CONDENSATION OF TRICYCLIC DIONES WITH METHYLNITRONATE ANION

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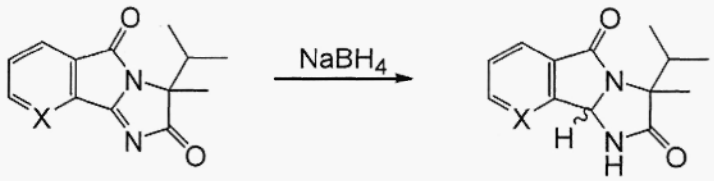
Abstract : 3-Isopropyl-3-methyl-9b-nitromethyl-1*H*,3*H*,9b*H*-imidazo-[1',2':1,2]-pyrrolo-[3,4-*b*]-pyridine-2,5-dione and 3-isopropyl-3-methyl-9b-nitromethyl-1*H*,3*H* 9b*H*-imidazo-[2,1-*a*]-isoindoline-2,5-dione are prepared in fair yields by addition of potassium methylnitronate to the azomethine linkage of the corresponding tricyclic precursors. A mechanistic rationale for the formation of the observed products is proposed.

Introduction

The imidazolinones comprise a class of compounds proven to inhibit branched-chain amino acid biosynthesis in plants and have been developed as commercial herbicides.[1] Structure-activity relationships for this chemical series have been well-developed and are detailed elsewhere.[2-4] During the work in this area, a great deal of effort was directed at understanding the chemistry of both the imidazolinones and their precursors. In this paper, the chemistry of the addition of methylnitronate anion to imidazolinone precursor tricyclic pyrroloarene diones is described. While investigating the chemistry of these tricyclic ring systems, it was found that compounds **1** are readily reduced by sodium borohydride, affording a mixture of diastereomers **2** that is separable (Scheme-1).[5]



1a: X=N
1b: X=CH

2a: X=N
2b: X=CH

Scheme-1

This observation led to subsequent work revealing that soft nucleophiles (protic substrates such as alcohols, amines, and thiols) add to the azomethine linkage leaving the tricyclic skeleton intact, while hard nucleophiles, such as alkoxides, add preferentially to the aroyl carbonyl group leading to tricycle fragmentation and the formation of substituted imidazolinones (Figure-1). Based on these results, a study was undertaken to ascertain the mode of addition of stabilized carbon nucleophiles to the pyrroloarene dione system, focusing on methylnitronate anions (Scheme-2).

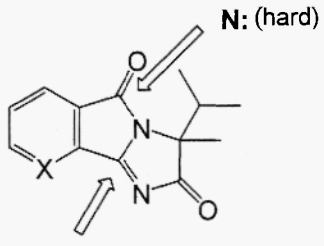
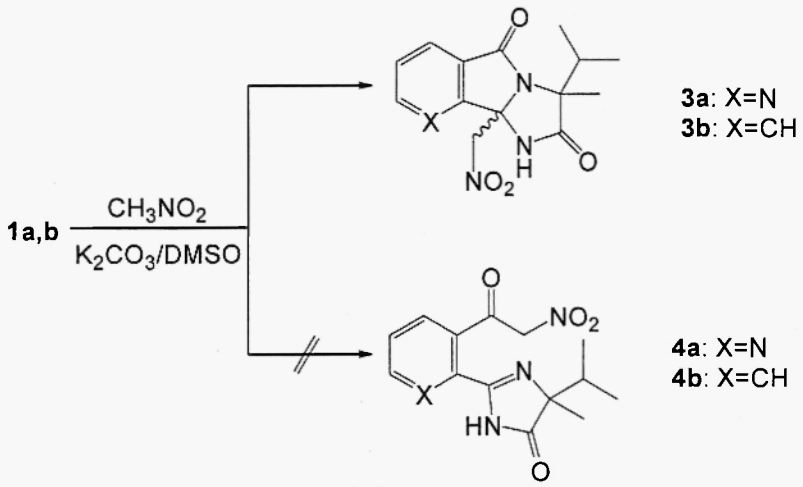


