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An Efficient Synthetic Method of Jasmone Analogues and 2,5-Dialkylpyrrolidine Alkaloids Using 1-Benzyl-2,5-dicyanopyrrolidine

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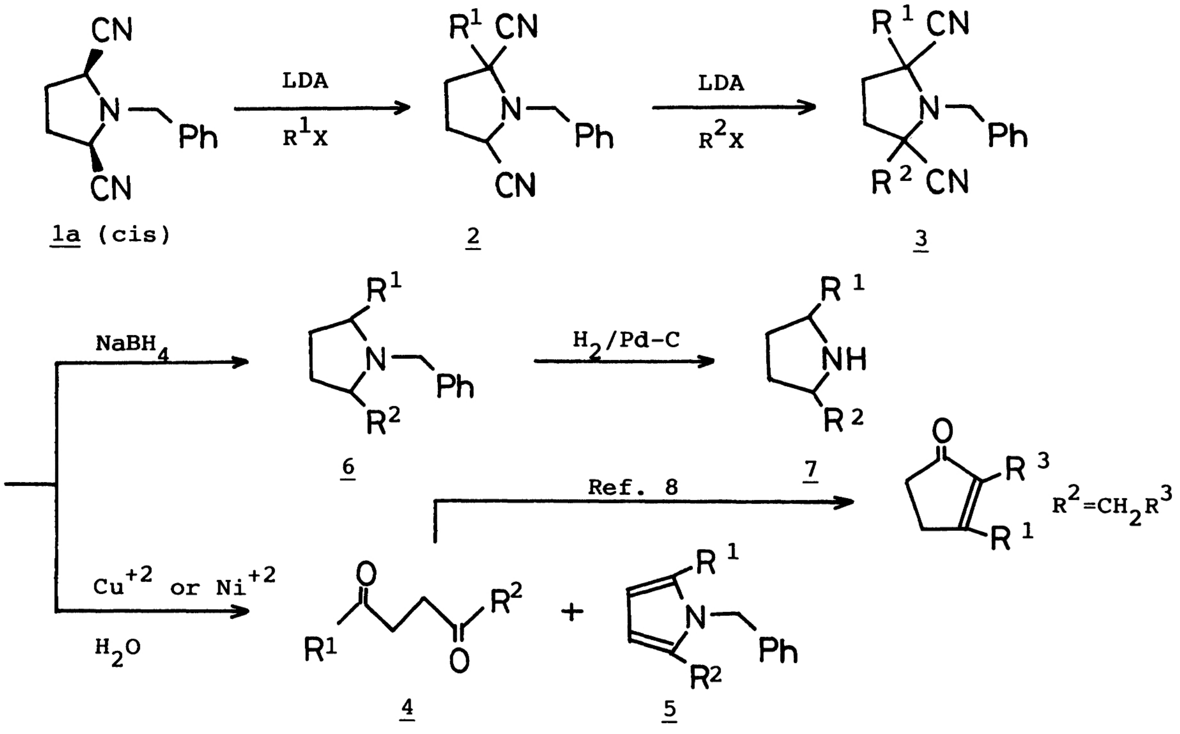
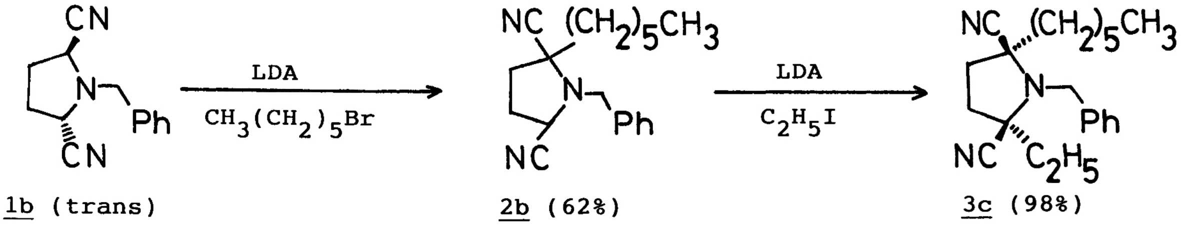
Reaction of 1-benzyl-2,5-dicyanopyrrolidine with alkyl halides give unsymmetrical 2,5-dialkylated products (3) in high yields. Hydrolysis of 3 gives γ-diketones which serve as precursors for jasmone analogues having a cyclopentenone framework, while decyanation and debenzylation of 3 lead to 2,5-dialkylpyrrolidine alkaloids in high yields.

