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Technical Notes

A New and Improved Synthesis of Bidisomide

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Abstract:

Bidisomide, an antiarrhythmic and defibrillating agent, has been synthesized by a new approach. One of the key intermediates in this synthesis is 2-(*N*-isopropyl-*N*-allylamino)ethyl chloride. The distinct advantages of this new process over the existing one are described.

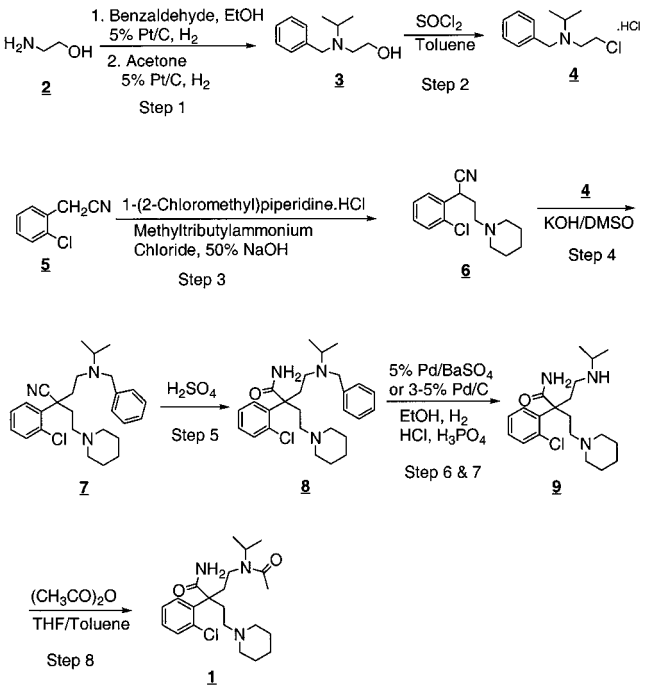
Introduction

Bidisomide or (±)-α-[2-[acetyl(1-methyl ethyl)amino]-ethyl]-α-(2-chlorophenyl)-1-piperidinebutanamide is a new antiarrhythmic and atrial defibrillating agent. Although currently not in clinical trials, earlier animal and human studies had indicated that bidisomide may be a promising drug due to its therapeutic profile.[1] This realization triggered the development of several synthetic routes.[1−4] The route used to prepare development supplies is illustrated by Scheme 1.

However, associated with this process were two major flaws that were absolutely unacceptable from a large-scale production point of view. The first problem was the *N*-benzyl protection of 2-aminoethanol in step 1. This, despite extensive efforts, involved an uncontrollable double hydrogenation and 52 h of reaction time. The second major issue was the palladium-catalyzed hydrogenation (step 6) to remove the benzyl-protecting group. This was accompanied by a significant amount of undesired deschloro product. Once the dechlorination occurs, the product cannot be purified in any known fashion to remove the deschloro impurity. This reality reduced dramatically the probability of meeting product specifications and increased the process cost. Thus, there was a pressing need to design and reduce to practice a new process for the synthesis of bidisomide, lacking the issues encountered in the existing process. Replacing the benzyl-protecting group by a functionality that did not require hydrogenation for removal was critical to our success.

This report deals with a new synthesis of **1** which completely eliminates the need of any hydrogenation.

Scheme 1. **Existing process**



Results and Discussion

Our initial approach involved the use of an allyl group as an amino-protecting group[5] and incorporated this into a new synthetic route (Scheme 2).

This synthesis started with the condensation of allylbromide (**11**) with 2-*N*-isopropylaminoethanol (**10**) to afford 2-*N*-isopropyl-*N*-allylaminoethanol (**12**) followed by chlorination with thionyl chloride to produce 2-(*N*-isopropyl-*N*-allylamino)ethyl chloride (**13**) in almost quantitative yield. The common intermediate **6** in both syntheses was then alkylated with **13** to produce **14**. The cyano intermediate **14** was then hydrolyzed to amide **15**. Deallylation of **15** was then carried out using Wilkinson's catalyst to generate the second common intermediate **9**. *N*-Acylation of secondary amine (**9**) yielded racemic bidisomide (**1**).

