Pergamon

Tetrahedron 55 (1999) 10915–10924

TETRAHEDRON

Synthesis of N-Substituted Pyrrole and Tetrahydroindole Derivatives from Alkenyl β-Dicarbonyl Compounds

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Received 7 April 1999; revised 4 May 1999; accepted 8 July 1999

Abstract: The iodocyclization of a series of alkenyl-substituted β-enamino esters and ketones, followed by base-promoted dehydroiodination, led to the formation of the corresponding pyrrole or tetrahydroindole derivatives. In the absence of base, the iodo-β-enamino esters **5** and **7** underwent spontaneous aromatization after dehydroiodination, furnishing the 4, 5, 6, 7-N-substituted-tetrahydroindoles **19** and **20**. All the elimination reactions proceeded smoothly, in yields ranging from 71% to 99%. Starting from the β-allyl-dimedone **21**, it was possible to prepare the oxotetrahydroindole **24**, in moderate overall yield.

Keywords: nitrogen heterocycles; enamino esters; cyclization; elimination reactions.

β-Enamino-carbonyl derivatives are useful intermediates in organic synthesis, due to their versatility in reacting both with nucleophilic and electrophilic species[1]. The reactivity and synthetic applications of these compounds are the subject of continuous studies by several research groups, as attested by the large number of recent papers[2-6]. In a previous paper[7] we described the reaction of five alkenyl-substituted β-enamino esters or ketones with iodine, which led to the corresponding iodocyclic derivatives, through an electrophilic cyclization[8]. In the same paper, we have also shown that the dehydroiodination of one of these products, namely the iodo-β-enamino ester **1a**, affords the corresponding N-benzyl pyrrole **2a**, by spontaneous aromatization of the initial elimination product (Scheme 1).

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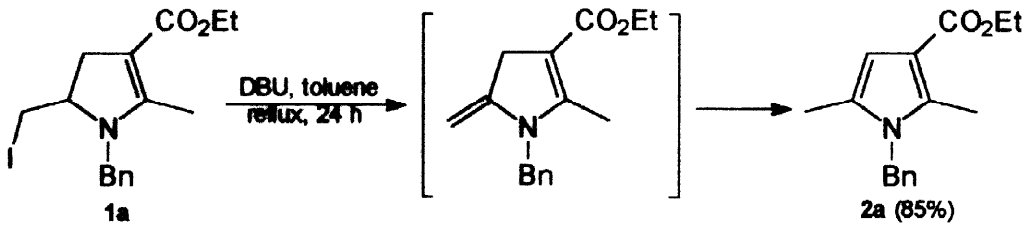
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00625-0

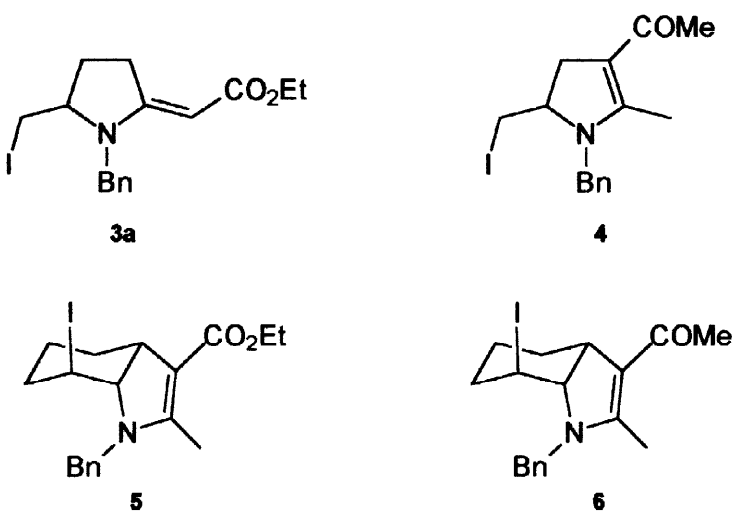
Scheme 1



In the present paper we wish to disclose our results[9] concerning the extension of the above mentioned dehydroiodination to other substrates, including those previously reported, as well as others herein described for the first time. The final products obtained by this sequence are pyrrole and tetrahydroindole derivatives, which constitute important building blocks in natural products synthesis[10].

