AN ANOMALOUS PREPARING OF A TETRAHYDRO-2*H*-OXOCINE FUSED PYRROLE DERIVATIVE AND ITS ACID-CATALYZED REARRANGEMENT

Shan-Yen Chou ,* Lien-Shange Chang , and Shyh-Fong Chen
Development Center For Biotechnology, 102, Lane 169, Kang Ning St., Hsichih, Taipei Hsien, Taiwan, R.O.C.

Abstract- Condensation of 5-methylthio-2-benzoylpyrrole (**1**) with spiro[2.5]-5,7-dioxa-6,6-dimethyloctane-4,8-dione (**3**) using excess amount of NaH in DMF gave an anomalous tetrahydro-2*H*-oxocine fused pyrrole (**10**), which then undergoes an acid-catalyzed rearrangement in refluxing toluene/methanol (10:1, v/v) to afford the unexpected anti-aromatic compounds (**15** and **16**).

In the preparation of Ketorolac,[1] an analgesic markted by Roche Co., for the pharmacological studies, one of the literature procedures was followed by us.[2-4] Among the multi-step transformations, one of the key steps is the *N*-alkylation of 5-methylthio-2-benzoylpyrrole (**1**) with sipro[2.5]-5,7-dioxa-6,6-dimethyloctane-4,8-dione (**3**).[5,6] We report herein an anomalous medium-ring fused pyrrole formation during the validation of this transformation and the subsequently rearrangement of one of the resulting fused pyrrole.

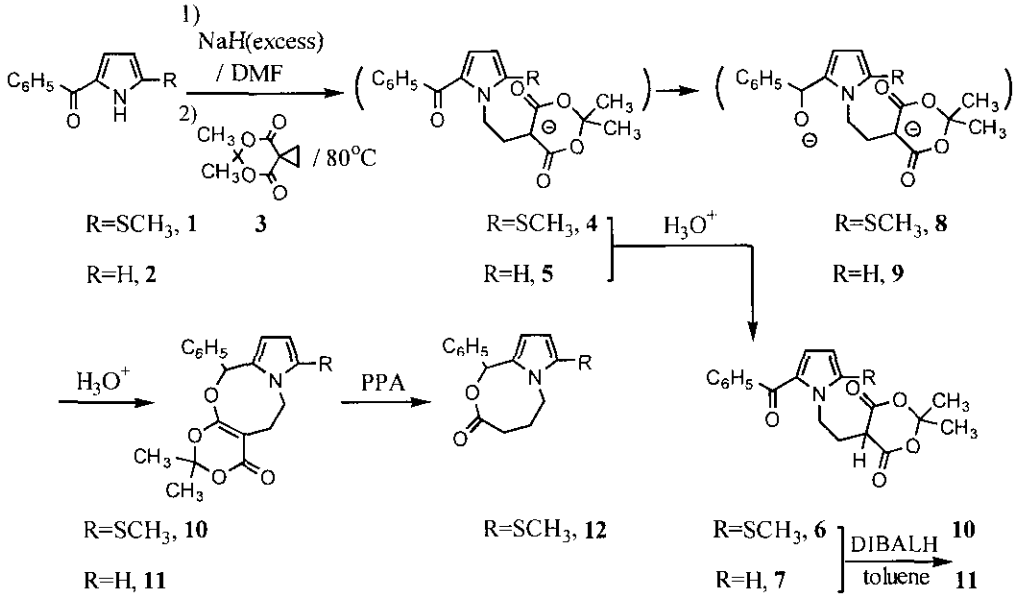
During our initial attempt of the deprotonation of **1** using stoichiometry amount of NaH in DMF, we found that the reaction remains incomplete after a long period of stirring (> 72 h). In order to accelerate the deprotonation process, an excess amount of NaH was employed. Under this condition, we found that the reaction of pyrrole anion and reagent (**3**) gave an unexpected tetrahydro-2*H*-oxocine fused pyrrole (**10**) as the major product (40 %).[7] The desired chain-extension product (**6**) was obtained in comparable yield . The ^{1}H-NMR peaks attributable to four multiplets (4.51, 4.08, 2.91 and 2.48 respectively) of **10** are characteristic of the strained tetrahydrooxocine ring. In order to broaden the scope of this unexpected reaction, **11** was prepared from 2-benzoylpyrrole (**2**)[8] by the similar procedure as that described for the preparation of **10**, but the yield is low (17.5 % based on recovered **2**). As judged from the structures of the condensation products (**10** and **11**), we proposed that the normal chain-extension intermediate (**4**) was

