Enantioselective method of synthesizing methylphenidate and derivatives

Abstract

Process for the preparation of enantioselective method of making methylphenidate and derivatives . The method involves use of a rhodium catalyst, and selectively produces the D-enantiomer of the methylphenidate derivative in excess of the L-enantiomer . Furthermore, the method selectively produces the threo-diastereomer in excess of the erythro-diastereomer. The method is thus suitable for synthesis of D-threo-methylphenidate (the biologically active form of this compound) and derivatives

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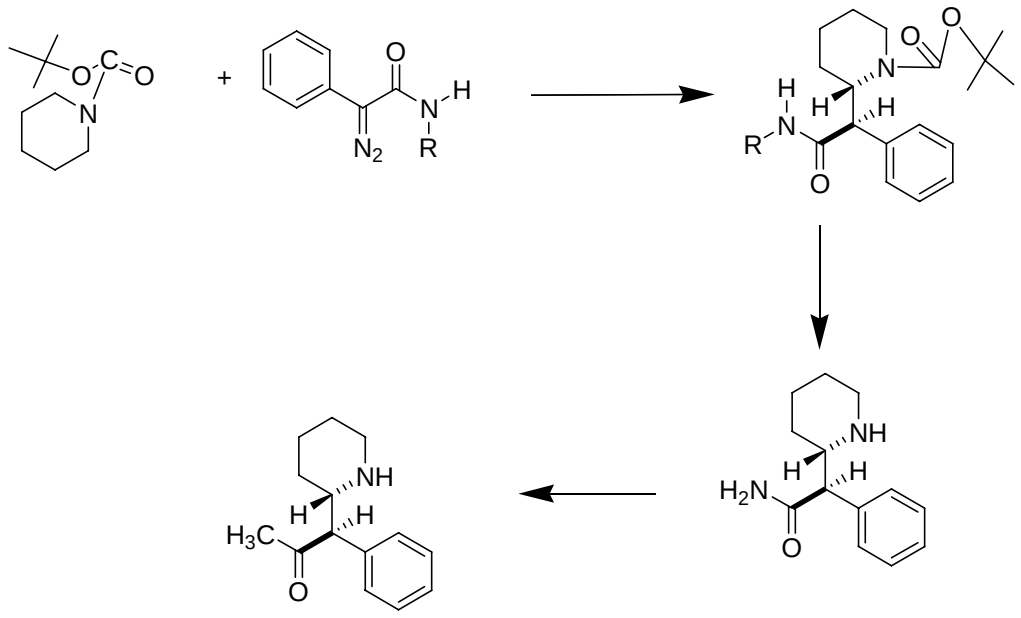
Introduction

Methylphenidate (Ritalin,™ Ciba-Geigy Corporation, Summit, N.J.) is the most commonly prescribed psychotropic medication for children in the United States. It is used primarily for the treatment of children diagnosed with attention deficit disorder (ADD). Methylphenidate is synonymous with methyl α-phenyl-2-piperidineacetate, α-phenyl-2-piperidineacetate methyl ester, methyl phenidylacetate, and methylphenidan. The biologically active form of methylphenidate is the D-threo enantiomer. Methylphenidate is sold, in the form of the hydrochloride salt, as the product Ritalin™ and its generic equivalents. A comprehensive description of the compound is found in Padmanabhan (1981, Analytical Profiles of Drug Substances v. 10, Florey, Ed., Academic Press, New York).

FIG-1



These methods have various shortcomings, including low yield, the necessity to interconvert diastereomers of methylphenidate following synthesis, and the necessity to resolve enantiomers of methylphenidate. Furthermore, investigation of methylphenidate analogs has been hampered by the fact that these methods can be used to synthesize only a narrow range of analogs, such as methylphenidate analogs having ester modifications or phenyl ring substitutions

The present invention overcomes the shortcomings of these synthetic methods, and provides D-threo-methylphenidate and numerous D-threo-methylphenidate derivatives, including efficacious cocaine antagonists and analogs useful for treatment of various neurological disorders

EXAMPLE 1

Synthesis of D-threo-methylphenidate

An enantioselective synthesis of a composition comprising D-threo-methylphenidate is described in this Example. This method yields a substantially greater proportion of the D-enantiomer of methylphenidate than non-enantioselective methods, and does not require chromatographic purification of this product from similar products in the reaction mixture. Furthermore, each of the synthetic steps is amenable to large-scale industrial chemical production methods and apparatus.

The synthetic method described in this Example is outlined in FIG. 1.

