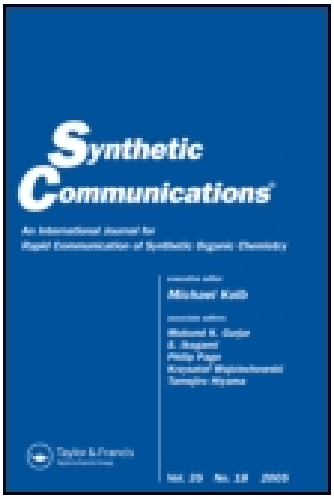

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STEREOSELECTIVE BROMINATION OF 2-VINYL CHROMONES USING NBS

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A simple one-step synthetic methodology for stereoselective synthesis of* E- *and* Z-*3-bromo-2-vinyl chromones in quantitative yield in polar solvents under ambient conditions without the use of catalysts is reported.

Keywords: N-Bromosuccinimide; stereoselective bromination; vinyl chromones

INTRODUCTION

Vinyl analogs of chromones, a rare class of oxygen heterocycles, possess a wide spectrum of biological activity. The natural and synthetic analogs of vinyl chromones have been reported to exhibit antineoplastic, antiallergic, antihepatoprotective, and estrogenic activity.[1] In view of our ongoing study to evaluate the biological activity of these compounds, we were interested in the preparation of 3-halogenated-2-vinyl chromones. Although synthetic methodologies for 3-halogenated chromones that lack substitution at C-2 have been reported,[2] efficient methodologies for preparation of 3-halogenated-2-vinyl chromones were not available.

Literature reports indicated that the chemical reactivity of vinyl chromones had been reasonably explored.[3] The reactive center exploited in these reactions was the acidic Cα=Cβ of vinyl chromone. The challenge in carrying out electrophilic/nucleophilic reactions on vinyl chromones was the acidic Cα=Cβ bond, which was more susceptible to attack by various electron-acceptor and electron-donor systems. Electrophilic attack on the pyran ring is influenced by ring substituents, and electron donors at C-2 and C-3 were reported to activate the adjacent ring position.[4] Based on these reports, it was considered worthwhile to explore the reactivity of 3-hydroxy-2-vinyl chromones in the presence of brominating agents. Herein, we report a one-step stereoselective bromination reaction of *E*-3-hydroxy-2-vinyl chromones to obtain quantitative yield of *E*- and *Z*-3-bromo-2-vinyl chromones using N-bromosuccinimide (NBS) as the brominating agent.

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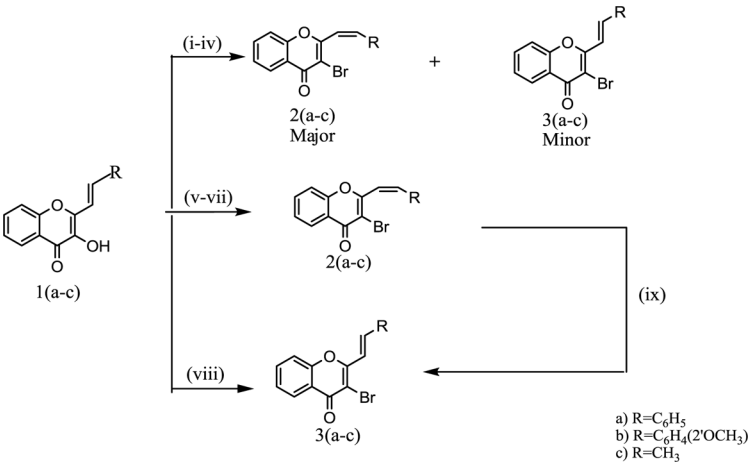
RESULTS

