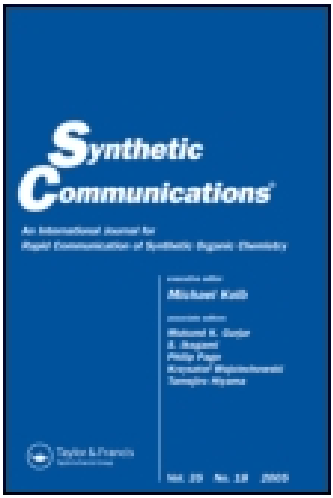

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Rapid Access of Some Chloro-substituted Isocoumarins and Biological Activity Toward Some Pathogenic Systems

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Abstract: Sulphuric acid–catalyzed chloralhydrate condensation with different *m*-substituted benzoic acids formed trichlorophthalides **1**, from which Zn + AcOH reduction afforded various dichloro derivatives **2**. These derivatives **2** on treatment with alkaline $Hg(OAc)_2 + I_2$ furnished different substituted isocoumarins **4**.

Keywords: 2-(2,2′-dichloroethenyl)-5-substituted benzoic acid, 3-chloro substituted isocoumarins

Isocoumarins are widely distributed microbial metabolites in nature that are associated with different structures[1] and biological profiles.[2–4] They are also found to be associated with pesticidal activities.[4,5] Many synthesis of isocoumarins and dihydroisocoumarins were reported. Larock et al.[6] have reported a convenient route for the synthesis of some isocoumarins and 3,4-dihydroisocoumarins using the toxic metal thallium for thallation and subsequent olefination of benzoic acids. In 1998 Mali et al.[7] devised the condensation of phthalides with butyraldehyde or acetaldehyde in the presence of LDA and acid hydrolysis to obtain isocoumarins. Recently, a simple method was devised by Purohit[8] for the fabrication of 3-aroyl-4-alkylisocoumarins by refluxing *o*-acylbenzoic acid with phenaceyl bromide in the presence of

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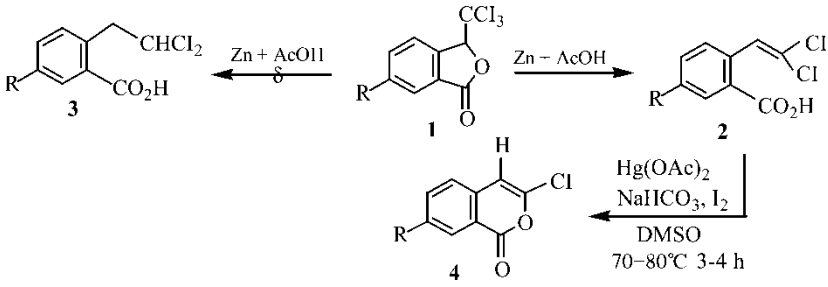
anhyd. potassium carbonate. Undoubtedly, all the methods added to the field of isocoumarins synthesis. We felt the need to develop a new method for the synthesis of chloro-substituted isocoumarin, which is described herein.

RESULTS AND DISCUSSION

While performing the known reaction[9] of the Zn and AcOH reduction to 3-(trichloromethyl)-6-methoxyphthalide, we isolated a new compound, 2-(2,2′-dichloroethenyl)-5-methoxybenzoic acid **2**, and not the reported compound **3**. The ^{1}H NMR and ^{13}C NMR (Dept) spectral analyses proved the structure of **2**. In addition the mass spectrum also supported the structure of **2**. Further information by conducting Baeyer and Br_2 + water tests were conclusive.

Subsequent reaction of **2a** with alkaline $Hg(OAc)_2$ in DMSO followed by acid workup gave **4a** in an 85% yield. In the infrared spectrum, peaks at 1728 and 1687 cm^{-1} for the C=O group and double bond were observed. The ^{1}H NMR spectrum indicated peak because of methoxy at 3.81 ppm. In the ^{13}C NMR spectrum, ten carbons were detected with C=O at 170.23 ppm. The double-bonded carbons were observed at 102.2 and 107.3 ppm. The HRMS was in agreement with the given structure of **4a**. Isocoumarins **(4)** were screened for biological activity. In the MIC test all the compounds **(4a–c)** showed moderate biological activity with respect to *Shigella dysenteriae, Bacillus subtilis, Salmonella typhi*, and *Escherichia coli* at a molar concentration of 20–25 μg/mL. Therefore, we state in conclusion that the present article describes a simple strategy for the preparation of chloro-substituted isocoumarins (Scheme 1).



4a. R = OMe, **4b.** R= OH
4c. R = OCH_2Ph

Scheme 1.

EXPERIMENTAL

General

The melting points were determined on a capillary melting-point apparatus and are uncorrected. Infrared spectra were recorded using KBr pellets for solids and neat for liquids on FTIR-8400 and Perkin-Elmer 883 grating spectrometers. ^{1}H NMR and ^{13}C NMR spectra were taken on AC Bruker 200-MHz spectrometer in $CDCl_3$, containing TMS as the internal standard. Mass spectra were taken on Kratos MS 80 and JEOL JMS-DX 303/JMA-DA-5000 system. All J values are given in Hz, chemical shifts are all in δ units. Reactions were monitored by TLC and column chromatography carried out on 60–120 mesh E. Merck silica gel. No hazardous chemicals or procedures have been adopted during the work.

