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New Synthesis of 4-Methoxyisophthalic Acid[1]

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Abstract—A new synthetic route to 4-methoxyisophthalic acid, the key intermediate in the synthesis of Picotamide, is reported. The new protocol starts from commercially available and cheap 4-methylphenol and includes four steps: esterification, Fries rearrangement, methylation, and oxidation; the overall yield is 49%. Unlike the traditional Blanc chloromethylation/oxidation scheme, the proposed procedure avoids using volatile and corrosive hydrochloric acid.

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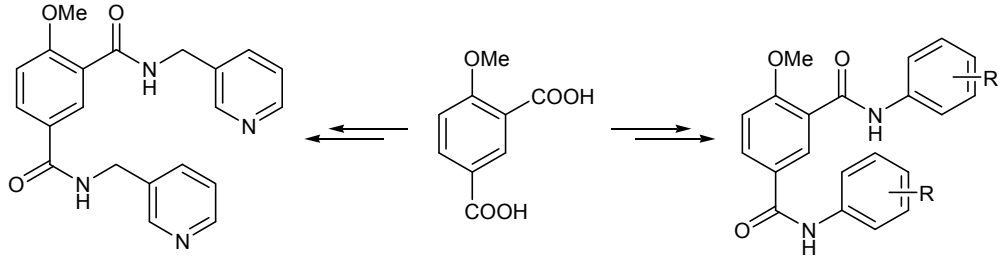
Picotamide (**1**), also known as *N*,*N*′-bis(3-picolyl)-4-methoxyisophthalamide, is an antiplatelet drug with dual inhibitory effects [1, 2]. Picotamide can inhibit thromboxane A_2 (TXA_2) receptors and the synthesis of TXA_2, and it has no influence on the endothelial prostacyclin (PGI_2) production [3, 4]. We have reported the synthesis of a series of structural analogs **2** of Picotamide by replacing its two 3-picolyl groups by substituted phenyl groups. Some of these analogs exhibited higher antiplatelet aggregation activities than Picotamide itself [5–8]. 4-Methoxyisophthalic acid (**3**) is the key intermediate in the synthesis of Picotamide and its analogs [5–8] (Scheme 1).

The most common method to synthesize 4-methoxyisophthalic acid is Blanc chloromethylation/methylation/oxidation sequences using anisole [9], 2-methylanisole, or 4-methylanisole [10] as starting materials (Scheme 2). A drawback of these methods is the use of volatile hydrogen chloride in the Blanc chloromethylation. Hydrogen chloride is not only difficult to handle but it also causes corrosion of the experimental equipment. Storage of a large volume of waste acid is also troublesome when the reaction is carried out on a large scale. Moreover, it is dangerous to use Blanc chloromethylation for industrial process because of using a large volume of bubbling hydrogen chloride. Direct oxidation of 2,4-dimethylphenol with potassium permanganate to produce 4-methoxyisophthalic acid was also reported; however, the yield is low (25%), and 2,4-dimethylpenol is a relatively expensive reagent [10]. Herein, we would like to introduce a new and safer method to synthesize 4-methoxyisophthalic acid using Fries rearrangement as the key step (Scheme 3). The proposed procedure allows preparation of 4-methoxyisophthalic acid on a large scale without using chromatographic purification, and the overall yield is 49% based on 4-methylphenol.

As shown in Scheme 3, 4-methylphenol (**4**) was used as starting material. Acetylation of **4** with acetic anhydride gave 4-methylphenyl acetate (**5**) which was

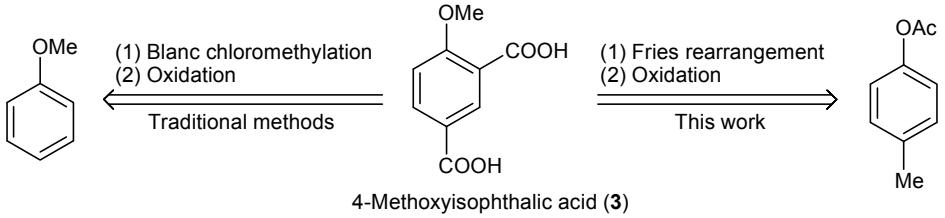
Scheme 1.



