Turk J Chem
29 (2005) , 171 – 175.

Synthesis of Some Novel Optically Active Isocoumarin and 3,4-Dihydroisocoumarin Containing L-valine and L-leucine Moieties

Khosrow ZAMANI*, Khalil FAGHIHI, Satar EBRAHIMI
Organic Synthesis Laboratory, Department of Chemistry, Faculty of Science, Arak University, Arak-IRAN
e-mail: K-Zamani@Araku.ac.ir

Received 15.07.2004

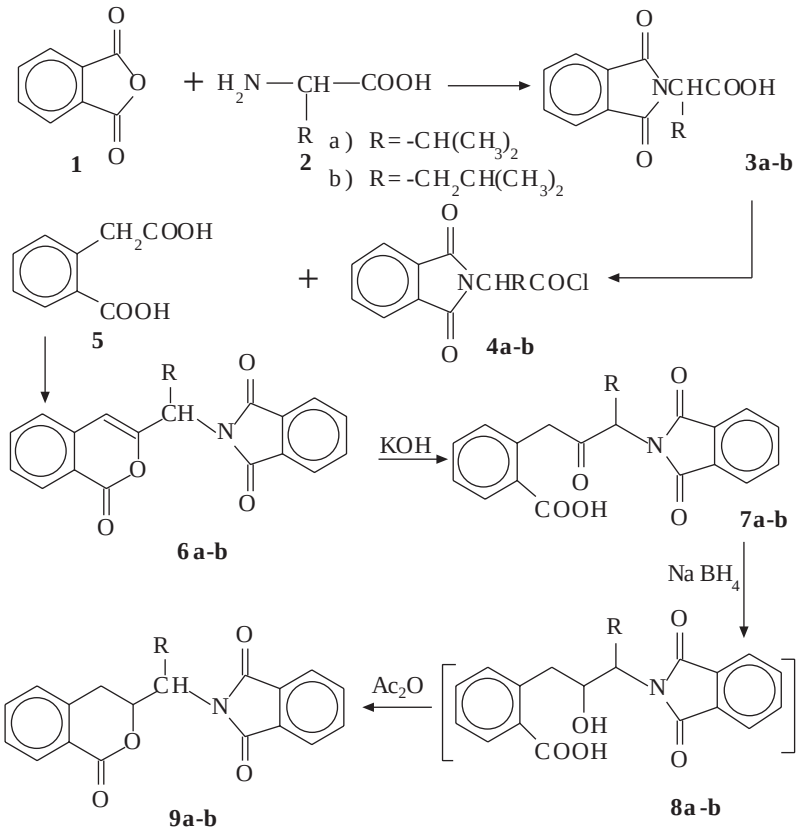
Phthalic anhydride was reacted with L-Valine and L-Leucine in a mixture of acetic acid and pyridine at room temperature, and then was refluxed at 90-100 °C and N-phthaloyl-L-valine or N-phthaloyl-L-leucine were obtained in quantitative yields. The imide-acids were converted to N-phthaloyl-L-valine acid chloride and N-phthaloyl-L-leucine acid chloride by reaction with thionyl chloride. Then 2 new derivatives of the chiral isocoumarin with L-valine and L-leucine moieties were synthesised by the condensation reaction of homophthalic acid with respective imide-acid chloride. Furthermore these isocoumarins were converted to 2 new chiral substituted 3,4-dihydroisocoumarins. Biological screening tests reveal that the compounds (3a, 9a) have not potential as antifungal activity against *Candida albicans* and *aspergillus niger*.

Key Words: Isocoumarin, Dihydroisocoumarin, Homophthalic, Amino acid.

Introduction

In recent years, there has been increasing interest in the synthesis of natural products, since they are an excellent and reliable source for the development of new drugs. Isocoumarins and 3,4-dihydroisocoumarins are a class of natural products that often occur as microbial metabolites and that have been found to exhibit interesting biological properties [1-7], including anti-fungal, anti-inflammatory, anti-allergic, necrotic, anti-angiogenic, anti-malaria [8], anti-bacterial [9], anti-cancer, anti-virus [10] and anti-microbial activities [11]. In view of their natural occurrence, biological activities, and utility as synthetic intermediates, we report some novel isocoumarin and 3,4-dihydroisocoumarins as shown in the Scheme.