---

#Dedicated to professor **Sheng-Hsu Zee** at National Tsing Hua University on the occasion of his 70 birthday.

reduced by the supplementary NaH to give the intermediate (**8**),[9,10] which was extracted into aqueous phase and spontaneously undergo ring closure during acidic work-up (see EXPERIMENTAL). Compound(**10**)(or **11**) could also been obtained by reduction of **6** (or **7**[3,4,11]) using DIBALH in toluene and followed by acidic work-up. Thus the envisaged mechanism was indirectly proved. At this point, we are interesting to prepare the medium-lactone fused pyrrole (**12**) by the hydrolysis of the dioxinone ring of **10**. Several articles describes the preparation of α-methoxycarbonyl lactones from the structure-related dioxinones.[12-14] However our attempts to accomplish this transformation by using the reaction condition (*p*-TSA·H_2O (cat)/MeOH, reflux) gave recovered starting material and/or complex mixture . Alternatively, upon hydrolysis and decarboxylation of **10** in polyphosphoric acid gave the oxocan-2-one fused pyrrole (**12**), however, the yield is low (~ 18 %) (Scheme 1).

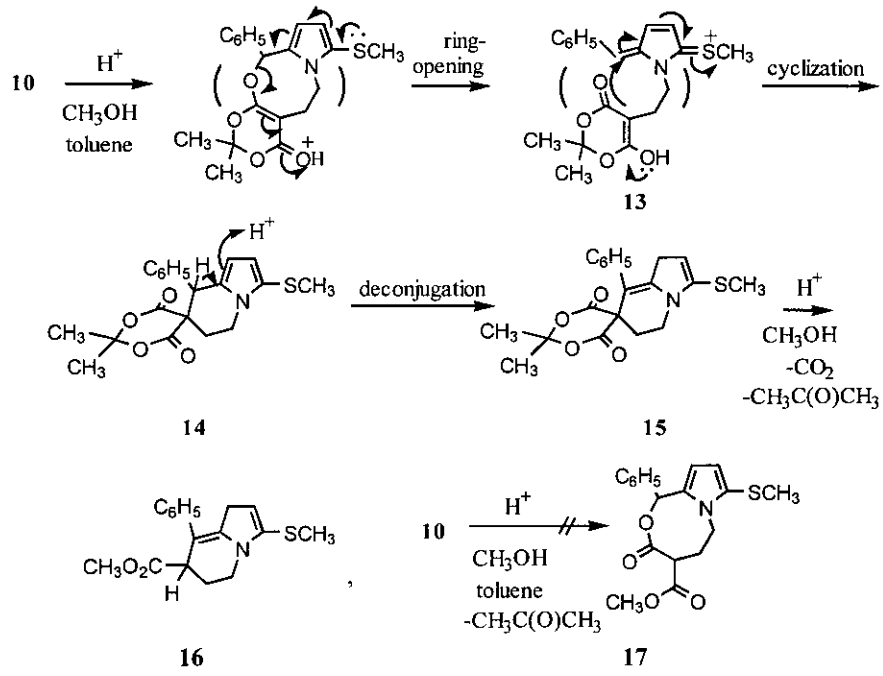
Scheme 1



Interestingly, when **10** was refluxed in a mixture of toluene and methanol (10:1, v/v) in the presence of catalytic amounts of *p*-TSA·H_2O, the acid-catalyzed rearrangement with concomitant ring-contraction and migration of pyrrole double bond to *exo* position of the pyrrole ring were observed (see **15** and **16**, Scheme 2).[14] The desired α-methoxycarbonyl lactone (**17**) and aromatic compound (**14**) were not obtained. The compound (**10**) fails to undergo the abnormal rearrangement in the absence of methanol and/or acid. For comparison purposes, we also examined the rearrangement of **11** under the same conditions. Surprisingly, most of **11** was recovered and no such abnormal rearrangement product was isolated. These results suggest that methanol might catalyze or stabilize the cation center of the charged intermediate (**13**) and methylthio group plays an important role in reaction. Our proposed mechanism is

outlined in Scheme 2.

Scheme 2