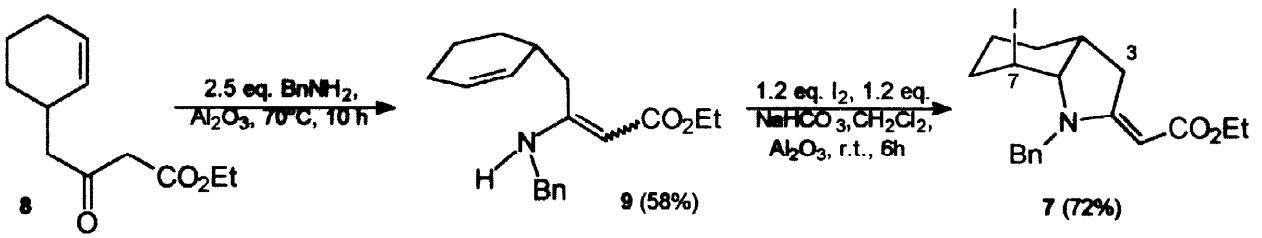
The substrates **3a**, **4**, **5** and **6** (Chart 1) were prepared as described earlier[7].

Chart 1



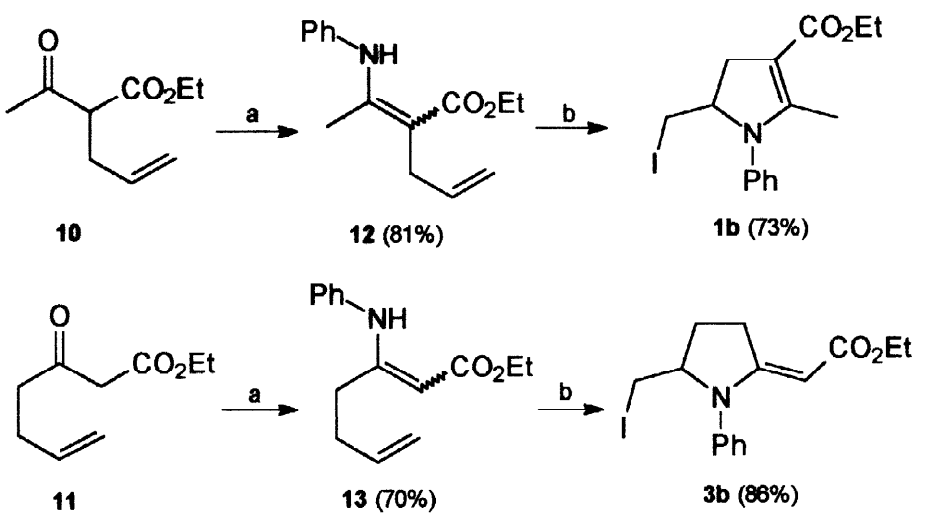
The bicyclic derivative **7** was achieved in two steps from the β-keto ester **8**, by a slight modification in the iodocyclization step (Scheme 2). The *E*-exocyclic double bond geometry in **7** was assigned on the basis of the chemical shifts of the vinylic proton[11] and of the C_3-ring methylene protons[12]. The stereostructure of **7** shown in Scheme 2 belongs to what we suppose to be the most stable conformer[13], based upon the analysis of ^{13}C and ^{1}H NMR spectra, and by analogy with the previously described bicycle **5**, whose stereostructure was recently confirmed by X-ray crystallography[14]. Particularly, H-C_7 appears as an apparent quartet (J = 5.7 Hz) at 4.40 δ, which is more consistent with an equatorial proton.

Scheme 2



In order to investigate the influence of the group attached directly to the nitrogen in the course of the iodocyclization, two N-phenyl-β-enamino esters were also prepared. Thus, condensation of the alkenyl β-keto esters **10** and **11** with aniline, under usual conditions, followed by treatment with iodine, gave rise to the desired iodocycles **1b** and **3b**, in good yield (Scheme 3).

