Synthesis of 3-chloro-2-oxo-butanoate

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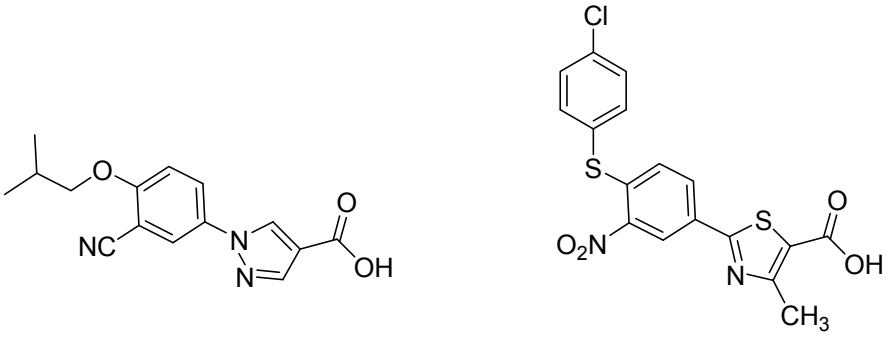
Abstract. 3-chloro-2-oxo-butyric acid ethyl ester **5** is an important intermediate in many biologically active compounds such as thiazole carboxylic acids. In this work, a rapid synthetic method for compound **5** was established. The compound **5** was synthesized from the commercially available diethyl oxalate through two steps including nucleophilic substitution, chlorinated. The structure was confirmed by MS and ^{1}HNMR. Furthermore, the synthetic method was optimized. The total yield of the two steps was30%

Introduction

Thiazole carboxylic acids is a new non-purine selective inhibitor of xanthine oxidoreductase，which exhibited significant therapeutic effect on xanthine oxidoreductase[1-5]. Xanthine oxidoreductase (XO) inhibitory activity of these compounds is one of the highest activity of the compounds 5 to inhibit the activity of XO reach 0.02nmol • L^{-1}[6-9]. The compounds belonging to XO long-lasting inhibitor of XO inhibition is highly selective, with high safety, has been listed in Europe, Japan and other countries[10-15]. Tamura Y [16] ,*et al*. reported a synthetic route of thiazole carboxylic acids intermediates. It was synthesized throught two steps, using diethyl oxalate as a starting material, including nucleophilic substitution, chlorinated to give the title compound. Most of the synthetic methods of 3-chloro-2-oxo-butyric acid ethyl ester which reported in the literature have the drawbacks such as long synthetic route, low yield and harmful to environment. 3-chloro-2-oxo-butyric acid ethyl ester 5 is a key intermediate for synthesizing thiazole carboxylic acids Therefore, the optimization of the synthetic route and methods of 3-chloro-2-oxo-butyric acid ethyl ester 5 is necessary.

In this study, we designed and optimized the synthetic methods for 3-chloro-2-oxo-butyric acid ethyl ester 5 and make it more suitable for industrial production. The structure of thiazole carboxylic acid was shown in Fig 1.



1 **2**

Fig. 1 Sructures of thiazole carboxylic acids

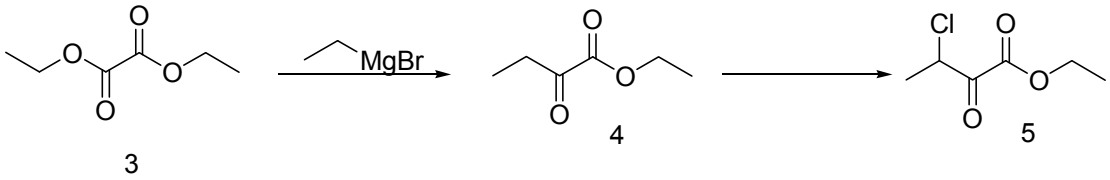
Materials and methods

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 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 5