Acid-catalyzed ring-opening of **10**, followed by intramolecular *C*-alkylation of **13** gives the enol-keto rearrangement intermediate (**14**), which undergoes acid-catalyzed deconjugation of the pyrrole ring to afford the product (**15**). Characteristic ^{1}H-NMR peaks appear at 3.94(s, 2H) and 6.05(s, 1H) , which are attributable to allylic CH_2 and olefinic CH respectively. Finally, fragmentation of **15** in a long period of heating affords **16**. We proposed that the torsional strain between the phenyl ring and the rigid dioxanone ring could be released if the pyrrole double bond migrates to *exo* position. In order to gain some insight of this assumption, energy minimization of the conformations of the aromatic compound (**14**) and anti-aromatic compound(**15**)indicates that **15** is 0.42 Kcal mol^{-1} more stable than **14**.[15] Moreover, we proposed that the lone pair electrons of pyrrole nitrogen in **15** could be delocalized to the phenyl ring system through the exocyclic double bond, which might contribute some energy preference. In summary, a reduction of the benzoylpyrrole derivatives (**6** or **7**) and the spontaneously acid-catalyzed cyclization illustrate a pathway to prepare the medium-ring fused pyrrole derivative (**10**).[16, 17] In comparison with the fact that the dioxinone ring be merely converted to α-methoxycarbonyl lactone by methanol,[12-14] the enol-keto rearrangement with concomitant deconjugation and/or fragmentation of the strained ring system **10** seem quite unusual.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 577 spectrophotometers, NMR spectra were recorded on a Bruker-AC 200 (200 MHz) spectrometer, $CDCl_3$ and DMSO-d_6 were used as solvents, and TMS was added as an internal standard. If determined, the type of carbon in ^{13}C NMR spectra is indicated in parentheses after the chemical shift : 0, quaternary, 1, methine, 2, methylene, and 3, methyl. Elemental analysis were determined by a Perkin-Elmer 2400. MS spectra and high-resolution MS spectra were measured on JEOL-JMS-D100 and JEOL-JMSD-HX100 instruments respectively. Melting points were measured in open capillary tubes using Buchi immersion apparatus, and are uncorrected. Separations by flash chromatography were performed on silica gel (230-400 mesh). All reagents were of commercial quality and were used as received.

The tetrahydro-2*H*-oxocine fused pyrrole derivative (10).

method A : preparation of **10** from **1** and **3** using NaH.