General Procedure for Dichloro Compounds: 2-(2,2′-Dichloroethenyl)-5-methoxybenzoic Acid 2a

Trichloromethyl-6-methoxyphthalide[9] **1a** (1 g, 3.55 mmol) acetic acid (15 mL) and Zn dust (2 equiv., 0.46 g) were heated at 116°C for 3 h, and then filtered and diluted with cold water. A white precipitate was cooled and filtered to give **2a** in a 90% yield (0.78 g). Mp. 166–167°C. IR: 1691, 1602 cm^{-1}; ^{1}H NMR (d_6-DMSO): 7.45–7.40 (m, 2 H, Ar-H), 6.90 (dd, 1 H, $J = 2$, 8 Hz, Ar-H), 4.53 (s, 1 H, =CH), 3.26 (s, 3 H, OMe); ^{13}C NMR: 167.5, 158.9, 131.2, 130.4, 128.8, 126.7, 119.4, 117.5, 115.4, 55.1. Calcd. for $C_{10}H_8O_3CI_2$: C, 48.58%; H, 3.24%; CI, 28.74%. Found C, 48.63%; H, 3.39%; CI, 28.78%. HRMS calculated for $C_{10}H_8O_3CI_2$, 247.0762; observed 247.0764.

2-(2,2′-Dichloroethenyl)-5-hydroxybenzoic acid 2b. 75% (0.65 g). Mp 183°C. IR: 3475 (broad), 1680 cm^{-1}; ^{1}H NMR: (d_6-DMSO), 7.47–7.35 (m, 2 H), 6.95 (dd, 1 H, $J = 2.6$, 8.4 Hz, Ar-H), 4.79 (s, 1 H, Ar-OH), 4.61 (s, 1 H, =CH); ^{13}C NMR: 168.6, 157, 131.5, 130.5, 128.8, 125.9, 119.6, 119.3, 117.8. Calcd. for $C_9H_6O_3CI_2$: C, 46.35%; H, 3.43%; CI, 30.47%. Found C, 46.40%; H, 3.48%; CI, 30.52%. HRMS calculated for $C_9H_6O_3CI_2$, 233.0494; observed 233.0497.

2-(2,2′-dichloroethenyl)-5-benzyloxybenzoic acid 2c. 70% (0.61 g). Mp 145°C. IR: 1687 cm^{-1}; ^{1}H NMR ($CDCI_3$): 8.03 (d, 1 H, $J = 8$ Hz, Ar-H), 7.46–7.35 (m, 7 H, Ar-H), 5.12 (s, 2 H, $-CH_2-$) 4.53 (s, 1 H, =CH); ^{13}C NMR: 169, 156, 145, 136.3, 133 (3 × C), 128.5 (2 × C), 128.1, 127.5, 126 (2 × C), 122.3, 117, 71.2. Calcd. for $C_{16}H_{12}O_3CI_2$: C, 59.44%; H, 3.71%; CI, 21.98%; Found C, 59.49%; H, 3.76%; CI, 22.03%. HRMS calculated for $C_{16}H_{12}O_3CI_2$, 323.1738; observed 323.1739.

General Preparation Procedure for Isocoumarins: 7-Methoxy-3-chloro Isocoumarin 4a

2-(2,2′-Dichloroethenyl)-5-methoxybenzoic acid **2a** (0.05 g, 0.203 mmol) and I_2 (0.025 g) were dissolved in DMSO (10 mL). Solid $NaHCO_3$ (0.017 g) and $Hg(OAc)_2$ (0.06 g) were added and the reaction mixture was heated between 70–80°C for 4 h (monitored by TLC). It was neutralized with 2 M of HCI, DMSO was removed, and the residue was extracted with EtOAc, washed with H_2O, dried over Na_2SO_4, and evaporated. The crude product was chromatographed on silica gel by eluting with *n*-hexane/ethylacetate (5 : 1) to afford **4a** (0.036 g, 85%), mp 131–132°C. IR: 1728, 1687 cm^{-1}; ^1H NMR ($CDCI_3$): 7.57 (d, 1 H, $J = 2$ Hz), 7.51 (d, 1 H, $J = 8$ Hz), 7.41 (s, 1 H, =CH), 7.06 (dd, 1 H, $J = 2$, 8 Hz), 3.81 (s, 3 H, OMe); ^{13}C NMR: 170.23, 166, 163, 144, 138, 107.3, 105, 104, 102.2, 52.3; HRMS calculated for $C_{10}H_7O_3CI$, 210.6153; observed 210.6150.

7-Hydroxy-3-chloro isocoumarin 4b. 78% (0.033 g), mp 103–104°C. IR: 3405 (broad), 1729, 1681 cm^{-1}, ^1H NMR ($CDCI_3$): 7.84–7.44 (m, 2 H), 7.50 (s, 1 H, =CH), 7.30 (s, 1 H, Ar-OH), 7.01 (dd, 1 H, $J = 2$, 8 Hz); ^{13}C NMR: 170.5, 163, 143, 137, 135, 133, 122, 107, 103; HRMS calculated for $C_9H_5O_3CI$, 196.5885; observed 196.5883.

7-Benzyloxy-3-chloro isocoumarin 4c. 80% (0.036 g), mp 109–111°C. IR: 1731, 1687; ^1H NMR ($CDCI_3$): 7.43–7.33 (m, 5 H), 6.86 (dd, 1 H, $J = 2.4$, 8 Hz), 6.73 (d, 1 H, $J = 2.4$ Hz), 6.69 (s, 1 H, =CH), 6.49 (dd, 1 H, $J = 2.4$, 8 Hz), 5.09 (s, 2 H); ^{13}C NMR: 172, 164, 161, 151, 141, 135.7, 128.7 (2 × C), 128.3, 127.5 (2 × C), 105.6, 104, 102.7, 102, 70.2; HRMS calculated for $C_{16}H_{11}O_3CI$, 286.7129; observed 286.7132.

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