Our studies were carried out on *E*-3-hydroxy-2-vinyl chromones, which were prepared by methods reported earlier in literature.[5] According to literature reports, *E*-3-hydroxy-2-vinyl chromones reacted with pyridinium tribromide to furnish dibromo and tribromo products. It was also reported that the type of substituent on ring B of vinyl chromone affected the product that was isolated.[6a] There were also reports that 3-bromo-2-vinyl chromones can be produced through cyclization of intermediate 2-bromo-1,3-diones using Br_2, dioxane, and as NBS/CCl_4. The products were obtained as mixtures that could not be separated even after repeated crystallization.[6b] The lack of an efficient one-step procedure with quantitative yields of product prompted us to explore this reaction further. In our initial studies, we attempted bromination with Br_2/CH_2Cl_2. In both cases, we obtained a mixture of products that was difficult to separate by column chromatography. The presence of more than one reactive center in the molecule prompted us to attempt bromination under milder conditions. In the light of reagents that had been used to carry out 3-halogenation in benzopyranones, it was concluded that NBS in the presence of various aprotic solvents had been used to get quantitative yield of 3-halogenated product. Therefore, as an alternative strategy, the bromination reactions were attempted using N-bromosuccinimide in the presence of α,α-azobisisobutyronitrile (AIBN) in benzene. Compounds **2** and **3(a–c)** were obtained in poor yield. A significant observation made during the course of this study: compounds **2** and **3(a–c)** were formed even in the absence of free radical initiator AIBN. Further, as a modification; the reaction was attempted with aprotic and dipolar aprotic solvents such as CH_3CN, dimethylformamide (DMF), and CH_2Cl_2. It was observed that if reaction was carried out in CH_2Cl_2 for 1 h, it led exclusively to the formation of compounds **2(a–c)**. Further exploration of the reaction conditions revealed that if compounds **2(a–c)** were suspended overnight in methanol, the products isolated were **3(a–c)**. Therefore, as a modification, the reaction of compounds **1(a–c)** was attempted in protic solvents for 1 h, and **3(a–c)** were obtained in good yield. A summary of the different reaction conditions explored is presented in Scheme 1.

The structure elucidations of the compounds were done spectroscopically. Compounds **2a** and **3a** were chosen as representative compounds, and detailed spectroscopic studies were carried out. The mass spectra of compound **2a** and **3a** indicated a molecular ion peak corresponding to the presence of a monobromo derivative. However, the possibility of bromination at the Cβ-position had to be ruled out. The infrared (IR) spectrum of compounds **2a** and **3a** exhibit peaks at 1738 cm^{-1}, 1628 cm^{-1}, and 1738 cm^{-1}, and 1633 cm^{-1} respectively for the C-4 carbonyl group and vinyl group along with similar fingerprint region. In comparison, compound **1a** exhibited corresponding group peaks at 1633 cm^{-1} and 1596 cm^{-1}. An increase in the absorption frequency of the carbonyl group suggests field effect in its vicinity. Also, if bromination had occurred at the Cβ-position it would have resulted in a decrease in absorption frequency of the Cα=Cβ bond because of the presence of bulky substituent[7] as compared to the starting compound **1a**, which was not observed. In our case, we have observed an increase in the absorption frequency of the Cα=Cβ bond in the product. Furthermore, the similarity in the fingerprint region of the spectrum suggests similar electronic environments in **2a** and **3a**.



Scheme 1. (i) C_6H_6, NBS, AIBN; (ii) DMF NBS, AIBN; (iii) CH_2Cl_2, NBS, AIBN; (iv) DMF, NBS, dark; (v) CH_2Cl_2, NBS, Dark; (vi) CH_2Cl_2, NBS, hν; (vii) CH_2Cl_2, NBS, 1 h; (viii) NBS, MeOH,1 h; (ix) MeOH, overnight.

