Organic Process Research & Development **2002**, *6*, 64–66

Structural Determination of a Process Impurity in a Furan−Pyrrole Heteroatom Exchange Reaction

Bryan Li,* Narasimhan Kasthurikrishnan, John A. Ragan, and Gregory R. Young

Chemical Research and Development, Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

Electron-deficient pyrrole (1) was derivatized by diazotization with *p*-nitrobenzene diazonium chloride. Reduction of the diazo intermediates gave 2- and 1-aminopyrroles (3 and 4). The 2-aminopyrrole (3) was determined to be the process impurity formed during a furan−pyrrole heteroatom exchange reaction. An oxidative mechanism for the impurity formation was hypothesized. Nitrogen sparging of the reaction mixture prior to heating eliminated formation of 3.

Introduction

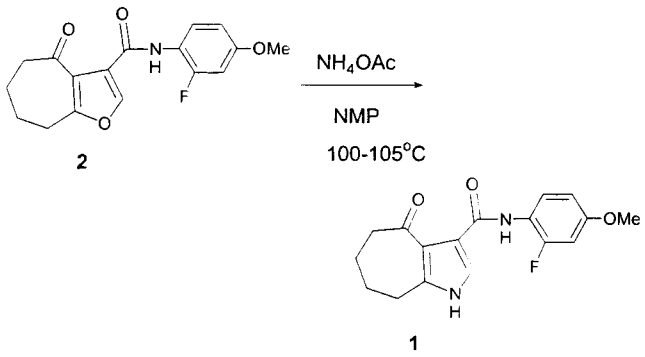
The preparation of **1**, involved heating the furan precursor **2** with ammonium acetate in *N*-methylpyrrolidinone at 100−105 °C (Scheme 1).[1] An impurity was formed in the reaction at 0.7% level (by HPLC area), which after recrystallization and Darco treatment, was still present at 0.5% level. The unknown impurity possessed a mass of M + NH, further MS/MS/MS fragmentation studies of the impurity identified the modification occurred at the pyrrole ring, and several structures were proposed (Figure 1).

Results and Discussion

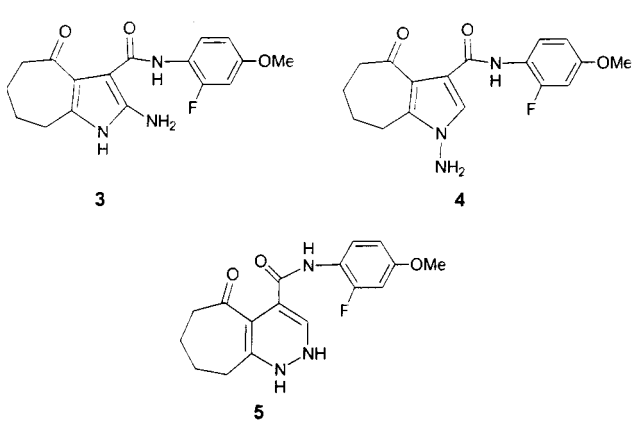
Structures **4** and **5** were viewed as possible byproducts from small quantities of hydrazine, which might be formed under the reaction conditions by adventitious O_2 (or other oxidants) and ammonium acetate.[2] However, when **2** was treated with hydrazine acetate in NMP, a new product (presumably **4** or **5**) was formed which had the same mass as the impurity, but did not coelute. Positive structural confirmation for the impurity came from the successful synthesis of 2-aminopyrrole **3**.

We reasoned that diazotization of the pyrrole ring would offer a convenient access to the amino derivative. A literature survey showed many examples of pyrrole diazotization, but mostly on electron-rich pyrrole systems.[3] The same transformation was lesser known for electron-deficient pyrroles.[4] When **1** was treated with *p*-nitrobenzenediazonium chloride prepared in situ from *p*-nitroaniline in 6 N HCl with sodium nitrite at 0 °C (Scheme 2), no reaction was observed. We felt that an elevated reaction temperature was needed for such an electron-poor pyrrole ring; indeed, warming to room temperature led to the 2-azo intermediate, although the reaction remained sluggish.[5] *N*-azo intermediate was also formed as a byproduct, which was an unexpected finding.[6] It is noteworthy that diazotizations of pyrroles had been reported to occur exclusively at C-2 when it is unsubstituted, and diazotization at the nitrogen of pyrroles is only preceded by an intramolecular diazotization to give 1,2,3-triazine from a 2-(1H-pyrrol-2-yl)aniline.[7] Upon treatment with $SnCl_2$ in acetic acid, **3** and **4** were obtained, respectively. It was gratifying to find that **3** coeluted with the unknown impurity. In addition, MS/MS/MS studies showed **3** to have identical fragmentation patterns to the unknown impurity. Also, the synthesized material was identical to the fractionated sample of the impurity by ^{1}H NMR and HPLC retention time.

