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Process Research Towards a Scalable Synthesis of the Muscarinic M_1 Receptor Subtype Selective Agonist MCD-386

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ABSTRACT: An efficient process for the M_1-selective muscarinic agonist MCD-386 has been developed that offers significant advantages over the original synthetic approach. The new process utilizes an improved preparation of a known symmetrical diamine ester, followed by elaboration to a symmetrical 5-substituted tetrahydropyrimidine. The new route avoids cryogenics and chromatography steps, circumvents an expensive protecting group strategy, and offers significant improvements in cost and throughput.

INTRODUCTION

MCD-386 (**7**), a potent, M_1-selective muscarinic receptor agonist, has potential for treating cognitive and memory impairments and as a disease-modifying therapy for Alzheimer's disease[1] and other neurological disorders.[2,3] MCD-386 recently entered clinical development, prompting a closer evaluation of process safety and scale-up efficiency factors. Initial scale-up work for clinical material utilized the original synthesis route[4] (Scheme 1) and kilo lab equipment to produce approximately 350 g of the active pharmaceutical ingredient (API) with approximately 20% overall yield. A number of operational problems were identified as impediments to large-scale production:

- The first step required the use of cryogenic (−100 °C) reaction conditions to install the 5-carboxyl group. At −90 °C the reaction suffered lower yields, and at −78 °C it failed altogether. Reliance on cryogenics was considered to be risky.
- Esterification of acid **3** in refluxing methanol was slow and had to be performed in repeated cycles over 2−3 days to complete the formation of ester **4**.
- The protecting group methoxytrityl (MMTr) is expensive, and yields for both the installation step and the deblocking step were low. The less expensive trityl protecting group was explored, but yields were lower compared to those with methoxytrityl.
- Sodium hydride, used for oxadiazole ring formation, posed a fire hazard.
- Two steps involving MMTr intermediates required inconvenient chromatographic purification.
- The final MMTr-deblocking step produced poor-quality material which required multiple solvent extractions and charcoal treatment prior to recrystallization and isolation.

These factors made the route unsuitable for further scale-up and long-term supply of API. Our retrosynthetic analysis of MCD-386 was directed towards alternative methods for constructing the tetrahydropyrimidine ring which would avoid the use of expensive protecting groups. The use of 1,3-diamines in ring-closure reactions with orthoformate reagents attracted our attention as a practical approach to forming the cyclic amidine moiety. An initial assessment of alternative routes focused on the use of diamine ester **10** which contains the functionalities from which both the oxadiazole ring and the tetrahydropyrimidine ring could be constructed. Herein we report the development of a safe and scalable preparation of the key intermediate **10** that enabled the completion of a novel, concise process for MCD-386.

RESULTS AND DISCUSSION

Diamine **10** is a well-known versatile building block,[5] which was first made from a diazide precursor. Subsequent reports describe only small-scale preparations, from diazide[6,7] and dinitrile[8,9] precursors, using methods unsuitable for large-scale production. It was postulated that the diamine nitrogen atoms might be installed via direct double displacement[10] with primary amines using the commercially available dibromide **8**. Several attempts were made to displace bromide with ammonia, in various solvents and at various temperatures, which resulted in degradation of the starting material. Allylamine worked well for the displacement, but removal of the allyl groups proved cumbersome and inefficient. Initially, benzylamine was found to work well in the displacement using chloroform as solvent. A number of alternative solvents were screened, and only acetonitrile (ACN) provided favorable yields for the reaction[11] (Scheme 2).

A series of experiments were conducted in ACN, varying the amount of benzylamine (2.0−4.0 equiv), reaction temperature (5 °C to reflux), and the order of addition, resulting in variable yields of desired product and unwanted byproduct.[12] Diisopropylethylamine (Hünig's base, 2 equiv) was then incorporated in the reaction which improved the conversion. The amount of benzylamine was examined again (2−4 equiv), and the optimal amount was determined to be 3.0 equiv. The displacement reaction was found to be relatively fast and exothermic. In order to control the reaction exotherm, the dibromide **8** was added slowly[13] to a refluxing solution of benzylamine and Hünig's base in ACN. After removing most of the solvent by vacuum

