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Regioselective Diastereotopic Michael Reaction as Building Blocks in Heterocyclic Synthesis

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ABSTRACT

The present work deals with generation and synthesis of 2-(2-camphoryl)-4-(4-aryl)-4-oxobutanoic acids *via* Michael reaction condition depending on the type of nucleophilic reagents and medium (acidic or basic). The adducts are used as a key starting materials to synthesize some hetrocycles include pyridazinone, furanone, 1,2-oxazin-5-one, 1.2-diazapine, pyrane and hydroxyl pyridine derivatives. Steric factor plays an important role in regioselectivity. The structure of newly synthesized compounds were elucidated by elemental analysis and spectroscopic data.

KEYWORDS

4-Aryl-4-oxo-but-2-enoic acid, Camphor, Pyridazin-3-one, Furanone, 1,2-Oxazinone.

INTRODUCTION

β-Aroylacrylic acids have an antiproliferative action against the human cervix carcinoma (Hela cells) [1], cytostatic activity used as an aid to study and determine factors affecting the human eye's UV filters [2], as *Aspergillus* controller [3] and inhibitors of phospholipase [4]. Moreover they have a marked increase *in vitro* activity against as Gram-positive bacteria [5] and anticancer [6]. They are used a key starting material due to their high electrophilicity, where the β-aroylacrylic acids react readily with nucleophilies including nitrogen and carbon nucleophiles afford either cyclic or normal Michael adducts depending on the nature of the attacking nucleophiles and the reaction medium (neutral, basic, acidic). As the Michael addition reaction may be considered an efficient tandem strategy for the construction of ring structures [7-9]. Therefore, this starting material will be directed to prepare the more interesting heterocyclic compounds of important biological activities which bearing 3(2*H*)-pyridazinone moiety [10].

EXPERIMENTAL

All the melting points are uncorrected and determined on Stuart electric melting point apparatus. Elemental analyses were carried out at the Microanalytical Center, National Research Center, Cairo, Egypt. By Elementar Viro El Microanalysis IR spectra (KBr, ν_{max}, cm^{-1}): were recorded on infrared spectro-

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meter FT-IR 400D using OMNIC program and are reported frequency of absorption in terms of cm^{-1} and ^1H NMR spectra recorded on a Bruker spectrophotometer at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent δ = 7.26 ppm for $CDCl_3$ and δ 2.51 ppm for DMSO-d_6. ^{13}C NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent signals δ = 77 ppm for $CDCl_3$ and δ 39.50 ppm for DMSO-d_6. DEPT ^{13}C NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^1H NMR and ^{13}C NMR spectra. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 e.v using the electron ionization technique. Homogeneity of all compounds synthesized was checked by TLC.

General procedure of starting material in literature [11]

General procedure of synthesis of the compounds 2 and 3: A mixture of 4-(4-benzoylamino/bromo-3-methylbenzoyl)-4-oxobut-2-enoic acids (**1**) (0.01 mol), active methylene precursor, *e.g.*, R(+) camphor (0.01 mol), (50 %) NaOH (8 mL) and ethanol (50 mL) was refluxed for 3 h and left for 3 days. The reaction mixture was poured into ice/HCl, filter the crude product and washed by petroleum ether (b.p. 40-60 °C) and then crystallized.

(2R,3R)4-[4-(Benzoylamino)phenyl]-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (2a): m.p.: 184-186 °C. IR (KBr, ν_{max}, cm^{-1}): 1712, 1668, 1599 (C=O), 3436 (OH). ^1H NMR spectrum ($CDCl_3$): δ 0.92 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.73 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.98 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2.71 (2dd, 1Ha and 1Hb methylene protons, CH_2-C=O, diastereotopic protons), 2.92 (2dt, CH-COO, sterogenic methine proton), multiplet at 7.47-7.75 assigned for 9ArH aromatic protons, singlet at 8.0 and 8.2 (a acidic protons which exchanged in D_2O). Anal. calcd. (%) for $C_{27}H_{29}NO_5$: C 68.57, H 7.01; found (%): C 68.46, H 7.00. MS: *m/z* 446 [M].

