Improved synthesis of 1-[hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl]-3-(4-methylbenzenesulfonyl)urea

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1-[Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl]-3-(4-methylbenzenesulfonyl)urea (Gliclazide) was synthesised over three steps from the starting material of cyclopentane-1,2-dicarboxylic anhydride. *N*-aminocyclopentane-1,2-dicarboximide was obtained from the condensation reaction between the material and 80% hydrazine hydrate. The reduction of *N*-aminocyclopentane-1,2-dicarboximide and followed by the condensation with *p*-toluenesulfonyl urea generated Gliclazide. Every step was modified to be more simple and gave a 60% overall yield. The procedure is suitable for large-scale production.

Keywords: gliclazide, cyclopentane-1,2-dicarboxylic anhydride, hydrazine hydrate, reduction, condensation

Gliclazide, 1-[hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl]- 3-(4-methylbenzenesulfonyl)urea(**1**), which is the second generation of sulfonylureas, is an oral antidiabetic agent. It improves the function of blood coagulation, has hypoglycemic effect and thus has been widely used in clinical treatment. Several partial and total syntheses of Gliclazide had been reported.[1-4]

Hexahydrocyclopenta[*c*]pyrrol-2-amine(**4**) is a key intermediate used in the synthesis of (**1**).[5-8] A simple and efficient synthesis of (**4**) by four steps has keen reported[5-8] using the starting material cyclopentane-1,2-dicarboxylic anhydride (see Scheme 1, route 1). The synthesis utilises operationally simple procedures, and is suitable for large-scale preparation. However, expensive or hazardous reagents were used, such as $LiAlH_4$, BH_3 and H_2(at high pressure and temperature).

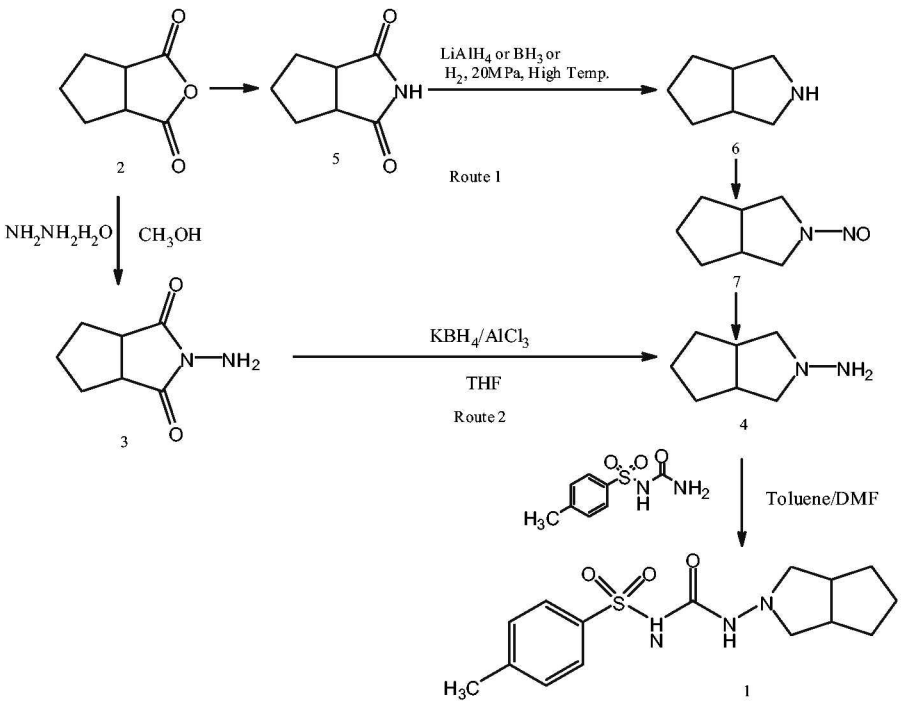
The synthesis of (**4**) formed the basis for our efforts to devise an improved practical synthesis (Scheme 1, route 2)

According to Hanson *et al.*,[9] imide could be prepared by reacting anhydride hydrazine hydrate in alcohols. *N*-aminocyclopentane-1,2-dicarboximide (**3**) was obtained from the condensation reaction between the material (**2**) and 80% hydrazine hydrate. The reduction of *N*-aminocyclopentane-1,2-dicarboximide (**3**) followed by the condensation with *p*-toluenesulfonyl urea generated Gliclazide (**1**). The new route for synthesis of (**1**) was accomplished in only three steps from readily available and relatively inexpensive raw material, cyclopentane-1,2-dicarboxylic anhydride (**2**), with an overall yield of 60% (better than the previous ones[5-8,10] of 55%). The presented synthesis utilised operationally simple procedures that would be more suitable for industralisation.

