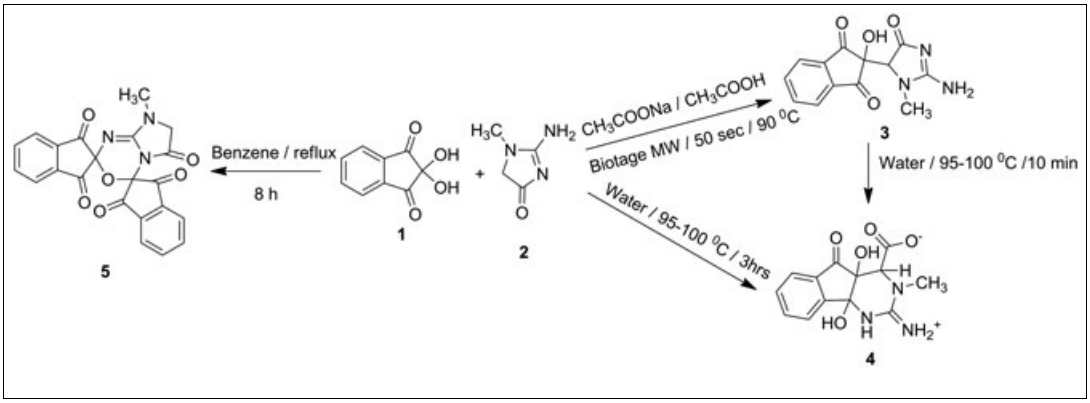
Solvent-Specific C-N Bond Formation: Synthesis of Novel Ninhydrin–Creatinine Heterocyclic Condensation Products

Narsimha Reddy Penthala,[a] Thirupathi Reddy Yerramreddy,[a] Sean Parkin,[b] and Peter A. Crooks[a]*

[a]Department of Pharmaceutical Sciences, College of Pharmacy University of Arkansas for Medical Sciences Little Rock, AR-72205, USA
[b]Department of Chemistry, University of Kentucky, Lexington, KY 40506, USA
*E-mail: pacrooks@uams.edu

Additional Supporting Information may be found in the online version of this article.
Received March 3, 2011
DOI 10.1002/jhet.1107
Published online 2 April 2013 in Wiley Online Library (wileyonlinelibrary.com).



Novel ninhydrin–creatinine heterocyclic condensation products (**3–5**) were synthesized under different solvent conditions. The compound 2-(2-amino-1-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-5-yl)-2-hydroxy-1*H*-ind-ene-1,3(2*H*)-dione (**3**) was formed by reacting ninhydrin (**1**) with creatinine (**2**) in the presence of sodium acetate in acetic acid. The same reactants afforded the zwitterionic compound **4** when the reaction was carried out in water, and a novel oxadiazine ring system (product **5**) was generated when benzene was used as solvent.

J. Heterocyclic Chem., **50**, E156 (2013).

INTRODUCTION

Ninhydrin (**1**) has been reported as a useful compound in organic, biochemical, analytical, and forensic sciences [1]. Ruhemann initially reported the color reaction of ninhydrin (1,2,3-indantrione monohydrate) with amino acids and peptides [2]. Because of its ability to react with amino acids to form Ruhemann's purple, ninhydrin has gained importance in the identification of fingerprints. Friedman reported the application of ninhydrin in the analysis of amino acids, peptides, and proteins to agricultural and biomedical sciences [3]. Prior research has shown that the reaction of ninhydrin with amino heterocycles can afford novel heterocyclic ring systems; the products from the reaction of ninhydrin with guanine [4], 1,1-dimethyl urea [5,6] and cytosine [7], are shown in Figure 1 (structures A, B and C, respectively). Ninhydrin has been utilized in the synthesis of some novel spirooxindoles containing chromene or pyran ring fragments [8]. We have previously reported on the reaction of *N*-alkylacetamides [9] and ureas [6] with ninhydrin and on the synthesis of 3-(2-amino-1-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-5-yl)-3-hydroxyindolin-2-one from the reaction of isatin with creatinine (**2**) [10]. In continuation of our work, we are currently investigating the reactions of ninhydrin with various amino azaheterocycles. We now report the formation of some novel heterocyclic condensation products from the reaction of ninhydrin with creatinine.

