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ZAHID SHAFIQ

MUHAMMAD ARFAN

NASIM HASAN RAMA

SHAHID HAMEED

GHULAM ABBAS

*See next page for additional authors*

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## Synthesis of Some New Dihalophenyl- and Dihalobenzylisocoumarins and Their (dl)-3,4-Dihydroderivatives

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## Synthesis of Some New Dihalophenyl- and Dihalobenzylisocoumarins and Their (dl)-3,4-Dihydroderivatives

Zahid SHAFIQ<sup>1</sup>, Muhammad ARFAN<sup>1</sup>, Nasim Hasan RAMA<sup>1\*</sup>, Shahid HAMEED<sup>1</sup>, Ghulam ABBAS<sup>1</sup>, Muhammad Tahir HUSSAIN<sup>2</sup>

<sup>1</sup>Department of Chemistry, Quaid-i-Azam University,  
Islamabad-45320 PAKISTAN

e-mail: nasimhasanrama@hotmail.com

<sup>2</sup>Department of Chemistry, National Textile University,  
Faisalabad-37610, PAKISTAN

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3-Dihalophenyl- and dihalobenzylisocoumarins (**3a-c**) were synthesized by condensation of homophthalic acid (**1**) with dihalobenzoyl- and dihalophenylacetyl chlorides (**2a-c**), respectively. The alkaline hydrolysis of these isocoumarins (**2a-c**) afforded keto-acids (**4a-c**). (dl)-3-(Dihalophenyl)- and (dl)-3-(dihalobenzyl)-3,4-dihydroisocoumarins (**6a-c**) were obtained by reduction of keto-acids (**4a-c**) to racemic hydroxy-acids (**5a-c**) followed by cyclodehydration using acetic anhydride.

**Key Words:** Dihaloisocoumarins, Dihydrodihaloisocoumarins, synthesis

### Introduction

Halogen substituted isocoumarins in general, and chlorosubstituted isocoumarins and dihydroisocoumarins in particular, have been used for various biological applications. 3-Fluoro-5,8-dimethoxy-3,4-dihydroisocoumarin is reported<sup>1,2</sup> to be effective as an inflammation inhibitor. Among chlorosubstituted isocoumarins and dihydroisocoumarins, 4-chloro-3-[(4-fluorophenyl)methoxy]isocoumarin is an effective inhibitor<sup>3</sup> for human Q31 granzyme A. It has also been found<sup>4</sup> useful in the treatment of emphysema and as a serine protease inhibitor. 6-(2-Chloro-4-trifluoromethylphenoxy)-3,4-dihydroisocoumarin has shown<sup>5</sup> effective herbicidal activity, almost totally controlling the growth of *Schinochloa crusgalli*, *Sinapis alba* and some other weeds. Isocoumarins substituted with chloro and basic groups such as guanidine are inhibitors<sup>6</sup> of complement serine proteases while their 3,4-dihydroisocoumarin derivatives are general serine protease inhibitors. Certain 6- or 7-chlorosubstituted-4-carboxyisocoumarins have been reported<sup>7</sup> as phytotoxic to radish and rice plants.

In order to further explore the activity of chlorosubstituted isocoumarins, and in continuation of our previous studies<sup>8-11</sup>, we hereby report the synthesis of some novel dihalophenyl- and dihalobenzyliso-

\*Corresponding author

coumarins (**3a-c**) and their (*dl*)-3,4-dihydroderivatives (**6a-c**). The synthesis of these compounds was carried out according to the scheme given in Figure 1.

