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Research Paper

A Facile Synthesis of Norbuprenorphine

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Abstract: A short and efficient synthesis of norbuprenorphine, a primary active metabolite of buprenorphine, using von Braun N-dealkylation is disclosed.

Introduction

Buprenorphine (BUP, **1**) (Figure 1), a thebaine derivative and an opioid class analgesic acts as a partial agonist at the μ- and δ-receptors and has a competitive antagonist activity at the κ-receptors.[1] It is used at low doses (ranging from 0.3– 0.6 mg) in the treatment of moderate to severe pain by intravenous, intramuscular, and sublingual routes and at high doses by the sublingual route (up to 16 mg/day, in combination with naloxone in some countries) in opioid replacement therapy.[2] The rapid metabolism of BUP through *N*-dealkylation in the liver primarily by CYP3A4 isozyme of the cytochrome P450 enzyme system produces norbuprenorphine (Nor-BUP, **2**).[3] Subsequently, BUP **1** and nor-BUP **2** undergo extensive phase II metabolism to form *O*-glucuronides; buprenorphine-3-β-D-glucuronide (BUP-GLU, **3**) and norbuprenorphine-3-β-D-glucuronide (Nor-BUP-GLU, **4**).[4] These metabolites **2-4** (Figure 1) are present in the circulation at concentrations greater than or equal to that of BUP **1**. Recent studies have demonstrated that all these metabolites, specially nonbuprenorphine, are biologically active.[5] Norbuprenorphine is a full agonist[1] at the μ- and δ-receptors and partial agonist at the κ-receptors and because of its clinical importance, along with buprenorphine it is being studied extensively.[6] Being a narcotic class of compounds, the availability and supply of norbuprenorphine is highly regulated. Besides, the available material from some vendors is very expensive. This hampers research using norbuprenorphine as starting material in chemistry and test item in drug discovery field. Recently short synthesis of buprenorphine (**1**)[7] and Nor-BUP-GLU (**4**)[8] were reported in literature. But to the best of

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our knowledge, there is no report on the synthesis of norbuprenorphine in literature. We describe herein a short and efficient synthesis of norbuprenorphine **2** from buprenorphine **1**.

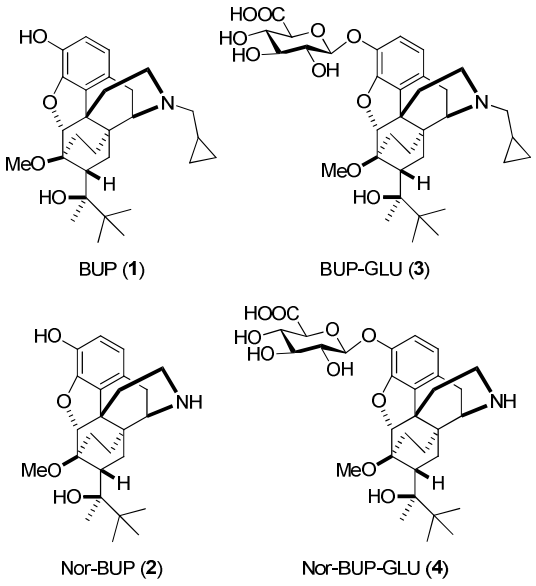
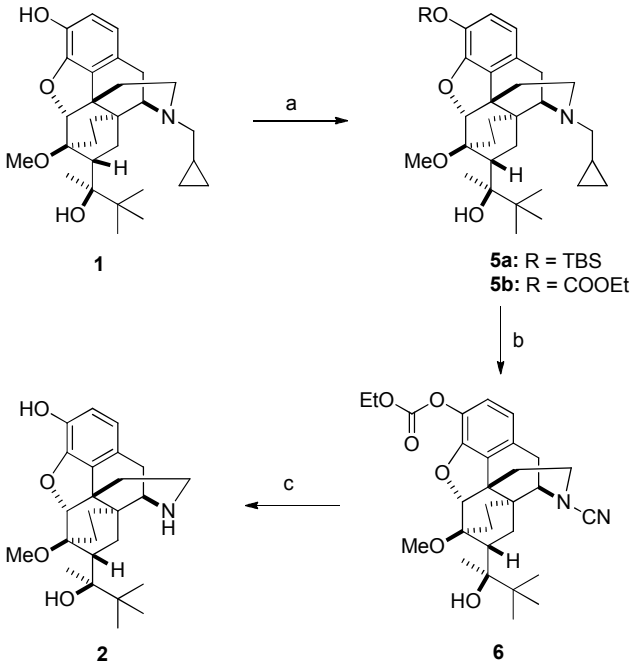


