A NEW STRATEGY FOR THE SYNTHESIS OF TRICYCLIC AND TETRACYCLIC SYSTEMS OF INDOLE ALKALOIDS

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Abstract

Reaction of tryptamine **1** with dimethyl -3-methoxyallylidenemalonate **2** afforded N^{β}-[4,4-bis (methoxycarbonyl)-1,3-butadienyl] tryptamine **3** which in combination with acetylchloride and pyridine in dichloromethane gave N^{β}, N^{β}-[acetyl]-[(4,4-dinethoxycarbonyl) 1,3butadienyl] tryptamine **4**. Treatment of **3** with sodium hydroxide afforded 2H[N-(3-indolyl) ethyl] 2-oxo-3-methoxy-carbonyl-1-pyridine **5**. Cyclization of **2** with trifluoroacetic acid gave methyl-2-(methoxycarbonyl) 4-(2,3,4,9-tetrahydro-1H-pyrido [3,4-b] indole-1-yle) butano-ate **6**. Heating of the latter in ethylacetate at reflux temperature afforded a new tetracyclic system methyl 4-oxo 1, 4, 6, 7, 12, 12b-hexahydro indolo [2, 3-a] quinolidine 3 carboxylate **7**.

Introduction

The area of indole alkaloids has fascinated organic chemists for the last 100 years [1]. From Historical point of view, total synthesis of reserpine by Woodward and his coworkers [2] is often cited as a model strategy in preparative organic chemistry. The first total synthesis of yohimbine by Van Tamelen *et al.* [3] also showed a high level of accomplishment meanwhile, tryptamine 1 is a key precursor for the synthesis of several clinically useful alkaloids [3-5] . It has been shown that cyclization of N - acetyl tryptamines afford spirocyclic indolines in almost quantitative yields [6]. The aim of this work is to develop a synthetic route leading to the tricyclic and tetracyclic systems derived from indoles by forming the 2,3 bond via attacking a nucleophilic center at C- 2. This approach has been exploited in several independent studies [8-11] including synthesis of strychnine by Woodward *et al.* [7]. In the present study, we report our work on the synthetic route leading to tricyclic and tetracyclic compounds derived from indole .

Keywords: Tryptamine; Indole; Alkaloids; Tricyclic; Tetracyclic

Results and Discussion

In the present work we began with attempts to condense tryptamine 1 with a compound with potential electophilic character such as 2 [13]. 3-methoxy-allylidene malonate 2 was prepared according to Corey's procedure [14] and was condensed with tryptamine 1 in the presence of pyridine in dry CH_2Cl_2 to afford N^{β}-[4,4-bis (methoxycarbonyl)-1,3-butadienyl] tryptamine 3.

