SYNTHESIS OF POTENTIAL RELATED SUBSTANCES OF PIRFENIDONE

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ABSTRACT:
The synthesis of five contaminants of pirfenidone (2), formed during the preparation of pirfenidone bulk drug, is described. The products were 1-(4-bromophenyl)-5-methylpyridin-2(1H)-one (3), 1-(3-bromophenyl)-5-methylpyridin-2(1H)-one (4), 1-(2-bromophenyl)-5-methylpyridin-2(1H)-one (5), 1,1'-(1,4-phenylene)bis(5-methyl pyridin-2(1H)-one) (6), 1,1'-(1,3-phenylene)bis(5-methyl pyridin-2(1H)-one) (7). The structures of these compounds were established on the basis of spectral data (IR, 1H-NMR and MS).

KEY WORDS: Pirfenidone, bromobenzene derivatives, bulk drug, synthesis, contaminants.

INTRODUCTION:
Pirfenidone 2, chemically known as 5-methyl-1-phenylpyridin-2(1H)-one, a pyridone compound, is an orally available pyridone derivative that exhibits anti-inflammatory, antioxidant and antifibrotic properties1-5. A large number of in vitro and animal experiments show that it is able to inhibit the synthesis of collagen, reduction in the generation of the multi-cell factor and blocks the cytokine driven desmocyte to stimulate the value, thereby preventing and even reverse the fibrosis scar formation. Several methods are reported in the literature for the preparation of pirfenidone,6-10 but the related compound synthesis was not discussed. The preparation and characterization data of these related substances has been necessary for the preparation of reference compounds for the quality assurance of bulk drugs and drug formulations.
EXPERIMENTAL:

General. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. All melting points were determined with Polmon melting point apparatus. 1H-NMR and 13C-NMR spectra were recorded on a Bruker 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. Mass spectra were measured on Thermo Finningan LCQ mass spectrometer. Infrared spectra were recorded on a Shimadzu spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. Analytical HPLC were run with Zorbax SB phenyl, 250 x 4.6 mm, 5 µ column at 230nm.

General procedure for alkylation of 5-methylpyridin-2(1H)-one (1).

5-Methyl-1-phenylpyridin-2(1H)-one (2). Mixture of Compound 1 (10 g, 91.7 mmol), K₂CO₃ (15.2 g, 110 mmol) and CuO (0.36 g, 4.5 mmol) in bromobenzene (21.6 g, 137.6 mmol) and DMF (50 mL) stirred at 125-130°C for 20 h, then cooled to 25°C and diluted with water (80 mL), adjusted pH to 12 to 13 with NaOH solution (30%), filtered through hyflow and washed with toluene (50 mL). Thus obtained filtrate was extracted with toluene followed by washing with NaCl solution (20%). The resulting toluene extract, after carbonization, evaporated to minimum volume (30 mL), cooled to 5-10°C, filtered the product and washed with precooled toluene (10 mL), dried, to yield 2 (12 g, 70%) as a off white solid; purity 99.9% (by HPLC); mp 110-112 °C (lit, 102-104°C); IR (KBr, cm⁻¹): 1670. ¹H-NMR (300 MHz, CDCl₃): δ 2.09 (s, 3H), 6.59 (d, 1H), 7.1-7.49 (m, 5H, Ar-H). ¹³C-NMR (75 MHz, CDCl₃): δ 16.8, 114.7, 121.2, 126.4, 128.1, 129.1, 135.1, 140.9, 142.4, 161.5. MS (ESI, m/z): 186 [M+H]+.

1-(4-Bromophenyl)-5-methylpyridin-2(1H)-one (3). This compound was prepared in a similar way to 2, using compound 1 (10 g, 91.7 mmol) and 1,4 dibromobenzene (32.4 g, 137.3 mmol), as a light brown solid (15.7 g, 65 %); purity 98.2% (by HPLC); mp 108-109 °C; IR (KBr, cm⁻¹): 1674. ¹H-NMR (300 MHz, DMSO): δ 2.04 (s, 3H), 6.43 (d, 1H, J=9.3), 7.38 (dd, 1H, J=2.4, 9.3), 7.40 (s, 1H), 7.43-7.67 (m, 4H, Ar-H). ¹³C-NMR (75 MHz, CDCl₃): δ 16.2, 114.2, 120.1, 120.8, 128.9, 131.8, 135.6, 140.1, 143.2, 160.2. MS (ESI, m/z): 266 [M+2]+; Anal. Calcd for C₁₂H₁₀BrNO (264.12): C, 54.57; H, 3.82; N, 5.30%. Found: C, 54.43; H, 3.88; N, 5.34%.

1-(3-Bromophenyl)-5-methylpyridin-2(1H)-one (4). This compound was prepared in a similar way to 2, using compound 1 (10 g, 91.7 mmol) and 1,3-Dibromobenzene (32.4 g, 137.3 mmol), as a light brown solid (13.3 g, 55 %); purity 98.4% (by HPLC); mp 108-109 °C; IR (KBr, cm⁻¹): 1674. ¹H-NMR (300 MHz, CDCl₃): δ 2.05 (s, 3H), 6.61 (d, 1H, J=9.6), 7.12 (s, 1H), 7.28 (dd, 1H, J=2.4, 9.3), 7.30-7.52 (m, 4H, Ar-H). ¹³C-NMR (75 MHz, CDCl₃): δ 16.2, 114.7, 121.2, 126.4, 128.1, 129.1, 135.1, 140.9, 142.4, 161.5. MS (ESI, m/z): 186 [M+H]+.