(2R,3R)4-(4-Bromo-3-methylphenyl)-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (2b): m.p.: 158-160 °C. IR (KBr, ν_{max}, cm^{-1}): 1680, 1712 (C=O) 3436 (OH). ^1H NMR spectrum ($CDCl_3$): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.78 (s, 3H, CH_3), 1.80 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2.25 (s, 3H, CH_3-Ar), 2.56 (dd, CHCO, camphor moiety), 2.78 (2dd, 1Ha, (*J* = 15.2, *J* = 7.2) and 1Hb methylene protons, CH_2-C=O, diastereotopic protons), 2.93 (2dt, CH-COO, sterogenic methine proton), multiplet at 7.67-7.71 assigned for 4ArH aromatic protons, singlet at 10.7 a acidic proton which exchanged in D_2O and ^{13}C NMR δ 22.8 (CH_3), 23.3 (CH_3), 28.3 (CH_3), 34.4 (CH_2) 38.6 (C), 43.4 (CH_2), 58.4 (CH_2), 67.4 (C), 102.3 (CH), 128.2 (CH), 129.2 (2CH), 129.5 (2CH), 134.4 (CH), 138.1 (C), 155.7 (C), 175.0 (C), 183.2 (C), 200.5 (C). Anal. calcd. (%) for $C_{21}H_{25}O_4Br$: C 58.96, H 5.65 ; found (%): C 58.93, H 5.62. MS: *m/z* 422 [M^++2], 420 [M+].

(2R,3S)4-[4-(Benzoylamino)phenyl]-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (3a): m.p.: 148-150 °C. IR (KBr, ν_{max}, cm^{-1}): 1598, 1668, 1710 (C=O), 3421 (OH). ^1H NMR spectrum ($CDCl_3$): δ 1.31 (s, 6H, $2CH_3$), 1.82 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.76 (s, 3H, CH_3), 2.20 (s, 3H, CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2.71 (2dd, 1Ha, (*J* = 15.2, *J* = 7.2) and 1Hb methylene protons, CH_2-C=O, diastereotopic protons), 2.92 (2dt, CH-COO, sterogenic methine proton), multiplet at 7.47-7.75 assigned for 4ArH aromatic protons, singlet at 11.2 and 13.11 (a acidic protons which exchanged in D_2O) and ^{13}C NMR δ 23.8 (CH_3), 25.4 (CH_3), 28.3 (CH_3), 32.0 (CH_3), 34.4 (CH_2), 37.1 (CH_2), 38.1 (C), 39.4 (CH_2), 45.0 (C), 58.4 (CH), 102.3 (CH), 108.2 (CH), 129.2 (2CH), 129.5 (2CH), 134.4 (C), 138.1 (C), 142.7 (C), 145.0 (C), 173.2 (C), 198.5 (C).

(2R,3S)4-(4-Bromo-3-methyllphenyl)-2-(1,7,7-trimethylbicyclo[2,2,1]heptan-2-on-3-yl)-4-oxobutanoic acid (3b): m.p.: 142-144 °C. IR (KBr, ν_{max}, cm^{-1}): 1598, 1680, 1710 (C=O), 3421 (OH). ^1H NMR spectrum ($CDCl_3$): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.83 (m, 4H, CH_2CH_2, camphor moiety), 1.78 (s, 3H, CH_3), 1.97 (m, 1H, CH, bridgehead methine, camphor moiety), 2.25 (s, 3H, CH_3-Ar), 2.73 (dd, CHCO, camphor moiety), 3.01 (2dd, 1Ha, (*J* = 15.2, *J* = 7.2) and 1Hb methylene protons, CH_2-C=O, (*J* = 15.2, *J* = 5.1) diastereotopic protons), 3.22 (2dt, CH-COO, sterogenic methine proton, *J* = 7.2, *J* = 5.1), multiplet at 7.72-7.78 assigned for 9ArH aromatic protons, singlet at 8.4 a acidic proton which exchanged in D_2O and Anal. calcd. (%) for $C_{21}H_{25}O_4Br$: C 59.11, H 7.01; found (%): C 59.26, H 7.09. MS: *m/z* 422 [M+2], 420 [M], 307, 198, 154, 105, 96.

