added portionwise to a well-stirred solution of 1.78 g **17** (9.82 mmol) in 15 cm^3 dry THF at 0 °C under argon. After 30 min, a solution of 1.76 g benzyl

bromide (10.31 mmol) in 12 cm^3 dry THF was added dropwise and the reaction mixture was allowed to stir at room temperature for 8 h. The reaction was then quenched with cold water, poured into a saturated solution of NH_4Cl, and extracted with ethyl acetate. The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo to yield 2.53 g **18** (95%) as a yellow oil. R_f = 0.4 (cyclohexane/ethyl acetate 9:1); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.04 (t, 2H, *J* = 6.9 Hz), 3.72 (t, 2H, *J* = 6.9 Hz), 4.56 (s, 2H), 7.24 (dd, 1H, *J* = 7.6, 8.0 Hz), 7.35 (m, 5H), 7.43 (d, 1H, *J* = 7.6 Hz), 7.62 (d, 1H, *J* = 8.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 34.2, 69.8, 73.3, 122.4, 126.5, 127.8, 128.0, 128.7, 130.75, 134.0, 138.5, 140.6, 151.7 ppm; MS: *m*/*z* calcd. for $C_{16}H_{19}NO_4$ [M+H_2O] 289.13, found 289.1.

Ethyl 3-[2-[2-(benzyloxy)ethyl]-6-nitrophenyl]-2-oxopropanoate (**19**, $C_{20}H_{21}NO_6$)

60% Sodium hydride (w/w) in mineral oil (1.28 g, 32.05 mmol) was added portionwise to a well-stirred solution of 1.74 g **18** (6.41 mmol) in 15 cm^3 dry DMF at 0 °C under argon. After stirring for 20 min at room temperature (reddish color), a solution of 7.50 g diethyl oxalate (51.31 mmol) in 15 cm^3 dry DMF was added dropwise and the reaction mixture was allowed to stir at room temperature for a further 8 h. The reaction was

then quenched with a saturated solution of NH_4Cl, diluted with water, and extracted with ethyl acetate. The collected organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 4:1) to afford 1.71 g (72%) **19** as a yellow oil. R_f = 0.5 (cyclohexane/ethyl acetate 8:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, 3H, J = 7.2 Hz), 2.97 (t, 2H, J = 6.6 Hz), 3.65 (t, 2H, J = 6.6 Hz), 4.37 (q, 2H, J = 7.2 Hz), 4.45 (s, 2H), 4.57 (s, 2H), 7.31 (m, 6H), 7.52 (d, 1H, J = 7.7 Hz), 7.90 (d, 1H, J = 8.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 30.0, 34.1, 39.5, 63.1, 70.3, 73.3, 123.7, 127.2, 127.8, 128.0, 128.7, 135.5, 138.1, 142.1, 150.1, 160.7, 189.8 ppm; MS: *m*/*z* calcd. for $C_{20}H_{20}NO_6^-$ $[M–H^+]^-$ 370.13, found 370.1.

2-[2-[2-(Benzyloxy)ethyl]-6-nitrophenyl]acetic acid (**20**, $C_{17}H_{17}NO_5$)

To an ice-cooled solution of 0.91 g **19** (2.46 mmol) in 5 cm^3 THF was added 2% NaOH (6.38 mmol). After stirring for 10 min at 0 °C, 30% H_2O_2 (4.92 mmol) was added and the solution was brought to room temperature and stirred for 1 h. The pH was then adjusted to 1.5 by careful addition of 2 N HCl and the reaction mixture was extracted with ethyl acetate. The pooled organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield 0.77 g (99%) **20** as an

orange oil. R_f = 0.5 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03 (t, 2H, J = 6.3 Hz), 3.69 (t, 2H, J = 6.3 Hz), 4.05 (s, 2H), 4.49 (s, 2H), 7.32 (m, 6H), 7.51 (d, 1H, J = 7.7 Hz), 7.86 (d, 1H, J = 8.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0, 34.0, 70.1, 73.4, 123.6, 127.7, 127.9, 128.2, 128.7, 128.8, 135.3, 138.0, 141.6, 150.6, 175.5 ppm; MS: *m*/*z* calcd. for $C_{17}H_{16}NO_5^-$ $[M–H^+]^-$ 314.10, found 314.1.