run A: To an ice cooled solution of **1** (10.6 g, 48.85 mmol) in DMF (600 mL) was carefully added NaH (10 g of 60 % in mineral oil, 250 mmol) in one portion. After 30 min, the ice-bath was removed and stirring was continued for 15 h at 25 °C. Then additional amount of NaH (4.0 g of 60 % in mineral oil, 100 mmol) was introduced and followed by addition of a solution of **3** (8.7 g, 51.2 mmol) in DMF (100 mL). The resulting mixture was stirred at 80 °C for 4 h and evaporated on vacuum. The residue was taken into ethyl acetate and water. The phases were separated. The aqueous phase was acidified with 3 N aqueous HCl and extracted three times with ethyl acetate. The combined extracts were washed successively with 5 % aqueous NaOH and water. The separated organic phase was dried ($MgSO_4$) and evaporated, the residue was purified by flash column chromatography using 1 : 5 (v/v) ethyl acetate-hexane to give **10** (7.2 g, 39.7 %) as a white powder, mp 196-197 °C (3:1 hexane/ethyl acetate). IR (KBr) ν_{max} : 1770, 1730 cm^{-1}.^{1}H-NMR ($CDCl_3$) : 7.30-7.40 (m, 5H), 6.39 (s, 1H), 5.67 (s, 1H), 4.95 (s, 1H), 4.51 (m, 1H), 4.08 (m, 1H), 2.91 (m, 1H), 2.48 (m, 1H), 2.33 (s, 3H), 1.63 (s, 3H), 0.83 (s, 3H). MS (70 eV) m/z (%): 371 (M^+, 100), 285 (50), 269 (40), 226 (40), 222 (20), 192(50). Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.69; H, 5.66; N, 3.77. Found : C, 64.66; H, 5.53; N, 3.65. The aqueous phase was acidified with 3 N HCl and extracted with ethyl acetate. The organic layer was washed twice with water, dried ($MgSO_4$) and evaporated. The residue was trituated with isopropyl ether to give **6** (7.18 g, 38.0 %) as a white powder, mp 122-124 °C (3:1 isopropyl ether/ethyl acetate). The spectra data are identical with literatures.[2]

run B : A scale up experiment was accomplished except that the reaction was carried out in a higher concentration and sodium hydride was added in one portion rather stepwisely. The amount of each reagent are listed as follows : **1** (21 g, 96.8 mmol), DMF (700 mL), sodium hydride (14 g of 60 % in mineral oil, 350 mmol), the solution of **3** (16.5 g in 100 mL DMF, 97.1 mmol). The yield of **10** is 16.7 g (44.6 %). Compound (**6**) (12.7 g, 34.0 %) was obtained by the similar procedures as that described in run A.

method B: preparation of **10** from **6** using DIBALH.

To an ice-cooled solution of **6** (1.0 g, 2.58 mmol) in toluene (15 mL) was injected DIBALH (1 M in hexane, 8.0 mL). After stirring for 2 h at 0 °C and rt for 5 h. The mixture was cooled to 0 °C and titrated carefully with 3 N HCl to pH 1 and stirred at 0 °C for 2 h. After standing at rt overnight , the mixture was filtered from Celite with the aid of ethyl acetate until the filtrate turned from yellow to colorless .The separated organic phase was washed twice with water, dried ($MgSO_4$) and evaporated to give a dark oil. Purification on silica gel using 1/8 (v/v) ethyl acetate-hexane gave in successively **10** (0.32 g, 46.4 % based on recovered **6**) and **6** (0.28 g, 28.0 % recovery).

The tetrahydro-2*H*-oxocine fused pyrrole derivative (11).

Method A: preparation of **11** from **2** and **3** using NaH.

The title compound (**11**) (0.9 g, 17.5 % based on recovered **2**) was prepared from **2** (4.32 g, 25.3 mmol) and **3** (4.5 g, 26.5 mmol) by the similar procedure as that described in the method A of the former procedures; white powder, mp 160-161 °C (1 : 5 ethyl acetate-hexane). IR (KBr) ν_{max}: 1740, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 7.50 (m, 2H), 7.40 (m, 3 H), 6.73 (s, 1H), 6.21 (s, 1H), 5.66 (s, 1H), 4.98 (s, 1H), 4.32 (m, 1H), 4.24 (m, 1H), 2.95 (m, 1H), 2.39 (m, 1H), 1.63 (s, 3H), 0.83 (s, 3H). MS (70 eV) m/z (%) 325 (M^+, 60), 239 (92), 223 (40), 194 (84), 168 (100). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.15; H, 5.85; N, 4.31. Found : C, 69.95; H, 5.76; N, 3.98. Compound (**7**) (1.4 g) was isolated from 5 % aqueous NaOH washings by the similar procedure as described for the isolation of **6**. It was obtained as a white powder, mp. 116-117 °C (isopropyl ether). The spectral data of **7** are identical with literature values.[3,4]

method B: preparation of **11** from **7** using DIBALH.