Compounds 4: A mixture of **2** (0.01 mol) and acetic anhydride (9.4 mL, 0.1 mol) compound refluxed on water bath for 2 h. The excess acetic anhydride was removed by distillation and the separated product was filtered, dried and were recrystallized from mix toluene-ethanol

5-[4-(Benzoylamino)phenyl]-3-(1,7,7-trimethylbicyclo-[2,2,1]heptan-2-on-3-yl)-2(3H)furanone (4a): m.p.: 234-236 °C. IR (KBr, ν_{max}, cm^{-1}): 1772, 1668 (C=O). ^1H NMR spectrum ($CDCl_3$): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.73 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.98 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2.92 (2dd, CH-COO, sterogenic methine proton), 5.4 (s, 1H.furanone proton), multiplet at 7.47-7.75 assigned for 9ArH aromatic protons, singlet at 13.2 (a acidic proton (NH) which exchanged in D_2O) and ^{13}C NMR δ 13.2 (CH_3), 18.3 (CH_3), 21.7 (CH_3), 23.9 (CH_2), 26.8 (CH_2), 38.4 (CH_3), 39.6 (CH), 46.6 (CH), 48.8 (CH), 50.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 132.2 (CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), 213.4 (C). Anal. calcd. (%) for $C_{27}H_{28}NO_4$: C 71.93, H 6.81; found (%): C 71.86, H 6.70. MS: *m/z* 428 [M].

5-(4-Bromo-3-methylphenyl)-3-(1,7,7-trimethylbicyclo[2,2,1]-heptan-2-on-3-yl)-2(3*H*)furanone(4b): m.p.: 218-220 °C. IR (KBr, ν_{max}, cm^{-1}): 1780, 1700 (C=O). ^1H NMR spectrum ($CDCl_3$): δ 1.06 (s, 3H, CH_3a), 1.2 (s, 3H, CH_3b), 1.78 (s, 3H, CH_3), 1.80 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2.25 (s, 3H, CH_3-Ar), 2.56 (dd, CHCO, camphor moiety), 2.93 (2dd, CH-COO, sterogenic methine proton), 5.4 (s, 1H, furanone proton), multiplet at 7.67-7.71 assigned for 4ArH aromatic protons and ^{13}C NMR δ 22.8 (CH_3), 23.3 (CH_3), 28.3 (CH_3), 34.4 (CH_2), 38.6 (C), 43.4 (CH_2), 67.4 (C), 102.3 (CH), 128.2 (CH), 129.2 (2CH), 129.5 (2CH), 131.3 (CH), 134.4 (CH), 138.1 (C), 155.7 (C), 175.0 (C), 183.2 (C), 200.5 (C). Anal. calcd. (%) for $C_{21}H_{23}O_3Br$: C 61.85, H 5.41; found (%): C 61.86, H 5.44. MS: *m/z* 403 [M^++2], 401 [M^+].

Compounds 5: A mixture of compound **2** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) was heated

under reflux for 5 h. The reaction mixture was allowed to cool and the separated product was filtered, dried and were recrystallized from ethanol.