In our previous paper,[1)] we reported an efficient synthetic method for preparation of 1-substituted 2,5-dicyanopyrrolidines and discussed their stereochemistry. We report here a new synthetic method for preparation of natural products such as jasmones and 2,5-dialkylpyrrolidine alkaloids using 1-benzyl-2,5-dicyanopyrrolidine (1). Reaction of 1 with various alkyl halides gave unsymmetrical 1-benzyl-2,5-dialkyl-2,5-dicyanopyrrolidines (3) in high yields. When hydrolyzed in aqueous



Scheme 1. Preparation of jasmone analogues and pyrrolidine alkaroids.



Scheme 2. Stereochemistry of 2,5-dialkyl-1-benzyl-2,5-dicyanopyrrolidine using trans 1-benzyl-2,5-dicyanopyrrolidine (1b).

ethanol in the presence of cupric sulfate or nikel acetate, 3 gave γ-diketones (4), which are important precursors of cyclopentenone derivatives such as cis- and dihydro-jasmones, together with 1-benzyl-2,5-dialkylpyrroles (5). On the other hand, when the alkylated products 3 were heated at 70 °C with sodium borohydride in isopropyl alcohol, decyanation took place to give 1-benzyl-2,5-dialkylpyrrolidines (6). The subsequent debenzylation by catalytic hydrogenolysis proceeded smoothly to give 2,5-dialkylpyrrolidine alkaloids (7), e.g., 2-ethyl-5-pentylpyrrolidine which is a component in the venom of the fire ant (Solenopsis punctaticeos).2) A synthetic method of unsymmetrical 2,5-dialkylpyrrolidines using vinyl ketones has been reported.3) However, 1 is an useful synthetic reagent not only for preparation of unsymmetrical γ-diketones but also for that of unsymmetrical 2,5-dialkylpyrrolidine alkaloids. The cis-isomer of 1 was mainly used in the present work, but the stereochemistry of 2 and 3 obtained using the trans-isomer of 1 was found to be the same as that obtained using the cis-isomer (see Scheme 2).

The alkylation of cis-1 gave monoalkylated products (2) selectively. The selective formation of 2 is important for the subsequent preparation of unsymmetrical dialkylated products (3). For example, the reaction of cis-1 with pentyl iodide in tetrahydrofuran (THF) containing lithium isopropylamide (LDA) gave 1-benzyl-2,5-dicyano-2-pentylpyrrolidine (2a) in a 71% yield. Likewise, the reaction of cis-1 with hexyl bromide gave 1-benzyl-2,5-dicyano-2-hexylpyrrolidine (2b) in a 62% yield. The physical properties of 2b obtained from trans-1 agreed with those obtained from cis-1. The monoalkylated products 2 isolated were found to consist of single isomers by means of column chromatography using Florisil and a mixture of benzene and hexane as a solvent. The configurations of the two cyano groups of each stereoisomer of 1 have been determined by ^{1}H-NMR (270 MHz):1) The benzylic methylene protons of cis-1 are equivalent, while those of the trans-1 are unequivalent, giving rise to two distinguishable doublets with a coupling constant of 13 Hz. The benzylic methylene protons of 2 give two doublets with a coupling constant of 14 Hz, but the exact configuration is yet to be determined.

Dialkylated products (3) were prepared in 97-99% yields by reaction of 2 with alkyl halides under conditions similar to those for the alkylation of 1, but they were also prepared by one-pot reaction from 1. For example, the reaction of 2a and 2b with ethyl iodide gave 2-pentyl- and 2-hexyl-1-benzyl-2,5-dicyano-5-ethylpyrrolidines (3a and 3c) in 97% and 98% yields, respectively. Likewise, the reaction of 2b with methyl iodide gave 1-benzyl-2,5-dicyano-2-hexyl-5-methylpyrrolidine (3b) in

