Asian Journal of Chemistry; Vol. 24, No. 12 (2012), 5473-5475

ASIAN JOURNAL OF CHEMISTRY

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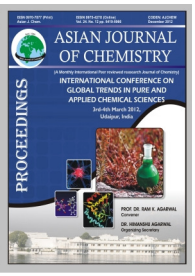

Synthesis and Characterization of 3-Formyl-1*H*-2-benzopyran-1-one†

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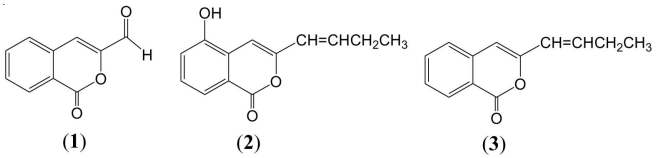
AJC-11671

Synthesis and characterization of 3-formyl-1*H*-2-benzopyran-1-one is reported through convenient three step method. Homophthalic acid and ethyloxalyl chloride were refluxed to afford isocoumarin 3-ethylcarboxylate, which was subsequently heated to reflux with ethanolic hydrazine hydrate to yield isocoumarin-3-hydrazide. The product is treated with ammoniacal solution of metaperiodate to synthesize 3-formyl-1*H*-2-benzopyran-1-one. All products were characterized by IR, NMR and mass spectral analysis. Physical and spectral data were in close agreement with those, reported in literature.

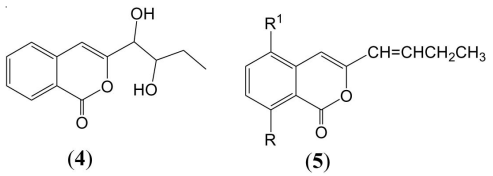
Key Words: Artimidinal, 3-Formyl-1*H*-2-benzopyran-1-one, Isocoumarin.

INTRODUCTION

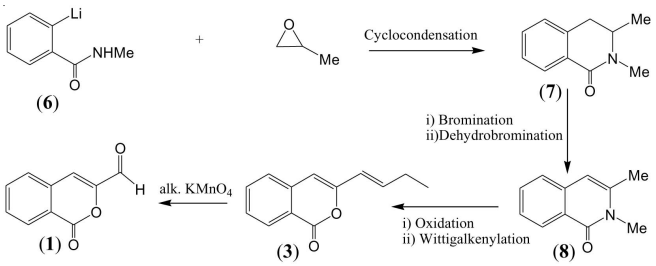
Artimisia dracunculus is a plant of family compositae. The crude extract from different parts of this plant, which is oily, is used in the form of tincture[1]. This oil is toxic when injected intraperitoneally to white rat and white mice[2]. This extract has *in vitro* antifungal activity. The leaves of this plant are used as appetizer agent. The isocoumarins also have anti-fungal and antioxidant properties. Artimidinal (**1**) was previously isolated[3] from the ground part of this plant by Mallabaev and Sidyakin[4], artimidinol (**2**) another isocoumarin derivative, which was isolated from *Artimisia dracunculus* and separated by chromatography. This isocoumarin has similar skeleton to that of Artimidinal. Artimidin (**3**), which was also isolated[5] during the process of isolation of artimidinal (**1**) from the ground parts of *Artimisia dracunculus*.



Mallabaev and Sidyakin[6] have also isolated artimidiol (**4**), a new isocoumarin, from the roots of *Artimisia dracunculus*. This compound (**4**) in combination with artimidinal has anti-allergic properties. Greger *et al.*[7] isolated isocoumarin (**5**) [R = R1= H (*cis* and *trans*), *trans*-R = OH, R[1]= H; R = H, R = OH] from *Artimisia dracunculus*.

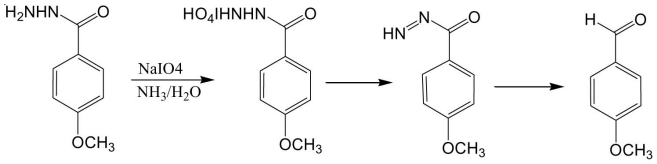


Bhasker *et al.*[8] reported a seven step synthesis of artimidinal (**1**). Sequential cyclocondensation of *N*-methyl-2-lithium-benzamide (**6**) with propylene oxide gave 2,3-dimthyl-3,4-dihydro-1-quinolone (**7**). The bromination and then dehydro-bromination of compound (**7**) yielded 2,3-dimethyl-1-quinolone (**8**). Oxidation and then wittig alkenylation of (**8**) resulted artimidin (**3**), which on treatment with alkaline potassium permanganate converted into artimidinal (**1**).