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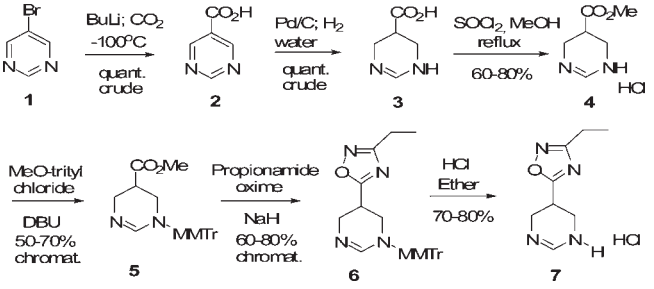
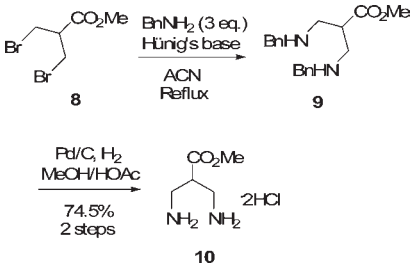
Scheme 1. Original medicinal chemistry route to MCD-386



Scheme 2. Preparation of diamine 10 from dibromide 8

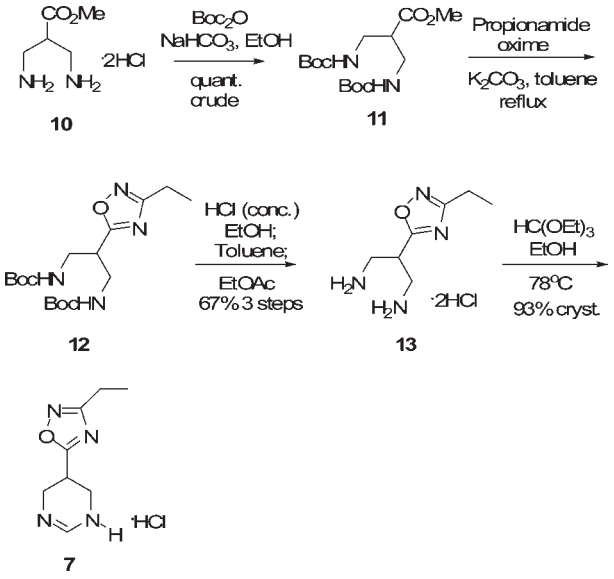


distillation, the addition of ethyl acetate (EtOAc) precipitated the unwanted HBr salt of Hünig's base which was then removed by filtration. To complete the workup, brine washes removed most of the excess benzylamine with little or no loss of the desired product **9**.

Initially, the free-base product solution of **9** in EtOAc was carried forward to hydrogenation with 10% Pd/C (wet) and acetic acid (HOAc) cosolvent. This resulted in partial loss of the ester by hydrolysis. When the EtOAc solvent was replaced with anhydrous methanol (MeOH), prior to hydrogenation with Pd/C and HOAc, the problem of ester hydrolysis was diminished, thus increasing the isolated yield of **10** from 60% to approximately 74% (for two steps). Confident in our results, we felt scale-up was now achievable in conventional equipment without the need for cryogenics or expensive chromatography.

To complete the synthesis, the amine groups require blocking prior to forming the oxadiazole ring. This was accomplished in high yield with inexpensive di-*tert*-butyldicarbonate (Boc anhydride), in ethanol (EtOH), with sodium bicarbonate, to afford ester **11** (Scheme 3). The crude Boc-protected ester **11** could be carried forward to the next step without purification. Two improvements were made regarding the oxadiazole formation step; first, the preparation of propionamide oxime was simplified by replacing hydroxylamine hydrochloride with aqueous hydroxylamine, which eliminated salt formation[14] and facilitated slow hydroxylamine addition.[15] Second, highly flammable sodium hydride was replaced with potassium carbonate as the base to promote oxadiazole ring formation. Treatment of **11** with propionamide oxime, in hot toluene, in the presence of potassium carbonate afforded oxadiazole **12** in 90% yield. Removal of the Boc-protecting groups was effected with concentrated HCl, which after azeotropic drying with toluene and precipitation from EtOAc afforded the stable diamine salt **13**. This transformation offered the opportunity to purify the advanced intermediate by crystallization, thereby reducing impurities going

Scheme 3. New route to MCD-386 from diamine 10



forward to the final step. Cyclization was completed using 3 equiv of triethylorthoformate in EtOH and provided crude **7** in high yield. The enhanced quality of crude **7**, as compared to that with the original medicinal chemistry process, avoided the need for solvent extractions and charcoal treatment to remove unwanted impurities. Recrystallization from ethanol/methyl *tert*-butyl ether afforded high-quality **7** in 92−94% yield. The overall yield for the six-step process, starting with 100 g of **8**, was 56%.

