A New and Efficient Approach to Cyclic β-Enamino Esters and β-Enamino Ketones by Iodine-Promoted Cyclization

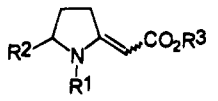
Helena M. C. Ferraz,*,† Eliseu O. de Oliveira,† M. Elena Payret-Arrua,† and Carlos A. Brandt‡

Instituto de Química, Universidade de São Paulo, C.P. 26.077, S. Paulo, 05599-970, SP, Brazil, and Instituto Butantan, S. Paulo, SP, Brazil

Received May 8, 1995

The development of new methods for preparing nitrogen five-membered rings, such as pyrrolidine and pyrrole derivatives,[1] continues to be an active research area, since they are useful intermediates for the synthesis of many natural products.

Cyclic β-enamino esters and ketones are the subject of continuous synthetic studies, as attested by a number of recent papers[2–6] dealing with reactivity and synthetic applications of these compounds. In particular, the exocyclic β-enamino ester of general formula **1**[7] has found widespread application in the synthesis of several alkaloids, such as pyrroloindoloquinones,[5,8,9] anatoxin-a,[10] camptothecin analogues,[11] and other pyrrolizidine[12] and indolizidine systems.[13,14]

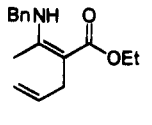
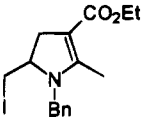
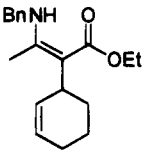
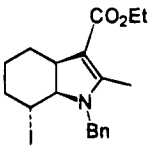
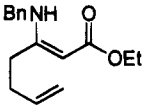
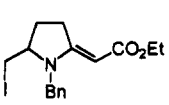
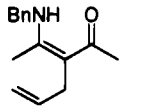
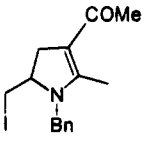
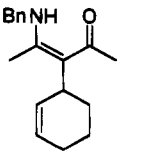
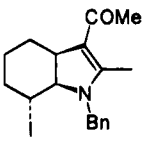


1 (R^1=H, alkyl; R^2=H, CO_2t-Bu; R^3=Me, Et, t-Bu)

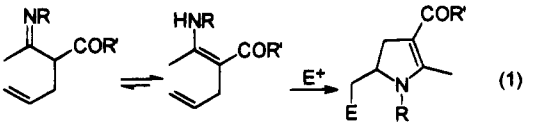
In this paper we wish to report an efficient approach to nitrogen heterocycles, consisting of a direct iodine-promoted cyclization of easily accessible acyclic alkenyl-substituted β-enamino esters and ketones. The products are cyclic β-enamino esters and ketones, and the above mentioned structural moiety **1** is represented in our series of examples by its analogous iodo-β-enamino ester **14** (see Table 1).

The basic strategy for the cyclization reactions exploits the imine–enamine tautomeric equilibrium, where the enamine form predominates (see Scheme 1). To our knowledge, these are the first examples of such an electrophile-promoted N-cyclization of β-enamino compounds. Similar reactions involving other nitrogen nucleophiles were already described.[15]

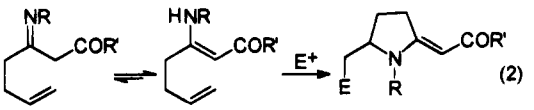
Table 1. Synthesis of Cyclic β-Enamino Esters 12–14 and β-Enamino Ketones 15 and 16

entry	substrate	product	yield (%)
1	 **7**	 **12**	84
2	 **8**	 **13**	84
3	 **9**	 **14**	78
4	 **10**	 **15**	60
5	 **11**	 **16**	72

Scheme 1



(1)



(2)

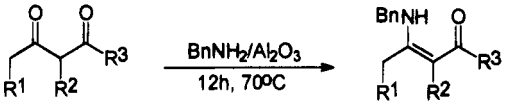
The usual preparation of enamines involves the reaction of the carbonyl compound with an amine in an aromatic hydrocarbon solvent, with azeotropic removal of water. In this work, we have prepared the acyclic β-enamino esters **7–9** and β-enamino ketones **10** and **11** by the reaction of the dicarbonyl compounds with benzylamine in the presence of neutral aluminum oxide,

† Universidade de São Paulo.
‡ Instituto Butantan.

