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An Improved Process for Preparation of Key Intermediates in the Synthesis of Praziquantel

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ABSTRACT

An improved greener method using toluene as the solvent for the bulk preparation of intermediates 2 and 3 for the synthesis of praziquantel (PZQ), the only drug used for schistosomiasis has been reported. The method will be of significant importance in the manufacture of PZQ by lowering manufacturing costs and reducing environmental problems.

Keywords: Schistosomiasis, PZQ, Improved process, Toluene

INTRODUCTION

Schistosomiasis is a neglected tropical disease and is a major public health problem in tropical and subtropical regions in particular of Sub-sahara Africa [1]. It is estimated that about 200 million people are infected each year, double the number of people are at risk and as high as 280,000 people die of this disease every year [2]. There were recent reports and evidences which showed that there is a high correlation in women with this disease and increased susceptibility to HIV/AIDs. Currently schistosomiasis can be treated only with a tetrahydoisoquinoline derivative Praziquantel (PZQ) which has been recommended by World Health Organization [3]. Every year about 100 tons of PZQ are required for millions of people affected with schistosomiasis. The high price of PZQ represented a major obstacle to the availability of PZQ in poor countries with endemic schistosomiasis. PZQ at an affordable price was a necessary condition to improve PZQs availability in poor countries. Further the manufacture of PZQ with a pollution free environment is also a required factor. This prompted us to undertake the present work to develop PZQ at lowering manufacturing costs and reducing environmental problems.

MATERIALS AND METHODS

General

All reagents are of commercial grade and were used without any purification. Chromatography was carried on silica gel (60-120 and 100-200 mesh). All the reactions were monitored by TLC. Proton Nuclear Magnetic Resonance (^{1}H-NMR) and ^{13}C-NMR spectra were recorded using Bruker Supercon Magnet DPX-200 spectrometers using Deuterated Chloroform ($CDCl_3$) and Deuterated Dimethyl Sulfoxide (DMSO-d_6) as solvents and Tetramethylsilane (TMS) as internal standard. Electrospray Ionization Mass Spectra (ESI-MS) were recorded on Thermo LCQ Advantage.

Preparation 2-chloro-N-phenethylacetamide 2

Method 1

To a solution of phenethylamine (1000.0 g, 8.2522 mol) and Na_2CO_3 (962.0 g, 9.076 mol) in toluene (600.0 ml) was added chloroacetyl chloride (1006.0 g, 8.8985 mol) dropwise at a temperature of 0-10°C. The reaction mixture was stirred with a mechanical stirrer for 1-2 h at room temperature. Water was poured into the reaction mass. The organic layer was separated and washed with brine. The organic layer was taken to the next stage and used *in situ* (1565.7 g, 96%).

Method 2

To a solution of phenethylamine (1000.0 g, 8.2522 mol) and Na_2CO_3 (1312.0 g, 12.3782 mol) in water (600.0 ml) was added drop wise chloro acetyl chloride (1025.20 g, 9.0774 mol) at room temperature. The reaction mixture was stirred with a mechanical stirrer for 1-2 h at room temperature. Toluene was added into the reaction mass. The organic layer was separated and washed with brine and taken to the next step.

Compound 2

White colourless needles; m.p. 59-63°C; IR (KBr): 3350, 1650 cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ=2.85 (2H, t, J=7.0 Hz), 3.55 (2H, q, J=6.7 Hz), 3.99 (2H, s), 6.73 (1H, br.s), 7.19-7.34 (5H, m); ^{13}C-NMR ($CDCl_3$): δ=35.51, 41.03, 42.68, 126.72, 128.75, 138.75, 165.91.

Preparation of 2-(2, 2-dimethoxyethylamino)N-phenethylacetamide 3

To a mixture of 2-chloro-N-phenethylacetamide 2 (1565.7 g, 7.9212 mol) prepared as above, amino acetaldehyde dimethyl acetals (1041.04 g, 9.9015 mol) and Na_2CO_3 (1091.53 g, 10.2975 mol) were added at room temperature. After stirring at 90-100°C for 5 h, toluene was recovered by distillation and the residual yellow oil was cooled to room temperature and diluted with dichloro methane (7900.0 ml). Then the organic phase (2004.3 g, 95%) was washed with water (3000.0 ml) followed by brine (2000.0 ml) then taken to the next step 3.