Scheme 3

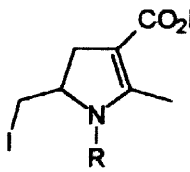
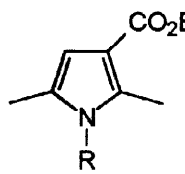
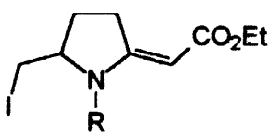
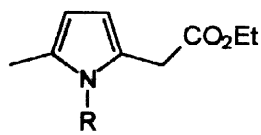
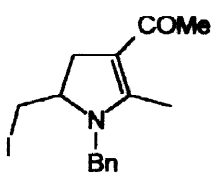
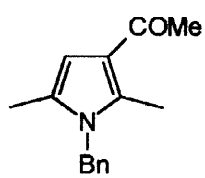
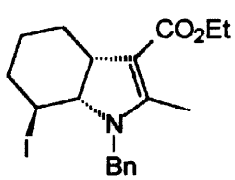
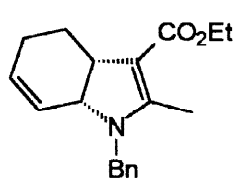
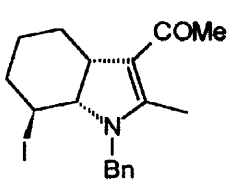
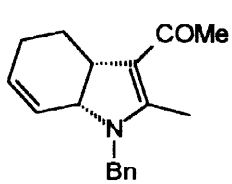
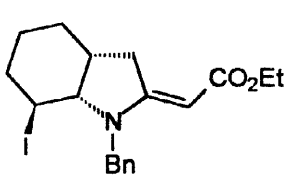
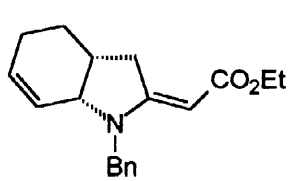


(a) 2.5 eq. aniline, Al_2O_3, 70°C (12 h for **10** and 8h for **11**)
(b) 1.1 eq. $NaHCO_3$, CH_2Cl_2, 1.1 eq. I_2, Al_2O_3, r.t. (60 min for **12** and 30 min for **13**)

The rate of the iodocyclization step increases significantly when changing from an aliphatic (24h for the N-benzylated **1a** and **3a**) to an aromatic group (30-60 min for the N-phenylated **1b** and **3b**), probably due to electronic effects. We plan to investigate further the role of other N-substituents, in order to verify this observation.

The cyclic iodo-β-enamino esters and ketones were then submitted to treatment with DBU, employing the same conditions earlier reported. Table 1 shows the results, including an improved run for substrate **1a** (cf. Scheme 1).

Table 1. Dehydroiodination of iodo-β-enamino carbonyl compounds[a]

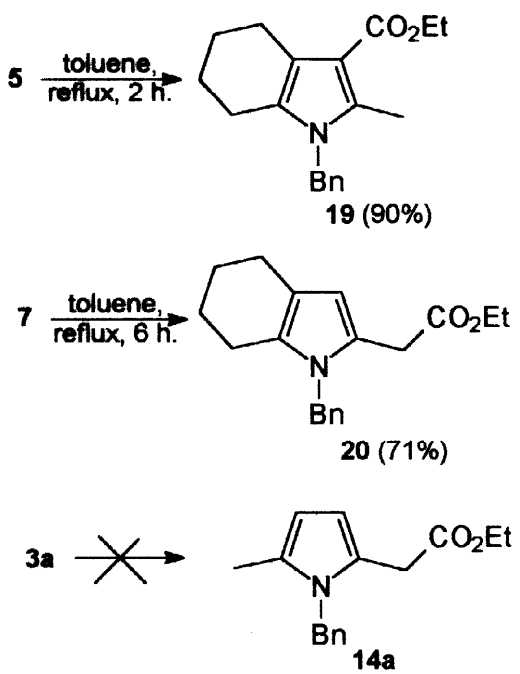
Entry	Substrate	Time	Product	Yield
1	 **1a**	16h	 **2a** (R=Bn)	93%
2	**1b**	2h	**2b** (R=Ph)	80%
3	 **3a**	4h	 **14a** (R=Bn)	99%
4	**3b**	1h	**14b** (R=Ph)	99%
5	 **4**	12h	 **15**	92%
6	 **5**	14h	 **16**	75%
7	 **6**	12h	 **17**	73%
8	 **7**	22h	 **18**	93%