The title compound (**11**) (0.17 g, 19.8 %) was prepared from **7** (0.9 g, 2.64 mmol)[3,4,13] by the similar procedure as that described in former procedure. No recovered **7** was isolated.

The oxocan-2-one fused pyrrole derivative (12). A mixture of **10** (0.66 g, 1.78 mmol) and 50 mL of 100 % polyphosphoric acid was heated at 55 °C for 15 h and 100 °C for 2 h. Then the cooled mixture was poured into ice water and extracted with dichloromethane. The organic layer was washed successively with 10% $NaHCO_3$ and water. The phases were separated and the organic phase was dried ($MgSO_4$) and evaporated to leave a dark oil. The oil was purified on silica gel using 1/1(v/v) ethyl acetate-hexane as eluent to give **12** (0.09 g, 17.6 %). mp 139-140 °C (1:1 ethyl acetate-hexane). IR (KBr) ν_{max}: 1700, 1438, 1300, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 7.25-7.35 (m, 5H), 6.63 (s, 1H), 5.58 (s, 1H), 4.34, 4.32 (each s, 1H), 4.16(m, 1H), 4.07(m, 1H), 2.97 (m, 1H), 2.34 (m, 3H), 2.31 (s, 3H). MS (70 eV) m/z (%): 287 (M^+, 100), 272 (10), 240 (100), 195 (36), 167 (20), 87 (72). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.89; H, 5.92; N, 4.87. Found: C, 66.87; H, 5.76; N, 4.76.

The anti-aromatic compound (15). A solution of **10** (0.28 g, 0.755 mmol) and *p*-TSA·H_2O (0.035 g, 0.18 mmol) in a mixture of methanol (5 mL) and dry toluene (25 mL) was refluxed under nitrogen atmosphere for 50 h. The mixture was evaporated to remove methanol. The residue was diluted with equal volume of ethyl acetate and washed twice with water. The organic layer was dried ($MgSO_4$) and evaporated, the residue was purified on silica gel using ethyl acetate-hexane (1:10, v/v) to give in successively recovered **10** (0.19 g, 68 % recovery) and **15** (0.05 g, 55.5 % based on recovered **10**). mp 146-147 °C (1 : 10 ethyl acetate-hexane). IR (KBr) ν_{max}: 3000, 2920, 1750 cm^{-1}.^{1}H-NMR ($CDCl_3$) : 7.22-7.40 (m, 5H), 6.05 (s, 1H), 4.02 (t, J=6.6 Hz, 2H), 3.94 (s, 2H), 3.06 (t, J=6.6 Hz, 2H), 2.21 (s, 3H), 2.02 (s, 3H), 1.83 (s, 3H), ^{13}C-NMR ($CDCl_3$) : 168.24 (0), 138.20 (0), 135.38 (0), 128.81 (0), 128.63 (1), 128.60 (1), 126.52 (1), 116.39 (1), 106.00 (0), 105.70 (0), 51.73 (0), 44.64 (2), 41.45 (2), 33.20 (2), 29.76 (3), 28.28 (3), 20.30 (3). Ms (70 ev) m/z (%) : 371 (M^+, 60), 286 (16), 269 (100), 241(40), 196 (20), 150 (26). Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.69; H, 5.66; N, 3.77. Found: C, 64.76; H, 5.57; N, 3.73.

