Synthesis of some N,N-diethoxyphthalimido-5-(substitutedphenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c] pyrazole-4-spiro-5-substituted-1H-indole-2-one

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Note

Isatin 1a,b reacted with 5-methyl-2,4-dihydro-3H-pyrazol-3-one in absolute alcohol to form a mixture of two compounds 2a,b and 4a,b. These compounds were separated out by dissolving in warm benzene. 3,5-Dimethyl-4,7-dihydro-1H-pyrazolo[4′,3′:5,6]pyrano[2,3-c]pyrazole-4-spiro-5-substituted-1H-indole-2-one 2a,b which were insoluble in benzene show intense bands at 3211, 3289 and 1235 cm⁻¹ for NH and C=O-C group respectively in IR region. Compounds 2a,b were refluxed with bromoethoxyphthalimide in the presence of K₂CO₃ to give N,N,N-triethoxyphthalimido-3,5-dimethyl-4,7-dihydro-1H-pyrazol-4-ylidene)-1,3-dihydro-2H-indol-2-one 4a,b which were soluble in benzene showed two absorption bands in IR region at 3289, 3211 cm⁻¹ and 1H NMR signal at δ 12.1 for NH moiety. These 4a,b when treated with substituted phenyldrazine in DMF and few drops of acetic acid furnished 5-(substitutedphenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-substituted-1H-indole-2-one 6a-f. Structure was supported by disappearance of NH bands in IR region and appearance of four triplets at δ 4.50 (t, 2H, O-CH₂), 3.2 (t, 2H, N-CH₂), 3.2 (t, 2H, N-CH₂), and 2.9 (t, 2H, N-CH₂) in 1H NMR spectrum. Compounds 5-substituted-3-(3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-indol-2-one 4a,b which were soluble in benzene showed two absorption bands in IR region at 3289, 3211 cm⁻¹ and 1H NMR spectrum of pyrazolopyrazole derivatives 5a-f by reaction with substituted phenyldrazine. These are finally condensed with bromoethoxyphthalimide in DMF and pyridine as a base to give titled compounds N,N-diethoxyphthalimido-5-(substituted phenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-substituted-1H-indole-2-one 6a-f. The structures of all the synthesized compounds are supported by spectral and analytical data.

Keywords: Isatin, pyrazole, bromoethoxyphthalimide, spectral data

Isatin derivatives possess antibacterial¹⁻³, antifungal⁴⁻⁶, antiviral⁷⁻⁹, anti HIV¹⁰⁻¹², anti-protozoal¹³⁻¹⁴, anticancer¹⁵, muscle relaxant¹⁶, anti-allergic activities¹⁷. The pyrazole unit is one of the core structures in a number of natural products. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, antifungal, anticoagulant, antitumor, sedative and hypnotic activity¹⁸⁻²¹. Spiro compounds are known to possess various biological activities e.g fungicidal²²⁻²⁵, herbicidal²⁶, bactericidal²⁶,²⁷⁻²⁸, anticonvulsant²⁹, anti-inflammatory³⁰, and antianxiety³¹. These heterocyclic rings attached to alkoxyphthalimide group have been synthesized³² and tested for antimicrobial³³ and antimalarial³⁴ activities.

Results and Discussion

Synthesis of some N,N-diethoxyphthalimido-5-(substitutedphenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c] pyrazole-4-spiro-5-substituted-1H-indole-2-one