1-(2-Bromophenyl)-5-methylpyridin-2(1H)-one (5). This compound was prepared in a similar way to 2, using compound 1 (10 g, 91.7 mmol) and 1,2-dibromobenzene (32.3 g, 137.3 mmol), as a light brown solid (15.7 g, 65 %); purity 98.4% (by HPLC); mp 108-109 °C; IR (KBr, cm⁻¹): 1674. ¹H-NMR (300 MHz, CDCl₃): δ 2.09 (s, 3H), 6.61 (d, 1H, J=9.6), 7.12 (s, 1H), 7.28 (dd, 1H, J=2.4, 9.3), 7.30-7.52 (m, 4H, Ar-H). ¹³C-NMR (75 MHz,
CDCl₃): δ 16.8, 114.7, 121.3, 126.3, 128.4, 129.1, 130.2, 133.5, 134.7, 135.1, 140.9, 161.5. MS (ESI, m/z): 266 [M+2]+; Anal. Calcd for C₁₂H₁₀BrNO (264.12): C, 54.57; H, 3.82; N, 5.30%. Found: C, 54.54; H, 3.80; N, 5.28%.

1,1’-(1,4-Phenylene)bis(5-methyl pyridin-2(1H)-one) (6). This compound was prepared in a similar way to 2, using compound 1 (10 g, 91.7 mmol) and 1,4-Dibromobenzene (10.8 g, 45.7 mmol), as a light brown solid 6 (18.7 g, 70%); purity 99.2% (by HPLC); mp 108-109 °C; IR (KBr, cm⁻¹): 1674. ¹H-NMR (300 MHz, DMSO): δ 2.07 (s, 3H), 6.45 (d, 2H, J=9.3), 7.39 (dd, 2H, J=2.4, 9.6), 7.49 (s, 2H), 7.53 (s, 4H, Ar-H). ¹³C-NMR (75 MHz, DMSO): δ 16.3, 114.2, 120.2, 127.3, 135.8, 140.2, 143.2, 160.4. MS (ESI, m/z): 293 [M+H]+; Anal. Calcd for C₁₈H₁₆N₂O₂ (292.33): C, 73.95; H, 5.52; N, 9.58%. Found: C, 73.86; H, 5.56; N, 9.63%.

1,1’-(1,3-phenylene)bis(5-methyl pyridin-2(1H)-one) (7). This compound was prepared in a similar way to 2, using compound 1 (10 g, 91.7 mmol) and 1,3-Dibromobenzene (10.8 g, 45.7 mmol) as a light brown solid 7 (18.2 g, 68%); purity 99.3% (by HPLC); mp 108-109 °C; IR (KBr, cm⁻¹): 1674. ¹H-NMR (300 MHz, DMSO): δ 2.06 (s, 3H), 6.44 (d, 2H, J=9.3), 7.39 (dd, 2H, J=2.4, 9.3), 7.48 (s, 2H), 7.49-7.63 (m, 4H, Ar-H), 7.50 (d, 1H), 7.51(d, 1H), 7.61 (s, 1H). ¹³C-NMR (75 MHz, DMSO): δ 16.27, 114.25, 120.22, 124.7, 126.2, 129.1, 135.8, 141.1, 143.2, 160.2. MS (ESI, m/z): 293 [M+H]+; Anal. Calcd for C₁₈H₁₆N₂O₂ (292.33): C, 73.95; H, 5.52; N, 9.58%. Found: C, 73.94; H, 5.50; N, 9.59%.

RESULTS AND DISCUSSION:

Pirfenidone 2 was prepared, by starting from 5-methylpyridin-2(1H)-one 1 by following the known method (Scheme 1). It was observed during the process development of pirfenidone 2 that some of the lab batches of 2 were contaminated with these impurities 3, 4, 5, 6 and 7 in the range from 0.1% to 0.5%. Therefore it is necessary to synthesize these impurities 3, 4, 5, 6 and 7 for the analytical method validation of pirfenidone 2. Then, a comprehensive study has been carried out to prepare these contaminants.

Scheme 1. i. DMF, K₂CO₃, bromobenzene, CuO, 125 °C; ii. DMF, K₂CO₃, 1,4 – dibromo benzene, CuO, 125 °C; iii. DMF, K₂CO₃, 1,3-dibromobenzene, CuO, 125 °C; iv. DMF, K₂CO₃, 1,2-dibromobenzene, CuO, 125 °C; v. DMF, K₂CO₃, 1,4-dibromobenzene, CuO, 125 °C; vi. DMF, K₂CO₃, 1,3-dibromobenzene, CuO, 125 °C.
Pirfenidone was prepared by treating bromobenzene with 5-methylpyridin-2(1H)-one using CuO and K$_2$CO$_3$. The presence of isomeric bromobenzene such as 1,4-dibromobenzene, 1,3-dibromobenzene and 1,2-dibromobenzene causes the formation of these related substances (Scheme 1).

In summary, we report a method for the preparation of the common contaminants of pirfenidone in quite good yield and purity. Also, the spectral data (IR, 1H-NMR and MS) of these compounds was described.

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REFERENCES:


Graphical Abstract

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<th>Synthesis of potential related substances of Pirfenidone</th>
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