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A Facile Synthesis of Some Spirooxoindole Derivatives *via* One-Pot Three-Component Reactions

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Tetrahydrospiro[chromene-4,3'-indole]-2-ones (**5a-c**) and spiro[indole-3,4'-pyrano(3',2'-*d*)pyrazole]-2-ones (**6a-b**) have been synthesized based on the one-pot three-component cyclocondensation reaction of 5-(un)substituted isatins (**1a-c**) with ethyl cyanoacetate (**2**) and 5,5-dimethylcyclohexane-1,3-dione (**3**) or 5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one (**4**) in absolute ethanol containing a catalytic amount of Et_3N carried out under both conventional heating and environmentally benign procedures. The structures of the resulting compounds were confirmed by spectral {IR, ^{1}H NMR, ^{13}C NMR, 2D NMR [^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY (HETCOR)] and electrospray ionization tandem mass [(±) ESI-MS/MS]} analysis.

Key Words: Isatin, Spirooxoindole, Ultrasound irradiation, Microwave irradiation, Retro diels-alder fragmentation.

INTRODUCTION

Five-membered nitrogen heterocycles, especially highly substituted pyrrolidines feature widely in pharmaceuticals, natural alkaloids, organocatalysts and are also useful building blocks in organic synthesis[1]. The indole moiety is probably the most well-known heterocyclic compound, a common and important feature of a variety of natural products and medicinal agents[2]. Compounds carrying the indole residue, such as isatin (1*H*-indole-2,3-dione) and its derivatives exhibiting antimicrobial,[3-18], antiviral[19-23] antiplasmodial[24] antitubercular[25-27] anticancer[28-35] anticonvulsant[36-41] antioxidant[42,43] activities. Due to the above mentioned diverse properties of isatins, we report herein the synthesis of some spirooxoindole compounds using simple, convenient and an efficient one-pot three-component reactions.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were acquired in open capillary tubes and were measured on an electro thermal digital melting point apparatus. Infrared data were obtained using Perkin-Elmer, FT-IR spectrometer, as KBr pellets. ^{1}H, ^{13}C and the 2D NMR spectra were recorded using a JEOL-NMR spectrometer at 300 MHz and 75 MHz, on solutions in DMSO-d_6 using TMS as an internal standard. Chemical shifts are given in ppm (δ-scale) and the coupling constants are given in Hertz. Results of DEPT-135 experiment is shown in parentheses where relative to DMSO-d_6, (+) denotes CH_3 or CH and (-) denotes CH_2. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-protected glass sheets (Type Si250F, 'BAKER' of 0.2 mm thickness) using ethanol-chloroform (1:9) as eluant. The spots were detected by exposure to UV-lamp at λ 254 nm for few seconds. Mass spectra were obtained using a quattro premier triple quadrupole mass spectrometer (UPLC-MS/MS) equipped with electrospray ion source using both positive and negative ion mode. Ultrasonication was performed in a J.P. Selecta ultrasound cleaner with a frequency of 60 Hz and an output power of, 770 W. The reaction flask was located in the maximum energy area in the cleaner, were the surface of reaction (reaction vessel) is slightly lower than the level of the water. The temperature of the water bath was controlled by the addition or removal of circulated water. Microwave irradiated reactions were carried out on a Galanz microwave oven, operating at 1000 W, generating 60 Hz frequency.

Synthesis of spirooxoindoles (5a-c and 6a-b): They were synthesized by following different methods.

Method A (conventional method): To a solution of 5-(un) substituted isatins (**1a-c**) (1 mmol), ethyl cyanoacetate (**2**) (0.13 g, 1 mmol) and triethylamine (3-4 drops) in absolute ethanol (25 mL), 5,5-dimethyl-cyclohexane-1,3-dione (**3**) (0.14 g, 1 mmol) or 5-methyl-2-phenyl-2,4-dihydro-pyrazole -3-one (**4**) (0.17 g, 1 mmol) was added and heated under

refluxed for about 2 h. The progress of the reaction was followed by TLC. After complication, the solvent was removed under reduced pressure and the residue was then washed well with ethanol, dried and recrystallized from methanol to afford pure products in cases (**5a-c**), while in cases (**6a,b**) the solid was treated with ether or petroleum ether (60-80 ºC) and recrystallized from water/methanol.

Method B (ultrasound irradiation method): A mixture of 5-(un)substituted isatins (**1a-c**) (1 mmol), ethyl cyanoacetate (**2**) (0.13 g, 1 mmol), **3** or **4** (1 mmol) and triethylamine (3-4 drops) in absolute ethanol (25 mL) was irradiated in an ultrasonic bath for 1 h. After completion of the reaction (as indicated by TLC), the solvent was removed under reduced pressure and the resulting solid was then washed well with ethanol, dried and recrystallized from methanol or water/methanol to afford pure products in most cases (**5a-c, 6a**), while in case (**6b**) the solid was treated with petroleum ether (60-80 ºC) and recrystallized from water/methanol.