4-(2-Hydroxyethyl)indolin-2-one (**2**)

A mixture of 0.51 g **20** (1.63 mmol) and 60 mg 10% Pd-C catalyst in 10 cm^3 EtOH was hydrogenated under balloon pressure at room temperature for 5 h. The catalyst was then removed by filtration on Celite® and the solvent evaporated in vacuo to afford 0.26 g (90%) **2** as a white solid. R_f = 0.3 (ethyl acetate); m.p.: 146-148 °C, crystallized from CH_3CN (Ref [7] 147-149 °C); ^{1}H NMR (300 MHz, CD_3OD): δ = 2.76 (t, 2H, J = 6.6 Hz), 3.48 (s, 2H), 3.76 (t, 2H, J = 6.6 Hz), 6.72 (d, 1H, J = 7.7 Hz), 6.86 (d, 1H, J = 7.7 Hz), 7.13 (dd, 1H, J = 7.7 Hz) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ = 35.0, 36.2, 61.8, 107.6, 122.8, 125.1, 127.8, 135.6, 143.1, 178.7 ppm; MS: *m*/*z* calcd. for $C_{10}H_{12}NO_2^+$ $[M+H^+]^+$ 178.09, found 178.1.

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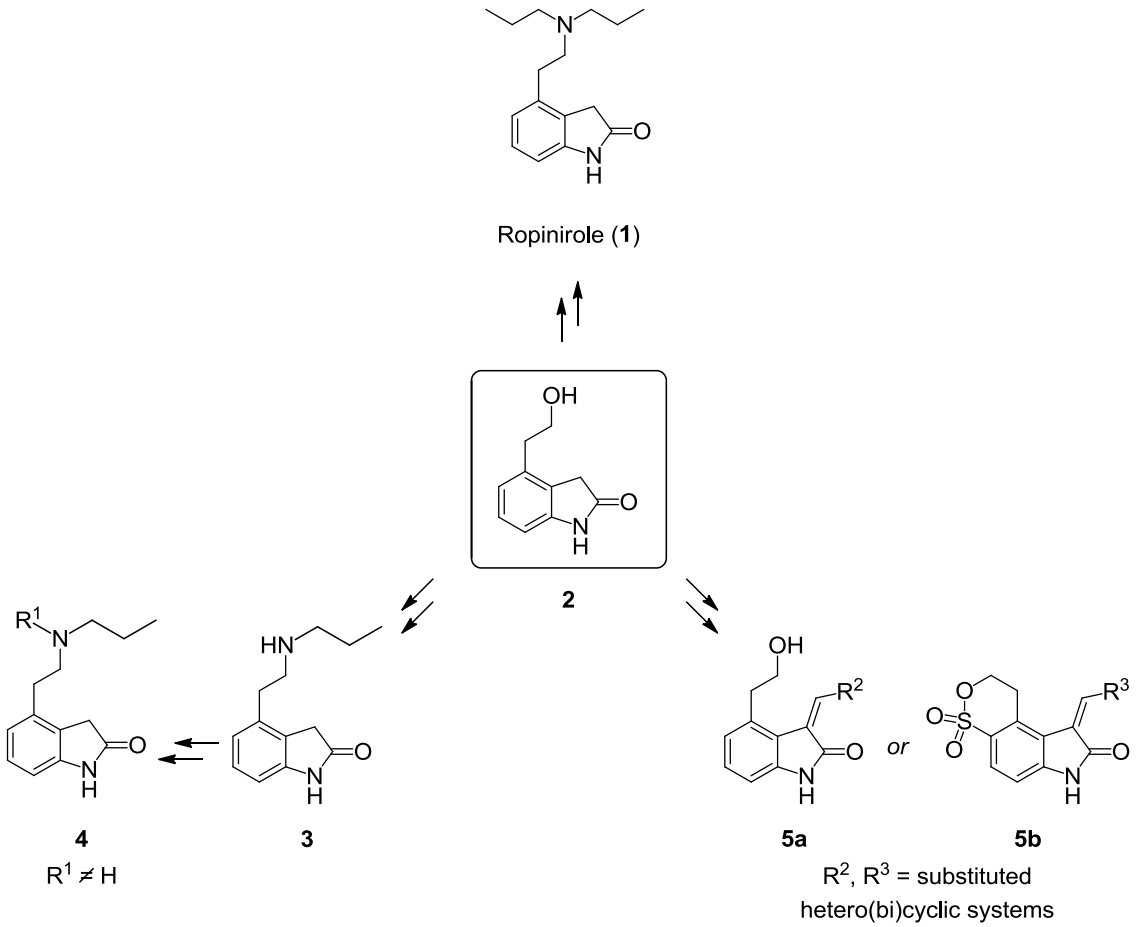
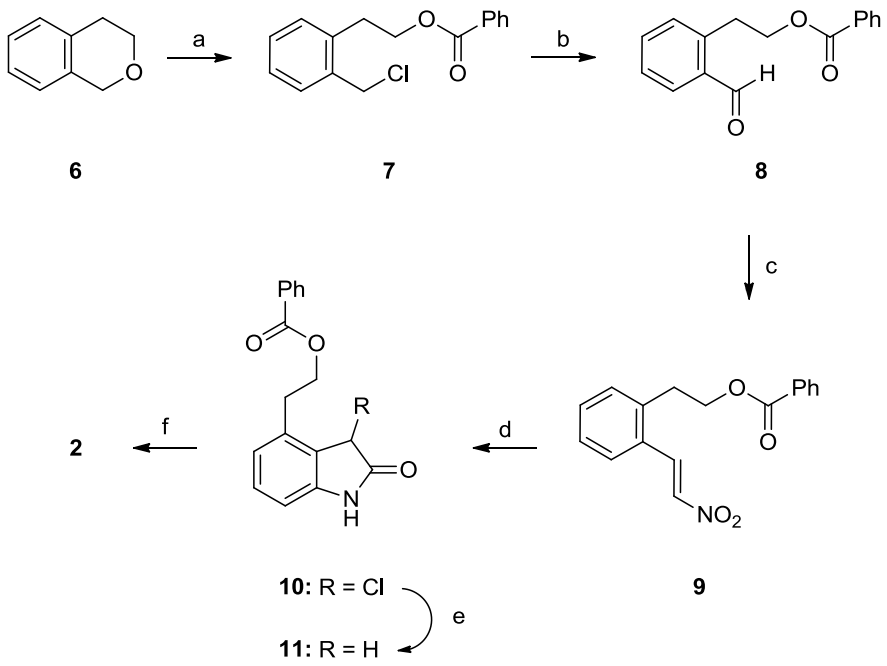
Figure caption

