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Green Synthesis of 6-[2-Aminothiazol-4-yl]-2-furylchromone

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Synthesis of 2-aminothiazoles through Hantzsch method involves the use of bromine. An 2-aminothiazole system 6-[2-aminothiazol-4-yl]-2-furylchromone has been synthesized green chemically from 6-chloroacetyl-2-furylchromone and 6-acetyl-2-furylchromone during present study. The structures of new compounds were elucidated on the basis of IR and PMR-spectra.

Keywords: 6-[2-Aminothiazol-4-yl]-2-furylchromone, 6-Chloroacetyl-2-furylchromone, 6-Acetyl-2-furylchromone.

INTRODUCTION

2-Aminothiazoles are key compounds in the synthesis of medicinally active compounds. Thiazoles are associated with curative effects under bad health conditions. For instance, they are anticancerous[1-3], antimicrobial[4-6], antiinflammatory[7-8], antitubercular[9-10] and antifungal[11]. Chromones are widely studied compounds with broad spectrum of medicinal activities[12-18]. Therefore, it was thought to develop 2-aminothiazole system at 6-position of chromone. Their synthesis by Hantzsch thiazole method involves use of the dangerous bromine. To eliminate the use of bromine environment friendly green chemical methods were developed according to the (**Scheme-I**).

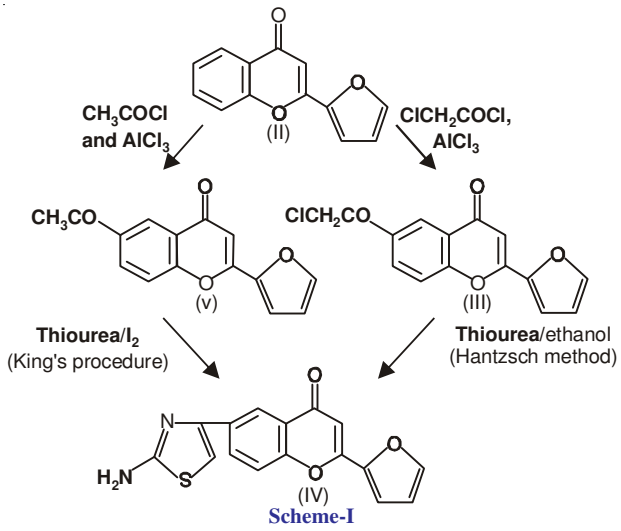
First method involved synthesis of title compound **4** through 6-chloroacetyl-2-furylchromone (**3**) which was obtained from 2-furylchromone (**2**) by Friedel Craft reaction with chloroacetyl chloride in presence of anhydrous aluminium chloride in carbon disulphide (CS_2) solvent. Compound **3** upon condensation with thiourea in ethanol yielded compound **4**.

In second method, compound **4** was obtained from 6-acetyl-2-furylchromone (**5**) by King's procedure. Here, compound **5** was condensed with thiourea under solvent free condition on water-bath by heating of 24 h. Compound **5** was prepared from compound **2** by Friedel-Craft reaction using acetyl chloride as acylating agent.

Structures of compounds **3**, **4** and **5** were elucidated by elemental analysis, IR and PMR-spectral data.

EXPERIMENTAL

All the melting and boiling points are uncorrected. Infrared spectra were recorded on SPECTRUM BX SERIES in KBr.



Scheme-I

Absorption frequency is recorded in cm^{-1}. The PMR-spectra were recorded in $CDCl_3$ and/or DMSO-d_6 on BRUKER AVANCE II 400 NMR spectrometer. The chemical shifts are expressed in ppm units (δ) downfield from internal tetramethyl silane (TMS) standard. Solvents and starting materials were purified using standard procedures. The purity of compounds was checked on TLC-plates coated with silica gel.

Synthesis of chalcone (1): Chalcone was synthesised from *o*-hydroxyacetophenone and furfural according to procedure described in literature[19].

Synthesis of 2-furylchromone (2): This compound was synthesised by refluxing 2g of **1** in DMSO in presence of 2-3 crystals of iodine for 10 min according to the procedure described in literature[20].

Synthesis of chloroacetyl chloride: In a 250 mL round bottom flask equipped with a reflux condenser and $CaCl_2$ guard tube was placed 0.1 mol (9.45 g) of chloroacetic acid. To the flask 8.5 mL of thionyl chloride was added in small portions with constant shaking. One or two drops of dry DMF were also added. Reaction mixture was refluxed on water-bath for 2 h. The excess of thionyl chloride was distilled off. Chloroacetyl chloride thus obtained is highly fumming and is immediately used for next step.