Figure-1 : Hard (C-acyl) versus soft (C-azomethine) modes of nucleophilic addition of methylnitronate anion

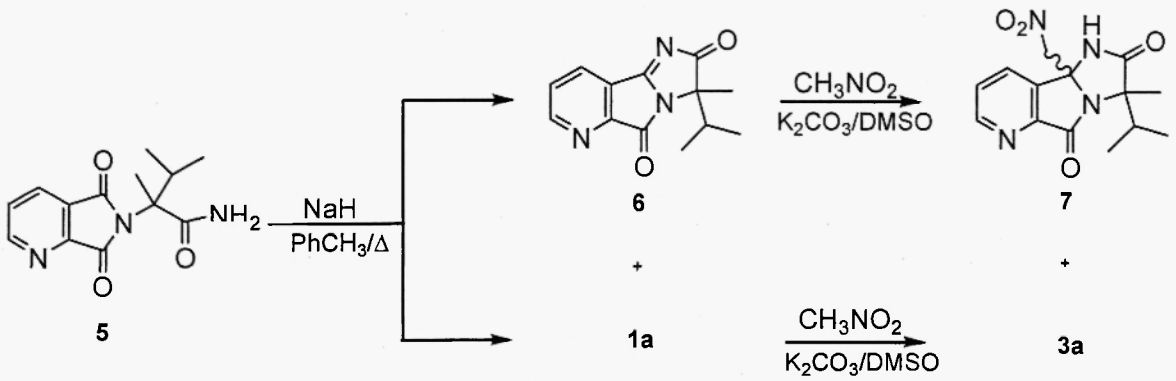
Results and Discussions

The reaction of 2,5-diones **1a** and **1b** with nitromethane in the presence of potassium carbonate in DMSO at room temperature affords the corresponding adducts **3a** and **3b** in good yield, the products arising from addition of the nitromethyl anion to the azomethine linkage (Scheme 2). No products arising from aroyl carbonyl addition