Scheme 1



2 **1**



3 **4** **5**

Figure 1.

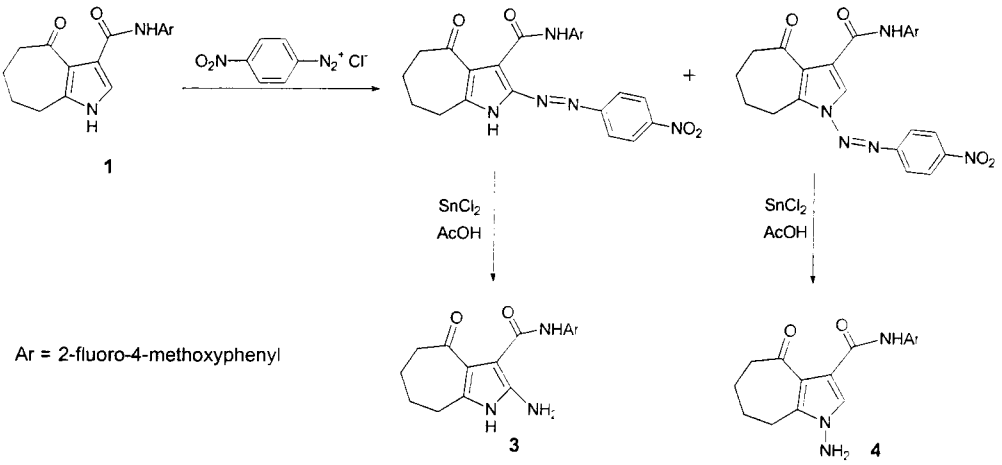
* To whom correspondence should be addressed. Fax: (860)715-7305. E-mail: bryan_li@groton.pfizer.com.

(1) Similar heteroatom exchange reactions had previously been reported: (a) Matsuura, T. Preparation of 4-Hydroxyindoles and their intermediates. Jpn. Kokai Tokkyo Koho JP 2000044555. (b) Hargis, D. C.; Shubkin, R. L. *Tetrahedron Lett.* **1990**, *31*, 2991. (c) Nagarajan, K.; Talwalker, P. K.; Goud, A. N.; Shah, R. K.; Shenoy, S. J.; Desai, N. D. *Indian J. Chem., Sect. B* **1988**, *27B*, 1113. (d) Bromidge, S. M.; Archer, D. A.; Sammes, P. G. *Synthesis* **1992**, *7*, 645. (e) Martin, A.; Luecke, B. *J. Chem. Soc., Chem. Commun.* **1993**, *23*, 1745.

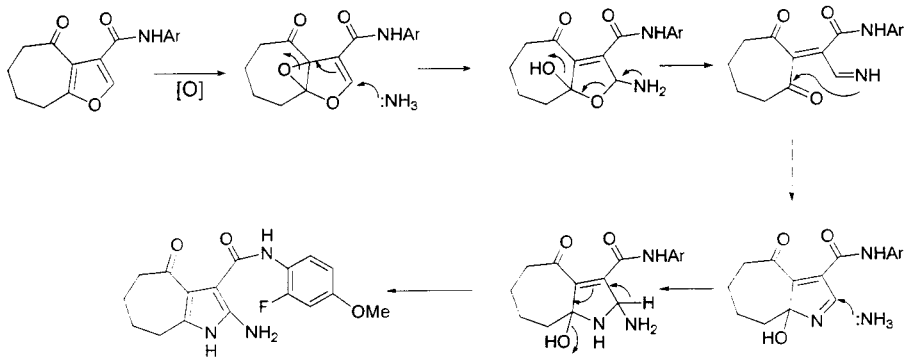
(2) There is no literature report of such a reaction, but a closely related example is known. Propane-1,3-diamine, oxidized by aqueous NaClO, gave pyrazolidine: Luettringhaus A.; Jander, J.; Schneider, R. *Chem. Ber.* **1959**, *92*, 1756.