Conclusions

In conclusion, the new and improved synthesis of bidisomide offers distinctive advantages over the published synthesis. This employs mild reaction conditions. Replacing the benzyl group by a different amino-protecting group that

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(4) Kowar, T. R. Application: US 95-433622 19950503, 1998; 455,731,435, 1998.
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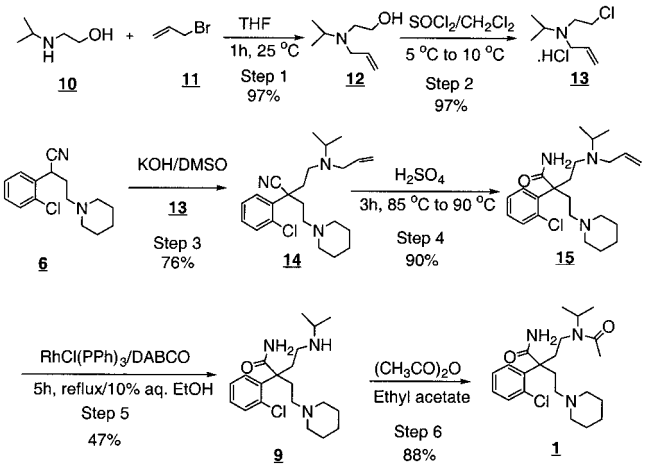
Scheme 2



eliminates the need for three hydrogenations significantly reduces batch cycle times. Towards the end, all of this and catalytic deallylation, probably via isomerization, offers potential cost savings and purity advantages.

Experimental Section

All chemicals were reagent grade and used as purchased. Compound **6** was procured from the Chemical Sciences department of Searle. All reactions were performed under an inert atmosphere of dry nitrogen, using distilled dry solvents unless otherwise stated. ^{1}H and ^{13}C NMR spectra were obtained on a Varian INOVA-400 instrument. Elemental analyses were determined by E. Zielinski and associates in the Physical Methodology department of our company. HPLC analysis was carried out by the group of J. Wysocki.

Preparation of 2-*N*-Isopropyl-*N*-allylaminoethanol (12). 2-(Isopropylamino)ethanol (34.94 g, 0.3 mol) was taken up in dry CH_2Cl_2 (100 mL). To this solution triethylamine (44.60 mL, 0.32 mol) and allyl bromide (25.96 mL, 0.3 mol) were added, and the reaction mixture was stirred at 25 °C. After 2 h of stirring, a saturated solution of $NaHCO_3$ was added to the reaction mixture. The CH_2Cl_2 layer was separated, washed with 2 × 50 mL of water, dried over $MgSO_4$, and filtered. Evaporation of the CH_2Cl_2 gave the product as an oil (22.0 g, 51% yield). ^{1}H NMR ($CDCl_3$) δ 5.8 (m, 1H), 5.15 (m, 2H), 3.5 (t, 2H), 3.15 (d, 2H), 3.05 (m, 1H), 2.6 (t, 2H), 1.0 (d, 6H).

In further optimization of this procedure, 2-(isopropylamino)ethanol was alkylated with allyl bromide in THF for 1 h to afford the desired product in 97% yield with >97% GC purity.

Preparation of 2-(*N*-Isopropyl-*N*-allylamino)ethyl Chloride Hydrochloride (13). 2-*N*-Isopropyl-*N*-allylaminoethanol (12) (22.0 g, 0.155 mol) was taken up in CH_2Cl_2 (50 mL). To this was added a solution of $SOCl_2$ (15 mL) in CH_2Cl_2 (50 mL), and the reaction temperature was maintained between 5 and 10 °C. After the addition was complete, the reaction mixture was stirred at 20 to 22 °C for 1 h and then concentrated on a rotary evaporator. The residue was taken up in CH_2Cl_2 (100 mL) and again concentrated to completely remove the $SOCl_2$. The so-obtained residue was taken up in acetone (300 mL), filtered, and dried to afford the product (30.0 g, 97% yield). ^{1}H NMR ($CDCl_3$) δ 6.35 (m, 1H), 5.55 (d, 2H), 4.15 (m, 2H), 3.7 (m, 2H), 3.3 (m, 3H), 1.5 (dd, 6H); ^{13}C NMR ($CDCl_3$) δ 127.17, 125.08, 54.93, 53.71, 50.05, 37.08, 17.00, 16.17; IR (KBr) (cm^{-1}) 3858, 2982, 1545; EI-MS 162 (M^+). Anal. Calcd for $C_8H_{17}Cl_2N$: C, 48.49; H, 8.65; N, 7.06; Cl, 35.80. Found: C, 47.76; H, 8.74; N, 7.06; Cl, 35.78.