5-Methyl-2,4-dihydro-3H-pyrazol-3-one reacts with isatin 1a,b in ethanol to give a solid product. On addition of warm benzene, one part (benzene soluble) is 4a,b and another part (benzene insoluble) is 2a,b. Compounds 3,5-dimethyl-4,7-dihydro-1H-pyrazolo[4′,3′:5,6]pyrano[2,3-c]pyrazole-4-spiro-5-substituted-1H-indole-2-one 2a,b on treatment with bromoethoxyphthalimide in DMF yield N,N,N-triethoxyphthalimido-3,5-dimethyl-4,7-dihydro-1H-pyrazolo[4′,3′; 5,6]pyrano[2,3-c]pyrazole-4-spiro-5-substituted-1H-indole-2-one 3a,b. 3-(3-Methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-indol-2-one 4a,b are converted to corresponding pyrazolopyrazole derivatives 5a-f by reaction with substituted phenyldrazine. These are finally condensed with bromoethoxyphthalimide in DMF and pyridine as a base to give titled compounds N,N-diethoxyphthalimido-5-(substituted phenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-substituted-1H-indole-2-one 6a-f. The structures of all the synthesized compounds are supported by spectral and analytical data.
Experimental Section
Melting points were obtained in open capillary tubes and are uncorrected. Homogeneity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spots were carried out in an iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 cm\(^{-1}\) range using KBr discs on Perkin Elmer FTIR spectrometer and \(^1\)H NMR were recorded on a Bruker DRX-300 MHz spectrometer (CDCl\(_3\)) using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Structure
of all the synthesized compounds was assigned on basis of their analytical and spectral data.

Synthesis of 3-(3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-1,3-dihydro-2H-indol-2-one, 2a and 3,5-dimethyl-4,7-dihydro-1H-pyrazolo[4',3':5,6]-pyrano[2,3-c]pyrazole-4-spiro-1H-indole-2-one, 4a

An equimolar mixture of Isatin 1a (0.01 mole) and 5-methyl-2,4-dihydro-3H-pyrazol-3-one (0.01 mole) was refluxed in absolute ethanol (30 mL) for 6-8 hr. Excess of the solvent was removed under reduced pressure. Crude product was a mixture of two compounds. These were separated out by dissolving in warm benzene. Compound 2a came out as insoluble white crystals and compound 4a as soluble violet crystals.

Similarly, compounds 2b and 4b were synthesized with minor change in refluxed time.

3,5-Dimethyl-4,7-dihydro-1H-pyrazolo[4',3':5,6]-pyrano[2,3-c]pyrazole-4-spiro-1H-indole-2-one, 4a: IR (KBr): 3292 (N-H str.), 3231 (N-H str.), 3080 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.); 1H NMR (CDCl3): δ 10.4 (s, NH), 2.44 (s, CH3), 8.7 (s, NH isatine) 7.05-7.78 (m, 4H, Ar-H); MS: [M]+ m/z 341, [M+2]+ 343.

5-Chloro-3-(3-methyl-5-oxo-1,5-dihydro-4H-pyrazolo[4',3'-5,6]-pyrano[2,3-c]pyrazole-4-spiro-1H-indole-2-one, 2b: IR (KBr): 3295 (N-H str.), 3229 (N-H str.) 3091 (C-H str., Ar-H), 1673 (C=O), 1662 (C=O), 1608 cm−1 (C=N str.); 1H NMR (CDCl3): δ 7.13 (s, NH), 8.4 (s, NH), 8.7 (s, NH isatine) 7.05-7.78 (m, 4H, Ar-H); MS: [M]+ m/z 227.

Synthesis of N,N,N-triethoxyphthalimido-3,5-dimethyl-4,7-dihydro-1H-pyrazolo[4',3':5,6]pyrano[2,3-c]pyrazole-4-spiro-1H-indole-2-one, 3a

A mixture of compound 2a (0.1 mole), bromoethoxyphthalimide (0.3 mole) and K2CO3 (0.3 mole) in
DMF was refluxed for 8 hr. The reaction mixture was then filtered and allowed to cool to RT. After some time, the mixture was poured into crushed ice, and isolated solid was dried and purified by recrystallized from methanol. Likewise, compound 3b was also synthesized by some modification in reflux time.