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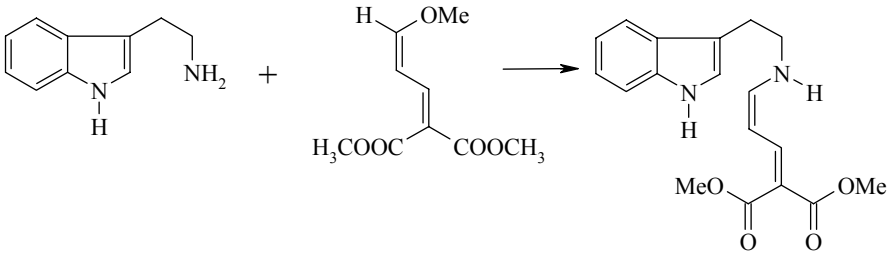
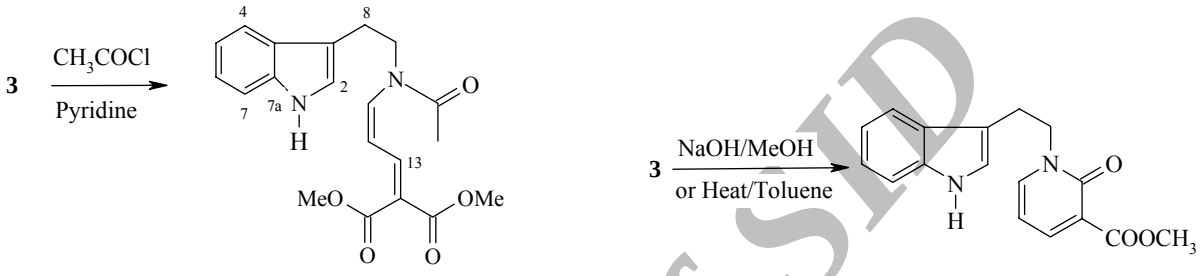
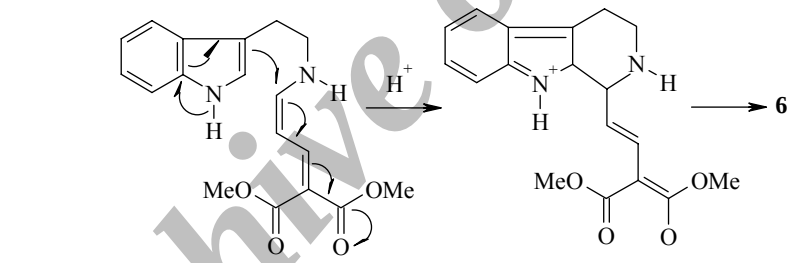


1 **2** **3**



4 **5**



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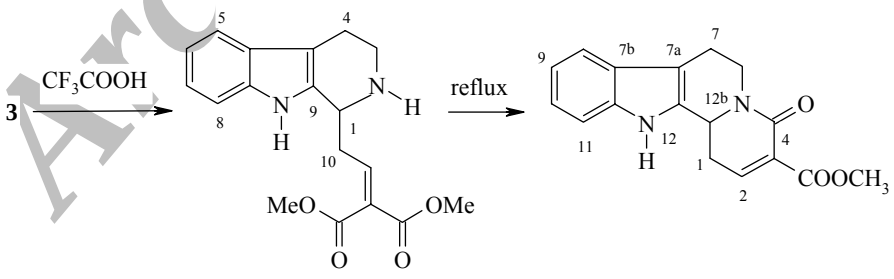

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This addition was reminiscent of the Michael type addition of amines to diethy1- 3-ethoxyallyliden-emalonate with subsequent elimination of alkoxy leading to a pyrone [13]. Compound 3 was successfully acetylated at nitrogen to give the N-acetyl derivative 4.

Compound 3 was heated in the presence of base to afford a single crystalline compound. This compound was identified as 2H[N-(3-indolyl) 2-oxo-3-methoxy-carbonyl-1-pyridine 5. In ^{1}H NMR of this compound the signal appeared only for one methoxy group, showing

the elimination of MeOH from compound 3.

To synthesize tricyclic compound from the indole derivatives we used the electrophilic activity at the indole 2-position for closure of 2,3-bond. The reagent of choice for this cyclization was trifluroacetic acid. This reaction resulted in compound 6. In the ^{1}H NMR spectrum of 6 a triplet was summarized at 6.3 ppm of 3.

When 6 was heated at reflux temperature a single crystalline compound was obtained. This compound was identified as methyl 4-oxo 1,4,6,7,12,12b-hexa-hydro indolo [2,3-a] quinolidine 3-carboxylate 7.

Experimental Section

All chemicals were purchased from Aldrich Chemical Co, unless otherwise specified. ^{1}H NMR spectra were collected at 90 and 400 MHZ. IR spectra were recorded on Perkin Elmer Spectrophotometer and elemental analyses were performed in the department of chemistry, University of Mazandaran at Babolsar.