Compound 3

Viscous oil; IR (KBr): 3340, 2975, 1670, 1530, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.42 (2H, d, J=5.4 Hz) 2.63 (2H, t, J=7.1 Hz), 3.1 (2H, s), 3.14 (6H, s) 3.29 (2H, q, J=6.9 Hz), 4.09 (1H, t, J=5.4 Hz), 6.98-7.10 (5H, m), 7.26 (1H, t, J=1.3 Hz); ^{13}C-NMR ($CDCl_3$) δ=35.57, 39.93, 50.99, 52.23, 53.72, 103.42, 126.21, 128.35, 128.57, 138.92, 171.34.

Preparation of 2,3,6,7-tetrahydro-1H-pyrazino [2,1-a]isoquinolin-4(11bH)-one 4

The organic phase solution obtained in the above step (**3**) (2004.0 g, 7.5242 mol) was taken in a round bottom flask and cooled to 10-15°C. Sulphuric acid (2212.1 g, 22.5726 mol) was added slowly and the reaction mass maintained at a temperature of 25-30°C for 4-6 h. The reaction mass was quenched into water (10020 ml) and adjust the aqueous layer PH to 8-9 with 25% sodium hydroxide solution. Then extract the compound praziquanamine with dichloromethane (10020 m) and the resulted solution was taken into next step as in-situ (1446.0 g, 95%).

Compound 4

White solid; m.p. 118-121°C; IR (KBr) 3340, 2975, 1670, 1530 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=2.45-2.74 (4H, m, J=5.4 Hz), 2.61 (2H, t, J=7.1 Hz), 3.0 (2H, s), 3.16 (6H, s) 3.31 (2H, q, J=6.8 Hz), 4.09 (1H, t, J=5.4 Hz), 6.98-7.10 (5H, m), 7.26 (1H, t, J=1.3 Hz); ^{13}C-NMR ($CDCl_3$); δ=35.57, 39.93, 50.99, 52.23, 53.72, 103.42, 126.21, 128.35, 128.57, 138.92, 171.34.

Preparation of cyclohexane carbonyl chloride

Cyclohexane carboxylic acid (1100.0 g, 8.5937 mol) and dichloromethane (2200.0 ml) were taken into a round bottom flask at room temperature and cooled to 10-15°C and slowly thionyl chloride (1125.0 g 9.4531 mol) was added for 30min, then the temperature of the reaction mass was raised to 35-40°C and maintained for 2-3 h.

Preparation of praziquantel 5

Compound 4 (1446.0 g, 7.1496 mol) and sodium carbonate(1515.7 g, 14.2992 mol) were taken in a round bottom flask at 25-30°C and the reaction mass was cooled to 0-10°C and cyclohexane carbonyl chloride (1153.0 g, 7.8645 mol) was added slowly and the temperature of the reaction mass was raised to 35-40°C and maintained for 4 h. The reaction mass was quenched into water and resulted layers were separated. The organic layer was given bicarbonate washing and then dried with sodium sulphate, concentrated. Cyclohexane was then added to isolate the compound PZQ (2009.0 g, 90%).

Praziquantel

Half white to white solid; m.p. 138-139°C; m/z: 313.5 $[M+H]^+$, ^{1}H-NMR ($CDCl_3$): δ=1.17 (br.s., 2H), 1.31 (m, 4H), 1.65-1.70 (m, 4H), 2.62 (m, 2H), 2.78 (m, 2H), 2.9 (m, 2H), 3.7 (m, 1H), 4.4 (m, 1H), 4.50 (m, 2H), 4.96 (m, 2H), 7.20 (m, 4H); ^{13}C-NMR: δ=173.84, 173.44, 164.70, 164.09, 135.12, 134.93, 133.51, 54.78, 53.70, 48.39, 47.99, 45.62, 29.20, 28.90, 25.52, 24.93.