 10.1021/op010227u CCC: $22.00
Published on Web 10/17/2001

Scheme 2



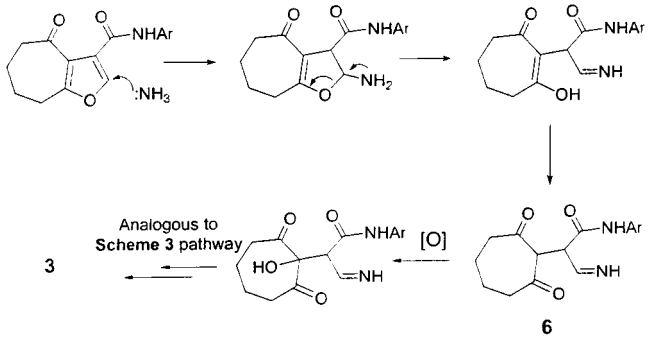
Scheme 3



While it remains unclear how **3** was formed during the furan−pyrrole heteroatom exchange reaction, furan epoxidations, well-documented in the literature,[8] suggested an oxidative mechanism. Several pathways can be postulated, one example is shown (Scheme 3). Other oxidative mechanisms are also plausible via a two-electron oxidation of the diketone **6** (Scheme 4).[9] The mechanism also highlighted optimization of the heteroatom exchange reaction shown in Scheme 1. Reaction conditions free of oxidants helped prevent the formation of the 2-aminopyrrole impurity; nitrogen sparging of the reaction mixture prior to heating eliminated the impurity formation.

In conclusion, we have found that electron-deficient pyrrole (**1**) can be diazotized at both 1- and 2-positions. The synthesis of the amino derivatives (**3** and **4**) provided unambiguous structural assignment to the process impurity, and the hypothesized oxidative mechanism for the impurity formation facilitated process development of the reaction.

Scheme 4



Experimental Section

^{1}H and ^{13}C NMR spectra were obtained in DMSO-d_6 with DMSO-d_6 (^{1}H, 2.49 ppm, ^{13}C, 39.5 ppm) as an internal reference using Varian 400. HPLC analyses were carried out using an Intersil C8 column (3.9 mm × 150 mm) with acetonitrile: pH 3.2 buffer (40/60) as mobile phase (1 mL/min) and detection at 205 nm wavelength. Preparative thin-layer chromatography was conducted using E. Merck precoated TLC plates (2 mm) using methylene chloride/acetic acid (95:5) as mobile phase. A Finnigan (San Jose, CA) LCQ ion trap instrument coupled to an HP 1100 liquid chromatograph was used for all MS data acquisition. LC/MS analysis

(3) (a) Butler, A. R.; Shepherd, P. T. *J. Chem. Soc., Perkin Trans. 2* **1980**, 113. (b) Bonnett, R.; North, S. A.; Newton, R. F.; Scopes, D. I. C. *Tetrahedron* **1983**, *39*, 1401.
(4) A relatively electron-deficient system, 3-acetyl-4-phenylpyrrole was reported: Cirrincione, G.; Almerico, A. M.; Diana, P.; Barrja, P.; Mingoia, F.; Grimaudo, S.; Dattolo, G. *J. Heterocycl. Chem.* **1996**, *33*, 161.
(5) LC/MS monitoring of reaction mixtures using an ion trap mass spectrometer.
(6) Cirrincione, G.; Almerico, A. M.; Barraja, P.; Diana, P.; Lauria, A. *J. Med. Chem.* **1999**, *42*, 2561.
(7) Dattolo, G.; Cirrincione, G.; Almerico, A. M.; D'Asdia, I.; Aiello, E. *Heterocycles* **1982**, *19*, 681.
(8) (a) Ruzo, L. O.; Casida, J. E.; Holden, I. *J. Chem. Soc., Chem. Commun.* **1985**, *22*, 1642. (b) Adam, W.; Sauter, M. *Tetrahedron* **1994**, *50*, 11441. (c) Adam, W.; Bialas, J.; Hadjiarapoglou, L.; Sauter, M. *Chem. Ber.* **1992**, 125231.
(9) (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P.; Foresti, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, *21*, 2845. (b) House, G. *J. Org. Chem.* **1958**, *23*, 879. (c) Adam, W.; Smerz, A. K. *Tetrahedron*, **1996**, *52*, 5799.

was performed using both atmospheric pressure chemical ionization (APCI) and electrospray ionization.

LC/MS Conditions. For unequivocal identification of the molecular weight of the unknown impurity, both negative and positive modes of ionization were used. The operating electrospray conditions were 890 V multiplier voltage, 5 kV source voltage, 220 °C capillary temperature, sheath gas flow rate setting of 60, auxiliary gas flow rate setting of 20, and a background pressure of 1.23×10^{-5} Torr. The operating APCI conditions were 890 V multiplier voltage, 3.5 kV source voltage, 3 kV capillary voltage, 150 °C capillary temperature, sheath gas flow rate setting of 80, auxiliary gas flow rate setting of 20, and a background pressure of 1.29×10^{-5} Torr. Data were acquired by scanning the mass spectrometer over the *m*/*z* range of 60−2000. Samples were introduced into the ion source of the mass spectrometer via HP 1100 autosampler. An Intersil C8 column (3.9 mm × 150 mm) and ammonium formate (pH 3)/acetonitrile gradient elution system was used for separation analysis.

