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NOVEL SYNTHETIC METHOD FOR PIMOBENDANE

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Abstract

The new route for synthesis of Pimobendane done by synthesis of key intermediate 4-(4-chlorophenyl)-3-methyl-4-oxobutanoic acid (4). This key int-4 was prepared by condensation and decarboxylation between less cost starting materials 1-(4-chlorophenyl)propan-1-one (2) with glyoxylic acid followed by reduction. Analogous and later synthesis was given proper references[1-7].

Key words

Pimobendane, Chlorobenzene, Glyoxalic acid

Introduction

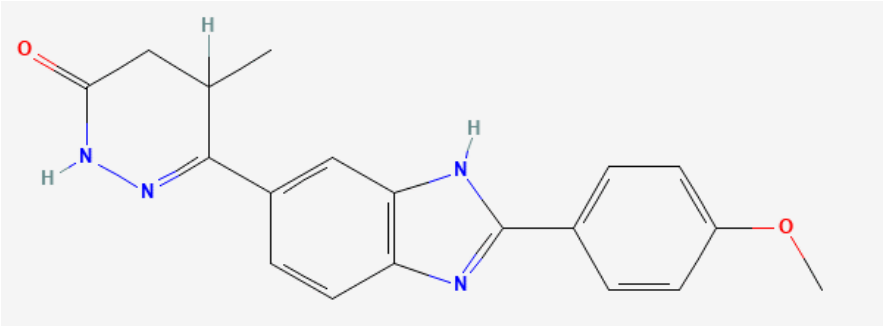
Pimobendan is a veterinary medication. It is a calcium sensitizer and a selective inhibitor of phosphodiesterase 3 (PDE3) with positive intropic and vasodilator effects.

Pimobendan is used in the management of heart failure in dogs, most commonly caused by myxomatous mitral valve disease, or Dilated cardiomyopathy [8]. Research has shown that as a monotherapy, pimobendan increases survival time and improves quality of life in canine patients with congestive heart failure secondary to mitral valve disease when compared with benazepril, an ACE inhibitor [9]. However, in clinical practice, it is often used in conjunction with an ACE inhibitor like enalapril or benazepril. Under the trade name Acardi, it is available for human use in Japan [10].

Pimobendan is both a positive inotrope and a vasodilator. The vasodilator effects occur via inhibition of Phosphodiesterase III (PDE III). Phosphodiesterase III is the enzyme that degrades cyclic adenosine monophosphate (cAMP); therefore its action is to increase intracellular concentrations of cAMP. There may be some inhibition of PDE V in the pulmonary circulation. The inotropic effects of pimobendan are attributed to its action as a calcium sensitizer rather than the PDE inhibition. By acting as a calcium

sensitizer, it increases the interaction of troponin C with contractile proteins and acts as an inotropic agent. The benefits in heart failure are caused by both positive inotropic effects and vasodilating properties. Other beneficial effects may include anti-inflammatory activity, increased sensitivity of baroreceptors, increased lusitropy, and decreased platelet aggregation. The cardiovascular effects occur after 1 hour and persist for 8-12 hours after administration. Pimobendan is absorbed best in an acidic environment. Fluctuating pH conditions in stomach and administration with food may produce inconsistent oral absorption.

