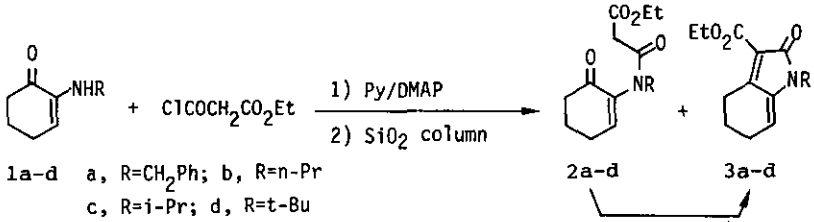
SYNTHESIS OF α,β-UNSATURATED γ-BUTYROLACTAMS BY KNOEVENAGEL CONDENSATION

Masazumi Ikeda,* Takamasa Uchino, Kazumi Maruyama, and Ayami Sato
Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Abstract— When 2-alkylaminocyclohex-2-enones **1a-d** were allowed to react with ethyl chloroformylacetate in the presence of pyridine and 4-(dimethylamino)pyridine, the carbamoylacetates **2a-d** and the 2H-indol-2-ones **3a-d** were obtained. Upon treating with ammonium acetate, **2a-d** were converted into **3a-d**. Reaction of **1a** and **1c** with cyanoacetyl chloride gave only the 1H-indol-2-ones **6a,c**. This reaction was extended to the synthesis of the erythrinan skeleton.

We have been interested in the synthesis of γ-butyrolactams to develop a new route to a variety of alkaloids.[1] Here we report a new entry to α,β-unsaturated γ-butyrolactams using a Knoevenagel condensation.[2]

2-Benzylaminocyclohex-2-enone (**1a**)[3] was allowed to react with ethyl chloroformylacetate in benzene in the presence of pyridine and 4-(dimethylamino)pyridine (DMAP) at room temperature,[4] followed by passing through a silica gel column to

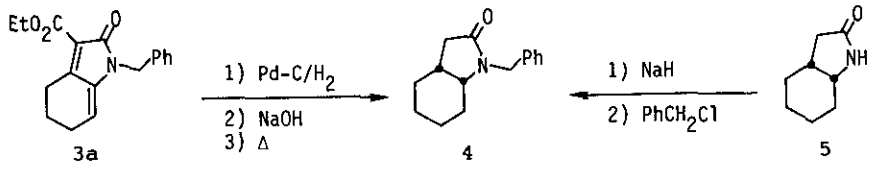


1a-d a, R=CH_2Ph; b, R=n-Pr; c, R=i-Pr; d, R=t-Bu

2a-d **3a-d**

give two products, the carbamoylacetate **2a** (37%) and the 1,4,5,6-tetrahydro-2H-indol-2-one **3a** (35%).[5] The former compound was transformed into the latter either by passing through a silica gel column (AcOEt-hexane=1:2) several times or, more conveniently, by treatment with ammonium acetate in ethanol at room temperature for 3 h. The structures of **2a** and **3a** were deduced from their spectroscopic evidence.[6] The structure **3a** was further confirmed by catalytic hydrogenation followed by alkaline hydrolysis and decarboxylation to cis-1-benzyloctahydro-2H-

indol-2-one (**4**). An authentic sample of **4** was synthesized from known cis-octahydro-2H-indol-2-one (**5**).[7]



3a **4** **5**

Similarly, the reaction of the aminoketones **1b-d**[3] with ethyl chloroformylacetate gave **2b-d** and **3b-d** in variable yields. The carbamoylacetates **2b-d** were converted by treatment with ammonium acetate in ethanol into the 2H-indol-2-ones **3b-d**. These results are summarized in Table.