Method C (microwave irradiation method): An equimolar mixture of 5-(un)substituted isatins (**1a-c**) (1 mmol), ethyl cyanoacetate (0.13 g, 1 mmol), **3** or **4** (1 mmol) and triethylamine (3-4 drops) in the minimum quantity of ethanol 96 % required to form a slurry was irradiated inside a microwave oven at 300 W for 5 min. After completion, the excess solvent was removed under reduced pressure and the activated solid was then recrystallized from methanol to afford pure products in cases (**5a-c**), while in cases (**6a,b**) the solid was treated with petroleum ether (60-80 ºC) and recrystallized from water/methanol.

Ethyl 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2'-one-3-carboxylate (5a) (Table-1, entry 1): Pale orange fine cubes, m.p. 264 ºC (from methanol); yield 59 %[A], 70 %[B], 95 %[C]; IR (KBr, ν_{max}, cm^{-1}) : 3369, 3235, 3179 (NH_2, NH), 1714 (C=O ester), 1687 (C=O ketone), 1671 (C=O γ-lactam); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.79 (3H, t, J = 5.7, OCH_2CH_3), 0.94 (3H, s, 7-CH_3), 1.01 (3H, s, 7-CH_3), 2.01 (1H, d, ^2J = 15.8, H_{ax}-8), 2.15 (1H, d, ^2J = 15.8, H_{eq}-8), 2.55 (2H, s, 6-CH_2), 3.70 (2H, q, J = 5.7, OCH_2CH_3), 6.67 (1H, d, ^3J = 7.1, H-7'), 6.74 (1H, td, ^3J = 7.1, ^4J = 1.1, H-5'), 6.83 (1H, d, ^3J = 7.1, H-4'), 7.01 (1H, td, ^3J = 7.1, ^4J = 1.1, H-6'), 7.86 (2H, br. s, NH_2, D_2O exchangeable), 10.14 (1H, br. s, NH, D_2O exchangeable); ^{13}C NMR, (75 MHz, DMSO-d_6) and DEPT-135: δ_C (ppm) 12.5 (OCH_2CH_3), 26.1, 27.2 [7-$(CH_3)_2$], 30.9 (C-7), 39.5 (C-6, overlapped with solvent signals), 46.1, 50.1 (C-8), 58.2 (OCH_2CH_3), 75.7 (spiro C), 107.5 (C-7'), 112.5, 119.9 (C-5'), 121.6 (C-4'), 126.6 (C-6'), 135.4, 143.4, 158.5, 161.8 (sp^2 carbons), 167.1 (CO ester)[44], 179.2 (CO 2'-oxoindole)[44], 194.1 (CO chromene)[44]; MS (+) ESI, *m/z* (%): 383 (2) $[M+H]^+$ ($C_{21}H_{22}N_2O_5$+H)$^+$, 367 (2) $[383-NH_2]^{+\bullet}$, 338 (7) $[383-OC_2H_5]^{+\bullet}$, 328 (67) $[383-C_2H_2-C_2H_5]^{+\bullet}$, 309 (29) $[383-CO_2C_2H_5-H]^+$, 293 (100) $[383-NH_2-CO_2C_2H_5-H]^{+\bullet}$, 139 (22) $[C_8H_{11}O_2]^+$, 115 (98) $[C_5H_9NO_2]^{+\bullet}$.

Ethyl 2-amino-5'-bromo-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2'-one-3-carboxylate (5b) (Table-1, entry 2): White powder, m.p. 288 ºC (from methanol); yield 62 %[A], 87 %[B], 95 %[C]; IR (KBr, ν_{max}, cm^{-1}): 3387, 3276, 3213 (NH_2, NH), 1726 (C=O ester), 1687 (C=O ketone), 1653 (C=O γ-lactam); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.82 (3H, t, J = 5.5, OCH_2CH_3), 0.96 (3H, s, 7-CH_3), 1.01 (3H, s, 7-CH_3), 2.07 (1H, d, ^2J = 15.9, H_{ax}-8), 2.14 (1H, d, ^2J = 15.9, H_{eq}-8), 2.53 (2H, s, 6-CH_2), 3.73 (2H, q, J = 5.5, OCH_2CH_3), 6.65 (1H, d, ^3J = 8.5, H-7'), 7.01 (1H, d, ^4J = 1.8, H-4'), 7.22 (1H, dd, ^3J = 8.5, ^4J = 1.8, H-6'), 7.93 (2H, br. s, NH_2, D_2O exchangeable), 10.32 (1H, br. s, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) and DEPT-135: δ_C (ppm) 12.9 (OCH_2CH_3), 26.9, 27.2 [7-$(CH_3)_2$], 30.8 (C-7), 39.9 (C-6, overlapped with solvent signals) 46.1, 50.3 (C-8), 58.7 (OCH_2CH_3), 74.9 (spiro C), 109.3 (C-7'), 111.3, 111.7, 124.3 (C-4'), 129.1 (C-6'), 137.8, 142.8, 158.4, 162.2 (sp^2 carbons), 166.7 (CO ester)[44], 178.7 (CO 2'-oxoindole)[44], 194.2 (CO chromene)[44]; MS (+) ESI, *m/z* (%): 461 (50) $[M+H]^+$ ($C_{21}H_{21}{}^{79}BrN_2O_5$+H)$^+$, 463 (54) $[461+2]^+$ ($C_{21}H_{21}{}^{81}BrN_2O_5$+H)$^+$, 443 (6) $[461-H_2O]^+$, 433 (12) $[461-CO]^+$, 416 (6) $[461-OC_2H_5]^{+\bullet}$, 389 (96) $[461-CO_2C_2H_5+H]^+$, 371 (4) $[461-NH_2-CO_2C_2H_5-H]^{+\bullet}$, 347 (4) $[461-C_5H_7NO_2-H$, RDA fragmentation$]^{+\bullet}$, 311 (5) $[389-Br+H]^+$, 295 (28) $[416-C_8H_{10}O+H$, RDA fragmentation$]^+$, 279 (54) $[295-NH_2]^{+\bullet}$, 259 (11) $[461-C_8H_{10}O-HBr$, RDA fragmentation$]^+$, 229 (24) $[259-NH-NH_2+H]^+$, 217 (100) $[295-Br+H]^+$, 213 (74) $[259-OC_2H_5-H]^+$, 201 (26) $[229-CO]^+$, 199 (31) $[259-NH_2-OC_2H_5+H]^{+\bullet}$, 169 (18) $[C_6H_5BrN-H]^{+\bullet}$, 157 (21) $[229-CO_2C_2H_5+H]^+$.