Preparation of (±)-α-(2-Chlorophenyl)-α-[2-[(-methyl-ethyl)(allyl) amino]ethyl]-1-piperidinebutanenitrile (14). To a round-bottom flask under argon atmosphere was added sequentially DMSO (48.3 mL, 0.561 mol), powdered anhydrous KOH (31.78 g, 0.566 mol), (±)-α-(2-chlorophenyl)-1-piperidinebutanenitrile (**6**) (26.8 g, 0.102 mol), and DMSO (10 mL). A solution of 2-(*N*-isopropyl-*N*-allylamino)ethyl chloride hydrochloride (**13**) (22.0 g, 0.111 mol) in DMSO (18 mL) was then added to the above reaction mixture by maintaining the reaction temperature below 20 °C. This mixture was then stirred for 10 h at 25 °C and then poured in to a cold stirred mixture of heptane (60 mL) and water (100 mL). The flask was rinsed with water (100 mL) and heptane (60 mL), and both rinses and the reaction mixture were combined. The layers were separated and the organic layer was filtered through Celite (2 g). The filter cake was washed with heptane (40 mL), and the wash was combined with the organic phase. The combined organic phase was then washed with water (2 × 50 mL) and dried over anhydrous $MgSO_4$ for 1 h, filtered, and concentrated to give the crude product as a yellow oil (30 g, 76% yield). ^{1}H NMR ($CDCl_3$) δ 7.7 (dd, 1H), 7.4 (dd, 1H), 7.25 (m, 2H), 5.7 (m, 1H), 5.15 (dd, 2H), 3.0 (d, 2H), 2.9−2.5 (m, 5H), 2.4−2.0 (m, 8H), 1.6−1.2 (m, 6H), 0.9 (dd, 6H); ^{13}C NMR ($CDCl_3$) δ 137.24, 132.39,131.97, 131.17, 129.11, 126.98, 122.33, 116.28, 55.20, 54.61, 53.76, 50.61, 45.65, 36.46, 34.22, 25.82, 24.20, 18.32, 18.19; IR (KBr) (cm^{-1}) 2980, 2240; EI-MS 388 (M^+). Anal. Calcd for $C_{23}H_{34}ClN_3 \cdot 0.5H_2O$: C, 69.58; H, 8.89; N, 10.58; Cl, 8.93. Found: C, 70.00; H, 9.45; N, 10.53; Cl, 8.87.

Preparation of (±)-α-(2-Chlorophenyl)-α-[2-[(-methyl-ethyl)(allyl)amino]-ethyl]-1-piperidinebutaneamide (15). To a round-bottom flask under argon was added (±)-α-(2-chlorophenyl)-α-[2-[(-methyl-ethyl)(allyl)amino]ethyl]-1-piperidinebutanenitrile (**7**) (10.0 g, 0.026 mol) followed by the cautious addition of concentrated H_2SO_4 (15 mL). The reaction mixture was stirred at 85 to 90 °C for 3 h and then slowly poured into a stirred mixture of water (42 mL) and toluene (50 mL). The flask was rinsed with water (20 mL), and this wash was combined with the reaction mixture. Aqueous NaOH (29 mL, 50 wt %) was then added to the above reaction mixture, maintained between 35 and 40 °C to bring the pH to 12. The reaction mixture was then warmed to 45 °C for 15 min, and the layers were separated. The aqueous phase was washed with toluene (2 × 15 mL), and the toluene wash was combined with the organic phase. This solution was dried over anhydrous Na_2SO_4 (4.0 g), filtered through Celite (2.0 g), and concentrated to give the crude product as a brown oil (9.56 g, 90% yield). ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1H), 7.34 (d, 1H), 7.25 (m, 2H), 6.3 (bs, 1H), 5.8 (m, 1H), 5.3 (bs, 1H), 5.05 (dd, 2H), 3.0 (d, 2H), 2.9 (m, 1H), 2.5−2.7 (m, 12H), 1.6−1.2 (m, 6H), 0.9 (dd, 6H); ^{13}C NMR ($CDCl_3$) δ 175.95, 138.88, 137.37, 134.48, 131.48,

