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Research article

Novel synthetic and commercial oriented synthesis of substituted benzofuran moiety

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Key words: Pongamol, Substituted benzofuran moiety, retention time (RT), reflux, semisynthetic, industrial friendly process.

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Abstract

Substituted benzofuran moiety i.e. Pongamol the target nucleus is reported to having various biological activity like anti-convulsant, sedative (prologation of sleeping time), anti oxidant and dislipidemic etc. due to structural correlation to CNS acting drugs. All the available data of Pongamol were based from natural or semisynthetic source. This encourages going for a synthesis of Pongamol with industrial friendly process. Pongamol is prepared synthetically using easily available source and quick, cost effective and high yielding process.

Introduction

Pongamol is obtained from extracts of fruits of *Pongamia pinnata* syn. and *P. glabra* (family: Leguminoceae/ Fabaceae). This plant has been used in traditional medicine for bronchitis, whooping cough, rheumatic joints, and to quench dipsia in diabetes (1995, Kirtikar and Basu). Pongamol is reported to have anticonvulsant [1], antioxidant and dislipidemic [2], anti hyperglycaemic [3], antiviral [4], anticancer [5] properties which suggest it to be a potential moiety having multiple biological activity. All the available data of pongamol were based from natural or semisynthetic source. This encouraged towards going for a synthetic source pongamol and with industrial friendly process. The synthetic routes were using easily available source and quick, cost effective and high yielding.

Experimental

3-(bromomethyl)-4-hydroxy-2-methoxybenzoic acid, Acetophenone, Triphenyl phosphine, 3-formyl-4-hydroxy -2-methoxybenzoic acid, Diazoacetone, solvents used in chemical synthesis (Dimethyl formamide, Toluene, Methyl tert-Butyl Ether, Dimethyl sulphoxide, Tetrahydro furan, Methanol, Ethanol, Isopropanol and Dichloromethane were purchased from local source of commercial grade. The chemicals were used as received without purification. Rests of the chemicals used were of analytical grade.

Melting points were determined in open capillary on Lab-India electronic apparatus. Purity of the compounds was verified by running TLC, using precoated plates and HPLC using reverse phase chromatography. The IR spectra of the compounds were recorded on Thermo electron (omnic) FT-IR Spectrophotometer using KBr (cm^{-1}). ^{1}HNMR Spectra was recorded in DMF using NMR (Bruker FT-400 MHz spectrometer at 400 MHz for 1H) using TMS as internal standard (chemical shifts in _ ppm).

Synthesis of 1-(4-methoxybenzofuran-5-yl)-3-phenyl propane-1,3-dione (1a-c)

Solution of acetophenone in dimethyl formamide was added to the stirred solution of 3-(bromomethyl)-4-hydroxy-2-methoxybenzoic acid in dimethylformamide (15 volume) at room temp and the whole reaction was refluxed for about 8 hrs. The resultant was dissolved in toluene (20 vol) and excess of triphenyl phosphine (1.1M) leading to formation of an in situ Intermediate, to the toluene solution, formaline was added dropwise at a temperature of 60-80^{o}C on continuous stirring.

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1-(3-(bromomethyl)-4-hydroxy-2-methoxyphenyl)-3-phenylpropane-1,3-dione (1a)

Solution of acetophenone into solution of 3-(bromomethyl)-4-hydroxy-2-methoxybenzoic acid in dimethyl formamide was added with constant stirring at room temperature. The reaction mixture was then refluxed for 8 hours. Reaction continues until acetophenone completely used up. Yellowish white powder, % yield was 65.03; Rf was 0.31 in Hexane: Ethyl acetate: Methanol (6:3:1) Retention time was 11 mins. IR (KBr): 3423 (OH Stretch) and 1725 (-C=O Stretch), 1252 (O-C Stretch), 2898 (C-H Stretch)

Synthesis of in situ Intermediate of 1-(4-methoxy benzofuran-5-yl)-3-phenylpropane-1,3-dione (1b)

1a was dissolved in toluene (20 volume) and excess of triphenyl phosphine (1.1M) was added, reaction is monitored till 1a gets consumed leading to formation of an Intermediate (1b).