CONCLUSION

A new process for MCD-386 has been identified which eliminates barriers to scale-up such as cryogenic reaction conditions, flammable reagents, silica gel chromatography, and an expensive protecting group. The process employs readily available and inexpensive materials, and greatly reduces solvent usage and waste-stream volumes. Two of the intermediate steps provide crystalline products which facilitate purification and storage of advanced intermediates. This new process appears to be a viable route for large-scale production of API. Future work on this new process will focus on streamlining steps involving isolation of crude intermediates. We believe this can be addressed with simple solvent exchange operations that allow crude intermediates to be carried forward as solutions. Prior to further scale-up, thermal stability studies are planned which may help set temperature limits for some of the process steps.

EXPERIMENTAL SECTION

^{1}H NMR data were collected at 400 MHz. The following HPLC column and conditions were employed: Altima C18 reverse phase 4.6 × 150 mm; UV detection at 210 nm; ACN/water with 0.1% TFA buffer; 1 mL/min flow rate; 5% ACN to 50% ACN gradient over 10 min with 2 min hold.

Methyl 3-(Benzylamino)-2-((benzylamino)methyl)propanoate (9). Benzylamine (123.6 g, 1.15 mol), Hünig's base (99.3 g, 0.77 mol), and ACN (550 mL) were combined and heated to reflux with rapid stirring. A solution of dibromo methyl ester **8** (100.0 g, 0.385 mol) in ACN (140 mL), was added over 27 min, while reflux (81 °C) was maintained. The mixture was

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cooled below 40 °C over 30 min. The solvent was distilled under reduced pressure (by rotary evaporator) until reaching about one-third of the original volume. EtOAc (700 mL) was added and the mixture stirred at 10−15 °C for 10 min. The solids were filtered and washed with EtOAc (2 × 200 mL). The filtrate was washed with 20% brine (2 × 150 mL) and with saturated brine (75 mL). The organic layer was dried with sodium sulfate (120 g), filtered, and concentrated under reduced pressure to approximately 200 mL. The crude product solution was sampled for HPLC analysis and used directly in the next step. HPLC analysis indicated 94.2% purity.

Methyl 3-Amino-2-(aminomethyl)propanoate Dihydrochloride (10). Product solution containing **9** in EtOAc (0.385 mol theoretical) was concentrated to about 175 mL (yellow oil) and treated with MeOH (300 mL). The solution was transferred to a Parr bottle containing 36.0 g of wet 10% Pd/C and HOAc (600 mL). The mixture was hydrogenated for 15 h at 38 °C, starting at 50 psi hydrogen pressure. The mixture, upon cooling, was filtered through Celite and washed with MeOH (4 × 100 mL). The filtrate was concentrated at 30 mbar pressure with the bath at 45 °C, until no more distillate collected. The residue was treated with ACN (1 L) and concentrated to remove HOAc. The co-evaporation was then repeated with additional ACN (1 L). The residue was dissolved in MeOH (500 mL), cooled below 15 °C, and treated slowly (dropwise) with conc. HCl (95 mL), keeping the temperature below 26 °C. The mixture was concentrated until the distillate stopped collecting (30 mbar, 45 °C bath temp). The HCl exchange cycle was repeated, again with MeOH (500 mL) and conc. HCl (95 mL), and the batch was concentrated until the distillate stopped collecting. The residue was taken up in ACN (500 mL) and concentrated to remove water. The residue was treated with another portion of ACN (500 mL) and concentrated until the distillate stopped collecting. The residue was taken up in MeOH (400 mL) and refluxed for about 15 min to dissolve solids. The heat was turned off, and the solution was treated slowly with EtOAc (400 mL). Solids formed as the mixture cooled; stirring was continued at ambient temperature overnight. Solids were collected and washed with cold EtOAc/MeOH (75:25, 200 mL) and then with EtOAc (200 mL). The solids were dried for 18 h at ambient temperature under high vacuum (<1 mbar) to 54.8 g of white solid. The mother liquors were condensed, and a second crop of solids was obtained from MeOH (100 mL, hot) and EtOAc (100 mL). The second crop dried to 4.0 g of white solid. The total yield was 58.8 g (74.5% for two steps). MS (ESI) m/z 133 $[M + 1]^+$. ^{1}H NMR (DMSO-d_6) 3.05−3.25 (m, 5 H), 3.70 (s, 3 H), 8.37 (bs, 6H). Anal. Calcd for $C_5H_{14}Cl_2N_2O_2$ (205.08): C 29.28; H 6.88; Cl 34.57; N 13.66. Found: C 29.64; H 6.87; Cl 34.17; N 13.42.