*Corresponding author

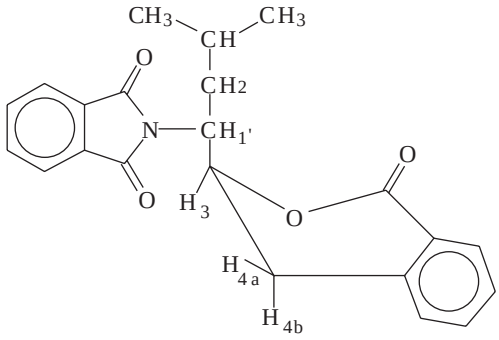


Scheme

Results and Discussion

Direct condensation of acid chlorides [12-13] **(4a-b)** with homophthalic acid **(5)** at 200 °C afforded 3-substituted isocoumarins **(6a-b)** by the method of Nakajima *et. al.* [14]. The isocoumarins **(6a-b)** showed a characteristic 1H singlet at δ 6.61 ppm for C_4-H of compounds **(6a-b)**. In the infrared spectrum of the compounds **(6a-b)** the lactonic carbonyl absorptions were observed at 1730 and 1725 cm^{-1}. Alkaline hydrolysis of the isocoumarins **(6a-b)** yielded the keto-acids **(7a-b)**. In the IR spectrum the absorption bands for ketonic and acidic carbonyl groups were observed at 1680 and 1699, 1740 and 1730 cm^{-1} respectively. In the ^{1}H-NMR of these compounds **(7a-b)** a 2H singlet at δ 3.9 and 2.59 ppm and a 1H broad singlet at δ 8.93 and 8.86 ppm were observed for methylene and hydroxyl protons, respectively. Sodium borohydride reduction of keto-acids **(7a-b)** should have afforded the corresponding hydroxy-acids **(8a-b)** which were not isolated and treated directly with acetic anhydride, and after separation and purification with TLC these afforded the optically active 3,4-dihydroisocumarins **(9a-b)**. These dihydroisocoumarins **(9a-b)** showed carbonyl absorption at 1712-1715 cm^{-1} and the typical AB pattern of C_3-H and typical ABX pattern for C_4-H protons in ^{1}H-NMR spectra. In **9b** H-4 showed two doublets of doublet (dd) at 2.83 and 3.21 ppm while H-3 appeared as a ddd at 5.15 ppm. The coupling constants observed between H-3 with H-4a, H-4b and H-1″ are 3.34, 1.47 and 3.35 Hz. This coupling constant, which is less than 5 Hz is a strong evidence of the presence of an equatorial hydrogen atom at carbon-3. If the proton attached to carbon-3 was in axial position we should have a relatively high coupling constant (8-12 Hz) for axial-axial coupling between H-3

and one of the H-4 protons, which was not observed. Therefore structure (A) is the proposed structure of **(9b),** which should be the subject of more investigation. Each of the C_4-H in **9b** showed corresponding protons.



9b (A)

Experimental

All chemicals were purchased from Aldrich (Milwaukee, WI, USA) and Merck (Germany). Melting points were determined using an electrothermal digital melting point apparatus and are uncorrected. Fourier transform infrared (FTIR) spectra were recorded on a Galaxy series FTIR 5000 spectrophotometer (England) as KBr discs. ^{1}H-NMR spectra (500MHz) were recorded on a Bruker instrument using TMS as internal standard and DMSO-d^6as solvent. The EIMS were determined on a MAT-112-s machine.

Synthesis of 3-substituted isocoumarins (6a-b)

General procedure: A mixture of homophthalic acid (2.8×10^{-3} mol) and acid chloride **(4a-b)** (0.0126 mol) was heated under reflux at 200 °C and stirred for 4 h. The residue was chromatographed over silica gel using ethyl acetate, pet. ether (60-80 °C) as eluent. The solid obtained was recrystallised from methanol to afford 3-substituted isocoumarins **(6a-b)**.

3-[2-(1,3-dioxoisoindolin)-3-methyl butyl] isocoumarin (6a): Yield (37%), mp 268-270 °C, $[\alpha a]_D^{25}$ -20° (20 mg/10mL DMSO), IR (cm^{-1}): 3010, 2970, 1780, 1730, 1710, 1489, 1288, 1273; ^{1}H-NMR (δ, ppm): 0.97-1.00 (dd, 6H, J = 6.7 Hz), 2.75-2.85 (m, 1H), 4.6-4.7 (d, 1H, J = 8.7 Hz), 6.61 (s, 1H), 7.27-8.16 (m, 8H); MS (%): 347 ($M^{\cdot+}$, 5%), 249 (7), 248 (6), 202 (42), 216 (10), 175 (18), 163 (38), 160 (75), 150 (15), 149 (90), 131(149), 131 (37), 130 (100), 104 (72), 90 (18), 76 (44).