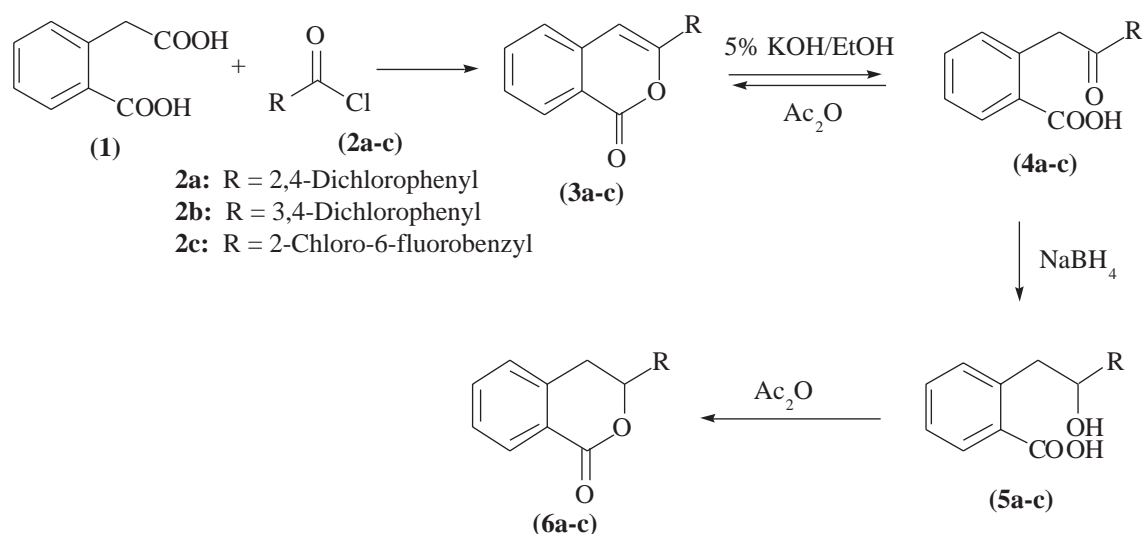


Figure 1

## Experimental

**General:** Melting points of the compounds were determined in open capillaries using Gallenkemp melting point apparatus and are uncorrected. The infrared spectra were recorded on a Hitachi model 270-50 spectrophotometer as KBr disks or as neat liquids. <sup>1</sup>H-NMR (500 MHz) spectra were recorded on a Bruker AM-500 as CDCl<sub>3</sub> solution using TMS as an internal standard while EIMS were recorded on a MAT-112-S machine. The petroleum ether used corresponds to the fraction with a boiling range of 40 to 60 °C.

### General procedure for preparation of dihalophenyl- and dihalobenzylisocoumarins (**3a-c**):

A mixture of homophthalic acid (**1**) (11.2 mmol) and acid chloride (**2a-c**) (47 mmol) was heated under reflux at 200 °C for 3 h. The residue after concentration was chromatographed on silica gel using petroleum ether (bp 60-80 °C) to give the isocoumarin (**3a-c**) as a colorless solid.

*3-(2',4'-Dichlorophenyl)isocoumarin (3a):* Yield 60%; mp 118 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 7.25, (s, 1H), 7.31 (d, J=2.0 Hz, 1H), 7.35 (ddd, J=0.8, 1.1, 6.3 Hz, 1H), 7.51 (dd, J=2.0, 7.8 Hz, 1H), 7.55 (ddd, J=1.2, 6.2, 7.3 Hz, 1H), 7.75 (ddd, J=1.3, 6.1, 7.4 Hz, 1H), 7.69 (d, J=8.4 Hz, 1H), 8.33 (ddd, J=0.6, 1.3, 6.6 Hz, 1H); IR (KBr): 1694, 684; MS (70ev) m/z (%) = 294 [M<sup>+</sup>+4 (7)], 292 [M<sup>+</sup>+2 (38)], 290 (M<sup>+</sup>, 57), 266 (4), 264 (20), 262 (31), 250(1), 248 (2), 246 (3), 229 (8), 227 (25), 193 (4), 178 (1), 177 (10), 176 (5), 175 (64), 174 (8), 173 (100), 149 (4), 147 (21), 145 (33).

*3-(3',4'-Dichlorophenyl)isocoumarin (3b):* Yield 62%; mp 178 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 6.90 (s, 1H), 7.42 (dd, J=1.7, 7.5 Hz, 1H), 7.53-7.61 (m, 2H), 7.80 (dd, J=1.7, 8.0 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H), 8.14 (dd, J=1.3, 7.2 Hz, 1H), 8.25 (d, J=1.5 Hz, 1H); IR (KBr): 1702, 1099; MS (70ev): m/z (%) = 294 [M<sup>+</sup>+4 (7)], 292 [M<sup>+</sup>+2 (38)], 290 (M<sup>+</sup>, 57), 177 (10), 175 (64), 173 (100), 149 (4), 147 (21), 145 (33).

*3-(2'-Chloro-6'-fluorobenzyl)isocoumarin (3c)*: Yield 56%; mp 102 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 3.88 (s, 2H), 6.30 (s, 1H), 7.39 (ddd, J=1.2, 6.1, 7.3 Hz, 1H), 7.63 (ddd, J=1.9, 7.3, 7.8 Hz, 1H), 7.22-7.35 (m, 4H), 8.22 (ddd, J=0.6, 1.3, 6.6 Hz, 1H); IR (KBr) 1702; EIMS (70ev): m/z (%) = 290 [M<sup>+</sup>+2 (2)], 288 (M<sup>+</sup>, 6), 246 (1), 244 (3), 172(1), 170 (2), 145 (70), 143 (100), 117 (15), 89 (17).