The NMR of compounds **2a** and **3a** characteristically depicted the absence of a hydroxyl group at 12.2 ppm and a downfield shift in the position of Hα to δ 7.47, 7.45 and δ 7.51, 7.47, respectively as compared to δ 6.80 in **1a**. The $^3J_{CH}$ coupling constants for Hα and Hβ protons were 9.9 Hz for **2a** and 18.9 Hz for **3a** suggesting them to be *Z*- and *E*-isomers, respectively. Long-range coupling with C-2′ in **2a** and C-2′ and C-6′ in **3a** was also observed, leading to a difference in multiplicity pattern of Hβ. ^{13}C experiments on **2a** and **3a** revealed that Cα and Cβ appeared at 129 ppm, 147 ppm and 138 ppm, 146 ppm, respectively. An unusual downfield shift in the position of C-8 was also observed at 141 ppm and 128 ppm for **2a** and **3a**, respectively. Compound **2a** can exist in two possible conformations: **I** and **II**. Earlier reports[5] had concluded conformations **I** based on energy calculations and upfield shift of H-8, which was contrary to results obtained in our case. In our case, the energy minimizations for **2a** and **3a** were conducted with Macromodel software[8] using Optimized Potentials for Liquid Simulations 2005 (OPLS 2005) force field. The convergence threshold used was the rms gradient of 0.01. The energy calculation using truncated Newton conjugate gradient (TNCG) reveals that conformation **I** has energy −8781 kJ/mol, and **II** has −8799 kJ/mol, while **3a** has energy −8788.15 kJ/mol. Our preference for conformation **II** is based on the spectroscopic data and energy calculations. The energy-minimized structures using TNCG of **2a** and **3a** are depicted in Fig. 1.

Detailed correlation spectroscopy (COSY) experiments were also performed on **2a** and **3a**. In the case of compound **2a**, correlation peaks were observed between H-2′ at δ 7.15 and H β at 7.75; however, no correlation peaks were observed between H-6′ at δ 7.53 and Hβ at δ 7.73. Correlation peaks were also observed between δ 7.50 and δ 7.70, indicating correlation between Hα and Hβ protons. In the case of compound **3a**, correlation peaks were observed between H-2′ at δ 6.90 and Hβ at δ 7.70; H-6′ at δ 7.04 and H β at δ 7.69; and Hα at δ 7.44 and Hβ at δ 7.76.

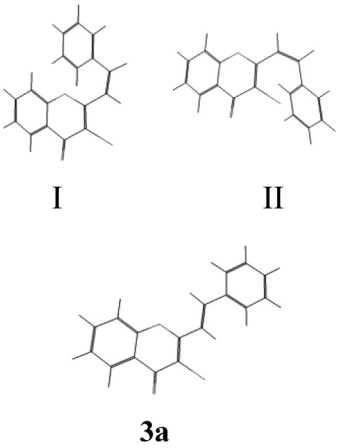


Figure 1. Energy-minimized structures of compounds **2a** and **3a**. I and II are the energy-minimized conformations of compound **2a**.

DISCUSSION

The two important observations made during the course of the study were that reactions invariably occurred at the C-3 position, however, there was a difference in the stereochemical outcome of products **2** and **3**. Bromination reactions using NBS occur by a free radical mechanism involving allylic or benzylic protons and electrophilic addition. Our observation of the occurrence of a reaction in the absence of light or free radical initiator (although slight variation in the reaction time was observed) and the presence of an intact Cα=Cβ bond in the products suggested that the reaction was not occurring by free radical or electrophilic mechanism. Based on these facts, the question arises with regard to the reactive species involved in bromination. The mechanism of NBS decomposition has been studied under different reaction conditions in detail, and several mechanisms have been proposed.[9] It has been observed that the results of bromination reactions using NBS were influenced by radical intermediates other than the bromine atoms.[10] Goldfinger had earlier suggested that NBS reacted rapidly with HBr to generate a low concentration of bromine to facilitate chain propagation but prevent ionic addition to olefin. It has also been suggested that a succinimidyl radical may be a possible chain carrier. Competitive brominations in methylene chloride, a solvent in which NBS has minimal solubility, has been known to consume bromine as bromodichloromethane.[11] These observations lead us to conclude that the when dichloromethane is being used as solvent, the possible intermediate was bromodichloromethane formed by hydrogen abstraction from dichloromethane, further leading to the formation of HBr, which was the reactive species leading to the bromination product. The change in stereochemistry from $E \rightarrow Z$ may be due to a second attack of HBr on the vinylic carbon. It has been reported that vinylic systems usually undergo nucleophilic addition elimination reaction, which leads to products of opposite stereochemistry because of olefin inversion. Olefin inversion is known to occur by various mechanisms, which include thermal–chemical, photoisomerization, and addition elimination reactions.[12]

