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SYNTHESIS OF 3-ACETYL-6-IODO-COUMARIN AND IT'S DERIVATIVES

Nguyen Tien Cong, Tran Thi Duong, Nguyen Anh Tien

Ho Chi Minh City University of Pedagogy, Viet Nam

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Abstract. Iodination of the 2-hydroxybenzaldehyde formed 2-hydroxy-5-iodobenzadehyde (2). Cyclization of (2) with ethyl acetoacetate gave 3-acetyl-6-iodocoumarin (3). 3-(Bromoacetyl)-6-iodocoumarin (4), the product formed when bromination of (3) was transformed into five derivatives containing thiazole ring (6a-e). The structures of the compounds were identified by IR, 1H-NMR and HR-MS spectral data.

Keywords. 3-acetyl-6-iodocoumarin, 3-(bromoacetyl)-6-iodocoumarin, 3-(2-aminothiazol-4-yl)-6-iodocoumarin, 3-[2-(2-arylidenhydrazinyl]thiazol-4-yl]-6-iodocoumarin

Coumarin derivatives have been focused recently due to potential activities exhibited by them. Modifications on the 3-position of coumarin nucleus have resulted in a large number of compounds having diverse pharmacological activities [1]. Thiazole displayed broad range of biological activities as as antitumor, antimicrobial, antifungal, anti-inflammatory, anticonvulsant activity [2]. Therefore, many 3-substituted coumarins' derivatives bearing thiazole heterocycle were synthesized with hope of increasing their valuable pharmacological activities [3-10]. Herein, we report on the synthesis of 3-acetyl-6-iodocoumarin and the transformation of which into *N*-substituted 3-(2-amino-1,3-thiazol-4-yl)-6-iodo-coumarin derivatives.

EXPERIMENT

Melting points were determined in open capillaries and the values are uncorrected. IR spectra of all synthesized compounds were recorded on KBr disks using a Shimadzu FTIR 8400S spectrometer. ^{1}H-NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz) using DMSO-d_6 as solvent and TMS (0.00 ppm) as an internal standard. HRMS were determined on a Bruker micrOTOF-Q 10187 mass spectrometer.

2-Hydroxy-5-iodobenzaldehyde (2):

5-iodosalicyaldehyde was prepared according to the procedure reported previously [11]. To a 500 ml round bottom flask, add 14 ml (0.134 mol) salycilaldehyde and 365 ml methanol. Using a magnetic stir bar, stir until dissolved. Add 22.24g (0.134 mol) potassium iodide, and continue to stir. After the potassium iodide has dissolved into solution, put the round bottom flask on an ice/water bath, positioned over the magnetic stirrer so that the solution is still stirring. Carefully add 90 ml of the sodium hypochlorite solution dropwise to the round bottomed flask over a period of 120 minutes. During this time, add ice to the ice bath as necessary to maintain a mixture with enough water that the surface area of the round bottomed flask is covered and enough ice that the bath is still 0°C. Also, check occasionally that the solution is still stirring, as some will thicken as the reaction progresses. After the addition of the sodium hypochlorite solution is complete, continue to stir the solution at 0°C for 60 minutes. Remove the ice/water bath, and add 100ml of a 10% (w/w) solution of sodium thiosulfate. Allow the solution to stir for 5 minutes. With continued stirring, acidify with a 2 M solution of hydrochloric acid in 10ml portions to pH 3-4. The iodophenol precipitated out was filtered off, washed with water and crystallized from mixture of ethanol-water to give (**1**) as light yellow crystals in 45% yield. M.p. 98^{o}C. IR (ν cm^{-1}): 3220 (broad, O-H), 2974 (CH aliphatic), 1668 (C=O), 1604 (C=C aromatic), 557 (C-I). ^{1}H-NMR (DMSO, 500 Hz): δ 10.93 (1H, *s*, OH), 10.16 (1H, *s*, CHO), 7.87 (1H, *d*, *J*=2.5, Ar-H), 7.77 (1H, *dd*, *J*=9.0, *J*=2.5, Ar- H), 6.85 (1H, *d*, *J*=9.0, Ar-H).

