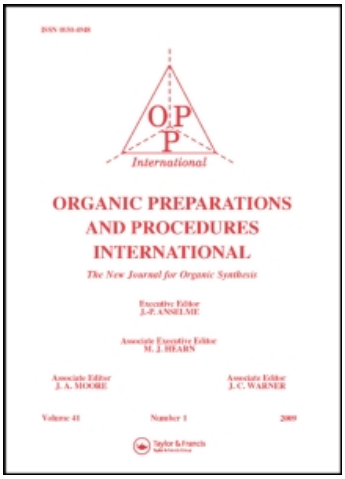

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NOVEL SYNTHESIS OF FUNCTIONALIZED 2-PYRROLIDINONES *via* UNSATURATED IMIDOYL CYANIDES

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NOVEL SYNTHESIS OF FUNCTIONALIZED 2-PYRROLIDINONES *via* UNSATURATED IMIDOYL CYANIDES

Submitted by (12/03/01)

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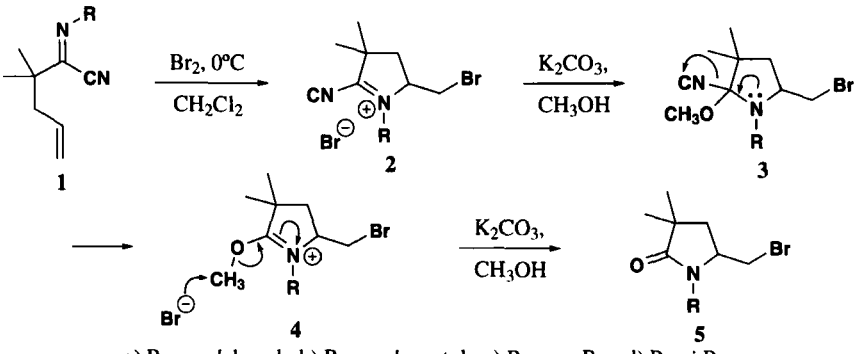
Several compounds with biological and pharmaceutical usefulness, such as psychotropic agents,[1] muscarinic acid antagonists,[2] and antihypertensive agents,[3] possess a γ-lactam framework. On account of their extensive occurrence and assorted scope of biological activities, functionalized pyrrolidinones are appealing targets as starting materials for the synthesis of other biologically active molecules such as γ-lactam bridged dipeptides,[4] γ-lactam analogs of β-lactam antibiotics[5] and substituted pyrrolidines.[6] 2-Pyrrolidinones have been usually prepared by cyclization through acyl-nitrogen bond formation,[7] by substitution of γ-butyrolactones with ammonia or amines,[8] or by cyclization of α-functionalized (*e. g.* halogenated) *N*-allylamides[9] or other radical routes.[10] This paper discloses a new synthesis of 1-alkyl-5-bromomethyl-2-pyrrolidinones **5**.

The required imidoyl cyanides **1** were prepared according to a procedure previously reported.[11] Treatment of the unsaturated imidoyl cyanides **1** with one equivalent of bromine in dry dichloromethane presumably led to the pyrrolinium bromides **2**, which were then treated with two equivalents of potassium carbonate in dry methanol to afford 2-pyrrolidinones **5** in reasonable yields after purification by flash chromatography. None of the *endo-trig* cyclization product, *i.e.* the 1-alkyl-6-bromo-3,3-dimethyl-2-piperidinone analogue could be detected in any of the reactions.

The formation of 2-pyrrolidinones **5** may be rationalized as shown below. Similar dealkylations (**4** → **5**) of open-chain imidates have been reported previously in the literature.[12] γ-Lactam **5c** was isolated as a 1:1 diastereomeric mixture. Attempts to separate and or to resolve it into



a) R = *cyclo*hexyl b) R = *cyclo*pentyl c) R = *sec*-Bu d) R = *i*-Pr

Scheme 1

its components were not successful (flash chromatography and GC). The pseudo-quartet at δ 0.94 of its ^{1}H NMR ($CDCl_3$) corresponds to an overlapped set of triplets. This fact was confirmed by recording the ^{1}H NMR spectrum in deuterated benzene, which resulted in a splitting of the signal into two triplets at δ 0.61 and δ 0.71, respectively.