Reagents and conditions: (a) 10% diluted hydrochloric acid, diethyl oxalate, dry tetrahydrofuran, magnesium turnings, ethyl bromide, iodide, 60 ℃. (b) 2- oxobutanoate, dichloro-methan

2-oxobutanoate 4

Freshly activated magnesium turnings (24g), bromoethane (22g) and a catalytic amount of iodine were suspended in anhydrous tetrahydrofuran (50mL), after heated to 60 ℃, bromoethane 44.4g(607mmol) which was dissolved in absolute tetrahydrofuran(140ml) was added slowly in such degree.After the reaction completed, stirring was continued for one hour to obtain a Grignard reagent. Then diethyl oxalate (87.6g ,600 mmol) was dissolved in anhydrous tetrahydrofuran (150mL). After cooled to -5 ~ -10 ℃, sufficiently stirred and then poured slowly into a Grignard reagent. When added was completed, the mixture was stirred at room temperature for 4 h. 10% hydrochloric acid was added to the solution,extracted with dichloromethane(300mL * 2), and the dichloromethane layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give yellow oily liquid. Vacuum distillation, collecting 75 ~ 78 ℃ fraction to obtain a colorless oily liquid(25g). Yield 32%, MS (ESI): m/z 131.2$[M+H]^+$.

3-chloro-2-oxo-butyric acid ethyl ester 5

2-oxobutanoate (26g) was added to a three-necked flask, after cooling to 0 ℃, dichloro-sulfonyl (27g ,200 mmol) was slowly added to the solution. and the mixture was stirred at room temperature. When the reaction completed, the solution was concentrated under reduced pressure to give yellow liquid (32g), yield 93%. MS (ESI): m/z 165.0$[M+H]^+$, 166.9$[M+H]^+$, 163.1$[M-H]^{-1}$, 165.0$[M-1]^{-1}$.

Conclusions

In conclusion, 3-chloro-2-oxo-butyric acid ethyl ester **5** was synthesized from the commercially available Diethyl oxalate through two steps including nucleophilic substitution, chlorinated. The synthetic method of compound 5 and the reactions conditions were optimized, the purity of the product was much more higher. Its structure was confirmed by MS and ^{1}HNMR spectrum.

Acknowledgments

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Reference

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

[2] 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.

[3] 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.

[4] 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.

[5] 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.

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

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

[8] 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.

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

[10] Ahmed I,Khazi M, Mahajanshetti C S, *et al*.Synthesis and antimicyobical acting of some 2-(substituted Carbox-amidomethyl/thyithio)-5-(2-thienyl)-1.3.4-oxadiazole *[J].Indian J Hetercocycli Chem.*2003,13(1);87-88

[11] Cesur N,Cesur Z, Guner H, *et al*. Fused heterocy-cles; Sythesis of some new imidazothiazole *[J]. Heterocyclic Communications* ,2002,85:433-438

[12] Cussia S, Halay G J,Barnes K D, *et al*. Thia2010[4,5-b] paridnes as.fundicides *[P].JP* 03647023.2003

[13] Sasaki E, Imai T, Hori N, *et al*. Method for producing 2-substituted carbapenem derivative *[P]. JP* 26686,2003

[14] SongY,Kim D S, *et al*. Fungicidal composition containing n-(a-cyano-2-thenyl)-4-enthyl-2-enthy/amino-5-thiazole carboxamide (ethaboxam) and as an adjust polyxyaky –lenealkye ether *[P]. US* 2003.0203949,2003

[15] Kazzouli E S, Berteina-Rabion S, Mouaddib A, *et al.* Sol-id support synthesis of 2,4-disubstituted thiazoles and aminothiazoles. *Tetrahedron Lett* 2002,43;3193-3196

[16] Tamura Y, Kawasaki T, Adachi M, et al. Reaction of Gri-gnard reagents with the combined reagent triphenylphos-phine thiocyanate; a versatile route to N-unsubstituted thioamides. *Synthesis*,19799(11):887-9.