2D Structure



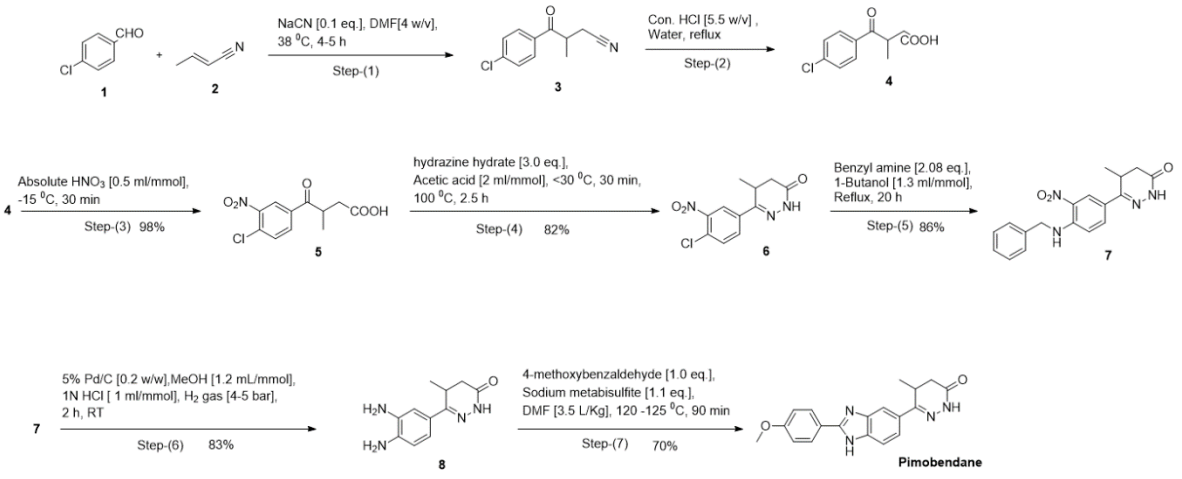
Mechanism of action

A positive inotrope is Pimobendan (which increases myocardial contractility). Ca2+ boosts cardiac troponin's affinity for the myofibril's calcium ions, making it more effective at binding calcium ions. In healthy hearts, it boosts oxygen and energy consumption to the same extent as dobutamine, but this may not be the case in sick hearts (DeFrancesco et al., 2013). Peripheral vasodilation is also a side effect of pimobendan since it inhibits PDE3. By decreasing blood flow resistance via peripheral arteries, afterload (the workload of the failing heart) and mitral regurgitation are both reduced.

Previous approaches

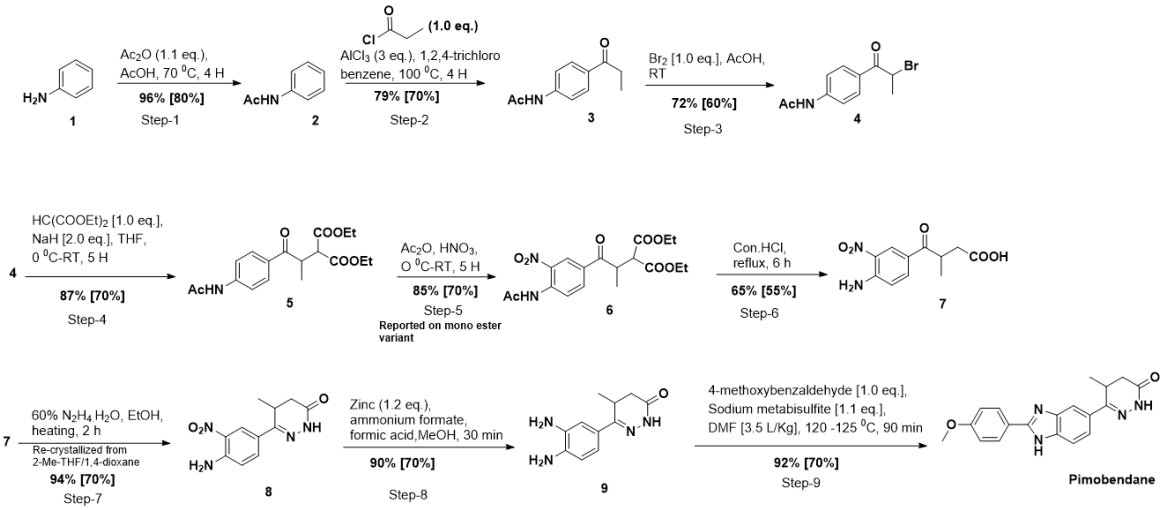
Previous approaches are shown below has more synthetic cost and taking more time for synthesis.