Table 1. Physical properties of new compounds

Compd.[a)]	Yield %	Mp °C	IR, ν/cm^{-1}	^{1}H-NMR(CDCl$_3$, 270 MHz),[b)] δ units [ppm]
2a: $R^1=CH_3(CH_2)_4$	71	78.2-79.0	ν_{CN}(KBr) 2220	3.85(d,1H,J=14 Hz,PhC$\underline{H}_2$), 3.85(m,1H,α-C$\underline{H}$ to CN), 4.17(d,1H,J=14 Hz,PhC$\underline{H}_2$)
2b: $R^1=CH_3(CH_2)_5$	80	78.0-78.3	ν_{CN}(KBr) 2240	3.82-3.85(m,1H,α-C$\underline{H}$ to CN), 3.87(d,1H, J=13.4 Hz,PhC$\underline{H}_2$), 4.13(d,1H,J=13.4 Hz, PhC$\underline{H}_2$)
3a: $R^1=CH_3(CH_2)_4$ $R^2=C_2H_5$	97	oil	ν_{CN}(neat) 2230	4.13(s,2H,PhC$\underline{H}_2$ of cis-form)
3b[c)]: $R^1=CH_3(CH_2)_5$ $R^2=CH_3$	99	oil	ν_{CN}(neat) 2220	1.34(s,2H,α-CH$_3$ of trans), 1.37(s,1H,α-C$\underline{H}_3$ of cis), 3.87 and 4.14(d,0.67H,J= 13.5 Hz,PhC$\underline{H}_2$ of trans), 4.13(s,0.67H, PhC$\underline{H}_2$ of cis)
3c: $R^1=CH_3(CH_2)_5$ $R^2=C_2H_5$	98	oil	ν_{CN}(neat) 2220	4.13(s,2H,PhC$\underline{H}_2$ of cis)
4a: $R^1=CH_3(CH_2)_4$ $R^2=C_2H_5$	47[d)]	31.5	ν_{CO}(KBr) 1700	2.67(s,4H,-OC-C$\underline{H}_2$-C$\underline{H}_2$-CO-)
5b: $R^1=CH_3(CH_2)_5$ $R^2=CH_3$	47[e)]	oil	$\nu_{=CH}$(neat) 3050	2.02(s,3H,α-CH$_3$), 4.89(s,2H,PhC$\underline{H}_2$),5.5-5.9(m,2H,β-C$\underline{H}$ x 2)
6a[c)]: $R^1=CH_3(CH_2)_4$ $R^2=C_2H_5$	86	oil	ν_{CH}(neat) 2924	3.69 and 3.81(d,0.33H,J=13 Hz,PhC$\underline{H}_2$ of trans), 3.77(s,1H,PhC$\underline{H}_2$ of cis)

a) All new compounds gave satisfactory elemental analysis (C±0.21, H±0.18, N±0.34). b) Only data of characteristic protons are listed. c) These compound of 3b and 6a are obtained as a mixture of cis- and trans-isomers. d) obtained by hydrolysis using Cu^{2+}. e) obtained by hydrolysis using Ni^{2+}.

a 99% yield. Both of 3a and 3c, obtained as single isomers, are found to be cis-form, as a result of stabilizing anomeric effects,[4)] because their benzylic methylene protons give rise to a singlet at δ 4.13 ppm. On the other hand, 3b was obtained as a mixture of cis- and trans-isomers in a molar ratio of 1 : 2 (see Table 1).

When the dialkylated product 3a was heated at 70 °C for 2 h with sodium borohydride in isopropyl alcohol, decyanation[5)] took place to give a mixture of cis- and trans-isomers of 1-benzyl-2-ethyl-5-pentylpyrrolidine (6a) in a combined yield of 83%. The molar ratio of cis to trans was 2 : 1. The subsequent debenzylation of 6 was carried out by modification of the procedure reported in the literature.[6)] For examples, 6a was hydrogenated at room temperature for 4 h in a mixture of 15% hydrochloric acid and ethyl alcohol (1:10 v/v) in the presence of 5% palladium-carbon and hydrogen at an initial pressure of 50 atm; 2-ethyl-5-pentylpyrrolidine (7a) was obtained as a mixture of cis- and trans-isomers in a combined yield of 88%.

When dialkylated products 3 were heated at 70 °C in an aqueous solution of cupric sulfate or nickel acetate containing ethanol as a cosolvent, γ-diketones 4 were obtained. Cupric ions presumably remove cyanide from 3, giving insoluble $[Cu(CN)_4]^{-3}$ salts,7) and the subsequent hydrolysis takes place to give 4. For example, the hydrolysis of 3a in the presence of cupric sulfate gave 3,6-undecanedione (4a) in a 47% yield. The formation of 1-benzyl-2-ethyl-5-pentylpyrrole (5a) together with that of 4a was confirmed by ^{1}H-NMR. Product 5a, however, was not isolated. On the other hand, the hydrolysis of 3b in the presence of cupric sulfate or nickel acetate afforded 2,5-undecanedione (4b) and 1-benzyl-2-methyl-5-hexylpyrrole (5b) in 20-25% and 47% yields, respectively. The formation of pyrroles 5 is due to elimination of β-hydrogen of an iminium intermediate. The formation of dihydrojasmone using 4b has been established via an intramolecular condensation of 4b prepared by a different synthetic method.8)

The present method was thus found to be useful for preparation of unsymmetrical 2,5-dialkylpyrrolidine alkaloids (7) and unsymmetrical γ-diketones (4) which are precursors of jasmone analogues.

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