In summary, a two-step one-pot route to 1,3,3,5-tetrasubtituted-γ-lactams from γ,δ-unsaturated imidoyl cyanides has been developed. The mild conditions, the readily availability of the starting materials and the simplicity of the synthesis make this approach a practical and convenient protocol for the preparation of this type of compounds.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 (270 and 68 MHz, respectively) nuclear magnetic resonance spectrometer at ambient temperature using TMS as internal standard and $CDCl_3$ as solvent, unless otherwise noted. High resolution mass spectrometry (70 eV) was carried out on a Finnigan MAT-8200 spectrometer. IR spectra were recorded on a Perkin Elmer Spectrum One spectrometer (entries **2a-c**) and a Perkin Elmer 1310 spectrometer (entry **2d**). Reagents and solvents were of analytical grade and were used without further purification. Dichloromethane was distilled over calcium hydride before use. Absolute methanol was purchased from Aldrich Chemical Co. Acros Organics Kieselgel (0.035-0.070 mm) was used for flash column chromatography, monitored with Merck Kieselgel 60F 254 pre-coated TLC plates. The purity of all compounds was checked by means of capillary gas chromatography on a Delsi DI 200 gas chromatograph equipped with a coated fused silica capillary column (30 m x 0.25 mm i.d., film thickness 1μm), N_2 as carrier gas, FID detector, H_2; and was in all cases +95%.

General Procedure for the Synthesis of 1-Alkyl-5-bromomethyl-3,3-dimethyl-2-pyrrolidinones 5.- To a solution of 1 mmol of imidoyl cyanide **1** in 3 mL of dichloromethane, 160 mg. (1 mmol) of bromine, dissoved in 1 mL of CH_2Cl_2, was added dropwise at 0°. After 20 min stirring at room temperature, the solvent was evaporated and the residue was dissolved in 3 mL of dry methanol. Then 276 mg (2 mmol) of K_2CO_3 were added and this mixture was kept stirring at room temperature for 4 h. After filtering the reaction mixture, the filtrate was evaporated and 5 mL of dry diethyl ether was

added to the residue. Filtration of the remaining potassium carbonate and evaporation of the solvent, followed by flash chromatography of the crude product resulted in 2-pyrrolidinones **5**.

5-(Bromomethyl)-1-cyclohexyl-3,3-dimethyl-2-pyrrolidinone (5a): light-yellow oil, 72%, ^{1}H NMR ($CDCl_3$): δ 1.11 and 1.22 (6H, 2 x *s*, 2 x CH_3); 1.25-1.85 (10H, *m*, $(CH_2)_5$); 1.82 (1H, *dd* overlapped, J_1=13.2 Hz, J_2=5.3 Hz, HC(H)C$(CH_3)_2$); 2.07 (1H, *dd*, J_1=7.9 Hz, J_2=13.2 Hz, HC(H)C$(CH_3)_2$); 3.30 (1H, *dd*, J_1=8.6 Hz, J_2=10.0 Hz, CH(H)Br); 3.55-3.60 (1H, *m*, NCH_{cyclo}); 3.64 (1H, *dd*, J_1=3.1 Hz, J_2=10.0 Hz, CH(H)Br); 3.76-3.85 (1H, *m*, NCH). ^{13}C NMR ($CDCl_3$): δ 25.75 and 26.27 (2 x CH_2); 26.33 and 26.65 (2 x CH_3); 30.19 and 32.06 (2 x CH_2); 36.91 (CH_2Br); 39.86 ($CH_2C(CH_3)_2$); 40.18 ($C(CH_3)_2$); 53.68 (NCH); 55.11 ($NCHCH_2Br$); 180.54 (C=O). MS (70 eV) m/z (%): 287/9 (M^+, 14); 244/6 (10); 206/8 (89); 194 (100); 180 (12); 126 (10); 112 (69); 84 (17); 83 (16); 82 (11); 81 (17); 69 (17); 67 (21); 55 (41); 54 (15). IR (NaCl, cm^{-1}): 1682 (C=O); Rf=0.25 (Hex/AcOEt : 8/2). $C_{13}H_{22}BrNO$: calcd. 287.08848; found 287.08849 (HRMS).