Synthesis of 6-chloroacetyl-2-furylchromone (3): 1.272 g (6 mmol) of 2-furylchromone and 0.678 g [6 mmol, 48 mL] of chloroaetyl chloride as well as 40 mL of CS_2 were taken in a 100 mL round bottom flask. To it was added 1 g of anhydrous $AlCl_3$ in portions with shaking. This reaction mixture was refluxed on water bath for 4 h. CS_2 was distilled off. Now reaction mixture was cooled and poured on crushed ice containing HCl. Solid was allowed to separate and was filtered, washed with water and recrystallized with ethanol. m.p. = 207-208 ºC, yield = 75 %, M.F. $C_{15}H_9O_4Cl$ required %: C = 62.39, H = 3.12. Found (%) : C = 62.25, H = 3.10. IR (KBr, ν_{max}, cm^{-1}): 1690 [C=O, str. -$COCH_2Cl$], 1640 [C=O str. chromone], 750 [C-Cl str. -$COCH_2Cl$], PMR[$CDCl_3$]: δ 4.66 [s, 2H, -CH_2 protons of -$COCH_2Cl$], 6.91 [s, 1H, C_3-H of chromone], 7.20-7.53 [m, 4H, protons of furyl ring and C_8-H of chromone], 7.71 [dd, 1H, C_7-H of chromone] 8.21 [d, 1H, C_5-H of chromone].

Synthesis of 6-[2-aminothiazol-4-yl]-2-furylchromone (4) (Hantzsch method without bromine): A mixture of 0.2885 g [1 mmol] of **3** and 0.076 g [1 mmol] of thiourea in 10 mL of alcohol was refluxed for 5 h. Solid separated on cooling was filtered and crystallized from ethanol. m.p. = 319-320 ºC; yield = 72 %; M.F. $C_{16}H_{10}O_3N_2S$ requires (%): C = 61.94, H = 6.23, N = 9.03, S = 10.32; Found (%): C = 61.98, H = 6.22, N = 9.02, S = 10.30; IR (KBr, ν_{max}, cm^{-1}): 3400 and 3309 [-NH str. of -NH_2 group], 1640 [C=O str. of chromone], 2367 [-N=C-S- str. of thiazole] PMR [DMSO-d_6]: δ 2.50 [s, 2H, -NH_2 protons on thiazole], 6.80-7.40 [m, 4H, C_3-H of chromone, C_3-H C_4-H and C_5-H of furyl ring], 7.50-7.69 [m, 2H, C_8-H of chromone and C_5-H of thiazole], 7.84 [dd, 1H, C_7-H of chromone], 8.05 [d, 1H, C_5-H of chromone].

Synthesis of 6-acetyl-2-furylchromone (5): 2.12 g [10 mmol] of 2-furylchromone and 1.33 g [15 mmol] of powdered Anh. $AlCl_3$ were mixed together in 50 mL of CS_2 in 100 mL round bottom flask. 1 mL of CH_3COCl was added dropwise to the mixture. The mixture was refluxed on water bath for an hour. CS_2 was distilled off and remaining solid was dropped into chilled water. Solid product was separated by filtration and recrystallized from ethanol. m.p. = 162-164 ºC; yield = 70 %; M.F. $C_{15}H_{10}O_4$ requires (%): C = 70.86, H = 3.94; Found (%): C = 70.83 and H = 3.93. IR (KBr, ν_{max}, cm^{-1}): 1680 [C=O str. -$COCH_3$], 1640 [C=O str. of chromone]. PMR [$CDCl_3$] (δ): 2.68 [s, 3H, -$COCH_3$], 6.61-6.76 [m, 2H, C_4-H of furan and C_3-H of chromone ring], 7.73-7.70 [m, 3H, C_3-H and C_5-H of furan and C_8-H of Chromone ring], 8.40-8.43 [dd, 1H, C_7-H of chromone] and 8.84 [d, 1H, C_5-H of chromone].

Synthesis of 6-[2-aminothiazol-4-yl]-2-furylchromone by King's procedure: An intimate mixture of 0.254 g [1 mmol] of **5**, 0.152 g [2 mmol] of thiourea and 0.254 g [1 mmol] of iodine was heated on water-bath under solvent free condition for 24 h. The reaction mixture was then washed with ether to remove unreacted acetyl compound. Now reaction mixture was treated with hot water accompanied by agitation with glass rod and was filtered. This process was repeated 5 times. Now hot filtrate was treated with liquor ammonia to precipitate the compound. Solid thus obtained was filtered, washed with water and recrystallized from ethanol. m.p. = 318-319 ºC; yield = 65 %; m.f. $C_{16}H_{10}O_3N_2S$ required (%): C = 61.94, H = 6.23, N = 9.03, S = 10.32; Found (%): C = 61.93, H = 6.21, N = 9.01 and S = 10.29. IR (KBr, ν_{max}, cm^{-1}) and PMR DMSO-d_6 (δ) conformed with compound **5** obtained by Hantzsch thiazole method.