[a] *2 eq of DBU, toluene, reflux.*

From Table 1, it is possible to note that the monocyclic substrates **3a** and **3b**, although bearing an exocyclic double bond, also lead to aromatic products (**14a** and **14b**), similarly to what occurs with **1** and **4**. On the other hand, the products **16-18**, originating from the secondary iodides **5-7**, do not undergo migration of the double bond. However, running the reaction of **5** and **7** in the absence of base allowed the aromatization of the system, resulting in prompt formation of products **19** and **20**[15]. Under the same conditions, **3a** failed in undergoing elimination, the starting material being recovered unchanged, even after several hours under reflux in toluene (Scheme 4).

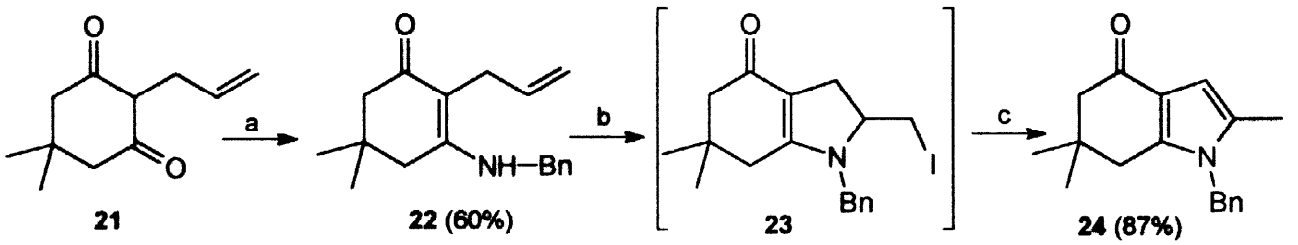
Therefore, the nature of the products seems to be strikingly dependent upon the employed conditions, the mechanism of the elimination reaction changing from E_2 (basic medium) to E_1 (absence of base). This proposal is in agreement with the lack of reactivity of the primary iodide **3a** in the absence of DBU.

Scheme 4



Finally, starting from the β-allyl-dimedone **21**, it was possible to prepare the indolone **24**, as depicted in Scheme 5. In contrast to analog **4** and **6**, the iodo-β-enamino ketone **23** proved to be very unstable, and was submitted without any purification to treatment with DBU, affording **24** in 87% overall yield from **22**. To our delight, this sequence constitutes a short and promising route for constructing oxotetrahydroindoles, which are important structural moieties[16]. Further experimentations using unsymmetrical β-diketones are planned, in order to check the scope and limitations of this approach.

Scheme 5



(a) 1 eq. $BnNH_2$, benzene, reflux, 8 h; (b) 1.2 eq. Et_3N, 1,2 eq. I_2, r.t., 24 h; (c) 2 eq. DBU, toluene, reflux, 12 h.

In conclusion, the developed methodology provides a straightforward entry into synthetically valuable functionalized nitrogen heterocycles. Moreover, depending upon the experimental conditions, it is possible to achieve different patterns of tetrahydroindole derivatives.

At present, we are investigating the extension of the reactions herein described for constructing heterocycles other than five-membered rings.

Experimental Section

General. All solvents were dried by the standard methods. Et_3N was freshly distilled from CaH_2 prior to use. NMR spectra were recorded on Bruker AC-200 and DPX-300, in $CDCl_3$. Elemental analyses were carried out in a Perkin Elmer-2400/CHM. IR spectra were recorded on a Perkin Elmer-FTIR. For column chromatography, 70-230 mesh silica gel Merck was employed. Preparation of the starting unsaturated-β-dicarbonyl compounds **8** and **11** was carried out employing the procedure described by Huckin and Weiler[17]; **10** and **21** were prepared according to *Organic Syntheses*[18] and Barrios et al.[19] procedures, respectively.

General Procedure for Preparation of the Acyclic β-Enamino Esters. Benzylamine (15 mmol) or aniline (20 mmol) was added slowly to a stirred suspension of the appropriate β-keto ester (10 mmol) in Al_2O_3 (4.0 g) and stirring was continued for 8-12 h at 70°C. The reaction mixture was then filtered and washed with CH_2Cl_2, and the filtrate was evaporated. The crude product was separated from the excess of amine and unreacted starting material by fractional distillation at reduced pressure [bp 175°C/0.30 mmHg (**9**); bp 180°C/0.30 mmHg (**12**); bp 165°C/0.30 mmHg (**13**)].

