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Photocyclization of α,β-Unsaturated Amide Aldehydes Synthesis of Jatropham

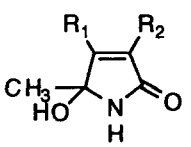
James P. Dittami*, Feng Xu, Hua Qi, Matthew W. Martin
Department of Chemistry
Worcester Polytechnic Institute
Worcester, Massachusetts 01609

and

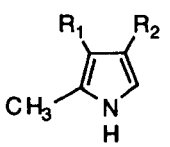
Jon Bordner, Debra L. Decosta, Jeffrey Kiplinger, Philip Reiche, Richard Ware
Pfizer Central Research
Groton, Conn. 06340

Abstract: α,β-unsaturated amide aldehydes undergo photoisomerization and intramolecular cyclization to provide hydroxy substituted pyrrolidinone systems. A synthesis of the natural product jatropham was accomplished by application of this procedure.

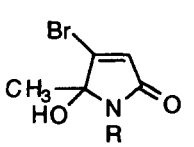
Derivatives of N-alkyl pyrrolidinones exhibit widespread and varied biological activity. Oxidized pyrroles **1** derived from kryptopyrroles **2a** reportedly induce behavioral, hypnotic and hypothermic changes. Compound **1a** is reported to induce porphyria and derivatives of hemopyrroles **2b** have been linked to psychiatric disorders. Thus compound **1b** was identified in the urine of schizophrenics and patients suffering from acute intermittent porphyria.[1] The structurally related 3-bromo-5-hydroxy-pyrrolin-2-ones **3** were evaluated for antineoplastic activity in tumor cells of white mice.[2] Derivatives such as **4** have been identified as metabolites of premazepam, a pyrrolodiazepine which reportedly exhibits anxiolytic activity.[3] The natural product jatropham, an antitumor alkaloid was isolated from *Jatropha macrorhiza*. in 1973 by Cole *et al.* and assigned structure **5a**.[4a] In 1980, Furukawa *et al.* suggested a revised structure for jatropham as 5-hydroxy-3-methyl-3-pyrrolin-2-one **5b**.[4b] Subsequent reports on the syntheses of both 5-hydroxy-4-methyl-3-pyrrolin-2-one **5a** and 5-hydroxy-3-methyl-3-pyrrolin-2-one **5b** confirm the revised structure assignment.[4c]



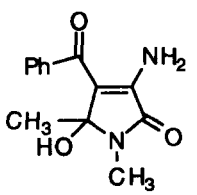
1a, R_1=C_2H_5 R_2=CH_3
b, R_1=CH_3 R_2=C_2H_5



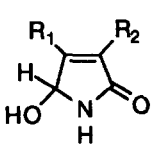
2a,b



3, R=CH_3,n-C_3H_7, n-C_4H_9, n-$C_{12}H_{25}$, cyclohexyl



4

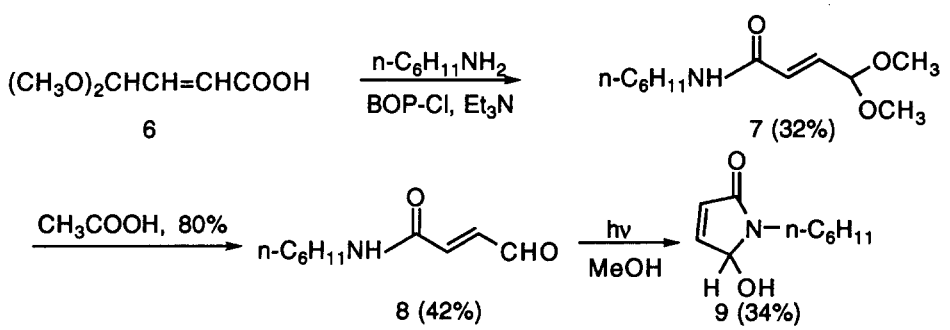


5a, R_1=CH_3 R_2=H
b, R_1=H R_2=CH_3

To date synthetic approaches to these 5-hydroxy-pyrrolin-2-ones have included sensitized photooxygenation of pyrroles[5] and diazepines[6], photooxidation of 2-furylcarbamates[7], conversion of lactones to lactams[2,8] and Grignard addition to maleimide derivatives.[9] We recently reported that photolysis of γ-keto-α,β-unsaturated amides provides N-alkyl 5-methyl-5-hydroxy-3-pyrrolin-2-ones.[10] Herein we detail an extension of

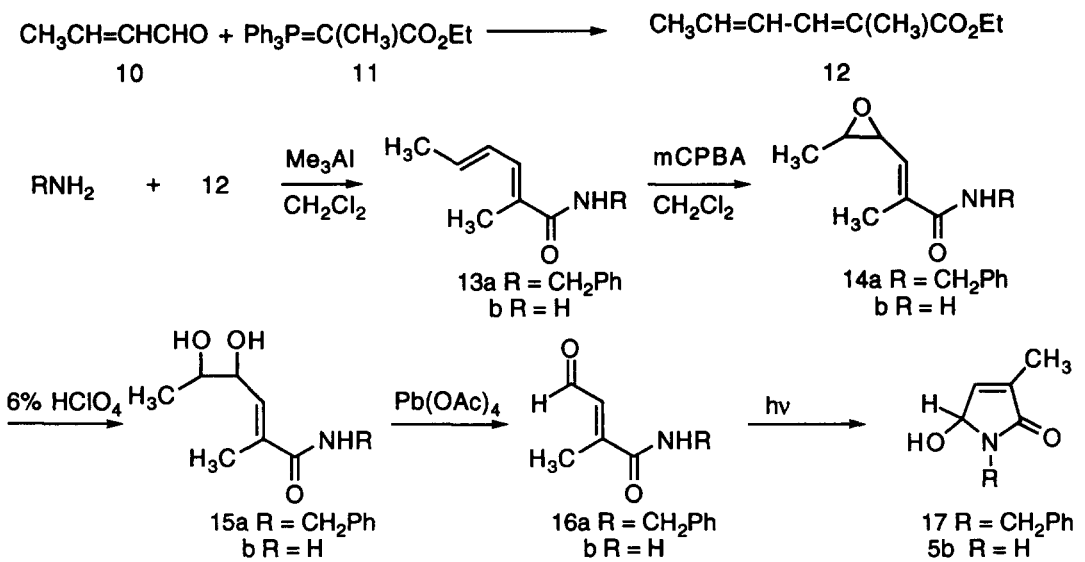
this procedure to include cyclization of α,β-unsaturated amide aldehydes. In demonstration of the utility of the photocyclization a total synthesis of the natural product jatropham has been completed.