6-(4-Benzoylaminophenyl)-4-(1,7,7-trimethyl-3-oxobicyclo[2,2,1]hepta-2-yl)-2,3,4,5-tetrahydro-3-oxopyridazine (5a): m.p.: 204-206 °C. IR (KBr, ν_{max}, cm^{-1}): 1676, 1706 (C=O), 3390 (N-H). ^{1}H NMR (DMSO-d_6): 0.94 (s, 3H, CH_3a), 1.17 (s, 3H, CH_3b), 1.26 (s, 3H, CH_3.), 1.48-1.71 (m, 4H, $2CH_2$), 1.87 (m, 1H, methine bridge head), 2.56 (2dd, 1Ha and 1Hb methylene protons, CH_2-C=N, diastereotopic protons in pyridazinone moiety), 3.17 (2dd, CH-, sterogenic methine proton), 3.25 (dt, 1H, attached, camph), 7.48-7.56 (m, 4H, Ar-H), 12.34 (brs, 2H, 2NH of acetamido and pyridazine moieties) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), 213.4 (C). Anal. calcd. (%) for $C_{27}H_{30}N_3O_3$: C 69.29, H 7.08; found (%): C 69.15, H 7.00. MS: *m/z* 442 [M], 267, 175, 137.

6-(4-Bromo-3-methylphenyl)-4-(1,7,7-trimethyl-3-oxobicyclo[2,2,1]hepta-2-yl)-2,3,4,5-tetrahydro-3-oxopyridazine (5b): m.p.: 196-198 °C. IR (KBr, ν_{max}, cm^{-1}): 1690, 1706 (C=O), 3421 (N-H). ^{1}H NMR (DMSO-d_6): 1.1 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.59-1.71 (m, 4H, $2CH_2$), 1.98 (t, 1H, methine bridgehead), 2.25 (s, 3H, CH_3-Ar), 2.75 (2dd, 1Ha, (*J* = 15.2, *J* = 7.9) and 1Hb methylene protons, CH_2-C=O, diastereotopic protons), 3.17 (2dd, CH-COO, sterogenic methine proton), 3.25 (dt, 1H, attached), 7.68-7.80 (m, 4H, Ar-H), 11.34 (brs, 1H, NH) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 213.4 (C). Anal. calcd. (%) for $C_{21}H_{25}N_2O_2Br$: C 59.70, H 5.72; found (%): C 59.65, H 5.67. MS: *m/z* 416 [M], 251, 175, 156.

Compound 6: A mixture of compound **2** (0.01 mol) and hydroxylamine (1.03 g; 0.015 mol) in pyridine (20 mL) was refluxed for 3 h. The reaction mixture was poured onto ice/HCl and the separated solid was filtered, dried and were recrystallized from ethanol

3-(4-Benzoylaminophenyl)-5-(1,7,7-trimethyl-3-oxobicyclo[2,2,1]hepta-2-yl)- 4,5,6-trihydro-1,2-oxazin-6-one (6a): m.p.: 254-256 °C. IR (KBr, ν_{max}, cm^{-1}): 1706, 1676 (C=O), 3362 (N-H). ^{1}H NMR (DMSO-d_6): 0.94 (s, 3H, CH_3a), 1.17 (s, 3H, CH_3b), 1.26 (s, 3H, CH_3), 1.48-1.71 (m, 4H, $2CH_2$), 1.87 (m, 1H, methine bridgehead), 2.56 (2dd, 1Ha and 1Hb methylene protons, CH_2-C=N, diastereotopic protons in oxazinone moiety), 3.17 (2dd, CH-, sterogenic methine proton), 3.25 (dt, 1H, attached, camph), 7.52-7.61 (m, 4H, Ar-H), 12.34 (brs, 1H, NH of acetamido moiety) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), 213.4 (C). Anal. calcd. (%) for $C_{27}H_{28}N_2O_4$: C 69.11, H 6.81;found (%): C 69.05, H 6.72. MS: *m/z* 443 [M], 267, 175, 137.