A mixture of ninhydrin and creatinine was irradiated utilizing a microwave initiator (Biotage) in the presence of sodium acetate and acetic acid for 50 s at 90°C to afford 2-(2-amino-1-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-5-yl)-2-hydroxy-1*H*-indene-1,3(2*H*)-dione (**3**) (Scheme 1). Compound **3** was initially recrystallized from methanol and the structure was characterized by ^{1}H NMR, ^{13}C NMR spectral analysis, and CHN combustion analysis. Single crystal X-ray diffraction analysis confirmed the structure as a monoclinic crystal system with a C 2/c space group (Fig. 2). During recrystallization of compound **3** from hot water at 95–100°C, the molecule was quantitatively transformed into the novel tricyclic analog, 4a,9b-dihydroxy-2-imino-3-methyl-5-oxo-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*d*] pyrimidine-4-carboxylate (**4**). The structure of **4** was determined from ^{1}H NMR and ^{13}C NMR analysis and confirmed by single crystal X-ray diffraction. Compound **4** exists as a zwitterion in a monoclinic crystal system, with a P 21/c space group (Fig. 2). A significant difference in solubility was observed between compound **3** and **4**; the former compound

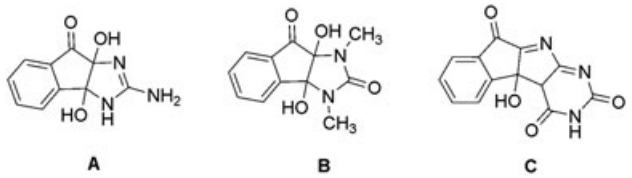


Figure 1. Ninhydrin condensation products with ureas and amino azaheterocycles.

is readily soluble in DMSO, whereas compound **4** could only be solubilized in a mixture of DMSO and trifluoroacetic acid.

We successfully synthesized **4** directly from **1** and **2** after reaction in water at 95–100°C for 3 h (Scheme 1). The likely mechanism of formation of zwitterion **4** from **3** in water is via initial hydrolytic ring opening of the creatinine moiety in compound **3** followed by N^1-C2 bond formation to afford the **4** (Scheme 2). Compound **4** contains the novel 2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-d]pyrimidine ring system.

We also studied the reaction between ninhydrin and creatinine in nonpolar solvents. Reaction of **1** with **2** in benzene was carried out at reflux temperature for 8 h by using a Dean–Stark apparatus. The product was identified as the *bis-spiro*-ninhydrin-creatinine condensation product **5** (Scheme 3) and fully characterized by ^{1}H NMR, ^{13}C NMR and CHN combustion analysis. Single crystal X-ray analysis confirmed this structure (Fig. 2), which represents a novel heterocyclic ring system. The formation of **5** likely involves initial generation of the addition product **6**, which results from nucleophilic attack of the creatinine 2-amino group, followed by reaction with a second equivalent of ninhydrin and subsequent intramolecular cyclization, as illustrated in Scheme 3.

EXPERIMENTAL

Procedure for the synthesis of 2-(2-amino-1-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-5-yl)-2-hydrox-y-1*H*-indene-1,3(2*H*)-dione (3). A mixture of ninhydrin (0.178 g, 1.0 mmol), creatinine (0.124 g, 1.1 mmol), and sodium acetate (0.098 g) in acetic acid (1 mL) was irradiated in a microwave-ready pressure vial equipped with a stir bar in a Biotage microwave initiator for 50 s at 90°C and at a power level of 25–29 W and 3 bar pressure. The cooled reaction mixture was taken out of the initiator, basified with saturated $NaHCO_3$, and filtered to afford a crude white solid. Crystallization from alcohol afforded **3** as a white crystalline

Scheme 1. Reaction of ninhydrin with creatinine in polar and nonpolar solvents.