Ethyl 2-amino-5'-chloro-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2'-one-3-carboxylate (5c) (Table-1, entry 3): White powder, m.p. 278 ºC (from methanol); yield 70 %[A], 70 %[B], 62 %[C]; IR (KBr, ν_{max}, cm^{-1}): 3384, 3276, 3215 (NH_2, NH), 1725 (C=O ester), 1688 (C=O ketone), 1650 (C=O γ-lactam); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.82 (3H, t, J = 5.5, OCH_2CH_3), 0.96 (3H, s, 7-CH_3), 1.01 (3H, s, 7-CH_3), 2.07 (1H, d, ^2J = 15.7, H_{ax}-8), 2.14 (1H, d, ^2J = 15.7, H_{eq}-8), 2.53 (2H, s, 6-CH_2), 3.73 (2H, q, J = 5.5, OCH_2CH_3), 6.68 (1H, d, ^3J = 8.3, H-7'), 6.90 (1H, d, ^4J = 1.9, H-4'), 7.09 (1H, dd, ^3J = 8.3, ^4J = 1.9, H-6'), 7.93 (2H, br. s, NH_2, D_2O exchangable), 10.31 (1H, br. s, NH, D_2O exchangable); ^{13}C NMR (75 MHz, DMSO-d_6) and DEPT-135: δ_C (ppm) 12.4 (OCH_2CH_3), 26.3, 26.7[(7-$(CH_3)_2$], 30.9 (C-7), 39.3 (C-6, overlapped with solvent signals), 43.1, 49.8 (C-8), 58.2 (OCH_2CH_3), 75.1 (spiro C), 108.7 (C-7'), 111.8, 121.7 (C-4'), 123.7, 126.3 (C-6'), 137.5, 142.5, 158.5, 162.2 (sp^2 carbons), 166.8 (CO ester)[44], 178.9 (CO 2'-oxoindole)[44], 194.2 (CO chromene)[44]; MS (-) ESI, *m/z* (%): 415 (36) $[M-H]^-$ ($C_{21}H_{21}{}^{35}ClN_2O_5$-H)$^-$, 417 (14) $[415+2]^-$ ($C_{21}H_{21}{}^{37}ClN_2O_5$-H)$^-$, 401 (4) $[415-CH_3+H]^-$, 387 (8) $[415-CO]^-$, 370 (6) $[415-OC_2H_5]^{-\bullet}$, 369 (28) $[387-H_2O]^-$, 362 (100) $[415-H_2O-Cl]^{-\bullet}$, 360 (10) $[415-C_2H_2-C_2H_5]^{-\bullet}$, 343 (32) $[415-CO_2C_2H_5+H]^-$, 325 (12) $[415-NH_2-CO_2C_2H_5-H]^{-\bullet}$, 309 (52) $[343-Cl+H]^-$, 302 (3) $[415-C_5H_7NO_2$, RDA fragmentation$]^-$, 293 (22) $[415-C_8H_{10}O$, RDA fragmentation$]^-$.

Ethyl 6'-amino-3'-methyl-1'-phenylspiro[indole-3,4'-pyrano(3',2'-*d*)pyrazole]-2-one-5'-carboxylate (6a) (Table-1, entry 4): Pale brown powder, m.p. 190 ºC (from water/methanol); yield 50 %[A], 95 %[B], 95 %[C]; IR (KBr, λ_{max}, cm^{-1}): 3352, 3254, 3211 (NH_2, NH), 1697 (C=O ester), 1640 (C=O γ-lactam); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.75 (3H, t, J = 6.9, OCH_2CH_3), 1.57 (3H, s, 3'-CH_3), 3.75 (2H, q, J = 6.9, OCH_2CH_3), 6.85-6.91 (2H, m, H-5,7), 6.97 (1H, d, ^3J = 7.3, H-4), 7.17 (1H, t, ^3J = 7.3, H-6), 7.34 (1H, t, ^3J = 7.3, H-4"), 7.51 (2H, t, ^3J = 8.1, H-3",5"),7.81 (2H, d, ^3J = 8.1, H-2",6"),