Synthesis of 1-(4-methoxybenzofuran-5-yl)-3-phenyl propane-1,3-dione(1c)

To 1b solution in toluene, formaldehyde was added dropwise at a temperature of 60-80^{o}C on continuous stirring. Reaction was monitored continuously for consumption 1b. Off white powder. Very soluble in methanol, ethanol, isopropanol, acetonitrile, tetrahydro furan, dichloromethane and toluene. % yield was 67.54; M.P. was 125^{o}C; Rf was 0.52 in Hexane: Ethyl acetate: Methanol (6:3:1), RT was 10.2 min, IR(KBr) : 3000-2800 (CH) and 1550-1750 (-C=O), 1279 (OCH3), 1H NMR: δ 7.94-7.79 (m, 3H, Ar-H), 7.23 (s, 1H, Ar-H), 6.43 (m, 3H, Ar-H), 6.40-6.34 (m, 2H, Ar-H), 3.82 (s, 2H, -CH_2), 3.41 (s, 3H, -OCH_3).

Alternate route for synthesis of 1-(4-methoxy benzofuran-5-yl)-3-phenylpropane-1,3-dione (2a-b)

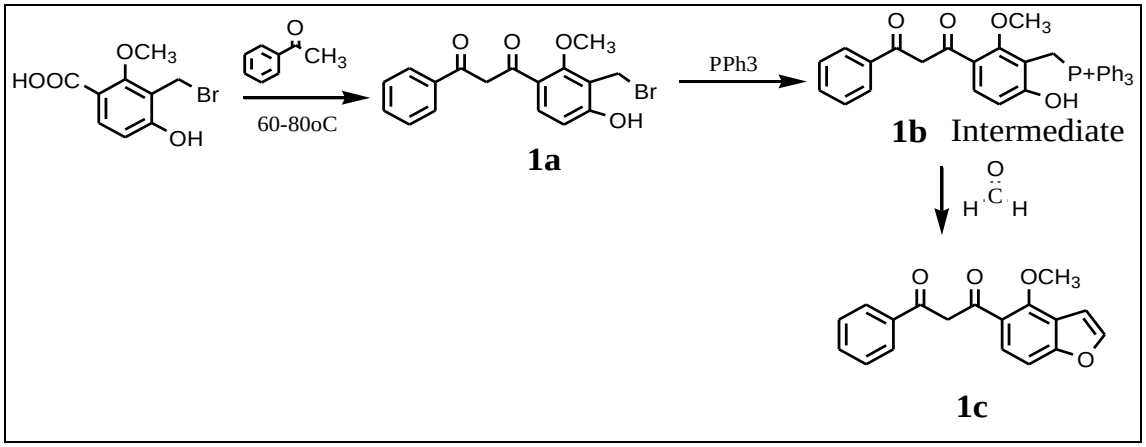
Synthesis of 4-methoxybenzofuran-5-carboxylic acid (2a)

Substituted salicylaldehyde as in scheme-II, was used as key raw material obtained as free sample from local market was taken in 12 volume of dichloromethane and excess of diazoacetone (1.5M) was added drop wise under continuous stirring at a temp of 40^{o}C to form 4-methoxybenzofuran-5-carboxylic acid. % yield was 37.44, dark coloured semi-solid mass. Very much soluble in all range of solvents.

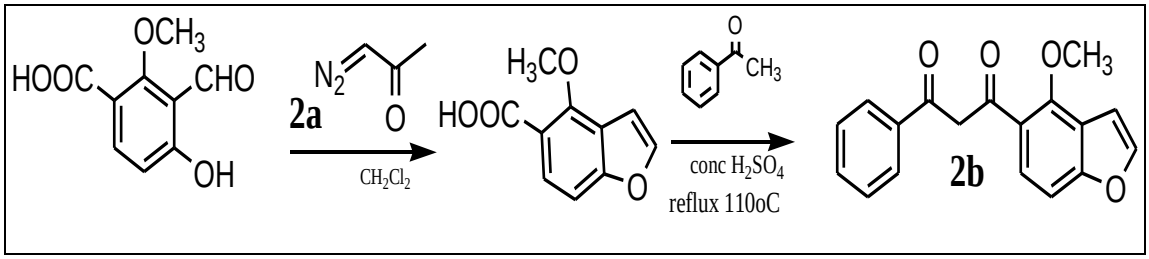
Synthesis of 1-(4-methoxybenzofuran-5-yl)-3-phenyl propane-1,3-dione(2b)

To the concentrated mass of 2a, DMF (15 volume) was added and made it to dissolve with continuous stirring. After complete dissolution, acetophenone, dissolved in 5 volume of DMF was added followed by dropwise addition of conc. H_2SO_4 then refluxed to 110^{o}C for 6 hrs.