### General procedure for preparation of 2-(substituted)benzoic acids (4a-c):

A solution of 5.3 mmol of the isocoumarin (**3a-c**) in ethanol (50 mL) and potassium hydroxide (5%, 100 mL) was refluxed for 4 h. Ethanol was removed from the reaction mixture by distillation. Ice cold water (20 mL) was added and the reaction mixture was acidified with hydrochloric acid. The reaction mixture was then extracted with dichloromethane (3 x 20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent rotary evaporated to yield a crude solid (**4a-c**) recrystallized from methanol.

*2-(2',4'-Dichlorobenzoylmethyl)benzoic acid (4a)*: Yield 59%; mp 150 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 4.02 (s, 2H), 7.16 (dd, J=8.4, 2.0 Hz, 1H), 7.23 (dd, J=8.0, 1.8 Hz, 1H), 7.31 (d, J=2.0 Hz, 1H), 7.35 (ddd, J=7.8, 6.0, 1.3 Hz, 1H), 7.49 (ddd, J=7.8, 6.0, 1.4 Hz, 1H), 7.71 (d, J=8.4 Hz, 1H), 8.09 (dd, J=7.8, 1.4 Hz, 1H), 11.4 (bs, 1H, D<sub>2</sub>O exchangeable); IR (KBr): 3200-2500, 1689; EIMS (70ev): m/z (%) = 310 [M<sup>+</sup>+2 (1)], 308 (M<sup>+</sup>, 2), 294 (2), 292 (11), 290 (2), 177 (10), 176 (6), 175 (64), 174 (17), 173 (100), 149 (12), 147 (41), 145 (64).

*2-(3',4'-Dichlorobenzoylmethyl)benzoic acid (4b)*: Yield 65%; mp 210 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 3.85 (s, 2H), 6.85 (dd, J=2.1, 8.6 Hz, 1H), 7.18 (d, J=1.9 Hz, 1H), 7.20 (d, J=8.4 Hz, 1H), 7.23 (dd, J=1.3, 6.7 Hz, 1H), 7.48 (ddd, J=2.1, 7.8, 8.1 Hz, 1H), 7.59 (ddd, J=1.3, 7.1, 8.6 Hz, 1H), 7.82 (dd, J=1.5, 8.7 Hz, 1H), 10.4 (bs, 1H, D<sub>2</sub>O exchangeable); IR (KBr): 1712, 1099; MS (70ev) m/z (%) = 312 [M<sup>+</sup>+4 (2)], 310 M<sup>+</sup>+2 (2)], 308 (M<sup>+</sup>, 3), 294 (2), 292 (11), 290 (22), 192 (84), 177 (10), 175 (64), 173 (100), 164 (4), 179 (12), 147 (41), 145 (64).

*2-[2'-Oxo-3'-(2"-chloro-6"-fluorophenyl)propyl]benzoic acid (4c)*: Yield 46%; mp 96 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 4.01 (s, 2H), 4.18 (s, 2H), 7.23 (dd, J=8.0, 1.8 Hz, 1H), 7.35 (ddd, J=1.3, 6.0, 7.8 Hz, 1H), 7.49 (ddd, J=1.4, 6.0, 7.8 Hz, 1H), 8.09 (dd, J=1.4, 7.8 Hz, 1H), 6.95-7.04 (m, 3H), 10.40 (bs, 1H, D<sub>2</sub>O exchangeable); IR (KBr): 1712; MS (70ev): m/z (%) = 308 [M<sup>+</sup>+2 (2)], 306 (M<sup>+</sup>, 6), 290 (2), 288 (5), 188 (68), 155 (20), 153 (62), 145 (67), 143 (100), 117 (21).

### General procedure for preparation of (dl)-3-(substituted)-3,4-dihydroisocoumarins (6a-c):

The keto-acid (2.07 mmol) was dissolved in potassium hydroxide solution (1%, 25 mL), sodium borohydride (0.25 g) was added and the mixture stirred for 1 h at room temperature. After acidification with hydrochloric acid the reaction mixture was extracted with ethyl acetate (2 x 50 mL). The usual workup gave the crude hydroxy-acid (**5a-c**), which was dissolved in acetic anhydride (1 mL) and heated under reflux for 2 h. The reaction mixture was cooled, water (25 mL) was added and the mixture stirred overnight. The crystals that deposited were collected by filtration and the filtrate was extracted with dichloromethane (2 x 20 mL). The solvent was removed by vacuum distillation. The crude dihydroisocoumarin (**6a-c**) was purified by column chromatography on silica gel using petroleum ether as an eluent.