N^{ß}-[4,4-bis(methoxycarbonyl)-1,3-butadienyl] Tryptamine (3)

Tryptamine 1 (2.4g,15 mmol) was added to a solution of 2(3.0 g, 15 mmol) and freshly distilled Toluene (75ml). The resulting solution was deoxygenated (3x) and maintained under argon at room temperature for 3.5 h. Progress of the reaction was monitored by TLC. Evaporation of the solvent, and purification with a silicagel column (EtOH: Hexane 1:1) gave a solid which on crystallization from MeOH afforded 1.97 (82%) of compound 3: mp 121-122°C: ^{1}H NMR (400 MHZ,$CDCl_3$) δ 8.3 (br.s indole NH), 7.6 (d ,1H, H-13), 7.6 (d, 1H, aromatic), 7.1-7.4 (m, 3H, aromatic), 7.0 (s, 1H, H-2), 6.9 (br.t, 1H, H-11), 6.3 (t, 1H, H-12), 5.2 (br.s,NH), 3.8 (s, 2Me Ester), 3.5 (t, 2H, H-9) , 3.1 (t, 2H, H-8), FTIR: 3558.4, 3413.8, 2947.0, 1704.9, 1591, 1556.4, 1265.2, 1176.5, 1076.2 cm^{-1}. Analysis calculated for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65. 73; H, 6.03; N, 8.50.

N^{ß} N^{ß}-[acetyl}-[(4,4-dimethoxycarbonyl)1,3-butadienyl] Tryptamine (4)

A solution of compound 3 (1.312g, 4 mmol)in dry CH_2Cl_2 (40 ml) and pyridine (0.632g , 8 mmol) was placed in a flask. A Solution of freshly distilled acetylchloride (0.471g, 6 mmol) in dry CH_2Cl_2 (5ml) was added dropwise to the above solution under nitrogen atmosphere. After the addition was complete the reaction mixture was warmed to room temperature and stirred for 6 h. After completion of the reaction (monitored by TLC) sodium hydroxide solution (0.1N) was added to PH~ 7.5. The organic layer was washed with distilled water (50ml), brine (50ml), dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized from methanol to afford 1.02g (78%) of compound 4: mp 153-4 ºC, ^{1}H NMR (100 MHZ, DMSO-d^6) δ 10.8 (s, indole NH), 8.1-7.1 (m, 7H, aromatic 5H & H-13 & H-11), 6.4 (t, 1H, H-12), 3.9 (t, 2H, H-8), 3.8 & 3.3 (2s, 6H, Me Ester), 2.9(m, 2H, H-9), 2.3 (s, 3H, Me Carbonyl), ^{13}C NMR: δ 170.1 (amid C = O); 147.8 (C-13 & C-11); 136.2 (C-7a); 127 (C-3b); 123.1 (C-6); 121.1 (C-5); 118.5 & 118.1 (C-4 & C-2); 111.5 (C-7) 110.6 (C-3a & C-14); 104.7 (C-12); 51.8 & 51.7 (Ester CH_3 & C-9); 22.3 (C-8); 21.9 (Amid-CH_3). Analysis calculated for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.98; N, 7.56. Found: C, 64.33; H, 5.83; N, 7.67

2H [N-(3 indolyl) ethyl] 2-oxo-3-methoxycarbonyl-1-pyridine(5)

Procedure 1. To a solution of Compound 3 (1.30g, 4 mmol) in dry THF (30ml) was added 2 Portion of Sodium hydroxide (0.2g) in methanol (25ml). The reaction was completed after 30 minutes (monitored by TLC) at room temperature. The solvent was evaporated to dryness to afford a solid which was crystallized from methanol to give 1.235g (95%) of compound 5.