3-(4-Bromo-3-methylphenyl)-5-(1,7,7-trimethyl-3-oxobicyclo[2,2,1]hepta-2-yl)-4,5,6-trihydro-1,2-oxazin-6-one (6b): m.p.: 232-234 °C. IR (KBr, ν_{max}, cm^{-1}): 1706, 1690 (C=O), 3331 (N-H). ^{1}H NMR (DMSO-d_6): 1.1 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.59-1.71 (m, 4H, $2CH_2$), 1.98 (t, 1H, methine), 2.25 (s, 3H, CH_3-Ar), 2.75 (2dd, 1Ha, (*J* = 15.2, *J* = 7.9) and 1Hb methylene protons, CH_2-C=O, (*J* = 15.2, *J* = 2.4) diastereotopic protons), 3.17 (2dd, CH-COO, sterogenic methine proton *J* = 9.7, *J* = 7.9, *J* = 2.4), 3.25 (dt, 1H, attached, *J* = 9.7), 7.71-7.79 (m, 4H, Ar-H) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 213.4 (C). Anal. calcd. (%) for $C_{21}H_{24}NO_3Br$: C 59.55, H 5.46; found (%): C 59.47, H 5.40. MS: *m/z* 417 [M], 251, 175, 156.

Compound 7: A mixture of compound **3** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL)and was heated under reflux for 5h. The reaction mixture was allowed to cool and the separated product was filtered, dried and were recrystallized from ethanol.

3-(4-Benzoylaminophenyl)-1,7,7-trimethyl-3-oxobicyclo[2,2,1]heptan[2,3-c]1,2-diazepine-5-carboxlic acid (7a): m.p.: 212-214 °C. IR (KBr, ν_{max}, cm^{-1}): 1668, 1706 (C=O). ^{1}H NMR (DMSO-d_6): 1, 12 (s, 3H, CH_3a), 1.23 (s, 3H, CH_3b), 1.30 (s, 3H, CH_3.), 1.52-1.78 (m, 5H, CH_2-CH_2), 2.56 (2dd, 1Ha and 1Hb methylene protons, CH_2-C=N), 3.17 (2dd, CH-, sterogenic methine proton, CHCOO), 3.00 (dt, 1H, attached, camph), 7.48-7.56 (m, 4H, Ar-H), 12.34 (s, 1H, NH of acetamido moiety) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), 213.4 (C). Anal. calcd. (%) for $C_{27}H_{29}N_3O_3$: C 69.29, H 7.08; found (%): C 69.29, H 7.00. MS: *m/z* 442 [M], 267, 175, 137.

3-(4-Bromo-3-methylphenyl)-1,7,7-trimethyl-3-oxobicyclo-[2,2,1]heptan[2,3-c] 1,2-diazepine-5-carboxlic acid (7b): m.p.: 200-202 °C. IR (KBr, ν_{max}, cm^{-1}): 1706 (C=O). ^{1}H NMR (DMSO-d_6): 1.1 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.59-1.71 (m, 4H, $2CH_2$), 1.98 (t, 1H, methine bridge-head), 2.25 (s, 3H, CH_3-Ar), 2.75 (2dd, 1Ha, (*J* = 15.2, *J* = 7.9) and 1Hb methylene protons, CH_2-C=O), 3.17 (2dd, CH-COO, sterogenic methine proton), 3.25 (dt, 1H, attached), 7.68-7.80 (m, 4H, Ar-H), 8.2 (bs, 1H, CO_2H) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 213.4 (C). Anal. calcd. (%) for $C_{21}H_{25}N_2O_2Br$: C 59.70, H 5.72; found (%): C 59.75, H 5.72. MS: *m/z* 416 [M], 251, 175, 156.

Compound 8: A mixture of compound **3** (0.01 mol) and acetic anhydride (9.4 mL, 0.1 mol) was refluxed on water bath for 2 h. The excess acetic anhydride was removed by distillation and the separated product was filtered, dried and were recrystallized from mix toluene-ethanol

