INDIRECT ELECTROREDUCTIVE CYCLIZATION FOR SYNTHESES OF KEY INTERMEDIATES OF SEVERAL INDOLE AND IPECAC ALKALOIDS

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Indirect electroreductive cyclization of η-bromo-α,β-unsaturated esters **1** - **6** using Co(III) or Ni(II) complex as an electron-transfer catalyst provided the six membered compounds **7** - **12**, which are useful synthetic intermediates of several indole and ipecac alkaloids.

KEY WORDS indirect electroreductive cyclization; alkaloid synthesis; VB_{12a}; Ni(II) complex; electron-transfer catalyst

It has been proven by a number of examples that radical cyclization is a highly versatile and often indispensable method.[1,2] Recently, we synthesized several alkaloids employing radical cyclization initiated by the use of Bu_3SnH or $(TMS)_3SiH$ in the presence of AIBN as the key step.[3-6] However, these chemical methods had the following drawbacks: (1) high toxicity of expensive reagents, (2) difficulty in purifying products from stuffs due to reagents, (3) the requirement of high diluted reaction conditions. In the hope of finding a practical procedure, we have studied the indirect electroreductive cyclization mediated by cobalt(III) and nickel(II) complexes, and wish to report successful results.

Cyclization of various η-bromo-α,β-unsaturated esters forming six membered rings was examined utilizing indirect electroreduction, and the results are summarized in Table I. Reactions were carried out in DMF containing supporting electrolyte (Et_4NClO_4; 0.1 M), halide as the substrate of reaction, proton source (NH_4ClO_4; 2 eq based on the halide) and vitamin B_{12a}[7] (0.1 eq for Method A) or the Ni(II) catalyst **13**[8,9] (0.5 eq for Method B) at -1.2 V vs. Ag/AgCl using a graphite electrode as the cathode in an H-shaped divided cell under N_2 atmosphere with mechanical stirring.

Treatment of the fumaric acid ester **1** under both conditions provided lactones **7**[3] as a 1 : 1 mixture of two stereoisomers in poor yields (Entries 1 and 2). A considerable mixture of polymers formed by reductive coupling between the electron-deficient olefinic carbons was produced by electrolysis. The coupling reaction was suppressed in the cases of the amide **2**[3] (Entries 3 and 4) and the hydroxycrotonic acid derivatives **3**[10] and **4**[10] (Entries 5 - 8). A diastereoisomeric mixture of lactams **8** was obtained in 37% (Entry 3) or 32% yield (Entry 4). The ratio of the two isomers was not determined by NMR spectroscopy because of rotational isomerism. The optically active indole alkaloid, tacamonine, had been synthesized starting with **8** in three steps.[3]

The 4-fluorophenyl ester **4** was subjected to cyclization reaction (Entries 7 and 8) in the hope of effecting a Michael type addition, but production of lactones **10** was not improved in comparison with ethyl ester **9** (Entries 5 and 6). Lactones **9** and **10** were obtained as about 2 : 1 mixtures of two stereoisomers in all cases.

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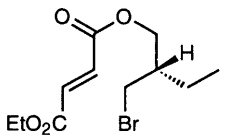
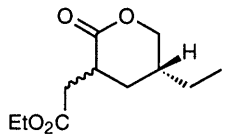
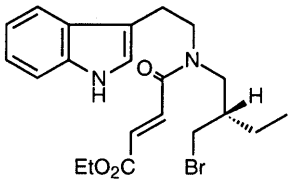
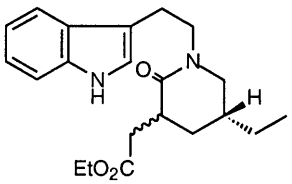
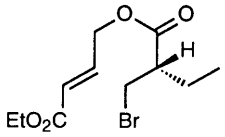
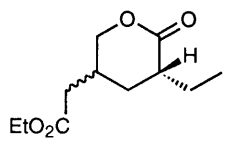
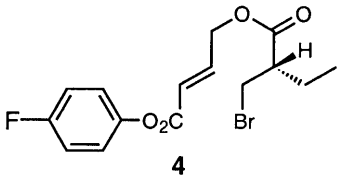
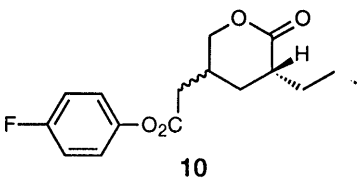
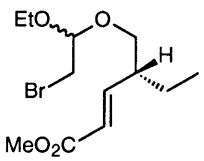
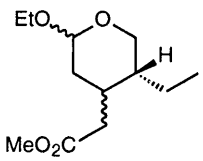
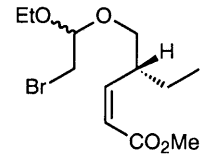
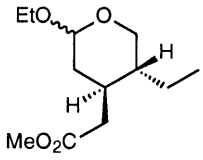
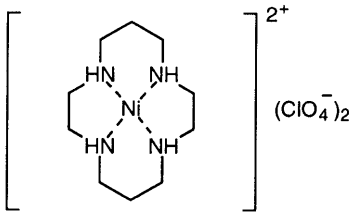
Table I. Indirect Electroreductive Cyclization Forming Six-Membered Compounds