Collision-Induced Dissociation Experiments. The optimum relative collision energy parameter was experimentally determined to be 28% by directly infusing standard solution of **1** at a rate of 5 μL/min. During MS/MS/MS experiments, the following ion trap parameters were used: Fixed ionization time, 400 ms; Isolation width, 3 amu; and AGC on with a target setting of 1×10^{-7} Torr.

4-Oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic Acid (2-Fluoro-4-methoxy-phenyl)amide (1). Under nitrogen atmosphere, a mixture of **2** (735 g, 2.32 mol) and ammonium acetate (1249 g, 16.22 mol) in *N*-methylpyrrolidinone (1.47 L) was heated to 100−105 °C for 24 h. The reaction was cooled to 25 °C, and water (13.2 L) was added. The resulting mixture was stirred for 17 h at 25 °C, and filtered. The filter cake was rinsed with water and dried under vacuum at 40−45 °C to give 729 g of crude product as dark brown solids (purity 94.8% by HPLC). The crude product was stirred in methanol (33.7 L), and filtered through Celite. To the filtrate was added 116 L of water, and the resulting slurry was stirred for 24 h. The mixture was filtered, and the solids were dried under vacuum at 40−45 °C to give 567 g of dark colored solids (purity 98.5% by HPLC). This crude product was stirred in acetone (17.0 L), and Darco G-60 (567 g) was added. After stirring for 30 min at 20−25 °C, the mixture was filtered. The filtrate was concentrated under vacuum to ~0.85 L and crystallization occurred. The mixture was granulated for 30 min and then filtered. The filter cake was rinsed with acetone (120 mL) and dried under vacuum at 50−60 °C to yield 320 g (1.01 mol, 43%) of **1** as off-white solids (purity 99.3% by HPLC). ^{1}H NMR δ 12.40 (s, 1H), 12.04 (s, 1H), 8.18 (t, J = 8.8 Hz), 6.91 (s, 1H), 6.89 (dd, 1H, J = 2.4 and 12.8 Hz), 6.72 (dd, 1H, J = 2.4 and 8.8 Hz); ^{13}C NMR δ 200.12, 161.12, 155.88, 155.78, 154.78, 152.34, 146.57, 126.16, 123.62, 120.21, 117.84, 109.55, 101.76, 101.54, 55.56, 40.93, 25.34, 23.11, 20.69 MS *m*/*z* 317 (M + 1), 177, 149.

2-Amino-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[*b*]pyrrole-3-carboxylic Acid (2-Fluoro-4-methoxy-phenyl)amide (3). To 4-nitroaniline (1.57 g, 11.4 mmol) in 6 N HCl (8.55 mL) at 0 °C was added dropwise with 30% $NaNO_2$ solution in water (wt/wt). After 10 min at 0 °C, **1** (1.20 g, 3.8 mmol) with NaOAc (2.50 g) in AcOH (50 mL) was added. The resulting reaction mixture was stirred at room temperature for 3 h and worked up by extraction with ethyl acetate. The 2-azo (47 mg) and *N*-azo (3.0 mg) intermediates were obtained by silica gel column chromatography; 0.87 g of **1** was recovered. The 2-azo intermediate (45 mg) was heated with $SnCl_2$ (100 mg) in AcOH (2 mL) at 80 °C for 1 h to give the desired product **3** (17.5 mg) after preparative TLC purification: ^{1}H NMR δ 12.29 (s, 1H), 8.14 (t, J = 9.2 Hz, 1H), 6.88 (dd, J = 12.8 and 2.8 Hz, 1H), 6.72 (dd, J = 9.2 and 2.8 Hz), 6.48 (s, 2H), 2.83−2.85 (s, 2H), 2.62−2.65 (s, 2H), 1.69−1.76 (s, 2H); ^{13}C NMR δ 198.28, 164.45, 155.07, 154.99, 154.33, 152.39, 148.24, 141.83, 123.38, 120.72, 116.39, 109.33, 101.57, 101.38, 55.52, 40.84, 25.22, 22.98, 20.70; MS *m*/*z* 331 (M + 1), 191, 163, 135.

Acknowledgment

We thank Andy Jessen and Linda Lohr for their technical support in NMR and Brian Chen and Mark Guinn for providing a fractionated sample.

Received for review September 4, 2001.

OP010227U