TABLE-1
SYNTHESIS OF **5a-c** AND **6a,b** *via* CLASSICAL HEATING, ULTRASOUND AND MICROWAVE IRRADIATION CONDITIONS

Entry	Products	R	Method A[a]		Method B[b]		Method C[C]	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1	5a	H	120	59	60	70	5	95
2	5b	Br	120	62	60	87	5	95
3	5c	Cl	120	70	60	70	5	70
4	6a	H	120	50	60	95	5	95
5	6b	Cl	120	73	60	95	5	95

[a]Method A: Refluxing in abs. ethanol; [b]Method B: Ultrasound irradiation at 25-30 ºC in abs. ethanol; [c]Method C: Microwave irradiation at 300 W (in the minimum quantity of ethanol 96 %)

8.21 (2H, br. s, NH_2, D_2O exchangeable), 10.51 (1H, br. s, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) and DEPT-135: δ_C (ppm) 10.9 (3'-CH_3), 12.3 (OCH_2CH_3), 46.7, 58.2 (OCH_2CH_3), 73.8 (spiro C), 97.4, 108.1 (C-7), 119.2 (C-2",6"), 120.9 (C-5), 122.4 (C-4), 125.6 (C-6), 126.9 (C-4"), 128.6 (C-3",5"), 135.1, 136.6, 141.4, 143.2 (C-1"), 143.5, 160.6 (sp^2 carbons), 167.1 (CO ester), 178.5 (CO 2-oxoindole); MS (-) ESI, *m/z* (%): 415 (54) $[M-H]^-$ ($C_{23}H_{20}N_4O_4$-H)$^-$, 400 (2) [415-CH_3]$^{-\bullet}$, 395 (100) [415-NH_2-4H]$^{-\bullet}$, 384 (43) [415-C_2H_5-2H]$^{-\bullet}$, 369 (28) [415-OC_2H_5-H]$^-$, 348 (400-2x C_2H_2]$^{-\bullet}$, 302 (39) [415-$C_5H_7NO_2$, RDA fragmentation]$^-$, 259 (23) [415-$C_{10}H_8N_2$, RDA fragmentation]$^-$.

Ethyl 6'-amino-5-chloro-3'-methyl-1'-phenylspiro[indole-3,4'-pyrano(3',2'-*d*)pyrazole]-2-one-5'-carboxylate (6b) (Table-1, entry 5): Dark brown powder, m.p. 200 ºC (from water/methanol); yield 73 %^{A}, 95 %^{B}, 95 %^{C}; IR (KBr, λ_{max}, cm^{-1}): 3355, 3254, 3194 (NH_2, NH), 1701 (C=O ester), 1640 (C=O γ-lactam); ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.79 (3H, t, J = 7.3, OCH_2CH_3), 1.63 (3H, s, 3'-CH_3), 3.78 (2H, q, J = 7.3, OCH_2CH_3), 6.87 (1H, d, ^3J = 8.1, H-7), 7.12 (1H, br. s, H-4, there is ^4J coupling but not resolved), 7.22 (1H, d, ^3J = 8.1, H-6, there is ^4J coupling but not resolved), 7.35 (1H, t, ^3J = 8.1, H-4"), 7.52 (2H, t, ^3J = 8.1, H-3",5"), 7.81 (2H, d, ^3J = 8.1, H-2",6"), 8.27 (2H, br. s, NH_2, D_2O exchangeable), 10.66 (1H, br. s, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) and DEPT-135: δ_C (ppm) 11.5 (3'-CH_3), 12.9 (OCH_2CH_3), 47.5, 58.8 (OCH_2CH_3), 73.7 (spiro C), 97.2, 109.9 (C-7), 119.7 (C-2",6"), 123.2 (C-4), 125.5, 126.1 (C-4"), 127.4 (C-6), 129.1 (C-3",5"), 137.1, 137.6, 140.8, 143.7 (C-1"), 143.8, 161.1 (sp^2 carbons) 167.4 (CO ester), 178.8 (CO 2-oxoindole); MS (-) ESI, *m/z* (%): 449 (76) $[M-H]^-$ ($C_{23}H_{19}{}^{35}ClN_4O_4$-H)$^-$, 451 (16) [449+2]$^-$ ($C_{23}H_{19}{}^{37}ClN_4O_4$-H)$^-$, 435 (2) [449-$CH_3$+H]$^-$, 421 (4) [449-CO]$^-$, 403 (6) [449-$OC_2H_5$-H]$^-$, 395 (9) [421-$C_2H_2$]$^-$, 382 (42) [435-2x C_2H_2-H]$^{-\bullet}$, 336 (100) [449-$C_5H_7NO_2$, RDA fragmentation]$^-$, 293 (9) [449-$C_{10}H_8N_2$, RDA fragmentation]$^-$, 245 (8) [293-CH_3-Cl+2H]$^-$, 219 (6) [245-C_2H_2]$^-$, 205 (8) [293-CONH-OC_2H_5]$^{-\bullet}$, 191 (16) [219-CO]$^-$, 159 (12) [205-$CONH_2$-2H]$^-$, 117 (65) [205-C_2H_2-CO-Cl+H]$^{-\bullet}$, 76 (14) $[C_6H_4]^{-\bullet}$.