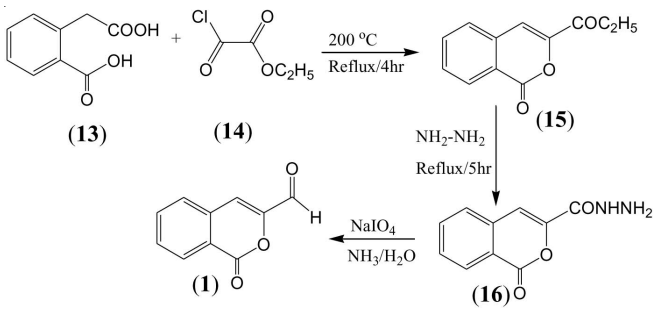


†Presented at International Conference on Global Trends in Pure and Applied Chemical Sciences, 3-4 March, 2012; Udaipur, India

A conversion of methyl 3,5-dimthoxybenzoate into 3,5-dimethoxybenzaldehyde by the action of hydrazine hydrate followed by benzenesulphonyl chloride and anhydrous sodium carbonate in ethylene glycol[9]. Wingfield *et al.*[10] have reported that pyridine-3-carboxylic acid hydrazide on oxidation with ammoniacal sodium metaperiodate yielded pyridine-3-aldehyde. Siedel *et al.*[11] also reported such reactions. Sodium metaperiodate is believed to react with hydrazide to form the intermediate (**10**), which decomposes in a manner dependant on the nature of the substituent group into aldehyde (**12**).



Various 3-arylisocoumarins and 3-alkylisocoumarins in high yields were synthesized by heating directly the homophthalic acid with aroyl or acyl chlorides at 200 ºC[12,13] in continuation of previous studies[13], herein we report a convenient three step synthesis of artimidinal (**Scheme-I**).



Scheme-I

EXPERIMENTAL

Melting points were determined on Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu model No. IR-460 serial No. 124127 spectrophotometer as KBr disc or neat liquids.

Isocoumarin-3-ethylcarboxylate (15): A mixture of homophthalic acid (**13**) (2.0 g, 11 mmol) and ethyl oxalyl chloride (**14**) (5 mL, 44 mmol) was heated under reflux for 4 h. The reaction mixture was then dissolved in ethyl acetate. Organic layer was separated, concentrated and chromatographed on silica gel using petroleum ether (b.p. 40-80 ºC) as eluent to afford isocoumarin-3-ethylcarboxylate (**15**), an oily mass (1.5 g, 6.7 mmol).

Yield: 61 %. Dense oil, IR (KBr, ν_{max}, cm^{-1}): 2998, 1735 and 1720. ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, *J* = 7.3 Hz, 3H, CH_3), 4.15 (q, 2H, *J* = 7.3 Hz, 2H, CH_2), 7.18 (s, 1H, C4-H), 7.22 (dd, *J* = 7.3 and 1.4 Hz, 1H, C5-H), 7.36 (ddd, *J* = 7.5 and 1.4 Hz, 1H, C7-H), 7.51 (ddd, *J* = 7.5 and 1.4 Hz, 1H, C6-H), 8.07 (ddd, *J* = 7.3, 1.4 and 0.4 Hz, 1H, C_8-H) ppm; $C_{12}H_{10}O_4$ EIMS (70 eV) *m/z* (%): 218 (10, M^+), 173 (39), 145 (60), 118 (100), 90 (85), 89 (70).

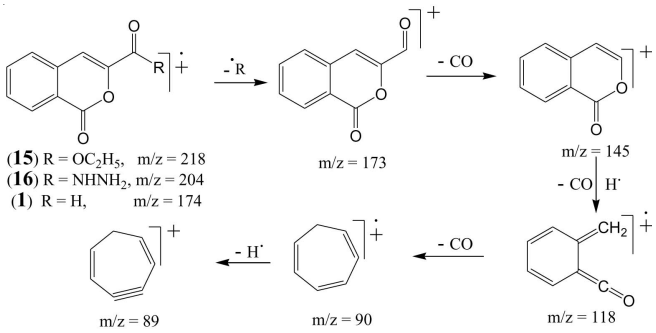
Isocoumarin-3-acid hydrazide (16): A mixture isocoumarin-3-ethyl carboxylate (**15**) (0.65 g, 3 mmol) and hydrazine hydrate (25 %, 8 mL) was refluxed in ethanol for 5 h. Precipitates were appeared during reflux. The mixture was cooled and filtered to afford isocumarin-3-acid hydrazide (**16**) (0.3 g, 1.47 mmol) mp 360 ºC Yield: 49 %. m.p. 360 ºC, IR (KBr, ν_{max}, cm^{-1}): 3440, 3350, 2995, 1732 and 1680. ^{1}H NMR ($CDCl_3$) δ: 2.30 (br, 2H, NH_2), 7.17 (s, 1H, C4-H), 7.22 (dd, *J* = 7.3 and 1.4 Hz, 1H, C5-H), 7.36 (ddd, *J* = 7.5 and 1.4 Hz, 1H, C7-H), 7.51 (ddd, *J* = 7.5 and 1.4 Hz, 1H, C6-H), 8.07 (ddd, *J* = 7.3, 1.4 and 0.4 Hz, 1H, C_8-H), 9.21 (br, 1H, NHCO) ppm; $C_{10}H_8N_2O_3$ EIMS (70 eV) *m/z* (%): 204 (25, M^+), 173 (45), 145 (64), 118 (100), 90 (95), 89 (75).