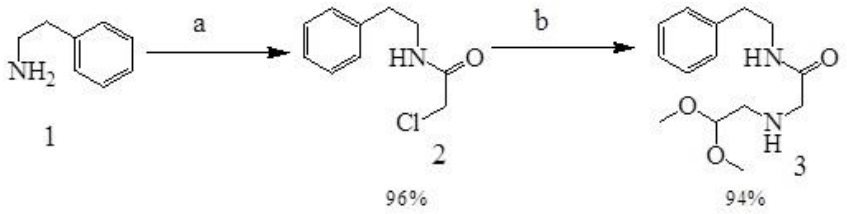
RESULTS AND DISCUSSION

PZQ is a simple molecule and has been prepared by several different synthetic routes [4-11], from those reported in the original patent [4], to a recent synthesis based on a multi component reaction [11]. Currently many companies manufacture the generic form of PZQ mainly via the process developed by Bayer [4]. Isoquinoline was used as the starting material in this process to prepare PZQ in six-steps. Apart from using a large quantity of benzene, it also consumes a large excess of potassium cyanide in a key step in the Reissert reaction and generates large volumes of cyanide waste. The disposal of the waste is a significant environmental problem especially because PZQ is produced in several ton quantities each year. Presently the cost of the drug and the pollution are the main two main problems encountered in the manufacturing of PZQ.

With all the available methods [5-11] which reported alternate routes to synthesize PZQ a fairly good procedure [8] involving mild conditions, less steps and high overall yield (50%) from using phenyl ethylene 1 as the starting material has become important for the production of PZQ. However this method suffers from limitations, like the use of large volumes of dichloromethane in the first step, low yield and employing two equivalents of reactant aminoacetldehyde dimethyl acetal in the second step. The poor yield of 3 was attributed to the use of the additional one equivalent of the aminoacetldehyde dimethylacetal in the second step which is not an effective acid scavenger to accelerate the formation of 3 efficiently. A slightly modified procedure [3] was tried to improve the yields of 2 and 3 under mild conditions (Scheme 1). Here the amidation of chloroacetyl chloride with phenethylamine 1 was conducted in a biphasic system comprising of water and dichloromethane to yield 2. Potassium carbonate was used as an acid scavenger. Further Dimethylformamide (DMF) was used as solvent in the step 2 which involves the subsequent amination of 2 with amino acetaldehyde dimethyl acetal to yield 3.

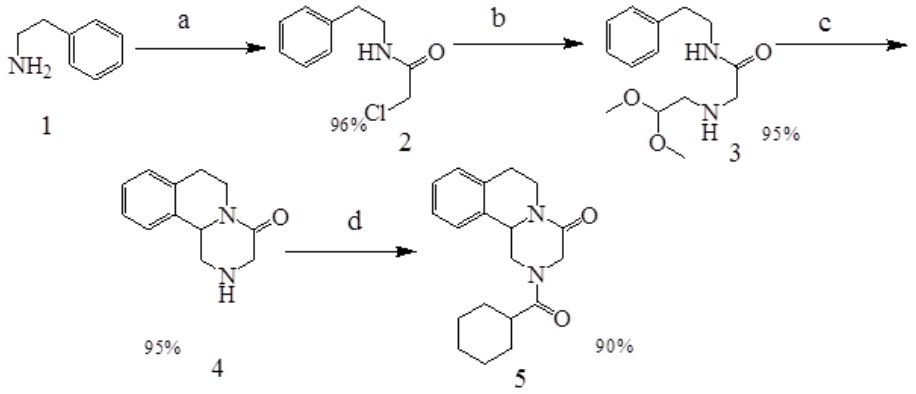
However, this method suffers from some serious drawbacks, such as the use of water and dichloromethane as the biphasic system in step 1 and the use of DMF as the solvent in the step 2. In the first step after the completion of the reaction dichloromethane has to be distilled out and in the second step, the removal of DMF is very difficult and even it is recovered it cannot be reused. Both of them increase the cost of the final product. Further in this process impurities like compounds 6, 7 and 8 are possible in the step 2 and compounds 9 and 10 are possible along with the end product. In the present work our efforts were focused on improving the preparation, especially in the preparation of the intermediates 2 and 3 in high yields under much mild condition (Scheme 2). As in other methods cyclization of 3 in large amount of H_2SO_4 afforded 4, whose acylation with cyclohexane carbonyl chloride gave the final product PZQ.

