Asian Journal of Chemistry; Vol. 24, No. 4 (2012), 1538-1540

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

A Novel Method for the Synthesis of Actarit

LI-YI ZHOU[1,2], JUN YANG[1,2,*], XI-QING YAN[1], YAN-JUAN PAN[1], FENG WU[2], JING ZHANG[2], FU-LIN YAN[1] and GUANG-ZHOU LU[1]

[1]College of Pharmacy, Xinxiang Medical University, Xinxiang 453003, Henan, P.R. China
[2]KAMP Institute for Medical Research, Changsha 410008, Hunan, P.R. China

*Corresponding author: Fax: +86 373 3831682; Tel: +86 373 3831665; E-mail: bcd2009@126.com

(*Received*: 24 February 2011; *Accepted*: 23 November 2011) AJC-10709

The specific synthetic route to synthesize the actarit (4-acetyl-amino phenylacetic acid) by acylation was designed in which *p*-amino benzaldehyde (a) and nitromethane (b) was used as the raw materials, through Knoevenagel reaction. The selective reduction of potassium borohydride and *p*-amino phenylacetic acid to be oxidated under the acidic conditions. After optimization of the synthetic conditions, the yield of each step was more than 85 %. The synthesized compound was confirmed by the elemental analysis and nuclear magnetic resonance. Because of the readily available raw materials, simple operations, high yield and avoiding highly toxic reagents in the synthesis of actarit (4-acetyl-amino phenylacetic acid), the synthetic route is suitable for the industrial production.

Key Words: Actarit, Knoevenagel reaction, Selective reduction, Reaction mechanism.

INTRODUCTION

Actarit(A1-4), 4-acetyl-amino phenylacetic acid was studied as an immunomodulator by Japan's Nippon Shinyaku in 1994. Its main clinical role has been using for the chronic rheumatoid arthritis treatment, because it can inhibit the allergic reaction, *i.e*. it can prevent the progressive articular cartilage destruction and the enhance T-lymphocyte activation and the interleukin-2 effect[1-3].

The main synthetic route of actarit is as follows: 1) The actarit(A1-4) is obtained, which total yield is 67 %, through 4-nitrophenyl acetate reduction, esterification, acylation and hydrolysis reaction[2]. 2) The actarit(A1-4) is obtained, which total yield is 60.6 %, through 4-nitrophenyl acetic acid combining with ethanol to become ester by hydrogen chloride, reduction by iron, acylation by acetic anhydride and hydrolysis by alkaline[3]. 3) The actarit(A1-4) is obtained, which total yield is 46.7 %, through 4-nitrophenyl acetonitrile obtained by nitration of benzene acetonitrile and then hydrolysis, reduction and acylation reaction[4]. Reference to many studies[5-7], this experiment was designed to synthesize actarit by acylation, which the *p*-amino benzaldehyde (a) and nitromethane (b) was used as the raw materials, through Knoevenagel reaction to generate aromatic-β-nitrostyrene, the selective reduction of the double bond of potassium borohydride to form aromatic-(β-nitro-ethane) and *p*-amino phenylacetic acid to be oxidated under the acidic conditions. The specific synthetic route is as Fig. 1.

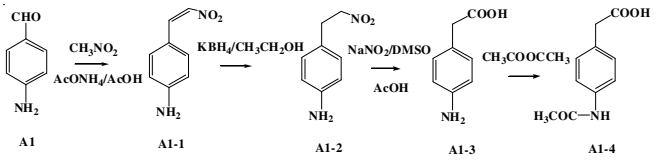

Fig. 1. Route of actarit(A1-4) synthesis

EXPERIMENTAL

XR-01 WRP melting point apparatus, Shanghai Precision Scientific Instrument Co. Ltd.; Vario-ET-III type elemental analyzer, Germany Elementear Inc. for determination of C,H,N content; Vario-ET-III type ^{1}HNMR, 400 MHz U.S. Vanian, Inc., TMS as internal standard, CCl_3 as solvent; Lab Tech P600 HPLC, Beijing Lab Tech Instruments.

p-Amino benzaldehyde (chemical pure), Suzhou Jaynes Chemical Co. Ltd., China; Nitro methane (AR), Shanghai Chemical Reagent Co. Ltd., China; Glacial acetic acid (AR), Tianjin Chemical Reagent Da Mao Plants, China; Acetic anhydride (reagent grade), Guangzhou Medical Station Chemicals Company, China; DMSO (AR), Tianjin Chemical Reagent Da Mao Plants, China; Potassium borohydride (AR), Tianjin Chemical Reagent Institute; Sodium nitrite (AR), Tianjin Chemical Reagent Da Mao Plants, China.