N,N,N-triethoxypthalimido-3,5-dimethyl-4,7-dihydro-1H-pyrazolo[4′,3′;5,6]pyrano [2,3c]pyrazole-4-spiro-1H-indole-2-one, 3a: IR (KBr): 3110 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.), 1238 cm\(^{-1}\) (C-O-C str.); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.30-8.1 (m, Ar-H), 4.89 (t, 2H, O-CH\(_2\)), 4.53 (t, 2H, O-CH\(_2\)), 3.4 (t, 2H, N-CH\(_2\)), 3.1 (t, 2H, N-CH\(_2\)), 1.40 (s, 3H, CH\(_3\)); MS: \([M]^+ m/z\) 353.1, \([M+2]^+\) 355.

5-(2,4-Dinitrophenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-chloro-1H-indol-2-one, 5d: IR (KBr): 3292 (N-H str.), 3233 (N-H str.), 3089 (C-H str., Ar-H), 1682 (C=O), 1635 (C=N str.), 792 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.22 (s, NH isatine), 7.18 (s, NH), 1.1 (s, CH\(_3\)), 6.37-7.59 (m, 8H, Ar-H), 2.3 (s, CH); MS: \([M]^+ m/z\) 351, \([M+2]^+\) 353.

5-(2,4-Dinitrophenyl)-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-chloro-1H-indol-2-one, 5e: IR (KBr): 3288 (N-H str.), 3235 (N-H str.), 3089 (C-H str., Ar-H), 1677 (C=O), 1632 (C=N str.), 781 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.25 (s, NH isatine), 7.2 (s, NH), 1.1 (s, CH\(_3\)), 6.58-7.59 (m, 8H, Ar-H), 2.3 (s, CH); MS: \([M]^+ m/z\) 351, \([M+2]^+\) 353.

5-(Phenyl)-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-chloro-1H-indol-2-one, 5f: IR (KBr): 3292 (N-H str.), 3233 (N-H str.), 1682 (C=O), 1635 (C=N str.), 792 cm\(^{-1}\) (C-Cl); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.2 (s, NH isatine), 7.2 (s, NH), 1.2 (s, CH\(_3\)), 6.37-7.53 (m, 7H, Ar-H), 2.4 (s, CH); MS: \([M]^+ m/z\) 387, \([M+2]^+\) 391.

Synthesis of 5-(2,4-dinitrophenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-1H-indol-2-one, 5a

An equimolar mixture of compound 4a (0.01 mole) and substituted phenyl hydrazine (0.01 mole) were dissolved in DMF. A few drops of CH\(_3\)COOH were added to the reaction mixture. Then the reaction mixture was refluxed for 10 hr, filtered, cooled, dried and purified by recrystallization from ethanol. Compounds 5b-f were also synthesized by similar procedure with some change in reflux time.

5-(2,4-Dinitrophenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-1H-indol-2-one, 5a: IR (KBr): 3298 (N-H str.), 3238 (N-H str.), 3110 (C-H str., Ar-H), 1685 (C=O), 1638 (C=N str.), 1392-1548 cm\(^{-1}\) (NO\(_2\) str.); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.3 (s, NH), 7.4 (s, NH isatine), 1.3 (s, CH\(_3\)), 6.96-7.59 (m, 4H, Ar-H), 2.3 (s, CH); MS: \([M]^+ m/z\) 407.

5-(Phenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-1H-indol-2-one, 5b: IR (KBr): 3289 (N-H str.), 3231 (N-H str.), 3085 (C-H str., Ar-H), 1632 (C=O), 1632 cm\(^{-1}\) (C=N str.); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.2 (s, NH isatine), 7.15 (s, NH), 1.1 (s, CH\(_3\)), 6.31-7.50 (m, 9H, Ar-H), 2.2 (s, CH); MS: \([M]^+ m/z\) 317.

5-(4-Chlorophenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-1H-indol-2-one, 6a: IR (KBr): 3110 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.), 1238 cm\(^{-1}\) (C-O-C str.); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.2 (s, NH isatine), 7.15 (s, NH), 1.1 (s, CH\(_3\)), 6.31-7.50 (m, 9H, Ar-H), 2.2 (s, CH); MS: \([M]^+ m/z\) 317.