2-(4-(Benzoylamino)phenyl)-1,7,7-trimethylbicyclo-[2,2,1]heptan[2,3-b](4*H*)pyran-4-carboxylic acid (8a): m.p.: 180-182 °C. IR (KBr, ν_{max}, cm^{-1}): 1712 (C=O). ^{1}H NMR spectrum ($CDCl_3$): δ 1.11 (s, 3H, CH_3a), 1.22 (s, 3H, CH_3b), 1.73 (m, 5H, $CHCH_2CH_2$, camphor moiety), 1.98 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CON-), 2.43 (dd, CHCO, camphor moiety), 2, 92 (2dd, CH-COO, sterogenic methine proton), 5.4 (s, 1H, furanone

proton), multiplet at 7.47-7.75 assigned for 4ArH aromatic protons, singlet 10.8, 13.2 (brs, 2H, a acidic protons COOH and NH which exchanged in D_2O) and ^{13}C NMR δ 13.2 (CH_3), 18.3 (CH_3), 21.7 (CH_3), 23.9 (CH_2), 26.8 (CH_2), 38.4 (CH_3), 39.6 (CH), 46.6 (CH), 48.8 (CH), 50.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 132.2 (CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), 213.4 (C). Anal. calcd. (%) for $C_{27}H_{27}NO_4$: C 71.93, H 6.81; found (%): C 71.97, H 6.81. MS: *m/z* 428 [M].

2-(4-Bromo-3-menthylphenyl)-1,7,7-trimethylbicyclo[2,2,1]heptan[2,3-b](4*H*)pyran-4-carboxylic acid (8b): m.p.: 154-156 °C. IR (KBr, ν_{max}, cm^{-1}): 1715 (C=O). ^1H NMR spectrum ($CDCl_3$): δ 1.10 (s, 3H, CH_3a), 1.20 (s, 3H, CH_3b) 1.82 (s, 3H, CH_3), 1.98 (m, 5H, $CHCH_2CH_2$, camphor moiety), 2.25 (s, 3H, CH_3-Ar), 2.93 (2dd, CH-COO, sterogenic methine proton), 6.2 (s, 1H, pyrane proton), multiplet at 7.67-7.71 assigned for 4ArH aromatic protons, 11.2 (s, 1H, COOH) and ^{13}C NMR δ 22.8 (CH_3), 23.3 (CH_3), 28.3 (CH_3), 34.4 (CH_2) 38.6 (C), 43.4 (CH_2), 67.4 (C), 102.3 (CH), 128.2 (CH), 129.2 (2CH), 129.5 (2CH), 131.3 (CH), 134.4 (CH), 138.1 (C), 155.7 (C), 175.0 (C), 183.2 (C), 200.5 (C). Anal. calcd. (%) for $C_{21}H_{23}O_3Br$: C 61.85, H 5.41; found (%): C 61.73, H 5.32. MS: *m/z* 403 [M^++2], 401 [M^+].

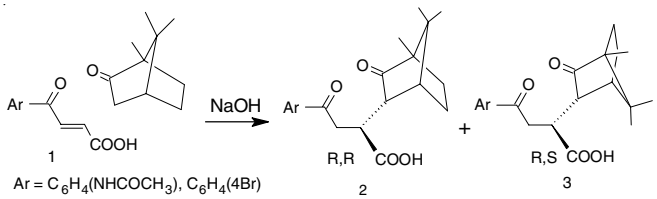
Compound 9: A mixture of compound **3** (0.01 mol) and hydroxylamine (1.03 g; 0.015 mol) in pyridine (20 mL) and refluxed for 3 h. The reaction mixture was poured onto ice/HCl and the separated solid was filtered, dried and were recrystallized from ethanol