RESULTS AND DISCUSSION

In our initial endeavor, we have investigated a three-component reaction of 5-(un)substituted isatins (**1a-c**) with ethyl cyanoacetate (**2**), 5,5-dimethylcyclohexane-1,3-dione (**3**) and Et_3N in absolute ethanol by using several methods such as thermal heating (Method A), ultrasound irradiation (method B) and microwave irradiation (method C) conditions to afford functionalized spirooxoindole derivatives (**5a-c**) (**Scheme-I**, Table-1). In comparison, the reaction realized under ultrasound and microwave irradiation had higher yields than those performed under classical conditions for less time and temperature. However, each of them gave the desired **5** and **6** as the single products. Proposed mechanism for the synthesis of **5** was described in (**Scheme-II**)[45]. The process represent a typical cascade reaction in which the isatin **1** first condenses with ethyl cyanoacetate (**2**) to produce non-isolated isatylidene derivative **7** in absolute ethanol in the presence of Et_3N. This step was regarded as a fast knoevenagel condensation. Then, **7** is attacked *via* Michael addition of **3** to give the intermediate **8** followed by the cycloaddition of hydroxyl group to the cyano moiety to form the desired product **5**. Structural elucidation of spiro[chromene-4,3'-indole]-2-ones (**5a-c**) was accomplished using 1D and 2D NMR spectrometric studies as described for **5b** (Fig. 1).

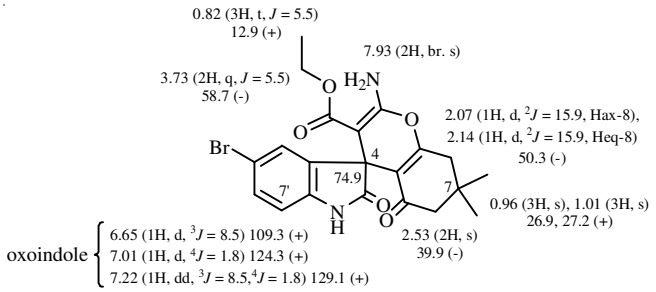
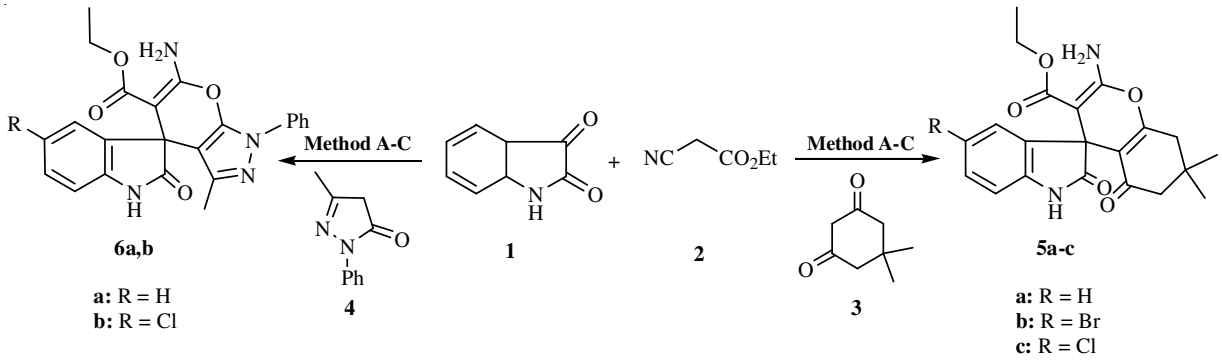