129.54, 128.41, 126.73, 116.30, 54.80, 54.72, 54.71, 53.67, 50.56, 44.85, 32.66, 30.43, 25.82, 24.30, 18.33, 18.21; IR (KBr) (cm^{-1}) 2980, 1680; EI-MS 406 (M^+). Anal. Calcd for $C_{23}H_{36}ClN_3O$: C, 68.04; H, 8.94; N, 10.35; Cl, 8.73. Found: C, 68.34; H, 10.11; N, 9.46; Cl, 8.12.

Preparation of (±)-α-(2-Chlorophenyl)-α-[2-[-(methyl-ethyl) amino]ethyl]-1-piperidinebutaneamide (9). To a round-bottom flask under argon were added (±)-α-(2-chlorophenyl)-α-[2-[(-methyl-ethyl)(allyl)amino]ethyl]-1-piperidinebutaneamide (15) (5.88 g, 0.0145 mol), DABCO (337 mg, 0.003 mol), rhodiumtriphenylphosphine chloride (925 mg, 0.001 mol), and 10% aqueous ethanol (40 mL). The reaction mixture was heated at reflux temperature for 5 h and cooled. Ethanol (∼20 mL) was then evaporated, and water (100 mL) was added. Reaction mixture was extracted with diethyl ether (3 × 100 mL), and the combined ether layers were washed with brine (2 × 20 mL) and 1 N HCl (15 mL). It was then dried over anhydrous $MgSO_4$, filtered, and evaporated to give a yellow solid. This solid was recrystallized with 50% ethyl acetate in heptane to give the desired product (2.5 g, 47% yield). ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 1H), 7.47 (d, 1H), 7.35 (d, 1H), 7.25 (m, 2H), 6.3 (bs, 1H), 5.3 (bs, 1H), 2.8 (m, 1H), 2.5−2.7 (m, 12H), 1.6−1.2 (m, 6H), 1.0 (dd, 6H); ^{13}C NMR ($CDCl_3$) δ 177.02, 139.55, 134.27, 131.58, 129.35, 128.87, 126.33, 54.70, 54.69, 48.65, 42.87, 34.70, 30.47, 25.90, 24.25, 22.77, 22.51; IR (KBr) (cm^{-1}) 3500, 2980, 1690; EI-MS 366 (M^+). Anal. Calcd for $C_{20}H_{32}ClN_3O·0.5\ H_2O$: C, 64.07; H, 8.87; N, 11.21; Cl, 8.46. Found: C, 64.14; H, 8.38; N, 10.44; Cl, 9.65.

Preparation of (±)-α-[2-[Acetyl(1-methylethyl)amino]-ethyl]-α-(2-chlorophenyl)-1-piperidinebutaneamide (1) or (Bidisomide). To a round-bottom flask under argon were added (±)-α-(2-chlorophenyl)-α-[2-[(-methyl-ethyl) amino]-ethyl]-1-piperidinebutaneamide (1.83 g, 0.005 mol), ethyl acetate (15 mL), and acetic anhydride (2 mL, 0.02 mol). The reaction mixture was stirred at 25 °C for 6 h and then diluted with water (10 mL). The ethyl acetate was removed under removed pressure, and a solution of K_2CO_3 (2.5 g) in water (10 mL) was added to the residue. It was then extracted with ethyl acetate (3 × 35 mL), and the combined extracts were dried over anhydrous Na_2SO_4 (4.0 g) and filtered through Celite (2.0 g). Evaporation of the ethyl acetate gave the product as an off-white solid (1.8 g, 88% yield). NMR and HPLC of the product were identical to those of an authentic sample of bidisomide. ^{1}H NMR ($CDCl_3$) δ 7.9−7.1 (m, 4H), 3.9 (m, 1H), 2.2 and 1.9 (2 s, 3H), 1.1 (d, 6H); ES-MS 408 (M + H).

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