3-[2-(1,3-dioxoisoindolin)-4-methyl pentyl] isocoumarin (6b): Yield (42%), mp 172-174 °C, $[\alpha]_D^{25}$ -22 °(20 mg/10 mL DMSO); IR (cm^{-1}): 3015, 2992, 1780, 1725, 1710, 1490, 1285, 1270; ^{1}H-NMR (δ, ppm): 1.01-1.02 (d, 3H, J = 6.7 Hz), 1.03-1.04 (d, 3H, J = 6.6 Hz), 1.99-2.00 (m, 1H), 2.55-2.56 (ddd, 2H, J = 3.3, 3.0, 2.1 Hz), 5.33-5.36 (dd, 1H, J = 4.7, 4.7 Hz), 6.61 (s, 1H), 7.42-8.26 (m, 8H); MS (%): 361 ($M^{\cdot+}$, 7%), 309 (2.5), 261 (12), 197 (6), 180 (16), 179 (100), 178 (58), 155 (10), 146 (12), 119 (17), 105 (42), 76 (25), 57 (11).

Synthesis of 2-[2-(1,3-dioxo-1,3-dihydroisoindolin) alkynoyl] benzoic acid (7a-b)

General procedure: Potassium hydroxide (5% w/w, 50 mL) was added to a solution of isocoumarins **(6a-b)** (3.13×10^{-4} mmol) in ethanol, and the reaction mixture was refluxed for 5 h. Then solution was evaporated under reduced pressure to remove ethanol, and then cold water (20 mL) was added and the reaction mixture was extracted with ethyl acetate. The aqueous layer was acidified with dilute hydrochloric acid. The mixture was extracted with CH_2Cl_2 (2×15 mL), the organic phase was dried (Na_2SO_4) and the solvent distilled in vacuo to afford a solid substance. The solid was recrystallised from ethyl acetate and pet. ether (40:60) to yield 2-substituted benzoic acid **7(a-b)**.

2-[2-(1,3-dioxo-1,3-dihydroisoindolin)-3-methyl butyryl] benzoic acid (7a): Yield (48%), mp 134-136 °C; IR (cm^{-1}): 3300, 2908, 1780, 1740, 1701, 1680; ^{1}HNMR: (δ, ppm): 0.85-0.87 (d, 3H, J = 7.1 Hz), 0.94-0.97 (t, 3H, J = 7.6 Hz), 2.11-2.17 (m, 1H), 3.9 (s, 2H), 4.29-4.31 (d, 1H, J = 7.8 Hz), 7.32-8.55 (m, 8H), 8.93 (bs, 1H).

2-[2-(1,3-dioxo-1,3-dihydroisoindolin)-4-methyl pentanoyl] benzoic acid (7b): Yield (47%), mp 170-173 °C; IR (cm^{-1}): 3178, 3076, 2995, 1730, 1699, 1641; ^{1}H-NMR (δ, ppm): 0.91-0.94 (t, 6H, J = 6.5 Hz), 2.59 (s, 2H), 1.80-1.82 (m, 1H), 4.34-4.36 (ddd, 2H, J = 3.3, 3.1, 3.2 Hz), 4.52 (bs, 1H), 7.25-7.92 (m, 8H), 8.86 (bs, 1H, D_2O exchenged); MS (%): 379 ($M^{\cdot+}$ 6.0%), 363 (8), 362 (12), 319 (22), 304 (17), 217 (19), 174 (100), 160 (64), 162 (15), 148 (8), 146 (7), 130 (19), 104 (13), 89 (12).

Synthesis of 3-substituted 3,4 -dihydroisocoumarins (9a-b)

General procedure: A solution of substituted keto-acids **(7a-b)** (1.48×10^{-4} mol) in potassium hydroxide solution (1%, 10 mL) and sodium borohydride (1.48×10^{-4} mol) in absolute ethanol (20 mL) was refluxed for 6 h. The solvent was evaporated and cooled water (20 mL) was added. The reaction mixture was acidified with dilute hydrochloric acid, and then extracted with ethyl acetate (2×20 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to leave oil. The obtained oily product was dissolved in acetic anhydride (2 mL), and heated under reflux for 2 h. The reaction mixture was cooled and water (20 mL) was added. Then the reaction mixture was extracted with dichloromethane (2×20 mL). The organic layer was separated and washed with sodium bicarbonate solution (2×10 mL, 5%), and water (2×25 mL), and then dried (Na_2SO_4). The solvent was removed by vacuum distillation to give an oily compound. The oily product was purified with thin layer chromatography using silica plates. The solid obtained was recrystallised from ethyl acetate-pet. ether (2:3).