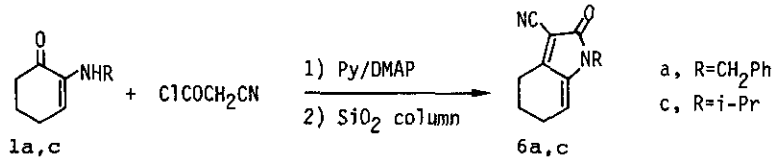
Table. Synthesis of the carbamoylacetates **2a-d** and the 2H-indol-2-ones **3a-d**

		Isolated Yield (%)		
	R	**2**[a]	**3**[a]	**2**→**3**[b]
a	CH_2Ph	37	35	72
b	n-Pr	36	34	72
c	i-Pr	31	31	60
d	tert-Bu	53	32	69

a) Ethyl chloroformylacetate (0.19 ml, 1.5 mmol) was added dropwise at 0°C to a mixture of pyridine (0.24 ml), DMAP (37 mg), and **1** (1 mmol) in benzene (5 ml). The reaction mixture was stirred at room temperature overnight. Isolated yields after chromatography under pressure (silica gel: *AcOEt-hexane*=1:2) were shown in the Table.

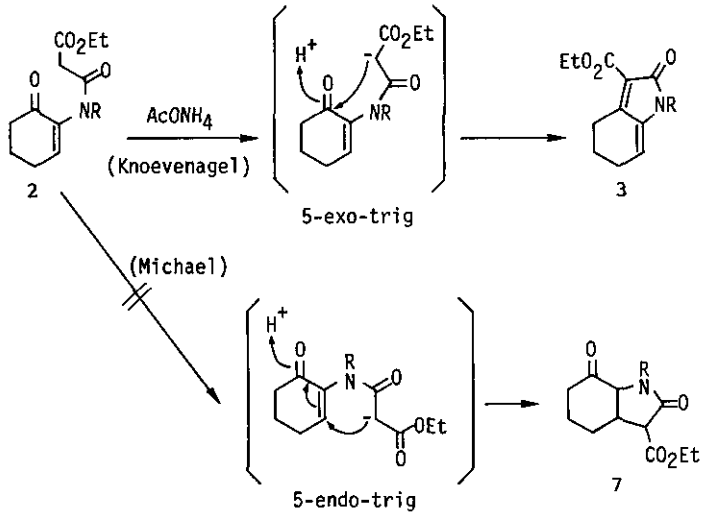
b) A mixture of **2** (1 mmol) and ammonium acetate (193 mg, 2.5 mmol) in ethanol (5 ml) was stirred at room temperature for 3h to 3 days until the starting material disappeared.

Similar treatment of **1a,c** with cyanoacetyl chloride gave only the cyclized products **6a**, mp 101-102°C, and **6c**, mp 135-136°C, in 16 and 32% yields, respectively. The low yields may be, in part, due to instability of cyanoacetyl chloride.

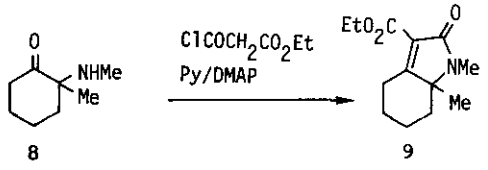


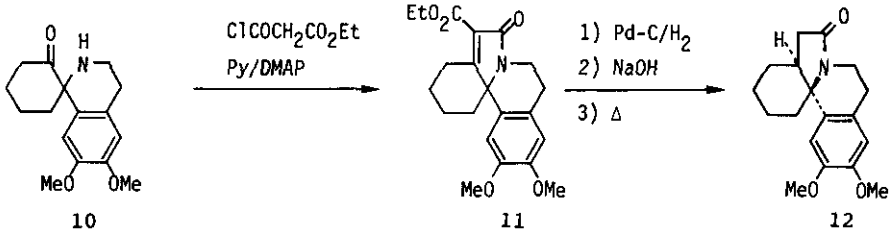
1a,c **6a,c**

For the ring-closure of the carbamoylacetates 2, there are two possibilities, the intramolecular Knoevenagel condensation (5-exo-trig) and the intramolecular Michael addition (5-endo-trig). According to the Baldwin's rule,[8] the 5-endo-trig cyclization is labelled as a disfavored process. Indeed, the Michael addition product 7 was not observed.