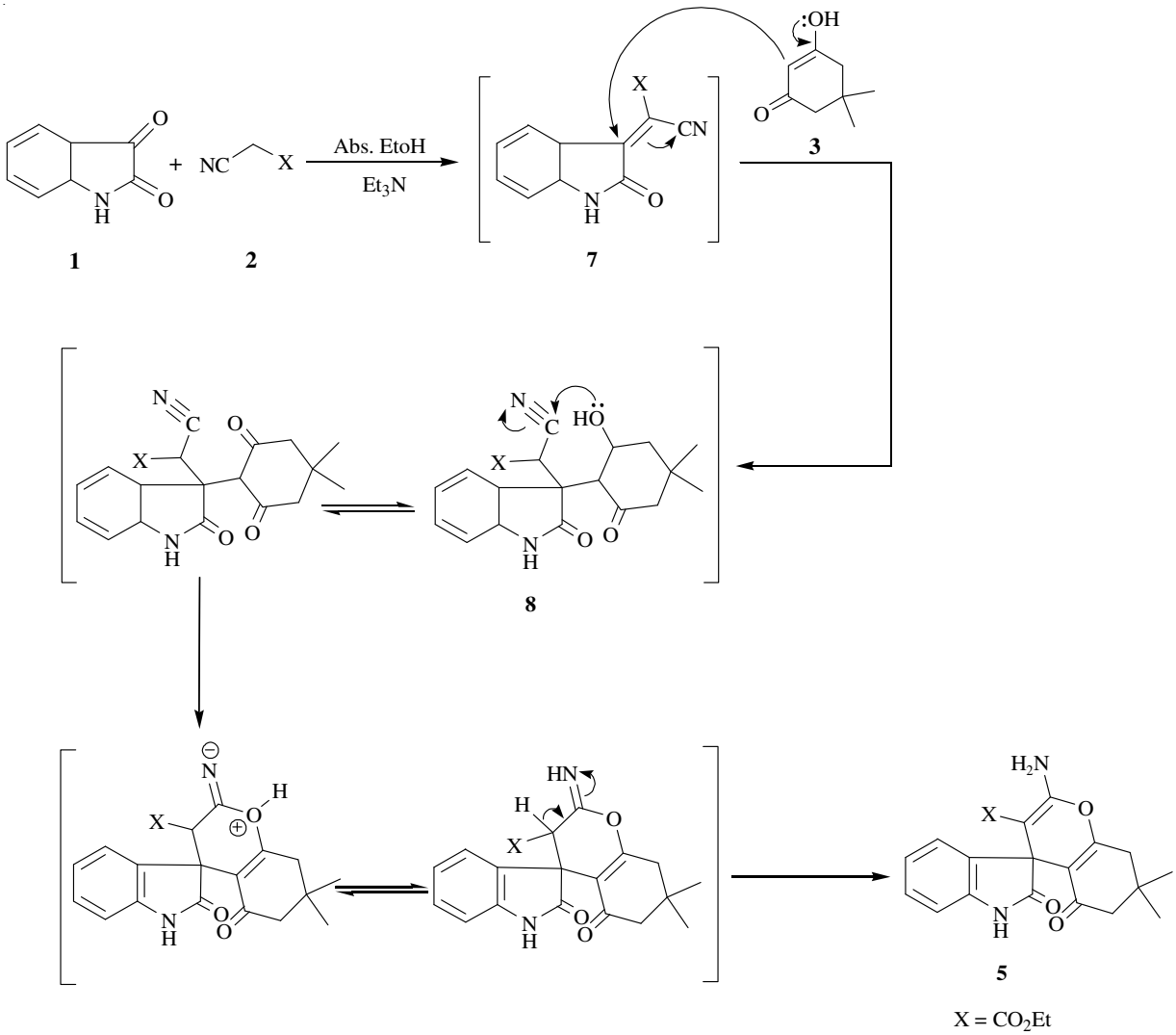
Fig. 1. Selected ^1H and ^{13}C NMR/DEPT-135 chemical shifts of **5b**

The IR spectra of **5** showed absorption bands at 3387-3179 cm^{-1} corresponding to the NH_2 and N-H stretching, in addition to bands in the range 1726-1650 cm^{-1}, which are characteristic to C=O groups. In the ^1H NMR spectrum of **5b** demonstrated a triplet at 0.82 ppm (J = 5.5 Hz) duo to 3-CH_3 protons of ester group. These protons showed ^1H-^1H COSY correlations with 3-CH_2 and ^1H-^{13}C COSY correlations with carbon signal at 12.9 (+) ppm. The two singlet at 0.96 and 1.01 ppm were assigned to 7-$(CH_3)_2$ chromene protons from their ^1H-^{13}C COSY correlations with C-7 at 26.9 (+) and 27.2 (+) ppm. The 8-CH_2 protons appeared as doublets at 2.07 and 2.14 ppm (^2J = 15.9 Hz) and showed ^1H-^{13}C COSY correlations with carbon signal at 50.3 (-) ppm. While, 6-CH_2 protons appeared as singlet at 2.53 ppm and showed ^1H-^{13}C COSY correlations with C-6 at 39.9 (-) ppm. The quartet at 3.73 ppm (J = 5.5 Hz), related by ^1H-^1H COSY correlations with 3-CH_3 protons of ester group, duo to 3-CH_2 showed ^1H-^{13}C COSY correlations with carbon signal at 58.7 (-) ppm. The H-7', 4' and 6' of the oxoindole ring occurred as two doublets at 6.65



A: Et_3N, Abs. EtOH, reflux, 2 h; B: Et_3N, Abs. EtOH, US, 1 h; C: Et_3N, Abs. EtOH, MW, 300 W, 5 min