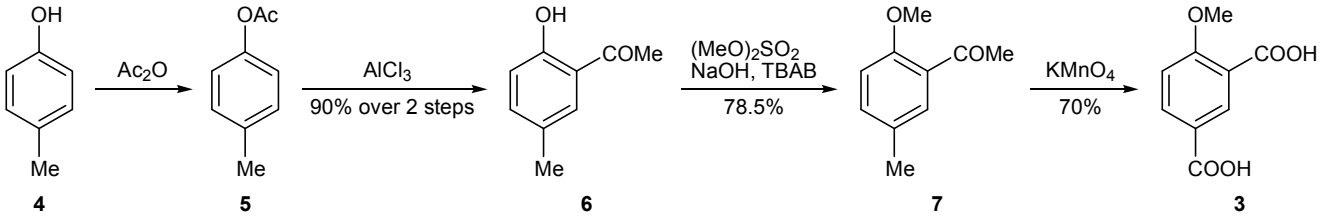
Picotamide (**1**) 4-Methoxyisophthalic acid (**3**) Picotamide analogs (**2**)

[1] The text was submitted by the authors in English.

Scheme 2.



Scheme 3.



subjected to Fries rearrangement to 5-methyl-2-hydroxyacetophenone (**6**) in the presence of $AlCl_3$ [11]. The yield was 90% over two steps. Compound **6** reacted with dimethyl sulfate in aqueous sodium hydroxide using tetrabutylammonium bromide (TBAB) as catalyst to produce 2-methoxy-5-methylacetophenone (**7**) in 78.5% yield. Oxidation of the methyl and acetyl groups in **7** afforded the target 4-methoxyisophthalic acid (**3**) which can be isolated in the pure state by recrystallization from ethanol. The structure of 4-methoxyisophthalic acid was fully characterized.

This new synthesis of **3** has several advantages. First of all, all steps are chromatography-free, and intermediate products **5**, **6**, and **7** can be used in the following steps without purification; therefore, the procedure is readily scalable. Moreover, the Fries rearrangement gives **6** as the only product. The known Blanc chloromethylation procedures usually give mixtures of mono- and disubstituted products. The new route reported in this paper avoids using difficult-to-handle gaseous hydrogen chloride which might cause corrosion of the equipment and environmental problems.

EXPERIMENTAL

All reagents were purchased from Aladdin Industrial Corporation (P.R. China), Shanghai Darui Fine Chemical (P.R. China), and Tianjin Kewei (P.R. China) and used without further purification. The melting points were determined with a Kofler micro melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded with a Bruker AM 400 spectrometer (400 MHz for ^{1}H) using tetramethylsilane as internal standard. The IR spectra were recorded on a Perkin Elmer 157 spectrometer. The mass spectra (electrospray ionization) were measured on Agilent 6310 Ion Trap and Shimadzu LC-MS instruments.

4-Methylphenyl acetate (5) and 1-(2-hydroxy-5-methyl)ethanone (6). A mixture of 4-methylphenol (**4**) (37.0 mmol, 4.0 g) and acetic anhydride (38.2 mmol, 3.6 mL, 3.9 g) was refluxed for 3 h. Aluminum trichloride (44.0 mmol, 6.0 g) and 36% hydrochloric acid (129.3 mmol, 4.0 mL, 4.7 g) were then added to the resulting solution, and the mixture was heated at 110°C for 8 h. The mixture was cooled and extracted with methylene chloride, the extract was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give 4.95 g (36.7 mmol, 90%) of yellow crude product **6**. Compound **6** was used directly in the following step without further purification.

1-(2-Methoxy-5-methylphenyl)ethanone (7). A 150-mL round bottom flask was charged with compound **6** (35.3 mmol, 5.3 g), sodium hydroxide (36.0 mmol, 1.4 g), and dimethyl sulfate (47.1 mmol, 5.2 g) in aqueous ethanol (15 mL), and tetrabutylammonium bromide (3.5 mmol, 1.1 g) was then added as catalyst. The mixture was stirred first at 40°C for 30 min and then at 75°C for 4.5 h and extracted with ethyl acetate, and the extract was washed with 15 ml of 5% aqueous NaOH and 50 mL of water three times in succession. The organic layer was dried with anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure to leave 4.55 g (78.5%) of crude compound **7**. ^{1}H NMR spectrum

($CDCl_3$), δ, ppm: 2.31 s (3H, CH_3), 2.63 s (3H, CH_3), 3.89 s (3H, OCH_3), 6.87 d (1H, H_{arom}, J = 8.2 Hz), 7.27 d.d (1H, H_{arom}, J = 2.0, 8.2 Hz), 7,54 d (1H, H_{arom}, J = 2.0 Hz). Compound **7** was used in the next step without further purification. The ^{1}H NMR spectrum of **7** was identical to that reported in [12].