Experimental

^{1}H NMR spectra were obtained on a Bruker AC-400. Chemical shifts are given in ppm, with respect to internal TMS, *J* values are quoted in Hz. IR spectra were obtained neat with a Nicolet NEXUS-670 spectrophotometer, only the most significant absorptions in cm^{-1} are indicated. Mass spectra were obtained on a Trace DSQ GC-MS spectrometer.

N-aminocyclopentane-1,2-dicarboximide (**3**): 14 g (0.1 mol) cyclopentane-1,2-dicarboxylic anhydride and 50 ml methanol were



Scheme 1

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mixed, and 6.6 ml (0.11 mol) 80% hydrazine hydrate was added in succession at 65 °C. The reaction mixture was stirred at refluxing temperature for 6 h after which time the starting material had been consumed, as evidenced by gas chromatographic analysis. The mixture was then cooled, and the solvent removed *in vacuo* to give the crude product. Recrystallisation with methanol : water = 3 : 1 (v/v) afforded *N*-aminocyclopentane-1,2-dicarboximide 13.5 g. The obtained yields were 87.7%. M.p. 113.2–114.9 °C.

N-aminocyclopentane-1,2-dicarboximide: IR(KBr) 3297.35, 1706.96, 1223.31 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.56–1.83 (6H, m), 2.71–2.89 (2H, m), 3.89 (2H, s). GC–MS(EI, 70Ev): *m/z*(%) = 155 (M^+ + H, 12), 154(M^+, 100), 98(32), 82(12), 67(59).

Hexahydrocyclopenta[c]pyrrol-2-amine (**4**): 12 g (0.22 mol) of KBH_4, to a solution of 25 g (0.19 mol) of $AlCl_3$ in 80 ml THF at 50 °C, and then 15.4 g (0.1 mol) of *N*-aminocyclopentane-1,2-dicarboximide(**3**) were added in succession. The reaction mixture was stirred for 5 h at refluxing temperature. The reaction solution was concentrated on a rotary evaporator at 45 °C and acidified to pH 12 with 1N NaOH. The mixture was then extracted with toluene (3 × 50 ml).The extract liquid was acidified to pH 2.5 with 1N HCl and concentrated on a rotary evaporator, leaving the crude product. Recrystallisation with ethanol afforded hexahydrocyclopenta[*c*] pyrrol-2-amine hydrochloride 12.8 g. The obtained yields were 78.5%. M.p. 154.5–156.1 °C.

Hexahydrocyclopenta[*c*]pyrrol-2-amine hydrochloride: ^1H NMR (CD_3OD): δ1.59–1.77 (6H, m), 2.92 (4H, s), 3.62–3.66 (2H, t, br), 4.62 (2H, s). MS-ESI: *m/z*(%) = 127.2(M^+ + H).

Gliclazide (**1**): 16.5 g (0.1 mol) of hexahydrocyclopenta[*c*]pyrrol-2-amine hydrochloride, 24 g (0.11 mol) of *p*-toluenesulfonylurea, 20 ml DMF and 100 ml toluene was mixed. The mixture was stirred at refluxing temperature for 2 h. Then the toluene was removed on a rotary evaporator and 100 ml water was added to the mixture. The solid was removed by suction filtration. and washed with dichloromethane (2 × 50 ml). Recrystallisation with ethyl acetate gives Gliclazide (**1**) 28.2 g. The obtained yields were 87.2%.M.p. 179.2–181.5 °C (lit.[11] 180–182 °C). ^1H NMR($CDCl_3$): δ8.70–8.83 (1H, d), 7.92–7.94 (2H, d), 7.28–7.30 (2H, d), 6.24–6.33 (1H, d), 2.54–3.25(5H, m), 2.40 (3H, s), 1.83–1.95 (2H, d), 1.23–1.65 (5H, m). ^{13}C NMR ($CDCl_3$): δ152.3, 144.4, 136.3, 129.3, 129.2, 128.1, 128.2, 63.0, 62.7, 40.2, 34.3, 30.9, 27.2, 24.3, 21.6. MS-ESI: *m/z* = 321.9(M^+-H).

Conclusions

In a previous route, from the starting material of hexahydrocyclopenta[*c*]pyrrol-2-amine, cyclopentane-1,2-dicarboxylic anhydride is obtained in four steps. Some expensive or hazardous reagents were used to synthesise the desired compound (**1**). On the base of above analysis, we have designed an improved process from the starting material of cyclopentane-1,2-dicarboxylic anhydride to synthesise the desired compound (**1**) without using special reagents, and every step was modified to be simpler and to give high yields. Hence, we think the present procedure is more effective, competitive, and more suitable for large-scale production.

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