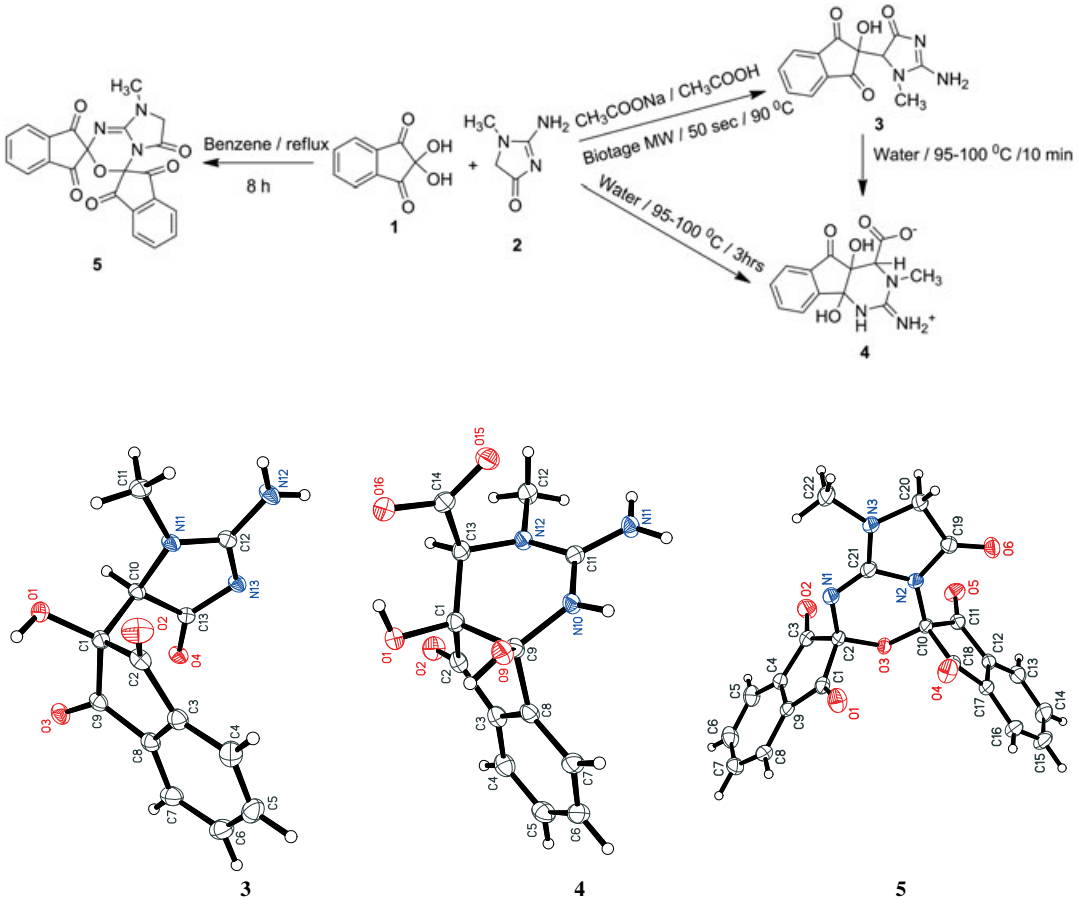
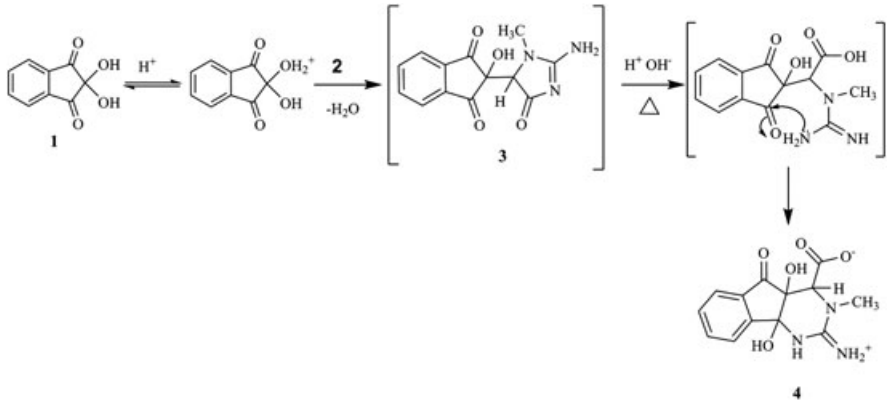
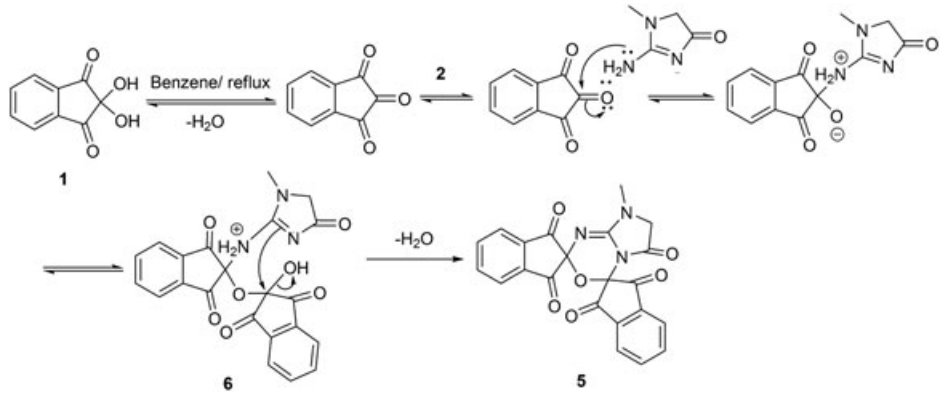


Figure 2. Single crystal X-ray diagrams of compounds **3**, **4** and **5**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 2. Possible mechanism for the formation of zwitterion (**4**) in water.