Fig. 1 Structure of target compound **2** and its application in medicinal chemistry

Figure 1

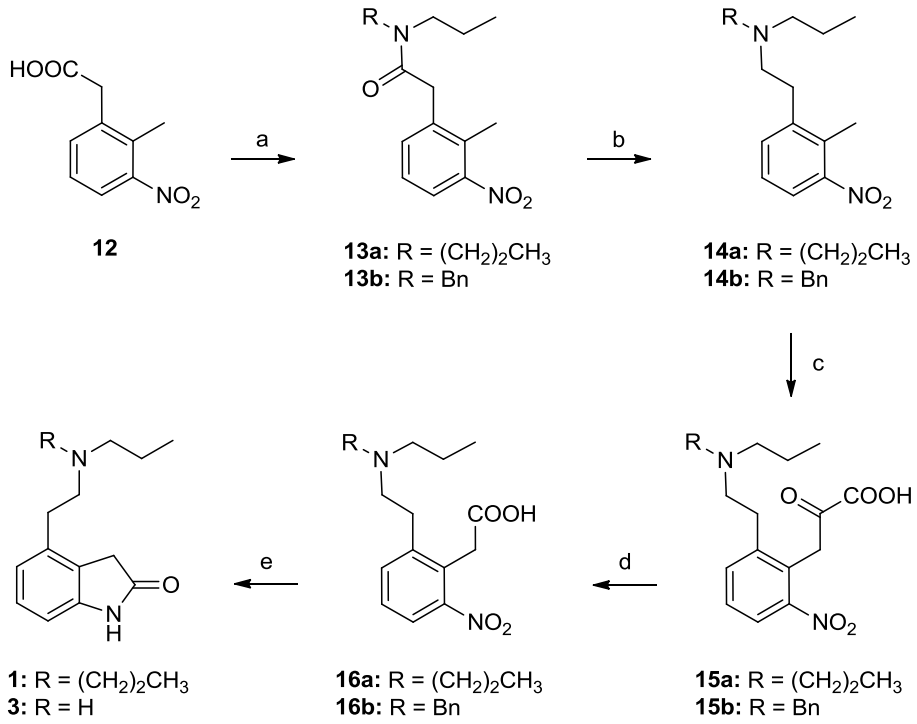


Scheme 1



Reagents and conditions: (a) cat. $ZnCl_2$, PhCOCl, CH_2Cl_2, reflux; (b) hexamethylenetetramine, EtOH, then 50% aq. AcOH; (c) nitromethane, *n*-butylamine, AcOH, MeOH, 20 °C; (d) $FeCl_3$, AcCl, CH_2Cl_2, 0-5 °C; (e) $N_2H_4xH_2O$, 10% Pd-C, MeOH; (f) NaOH, H_2O, MeOH, reflux.