3-Acetyl-6-iodocoumarin (3): To a mixture of 5-iodosalicyaldehyde (6.20 gr, 0.025 moles) and ethyl acetoacetate (3.20 mL, 0.025 moles) was added catalytic amount of piperidine (0.2 mL, 1.64 mmoles) and swirled thoroughly. The mixture was irradiated in microwave oven at 450 W for 90 seconds. The solid

product was filtered, and recrystallized from mixture of dioxane-water to afford pure 3-acetyl-6-iodo-2*H*-chromen-2-one in 79% yield. M.p. 203-204^{O}C. IR (ν, cm^{-1}): 3057, 3039 (C-H aromatic and olefinic), 2997. 2918 (C-H aliphatic), 1728, 1725 (C=O), 1604 (C=C aromatic), 557 (C-I). ^{1}H-NMR (DMSO, 500 Hz): δ 8.58 (1H, *singlet*, H-pyrole ring), 8.35 (1H, *doublet*, ^{4}J = 2,0, ArH); 8.02 (1H, *doublet-doublet*, ^{3}J = 8.5, ^{4}J = 2,0, Ar-H); 7.29 (1H, *doublet*, ^{3}J = 8.5, Ar-H); 2.58 (3H, *singlet*, $COCH_3$). HR-MS ($C_{11}H_7IO_3$): *m/z* (rel int %) 314.9547 [M+H] (100), 315.9554 [M+H+1] (7.20).

3-(Bromoacetyl)-6-iodocoumarin (4): To a solution of compound **3** (3.14 gr, 0.01 mol) in 30 mL dioxane, bromine (1.6 gr, 0.01 mol) in 30 ml dioxane was added with intermittent shaking. After adding all the bromine, the reaction mixture was heated on water bath to give off all the hydrobromic acid. Then the mixture was cooled and added to ice-cold water. The precipitate was filtered then recrystallized from mixture of dioxan-water to give colorless needles (**4**). Yield: 46%. M.p. 189-190^{O}C. IR (ν, cm^{-1}): 3064, 3017 (C-H aromatic and olefinic), 2943 (C-H aliphatic), 1728, 1676 (C=O), 1600 (C=C aromatic), 684 (C-Br), 559 (C-I). ^{1}H-NMR (DMSO, 500 Hz): δ 8.74 (1H, *singlet*, H-pyrole ring), 8.37 (1H, *doublet*, ^{4}J = 2,0, Ar-H); 8.04 (1H, *doublet-doublet*, ^{3}J = 8.5, ^{4}J = 2,0, Ar-H); 7.31 (1H, *doublet*, ^{3}J = 8.5, ArH); 4.88 (2H, *singlet*, $COCH_2Br$).

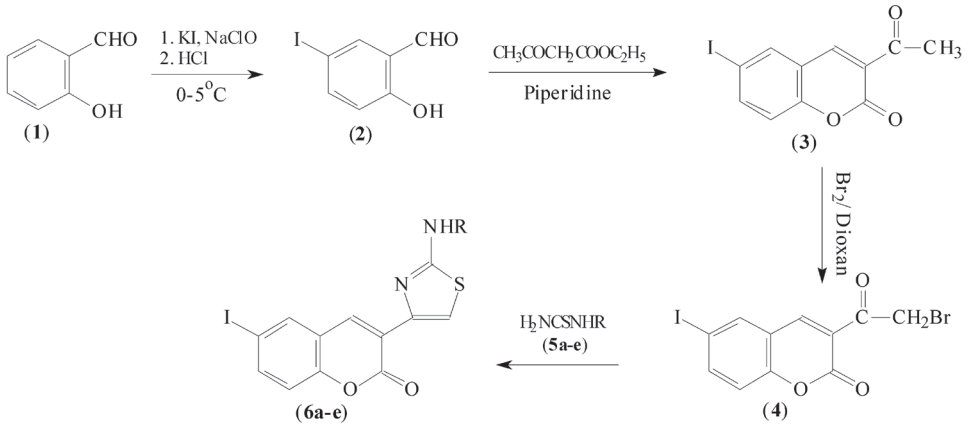
Thiosemicarbazone compounds (**5b-e**): An equimolecular mixture of thiosemicarbazide and respective aromatic aldehyde in ethanol was re-fluxed for 2.0 hrs. The precipitate was filtered then recrystallized from ethanol. Their preparation was confirmed by comparing the melting points from literature [12, 13].

