A facile one-pot synthesis of 7-substituted-5-methoxycarbonyl-1H-2, 3-dihydro-1, 4-benzodiazepin-2-ones from 5-substituted-N-chloroacetyl isatins

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7-Substituted-5-methoxycarbonyl-1H-2, 3-dihydro-1, 4-benzodiazepin-2-ones 3a-c have been prepared in one-pot from 5-substituted N-chloroacetyl isatins 2a-c.

1, 4-Benzodiazepines and their oxo derivatives have acquired pharmacological importance as potential tranquilizers, CNS depressant, anti-inflammatory, anti-convulsant, anti-spasmodic, muscle relaxant, hypnotic and sedative agents. The recent demonstration that these compounds can serve as a potential agents for the control and treatment of AIDS has stimulated further interest in these compounds.

The usefulness of isatin in the synthesis of a variety of heterocyclic compounds has been well documented. Its use in 1, 4-benzodiazepine synthesis was known after Ogata et al. showed that it could be employed in the synthesis of 1, 4-benzodiazepines through sequential N-chloroacetylation and amination with hexamine. This approach is based on the ring opening of substituted N-acyl isatins with nucleophilic reagents and concomitant ring expansion to form six or seven membered heterocyclic rings. This technique of a convenient one-step synthetic entry into the 1, 4-benzodiazepine nucleus, prompted us to explore the possibility of employing this procedure as a synthetic tool to the preparation of several other 1, 4-benzodiazepines. This paper describes its application to the synthesis of 5-methoxycarbonyl-1H-2, 3-dihydro-1, 4-benzodiazepin-2-one 3 (R = Me, OMe, NO₂) (Scheme I). The 5-methoxycarbonyl substituted 1, 4-benzodiazepines are important in view of their utility as novel synths in the synthesis of 5-pyrrolo substituted 1, 4-benzodiazepines class of anti-HIV.
agents. Structure of 3 was established through its conversion to known 5 and subsequent oxidation to 6.

**Results and Discussion**

Application of Sandmeyer's procedure\(^9\),\(^6\) afforded the required isatin derivatives 1. Compound 2 was formed from 1 on treatment with chloroacetyl chloride\(^7\) which on treatment with methanolic solution of hexamine afforded 5-methoxycarbonyl-1H-2, 3-dihydro-1, 4-benzodiazepin-2-one 3 in moderate to good yield (Scheme I). A tentative mechanism to account the formation of 3 from 2 has been proposed (Scheme II). It is presumed that the reaction proceeds through the initial cleavage of isatin ring with methanol under the influence of hexamine to give an intermediate 7, which subsequently reacts with hexamine to form hexamethylene tetraminium salt 8. Hydrolysis of salt 8 with methanol gives 3. This is in accord to a similar mechanism reported for an analogous cyclization of hexaminium salts of 2-chloroacetamido-5-chlorobenzophenone.\(^8\)

The compound 2(R=H) reacted with hexamine in t-buty1 alcohol to give t-buty1 ester 4 which on treatment in situ with TFA\(^9\) afforded 1H-2, 3-dihydro-1, 4-benzodiazepin-2-one 5. Oxidation of 5 with MCPBA gave corresponding N-oxide derivative 6. Structure of compounds 3a-c, 5 and 6 were established on the basis of elemental analysis, IR, \(^1\)H NMR and mass spectral data.