Previous Route-1[11]



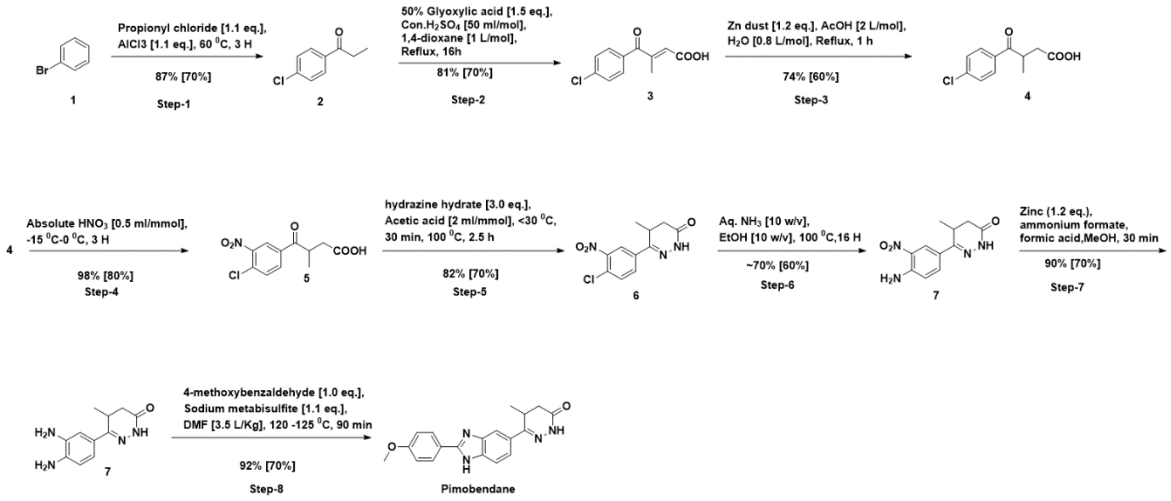
Route-1 abandoned due to the expensive cost of trans-Croton nitrile in the first step Which almost 80% of the total cost for synthesis. [200 ml costing more than Rs.20000/- Where, as 100 g compound preparation estimated as costing ~32,000/-. Though it is a nice route for the synthesis of the compound, the route is not affordable commercially for us.

Previous Route-2[12]



The route-2 estimated to be cheaper on larger scale and looks commercially feasible for us to some extent [looks to obtain 1 kg about 55,000/- to 60,000/-] on 10 kg scale estimation. The scheme was initiated and proceeded to step-6. It was observed that at step-2 [Friedel craft's acylation] the reaction is not working Without using 1,2,4-trichloro benzene solvent and at 100 °C the product formation Is there along with some impurity formation [~20% by TLC]. The reaction was performed at 80 ° C and obtained the product as the major one by excluding the non-polar impurity formation. This route also abandoned, because of impurities forming in step-2 if not used 1,2,4-trichloro benzene.

Proposed Route



In the proposed route cost of 4-Chloro benzene (**1**) (1 kg 30 USD) and yield of this Friedel craft[13] reaction step-(1) also around 87%. For the isolation not required any silica purification directly afforded 4-Chloroacetophenone with in the aq. work-up. Key Int Acid-4 fallowed by Enoic acid-3 are also afforded with good yileds. Overally Key Int Acid-4 obtained 4.25 kg from only 7.66 kg of 4-Chloro benzene (**1**).

Materials and Method

Preparation of 1-(4-chlorophenyl)propan-1-one (2)[14]

To the stirred solution of chlorobenzene (7.66 kg, 68.4 mol) was added propionyl chloride (6.96 L, 75.24 mol) at 0°C and after that added $AlCl_3$ (10.03 kg, 75.24 mol) pinch wise at same temperature. Raised the temperature to 60°C and maintained for 3h. The progress of the reaction was monitored by TLC. The reaction mixture was reverse quenched with ice cold water (10 L) and extracted with ethyl acetate (2 x 2 L), combined organic layers were washed with brine solution (1 L), dried over sodium sulphate and evaporated under reduced pressure to afford 1-(4-chlorophenyl)propan-1-one (8.03 kg, 47.8 mol, 70%). as crystalline semi solid.