Preparation of the Acyclic β-Enamino Ketone 22. Benzylamine (10 mmol) was added to a stirred solution of **21** (10 mmol) in benzene (50 mL). Water was removed by azeotropic distillation in a Dean Stark system, by refluxing the mixture for 8 h. The solvent was evaporated and the crude product was recrystallized from benzene/hexane, giving **22** (mp 119-120°C) in 60% yield. IR (KBr)

ν_{max} 1638; 1565; 1273 cm^{-1}; ^{1}H-NMR (δ) 1.02 (s, 6H); 2.23 (s, 2H); 2.30 (s, 2H); 3.17 (d, *J* = 6.0 Hz, 2H); 4.43 (d, *J* = 6.2 Hz, 2H); 4.97-5.06 (m, 2H); 5.19 (br s, 1H); 5.65-5.80 (m, 1H); 7.20-7.40 (m, 5H); ^{13}C-NMR (δ) 27.0; 28.5; 31.9; 38.9; 46.9; 49.7; 105.5; 114.5; 126.5; 127.7; 128.9; 136.6; 138.2; 160.3; 193.7. Anal. calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 79.96; H, 8.61; N, 5.53.

General Procedure for Preparation of Cyclic Iodo-β-Enamino Esters. To a solution of the appropriate acyclic β-enamino ester (1 mmol) in anhydrous CH_2Cl_2 (15 mL) were added solid $NaHCO_3$ (1.1 mmol), Al_2O_3 (1 g) and I_2 (1.1 mmol). After stirring at room temperature for the times indicated in the schemes, the reaction mixture was extracted with ethyl acetate, washed with aqueous $NaHSO_3$, aqueous $NaHCO_3$, saturated NaCl solution, dried over $MgSO_4$, filtrated and concentrated. The crude product was purified as described below.

1-Benzyl-(*E*)-2-carbethoxymethylene-7-iodo-2,3,4,5,6,7,3a,7a-octahydroindole (7). The solid residue was recrystallized from cold ethanol, giving pure **7** (mp 93-94 °C) in 72% yield. IR (KBr) ν_{max} 1679; 1602; 1138; 1059 cm^{-1}; ^{1}H-NMR (δ) 1.22 (t, *J* = 7.1 Hz, 3H); 1.42-1.84 (m, 6H); 2.50-2.60 (m, 1H); 3.01 (dd, *J* = 17.2 and 6.5 Hz, 1H); 3.13 (ddd, *J* = 17.2, 7.2 and 1.3 Hz, 1H); 3.83 (t, *J* = 5.7 Hz, 1H); 4.06 (q, *J* = 7.1 Hz, 2H); 4.40 (q, *J* = 5.7 Hz, 1H); 4.47 (d, *J* = 16.5 Hz, 1H); 4.67 (d, *J* = 16.5 Hz, 1H); 4.75 (s, 1H); 7.17-7.35 (m, 5H); ^{13}C-NMR (δ) 14.6; 21.8; 26.5; 30.6; 34.4; 35.4; 36.1; 49.5; 58.5; 68.9; 82.2; 126.8; 127.3; 128.7; 136.5; 165.4; 169.3. Anal. calcd for $C_{19}H_{24}O_2NI$: C, 53.65; H, 5.65; N, 3.29. Found: C, 53.59; H, 5.67; N, 3.41.

1-Phenyl-2-methyl-5-(iodomethyl)-4,5-dihydropyrrole (1b). The crude product was purified by column chromatography (hexane:ethyl acetate 5:1 as eluent), giving **1b** (oil) in 73% yield. IR (film) ν_{max} 1678; 1590; 1237; 1077 cm^{-1}; ^{1}H-NMR (δ) 1.29 (t, *J* = 7.3 Hz, 3H); 2.07 (s, 3H); 2.66 (ddd, *J* = 1.5, 8.1 and 15.1 Hz, 1H); 3.06-3.21 (m, 1H); 3.13 (dd, *J* = 2.9 and 10.3 Hz); 3.25 (dd, *J* = 7.3 and 10.3 Hz); 4.17 (q, *J* = 7.3 Hz, 2H); 7.13-7.43 (m, 5H); ^{13}C-NMR (δ) 11.3; 13.8; 14.6; 35.2; 58.7; 64.2; 98.5; 126.8; 127.3; 129.4; 140.2; 157.5; 166.7. This product undergoes spontaneous elimination to **2b** in few hours, thus precluding determination of elemental analysis and/or HRMS.