2-(4-(Benzoylamino)phenyl)-1-(hydroxy)-1,7,7-trimethylbicyclo[2,2,1]heptan[2,3-b]1,4-dihydropyridine-4-carboxylic acid (9a): m.p.: 242-244 °C. IR (KBr, ν_{max}, cm^{-1}): 1676, 1710 (C=O), 3420 (O-H). ^1H NMR (DMSO-d_6): 1.12 (s, 3H, CH_3a), 1.19 (s, 3H, CH_3b), 1.31 (s, 3H, CH_3.), 1.58-1.84 (m, 4H, $2CH_2$), 2.01 (m, 1H, methine bridgehead), 2.56 (s, 3H, CH_3) 3.17 (s, 1H, CHCOO),) 4.4 (s, 1H, proton of pyridine moiety), 4.8 (brs, 1H, OH), 7.52-7.61 (m, 4H, Ar-H), 11.8 (brs, 2H, NH of acetamido moiety and -COOH) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH_3), 39.6 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 201.5 (C), 213.4 (C). Anal. calcd. (%) for $C_{27}H_{28}N_2O_4$: C 69.11, H 6.81;found (%): C 69.17, H 6.81. MS: *m/z* 443 [M], 267, 175, 137.

2-(4-Bromo-3-methylphenyl)-1-(hydroxyl)-1,7,7-trimethylbicyclo[2,2,1]heptan[2,3-b]1,4-dihydro)pyridine-4-carboxylic acid (9b): m.p.: 226-228 °C. IR (KBr, ν_{max}, cm^{-1}): 1710 (C=O), 3412 (O-H). ^1H NMR (DMSO-d_6): 1.12 (s, 3H, CH_3a), 1.19 (s, 3H, CH_3b), 1.31 (s, 3H, CH_3.), 1.58-1.84 (m, 4H, $2CH_2$), 2.01 (m, 1H, methine bridgehead), 2.25 (s, 3H, CH_3-Ar), 3.17 (s, 1H, CHCOO), 4.4 (s, 1H, proton of pyridine moiety), 4.8 (brs, 1H, OH), 7.52-7.61 (m, 4H, Ar-H), 11.2 (s, 1H, COOH) and ^{13}C NMR δ 11.8 (CH_3), 18.3 (CH_3), 18.7 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.8 (CH), 48.2 (C), 56.8 (C), 129.7 (C), 130.4 (2CH), 131.8 (2CH), 136.2 (C), 178.8 (C), 195.7 (C), 213.4 (C). Anal. calcd. (%) for $C_{21}H_{24}NO_3Br$: C 59.55, H 5.46; found (%): C 59.38, H 5.37. MS: *m/z* 417 [M], 251, 175, 156.