(1) Bean, G. P. The Synthesis of 1*H*-Pyrroles. In *Heterocyclic Compounds, Vol 48, Part 1 "Pyrroles"*; Jones, R. A., Ed.; Interscience Publishers: New York, 1990; Ch. 2; p 105–294.
(2) Fasseur, D.; Cauliez, P.; Couturier, D.; Rigo, B.; Defretin, S. *J. Heterocycl. Chem.* **1994**, *31*, 829.
(3) Bartoli, G.; Bosco, M.; Dalpozzo, R.; De Nino, A.; Palmieri, G. *Tetrahedron* **1994**, *50*, 9831, and refs cited therein.
(4) Brunerie, P.; Célérier, J.-P.; Huché, M.; Lhommet, G. *Synthesis* **1985**, 735.
(5) Murphy, W. S.; O'Sullivan, P. J. *Tetrahedron Lett.* **1992**, *33*, 531.
(6) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613.
(7) Roth, W.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(8) Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.* **1983**, *105*, 2859.
(9) Coates, R. M.; MacManus, P. A. *J. Org. Chem.* **1982**, *47*, 4822.
(10) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.
(11) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1974**, *39*, 3430.
(12) Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.* **1978**, *43*, 4662.
(13) Célérier, J. P.; Eskénazi, C.; Lhommet, G.; Maitte, P. *J. Heterocycl. Chem.* **1979**, *16*, 953.
(14) Howard, A. S.; Gerrans, G. C.; Michael; J. P. *J. Org. Chem.* **1980**, *45*, 1713.
(15) Engman, L. *J. Org. Chem.* **1993**, *58*, 2394, and refs cited therein.

0022-3263/95/1960-7357$09.00/0

Scheme 2



2	(R^1=H; R^2=allyl; R^3=OEt)	**7**	81%
3	(R^1=H;R^2=2-cyclohexenyl;R^3=OEt)	**8**	72%
4	(R^1=allyl; R^2=H; R^3=OEt)	**9**	63%
5	(R^1=H; R^2=allyl; R^3=Me)	**10**	70%
6	(R^1=H;R^2=2-cyclohexenyl;R^3=Me)	**11**	78%

following an improved method developed by Braibante et al.[16] By this procedure, the products can be separated easily from the excess benzylamine and are sufficiently pure for further reactions (Scheme 2).

The starting alkenyl-substituted β-dicarbonyl compounds **2**–**6** were obtained from ethyl acetoacetate or acetylacetone, by known procedures.[17–19]

The β-enamino esters **7**–**9** were cyclized smoothly by treatment with iodine, in the presence of anhydrous sodium hydrogen carbonate. On the other hand, cyclization of the β-enamino ketones **10** and **11** was best carried out by changing the base from bicarbonate to triethylamine (both the conditions involve kinetic control). The cyclic products **12**–**16** were formed in moderate to good yields, and in a highly regioselective manner (Table 1).

The *E* exocyclic double bond geometry in **14** was assigned on the basis of the chemical shifts of the vinylic proton[10] and of the C3-ring methylene protons,[8] in the 200 MHz ^{1}H-NMR spectra.

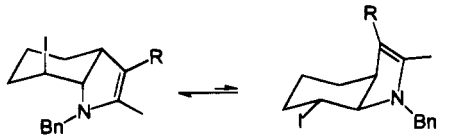
The bicyclic products **13** and **16** exhibit *cis*-fused rings, as a consequence of the mechanism of the iodocyclization reaction, which is believed to proceed *via* a kinetically controlled *trans*-diaxial addition to the double bond.[20–22]

To aid in the interpretation of NMR spectra, we also calculated minimum energy conformations for these products using MMX.[23] The results of molecular mechanics calculations showed that in the most stable conformers the iodine atom occupies the axial position. In fact, ^{1}H and ^{13}C NMR spectra are consistent with the existence of only **13a** and **16a** (Scheme 3).

In order to check the potentiality of the cyclic iodo-β-enamino derivatives as precursors for the pyrrole nucleus, compound **12** was treated with DBU, resulting in prompt formation of the 2,3,5-trisubstituted *N*-benzylpyrrole **17** (Scheme 4). The extension of this dehydroiodination to other substrates is under way.

In conclusion, the developed methodology provides a simple and efficient entry into synthetically valuable cyclic β-enamino esters and ketones and can also be employed for the synthesis of pyrrole derivatives.