Preparation of α,β-unsaturated amide aldehydes can be carried out from fumaraldehydic acid dimethyl acetal **6**. Compound **6** was prepared from furan via i) oxidative cleavage with bromine in methanol to provide fumaraldehyde bis(dimethyl acetal) (85 %) ii) hydrolysis with Amberlyst® 15 in acetone to give the monodimethyl acetal (99 %) and iii) oxidation with sodium chlorite-hydrogen peroxide to afford fumaraldehydic acid dimethyl acetal **6** (82 %).[11] Compound **6** was converted to the amide **7** in 32 % yield on treatment with n-hexylamine, triethylamine and bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl). Hydrolysis of the acetal **7** in 80 % acetic acid provided the amide aldehyde **8** (42 %). Irradiation of a solution of **8** in methanol through Pyrex provided the lactam **9** in 34 % yield after chromatography. Encouraged by the success of this photocyclization we turned our attention to the preparation of jatropham.



The synthesis of jatropham was approached via modification of ethyl 2-methyl sorbate **12** to provide the requisite unsaturated amide aldehyde photoprecursor. Compound **12** was prepared in 93 % yield via Wittig olefination of crotonaldehyde with **11**.[12] Aminolysis of **12** with trimethyl aluminum and benzyl amine provided **13a** (72 %). Selective epoxidation of **13a** was carried out with meta chloroperoxybenzoic acid in methylene chloride to provide **14a** (32 %). Hydrolysis of the epoxide with perchloric acid (6 %) provided the diol **15a** (71 %) which was treated with lead tetraacetate to afford aldehyde **16a** (90 %). Photolysis of aldehyde **16a** in methanol provided lactam **17** (50 %). However, attempts to convert **17** to **5b** via removal of the N-benzyl group were not successful. Accordingly **12** was transformed to the amide derivative **13b** with trimethylaluminum and ammonia (53 %). Epoxidation of **13b** with mCPBA gave **14b** (64 %) which was converted via the diol **15b** to the aldehyde **16b** (44 %). Photolysis of **16b** provided product (86 %) which had structural and physical data consistent with that reported for the natural product jatropham **5b**.[13-14]

In summary we have demonstrated that synthesis of 5-hydroxy-2-pyrrolidinones can be accomplished by photocyclization of either γ-keto-α,β-unsaturated amides[10] or α,β-unsaturated amide aldehydes. The photocyclization can be carried out with either primary or secondary amides to provide either unsubstituted or N-alkyl substituted pyrrolidinone derivatives.



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13. All products gave spectral data (^{1}H NMR, IR, MS) which were consistent with the assigned structures. Satisfactory combustion analyses or high resolution mass spec data were obtained for all new products.
14. Physical and spectral data is provided for **16b** and **5b** (jatropham). Comparative literature data is also provided for jatropham:

    Compound **16b** white solid: mp 98-99°C; IR (film, CH_3CN) 3626, 3001, 2943, 1678, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.37 (d, 3 H, J = 1.5 Hz), 5.75 (s, 2 H), 6.46 (dd, 1 H, J = 7.3 and 1.5 Hz), 10.16 (d, 1 H, J = 7.3 Hz); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 13.6 (CH_3), 130.3 (CH), 151.4 (C), 170.6 (C=O), 193.0 (C=O); UV (EtOH) λmax (e) 231 (4500), 204 (8100) nm; HRMS calcd for $C_5H_7O_2N$, 113.0475 found 113.0475.

    Compound **5b** (jatropham): mp 112-113 °C; IR (film): 3616, 3530, 3429, 1715, 1656 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.74 (m, 3 H), 4.85 (d, 1 H, J = 9.0 Hz), 5.45 (dd, 1 H, J = 9.0 and 1.6 Hz), 6.59 (m, 1 H), 7.45 (s, 1 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 10.4 (CH_3), 79.1 (CH), 136.2 (C), 142.0 (CH), 173.4 (C=O); HRMS calcd for $C_5H_7O_2N$, 113.0475 found 113.0475.

    Data reported for jatropham by Furukawa, H. et. al. Heterocycles **1981**, *16*, 1157: mp 115-118 °C; IR (CH_3CN) cm^{-1} 3600, 3520, 3420, 1715, 1645 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 1.78 (s, 3 H), 4.92 (d, 1H, J = 8 Hz), 5.48 (br d, J = 8 Hz), 6.59 (s, 1H), 7.54 (br, 1H); ^{13}C NMR (acetone-d_6) 10.41 (CH_3), 79.33 (CH), 136.25 (C), 142.16 (CH), 173.58 (C=O); UV (EtOH) λmax 230 nm.

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