# Synthesis of 3-bromo-4-isobutyloxyphenyl carbothioamide

Qinqin Wang[1], Yuping Guo[1], Min Wang[1], Wufu Zhu [1] and Shan Xu[1,a]

[1]School of Pharmacy, Jiangxi Science & Technology Normal University, Nanchang 330013, China

[*a]shanxu9891@126.com

**Keywords:** 3-bromo-4-isobutyloxyphenyl carbothioamide, Synthesis

**Abstract.** 3-bromo-4-isobutyloxyphenyl carbothioamide **1** is an important intermediate in many biologically active compounds such as febuxostat. In this work, a rapid synthetic method for compound **1** was established. The compound **1** was synthesized from the commercially available 4-hydroxybenzonitrile **2** through three steps including bromination, oxyalkylation and thioamidation. The structure was confirmed by MS and $^1$HNMR. Furthermore, the synthetic method was optimized. The total yield of the three steps was 49.2%.

## Introduction

Febuxostat is a new urate lowering therapy drugs which exhibited significant therapeutic effect on gout[1-12]. As more and more people have been plagued by gout, developing gout inhibitors is one of the research hotspots for the treatment of gout. Konda S *et al* reported a synthetic route of febuxostat. It was synthesized throught eight steps, using 4-hydroxy-3-nitrobenzaldehyde as a starting material, febuxostat was prepared by dehydration, thioformylation, cyclization, oxygen alkylation, catalytic hydrogenation, followed by diazotized, hydrolysis, acidification. On the other hand , used p-hydroxy thiobenzamide as a starting material, febuxostat was obtained after cyclization, formylation, etherification, oximation dehydration and hydrolysis[14-15]. Chen Y *et al* established a synthetic route of febuxostat using methyl 4-hydroxybenzoate as raw material, through bromintion, oxyalkylation, cyanide, hydrolysis, chlorination and aminolysis reaction, thioamidation, cyclization, hydrolysis and acidification to give the title compound[16].

Most of the synthetic methods of 3-bromo-4-isobutyloxyphenyl carbothioamide which reported in the literature have the drawbacks such as longer synthetic route, lower yield and harmful to environment. 3-bromo-4-isobutyloxyphenyl carbothioamide **1** is a key intermediate for synthesizing Febuxostat. Therefore, the optimization of the synthetic route and methods of 3-bromo-4-isobutyloxyphenyl carbothioamide **1** is necessary.

In this study, we designed and optimized the synthetic methods for 3-bromo-4-isobutyloxyphenyl carbothioamide **1** and make it more suitable for industrial production. The structure of febuxostat was shown in Fig. 1

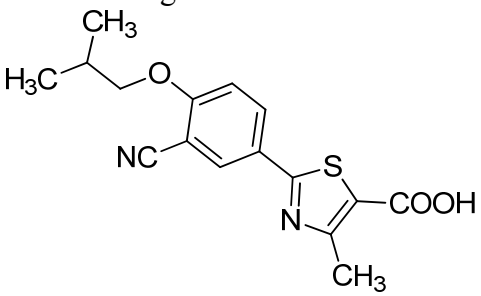



Fig. 1 Sructure of febuxostat

## Materials and methods

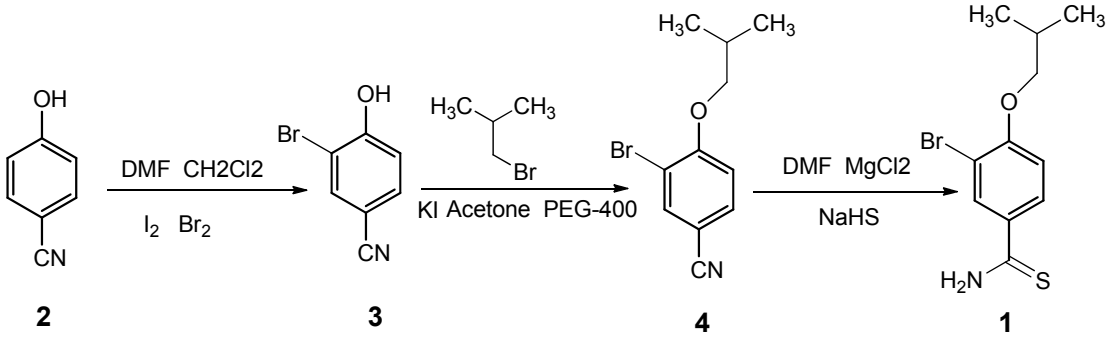
NMR spectra were performed using Bruker 300 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a

© 2016. The authors - Published by Atlantis Press 

Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China).