Methyl 3-(*tert*-Butoxycarbonylamino)-2-((*tert*-butoxycarbonylamino)methyl)propanoate (11). The diamine HCl **10** (58.6 g, 0.285 mol) was stirred vigorously with 95% EtOH (600 mL) and treated with sodium bicarbonate (72.0 g, 0.857 mol) and di-*tert*-butyl dicarbonate (127.8 g, 0.585 mol). A rinse with 95% EtOH (285 mL) completed the transfer of solids. The mixture was stirred vigorously for 3 h at 45−48 °C. The mixture was condensed to about 200 mL, resulting in a thick, free-flowing slurry. EtOAc (700 mL) was added and the mixture extracted with D.I. water (580 mL). The organic layer was washed with water (290 mL) followed by saturated brine (290 mL), dried over sodium sulfate, and filtered. The organic solution was concentrated to approximately 200 mL. The crude product was taken directly to the next step. In preparation for the next step, toluene (200 mL) was added and the solution concentrated again to approximately 100−125 mL. Toluene was added to a final volume of approximately 350 mL. A purified sample of **11**, obtained from silica gel chromatography, solidified upon standing overnight at ambient temperature; MS (ESI) m/z 333 $[M + 1]^+$. ^{1}H NMR ($CDCl_3$) 1.43 (s, 18 H), 2.71−2.77 (m, 1 H), 3.17−3.26 (m, 2 H), 3.50−3.58 (m, 2 H), 3.71 (s, 3 H), 5.22 (s, 2 H).

***tert*-Butyl 2-(3-Ethyl-1,2,4-oxadiazol-5-yl)propane-1,3-diyldicarbamate (12).** *Propionamide Oxime.* Propionitrile (55.0 g, 0.998 mol) was combined with MeOH (440 mL) and the solution brought to reflux. A solution of 50% aqueous hydroxylamine (50.7 g, 0.768 mol) was added dropwise over 20 min. The mixture was refluxed for 8 h, cooled, and partially concentrated under vacuum. The residue was co-evaporated with toluene (300 mL). Co-evaporation was repeated with additional toluene (300 mL), and the resulting oil was dried for 16 h under high vacuum (<1 mbar) at ambient temperature to 56.8 g of oil which solidified upon cold storage. MS (ESI) m/z 89 $[M + 1]^+$. ^{1}H NMR (DMSO-d_6) 1.01 (t, 3H), 1.96 (q, 2H), 5.29 (s, 2H), 8.68 (s, 1H).

Oxadiazole Formation. The toluene solution of *N*-Boc-methyl ester **11** (0.285 mol theoretical) was combined with crude propionamide oxime (62.7 g, 0.71 mol) and the mixture further diluted with additional toluene to a total volume of about 580−600 mL. The reaction vessel was fitted with a Dean−Stark trap and condenser. Potassium carbonate (177.7 g, 1.285 mol) was charged and the reaction heated to reflux with vigorous stirring for 5 h. The mixture was extracted with D.I. water (370 mL) and EtOAc (315 mL). The organic layer was washed with 5% citric acid (2 × 160 mL), followed by saturated sodium bicarbonate solution (160 mL) and finally with saturated brine (160 mL). The organic layer was dried (sodium sulfate), filtered, and concentrated to about 90 g of oil. The crude product was used directly in the next step. A pure sample was obtained from silica gel chromatography (25% EtOAc/hexane); MS (ESI) m/z 371 $[M + 1]^+$. ^{1}H NMR ($CDCl_3$) 1.30−1.34 (m, 3H), 1.44 (s, 18 H), 2.72−2.78 (m, 2 H), 3.33 (m, 4 H), 3.74−3.78 (m, 1 H), 7.26 (s, 2 H).