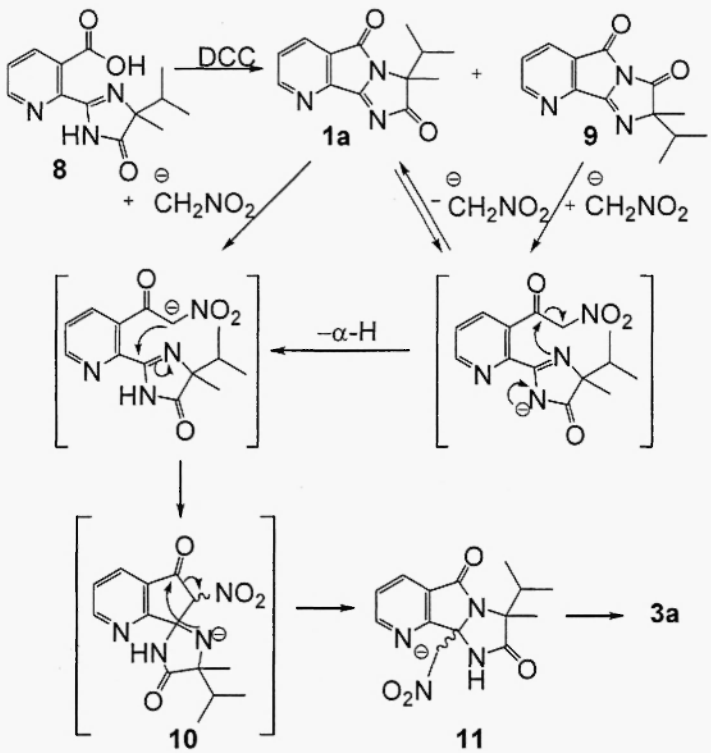


Scheme-2

(**4a, b**) were detected by NMR spectroscopy. The diastereomeric nature of the products **3a,b** was evident from the ^{1}H and ^{13}C NMR spectra. In the case of the pyrrolopyridine **6**, a by-product resulting from the cyclization of the requisite β-phthalimidocarboxamide **5** during the preparation of **1a**, namely regioisomer **7**, was isolated in 13% yield, resulting from methylnitronate anion addition to the regioisomeric pyrrolopyridine 3,5-dione **6** (Scheme-3).[6] Investigation of the chemistry of the pyrrolopyridine 3,5-dione **9** (Scheme-4), prepared devoid of the regioisomer corresponding to **6** from the imidazolinone carboxylic acid **9** *via* DCC-mediated cyclodehydration,[7] has indicated that these systems are more susceptible to nucleophilic ring opening compared to the isomeric 2,5-dione **1**.[8] Based on this observation, it appeared that nitromethyl anion addition to the 3,5-dione may be a viable entry to the nitromethyl ketone **4a**. However, the same adduct arising from nitromethyl anion addition to the 2,5-dione (**3a**) was the sole isolated product. Two plausible explanations for this observation are: (a) a substantial amount of **1a** is formed with **9** from the DCC-mediated ring closure of acid **8**, and products arising from **9** are either soluble during workup or are converted to other non-isolable products, or: (b) the nitromethyl ketone is formed as a transient intermediate, cyclizes to the spirocyclic anion **10**, and then rearranges to the penultimate anion **11**.



Scheme-3



Scheme-4

Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. Proton NMR spectra were recorded on a Varian Unity 300 spectrometer at 300 MHz; carbon NMR spectra were recorded at 75 MHz. Chemical shifts were measured in ppm relative to TMS using $CDCl_3$ as the deuterium lock. Infrared spectra were recorded on a Perkin-Elmer Model 1420 spectrophotometer. Mass spectra were obtained on a Finnigan Model MAT 95S at 70eV. Elemental analyses were obtained from Robertson Microlit Laboratories, Madison, NJ.

General Procedure

A mixture of the tricyclic dione (**1a**, **1b**, **9**), K_2CO_3, nitromethane, and DMSO were stirred under a $CaCl_2$ drying tube at room temperature for 4 h. The resulting tan-yellow mixture was diluted with H_2O, and the pH of the mixture was adjusted to 6 by the addition of concentrated HCl. Upon cooling, the product was either: (a) collected by suction filtration and air-dried or, (b) isolated by extraction with dichloromethane, washing the extract with 10% $NaHCO_3$, drying ($MgSO_4$), filtering, concentrating *in vacuo*, and crystallizing the product from Et_2O.

3-Isopropyl-3-methyl-9b-nitromethyl-1H,3H,9bH-imidazo-[1',2':1,2]-pyrrolo-[3,4-b]-pyridine-2,5-dione (3a).

A. From 3-Isopropyl-3-methyl)-3H-imidazo-[1',2':1,2]-pyrrolo-[3,4-b]-pyridine-2,5-dione (1a).
The reaction of the dione **1a** (12.13g; 0.050 mol), K_2CO_3 (20.66g; 0.150 mol), nitromethane (7.55g; 0.124 mol), and DMSO (50 mL) afforded a tan powder after filtration and air-drying (10.70g, 70%). Chromatography on silica gel (95:5 $CHCl_3/CH_3OH$) afforded the nitromethane adduct **3a** (8.62g, 57%) as a light tan powder; mp 165-168 °C; IR (KBr) ν 1733, 1710, 1601, 1591, 1551, 1471, 1443, 1374 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, i-Pr CH_3), 1.56 (3H, s, CH_3), 2.13 (1H, m, i-PrCH), 4.80 (1H, d, $J_{a,b}$=12 Hz, prochiral CH_aNO_2), 5.28 (1H, d, $J_{a,b}$=12 Hz, prochiral CH_bNO_2), 7.50 (1H, dd, 5-pyCH), 8.10 (1H, dd, 4-pyCH), 8.83 (1H, dd, 6-pyCH), 9.42 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ

17.1, 17.2, 18.8, 35.2, 70.3, 81.0, 126.1, 127.0, 133.7, 154.2, 162.8, 169.2, 176.9. *Anal.* Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.53; H, 5.66; N, 18.79.