% yield was 47.12; M.P. was 131°C, Off-white powder and have same RT as 1c.



Scheme 1. Synthesis of substituted benzofuran (1c)



Scheme 2. Synthesis of substituted benzofuran (2b)

Analytical Methodology and its validation

The analytical method involved for testing as in scheme I and II, during reaction monitoring, impurity profile and estimation was validated using HPLC system (shimadzu, class VP software) with buffer composition of 20mM K_2HPO_4 in water pH adjusted to 7.00±0.05 by dil. H_3PO_4; Eluent A comprising 90:10 Buffer: Acetonitrile, Eluent B 70:30 Buffer: Acetonitrile; Diluent (50:50 water: Acetonitrile, Column used was Brava C18, 100 x 3.5 mm, 5micron; Column temp was 45°C, Sample Temp was 10°C, Flow Rate was 1.2 ml/min, Wavelength was 305 nm; Sample concentration was 0.4 mg/mL.

Gradient Table

Time	0	6	11	12	15
% Eluent B	20	40	80	20	20

Specificity

All the known components were injected at 0.1% concentration (quantitative concentration) along with diluent as blank. No unknown impurities were found at the retention of known analyte peaks in the chromatogram of blank and peak purity of all components were passing therefore suggesting specificity of the method (Table 1).

Precision

Six replicates of Pongamol (Substituted benzofuran moiety) standard solution in diluent were injected. Area counts as obtained from the Pongamol at a concentration of 0.4 mg/mL were given in table 2.

Method Precision

Six different preparation of sample of Substituted benzofuran moiety at concentration of 0.4 mg/mL were prepared and injected. Data are in the Table 3.

Linearity

Solutions prepared by dissolving desired amount of impurities and API in diluent in the concentration range from 0.178µg/ml to 478µg/ml of sample concentration and injected. Data are in the Table 4.

Accuracy

Recovery solution are prepared by spiking desired amount of impurities and API in diluent in the concentration range from Accuracy was shown with all known impurities from 50 to 150% of specific concentration of 0.1%. Data are in the Table 5.

Results and Discussion

In the synthesis of 1a, stirring plays a important role, with uniform stirring above 45rpm at room temperature with creating proper surface area and mixing of reaction materials. Reaction proceeds with various solvents like Tetrahydrofuran, Toluene, Methyl tert Butyl ether, Dimethyl sulphoxide which were tried one by one. In the synthesis of 1b which is a in situ intermediate, nitrogen environment seemed faster rate of reaction but still there was not much improvement in overall yield. Volume of solvent used i.e toluene was important as it results in proper solubility and increasing interface for reaction and workup. The triphenyl phosphine was very much essential for removal, as it resulted in large precipitation in trouble some in uniform stirring and solubility issues and resulted in formation of various impurities. Excess of triphenyl phosphine was removed by manual process. The reaction was monitored through TLC as well as HPLC. HPLC played an important role in monitoring exactly the reaction progress. In the step of formation of 1c toluene was found most suitable solvent, though different solvents like dichloromethane, dimethyl formamide, various alcohols were found suitable as well. But the handling of triphenyl phosphine and intermediate was effective in toluene.

In the alternative scheme for synthesis of Pongamol, substituded salicylaldehyde was dissolved in dichloromethane, which was found best suitable in terms of its solubility and handling during workup for removal of impurities, biproducts and excess of diaoacetone. The addition was in drop wise fashion in 2-3 aliquots until complete conversion to 2a is achieved. The temperature was optimised at 40°C looking into the yield and byproducts generated. The resulting mass was concentrated.

During validation of HPLC method used for testing and reaction monitoring for specificity parameter the peak was found pure which can be seen in table 1.