3-(1,3-Thiazol-4-yl)-6-iodo-coumarin derivatives (6a-e): To a solution of compound **4** (0.393 gr, 1 mmol) and sodium acetate (0.082 gr, 1 mmol) in 20 mL dioxane, thiourea or different thiosemicarbazone derivatives (1 mmol) in 10 mL dioxane was added. The mixture was refluxed for 1 hour, cooled and filtered then recrystallized from mixture DMF-water to give (**6a-e**) respectively as shown in the scheme 1.

3-(2-aminothiazol-4-yl)-6-iodocoumarin (**6a**): yield: 48%; mp: 183-184°C; IR: 3464, 3334, 1712 cm^{-1}; ^{1}H-NMR: δ 8.42 (1H, *singlet*, H-pyrole ring), 8.23 (1H, *doublet*, ^{4}J = 2,0, Ar-H), 7.87 (1H, *doublet-doublet*, ^{3}J = 8.5, ^{4}J = 2,0, Ar-H), 7.25 (1H, *doublet*, ^{3}J = 8.5, ArH), 7.53 (1H, *singlet*, H-thiazole ring), 7.17 (2H, *singlet*, NH_2).

3-{2-[2-(4-chlorobenzyliden)hydrazinyl]thiazol-4-yl}-6-iodocoumarin (**6b**): yield: 52%; mp: 282-283°C; IR: 3600, 3360, 1717 cm^{-1}; ^{1}H-NMR: δ 12.32 (1H, *singlet*, NH), 8.45 (1H, *singlet*, H-pyrole ring), 8.06 (1H, *singlet*, CH=N), 8.25 (1H, *doublet*, ^{4}J = 2,0, Ar-H), 7.89 (1H, *doublet-doublet*, ^{3}J = 8.5, ^{4}J = 2,0, Ar-H); 7.27 (1H, *doublet*, ^{3}J = 8.5, ArH), 7.81 (1H, *singlet*, H-thiazole ring), 7.68 (2H, *doublet*, ^{3}J = 8.5, ArH), 7.50 (2H, *doublet*, ^{3}J = 8.5, ArH); HR-MS ($C_{19}H_{11}ClIN_3O_2S$): *m/z* (rel int %) 507.9362 [M+H] (100), 509.9353 [M+H+2] (39.35).

3-{2-[2-(4-methoxybenzyliden)hydrazinyl] thiazol-4-yl}-6-iodocoumarin (**6c**): yield: 50%; mp: 247-248°C; IR: 3600, 3400, 1724 cm^{-1}; ^{1}H-NMR: δ 12.08 (1H, *singlet*, NH), 8.45 (1H, *singlet*, H-pyrole ring), 8.03 (1H, *singlet*, CH=N), 8.26 (1H, *doublet*, ^{4}J = 2,0, Ar-H), 7.89 (1H, *doublet-doublet*, ^{3}J = 8.5, ^{4}J = 2,0, Ar-H); 7.27 (1H, *doublet*, ^{3}J = 8.5, ArH), 7.78



(***5a, 6a***: *R = H;* ***5b, 6b***: *R = 4-ClC$_6$H$_4$CH=N,* ***5c, 6c***: *R = 4-CH$_3$OC$_6$H$_4$CH=N,* ***5d. 6d***: *R = 2-O$_2$NC$_6$H$_4$CH=N.* ***5e. 6e***: *R = 2-HO-5-BrC$_6$H$_3$CH=N*)

Scheme 1. Pathways for synthesis

(1H, *singlet*, H-thiazole ring), 7.61 (2H, *doublet*, ^3J = 8.5, ArH), 7.01 (2H, *doublet*, ^3J = 8.5, ArH), 3.80 (3H, *singlet*, CH_3O).