**Synthesis of compounds**

The structures and the synthetic route were shown in Scheme 1.




Scheme 1. The synthetic route of compound **1**

**Reagents and conditions:**(a) DMF, $CH_2Cl_2$, $I_2$, $Br_2$, -5℃-10℃, 10h; (b) KI, Acetone , 1-bromo-2-methylpropane, PEG-400, 8h; (c) DMF, $MgCl_2$, NaHS.

**3- bromo-4-hydroxybenzonitrile(3)**

To the mixture of 4-hydroxybenzonitrile(2.95 g, 24.8 mmol), dichloromethane(5 mL), *N*,*N*-dimethylformamide(1 mL), iodine (0.16 g, 1.3 mmol), bromine (7.50 g, 6.9 mmol ) was added drop-wise with stirring maintaining the temperature below 10℃ and keep the temperature for 10h, After completion of reaction as indicated by TLC, the mixture was poured into 16% sodium bisulfite solution(38 mL) and stirred for 0.5h at room temperature, the mixture was then filtreed and the filter cake was washed with dichloromethane for 0.5h with strong stirring, then filtreed and dried to obtain **3** as white solid(4.33 g, 88.2%). MP 152.4-154.5℃, ESI-MS m/z: $[M+H]^+$197.5.

**3- bromo-4-isobutoxy benzonitrile(4)**

A solution of 3-bromo-4-hydroxybenzonitrile **3**(15.00 g, 75.8 mmol), anhydrous potassium carbonate(41.0 g, 296.7 mmol) and acetone(120 mL) was stirred at room temperature for 0.5h. Then Potassium iodide(1.20 g, 7.2 mmol), PEG-400, 1-bromo-2-methylpropane(15.53 g, 133.3 mmol) were added and refluxed for 8h and monitored by TLC. The heated mixture was then filtered and two-thirds of the organic layer was concentrated under reduced pressure. The remaining reaction was added to water with vigorous stirring yielding a precipitate. The mixture was then filtered to yield **4** as light yellow solid (17.0 g, 89.3%). ESI-MS m/z: $[M+H]^+$254.1 and ESI-MS m/z: $[M+Na]^+$278.1. $^1$H-NMR(600MHz, DMSO-d6): δ(ppm) 0.99-1.00(d, *J*=6.5Hz, 6H), 2.02-2.08(m, 1H),3.83-3.86(d, *J*=5.8Hz, 2H), 7.20-7.22(d, *J*=8.6Hz, 1H), 7.9-8.1(dd, *J*=8.6Hz, 1H),8.2(s, 1H).

**3-bromo-4-isobutyloxyphenyl carbothioamide(1)**

To the solution of 3-bromo-4-isobutoxy benzonitrile **4**(6.33 g, 24.92 mmol), *N*,*N*-dimethylformamide(75 mL), anhydrous magnesium chloride(2.98 g, 31.25 mmol) , sodium hydrosulfide(5.6 g, 100 mmol) was stage added and stirred at room temperature for 10h. After completion of reaction as indicated by TLC, the solution was poured into ice-water(300 mL) with strong stirring for 0.5h. The mixture was then filtered to furnish crude product and the crude product was recrystallized with anhydrous methanol and dried to give **5** as light solid(4.95 g, 62.5%). ESI-MS m/z: $[M-H]^-$285.6. $^1$H-NMR(600MHz, DMSO-d6):δ(ppm) 1.01 (d, *J*=6.7Hz, 6H), 2.0-2.1(m, 1H), 3.90-3.91(m, 2H), 7.12-7.14(m, 1H), 7.96-7.98(m, 1H), 8.21(d, *J*=2.3Hz, 1H), 9.49(s, 1H), 9.76(s, 1H).

## Conclusions

In conclusion, 3-bromo-4-isobutyloxyphenyl carbothioamide **1** is a key intermediate of febuxostat. It was synthesized from the commercially available 4-hydroxybenzonitrile **2** through three steps including bromination, oxyalkylation and thioamidation. The synthetic method of compound **1** and the reactions conditions were optimized, after recrystallization, the purity of the product was much more higher. Its structure was confirmed by MS and $^{1}$HNMR spectrum.