2-(3-Ethyl-1,2,4-oxadiazol-5-yl)propane-1,3-diamine Dihydrochloride (13). Crude **12** (*N*-Boc oxadiazole, approximately 90 g) was taken up in EtOH (630 mL), stirred at ambient temperature, and treated slowly with conc. HCl (140 mL) over 15 min. The temperature increased to 34 °C during the addition. The mixture was warmed to 45−50 °C for 4.5 h then cooled below 25 °C. Toluene (700 mL) was added, and the mixture was concentrated under reduced pressure to about one-fourth the volume. The residue was treated with EtOAc (810 mL), causing a precipitate to form. The mixture was allowed to stand overnight at ambient temperature and then was stirred vigorously at 5 °C for 30 min. The solids were collected by filtration, washed with EtOAc, and dried for 20 h under vacuum. The mother liquors were condensed and co-evaporated with EtOH (150 mL), and a second crop of product was obtained from EtOH/EtOAc. The first crop produced 41.61 g of white solid; the second crop provided 5.27 g of white solid. Total yield was 46.88 g (67.6% for three steps). MS (ESI) m/z 171 $[M + 1]^+$. ^{1}H NMR (CD_3OD) 1.32−1.36 (m, 3H), 2.81−2.83 (m, 2 H), 3.49−3.51 (m, 4 H), 3.90−3.96 (m, 1 H).

3-Ethyl-5-(1,4,5,6-tetrahydropyrimidin-5-yl)-1,2,4-oxadiazole Hydrochloride (MCD-386, 7). Oxadiazole diamine HCl, **13** (45.88 g, 0.189 mol), was treated with triethyl orthoformate (94.4 mL, 0.567 mol) and EtOH (460 mL). The mixture was

heated to reflux for 30 min and cooled (over 25 min) to below 25 °C. The mixture was concentrated under reduced pressure to form a thick slurry. The residue was taken up in EtOH (183 mL) and toluene (183 mL) and concentrated again to a thick slurry. Isopropanol (IPA, 140 mL) was added and the mixture heated to reflux. External heat was turned off, and MTBE (275 mL) was slowly added, resulting in the formation of a precipitate. The mixture was cooled slowly to ambient temperature and further cooled to 5 °C for an additional 30 min. Solids were collected, washed with MTBE (275 mL), and briefly air-dried with suction. The wet cake was dissolved in hot IPA (174 mL) and filtered, and the filter was rinsed with hot IPA (30 mL). The filtrate was heated and, upon cooling, was treated slowly with MTBE (408 mL). The resulting slurry was stirred about 30 min at ambient temperature and an additional 30 min at 5 °C. Solids were collected, washed with MTBE, and dried with heat and vacuum to provide 38.41 g of white solid (93.8% yield, 99.8% HPLC PA% purity). The overall yield for six steps was 55.5%. MS (ESI) m/z 181 $[M + 1]^+$. ^{1}H NMR (DMSO-d_6) 1.20−1.24 (m, 3H), 2.71−2.75 (m, 2 H), 3.63−3.91 (m, 5 H), 8.24 (s, 1 H), 10.10 (bs, 2H).

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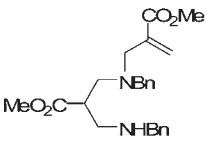
(11) Chloroform posed environmental issues which prompted the screening of the following alternative solvents: water, MeOH, EtOH, DMF, THF, EtOAc, ACN, and toluene.
(12) The byproducts were not isolated and fully characterized. HPLC analysis of reaction mixture samples revealed two late-eluting impurities. Mass spectral analysis of the samples revealed two high-molecular weight(410 and 517) impurities for which structures were tentatively assigned as **14** and **15**.



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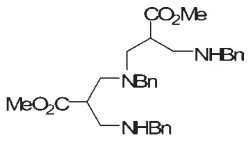

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(13) After reflux temperature (80 °C) was reached, the heat source was turned off, and dibromide solution was added a rate sufficient to maintain reflux. On a 100-g scale the charge was carried out over 27 min.
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