1-Phenyl-(*E*)-2-carbethoxymethylene-5-iodomethylpyrrolidine (3b). The solid residue was recrystallized from cold ethanol, giving pure **3b** (mp 122-124 °C) in 86% yield. IR (KBr) ν_{max}1685; 1604; 1578; 1136 cm^{-1}; ^{1}H-NMR (δ) 1.19 (t, *J* = 7.3 Hz, 3H); 1.90-2.07 (m, 1H); 2.28-2.45 (m, 1H); 3.04 (dd, *J* = 10.2 and 6.6 Hz, 1H); 3.23 (dd, *J* = 10.2 and 2.2, 1H); 3.29-3.45 (m, 1H); 3.90-4.10 (m, 1H); 4.04 (q, *J* = 7.3 Hz, 2H); 4.54 (s, 1H); 7.22-7.47 (m, 5H); ^{13}C-NMR (δ) 10.5; 14.5; 28.1; 30.3; 58.3; 64.5; 81.7; 127.3; 127.5; 129.8; 138.7; 165.2; 168.9. Anal. calcd for $C_{15}H_{18}O_2NI$: C, 48.49; H, 4.85; N, 3.77. Found: C, 48.62; H, 4.68; N, 3.94.

General Procedure for the Dehydroiodination Reaction with Base. To a solution of the appropriate cyclic iodo-β-enamino ester or ketone (0.6 mmol) in toluene (5 mL) was added DBU (0.18 g, 1.2 mmol). The mixture was stirred at reflux for the time indicated in Table 1 (monitored by GC), and then was filtered. The filtrate was diluted with CH_2Cl_2, washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (hexane:ethyl acetate (4:1) as eluent).

1-Phenyl-2,5-dimethyl-3-carbethoxypyrrole (2b). Yield: 80% (mp 42-44 °C). IR (KBr) ν_{max} 1686; 1421; 1217; 1078 cm^{-1}; ^{1}H-NMR (δ) 1.34 (t, J = 7.3 Hz, 3H); 1.97 (s, 3H); 2.29 (s, 3H); 4.28 (q, J = 7.3 Hz, 2H); 6.37 (s, 1H); 7.15-7.54 (m, 5H); ^{13}C-NMR (δ) 12.3; 12.5; 14.5; 59.1; 107.5; 111.4; 128.1; 128.4; 128.6; 129.3; 136.1; 137.7; 165.6. Anal. calcd for $C_{15}H_{17}O_2N$: C, 73.98; H, 6.99; N, 5.75. Found: C, 73.88; H, 6.89; N, 5.66.

1-Benzyl-5-methyl-2-carbethoxymethylpyrrole (14a). Yield: 99%. Oil; IR (film) ν_{max} 1736; 1152; 1029 cm^{-1}; ^{1}H-NMR (δ) 1.16 (t, J = 7.1 Hz, 3H); 2.12 (s, 3H); 3.48 (s, 2H); 3.99 (q, J = 7.1 Hz, 2H); 5.10 (s, 2H); 5.91 (d, J = 2.9 Hz, 1H); 6.03 (d, J = 3.7 Hz, 1H); 6.82-7.31 (m, 5H); ^{13}C-NMR (δ) 12.5; 14.0; 33.2; 46.9; 60.9; 106.2; 107.9; 124.2; 125.5; 127.1; 128.7; 129.4; 138.2; 170.8.