Anal. Calcd for $C_{13}H_{22}BrNO$: C, 54.17; H, 7.69; N, 4.86. Found: C, 54.53; H, 7.41; N, 5.12

5-(Bromomethyl)-1-cyclopentyl-3,3-dimethyl-2-pyrrolidinone (5b): light-yellow oil, 77%, ^{1}H NMR ($CDCl_3$): δ 1.11 and 1.22 (6H, 2 x *s*, 2 x CH_3); 1.25-1.86 (9H, *m*, HC(H)C$(CH_3)_2$ and $(CH_2)_4$); 2.07 (1H, *dd*, J_1=8.0 Hz, J_2=13.4 Hz, HC(H)C$(CH_3)_2$); 3.31 (1H, *dd*, J_1=8.6 Hz, J_2=10.0 Hz, CH(H)Br); 3.56-3.61 (1H, *m*, NCH_{cyclo}); 3.64 (1H, *dd*, J_1=2.8 Hz, J_2=10.0 Hz, CH(H)Br); 3.76-3.85 (1H, *m*, NCH). ^{13}C NMR ($CDCl_3$): δ 26.07 and 26.40 (2 x CH_3); 25.50, 26.02, 29.91 and 31.81 ($(CH_2)_4$); 36.66 (CH_2Br); 39.59 ($CH_2C(CH_3)_2$); 39.93 ($C(CH_3)_2$); 53.42 (NCH_{cyclo}); 54.86 ($NCHCH_2Br$); 180.30 (C=O). MS (70 eV) m/z (%): 273/5 (M^+, 11); 206/8 (53); 194 (32); 181 (12); 180 (100); 126 (12); 113 (10); 112 (91); 84 (27); 83 (19); 81 (14); 69 (28); 68 (17); 67 (25); 57 (14); 56 (11); 55 (33); 54 (12); 43 (16); 41 (78). IR (NaCl, cm^{-1}): 1681 (C=O); Rf=0.21 (Hex/AcOEt : 8/2). $C_{12}H_{20}BrNO$: calcd. 273.07283; found 273.07263 (HRMS).

Anal. Calcd for $C_{12}H_{20}BrNO$: C, 52.56; H, 7.35; N, 5.11. Found: C, 52.73; H, 7.49; N, 5.02

5-(Bromomethyl)-1-*sec*-butyl-3,3-dimethyl-2-pyrrolidinone (2c): light-yellow oil, 65%, ^{1}H NMR ($CDCl_3$): δ 0.88 and 0.91 (2 x 3H, 2 x *t*, *J*=7.3 Hz, 2 x CH_2CH_3); 1.13 and 1.22 (2 x 6H, 2 x *s*, 2 x $C(CH_3)_2$); 1.24 and 1.31 (2 x 3H, 2 x *d*, *J*=7.0 Hz, 2 x $CHCH_3$); 1.41-1.74 (2 x 2H, *m*, 2 x CH_2CH_3); 1.82 (2 x 1H, *dd*, J_1=5.9 Hz, J_2=13.2 Hz, 2 x NCHCH(H)); 2.08 (1H, *dd*, J_1=2.6 Hz, J_2=7.9 Hz, NCHCH(H_a)); 2.13 (1H, *dd*, J_1=2.6 Hz, J_2=7.9 Hz, NCHCH(H_b)); 3.29 (2 x 1H, *dd*, J_1=9.3 Hz, J_2=17.3 Hz, 2 x CH(H)Br); 3.59-3.69 (2 x 2H, 2 x *m*, 2 x CH(H)Br and 2 x $NCHCH_3$); 3.73-3.86 (2 x 1H, 2 x *m*, 2 x $NCHCH_2$). ^{13}C NMR ($CDCl_3$): δ 11.52 and 11.59 (2 x CH_2CH_3); 17.74 and 19.87 (2 x $CHCH_3$); 26.06 and 26.09 and 26.25 and 26.33 (2 x $(CH_3)_2$); 36.15 and 36.53 (CH_2Br); 39.73 and 39.87 ($NCHCH_2$); 39.98 and 40.07 ($C(CH_3)_2$); 50.75 and 51.48 ($NCHCH_3$); 54.61 and 55.87 ($NCHCH_2Br$); 180.43 (C=O). MS (70 eV) m/z (%): 261/3 (M^+, 11); 232/4 (100); 206/8 (30); 204 (12); 182 (39); 168 (55); 149 (21); 148 (22); 126 (10); 112 (65); 84 (23); 83 (28); 82 (11); 81 (18); 69 (26); 57 (20); 56 (16); 55 (44); 54 (10); 44 (16); 42 (20); 41 (57). IR (NaCl, cm^{-1}): 1683 (C=O); Rf=0.15 (Hex/Et_2O : 8/2). $C_{11}H_{20}BrNO$: calcd. 261.07283; found 261.07461 (HRMS).