This reaction was then extended to the synthesis of the 1,4,5,6,7,7a-hexahydro-2H-indol-2-one ring system. Thus, the readily available aminoketones **8**[9] and **10**[10] were allowed to react with ethyl chloroformylacetate in the presence of pyridine and DMAP to give directly the corresponding cyclized products **9** (29 %), mp 64.5-65.5°C, and **11** (72%), mp 145.5-146.5°C.[11] The nmr spectra of both **9** and **11** showed no olefinic proton signal. Furthermore, catalytic hydrogenation of **11** followed by alkaline hydrolysis and decarboxylation gave known 15,16-dimethoxy-cis-erythrinan-8-one (**12**).[1a]





REFERENCES AND NOTES

1. (a) H. Ishibashi, K. Sato, M. Ikeda, H. Maeda, S. Akai, and Y. Tamura, J. Chem. Soc. Perkin Trans. 1, 1985, 605; (b) H. Ishibashi, K. Sato, K. Maruyama, M. Ikeda, and Y. Tamura, Chem. Pharm. Bull., 1985, **33**, 4593; (c) H. Ishibashi, S. Harada, K. Sato, M. Ikeda, S. Akai, and Y. Tamura, ibid., 1985, **33**, 5278; (d) H. Ishibashi, H. Ozeki, and M. Ikeda, J. Chem. Soc., Chem. Commun.,1986, 654; (e) H. Ishibashi, M. Ikeda, H. Maeda, K. Ishiyama, M. Yoshida, S. Akai, and Y. Tamura, J. Chem. Soc. Perkin Trans. 1, 1987, 1099; (f) H. Ishibashi, T. Sato, M. Irie, S. Harada, and M. Ikeda, Chem. Lett., 1987, 795.
2. G. Jones, Organic Reactions, 1967, **15**, 204.
3. **1a** (65%), bp 143-147°C/2 mmHg; **1b** (66%), bp 83-85°C/2 mmHg; **1c** (74%), bp 79-81°C/3 mmHg; **1d** (60%), bp 100-102°C/2 mmHg. (c.f., M. Ikeda, T. Uchino, M. Yamano, Y. Watanabe, H. Ishibashi, and M. Kido, Chem. Pharm. Bull., 1986, **34**, 4997.)
4. Use of triethylamine as a base gave a similar result.
5. An nmr spectrum of the crude reaction product of **1a** (before submitting to silica gel chromatography) indicated that a ratio of **2a:3a** is about 7:3.
6. **2a**: an oil, δ ($CDCl_3$); 1.24 (3H, t, J=7 Hz, $-OCH_2\underline{CH_3}$), 1.6-2.2 (2H, m, C_4-H), 2.2-2.7 (4H, m, C_5- and C_6-H), 3.23 (2H, bs, $-\underline{CH_2}CO_2Et$), 3.93, 5.33 (1H each, br. ABq, J=15 Hz, $-NC\underline{H_2}Ph$), 4.14 (2H, q, J=7 Hz, $-OC\underline{H_2}CH_3$), 6.61 (1H, br. t, J=4 Hz, C_3-H), 7.22 (5H, s, Ph).
   3a: an oil, δ ($CDCl_3$); 1.39 (3H, t, J=7 Hz, $-OCH_2\underline{CH_3}$), 1.7-2.2 (2H, m, C_4-H), 3.05 (2H, br. t, J=6 Hz, C_6-H), 4.38 (2H, q, J=7 Hz, $-OC\underline{H_2}CH_3$), 4.81 (2H, br. s, $-NC\underline{H_2}Ph$), 5.83 (1H, t, J=5 Hz, C_3-H), 7.29 (5H, s, Ph).
7. P.D. Kennewell, S.S. Matharu, J.B. Taylor, R. Westwood, and P.G. Sammes, J. Chem. Soc., Perkin Trans. 1, 1982, 2553.
8. J.E. Baldwin, J. Chem. Soc., Chem. Commun., 1976, 734.
9. C.L. Stevens, I.L. Klundt, M.E. Munk, and M.D. Pillai, J. Org. Chem., 1965, **30**, 2967.
10. Y. Zhang, S. Takeda, T. Kitagawa, and H. Irie, Heterocycles, 1986, **24**, 2151.
11. It has been claimed that treatment of the N-(ethoxycarbonylacetyl) derivative of **10** with sodium ethoxide in ethanol provides 8-oxo-15,16-dimethoxyerythrin-5-ene-7-carboxylic acid without evidence for the location of the double bond.[12]
12. S. Sugasawa and H. Yoshikawa, Chem. Pharm. Bull., 1960, **8**, 290.

Received, 24th June, 1988