Scheme 3. Possible mechanism of formation of oxadiazine analog **5** from the reaction of ninhydrin with creatinine.



product (85%); mp 190°C dec. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.12 (s, 3H, N-CH_3), 4.20 (s, 1H, CH), 6.70 (s, 1H, OH), 7.50–7.65 (bd, 2H, NH_2), 7.65–8.02 (m, 4H, Ar H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 31.96, 68.73, 76.40, 122.83, 135.71, 136.69, 139.94, 141.23, 170.94, 181.26, 197.20, 197.73 ppm. *Anal*. Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.34; H, 4.12; N, 15.31.

Procedure for the synthesis of 4a,9b-dihydroxy-2-imino-3-methyl-5-oxo-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*d*] pyrimidine-4-carboxylate (4). A mixture of ninhydrin (0.178 g, 1.0 mmol) and creatinine (0.124 g, 1.1 mmol) was refluxed in water (5 mL) at 95–100°C for 3 h. The resulting reaction mixture was cooled and filtered to afford **4** as a white crystalline solid (92%); mp: >300°C. ^{1}H NMR (300 MHz, DMSO-d_6 + TFA) δ 2.88 (s, 3H, N-CH_3), 4.45 (s, 1H, CH), 7.56 (bs, 2H, NH_2), 7.61 (dd, J = 4.5, 8.6 Hz, 1H, Ar H), 7.73–7.75 (1H, d, J = 7.2 Hz, Ar H), 7.79–7.86 (m, 2H, Ar H), 9.35 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6 + TFA): δ 37.46, 61.36, 78.95, 83.81, 114.09, 117.94, 124.39, 124.97, 131.61, 153.52, 153.92, 169.44, 198. *Anal*. Calcd for $C_{13}H_{13}N_3O_5$: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.63; H, 4.46; N, 114.44.

Procedure for the synthesis of compound 5. A mixture of ninhydrin (0.178 g, 1.0 mmol) and creatinine (0.124 g, 1.1 mmol) was refluxed in benzene (5 mL) for 8 h in a Dean–Stark apparatus. The resulting reaction mixture was cooled and filtered to afford **5** as a yellow crystalline solid (65%); mp 200°C dec. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.03 (s, 3H, N-CH_3), 3.96 (s, 2H, CH_2), 7.86–7.93 (m, 4H, Ar H), 8.01–8.08 (m, 4H, Ar H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.57, 51.22, 124.81 (3C), 125.02(3C), 136.81(3C), 137.11(3C), 139.91, 140.03, 147.24, 166.90(2C), 189.44, 193.25(2C) ppm. *Anal*. Calcd for $C_{22}H_{13}N_3O_6$: C, 63.62; H, 3.15; N, 10.12. Found: C, 63.59; H, 3.20; N, 10.20.

In summary, we have observed solvent-specific C-N bond formation in the reaction of ninhydrin with creatinine. When a polar solvent, such as acetic acid or water, is utilized in the reaction of ninhydrin with creatinine, the initial condensation product **3**, resulting from the reaction of the C5 methylene group of creatinine with the C2 keto group of ninhydrin, is formed. However, when this reaction is carried out in a covalent solvent, such as benzene, the addition product **6**, which likely results from the reaction of the 2-amino group of creatinine with the 2-keto group of ninhydrin, is formed. We have utilized these observations to generate the new heterocyclic ring systems **4** and **5**. To the best of our knowledge, the zwitterion **4** is the first example of a novel 2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-d] pyrimidine heterocyclic ring system, and compound **5** is also a new *bis-spiro*-oxadiazine ring system. Further studies that examine the use of other aromatic triones with creatinine and related compounds are currently being pursued to assess the diversity of new heterocyclic systems that can be generated via this facile synthetic approach.

SUPPORTING INFORMATION

Single crystal X-ray diffraction CIF files accompany the online version of this article.

Acknowledgment. We are grateful to the NIH for their financial support under grant number CA 140409.

REFERENCES AND NOTES

[1] Joullie, M. M.; Thompson, T. R.; Nemeroff, N. H. Tetrahedron 1991, 47, 8791.
[2] Ruhemann, S. J Chem Soc Trans 1910, 97, 2025.
[3] Friedman, M. J Agric Food Chem 2004, 52(3), 385.
[4] Shapiro, R.; Chatterjie, N. J Org Chem 1970, 35(2), 447.
[5] Polonovsky, M.; Gonnard, P.; Glotz, G. Bull Soc Chim Fr 1939, 6, 1557.
[6] Crooks, P. A.; Deeks, T. Chem Ind 1975, 793.
[7] Shapiro, R.; Agarwal, S. C. J Amer Chem Soc 1968, 90, 474.
[8] Ramin, G.; Tayebeh, A.; Ayoob, B. J Hetero Chem 2010, 47, 46.
[9] Crooks, P. A. Chem Ind 1975, 176.
[10] Penthala, N. R.; Yerramreddy, T. R.; Parkin, S.; Crooks, P. A. Acta Cryst 2009, E65, o552.