Oxidative addition to an olefin involving nucleophilic substitution followed by reductive elimination usually leads to an olefin with inverted geometry. Several mechanisms have been proposed that involve *syn*/*anti* addition and elimination, leading to different stereochemical outcomes. The addition of electrophilic reagents to olefins is usually *anti*.[12] Literature reports indicate that bromine and modified brominating reagents have been used for controlled *anti* addition of halogens olefins. It is proposed that HBr was first undergoing *anti* addition followed by *syn* elimination, leading to inversion in stereochemistry from $E \rightarrow Z$ in the product.

Analogously, when methanol was being used as solvent, the possible intermediate leading to the formation of HBr could be bromomethanol by hydrogen abstraction. However, in this case, because of the presence of protic solvents, the reaction was probably proceeding through a carbocation intermediate. The retention in stereochemistry further suggests possible neighboring group participation could be operational. The attack of the bromide ion led to the product with an overall retention in configuration.

EXPERIMENTAL

All the melting points were determined on a hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bruker instrument as KBr discs or neat. ^{1}H NMR spectra were recorded on a Bruker Spectrospin 300-MHz instrument. The solvent used was $CDCl_3$ unless mentioned otherwise. Compounds have been analyzed using 2D correlation spectroscopy unless mentioned otherwise. 4*H*-1-Benzopyran-4-one-3-hydroxy-2-(2-phenylethenyl) **1(a–c)** were prepared by reported procedures.[5]

Synthesis of *Z*-3-Bromo-2-(phenyl ethenyl) Benzopyran-4-ones (2a)

N-Bromosuccinimide (6.75 g, 0.038 mol) was added to the compound 3-hydroxy-2-(2-phenyl ethenyl) benzopyran-4-one (10.0 g, 0.038 mol) in dry CH_2Cl_2 (50 ml),and the mixture was stirred at room temperature for an hour. The reaction was monitored by thin-layer chromatography (TLC), and thereafter the excess CH_2Cl_2 was distilled off in vacuo. The reaction mixture was quenched with water and extracted with ethyl acetate (3×25 ml). The organic layers were pooled, washed with brine, and dried over anhydrous sodium sulfate to obtain the product. Yield 68.26%, mp 144–146 °C, $C_{17}H_{11}O_2Br$ 326 (M+), IR (cm^{-1}) 1738 cm^{-1}, 1644 cm^{-1}; NMR ($CDCl_3$) 7.85 (d, 1H, H-8), 7.80 (d, 1H, H5), 7.75, 7.69 (dd, $J = 9.6$ Hz, =Cβ *H*) 7.47, 7.45 (d, 2H, =Cα*H*, H-6′ ($J = 7.8$ Hz) merged), 7.33 (m, 3H, H4′, H5′, H7), 7.00–7.15 (m, 3H, H-2′, H-6, H-4); C^{13} ($CDCl_3$) 162.38 (C2), 122.64 (C3), 194.6 (C4), 130.96 (C5), 127.6 (C7), 141.02 (C8), 159.12 (C9), 110.20 (C10), 129.88 (Cα), 147.54 (Cβ), 135.57 (C1′), 126.23 (C2′), 121.99 (C-3′), 121.46 (C4′), 128.93 (C5′,6), 144.53 (C6′).

E-3-Bromo2-(2-phenyl ethenyl) Benzopyran-4-one (3a)

N-Bromosuccinimide (6.75 g, 0.038 mol) was added to the compound 3-hydroxy-2-(2-phenyl ethenyl) benzopyran-4-one (10.0 g, 0.038 mol) in methanol (50 ml), and the mixture was stirred at room temperature for an hour. The reaction