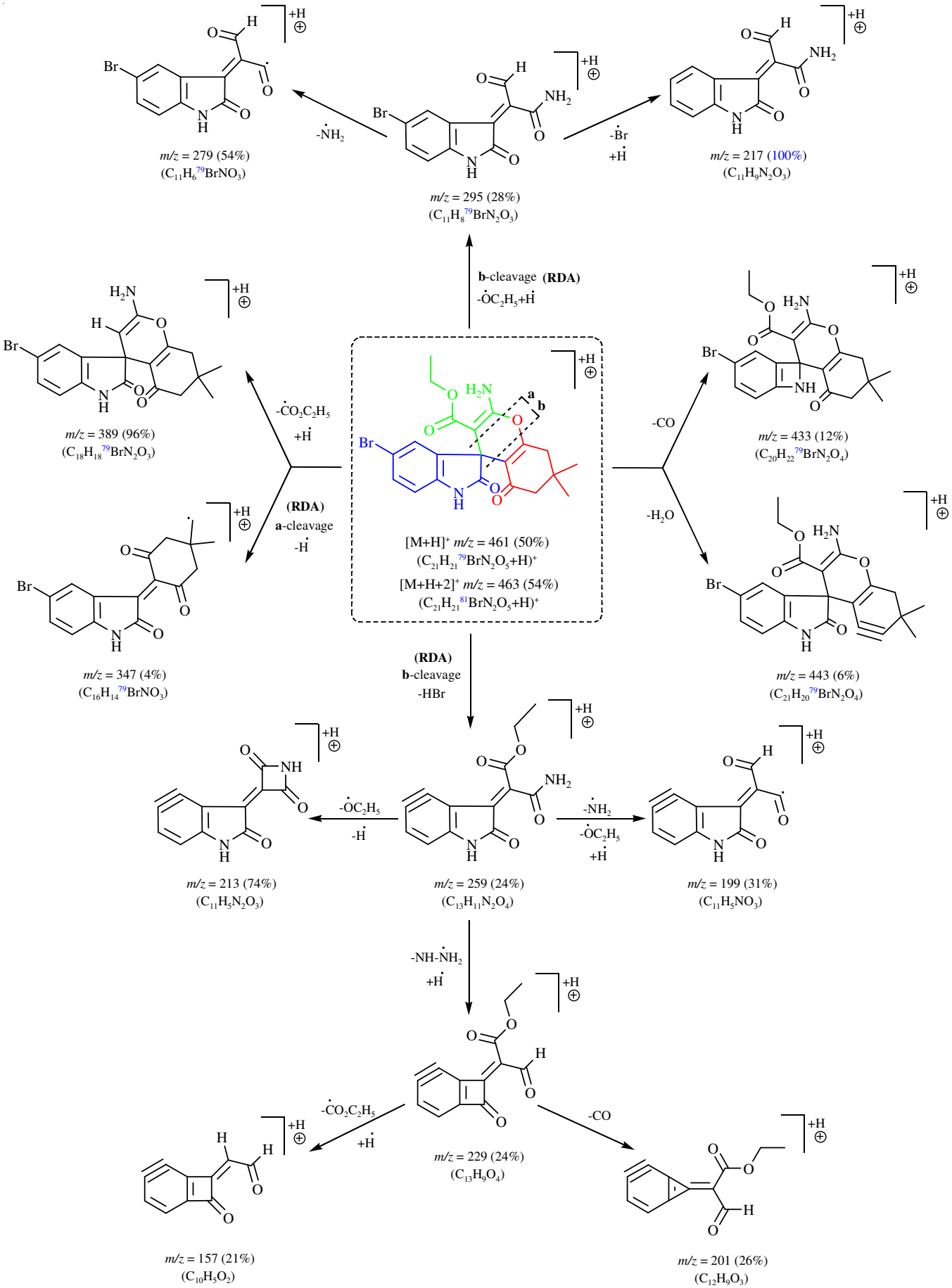
Scheme-I: Synthesis of spirooxoindole derivatives **5** and **6**



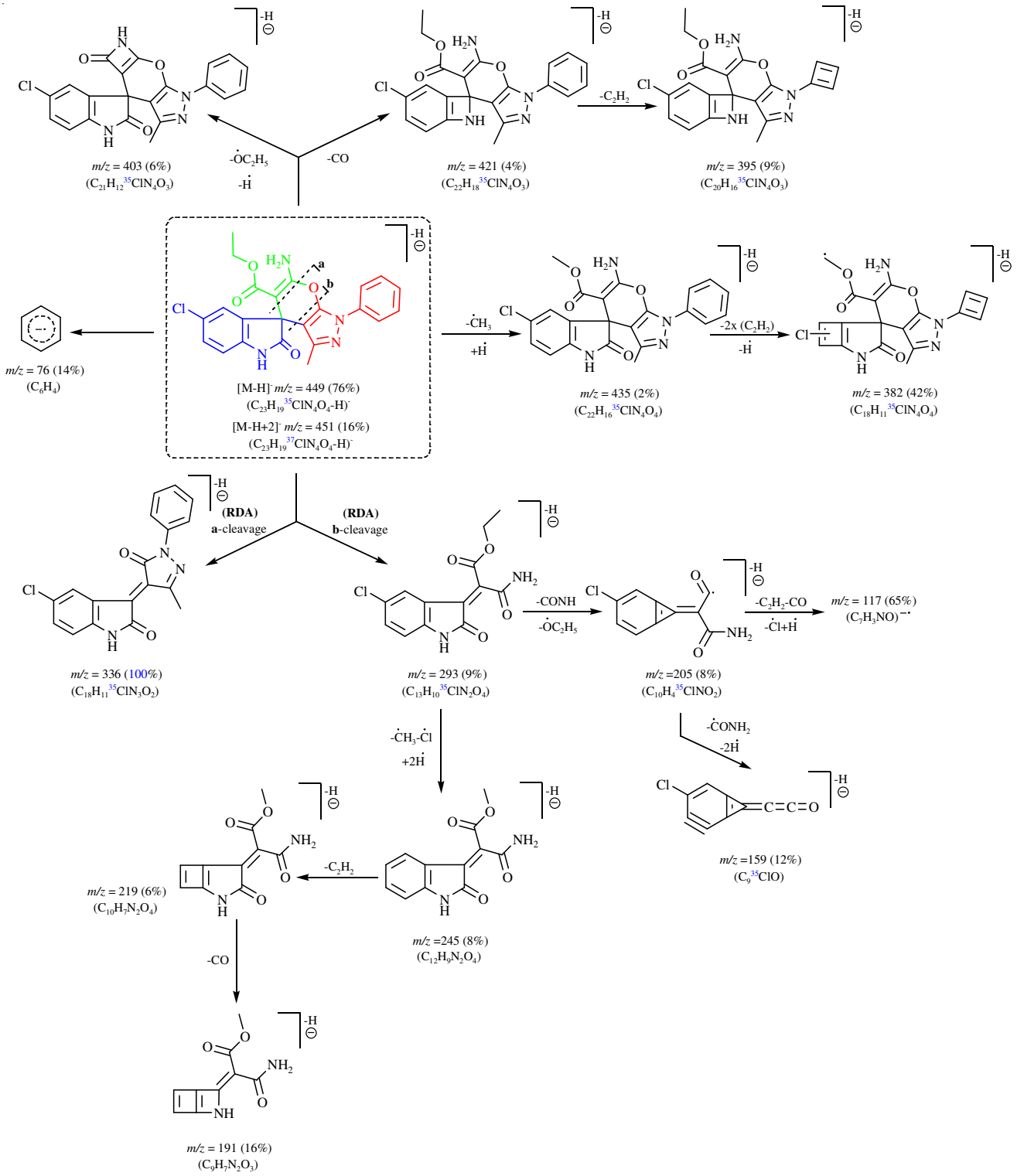
Scheme-II: Proposed mechanism for the formation of spiro[chromene-4,3'-indol]-2-ones **5**