## Acknowledgments

We gratefully acknowledge the generous support provided by The National Natural Science Funds (No. 81460527), Project supported by the Natural Science Foundation of Jiangxi Province (No. 20142BAB215020) , Doctoral Scientific Research Foundation of Jiangxi Science & Technology Normal University and Program of Key Laboratory of Drug Design and Optimization, Jiangxi Science & Technology Normal University（300098010306）and College Students' Science and Technology Innovation Project of Jiangxi Province


## Reference


[1] Pascual E, Siver F, Yasothan U, *et al.* Febuxostat [*J*]. *Nat Rev Drug Discov*, 2009, 8(3):191-192.

[2] Perez-Ruiz F, Dalbeth N, Schlesinger N. Febuxostat, a novel drug for the treatment of hyperuricemia of gout [*J*]. *Future Rheumatol*, 2008, 3(5):421-427.

[3] Burns C M, Wortmann R L, Gout therapeutics: new drugs for an old disease [*J*]. *Lancet*, 2011, 377(9760):175-177.

[4] Takano Y, Hase-Aoki K, Horiuchi H, *et al.* Selectivity of febuxostat, a novel non-purine inhibitor of xanthine oxidase/xanthine dehydrogenase [*J*]. *Life sci*, 2005, 76(16):1835-1847.

[5] Nepali K, Singh G, Turan A, *et al*. A rational approach for the design and synthesis of 1-acetyl-3,5-diaryl-4,5-dihydro(1H) pyrazoles as a new class of potential non-purine xanthine oxidase inhibitors [*J*]. *Bioorg Med Chem*, 2011, 19(6):1950-1958.

[6] Sato H, Ashizawa N, Iwanaga T, *et al*. Design, synthesis, and pharmacological and pharmacokinetic evalution of 3-phenyl-5-pyridyl-1,2,4,-triazole derivatives as xanthine oxidoreductase inhibitors [*J*]. *Bioorg Med Chem Lett,* 2009, 19(1):184-187.

[7] Bardin T. Current management of gout in patients unresponsive or allergic to allopurinol [*J*]. *Joint Bone Spine*, 2004, 71( 6) : 481-485.

[8] Chen L X, Schumacher H R. Gout: can we create an evidence-based systematic approach to diagnosis and management [*J*]. *Best Pract Res Clin Rheumatol*, 2006, 20( 4) : 673-684.

[9] Wortmann R L, Macdonald P A, Hunt B, *et al*. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials [*J*]. *Clin Ther,* 2010, 32( 14) : 2386-2397.

[10] Ernst M E, Fravel M A, Febuxostat: a selective xanthine-oxidase/xan-thine-dehydrogenase inhibitor for the management of hyperuricemia in adults with gout [J]. *Clin Ther*, 2009, 31( 11) : 2503-2518.

[11] Hosravavr R, Grabowski B, Wu J T, *et al.* Effect of food or antacid on pharmacokinetics and pharmaco dynamics of febuxostat in healthy subjects [*J*]. *Br J Clin Pharmacol*, 2008, 65(3):355- 363.

[12] Watabra K, Yarino A T, Hiramatsu T. Production of 2-(4-alkoxy-3-cyanophenyl) thiazole derivative: JP, 10045733 [P]. 1998-02-17.

[13] Konda S, Fukushima H, Hasegawa M, *et al*. 2-Arylthiazole derivative and pharmaceutical composition containing the same: EP, 0513379 [*P*]. 1992-06-11.

[14] Watanabe K, Fujii T, Tanaka T, *et al*. Preparation method of 2-(4-alkoxy-3-cyanophenyl) thiazol derives and novel intermdiates for the synthesis of them: JP, 1994329647 [P]. 1994-11-29.

[15] Watanabe K, Fujii T, Tanaka T, *et al*. Preparation method of 2-(4-alkoxy-3-cyanophenyl) thiazole derivatives: JP, 1998045733 [ P]. 1998 -02-17.

[16] Chen Y, Luo Y, Lu W. Synthesis of febuxostat [*J*]. *Chin Med Indus.* 2009, 40(1):1-5.