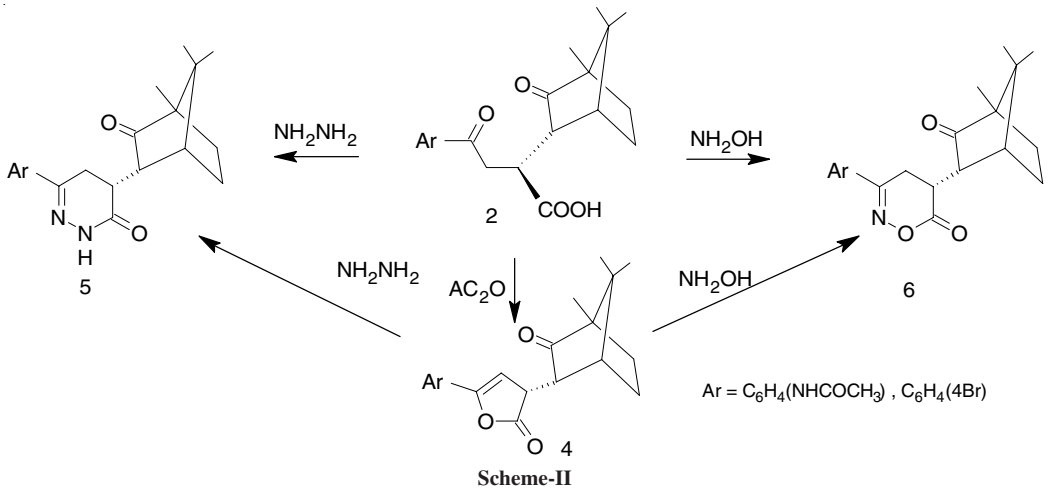
RESULTS AND DISCUSSION

Reports from our laboratory [11-17] and others [18,19] revealed that β-aroyl acrylic acids are convenient poly electrophilic reagents in the synthesis of heterocycles for the addition reaction of nucleophililes *e.g.*, carbon, nitrogen, sulfur, phosphoreoccurs exclusively at the α-carbon electrophilic center of carboxy precursors. With the aim of broading the synthetic potential of β-aroyl acrylic acids, we are reporting that the behaviour of benzoylamino/bromo-3-methylphenyl)-4-oxo-but-2-enoic acids (**1**) were allowed to react with active methylene precursors *e.g.*, R(+)-camphor in the presence of sodium hydroxide (basic medium) under Michael reaction conditions afford the diasteriomeric adducts, 2-camphoryl-4-aryl-4-oxo butanoic acids (**3**), *via* the formation of carbanion in the cyclic moiety that added to the activated double bond of acids **1**, that takes place under Michael reaction condition to afford diastereomeric Michael adducts **2** and **3** (**Scheme-I**).

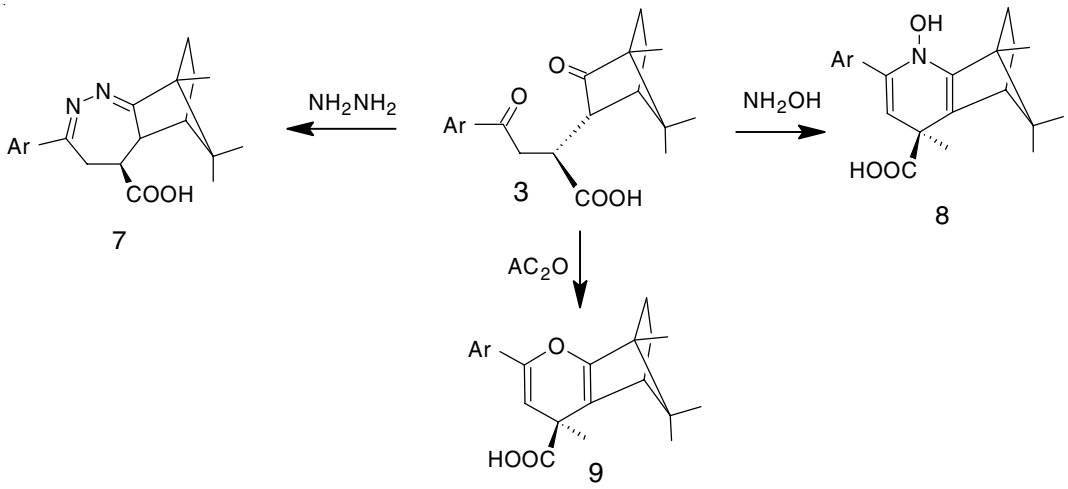


Scheme-I

When the (R,R) acids **2** were allowed to react with hydrazine hydrate in boiling ethanol and hydroxylamine in boiling



Scheme-II



Scheme-II

pyridine and/or *via* the furanone derivatives **4**, they afforded pyridazinone derivatives **5** and oxazinone derivatives **6** respectively (**Scheme-II**).

In the same manner, when the (R,S) acids (**3**) were allowed to react with hydrazine hydrate in boiling ethanol and hydroxylamine in boiling pyridine, afforded 1,2-diazapine **7** and pyridine (**8**) derivatives (**Scheme-III**). Formation of the 1,2-diazepine derivatives (**6**) *versus* pyridazinone **5** were due to the ketonic group of the camphor moiety is more reactive than carboxylic group. In **Scheme-II**, the steric crowding due to the bridged methyl group was outweigh the reactivity of carbonyl of camphor moiety and therefore, the isomers **2** can be preferred cyclization with the carboxylic group. The steric factor play an important role in regioselectivity. So, absence of the steric crowding of bridged methyl group in camphor moiety of the acids **3** became a driving force to afford regioselective isomers **7**, **8** and **9** respectively (**Scheme-III**).

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