1-Pheny-5-methyl-2-carbethoxymethylpyrrole (14b). Yield: 99%. Oil; IR (film) ν_{max} 1738; 1500; 1416; 1157 cm^{-1}; ^{1}H-NMR (δ) 1.06 (t, J = 7.3 Hz, 3H); 1.94 (s, 3H); 3.34 (s, 2H); 3.93 (q, J = 7.3 Hz, 2H); 5.98 (br, 1H); 6.01 (d, J = 2.9 Hz, 1H); 7.11-7.41 (m, 5H); ^{13}C-NMR (δ) 12.8; 14.0; 33.1; 60.5; 106.3; 107.8; 125.1; 127.9; 128.5; 129.0; 129.8; 138.3; 170.7. Anal. calcd for $C_{15}H_{17}O_2N$: C, 73.98; H, 6.99; N, 5.75. Found: C, 73.67; H, 7.34; N, 5.83.

1-Benzyl-2,5-dimethyl-3-acetylpyrrole (15)[20]. Yield: 92%. Oil; IR (film) ν_{max} 1649; 1574; 1420; 1031 cm^{-1}; ^{1}H-NMR (δ) 2.01 (s, 3H); 2.29 (s, 3H); 2.38 (s, 3H); 4.91 (s, 2H); 6.20 (s, 1H); 6.76-7.17 (m, 5H); ^{13}C-NMR (δ) 11.3; 11.7; 28.2; 46.1; 108.0; 119.9; 125.2; 127.0; 127.5; 128.5; 134.6; 136.4; 194.5.

1-Benzyl-2-methyl-3-carbethoxy-4,5,3a,7a-tetrahydroindole (16). Yield: 75%. Oil; IR (film) ν_{max} 1670; 1418; 1135; 1056 cm^{-1}; ^{1}H-NMR (δ) 1.28 (t, J = 7.0 Hz, 3H); 1.84-2.12 (m, 4H); 2.30 (s, 3H); 2.85-2.96 (m, 1H); 3.75-3.80 (m, 1H); 4.19 (q, J = 7.0 Hz, 2H); 4.29 (d, J = 16.7 Hz, 1H); 4.49 (d, J = 16.7 Hz, 1H); 5.73-5.77 (m, 1H); 6.03-6.07 (m, 1H); 7.15-7.36 (m, 5H); ^{13}C-NMR (δ) 12.5; 14.7; 23.7; 24.6; 38.6; 47.4; 58.3; 58.4; 101.8; 122.1; 126.9; 127.3; 128.8; 133.3; 137.3; 160.0; 167.3. Anal. calcd for $C_{19}H_{23}O_2N$: C, 76.72; H, 7.80; N, 4.71. Found: C, 76.47; H, 7.69; N, 4.59.

1-Benzyl-2-methyl-3-acetyl-4,5,3a,7a-tetrahydroindole (17). Yield: 94%. Oil; IR (film) ν_{max} 1643; 1414; 1181; 1020 cm^{-1}; ^{1}H-NMR (δ) 1.13-1.22 (m, 1H); 1.75-1.96 (m, 3H); 2.07 (s, 3H); 2.26 (s, 3H); 2.75-2.84 (m, 1H); 3.73-3.77 (m, 1H); 4.21 (d, J = 16.7 Hz, 1H); 4.45 (d, J = 16.7 Hz, 1H); 5.63-5.69

(m, 1H); 5.95-6.02 (m, 1H); 7.02-7.26 (m, 5H); ^{13}C-NMR (δ) 12.5; 22.9; 24.2; 27.5; 38.2; 46.1; 58.0; 112.6; 120.7; 125.9; 126.6; 127.9; 132.8; 135.8; 159.9; 190.5.

1-Benzyl-(*E*)-2-carbethoxymethylene-2,3,4,5,3a,7a-hexahydroindole (18). Yield: 93%. Oil; IR (film) ν_{max} 1682; 1452; 1128; 1042 cm^{-1}; ^{1}H-NMR (δ) 1.22 (t, *J* = 7.1 Hz, 3H); 1.48-1.76 (m, 2H); 1.93-2.19 (m, 2H); 2.40-2.47 (m, 1H); 3.06-3.14 (m, 1H); 3.22-3.31 (m, 1H); 3.88-3.91 (m, 1H); 4.06 (q, *J* = 7.1 Hz, 2H); 4.28 (d, *J* = 16.4 Hz, 1H); 4.49 (d, *J* = 16.4 Hz, 1H); 4.62 (s, 1H); 5.67-5.73 (m, 1H); 5.91-5.97 (m, 1H); 7.18-7.34 (m, 5H); ^{13}C-NMR (δ) 14.7; 22.7; 23.8; 33.1; 36.6; 47.8; 58.3; 59.5; 79.1; 123.0; 126.9; 127.2; 128.6; 132.1; 136.5; 164.5; 169.6. Anal. calcd for $C_{19}H_{23}O_2N$: C, 76.72; H, 7.80; N, 4.71. Found: C, 76.51; H, 7.65; N, 4.91.