3-[2-(isoindolin-1,3-dione)-3-methylbutyl]-3,4-dihydroisocoumarin (9a): Yield: 42%, mp: 99-100 °C; $[\alpha]_D^{25}$ -24° (20 mg/10 mL DMSO); IR (cm^{-1}): 3009, 2994, 1712, 1695, 1680; ^{1}HNMR (δ, ppm): 1.19-1.20 (d, 3H, J = 6.7 Hz), 1.29-1.35 (d, 3H, J = 6.8 Hz), 2.31-2.41 (m, 1H), 2.79-2.83 (dd, 1H, J = 6.78, 6.79 Hz), 4.22-4.29 (m, 1H), 4.61-4.62 (d, 1H, J = 8.3 Hz), 4.98-5.01 (dd, 1H, J = 4.34, 4.29 Hz), 7.27-8.33 (m, 8H); MS (%): 349 ($M^{\cdot+}$, 3.0), 219 (28), 218 (61), 216 (37), 205 (21), 203 (39), 191 (64), 188 (56), 175 (100), 163 (8), 162 (15), 160 (95), 150 (42), 133 (72), 130 (37), 104 (23), 88 (13), 76 (12).

3-[2-(isoindolin-1,3-dione)-4-methylpentyl]-3,4-dihydroisocoumarin (9b): Yield 47(%), mp 115-117 °C; $[\alpha]_D^{25}$ -26° (20 mg/10 mL DMSO); IR (cm^{-1}): 3012, 1715, 1695, 1680; ^{1}HNMR: (δ, ppm): 0.90-0.99 (d, 6H, J = 7.0 Hz), 1.28-1.31 (t, 2H, J = 7.18 Hz), 1.42-1.49 (m, 1H), 2.81-2.85 (dd, 1H, J =

2.91, 2.82 Hz), 3.19-3.23 (dd, 1H, J = 3.26, 3.30 Hz), 4.14-4.18 (q, 1H, J = 7.16 Hz), 5.13-5.18 (ddd, 1H, J = 3.34, 1.47, 3.35 Hz), 7.27-8.10 (m, 8H); MS (%): 363 ($M^{\cdot+}$, 20%), 362 (85), 320 (25), 319 (100), 304 (56), 301 (8), 171 (4), 144 (4), 128 (10).

Acknowledgement

The authors wish to express their gratitude to the Research Affairs Division of Arak University for its financial support.

References

1. R. S. Mali and K. N. Babu, **J. Org. Chem.**, **63**, 2488 (1998).
2. S. Noguchi, S. Kishimoto, I. Minamida and M. obayashi, **Chem. Pharm. Bull., 22**, 529 (1974).
3. G. R. Alien, **J. Med. Chem., 15**, 934 (1972).
4. M. E. J. Billingam, **J. Pharmcol., 72**, 523 (1981).
5. T. Kovacs and J. Sonnenbichler, **Liebigs Ann. Rcl.,** 211 (1997).
6. M. Stadler, H. Anke and O. Sterner, **J. Antibiot.**, **48**, 261 (1995).
7. R. P. Barry, **Chem. Rev., 64**, 229 (1964).
8. M. Chinworrungsee, P. Kittakoop, M. Isaka, R. Chanphen, M. Tanticharoen and Y. Thebtaranonth, **J. Chem. Soc. Perkin Trans.**, **1**, 2473 (2002).
9. N.H. Rama, R. Iqbal and Kh. Zamani, **J. Chem. Soc. Pak., 20**, 62 (1998).
10. P. Stephen Waters and M.C. Koslowski, **Tetrahedron Lett.**, **42**, 3567 (2001).
11. F. Karina, M. Devienne, G. Stela Raddi, A. Eliana and Z. Varand, **Nature Forsch, 57**, 85 (2002).
12. E. Haffmann and H. Schiffshenhav, **J. Org. Chem., 27**, 4686 (1962).
13. A. Hajipour, S. Mallakpour and G. Imanzadeh, **Indian. J. Chem., 40B,** 250 (2001)
14. H. Kaji, M. Yamada, K. Kawai and S. Nakajima, **Org. Prep. Proced. Int., 18**, 253 (1986).