A second fraction was isolated and identified as the regioisomeric nitromethane adduct 7 (1.98g, 13 %) as a white powder; mp 207.5-209.5 °C; IR (KBr) ν 1731, 1706, 1616, 1590, 1549, 1458, 1420, 1376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (6H, d, i-Pr CH_3), 1.45 (3H, s, CH_3), 2.20 (1H, m, i-PrCH), 5.00 (1H, d, $J_{a,b}$=15 Hz, prochiral CH_aNO_2), 5.30 (1H, d, $J_{a,b}$=15 Hz, prochiral CH_bNO_2), 7.62 (1H, dd, 5-pyCH), 8.18 (1H, dd, 4-pyCH), 8.87 (1H, dd, 6-pyCH), 9.67 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 17.1, 17.6, 19.3, 35.1, 70.8, 75.7, 81.7, 126.7, 132.1, 138.9, 150.3, 153.2, 169.1, 176.5. *Anal.* Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.62; H, 5.12; N, 18.84.

B. From 2-isopropyl-2-methyl-2H-imidazo-[1',2':1,2]-pyrrolo-[3,4-b]-pyridine-3,5-dione (9).

The water-quenched mixture from the reaction of the tricyclic dione **9** (5.00g, 0.021 mol), nitromethane (3.39g, 0.056 mol), K_2CO_3 (9.10g, 0.066 mol), and DMSO (50 mL) was processed by the extraction/recrystallization procedure to afford **3a** (2.87g, 46%) as a tan powder, mp 165-167 °C.

3-Isopropyl-3-methyl-9b-nitromethyl-1H,3H,9bH-imidazo-[2,1-a]-isoindoline-2,5-dione (3b).
The water-quenched mixture from the reaction of the tricyclic dione **1b** (1.50g; 6.20 mmol), nitromethane (1.00g, 6.20 mmol), K_2CO_3 (2.71g, 19.67 mmol), and DMSO (50 mL) was processed by the extraction/crystallization procedure to afford **3b** (1.24g, 66%) as a tan powder, mp 154-155 °C; ^1H nmr ($CDCl_3$) δ 1.94 (6H, overlapping d, i-pr CH_3), 1.54 (3H, s, CH_3), 2.07 (1H, m, i-pr CH), 4.58 (1H, d, $J_{a,b}$=11 Hz, prochiral CH_aNO_2), 5.01 (1H, d, $J_{a,b}$=11 Hz, prochiral CH_bNO_2), 7.58 (3H, m, ArH), 7.83 (1H, dd, ArH), 8.42 (1H, br s, NH). *Anal.* Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.00; H, 5.78; N, 13.38.

References and Notes

1. M. Los, O-(5-Oxo-2-imidazolin-2-yl)-arylcarboxylates: A New Class of Herbicides. in P.S. Magee, G.C. Kohn, and J.J. Menn, (Eds.), Pesticide Synthesis Through Rational Approaches, ACS Symposium Series 255, American Chemical Society, Washington, D.C., pp 29-44 (1984).
2. P. Wepplo, *Pestic. Sci.* **39**, 293 (1990)
3. B. Cross and D. Ladner, Development and Analysis of QSAR Models for Generating Pesticidal Synthesis Programs in W. Draber, T. Fujita, (Eds.), Rational Approaches to Structure, Activity, and Ecotoxicology of Agrochemicals, CRC Press, Boca Raton, pp 345-353 (1992).
4. The Imidazolinone Herbicides, D.L. Shaner, S.L. O'Connor (Eds.), CRC Press, Boca Raton (1991).
5. M. Los, Discovery of the Imidazolinone Herbicides in D.L. Shaner, S.L. O'Connor (Eds.), The Imidazolinone Herbicides, CRC Press: Boca Raton, p.4 (1991).
6. Reference 1, p 39.
7. M. Los, Herbicidal 2-(2-Imidazolin-2-yl)pyridine Derivatives, GB Patent Application 2,174,395A, November 5, p. 98 (1986).
8. D. Ladner, Structure-Activity Relationships Among the Imidazolinone Herbicides in D.L. Shaner, S.L. O'Connor (Eds.), The Imidazolinone Herbicides, CRC Press: Boca Raton, pp 47-48 (1991).

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