3-{2-[2-(2-nitrobenzyliden)hydrazinyl]thiazol-4-yl}-6-iodocoumarin (**6d**): yield: 57%; mp: 302-303°C; IR: 3620, 3360, 1730 cm^{-1}; ^{1}H-NMR: δ 12.61 (1H, *singlet*, NH), 8.48 (1H, *singlet*, H-pyrole ring), 7.48 (1H, *singlet*, CH=N), 8.29 (1H, *doublet*, ^4J = 2,0, Ar-H), 7.90 (1H, *doublet-doublet*, ^3J = 8.5, ^4J = 2,0, Ar-H); 7.28 (1H, *doublet*, ^3J = 8.5, ArH), 7.85 (1H, *singlet*, H-thiazole ring), 8.05 (2H, *doublet*, ^3J = 8.5, Ar-H), 7.80 (1H, *doublet-doublet*, ^3J = 8.5, Ar-H), 7.63 (1H, *doublet-doublet*, ^3J = 8.5, Ar-H).

3-{2-[2-(5-bromo-2-hydroxybenzyliden)hydrazinyl]thiazol-4-yl}-6-iodocou marin (**6e**): yield: 70%; mp: 306-307°C; IR: 3600, 3400, 1717 cm^{-1}; ^{1}H-NMR: δ 12.28 (1H, *singlet*, NH), 8.45 (1H, *singlet*, H-pyrole ring), 8.29 (1H, *singlet*, CH=N), 8.26 (1H, *doublet*, ^4J = 2,0, Ar-H), 7.90 (1H, *doublet-doublet*, ^3J = 8.5, ^4J = 2,0, Ar-H); 7.27 (1H, *doublet*, ^3J = 8.5, ArH), 7.80 (1H, *singlet*, H-thiazole ring), 7.75 (1H, *doublet*, ^4J = 2.5, Ar-H), 7.36 (2H, *doublet-doublet*, ^3J = 8.5, ^4J = 2.5, Ar-H), 6.87 (1H, *doublet*, ^3J = 8.5, Ar-H). HR-MS ($C_{19}H_{11}BrIN_3O_3S$): *m/z* (rel int %) 567.8825 [M+H] (100), 568.8833 [M+H+1] (11.15), 569.8819 [M+H+2] (98).

RESULTS AND DISCUSSION

The compound (**2**) was synthesized starting from salicylaldehyde according to method of iodination of the phenols discribed in literature [11]. Melting point of the yielded product has an good agreement with the characteristic of 2-hydroxy-5-iodobenzaldehyde in the Sigma-Aldrich' catalogue [14]. The ^{1}H-NMR of the product showed 3 signals in the aromatic area: the first one was a *doublet* at 7.87ppm with ^4J=2.5 Hz, the second one was a *doublet-doublet* at 7.77ppm with ^3J=9.0Hz and ^4J=2.5 Hz and the last one was a *doublet* at 6.85ppm with ^3J=9.0 Hz. These evidences firm that the iodine atom linked to the 5 position in the benzene ring of the 2-hydroxybenzaldehyde.