was monitored by TLC, and thereafter the insoluble solid was crystallized using hexane–ether mixture to obtain an insoluble solid, which was filtered off. Yield (88.63%), mp 152–153 °C, $C_{17}H_{11}O_2Br$ 326 (M+), IR (cm^{-1}) 1738 cm^{-1}, 1633 cm^{-1}; NMR ($CDCl_3$) 7.84 (d, 1H, H-5), 7.72 (m, 1H, Hβ), 7.51, 7.47 (m3H, Hα, H-6, H-8), 7.39 (m, 3H, Ar-H), 7–7.07 (m, 2H, Ar-H), 6.93 (t, 1H, Ar-H); C^{13} ($CDCl_3$) 159.12 (C2), 122.64 (C3), 193.723 (C4), 131.69 (C5), 129.67 (C6,5′), 127.6 (C7), 128.93 (C8), 162.38 (C9), 110.34 (C10), 138.7 (Cα), 146.47 (Cβ), 135.71 (C1′), 120.57 (C2′), 121.17 (C3′), 126.40 (C4′), 128.93 (C8), 143.71 (C6′).

Synthesis of *Z*-3-Bromo-2-[2-phenyl(-2′-methoxy) ethenyl] Benzopyran-4-ones (2b)

To the compound 3-hydroxy-2-(phenyl ethenyl)2′-methoxy benzopyran-4-one (10.0 g, 0.034 mol) in dry CH_2Cl_2 (50 ml), NBS (9.081 g, 0.051 mol) was slowly added. The reaction mixture was stirred at room temperature for 1.5 h. Reaction was monitored by TLC, and the excess CH_2CL_2 was distilled off in vacuo. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 25 ml). The organic layers were pooled, washed with brine, and dried over anhydrous sodium sulfate to obtain the product. Yield (76%) mp = 128–130 °C.

Synthesis of *E*-3-Bromo-2-[2-phenyl(-2′-methoxy) ethenyl] Benzopyran-4-ones (3b)

N-Bromosuccinimide (6.75 g, 0.038 mol) was added to the compound 3-hydroxy-2-(2-phenyl ethenyl) benzopyran-4-one (10.0 g, 0.038 mol) in methanol (50 ml) and the mixture was stirred at room temperature for 30 min. The reaction was monitored by TLC, and thereafter the insoluble solid was crystallized using hexane–CH_3OH to obtain an insoluble solid, which was filtered off. Yield (75%). ***E,Z*** mass 356 (M+); IR 1736 cm^{-1}; 1640; NMR ($CDCl_3$) δ 7.86, 7.78 (dd, $J = 8.1$ Hz, β *H*, 7.49, 7.46 (d, 2H, α*H*, Ar-H merged), 7.43–6.84 (m, 8H, Ar-H).

Synthesis of *Z*-3-Bromo-2-(2-methyl ethenyl) Benzopyran-4-one (2c)

N-Bromosuccinimide (8.81 g, 0.038 mol) in CH_2CL_2 (50 ml) was slowly added to compound 3-hydroxy-2-(methyl) benzopyran-4-one (10.0 g, 0.038 mol) in dry CH_2CL_2. The mixture was stirred at room temperature for 1 h. Reaction was monitored by TLC, and thereafter the excess CH_2CL_2 was distilled off in vacuo. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 25 ml). The organic layers were pooled, washed with brine, and dried over anhydrous sodium sulfate to obtain the product. Yield (78%), oil.

Synthesis of *E*-3-Bromo-2-(2-methyl ethenyl) Benzopyran-4-one (3c)

N-Bromosuccinimide (6.75 g, 0.038 mol) was added to the compound 3-hydroxy-2-(2-phenyl ethenyl) benzopyran-4-one (10.0 g, 0.038 mol) in methanol (50 ml), and the mixture was stirred at room temperature for an hour. The reaction

was monitored by TLC, and thereafter the insoluble solid was crystallized using hexane–MeOH to obtain an insoluble solid, which was filtered off. Yield (76%), oil.

E,Z mass 265 (M+); IR 1708 cm^{-1}, 1644 cm^{-1}; NMR ($CDCl_3$) 7.82, 7.77 (dd, $J = 8.1$ Hz, =Cβ *H*), 7.48, 7.46 (d, 2H, α*H*, Ar-H merged), 7.02–6.70 (m, 3H, Ar-H), 3.38 (s, 3H, CH_3).

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