Afforded as iol liquid compound with 87% yield. ^{1}H NMR (CDCl3): δ 7.84 (d, *J* = 2.4 Hz, 2H), 7.61 (d, *J*=2 Hz, 2H), 2.99 (q, 6.76, *J*=7.2, 2H), 1.24 (t, *J*=8 Hz, 3H).

LCMS (EI) m/z 169.25 (M+H, 99.32%).

13C NMR (CDCl3): δ 199.76, 135.67, 131.91, 129.58, 128.04, 31.83, 8.18

Preparation of (E)-4-(4-chlorophenyl)-3-methyl-4-oxobut-2-enoic acid (3)[15]

To the stirred solution of 1-(4-chlorophenyl)propan-1-one (2) (8.03 kg, 47.8 mol) in 1,4-dioxane (47 L) was added 50% glyoxylic acid (5.3 L, 71.7 mol) at 0°C and after that added Con.H_2SO_4 (2 L, 20.4 mol) dropwise at same temperature. Raised the temperature to 80°C and maintained for 16h. The progress of the reaction was monitored by TLC. The reaction mixture was reverse quenched with ice cold water (10 L) and extracted with ethyl acetate (2 x 3 L), combined organic layer was washed with brine solution (1 L), dried over sodium sulphate and evaporated under reduced pressure to afford (E)-4-(4-chlorophenyl)-3-methyl-4-oxobut-2-enoic acid (3) (7.48 kg, 33.4 mol, 70%). as light brown liquid.

Afforded as iol liquid compound with 87% yield. ^{1}H NMR (CDCl3): δ 7.84 (d, *J* = 2.4 Hz, 2H), 7.61 (d, *J*=2 Hz, 2H), 2.99 (q, 6.76, *J*=7.2, 2H), 1.24 (t, *J*=8 Hz, 3H).

LCMS (EI) m/z 169.25 (M+H, 99.32%).

13C NMR (CDCl3): δ 199.76, 135.67, 131.91, 129.58, 128.04, 31.83, 8.18

Preparation of 3-(4-chlorophenyl)-3-oxopropanoic acid (4) [16]

To the stirred solution of (E)-4-(4-chlorophenyl)-3-methyl-4-oxobut-2-enoic acid (3) (7.48 kg, 33.4 mol) in acetic acid (65 L) and water (26 L) was added zink dust (2.6 kg, 40.08 mol) at 0°C. Then raised the temperature to 80°C and maintained for 1h. The progress of the reaction was monitored by TLC. The reaction was cooled to RT, filtered throw celite bed, effluent was extracted with ethyl acetate (2 x 3 L) and separated the layers, combined organic layer was washed with sat. sodium bicarbonate (2 x 2 L), brine solution (1 L), dried over sodium sulphate and evaporated under reduced pressure to afford 3-(4-chlorophenyl)-3-oxopropanoic acid (4) (4.52 kg, 19.94 mol, 60%). as light brown liquid.

Afforded as iol liquid compound with 87% yield. ^{1}H NMR (CDCl3): δ 7.84 (d, *J* = 2.4 Hz, 2H), 7.61 (d, *J*=2 Hz, 2H), 2.99 (q, 6.76, *J*=7.2, 2H), 1.24 (t, *J*=8 Hz, 3H).

LCMS (EI) m/z 169.25 (M+H, 99.32%).

13C NMR (CDCl3): δ 199.76, 135.67, 131.91, 129.58, 128.04, 31.83, 8.18

Conclusion

In this work we reduce the overall cost of preparation and reduce the time for preparation of pimobendane by alternate approach with key intermediate 4-(4-chlorophenyl)-3-methyl-4-oxobutanoic acid (4).

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