Anal. Calcd for $C_{11}H_{20}BrNO$: C, 50.39; H, 7.69; N, 5.34. Found: C, 50.08; H, 7.92; N, 5.07

5-(Bromomethyl)-1-isopropyl-3,3-dimethyl-2-pyrrolidinone (2d): light-yellow oil, 67%, ^{1}H NMR ($CDCl_3$): δ 1.11 and 1.22 (6H, 2 x *s*, CH_3); 1.27 and 1.32 (6H, 2 x *d*, *J*=6.9 Hz, $CH(CH_3)_2$); 1.82 (1H, *dd*, J_1=13.2 Hz, J_2=8.2 Hz NCHCH(H)); 2.08 (1H, *dd*, J_1=13.2 Hz, J_2=7.9 Hz, NCHCH(H)); 3.33 (1H, *dd*, J_1=10.2 Hz, J_2=8.2 Hz, CH(H)Br); 3.62 (1H, *dd*, J_1=10.2 Hz, J_2=2.9 Hz, CH(H)Br); 3.78-3.84 (1H, *m*, $NCHCH_2$); 4.01 (1H, *septet*, *J*=6.9 Hz, $CH(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 19.42 and 21.33 (2 x $CHCH_3$); 25.84 and 26.14 ($(CH_3)_2$); 36.48 (CH_2Br); 39.42 ($NCHCH_2$); 39.89 ($C(CH_3)_2$); 44.87 ($NCH(CH_3)_2$); 54.64 ($NCHCH_2Br$); 180.14 (C=O). MS (70 eV) m/z (%): 247/9 (M^+, 9); 232/4 (10); 168 (17); 155 (15); 154 (100); 112 (61); 84 (27); 83 (14); 81 (9); 69 (15); 55 (20); 43 (23); 42 (15); 41 (33). IR (NaCl, cm^{-1}): ν_{max}=1672 (C=O).

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SELECTIVE TRANSESTERIFICATION OF METHYL AND ETHYL β-KETOESTERS

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Transesterification, one of the most effective methods of ester synthesis has wide applications both in academic and industrial research.[1] In general, it is accelerated by protic acids,[1] Lewis acids[1] and basic catalysts.[1] More recently various catalysts have been reported to effect transesterifications.[1,2] β-Ketoesters, a class of versatile intermediates used extensively in the agrochemical, pharmaceutical and dyestuff industries,[2] are useful and important building blocks for the synthesis of complex natural products.[2] Various methods have been reported for their preparation, mostly involving ester derivatives as starting materials.[3,4] Most of the reported methods of transesterification of β-ketoesters are not general and are equilibrium driven reactions that require an excess of one of the reactants to obtain good yields. For example, 4-(dimethylamino)pyridine (DMAP) catalyzed transesterification[5] required a large amount of catalyst whereas other methods[6] are restricted to tertiary butyl esters, thus lack generality. Although distannoxanes[7] leads to good yields of β-ketoesters, the catalysts are difficult to prepare. The synthesis of lignan lactones of significant cytotoxic activity required a variety of alkylbenzoyl acetates in larger amounts. However, there are few reports on the synthesis of the