Scheme 2



12

13a: R = $(CH_2)_2CH_3$
13b: R = Bn

14a: R = $(CH_2)_2CH_3$
14b: R = Bn

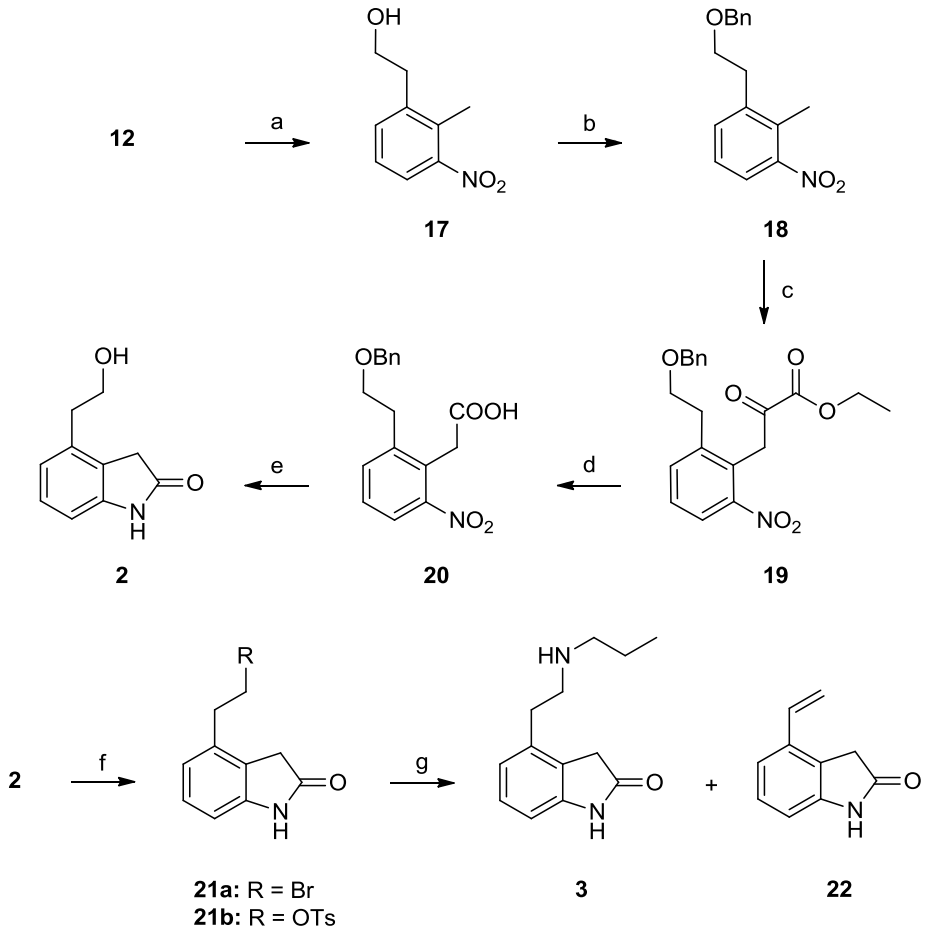
15a: R = $(CH_2)_2CH_3$
15b: R = Bn

16a: R = $(CH_2)_2CH_3$
16b: R = Bn

1: R = $(CH_2)_2CH_3$
3: R = H

Reagents and conditions: (a) 1. $SOCl_2$; 2. di-*n*-propylamine (for **13a**) or benzyl-*n*-propylamine (for **13b**) and Na_2CO_3, toluene, H_2O; (b) BH_3-THF; (c) K metal, abs. EtOH, dry Et_2O, diethyl oxalate; (d) 30% H_2O_2, 2% NaOH; (e) H_2, 5% Pd-C, EtOH.

1 *Scheme 3*



Reagents and conditions: (a) BH_3-THF; (b) benzyl bromide, 60% NaH, dry THF; (c) 60% NaH, dry DMF, diethyl oxalate, 0 °C to rt; (d) 30% H_2O_2, 2% NaOH; (e) H_2, 10% Pd-C, EtOH; (f) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt (for **21a**) or *p*-toluenesulfonyl chloride, pyridine, CH_2Cl_2, 0 °C to rt (for **21b**); (g) *n*-propylamine, reflux.

2

3

4

Graphics for use in the Table of Contents