Figure 1. Structure of buprenorphine, norbuprenorphine and their *O*-glucuronides

Results and discussion

The overall strategy to synthesize norbuprenorphine from buprenorphine involved cyanogen bromide mediated von Braun N-dealkylation of buprenorphine to N-nitrile intermediate followed by hydrolyze to the corresponding secondary amine. Though von Braun N-demethylation has appeared in literature repeatedly,[9] the dealkylation of N-cyclopropylmethyl group was unprecedented. To this endeavor, initially we employed TBS ether protection of phenolic hydroxyl group to afford compound **5a**. The treatment of **5a** with CNBr was very sluggish and the reaction was complicated due to desilylation of TBS ether under various conditions. This led us to choose more stable carbamate protecting group on phenolic moiety which was thought to be beneficial as well as it can easily be de-protected along with the *N*-nitrile group in the later stage employing alkaline conditions.



Scheme 1. Reagents and conditions: (a) TBDMSCl, Imidazole, DMF, 25 °C, 16 h, 81% (for **5a**) and $ClCO_2Et$, Et_3N, CH_2Cl_2, 25 °C, 2 h, 100% (for **5b**); (b) CNBr, K_2CO_3, CH_2Cl_2, 25 °C, 72 h, 74%; (c) KOH, Digol, 200 °C, 20 min, 31%.

Compound **1** was converted to compound **5b** in high yield by the treatment of 1.5 eq. of ethyl chloroformate in dichloromethane along with base at room temperature. Without further purification, compound **5b** was subjected to von Braun reaction using cyanogens bromide (6.0 eq.) in the presence of potassium carbonate as base at 25 ˚C. The conversion of *N*-cyano compound **6** from **5b** was found to be very sluggish and cyanogen bromide was required to be added in portion. It was also observed that if cyanogen bromide was added at a time into the reaction, the reaction did not proceed to completion whereas portion wise addition of cyanogens bromide at regular intervals showed noticeable increase in rate of reaction and the reaction

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proceeded to completion. The reaction progress was monitored by TLC and upon completion the compound **6** was isolated by column chromatography in 74% yield. With *N*-cyano compound **6** in hand, we turned our attention to its conversion to norbuprenorphine **2**. The compound **6** was suspended in digol at room temperature, and potassium hydroxide was added to suspension in one portion. The mixture was immersed in the preheated oil bath at 200 °C for 20 min. The reaction progress was monitored by TLC. It was noticed that prolong heating at high temperature or gradual increase of the bath temperature to 200 °C led to decomposition of the reaction mixture. Upon completion of the reaction (judged by the disappearance of compound **6**) the reaction mass was cooled to room temperature and worked up following usual process to furnish compound **2** in good yield. Pure sample of **2** (98% pure by HPLC) was obtained by crystallization from acetone as off white solid.

Conclusion

In conclusion, we have developed an efficient, simple and facile method for the synthesis of norbuprenorphine from buprenorphine in good yield. This process will allow researcher to quickly make norbuprenorphine which in turn will have significant impact on research using norbuprenorphine as starting material in chemistry and as a test item in drug discovery field.