Table 1. Specificity

Name of Components	Peak angle	Purity Threshold
Acetaminophen	0.123	1.098
3-(bromomethyl)-4-hydroxy-2-methoxybenzoic acid	0.145	2.223
1-(3-(bromomethyl)-4-hydroxy-2-methoxyphenyl)-3-phenylpropane-1,3-dione	1.761	5.431
Pongamol	4.723	10.320

Table 2. Precision

No. of Injections	Area counts
1	3520279
2	3487823
3	3562930
4	3487190
5	3535109
6	3519761
Mean	3518849
SD	28897.4
%RSD	0.8

Table 3. Linearity

Conc (mg/mL)	Area counts (µV*sec)
0.000178	1579
0.00323	28982
0.0421	392930
0.1423	1207190
0.2588	2235109
0.3984	3519761
0.47808	4223713.2
Slope	8815230
Intercept	-7723
CC	0.99987

Table 4. Method Precision

		% Area			
Sl no.	**Concentration**	**RT**	**Pongamol**	**Acetaminophen**	**1a**
1	0.39841	11.34	95.68	3.12	1.2
2	0.41223	11.35	95.64	3.13	1.23
3	0.39842	11.34	95.69	3.13	1.18
4	0.36844	11.35	95.67	3.12	1.21
5	0.40484	11.33	95.64	3.14	1.22
6	0.41934	11.35	95.66	3.12	1.22
Mean		**11.34**	**95.66**	**3.13**	**1.21**
Std Deviation		**0.008**	**0.021**	**0.008**	**0.018**
% RSD		**0.1**	**0**	**0.3**	**1.5**

Table 5. Accuracy

	Acetaminophen			**3-(bromomethyl)-4-hydroxy-2-methoxybenzoic acid**		
	Amount Added (µg/mL)	**Amount Recovered (µg/mL)**	**% Recovery**	**Amount Added (µg/mL)**	**Amount Recovered (µg/mL)**	**% Recovery**
	0.243	0.241	99.2	0.250	0.242	96.8
50%	0.198	0.194	98.0	0.204	0.195	95.6
	0.212	0.209	98.6	0.218	0.21	96.3
	0.396	0.393	99.2	0.408	0.395	96.8
100%	0.411	0.418	101.7	0.423	0.42	99.3
	0.443	0.441	99.5	0.456	0.443	97.1
	0.621	0.614	98.9	0.640	0.616	96.3
150%	0.594	0.583	98.1	0.612	0.585	95.6
	0.589	0.591	100.3	0.607	0.593	97.7

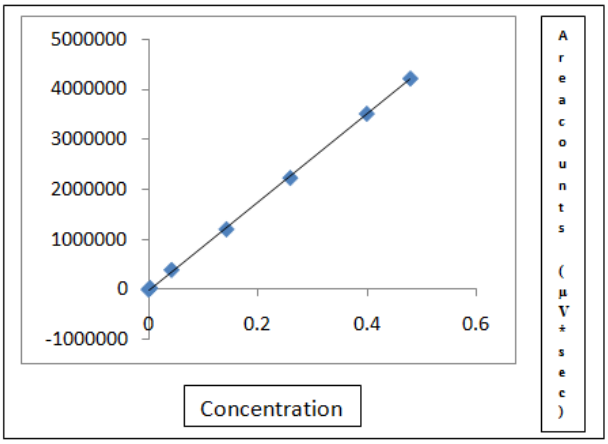


Figure 1: Figure for Linearity

In Linearity, various concentrations at range were in 0.178µg/ml to 478 µg/ml. In method precision, results of each injection of six preparation of sample solution in diluent is tabulated. In system precision, six injection of in working standard was injected six replicates in diluents. The % RSD obtained was 0.8. The % RSD of all % area are 0.0% (Pongamol), 0.3% (Acetaminophen), 1.5% (1a) and retention time are 0.0 % which are well below 10.0 suggesting precision of the method.

Conclusion

The above synthetic step was able to obtained desired purity of API with a satisfactory yield of 65% using all commercial grades of solvents and reagents. This suggests that the above scheme can be used for industrial purpose. The analytical method involved in testing of substances was validated. The method was found to be specific, precise, linear and accurate.

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