Entry	Substrates	Products	Method [a]	Yield (%)
1			A	15
2			B	21
	1	**7**		
3			A	37
4			B	32
	2	**8**		
5			A	45
6			B	39
	3	**9**		
7			A	39
8			B	40
	4	**10**		
9			A	64
10			B	74
	5	**11**		
11			A	66
12			B	86
	6	**12**		

a) Method A: e (-1.2 V), VB_{12a}, NH_4ClO_4, 0.1 M Et_4NClO_4 in DMF; Method B: e (-1.2 V) , Ni(II) complex **13**, NH_4ClO_4, 0.1 M Et_4NClO_4 in DMF.



13

Cyclization of (*E*)-esters **5**, carried out under both conditions, gave a 4 : 1 mixture of *trans*- and *cis*-substituted tetrahydropyrans **11**[4] in 64 and 74% yields, respectively (Entries 9 and 10). On the other hand, the *trans*-substituted compounds **12** were stereoselectively produced in 66 and 86% yields in a highly stereoselective manner by the indirect electroreductive cyclization of (*Z*)-esters **6** using both methods (Entries 11 and 12). The exclusive formation of the *trans*-isomers **12** from (*Z*)-esters **6** was previously explained in term of the least 1,3-allylic strain.[4] The *trans*-substituted cyclic acetals **12** had been correlated with (-)-protoemetine,[4] (-)-protoemetinol,[4] (-)-emetine,[4] (-)-tubulosine,[4] (-)-dihydrocorynantheol,[5] dihydroantirhine,[6] and quinine alkaloids.[6]

It was further demonstrated that cyclizations could be carried out at a higher concentration, 5 w/v %; cf. 0.1 and 1 w/v % for radical cyclizations using Bu_3SnH and $(TMS)_3SiH$, respectively.[3] On the basis of the above observations, the indirect electroreductive cyclization using Co(III) or Ni(II) as an electron-transfer catalyst would provide a useful methodology for preparation of natural products and medicinally important compounds.

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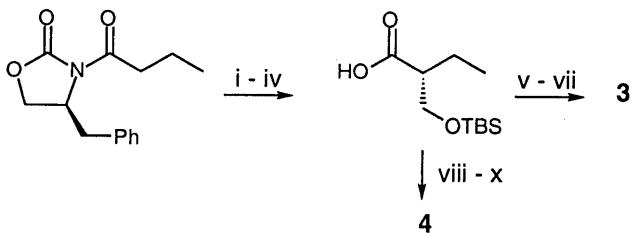
10) Esters **3** and **4** were prepared as follows.



Reagents; (i) $TiCl_4$, Et_3N, $BnOCH_2Cl$ (77%; > 99% de); (ii) H_2, Pd-C (100%); (iii) TBSCl, Et_3N, DMAP (100%); (iv) 30% H_2O_2, LiOH (97%); (v) $EtO_2CCH{=}CHCH_2OH$, DCC, DMAP (100%); (vi) dil. AcOH (96%); (vii) CBr_4, PPh_3 (95%); (viii) 4-F-$C_6H_4O_2CCH{=}CHCH_2OH$, DCC, DMAP (100%); (ix) dil. AcOH (100%); (x) CBr_4, PPh_3 (84%).

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