General Procedure for the Dehydroiodination Reaction without Base. A solution of the appropriate cyclic iodo-β-enamino ester (0.6 mmol) in toluene (5 mL) was stirred at reflux for the time indicated in Scheme 3 (monitored by GC), and then was filtered. The filtrate was diluted with CH_2Cl_2, washed with aqueous $NaHSO_3$, $NaHCO_3$ and then with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate 4:1 as eluent).

1-Benzyl-2-methyl-3-carbethoxy-4,5,6,7-tetrahydroindole (19)[21]. Yield: 90%. Oil; ^{1}H-NMR (δ) 1.33 (t, *J* = 7.1 Hz, 3H); 1.63-1.80 (m, 4H); 2.32-2.42 (m, 2H); 2.44 (s, 3H); 2.70-2.80 (m, 2H); 4.25 (q, *J* = 7.1 Hz, 2H); 4.97 (s, 2H); 6.88-7.30 (m, 5H); ^{13}C-NMR (δ) 10.2; 13.5; 20.8; 22.0; 22.5; 22.6; 45.3; 57.9; 108.6; 117.5; 124.6; 126.2; 126.7; 127.2; 127.7; 128.0; 133.9; 136.3; 165.4.

1-Benzyl-2-carbethoxymethyl-4,5,6,7-tetrahydroindole (20). Yield: 71%. Oil; ^{1}H-NMR (δ) 1.17 (t, *J* = 7.1 Hz, 3H); 1.67-1.84 (m, 4H); 2.35-2.43 (m, 2H); 2.48-2.53 (m, 2H); 3.47 (s, 2H); 4.00 (q, *J* = 7.1 Hz, 2H); 5.03 (s, 2H); 5.91 (s, 1H); 6.86-7.28 (m, 5H); ^{13}C-NMR (δ) 14.1; 22.1; 23.1; 23.4; 23.7; 32.9; 46.6; 60.9; 107.6; 116.9; 123.1; 125.8; 127.0; 128.6; 138.6; 170.9. Anal. calcd for $C_{19}H_{23}O_2N$: C, 76.72; H, 7.80; N, 4.71. Found: C, 76.67; H, 7.72; N, 4.67.

Preparation of 1-Benzyl-2,6,6-trimethyl-6,7-dihydro-4(*5H*)-indolone (24)[22]. To a solution of **22** (1 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (1.2 mmol) and I_2 (1.2 mmol). After stirring at room temperature for 24 h, the reaction mixture was extracted with ethyl acetate, washed with aqueous $NaHSO_3$, with NaCl solution, dried over $MgSO_4$, filtered and concentrated. The crude product was diluted in toluene (10 mL) and DBU (0.3 g, 2 mmol) was added. After stirring at reflux for 12 h, the mixture was filtered and submitted to the same work-up outlined above, giving **24** in 86% overall yield. IR (KBr) ν_{max} 1653; 1449; 1143 cm^{-1};^{1}H-NMR (δ) 1.07 (s, 6H); 2.13 (s, 3H); 2.33 (s, 2H); 2.50 (s, 2H); 5.02 (s, 2H); 6.33 (s, 1H); 6.89-7.33 (m, 5H); ^{13}C-NMR (δ) 12.0; 28.6; 35.5; 36.0; 47.0; 51.8; 103.5; 118.7; 125.5; 127.5; 128.9; 130.9; 136.7; 142.8; 193.5.

Acknowledgments

Financial supporting from FAPESP, CNPq and CAPES are gratefully acknowledged. We are indebted to Luiz F. Silva Jr. and Tiago O. Vieira for fruitful discussions.

References and Notes

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