(*dl*)-3-(2',4'-Dichlorophenyl)-3,4-dihydroisocoumarin (**6a**): Yield 89%; mp 105 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 2.96 (dd, J=4.4, 12.2 Hz, 1H), 3.08 (dd, J=3.2, 13.2 Hz, 1H), 5.71 (dd, J=3.2, 11.9 Hz, 1H), 7.12 (dd, J=2.0, 6.3 Hz, 1H), 7.18 (dd, J=2.1, 8.4 Hz, 1H), 7.25 (ddd, J=1.9, 7.5, 7.6 Hz, 1H), 7.27 (d, J=2.0 Hz, 1H), 7.43 (ddd, J=1.4, 6.1, 7.5 Hz, 1H), 7.47 (d, J=8.4 Hz, 1H), 7.92 (dd, J=1.2, 7.7 Hz, 1H); IR (KBr): 1675, 1500; MS (70ev): m/z (%) = 296 [M<sup>+</sup>+4 (1)], 294 [M<sup>+</sup>+2 (3)], 292 (M<sup>+</sup>, 5), 178 (8), 177 (22), 176 (13), 175 (83), 174 (16), 173 (90), 149 (13), 147 (37), 145 (57), 119 (29), 118 (100), 90 (76).

(*dl*)-3-(3',4'-Dichlorophenyl)-3,4-dihydroisocoumarin (**6b**): Yield 72%; mp 142 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 3.18 (dd, J=3.2, 12.1 Hz, 1H), 3.41 (dd, J=3.2, 13.2 Hz, 1H), 5.56 (dd, J=3.2, 11.9 Hz, 1H), 7.20 (dd, J=1.7, 8.0 Hz, 1H), 7.39-7.55 (m, 2H), 7.98 (dd, J=1.7, 8.2 Hz, 1H), 8.07 (dd, J=1.9, 7.7 Hz, 1H), 8.12 (d, J=7.6 Hz, 1H), 8.38 (d, J=1.7 Hz, 1H); IR (KBr): 1705, 1098 (C-Cl); MS (70ev): m/z (%) = 296 [M<sup>+</sup>+4 (1)], 294 [M<sup>+</sup>+2 (2)], 292 (M<sup>+</sup>, 3), 192 (75), 177 (21), 175 (79), 173 (92), 149 (15), 147 (63), 145 (78), 119 (28), 118 (100), 90 (57).

(*dl*)-3-(2'-Chloro-6'-fluorobenzyl)-3,4-dihydroisocoumarin (**6c**): Yield 80%; mp 88 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, δ-values): 2.87 (dd, J=9.8, 16.3 Hz, 1H), 3.06 (dd, J=10.8, 16.4 Hz, 1H), 3.23 (dd, J=7.9, 13.4 Hz, 1H), 3.41 (dd, J=6.4, 13.5 Hz, 1H), 4.81-4.84 (m, 1H), 6.94-7.04 (m, 3H), 7.20 (dd, J=1.7, 8.0 Hz, 1H), 7.38 (ddd, J=1.9, 6.6, 7.6 Hz, 1H), 7.48 (ddd, J=1.4, 6.1, 7.5 Hz, 1H), 8.07 (dd, J=1.9, 7.7 Hz, 1H); IR (KBr): 1705; MS (70ev): m/z (%) = 292 [M<sup>+</sup>+2 (1)], 290 (M<sup>+</sup>, 2), 248 (3), 246 (9), 190 (43), 172 (1), 170 (2), 145 (70), 143 (100), 126 (7), 124 (19), 117 (16).