IR spectrum of compound 3 on KBr pellet exhibited the bands characteristic of NH group, amide and ester carbonyl groups. A medium intensity band at 1260 cm\(^{-1}\) in the IR spectrum of 6 indicated the presence of N-oxide linkage. \(^1\)H NMR spectrum of 3 in CDCl\(_3\) (DMSO-\(d_6\)) displayed a singlet at around \(\delta\) 3.85 for methyl protons of the 5-methoxycarbonyl group and a singlet at \(\delta\) 4.15 for CH\(_2\) protons flanked by the two electronegative groups, CO on one side and C=N on the other side in this molecule. The signal for these protons in the starting material 2 was present at \(\delta\) 4.80. The upfield shift of this signal in 3 gave clear indication of its formation from 2. The two C\(_3\) protons in 5 and 6 appeared as a doublet due to its coupling with C\(_5\) (HC=N) proton. A multiplet for C\(_5\) (HC=N) proton was observed owing to its coupling with C\(_7\) and aromatic proton. \(^1\)H NMR spectra of 3, 5 and 6 showed the presence of broad signal for NH at \(\delta\) 10.55 which exchanged with D\(_2\)O and a multiplet for
four protons at δ 7.00-7.85 for a substituted benzene ring. Presence of O=C-NH linkage in 3 clearly established that cyclisation of 2 to 3 had taken place. The mass spectra of 3a-c, 5 and 6 exhibited correct m/z values for the molecular ion peaks. Fragment M-58 appeared as the base peak in 3a-c which could arise by the loss of COCH₃ from the parent ion. 6 had a strong peak at M-16 owing to the loss of oxygen.

Experimental Section

All the melting points are uncorrected. The purity of all the compounds was checked by TLC using the solvent systems (benzene: methanol, 9: 1 v/v) and silica gel G as adsorbent. IR spectra were recorded on a Pye Unican Model SP3-300 infrared in nujol and on KBr pellets; 1H NMR spectra on a Varian EM 360 L using CDCl₃ and DMSO-d₆ as internal reference; and mass spectra on a Jeol D-300(EI) spectrometer.

The preparation of 2. Isatins (0.068 mole) were vigorously refluxed with chloroacetyl chloride (70 mL, 0.089 mole) for 5 hr and the mixture was cooled for 2 hr in an ice-bath. The precipitate was filtered, washed with 20 mL portion of ether, then air dried and was recrystallised from ethyl acetate.

N-Chloroacetyl-5-methylisatin 2a: Yield 67%; m.p. 185-87°C. Anal. Found: C, 55.40; H, 3.25; N, 11.29 %. IR: 3200(-NH), 1730(COCl), 1700(CO)cm⁻¹; 1H NMR: δ 8.33-6.81(m, 3H, ArH), 2.85(s, 3H,-CH₃), 4.82(s, 2H,-CH₂).

N-Chloroacetyl-5-methoxyisatin 2b: Yield 58%; m.p. 223-25°C. Anal. Found: C, 52.15; H, 3.11; N, 5.52%. Calcd for C₁₁H₇NO₂Cl: C, 52.07; H, 3.15; N, 5.52%. IR: 1780(COCl), 1740(NCO), 1705(CO) cm⁻¹; 1H NMR: δ 8.30-6.78(m, 3H, ArH), 3.99(s, 3H,-OCH₃), 4.84(s, 2H,-CH₂).

N-Chloroacetyl-5-nitroisatin 2c: Yield 47%; m.p. 130°C. Anal. Found: C, 44.50; H, 1.34; N, 10.74. Calcd for C₁₀H₈N₂O₂Cl: C, 44.69; H, 1.86; N, 10.42%. IR: 1730 (COCl), 1685(NCO), 1655(CO), 1550(NO₂), 1345(NO₂) cm⁻¹; 1H NMR: δ 8.27-6.73(m, 3H, ArH), 4.87(s, 2H,-CH₂).

Preparation of 3. N-Chloroacetyl isatins 2 (0.01 mole) and hexamethylenetetramine (0.01 mole) in dry methanol (20 mL) were refluxed for 10-11 hr. Progress of the reaction was checked through TLC. After completion of reaction, solvent was removed under reduced pressure and the solid was chromatographed over alumina (neutral) in C₆H₆:MeOH (9:5:0.5) as an eluant, the product obtained was recrystallized from benzene.

7-Methyl-5-methoxyacarbonyl-1H-2, 3-dihydro-1, 4-benzodiazepin-2-one 3a: Yield 50%; m.p. 208°C. Anal. Found: C, 62.11; H, 6.13; N, 12.15. Calcd for C₁₂H₁₁N₂O₂: C, 62.06; H, 6.17; N, 12.06%. IR: 3210(-NH), 1720(CO of ester), 1680(CO of amide) cm⁻¹; 1H NMR: δ 10.54(br, 1H,-NH), 7.3-6.84(m, 3H, ArH), 3.83(s, 3H,-OCH₃ of ester), 3.23s(3H,-CH₃), 4.20 (2H,-CH₂); MS: m/z 232(M⁺), 174(base peak).