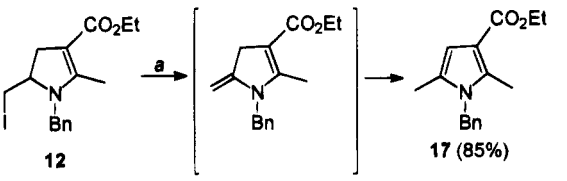
Scheme 3



13a (R=CO_2Et) **13b** (R=CO_2Et)

16a (R=COMe) **16b** (R=COMe)

Scheme 4



12 **17** (85%)

[a] DBU, toluene; reflux, 24h

Experimental Section

General. Melting points are uncorrected. Elemental analyses were performed by USP-Instituto de Química. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively, in $CDCl_3$, on a Bruker AC-200 spectrometer. All solvents were dried by the standard methods. Et_3N was freshly distilled from CaH_2 prior to use. For column chromatography, 70–230 mesh silica gel Merck was employed. Preparation of the starting α-alkenyl-β-keto esters **2** and **3**[17] and α-alkenyl-β-diketones **5** and **6**[18] was carried out according to *Organic Synthesis* procedures.[17,18] For the γ-alkenyl-β-keto ester **4** was employed the procedure of Huckin and Weiler.[19]

General Procedure for Preparation of the Acyclic β-Enamino Esters and Ketones (7–11). Benzylamine (15 mmol) was added slowly to a stirred suspension of the β-dicarbonyl compound (10 mmol) in Al_2O_3 (4.0 g), and stirring was continued for 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 benzylamine and unreacted starting material by fractional distillation at reduced pressure [bp 130 °C/0.15 mmHg (**7**); 185 °C/0.10 mmHg (**8**); 120 °C/0.10 mmHg (**9**); 125 °C/0.30 mmHg (**10**); 150 °C/0.30 mmHg (**11**)]. The products were characterized by IR, ^{1}H-NMR, and ^{13}C-NMR and were used in the next step without further purification.

General Procedure for Preparation of Cyclic β-Enamino Esters (12–14). To a solution of the acyclic β-enamino ester (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL) were added solid $NaHCO_3$ (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. The combined organic layers were washed with aqueous sodium hydrogen sulfite and then with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (hexane:ethyl acetate (1:1) as eluent). Analytical samples of **13** and **14** were obtained by recrystallization from light petroleum ether, but several efforts to recrystallize **12** have failed.

1-Benzyl-2-methyl-3-carbethoxy-5-(iodomethyl)-4,5-dihydropyrrole (12): oil; ^{1}H-NMR (δ) 1.27 (t, J = 7.1 Hz, 3H); 2.29 (s, 3H); 2.53 (dd, J = 7.2 and 15.1 Hz, 1H); 3.04 (dd, J = 11.2 and 15.1 Hz, 1H); 3.1–3.2 (m, 2H); 3.54–3.67 (m, 1H); 4.15 (q, 7.1 Hz, 2H); 4.20–4.56 (q AB J = 16.5 Hz, 2H); 7.14–7.35 (m, 5H); ^{13}C-NMR (δ) 10.9; 12.3; 14.6; 35.2; 47.9; 58.6; 60.7; 95.7; 126.7; 127.5; 128.8; 137.1; 159.6; 166.9.

1-Benzyl-2-methyl-3-carbethoxy-7-iodo-4,5-6,7-3a,7a-Hexahydroindole (13): mp 89–90 °C; ^{1}H-NMR (δ) 1.0–2.0 (m, 6H); 1.28 (t, J = 7.1 Hz, 3H); 2.28 (s, 3H); 3.07–3.13 (m, 1H); 3.73 (br d, J = 7.4 Hz, 1H); 4.15 (q, J = 7.1 Hz, 2H); 4.23–4.43 (q AB, J = 16.8 Hz, 2H); 4.74 (br s, 1H); 7.16–7.38 (m, 5H);

(16) Braibante; M. E. F.; Braibante, H. T. S.; Salvatore, S. J. S. A. *Quím. Nova* **1990**, *13*, 67.
(17) Marvel, C. S.; Hager, F. D. *Organic Syntheses*; Wiley: New York, 1948; Vol. 1, p 248.
(18) Johnson, A. W.; Markhan, E.; Price, R. *Org. Synth.* **1965**, *42*, 75.
(19) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(20) Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611.
(21) Still, W. C.; Schneider, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 948.
(22) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.
(23) Molecular mechanics calculations were performed with software PC Model 4.0. **13a**: $\Delta H_f°$ = −25.63 kcal/mol; SE (strain energy) = +23.86; **13b**: $\Delta H_f°$ = +62.77 kcal/mol; SE = +112.25 kcal; $\Delta\Delta H_f°$ (**13b**−**13a**) = +88.40; ΔSE (**13b**−**13a**) = +88.39. **16a**: $\Delta H_f°$ = +23.82 kcal/mol; SE = +23.10 kcal; **16b**: $\Delta H_f°$ = +114.37 kcal/mol; SE = +113.65 kcal; $\Delta\Delta H_f°$ (**16b**−**16a**) = +90.55; ΔSE (**16b**−**16a**) = +90.55.