Synthesis of actarit

Synthesis of 4-(2-nitrovinyl)benzenamine (A1-1): Added *p*-amino benzaldehyde (a) (100 mmol) into a100 mL flask with a reflux condenser, at the same time, added 7.32 g

nitromethane, 7.8 g ammonium acetate and 50 mL of acetic acid, stirring and reaction under 60 ºC for 1 h and then the mixture was cooled to room temperature and poured into 200 mL ice water. The sold precipitation was filtrated and dryed to constant weight under the vacuum, recrystallized with anhydrous ethanol and dried by vacuum and the products were obtained. m.p.:155-157 ºC; Elemental analysis (%): C, 58.45; N, 17.21; H, 4.70; Calculated for $C_8H_8N_2O_2$ (%) : C, 58.53; N, 17.06; H, 4.91.

Synthesis of 4-(2-nitroethyl)benzenamine (A1-2): The potassium borohydride 5.40 g (0.1 mol) by adding 40 mL ethanol and mechanical stirring in an ice bath, 4-(2-nitrovinyl) benzenamine (0.02 mol) was dissolved in 10 mL ethanol dropwise. Control the reaction temperature was not more than 5 ºC. After dropping to continue stirring, TLC tracking response to raw material disappeared. The solution was poured into 50 mL 10 % HCl-ice-water solution, stirred to stop the bubbles, filtration, spin dry ethanol, added 10 mL water, used 25 mL × 3 chloroform extraction, washed by 25 mL water, dried by anhydrous magnesium sulfate, spin dry solvent and then the crude product was crystallizated and the product was obtained by recrystallizated. m.p. : 179-182 ºC; Elemental analysis (%): C, 57.90; N, 16.82; H, 6.10; Calculated for $C_8H_{10}N_2O_2$ (%): C, 57.82; N, 16.86; H, 6.07.

Synthesis of 4-amino phenylacetic acid (A1-3) : The 4-(2-nitroethyl)benzenamine (0.01 mol), DMSO (20 mL) and acetic acid 6 g (0.1 mol) in turn were put into a reaction flask, added sodium nitrite 1.38 g (0.02 mol) under stirring, continued stirring at 35 ºC, TLC track the response until the raw material disappeared. Added 10 % HCl solution acidified to pH = 2, used 15 mL × 3 of ethyl acetate extraction, spin dry solvent and then the oily product was obtained. Used 10 % KOH to adjust pH to 9, washed with 15 mL of ethyl acetate. Used the concentrated hydrochloric acid to adjust pH = 2 under the ice bath. After the mixture in the refrigerator overnight, the precipitation was filtered, which was aromatic acetic acid. m.p.: 196.5-200.5 ºC; Elemental analysis (%): C, 63.63; N, 9.20; H, 5.95; Calculated for $C_8H_9NO_2$ (%): C, 63.56; N, 9.27; H, 6.00.

Synthesis of 4-acetyl-amino phenylacetic acid (A1-4): *p*-Amino phenylacetic acid (10 g, 0.07 mol), DMF (30 mL, 0.4 mol) and acetic anhydride (6.6 mL, 0.07 mol) in stirring heated to reflux 3 h. Steam the solvent, residue after cooling with cold water and then ethanol recrystallization, which was white crystals (10.2 g); m.p.: 172.5-173.8 ºC; Consistent with literature values[4]; The yield 95 %; The purity 99.86 % meaured with HPLC normalized method. Elemental analysis (%): C, 62.22; N, 7.21; H, 5.69; Calculated for $C_{10}H_{11}NO_3$ (%): C, 62.17; N, 7.25; H, 5.74; ^{1}H NMR analysis: 2.02 (s, J = 4.8, 3H), 3.49 (s, 2H), 7.04 (d, J = 7.2,2H), 7.52 (d, J = 6.8, 2H); 8.00 (s, 1H), 11.00 (s, 1H).

RESULTS AND DISCUSSION

Mechanism of Knoevenagel reaction and the selective reduction process: First step, depending on the mechanism[8], Knoevenagel reaction synthesizs the active methylene compounds with aldehydes, ketones of the form α, β unsaturated compounds by catalyzed of the ammonia, amine or carboxylate. The reaction mechanism is shown in Fig. 2. Namely, carbonyl compounds of the form the amines transition state by the catalytic of primary amine, secondary amine or ammonium salt and amine transition state with active methylene of the carbon anion were added.