An oven-dried 5 milliliter flask containing a stirring bar was fitted with a septum and flame-dried while being purged with argon. 0.35 Milliliters of N-butoxycarbonyl piperidine ("Boc-piperidine") was added to the flask and degassed. An equal volume (i.e. 0.35 milliliters) of freshly distilled cyclohexane was then added to the flask. Next, 2.3 milligrams (2.51 millimoles) of $Rh_2\{5R\text{-}MEPY\}_4$ catalyst was added to the flask, and the reaction mixture was maintained at 50 ° C. for 20 minutes. Preparation of this catalyst is described, for example, by Doyle et al., 1995, Reel. Trav. Chim. Pays-Bas 114:163-170.

70.4 Milligrams of 2-diazo -2-phenyl acetamide was injected into the reaction mixture over the course of 4 hours. About 10 milligrams of the compound was be added at the beginning of the reaction and about every 30 minutes thereafter (the balance was added 30 minutes after the last 10 milligram addition). During this period, the reaction mixture was maintained at 50° C. and had a blue color. After this period, the reaction mixture was allowed to cool to room temperature (e.g. about 20° C.) over the course of about 30 minutes. The cooled reaction mixture was filtered at room temperature through a column containing a silica bed. The cylindrical silica bed had a diameter of about 5 millimeters and a height of about 100 millimeters. The silica column packing was flash silica. After the reaction mixture had been filtered through the silica column, the silica was washed with diethyl ether. The rhodium catalyst did not pass through the column, and therefore

was not contained in the filtrate obtained from the silica column. This filtrate was concentrated in vacuo to yield a yellow oil. The yellow oil was purified by flash chromatography using a silica gel (EM Science; 244 mesh) column containing a bed having a diameter of 20 millimeters and a height of about 10 inches and a solution comprising 10% (v/v) diethyl ether and 90% petroleum ether (boiling point 30-60 C.). About 86 milligrams of boc-methylphenidate (i.e. ca. 64.5% yield) was obtained in the form of a green oil.

An oven-dried 15 milliliter flask containing a stirring bar was fitted with a septum, and 4.0 milliliters of methanol was added thereto. The methanol was cooled to 0° C., and HCl gas was bubbled through the cooled methanol for about 15 minutes. 2.2 milliliters of methanol was added to 206 milligrams (0.62 millimoles) of Boc-methylphenidate made as described above. This solution was added to the cooled acidified methanol solution, and this mixture was maintained at 0° C. for 30 minutes while stirring the mixture. The resulting liquid was concentrated in vacuo and triturated with ethyl acetate. The resulting white solid was washed with diethyl ether to yield 114.6 milligrams of the hydrochloride salt of D-threo-methylphenidate (i.e. 68.5% yield).

37.5 Milligrams (0.115 millimoles) of the salt was dissolved in 10 milliliters of a saturated solution of sodium bicarbonate, and then extracted twice with about 15 milliliters of diethyl ether to yield 30 milligrams of the free amine form of D-threo-methylphenidate (92% yield for the de-salting step).

The free amine form was applied to a Chiralcel ADTM analytical column (particle size ca. 10 micrometers) containing a bed having a diameter of about 4.6 millimeters and a length of 25 centimeters. The buffer applied to the column was a 98:2:0.1 mixture of hexane: isopropyl alcohol:diethyl alcohol, and the flow rate was 2.0 milliliters per minute. The retention times characteristic of the various enantiomers of methylphenidate under these column conditions are listed in Table 1. Chromatographic analysis of the free amine form of the reaction product indicated that at least 94% of the methylphenidate made using the methods described in this Example was the threo- diastereomer, and that at least 69% was the D-enantiomer. Thus, not less than about 63% of the methylphenidate made in this way was D-thieo-methylphenidate.

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. TABLE-1

Enantiomer of Methylphenidate	Retention Time, minutes
l-erythro	4.84
d-erythro	5.00
l-threo	6.61
d-threo	9.33

While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

REFERENCES

Padmanabhan (1981, Analytical Profiles of Drug Substances v. 10, Florey, Ed., Academic Press, New York).

Medical Economics Co., Inc., Montvale, N.J., 51st ed., 1997; PDR® Generics™,

U.S. Pat. No. 2,507,631

U.S. Pat. No. 2,838,519

U.S. Pat. No. 2,957,880

British Patent Nos. 788,226 and 878,167

Soviet Patent No. 466,229

WO9735836 ;

. WO9728124 o

Panizzon, 1944, Helv. Chim. Acta 27:1748-1756

Naito et al., 1964, Chem. Pharm. Bull. 12:588-590

Deutsch et al., 1996, J. Med. Chem. 39:1201-1209

Earle et al., 1969, J. Chem. Soc. (C) 2093-2098);