Experimental

Unless otherwise stated, all non-aqueous reactions and distillations were carried out under an atmosphere of dry nitrogen in dried glassware. Commercial grade reagents and solvents were used as received. When necessary, solvents and reagents were dried prior to use. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel aluminium support plates that have been bought from Merck. Visualization was accomplished by irradiation under a 254 nm UV lamp. ^{1}H NMR spectra were recorded on a Varian 400 MHz. ^{13}C NMR spectra were recorded at 100 MHz using Varian 400 MHz instrument. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. Unless otherwise noted, all "*J*" refers to $^{3}J_{HH}$ coupling constant. All reported compounds were homogeneous by thin layer chromatography (TLC) and by NMR. IR spectra were recorded as KBr pallet with a Shimadzu IR-Prestige-21 instrument and only diagnostic and/or intense peaks are reported. Mass spectra were obtained on a low resonance Q-trap machine in electron spray mode. HRMS spectra were with Waters LCT Premier XE (Micromass Oa-TOF) instrument.

Preparation of compound 5a: Buprenorphine hydrochloride (**1**) (0.107 g, 0.212 mmol) was suspended in DMF (5 mL) at room temperature, and to it was added imidazole (0.05 g, 0.735 mmol) followed by TBDMS chloride (0.035 g, 0.232 mmol). The reaction mixture was stirred at room temperature overnight, diluted with ethyl acetate (25 mL), and washed with brine solution (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum and the crude product was purified by column chromatography to give compound **5a** as a white solid (0.1 g, 80.6 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.60 (d, J = 7.8 Hz, 1H), 6.48 (d, J = 8.3 Hz, 1H), 5.90 (s, 1H), 4.45 (s, 1H), 3.54 (s, 3H), 3.00-2.80 (m, 3H),

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2.62 (dd, J = 11.9, 5.1 Hz, 1H), 2.37-2.10 (m, 5H), 1.77 (m, 1H), 1.35-1.20 (m, 5H), 1.05 (s, 9H), 0.98 (s, 9H), 0.86 (s, 2H), 0.81 (m, 1H), 0.72 (m, 1H), 0.52-0.45 (m, 2H), 0.198 (s, 3H), 0.164 (s, 3H), 0.13 (m, 2H); MS (ESI): *m/z* 582 (M + H).

Preparation of compound 5b: Buprenorphine hydrochloride (**1**) (1.08 g, 2.14 mmol) was suspended in dichloromethane (50 mL) at room temperature, and to it was added ethyl chloroformate (0.3 mL, 3.15 mmol) in one portion followed by triethylamine (0.9 mL, 6.45 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with dichloromethane (25 mL), and washed with saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was re-extracted with dichloromethane (20 mL), and the combined organic layer was dried over Na_2SO_4 and concentrated under vacuum to give compound **5b** as a white solid (1.1 g, 100%). IR (KBr, cm^{-1}): 3444, 3061, 2981, 2954, 2929, 1760, 1611.; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.90 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 5.90 (s, 1H), 4.45 (s, 1H), 4.29-4.27 (m, 2H), 3.54 (s, 3H), 3.02-3.01 (m, 2H), 3.00-2.98 (m,1H), 2.62 (dd, J = 11.9, 5.1 Hz, 1H), 2.37 (dd, J = 12.6, 6.0 Hz, 1H), 2.40-2.27 (m, 2H), 2.23 (dd, J = 18.3, 6.5 Hz, 1H), 2.17 (dd, J = 9.8, 9.8 Hz, 1H), 1.99 (ddd, J = 12.6, 12.6, 5.6 Hz, 1H), 1.86-1.84 (m, 1H), 1.78-1.76 (m, 1H), 1.69 (dd, J = 12.8, 2.5Hz, 1H), 1.36-1.34 (m, 6H), 1.32 (dd, J = 18.9, 9.2 Hz, 1H), 1.09-1.07 (m, 1H), 1.05 (s, 9H), 0.82-0.80 (m, 1H), 0.73-0.71 (m, 1H) ,0.52-0.45 (m, 2H), 0.14-0.12 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 153.1, 149.5, 134.7, 133.9, 131.8, 121.6, 119.2, 98.2, 80.6, 79.2, 64.8, 59.4, 58.0, 52.5, 46.2, 44.2, 43.4, 40.2, 35.9, 35.3, 33.3, 29.7, 26.3, 23.2, 19.8, 17.4, 14.1, 9.4, 4.1, 3.2; MS (ESI): *m/z* 540 (M + H); HRMS calcd for $C_{32}H_{46}NO_6$ 540.3325, found: 540.3320.