^{13}C-NMR (δ) 12.9; 14.6; 20.1; 28.7; 29.9; 31.4; 36.6; 48.7; 58.8; 69.6; 108.3; 126.8; 127.4; 128.7; 137.1; 159.8; 166.7. Anal. Calcd for $C_{19}H_{24}O_2NI$: C, 53.66; H, 5.69; N, 3.29. Found: C, 53.68; H, 5.72; N, 3.31.

1-Benzyl-(*E*)-2-(carbethoxymethylene)-5-(iodomethyl)-pyrrolidine (14): mp 83–84 °C; ^{1}H-NMR (δ) 1.22 (t, J = 7.1 Hz, 3H); 1.83–1.99 (m, 1H); 2.11–2.31 (m, 1H); 3.08 (dd, J = 10.3 and 8.0 Hz, 1H); 3.22–3.31 (m, 3H); 3.62–3.73 (m, 1H); 4.07 (q, J = 7.1 Hz, 2H); 4.21–4.56 (q AB, J = 16.5 Hz, 2H); 4.68 (br s, 1H); 7.15–7.38 (m, 5H); ^{13}C-NMR (δ) 9.0; 14.6; 27.9; 30.3; 48.1; 58.5; 63.4; 80.3; 126.9; 127.6; 128.8; 135.7; 165.0; 169.2. Anal. Calcd for $C_{16}H_{20}O_2NI$: C, 49.88; H, 5.23; N, 3.64. Found: C, 50.10; H, 5.19; N, 3.55.

General Procedure for Preparation of Cyclic β-Enamino Ketones 15 and 16. To a solution of the acyclic β-enamino ketone (1.0 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 submitted to the same procedure given above. Efforts to recrystallize **15** have failed, while an analytical sample of **16** was obtained by recrystallization from light petroleum ether.

1-Benzyl-2-methyl-3-acetyl-5-(iodomethyl)-4,5-dihydropyrrole (15): oil; ^{1}H NMR (δ) 2.11 (s, 3H); 2.36 (s, 3H); 2.60 (dd, J = 6.8 and 15.2 Hz, 1H); 3.0–3.2 (m, 3H); 3.6–3.7 (m, 1H); 4.22–4.62 (q AB, J = 16.8 Hz, 2H); 7.1–7.4 (m, 5H); ^{13}C (δ) 10.6; 13.0; 29.4; 35.9; 47.4; 60.7; 106.2; 126.6; 127.8; 128.8; 136.3; 160.0; 192.4.

1-Benzyl-2-methyl-3-acetyl-7-iodo-4,5,6,7,3a,7a-hexahydroindole (16): mp 108–109 °C; ^{1}H NMR (δ) 2.09 (s, 3H); 2.27 (s, 3H); 1.0–1.9 (m, 6H); 2.96–3.08 (m, 1H); 3.71 (br d, J = 7.1 Hz, 1H); 4.29 (s, 2H); 4.71 (br s, 1H); 7.1–7.3 (m, 5H); ^{13}C NMR (δ) 13.6; 19.8; 28.5; 28.9; 29.0; 30.8; 36.9; 47.9; 69.5; 116.7; 126.6; 127.4; 128.7; 136.2; 160.1; 192.7. Anal. Calcd for $C_{18}H_{22}ONI$: C, 54.69; H, 5.61; N, 3.54. Found: C, 54.80; H, 5.70; N, 3.56.

Preparation of 1-Benzyl-2,5-dimethyl-3-carbethoxypyrrole (17). To a solution of **12** (0.23 g, 0.6 mmol) in toluene (5 mL) was added DBU (0.18 g, 1.2 mmol). After being stirred at reflux for 24 h, the mixture was filtered. The filtrate was diluted with CH_2Cl_2, washed with saturated NaCl solution and dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel (hexane:ethyl acetate (3:1) as eluent), giving 0.13 g (85%) of pure **17**, as an oil. IR (film) ν_{max} 1701, 1692, 1606, 1581 cm^{-1}; ^{1}H-NMR (δ) 1.29 (t, J = 7.1 Hz, 3H); 2.09 (s, 3H); 2.45 (s, 3H); 4.26 (q, J = 7.1 Hz, 2H); 5.01 (s, 2H); 6.35 (s, 1H); 6.85–7.32 (m, 5H); ^{13}C-NMR (δ) 11.1; 11.9; 14.4; 46.6; 59.0; 107.6; 111.0; 125.4; 127.2; 127.8; 128.7; 135.3; 136.9; 165.5.

Acknowledgment. We thank FAPESP and CNPq for financial support, and Prof. Nicola Petragnani and Dr. Adrian M. Pohlit for helpful discussions.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **7**–**17** and DEPT and HETCORR spectra of **16** are available (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9508560