Prcedure 2. A Solution of Compound 3 (1.30g, 4 mmol) in dry toluene (25 ml) was refluxed under nitrogen for 4 h. Evaporation of solvent gave a solid which on Crystallization from methanol to afforded 1.20 g (%92) compound 5: mp 171-172˚C ^{1}H NMR (400MHZ ,$CDCL_3$) δ 10.9(s, indole NH), 8.0(dd, H-1); 7.8 (dd, 1H, H-13), 7.6 (d, 1H, H-4), 7.3 (d, 1H, H-7), 7.1 (s, 1H, H-2), 7.1 (t, 1H, H-6), 6.986 (t, 1H, H-5), 6.2 (t, 1H, H-14), 4.2 (t, 2H, H-9), 3.8 (s, 3H, Me Eseter), 3.1 (t, 2H, H-8) ^{13}C NMR δ 165.3 (Ester C = O); 158.1 (Lactam C = O) 144.2 & 143.9 (C-11 & C-13); 136.2 (C-7a); 127.6 (C-3b); 123.1 (C-2); 121 (C-6); 119.5 (C-12); 118.3 & 118.2 (C-4 & C-5); 111.4 (C-7); 110.2 (C-3a); 103.8 (C-14); 51.6 (Ester-CH_3); 50.2 (C-9); 24.4 (C-8); FTIR 3311.5, 1722.5, 1637.4, 1546, 1271cm^{-1}. Analysis calculated for $C_{17}H_{16}$ N_2O_3: C, 68.90; H, 5.54; N, 9.45. Found: C, 68.63; H, 5.43; N, 9.25.

Methyl-2 (methoxycarbonyl)4 -(2,3,4,9-tetrahydro-1H-pyrido [3,4- b] indole-1-yle) butanoate (6)

A Solution of 3 (1.30, 4 mmol) in dry CH_2Cl_2 (40ml) was deoxygented (3x) and cooled to-5˚C and freshly distilled trifluroroacetic acid (2.30g, 20 mmol) was added dropwise. After 25 min at –5˚C the solution was allowed to warm to room temperature and was washed with H_2O (50 ml), dried ($MgSO_4$), and concentrated to yield 1.274 g (%98) of crude 6 as a pale yellow solid: mp 176˚C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.5 (s, 1H, indole NH), 7.4 (d, 1H aromatic), 7.4 (d, 1H aromatic), 7.3 (t, 1H, CH = $C(CO_2Me)_2$), 7.2 (t, 1H, aromatic), 7.1 (dt, 1H, aromatic), 5.1 (br.s, 1H, Nb-H), 3.3 (dd, 1H, H-1), 3.8 & 3.7 (2s, 6H, Me Esters), 3.6 (m, 2H, H-4), 3.4

(m, 1H,H-3eq), 3.2 (m, 1H, H-3ax), 3.1 (m, 2H,H-10). Analysis calculated for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.77; H, 6.33; N, 8.49.

Methyl 4-oxo-1,2,6,7,12,12b-hexahydro indolo [2,3-a] quinolidine-3-carboxylate (7)

A Solution of 6 (0.565 g, 2 mmol) and dry ethylacetate (50 ml) was deoxygenated (3x). This solution was heated to reflux under argon for 30 min and concentrated to give 0.56 g (%99) as a yellow orange powdery solid: mp 235˚C; ^{1}H NMR (400) MHZ, DMSO-d^6) δ 7.52 (d, 1H, aromatic), 7.44 (d, 1H, H-2), 7.36 (d, 1H, aromatic), 7.29 (br.s, 1H, indole NH), 7.10-7.22 (m, 2H, aromatic), 5.10 (dd, 1H 6 eq), 4.90 (dd ,1H, H-12b), 3.82(s, 3H, Me Ester), 3.76(dd, 1H, H-1 eq),2.95-2.83(m,3H,H-6ax & H-7), 2.52 (ddd, 1H, H-1ax) ^{13}C NMR δ 165.0(Ester C = 0), 161.3 (C-4); 144.9(C-2); 136.8(C-11a); 132.8(C-12a); 129.5(C-3); 126.4 (C-7b); 121.6 (C-10); 119.1(C-9); 118.2 (C-8); 111.416(C-11); 107.8(C-7a); 52.2 (Ester-CH3); 51.2(C-12b); 39.2(C-6); 32.1(C-1); 21.0(C-7). Analysis calculated for $C_{17}H_{16}N_2O_3$: C, 68.90, H, 5.44, N, 9.45. Found: C, 68.77, H, 5.33; N, 9.41.

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