## Results and Discussion

Condensation of acid chlorides (**2a-c**) with homophthalic acid (**1**) at 200 °C afforded 3-(substituted)isocoumarins (**3a-c**). These isocoumarins (**3a-c**) showed a characteristic 1H singlet at δ 7.25, 6.90 and 6.50 respectively, for C<sub>4</sub>-H in <sup>1</sup>H-NMR. The aromatic protons appeared in the acceptable region of δ 6.9 to 8.1. In IR spectra, the lactonic carbonyl absorptions were observed at 1694, 1733 and 1702 cm<sup>-1</sup>, respectively. The mass spectra of the isocoumarins (**3a-b**) showed molecular ion peaks at m/z 290, while for (**3c**) the molecular ion peak was observed at m/z 288. It is noteworthy that in all the fragments containing chlorine atoms peaks corresponding to 2 isotopes of chlorine were observed. Alkaline hydrolysis of (**3a-c**) yielded the keto-acids (**4a-c**), which in <sup>1</sup>H-NMR spectra exhibited 2H singlets for benzylic -CH<sub>2</sub> at δ 4.0, 3.85 and 4.18, respectively. The molecular ion peaks for the keto-acids (**4a-b**) were observed at m/z 308 along with peaks at 310 (M<sup>+</sup>+2) and 312 (M<sup>+</sup>+4) and for keto-acid (**4c**) at m/z 306 (M<sup>+</sup>) and 308 (M<sup>+</sup>+2) due to 2 isotopes of chlorine. A characteristic [M<sup>+</sup>-H<sub>2</sub>O] fragment was also observed for these keto-acids. Isocoumarins (**3a-c**) were re-obtained on refluxing the keto-acids with acetic anhydride. The melting points, IR, <sup>1</sup>H-NMR and mass spectra of these compounds were the same as those for isocoumarins (**3a-c**). Sodium borohydride reduction of the keto-acids (**4a-c**) to racemic hydroxy-acids (**5a-c**) followed by cyclodehydration with acetic anhydride furnished (*dl*)-3-(substituted)-3,4-dihydroisocoumarins (**6a-c**) that exhibited the carbonyl absorptions at 1675, 1700 and 1705 cm<sup>-1</sup> in their IR spectra. The typical AB pattern for C<sub>3</sub>-H and typical ABX pattern for C<sub>4</sub>-H protons were observed in <sup>1</sup>H-NMR spectra of these compounds (**6a-c**). Thus each of the C<sub>4</sub> protons showed a double doublet at δ 2.96 and 3.08 for (**6a**) and at 3.18 and 3.41 for (**6b**). The second double doublets for C<sub>3</sub>-H were observed at δ 5.71 for (**6a**) and at δ 5.56 for (**6b**). In the case

of the dihydroisocoumarin (**6c**) 2 double doublets were observed for C<sub>4</sub>-H and C-1' at  $\delta$  3.23 and 3.41 and at  $\delta$  2.87 and 3.06, respectively, while a multiplet at  $\delta$  4.81-4.84 was observed for C<sub>3</sub>-H. The mass spectra showed molecular ion peaks at m/z 292 (M<sup>+</sup>), 294 (M<sup>+</sup>+2) and 296 (M<sup>+</sup>+4) for (**6a-b**) and at 290 (M<sup>+</sup>), 292 (M<sup>+</sup>+2) for (**6c**) due to 2 isotopes of chlorine. The antimicrobial activity of the synthesized compounds will be published in a separate paper.

### References

1. T. Furuta, Y. Asakawa and Y. Fukuyama, **Jpn. Kokai Tokyo Koho JP 60,142,976 [85,142,976]**. **Chem. Abstr.** 104, 88435v.
2. F. Fratev, V. Enchev, P. Nikolov and O.E. Polansky, **Z. Naturforsch A: Phys., Phys. Chem., Kosmophys** **39A**, 1143-1144 (1984).
3. S. Odake, C.M. Kam, L. Narasimhan, M. Poe, J.T. Blake, O. Krahenbuhl, J. Tschopp and J.C. Powers, **Biochemistry** **30**, 2217-2227 (1991).
4. D. Hudig, N.J. Allison, C. M. Kam and J.C. Powers, **Mol. Immunol.** **26**, 793-798 (1989).
5. M.T. Clark and I.J. Gilmore, GB 2207425. **Chem. Abstr.** 111, 19479v.
6. C.M. Kam, T.J. Oglesby, M.K. Pangburn, J.E. Volanakis and J.C. Powers, **J. Immunol.** **149**, 163-168 (1992).
7. H. Yoshikawa, E. Taniguchi and K. Maekawa, **Nippon, Noyaku Gakkaishi** **5**, 1-10 (1980). **Chem. Abstr.** 94, 65423a.
8. M.T. Hussain and N.H. Rama, **Indian J. Heterocyclic Chem.** **8**, 99-102 (1998).
9. A. Hussain, N.H. Rama, M.T. Hussain and A. Malik, **Indian J. Heterocyclic Chem.** **8**, 189-192 (1999).
10. M.T. Hussain, N.H. Rama and A. Malik, **Indian J. Chem.** **40B**, 372-376 (2001).
11. H.B. Ahmad, N.H. Rama, M. Hussain, M.T. Hussain, M.M. Qasim, S. Hameed, M.A. Malana and A. Malik, **Indian J. Chem.** **42B**, 611-615 (2003).