RESULTS AND DISCUSSION

Prompted by the fact that thiazoles and chromones are of immense medicinal value and from 2-aminothiazoles a number of medicinally active compounds come into existence, 6-[2-aminothiazol-4-yl]-2-furylchromone was synthesised green chemically by Hantzsch thiazole method (without bromine) and King's procedure[21]. 2-Furylchromone (**2**) was used as starting material which was prepared from chalcone (**1**) obtained by condensing *o*-hydroxy acetophenone with furfural in basic medium and alcoholic solution followed by cyclization of chalcone with iodine in DMSO. 2-Furylchromone upon Friedel-Craft reaction with chloroacetyl chloride yielded 6-chloroacetyl-2-furylchromone (**3**). Compound **3** in its IR-spectrum showed characteristic bands for C=O str. of chromone and -$COCH_2Cl$ side chain at 1640 and 1690 cm^{-1}, respectively in addition to the usual bands. C-Cl str. of -$COCH_2Cl$ in this compound appeared at 750 cm^{-1}. PMR spectrum of this compound in $CDCl_3$ showed -$COCH_2Cl$ protons at δ 4.66 as singlet. Other protons showed up in aromatic region. Signal at δ 6.91 can be assigned to C_3-H of chromone. C_8-H of chromone and three protons of furan ring appeared from δ 7.20 to 7.53 as multiplet. C_7-H of chromone is assignable to δ 7.71 doublet of doublet. Whereas, last signal at δ 8.21 which appeared as doublet can be safely assigned to C_5-H of chromone.

Compound **3** upon condensation with thiourea in alcoholic solution afforded 6-[2-aminothiazol-4-yl]-2-furylchromone (**4**). Compound (**5**) in its IR-spectrum predicted its formation as -$COCH_2Cl$ str. at 1690 cm^{-1} [C=O str.] and 750 cm^{-1} [C-Cl str] which were present in IR-spectrum of **3** are absent in it. Formation of 2-aminothiazole moiety is concluded by the fact that 2-NH stretching peaks appeared at 3400 and 3309 cm^{-1} [symmetric and asymmetric stretchings] and -N=C-S- str. of thiazole at 2367 cm^{-1} appeared in the IR-spectrum of **4**. PMR-spectrum fully advocated its formation. Compound **4** in its PMR-spectrum run in DMSO-d_6 showed signals for all the ten protons. Starting from highest field two proton singlet for C_2-NH_2 of thiazole appeared at δ 2.50. At 6.80-7.40 appeared C_3-H of chromone and C_3-H, C_4-H and C_5-H of furan ring. Other signals at δ 7.50 to 7.69 are assignable to C_8-H of chromone and C_5-H of thiazole rings. Signal (doublet of doublet) at δ 7.84 was for C_7-H of chromone and 8.05 doublet for C_5-H of chromone completed the proton count.

In other method **4** was synthesised through 6-acetyl-2-furylchromone (**5**) by using King's procedure[21]. Compound **5** was synthesised from 2-furylchromone (**2**) through Friedel-Craft acylation using acetyl chloride as acylating agent. Structure

of **5** was confirmed on the basis of elemental analysis IR and PMR spectral data. This compound in its IR-spectrum exhibited two absorption bands at 1680 and 1640 cm^{-1} assignable to C=O str. of -$COCH_3$ and C=O str. of chromone, respectively. The PMR of compound **5** recorded in $CDCl_3$ completely revealed its structure. A three proton singlet of -$COCH_3$ appeared at δ2.68 and C_6-H of 2-furylchromone [δ 7.42] also disappeared indicating that -$COCH_3$ group was introduced at C_6-position of chromone. The reason behind it is that instead of our assumption that C_3-position is more nucleophilic than C_6 due to driving force of C=O group of chromone, the C_6-position was found more nucleophilic due to greater resonance stabilization, hence, was attacked by $^{\oplus}COCH_3$ electrophilie.

Other protons appeared after δ 6.60. At 6.61-6.76 was two proton multiplet assignable to C_4-H of furan and C_3-H of chromone rings. In the region 7.70-7.73 appeared C_3-H and C_5-H of furan ring and C_8-H of chromone. At δ 8.40-8.43 [doublet of doublet J = 9 Hz and 2.5 Hz; *o*- and *m*-coupling] C_7-H of chromone appeared. At 8.84 doublet [J = 2.5 Hz, *m*-coupling] C_5-H of chromone appeared as the last signal.

Compound **5** was converted into compound **4** by condensing former with thiourea and iodine under solvent free condition [king's procedure]. Analytical data of compound **4** obtained by this method were in agreement with that obtained by Hantzsch thiazole method. Spectra of compound **4** obtained by two methods also conformed.

Conclusion

Out of two green chemical methods of synthesis of title compound though Hantzsch method is less time consuming; but King's procedure is more eco-friendly as well as cost-effective.

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