7-Methoxy-5-methoxyacarbonyl-1H-2, 3-dihydro-1, 4-benzodiazepin-2-one 3b: Yield 39%; m.p. 182-84°C. Anal. Found: C, 58.10; H, 4.19; N, 11.10. Calcd for C₁₂H₁₀N₂O₂Cl: C, 58.06; H, 4.03; N, 11.29 %. IR: 3200(NH), 1730(CO of ester), 1685(CO of amide) cm⁻¹; 1H NMR: δ 8.10-6.96(m, 3H, ArH), 3.89(s, 3H,-OCH₃ of ester), 3.79(s, 3H,-OCH₃ of ester), 4.22(s, 2H,-CH₂); MS: m/z 248(M⁺), 190(base peak).

7-Nitro-5-methoxyacarbonyl-1H-2, 3-dihydro-1, 4-benzodiazepin-2-one 3c: Yield 42%; m.p. 214°C. Anal. Found: C, 50.21; H, 3.28; N, 16.00. Calcd for C₁₁H₈N₂O₃Cl: C, 50.19; H, 3.42; N, 15.96 %. IR: 3185 (-NH), 1715(CO of ester), 1665(CO of amide), 1545(NO₂), 1340(NO₂) cm⁻¹; 1H NMR: δ 10.52(br, 1H,-NH), 7.08-6.81(m, 3H, ArH), 3.88(s, 3H,-OCH₃ of ester), 4.25(s, 2H,-CH₂); MS: m/z 263(M⁺), 205(base peak).

Preparation of 1H-2, 3-dihydro-1, 4-benzodiazepin-2-one 5. N-Chloroacetyl isatin 2 (R=H; 4.46g, 0.02 mole) and hexamethylenetetramine (2.80g, 0.02 mole) were taken in t-butanol (30 mL) and the reaction mixture was refluxed for 12 hr. Progress of the reaction was checked through TLC. After completion of reaction, t-butanol was removed under reduced pressure and the solid was chromatographed over alumina (neutral) in C₆H₆: MeOH (9:2.0:0.8) as an eluant, the crude product obtained was suspended in TFA (20 mL) and stirred overnight. It was basified with dilute NaOH solution, filtered, washed with water and recrystallized from benzene to give 5 in 76%(2.42g) yield; m.p. 214-15°C(lit17, m.p. 215-17°C). Anal. Found: C, 67.47; H, 5.04; N, 17.54. Calcd for C₁₀H₉N₂O₂: C, 67.50; H, 5.00; N, 17.50 %. IR: 3180(-NH), 1670(CO of amide) cm⁻¹; 1H NMR: δ 10.55(br, 1H,-NH), 7.80-7.00(m, 4H, ArH), 8.55(m, 1H, H=C=N), 4.1(d, J =1.5 Hz, 2H,-CH₂); MS: m/z 160(M⁺).

Preparation of 1H-2, 3-dihydro-2-oxo-1, 4-benzodiazepin-4-oxide 6. A solution of 5 (1.60g,
0.01 mole) in methylene chloride (60 mL) was stirred with m-chloroperbenzoic acid (3.44 g, 0.02 mole) for 1.5 hr. The mixture was extracted with 3x25 mL 1N HCl. The extracts were washed with ether, made alkaline with ammonia and extracted with methylene chloride. The solid that was obtained on drying and evaporation of solvent was recrystallized from chloroform to give 6 in 33% (0.58 g) yield; m.p. 284°C. Anal. Found: C, 61.20; H, 4.15; N, 16.02. Calcd for C9H9N2O2: C, 61.36; H, 4.55; N, 15.90%. IR: 3410 (N-H), 1710 (CO of amide), 1260 (N-O) em -1; 1H NMR: δ 11.55 (br, 1H, -NH), 8.00-7.01 (m, 4H, ArH), 8.40 (m, 1H, H-C=N), 4.1 (d, J=1.5Hz, 2H, CH2-); MS: m/z 176 (M+), 160 (base peak).

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