Synthesis of N,N-diethoxypthalimido-5-(substitutedphenyl)-3-methyl-1,3a,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-substituted-1H-indol-2-one, 6a

Compound 5a (0.01 mole) and bromoethoxypthalimide (0.02 mole) were dissolved in absolute ethanol along with 2 mL pyridine as a base. The reaction mixture was then refluxed for 6 hr. The excess of solvent was distilled off under reduced pressure and the residue was purified by recrystallization from methanol. Compounds 6b-f were synthesized in similar way with small changes in reflux time.
NOTES

N,N-Diethoxyphthalimido-5-(phenyl)-3-methyl-1,3α,4,5-tetrahydropyrazolo[3,4-c] pyrazole-4-spiro-1H-indol-2-one, 6b: IR (KBr): 3110 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.), 1238 cm⁻¹ (C-O-C str.); ¹H NMR (CDCl₃): δ 7.1-7.8 (m, Ar-H), 4.71 (t, 2H, O-CH₂), 4.45 (t, 2H, O-CH₂), 3.1 (t, 2H, N-CH₂), 2.8 (t, 2H, N-CH₂), 2.1 (s, 1H, CH), 1.5 (s, 3H, CH₃); MS: [M⁺] m/z 695.

N-Diethoxyphthalimido-5-(4-chlorophenyl)-3-methyl-1,3α,4,5-tetrahydropyrazolo [3,4-c]pyrazole-4-spiro-1H-indol-2-one, 6c: IR (KBr): 3110 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.), 1238 cm⁻¹ (C-O-C str.); ¹H NMR (CDCl₃): δ 7.1-8.0 (m, Ar-H), 4.80 (t, 2H, O-CH₂), 4.50 (t, 2H, O-CH₂), 3.3 (t, 2H, N-CH₂), 3.1 (t, 2H, N-CH₂), 2.2 (s, 1H, CH), 1.6 (s, 3H, CH₃); MS: [M⁺] m/z 731.

N,N-Diethoxyphthalimido-5-(2,4-dinitrophenoxy)-3-methyl-1,3α,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-chloro-1H-indol-2-one, 6d: IR (KBr): 3110 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.), 1238 cm⁻¹ (C-O-C str.); ¹H NMR (CDCl₃): δ 7.4-8.3 (m, Ar-H), 4.85 (t, 2H, O-CH₂), 4.60 (t, 2H, O-CH₂), 3.4 (t, 2H, N-CH₂), 3.1 (t, 2H, N-CH₂), 2.4 (s, 1H, CH), 1.8 (s, 3H, CH₃); MS: [M⁺] m/z 824.

N,N-Diethoxyphthalimido-5-(phenyl)-3-methyl-1,3α,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-chloro-1H-indol-2-one, 6e: IR (KBr): 3110 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.), 1238 cm⁻¹ (C-O-C str.); ¹H NMR (CDCl₃): δ 7.2-7.9 (m, Ar-H), 4.81 (t, 2H, O-CH₂), 4.50 (t, 2H, O-CH₂), 3.2 (t, 2H, N-CH₂), 2.9 (t, 2H, N-CH₂), 2.2 (s, 1H, CH), 1.6 (s, 3H, CH₃); MS: [M⁺] m/z 731.

N,N-Diethoxyphthalimido-5-(4-chlorophenyl)-3-methyl-1,3α,4,5-tetrahydropyrazolo[3,4-c]pyrazole-4-spiro-5-chloro-1H-indol-2-one, 6f: IR (KBr): 3110 (C-H str., Ar-H), 1672 (C=O), 1617 (C=N str.), 1238 cm⁻¹ (C-O-C str.); ¹H NMR (CDCl₃): δ 7.3-8.1 (m, Ar-H), 4.82 (t, 2H, O-CH₂), 4.53 (t, 2H, O-CH₂), 3.4 (t, 2H, N-CH₂), 2.9 (t, 2H, N-CH₂), 2.3 (s, 1H, CH), 1.65 (s, 3H, CH₃); MS: [M⁺] m/z 765.

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References