(^3J = 8.5 Hz) and 7.01 (^4J = 1.8 Hz) and doublet of doublets at 7.22 ppm (^3J = 8.5, ^4J = 1.8 Hz), respectively, which showed ^{1}H-^{13}C COSY correlations with C-7' at 109.3 (-), C-4' at 124.3 (-) and C-6' at 129.1 (-) ppm. The D_2O exchangeable protons at 7.93 and 10.32 ppm assigned to NH_2 and NH groups, respectively. Moreover, the ^{13}C NMR exhibited signal at 74.9 for the spiro carbon atom beside three signals in the range of 166.7-194.2 for the carbonyl groups. All other carbons in this spectrum appeared at their expected chemical shift. The mass spectrum of **5b** further confirmed its structure, which gave protonated (quasi-molecular) ion $[M+H]^+$ peak at *m/z* 461 as well as at *m/z* 463 for bromine isotope. The plausible mass fragmentation pattern of **5b** was described in **Scheme-III**.

Furthermore, we have applied this reaction on 5-methyl-2-phenyl-2,4-dihydropyrazole-3-one (**4**) instead of **3** under similar conditions to furnish the respective spiro[indole-



Scheme-III: Proposed fragmentation pathways of protonated **5b**



Scheme-IV: Proposed fragmentation pathways of deprotonated **6b**

3,4'-pyrano(3',2'-*d*)pyrazole]-2-ones derivatives (**6a-b**) (**Scheme-II**, Table-1). The structure of cycloadducts **6a-b** was confirmed through 1D and 2D NMR spectroscopic data (Fig. 2).

The IR spectra of **6** showed absorption bands in the 3355-3194 and 1701-1640 cm^{-1} regions resulting from the NH_2, NH and C=O functions, respectively. ^1H NMR spectrum of **6b** exhibited a singlet at 1.63 ppm due to the 3'-CH_3 protons of pyrazole ring. Further, 3'-CH_3 showed ^1H-^{13}C COSY correlations with carbon signal at 11.5 (+) ppm. This spectrum also appeared signals in the range 7.35-7.81 for the phenyl protons. The chemical shifts of other proton absorptions in the latter spectrum of **6b** as well as the whole carbon signals in the ^{13}C NMR spectrum were in complete consistent with its structure (cf. Experimental). Finally, the mass spectrum displayed distinguishing peaks at *m/z* = 449 and 451, which further supported the formation of **6b** (**Scheme-IV**).

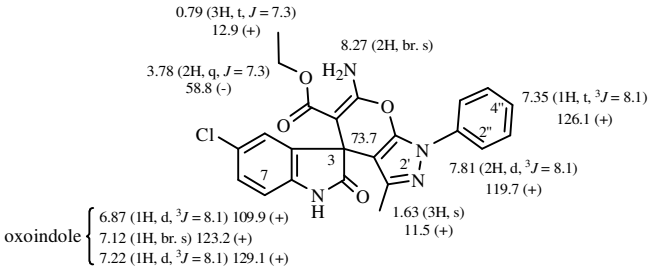


Fig. 2. Selected ^{1}H and ^{13}C NMR/DEPT-135 chemical shifts of **6b**

Conclusion

Herein we described an effective approach for constructing a class of spirooxoindole derivatives with high selectivity under conventional heating, ultrasound and also by microwave irradiation methods. In general, improvement in rates and yields of the reactions were observed by carrying out them under environmentally benign procedures. The biological evaluations of these derivatives are ongoing in our laboratory and will be reported in due course.

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