3-Acetyl-6-iodocoumarin (**3**) was synthesized by simple, fast procedure where 5-iodosalicylaldehyde was condensed with ethyl acetoacetate in the presence of piperidine under the microwave irradiation. The product was yellow solid with high melting point. The IR spectra of the compound (**3**) obtained from 2-hydroxy-5-iodobenzaldehyde (**2**) showed not only a lack of broad band at 3220cm^{-1} but also an appearance of the intense absorption band of lacton carbonyl group at 1728 cm^{-1}. The ^{1}H-NMR spectra of (**3**), 3 signals in the aromatic area with added appearance of *singlet* signals at 8.58 ppm (1H) and 2.58 ppm (3H) confirmed that the coumarin ring had clearly been formed.

3-(Bromoacetyl)-6-iodocoumarin (**4**), a key precursor of Hantzsch thiazole synthesis, was prepared in 46% yield by the electrophilic bromination of 3-acetyl-6-iodocoumarin, based on the method of preparing 3-(bromoacetyl)coumarin described in literature [3,7]. In the IR spectra of (**4**), the stretching vibration of the lactone C=O bond appeared at 1728cm^{-1} while stretching vibration of the C=O bond in the -C(O)CH_2Br group appeared at 1676cm^{-1}. In the ^{1}H-NMR spectra of (**4**), signal of the -C(O)CH_2Br group is shifted downfield corresponds to electronic withdraw effect of bromine atom.

Reaction of 2-bromoacetophenone compounds with thiourea or thiosemicarbazone derivatives was generally used to synthesize thiazole derivatives [3,4,7,10]. The IR spectra of (**6a-e**) showed absorption bands in the range 3300-3600 cm^{-1} which were attributable stretching vibrations of the N-H and O-H bonds. The lactone C=O bands of the coumarin ring were observed in the 1712-1730 cm^{-1} region. Besides that, there was a lack of strong stretching band at around 1676 cm^{-1}. These evidences confirmed that the thiazole ring had clearly been formed. The ^{1}H-NMR spectra of (**6a-e**) showed *singlets* at 7.78-7.81 ppm due to proton of the thiazole rings. While protons of the CH=N and NH-N groups in molecules of the (**6b-e**) showed *singlets* at 8.03-8.48 ppm and 12.08-12.61 ppm respectively, protons in the NH_2 group of (**6a**) appeared as a *singlet* at 7.53 ppm. Similar to the (**3**) and (**4**), proton in the pyrole ring of the (**6a-e**) resonate d as a *singlet* at 8.42-8.48 ppm. As the test results by Scifinder program at the K.U. Leuven, Belgium on April 26th 2012, all of the (**3**), (**4**) and (**6a-e**) compounds had not been found in any references.

CONCLUSION

Seven new compounds consist 3-acetyl-6-iodocoumarin, 3-(2-bromoacetyl)-6-iodocoumarin and five derivatives of the 6-iodo-coumarin containing thiazole heterocycle were synthesized. The structures of the compounds were identified by IR, ^{1}H-NMR and HR-MS.

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Нгуен Тьен Конг — д.х.н химического факультета Хошиминского государственного педагогического униеврситета, г. Хошиминь, Вьетнам; e-mail: congchemist@yahoo.com

Чан Тхи Зыонг — студент 4-го курса химического факультета Хошиминского государственного педагогического униеврситета, г. Хошиминь, Вьетнам, e-mail: duongmap156@gmail.com

Нгуен Ань Тьен — д.х.н химического факультета Хошиминского государственного педагогического униеврситета, г. Хошиминь, Вьетнам; e-mail: anhtien0601@rambler.ru

Nguyen Tien Cong — doctor of Chemical sciences, Chemical faculty of Ho Chi Minh City University of Pedagogy, Ho Chi Minh City, Viet Nam; e-mail: congchemist@yahoo.com

Tran Thi Duong — Fourth year student of chemical faculty, Ho Chi Minh City University of Pedagogy, Ho Chi Minh City, Viet Nam; e-mail: duongmap156@gmail.com

Nguyen Anh Tien — doctor of Chemical sciences, Chemical faculty of Ho Chi Minh City University of Pedagogy, Ho Chi Minh City, Viet Nam; e-mail: anhtien0601@rambler.ru