4-Methoxyisophthalic acid (3). A mixture of compound **7** (34.2 mmol, 5.6 g) and sodium hydroxide (100.0 mmol, 4.0 g) in 200 mL of water was stirred at room temperature for 30 min. The temperature of the solution was then raised to 80°C within 3 h, and potassium permanganate (170.0 mmol, 23.2 g) was added quickly in small portions. When the reaction was complete, 3 mL of ethanol was added through the top of the reflux condenser to consume unreacted $KMnO_4$. The precipitate of manganese dioxide was separated by filtration and washed with hot water (2×25 mL). The filtrate was combined with the washings, acidified with dilute aqueous hydrochloric acid to pH 1–2, and cooled, and the precipitate was filtered off. The product was additionally recrystallized from ethanol Yield 4.6 g (23.5 mmol, 69.6%), white solid, mp 260–261°C; published data [13]: mp 268–269°C. IR spectrum, ν, cm^{-1}: 3300 br (OH), 2955 (C–H), 1606 (C=O). ^{1}H NMR (DMSO-d_6), δ, ppm: 3.88 s (3H, OCH_3), 7.20 d (1H, H_{arom}, J = 8.8 Hz), 8.03 d.d (1H, H_{arom}, J = 8.8, 2.0 Hz), 8.21 d (1H, H_{arom}, J = 2.0 Hz), 12.9 s (2H, COOH). ^{13}C NMR (DMSO-d_6), δ_C, ppm: 56.2, 112,5, 121,1, 122.5, 132.3, 134.4, 161.6, 166.5, 166.6. Mass spectrum: m/z 195 $[M-H]^-$.

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REFERENCES

1. Milani, M., Longoni, A., and Maderna, M., *Br. J. Clin. Pharmacol*., 1996, vol. 42, p. 782.
2. Modesti, P.A., *Cardiovasc. Drug Rev*., 1995, vol. 13, p. 353.
3. Celestini, A. and Violi, F., *Vasc. Health Risk Manage*., 2007, vol. 3, p. 93.
4. Sartori, E., Camy, F., Teulon, J.M., Caussade, F., Virone-Oddos, A., and Cloarec, A., *Eur. J. Med. Chem*., 1993, vol. 28, p. 625.
5. Liu, X.J., Shao, Y.L., Wang, C., He, X., Si, H.Q., and Wang, S.J., *Chin. J. Med. Chem*., 2007, vol. 17, p. 354.
6. Liu, X.J., Shi, X.X., Zhong, Y.L., Liu, N., Liu, K., *Bioorg. Med. Chem. Lett*., 2012, vol. 22, p. 6591.
7. Deng, N., Liu, X.J., Shi, C.L., Zhang, F.X., and Liu, L.Z., *Chin. J. Med. Chem*., 2012, vol. 22, p. 191.
8. Liu, X.J., He, X., Shi, C.L., Meng, J., Shao, Y.L., Si, H.Q., and Hu, T., *Chin. Chem. Lett*., 2011, vol. 22, p. 1139.
9. Sprengling, G.R. and Freeman, J.H., *J. Am. Chem. Soc*., 1950, vol. 72, p. 1982.
10. Gray, R. and Bonner, J., *J. Am. Chem. Soc*., 1948, vol. 70, p. 1249.
11. Shaikh, M.H., Subhedar, D.D., Khedkar, V.M., Jha, P.C., Khan, F.A.K., Sangshetti, J.N., and Shingate, B.B., *Chin. Chem. Lett*., 2016, vol. 27, p. 1058.
12. Buchwald, S.L., Watson, B.T., Lum, R.T., and Nugent, W.A., *J. Am. Chem. Soc*., 1987, vol. 109, p. 7137.
13. Rao, K.V.J. and Row, L.R., *J. Org. Chem*., 1960, vol. 25, p. 981.