Preparation of compound 6: To a suspension of compound **5b** (1.0 g, 1.85 mmol) in chloroform (50 mL) at room temperature was added solid K_2CO_3 (0.4 g, 2.89 mmol) in one portion. After stirring for 10 min, cyanogen bromide (1.2 g, 11.3 mmol) was added portion wise. The reaction mixture was stirred at room temperature for 72 h and diluted with additional chloroform (50 mL). The solid was filtered off and the filtrate was concentrated under vaccum and the crude was purified by column chromatography (20% EtOAc in hexane) to afford compound **6** (0.7 g, 74%). IR (KBr, cm^{-1}): 3424, 3062, 2956, 2922, 2879, 2205, 1761, 1611, 1452; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.90 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 5.70 (s, 1H), 4.5 (s, 1H), 4.29-4.27 (m, 2H), 3.50 (s, 3H), 3.50-3.30 (m, 1H), 3.40-3.20 (m, 2H), 3.00-2.80 (m, 1H), 2.6 (dd, J = 11.9, 5.1 Hz, 1H), 2.20-1.81 (m, 4H), 1.61-1.41 (m, 3H), 1.36-1.34 (m, 6H), 1.31-1.29 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 149.0, 131.6, 131.0, 130.7, 122.0, 118.8, 116.9, 96.6, 64.1, 58.5, 51.7, 44.0, 42.9, 40.5, 39.4, 34.4, 32.0, 31.7, 31.0, 28.7, 27.9, 25.4, 19.0, 16.2, 13.2; MS (ESI): *m/z* 533 (M + Na).

Preparation of Norbuprenorphine (2): Compound **6** (0.58 g, 1.135 mmol) was suspended in digol (5 mL) at room temperature, and KOH (0.58 g; 10.3 mmol) was added to suspension in one portion and stirred for 5 min. The mixture was immersed in the preheated oil bath at 200 °C for 20 min. The mixture was allowed to cool to room temperature, and diluted with ethyl acetate (50 mL). The organic layer was washed with water (2x25 mL), brine and dried over Na_2SO_4 and concentrated under vacuum. Crystallization of the crude solid from acetone afforded desired compound **2** as a white solid (250 mg, 31%). IR (KBr, cm^{-1}): 3417, 3292, 2954, 2916, 2843, 2694, 2623, 1851, 1731, 1635, 1605, 1473; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.70 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 7.9 Hz, 1H), 5.81 (s, 1H), 4.40 (s, 1H), 3.50 (s, 3H), 3.00-2.80 (m, 7H), 2.70-2.50 (m,

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1H), 2.30-2.11 (m, 1H), 1.90-1.60 (m, 4H), 1.41-1.39 (m, 4H), 1.36-134 (m, 6H), 1.21-1.19 (m, 2H), 1.10-1.08 (m, 1H), 1.05 (s, 9H), 0.81-0.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 138.3, 131.8, 127.0, 119.9, 117.5, 96.6, 80.5, 66.7, 54.0, 52.5, 46.3, 43.0, 40.4, 36.7, 35.3, 34.8, 33.7, 33.0, 29.5, 26.4, 20.3,18.5; MS (ESI): *m/z* 414 (M + H).

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