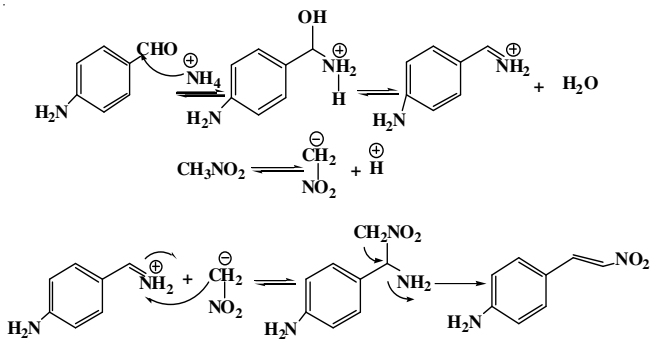

Fig. 2. Knoevenagel reaction mechanism

Second step, the reaction is selective reduction of carbon-carbon double bond, for acetylene, alkene reduction, widely used in catalytic hydrogenation and hydroboration[9]. Catalytic hydrogenation includes the nickel, palladium, platinum and other metals as catalysts of heterogeneous catalytic hydrogenation reaction and homogeneous organometallic catalysts hydrogenation. Hydroboration is the borane and carbon-carbon double bond to be added and formed the alkyl boranes, hydrolysis in the acidic environment of carbon-boron bond cleavage derived from saturated hydrocarbons. The borane reagent of sodium borohydride reduction method is more widely used. However, it shows many shortages such as low yield, high requirements on the solvent, high cost. Because of the mild reaction conditions of potassium borohydride, the solvent water requirements are not stringent that the price is cheap relatively, we tried to use potassium borohydride as reducing reagent, ethanol as solvent, reaction at room temperature. The reaction mechanism is as shown in Fig. 3.

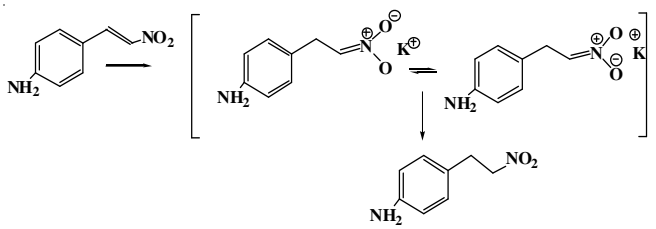

Fig. 3. Selective reduction mechanism of the potassium borohydride

Influence of reaction temperature on Knoevenagel-reaction: Reaction temperature on the yield is shown in Table-1. The higher yield, the higher temperature if the temperature is less than 60 ºC, whereas the lower yield, the higher temperature if the temperature is more than 60 ºC. Although the reaction is a nucleophilic reaction, elevated temperature on the reaction is favourable. The higher temperature of the molecular abnormalities stands, the faster response prone to side effects. The reaction temperature is influential, which must control the temperature 60 ºC up and down.

Influence of substrate molar ratio on Knoevenagel-reaction: Table-2 results show that the optimal reaction molar

ratio of n (a): n (b) = 1:1.2. If the ratio is lower or higher than this ratio, the yield decline. TLC also showed that the ratio in this reaction were only two points and the substrate reaction more thoroughly.

TABLE-1
INFLUENCE OF THE REACTION TEMPERATURE ON KNOEVENAGEL-REACTION

No.	Temperature (ºC)	n_a: n_b = 1:1.2	Yield (%)
1	25	1:1.2	40
2	40	1:1.2	50
3	50	1:1.2	70
4	60	1:1.2	85
5	70	1:1.2	67

TABLE-2
INFLUENCE OF SUBSTRATE MOLAR RATIO ON KNOEVENAGEL-REACTION

No.	$AcONH_4$ = N % m_a/g	n_a : n_b	Yield (%)
1	7.8	1:1	50
2	7.8	1:1.1	60
3	7.8	1:1.2	90
4	7.8	1:1.3	85

Conclusion

A novel route to synthesize the actarit(A1-4), which which *p*-amino benzaldehyde (a) and nitromethane (b) was used as the raw materials, through Knoevenagel reaction, the selective reduction of potassium borohydride and *p*-amino phenylacetic acid to be oxidated under the acidic conditions, was easy to operate, high yield (more than 85 %), avoiding the use of highly toxic sodium cyanide reagents and friend environment. The product structures were characterized by elemental analysis and ^{1}H NMR. The method was and suitable for the industrial production.

ACKNOWLEDGEMENTS

This work was supported by Xinxiang Medical University, Kamp Institute for Medical Research and grants from National Basic Research Program of China (2007CB936104) and the 863 National High Technology Research Development Program of China (2007AA021905).

REFERENCES

1. K.X. Gao, *Anthol. Med.*, **19**(s1), 31 (2000).
2. Y.-H. Hui, N.H. Huang, L. Ebbert, H. Bina, A. Chiang, C. Maples, M. Pritt, T. Kern and N. Patel, *J. Pharmcol. Toxicol. Method*, **56**, 256 (2007).
3. M. Mosharraf and C. Nyatröm, *Int. J. Pharm.*, **122**, 35 (1995).
4. R.B. Gupta and U.B. Kompella, Nanoparticle Technology for Drug Delivery, Taylor & Francis Group, New York, edn. 1, pp. 23-36 (2006).
5. C. Matt, A. Wagner and C. Mioskowski, *J. Org. Chem.*, **62**, 234 (1997).
6. A. Gissot, S. Gouela and C. Matt, *J. Org. Chem.*, **69**, 8997 (2004).
7. M.D. Nikalie, I.S. Ali and G.K. Dewkar, *Tetrahedron Lett.*, **41**, 959 (2000).
8. R. Wen, Organic Reactions for Drug Synthesis, Chemical Industry Press, Beijing, pp. 213-219 (2003).
9. R. Wen, Organic Reactions for Drug Synthesis, Chemical Industry Press, Beijing, pp. 365-371 (2003).