In the step 1 and step 2 of the present method (Scheme 2) toluene was used as the solvent. Two methods were followed for the step 1. In the first method toluene is used as the reaction medium and in the second method toluene is used to isolate the product. A significant improvement in this method is toluene need not to be removed after the step 1, the intermediate obtained can be used as such in the step 2. Potassium carbonate or sodium carbonate was used as an acid scavenger to get improved yield (96%) of 3. So, the present method reports that using toluene an eco-friendly media reduces pollution problem and the same time it lowers cost since toluene need not be recovered after the first step. Further in the second step after the completion of the reaction toluene is recovered and reused whereas DMF has its own limitations. This one again leads to a additional cost reduction of the process. Potassium carbonate or sodium carbonates which are used as acid scavengers are also of preferable choice because of their low reactivity, environmentally friendly by-product (KCl or NaCl and CO_2, low cost and convenience in storage.



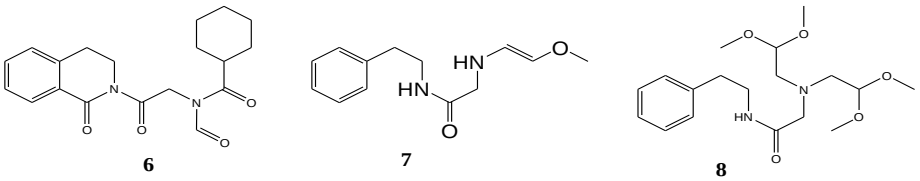
Scheme 1: Preparation of the intermediates 2 and 3

Conditions: (a) Phenyl ethylamine, chloroacetylchloride, potassium carbonate, DCM, water, 25-30°C, 2-3 h, (b) Amino acetaldehyde dimethylacetol, potassium carbonate, DMF, 75°C, 5 h.

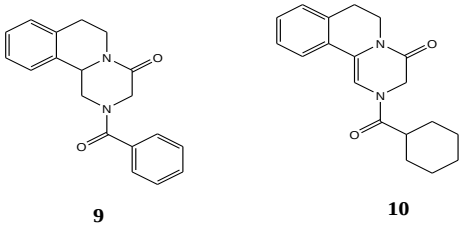


Scheme 2: Preparation of praziquantel

Conditions: (a) Chloroacetyl chloride, potassium carbonate, toluene, (b) Amino acetaldehyde dimethylacetol, potassium carbonate, toluene, 90-100°C, 4 h, (c) Sulphuric acid, DCM, 25-30°C, 3-6 h (d) Cyclohexane carbonyl chloride, DCM, sodium carbonate, 25-30°C, 3 h.



Possible impurities in step 2



Possible impurities along with 5

CONCLUSION

In conclusion, an improved greener method for the bulk preparation of intermediates 2 and 3 for the synthesis of PZQ has been reported. The method will be valuable in the manufacture if PZQ by lowering production costs and reducing environmental pollution.

REFERENCES

[1] P.J. Hotez, D.H. Molyneux, A. Fenwick, J. Kumaresan, S.E. Sachs, J.D. Sachs, L. Savioli, *N. Engl. J. Med*., **2007**, 357, 1018-1027.
[2] M.J. Van der Werf, S.J. DeVlas, S. Brooker, C.W. Looman, N.J. Nagelkerke, J.D. Habbema, D. Engels, *Acta Tropica*., **2003**, 86, 125-139.
[3] C. Yang, L. Zhang, Y. Zheng, S. Dequn, *Asian J. Chem*., **2013**, 25(16), 9415-9416.
[4] J. Seubert, R. Pohlke, F. Loebich, *Experientia*., **1977**, 33, 1036-1037.
[5] D. Frehel, J.P. Maffrand, *Heterocycles*., **1983**, 20, 1731-1735.
[6] F. Yuste, Y. Pallás, H. Barrios, B. Ortiz, R. Sanchez Obregon, *J. Heterocyc. Chem*., **1986**, 23, 189-190.
[7] W.F. Berkowitz, T.V. John, *J. Org. Chem*., **1984**, 49, 5269-5271.
[8] J.H. Kim, Y.S. Lee, H. Park, C.S. Kim, *Heterocycles*., **1998**, 48, 2279-2285.
[9] M.H. Todd, C. Ndubaku, P.A. Bartlett, *J. Org. Chem*., **2002**, 67, 3985-3988.
[10] J.K. Kim, Y.S. Lee, H. Park, C.S. Kim, *Tetrahedron*., **1998**, 54, 7395-7400.
[11] H. Liu, S. William, E. Herdtweck, S. Botros, A. Dömling, *Chem. Biol. Drug Des*., **2012**, 79(4), 470-477.