Artimidinal (1): Sodium metaperiodate (0.12 g) was dissolved with vigorous stirring in distilled water (10 mL), then chilled to 0 ºC. To this solution, ammonium hydroxide (27 %, 5 mL) was added lowly with stirring until white precipitates formed. A crystalline mass separated on continued cooling. Isocoumarin-3-carboxylic acid hydrazide (**16**) (0.1 g, 0.0005 mol) was dissolved in ammonium hydroxide (27 %, 15 mL), chilled and added to the ammonical sodium periodate mixture as rapidly as possible. The reaction mixture turned yellow with effervescence and the crystalline mass disappeared. After stirring and cooling for 5 min, the reaction mixture was kept in ice bath for 20 min, then precipitated with a solution of barium acetate (0.13 g) in distilled water (5 mL). The reaction mixture was filtered and pH of filtrate was adjusted to 8. It was then saturated with sodium chloride and extracted with ethyl acetate. The solvent was evaporated to obtain crystalline mass, *i.e.* artimidanal (**1**) (0.025 g, 0.00014 mol, 30 %), m.p. 76-77 ºC. Yield: 30 %. m.p. 77 ºC, IR (KBr, ν_{max}, cm^{-1}): 2960, 1685. ^{1}H NMR ($CDCl_3$) δ: 7.22 (dd, *J* = 7.3 and 1.4 Hz, 1H, C5-H), 7.26 (s, 1H, C4-H), 7.36 (ddd, *J* = 7.5 and 1.4 Hz, 1H, C7-H), 7.51 (ddd, *J* = 7.5 and 1.4 Hz, 1H, C6-H), 8.07 (ddd, *J* = 7.3, 1.4 and 0.4 Hz, 1H, C_8-H), 9.71 (s, 1H, HCO) ppm; $C_{10}H_6O_3$ EIMS (70 eV) *m/z* (%): 174 (33, M^+), 173 (48), 145 (42), 118 (100), 90 (90), 89 (71).

RESULTS AND DISCUSSION

Homophthalic acid (**13**) was condensed with ethyloxalyl chloride (**14**) by refluxing at 200 ºC to afford isocoumarin-3-ethylcarboxylate (**15**). The product was purified by column chromatography on silica gel to obtain oily mass. In IR spectrum this isocoumarin showed lactonic and ester carbonyl strong absorption bands at 1735 and 1720 cm^{-1}. The ^{1}H NMR spectrum shows characteristic absorption peak at 7.18 ppm, which indicates the formation of lactonic ring. The spectrum exhibits absorption signals at 1.29 (t, *J* = 7.3 Hz, 3H, CH_3) and 4.15 (q, 2H, *J* = 7.3 Hz, 2H, CH_2) ppm corresponding to 3-ethoxy carbonyl side chain at pyrone ring. The other signals in spectrum are in closely resemblance with the proposed structure of the isocoumarin (**15**). The EIMS spectrum shows molecular ion peak at *m/z* = 218. The mass fragmentation pattern is in close accord with the structure of the synthesized isocoumarin (**15**).

The isocoumarin was refluxed with hydrazine hydrate in ethanol for 5 h. Precipitates formed during reflux, were separated by filtration to afford isocoumarin-3-acid hydrazide (**16**). It was recrystallized from hot ethanol. IR spectrum showed lactonic and amide carbonyl absorption bands at 1732 and



1680 cm^{-1} respectively. Stretching for N-H bond was observed at 3440 and 3350 cm^{-1}. In ^1H NMR spectrum absorption signals at 1.29 (t, J = 7.3 Hz, 3H, CH_3) and 4.15 (q, 2H, J = 7.3 Hz, 2H, CH_2) ppm corresponding to 3-ethoxy carbonyl side chain at pyrone ring disappeared. Two new absorption bands appeared at 2.30 (br, 2H, NH_2) and 9.21 (br, 1H, NHCO) ppm indicating transformation of este into acid hydrazide (**4**). The EIMS spectrum exhibits molecular ion peak at *m/z* = 204. Finally the mass fragmentation pattern which is in close accord with the structure of the synthesized compound confirms this transformation into isocoumarin-3-acid hydrazide (**16**). The isocoumarin-3-acid hydrazide (**16**) was treated with ammonical solution of sodium metaperiodate in ice bath followed by the addition of barium acetate solution to afford artimidnal (**1**). The product was purified by preparative tlc. In IR spectrum, it showed a broad band at 1729 and 1685 cm^{-1} for lactonic carbonyl and α,β-unsaturatedaldehydic group. The appearance of absorption signal at 9.71 (s, 1H, HCO) ppm for aldehydic proton indicates the conversion of acid hydrazide (**16**) into the targeted synthesis of naturally occurring artimidinal (**1**). The EIMS spectrum exhibiting molecular ion peak at *m/z* = 174 and the mass fragmentation pattern confirms the structure of artimidinal (**1**). The spectroscopic data of the isolated one is similar to that of synthesized one which clearly indicates about the proposed structure of the targeted compound.

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