

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

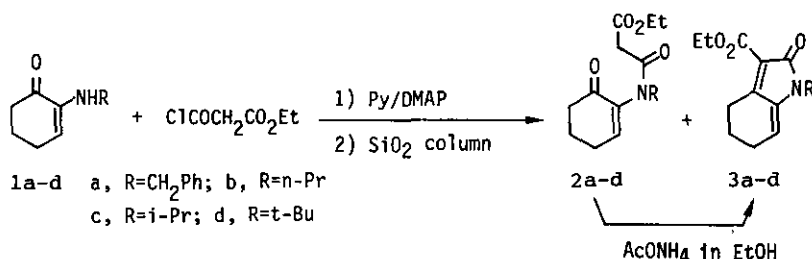
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Abstract—When 2-alkylaminocyclohex-2-enones **1a-d** were allowed to react with ethyl chloroformylacetate in the presence of pyridine and 4-(dimethylamino)pyridine, the carbamoylacetates **2a-d** and the 2H-indol-2-ones **3a-d** were obtained. Upon 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.

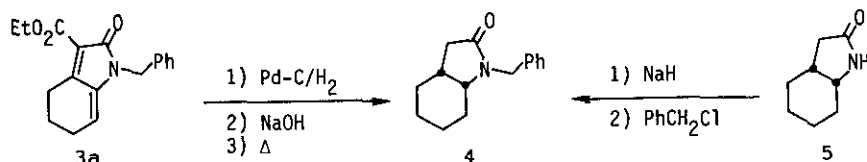
We have been interested in the synthesis of γ -butyrolactams to develop a new route to a variety of alkaloids.¹ Here we report a new entry to α,β -unsaturated γ -butyrolactams using a Knoevenagel condensation.²

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



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-benzyl-octahydro-2H-

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



Similarly, the reaction of the aminoketones 1b-d³ 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.

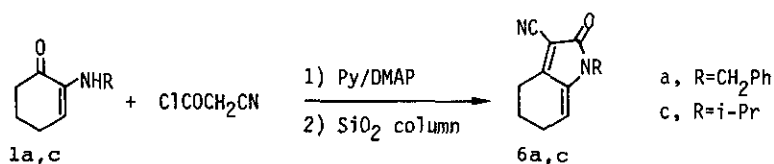
Table. Synthesis of the carbamoylacetates 2a-d and the 2H-indol-2-ones 3a-d

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

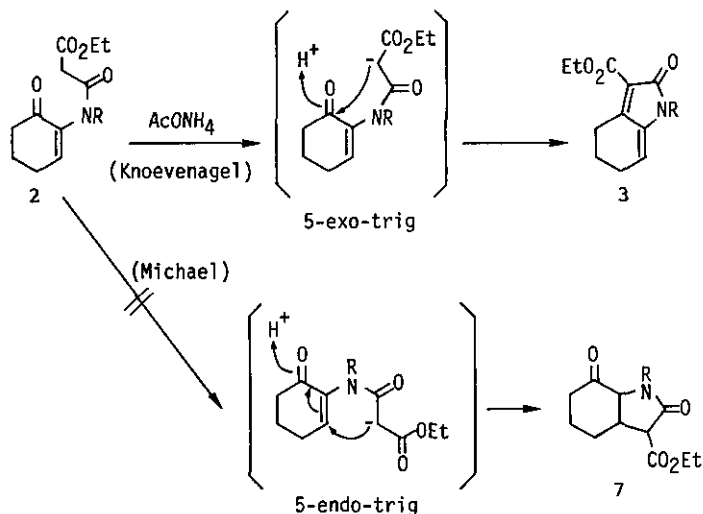
a) Ethyl chloroformylacetate (0.19 ml, 1.5 mmol) was added dropwise at 0°C to a mixture of pyridine (0.24 ml), DMAP (37 mg), and 1 (1 mmol) in benzene (5 ml). The reaction mixture was stirred at room temperature overnight. Isolated yields after chromatography under pressure (silica gel: AcOEt-hexane=1:2)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

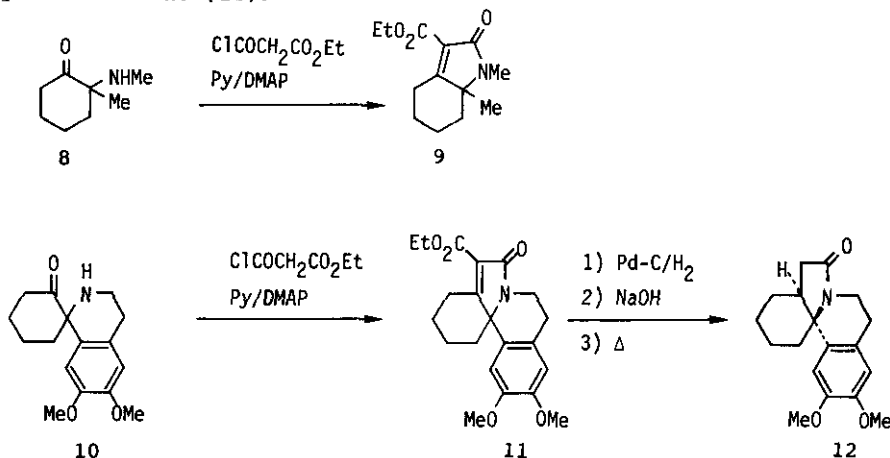
Similar treatment of 1a,c with cyanoacetyl chloride gave only the cyclized products 6a, mp 101-102°C, and 6c, mp 135-136°C, in 16 and 32% yields, respectively. The low yields may be, in part, due to instability of cyanoacetyl chloride.



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

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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 (CDCl₃); 1.24 (3H, t, J=7 Hz, -OCH₂CH₃), 1.6-2.2 (2H, m, C₄-H), 2.2-2.7 (4H, m, C₅- and C₆-H), 3.23 (2H, bs, -CH₂CO₂Et), 3.93, 5.33 (1H each, br. ABq, J=15 Hz, -NCH₂Ph), 4.14 (2H, q, J=7 Hz, -OCH₂CH₃), 6.61 (1H, br. t, J=4 Hz, C₃-H), 7.22 (5H, s, Ph).
3a: an oil, δ (CDCl₃); 1.39 (3H, t, J=7 Hz, -OCH₂CH₃), 1.7-2.2 (2H, m, C₄-H), 3.05 (2H, br. t, J=6 Hz, C₆-H), 4.38 (2H, q, J=7 Hz, -OCH₂CH₃), 4.81 (2H, br. s, -NCH₂Ph), 5.83 (1H, t, J=5 Hz, C₃-H), 7.29 (5H, s, Ph).
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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
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