The anti-aromatic compound (16). A solution of **10** (0.56 g, 1.51 mmol) and *p*-TSA·H_2O (0.07 g, 0.37 mmol) in a mixture of methanol (10 mL) and dry toluene (50 mL) was refluxed under nitrogen atmosphere for five days, and worked-up as described in compound **(15)**. The obtained crude product was purified on silica gel using ethyl acetate-hexane (1:20, v/v) to give in successively **16** (0.20 g, 60.1 % based on recovered **10**), **10** (0.15 g, 26.8 % recovery) and **15** (0.06 g, 14.6 % based on recovered **10**) . IR (film) ν_{max}: 2920, 1740, 1430, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : 7.20-7.30 (m, 5H), 6.00 (s, 1H), 4.03 (m, 1H), 3.87 (s, 2H), 3.84 (m, 1H), 3.76 (s, 3H), 3.67 (m, 1H), 2.70 (m, 2H), 2.28 (s, 3H). MS (70 eV) m/z (%): 301 (M^+, 52), 242 (100), 227 (12), 194 (20). HR-EIMS : Found 301.1136 (M^+), Calcd for $C_{17}H_{19}NO_2S$: 301.1137.

ACKNOWLEDGEMENTS

We would like thank to the Ministry of Economic Affairs, R.O.C. for their financial support. Analytical support by Dr. Yuh-Shan Chung's group of Development Center for Biotechnology is greatly appreciated.

REFERENCES AND NOTES

1. A more efficient process was developed recently, therefore, the process validation was discontinued, see: M. P. Fleming and H. N. Khatri, *Eur. Pat. Appl.*, 1989, 0284076 (*Chem. Abstr.*, 1989, **110**, 76304).
2. F. Franco, R. Greenhouse, and J. M. Muchowski, *J. Org. Chem.*, 1982, **47**, 1682.
3. J. M. Muchowski and I-S Cho, *U. S. Patent*, 1992, 5,082,950 (*Chem. Abstr.*, 1992, **116**, 255473).
4. J. M. Muchowski and I-S Cho, *U. S. Patent*, 1992, 5,082,951 (*Chem. Abstr.*, 1992, **116**, 214338).

5. R. K. Singh and S. Danishefsky, *J. Org. Chem.*, 1975, **40**, 2969.
6. R. K. Singh and S. Danishefsky, *Organic Syntheses*, Coll. Vol.,7, 1990, 411.
7. The problem has been resolved by using stoichiometric amounts of **1** and **3**, and slight excess amount of sodium hydride. In this instance only the desired chain-extension product (**6**) was obtained.
8. G. McGillivray and J. White, *J. Org. Chem.*, 1977, **42**, 4248.
9. Reduction of the carbonyl groups with sodium hydride has been observed only with aldehydes or ketones having no α-hydrogen, see: F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, 1946, **68**, 2647.
10. Several articles describe the scope of sodium hydride-containing "complex reducing agents", see: R. C. Larock, "*Comprehensive Organic Transformations*", VCH Publishers Inc., New York, 1989, p. 534, 540.
11. Compound (**7**) was prepared by the known method with slight modification (see ref. 7). The obtained crude product was purified by trituation with isopropyl ether to give a white powder, mp 116-117 °C. No precedent literature reported the purification and its melting point.
12. L. F. Tietze, G. V. Kiedrowski, K-G. Fahlbusch, and E. Voss, *Organic Syntheses*, Coll. Vol., **8**, 1993, 353.
13. S. Takano, T. Sugihara, S, Satoh, and K, Ogasawara, *J. Am. Chem. Soc.*, 1988, **110**, 6467.
14. A dioxinone derivative was converted into α-keto ester by heating in toluene containing catalytic amounts of *p*-TSA·H_2O and methanol, see: M. Sato, S. Sunami, S, Y. Sugita, and C. Kaneko. *Chem. Pharm. Bull.*, 1994, **42**, 839.
15. The conformational analyses were carried out by using geometry optimization and minimum energy conformations calculation within SYBYL.
16. Several literatures reported the construction of 8-11 membered cyclic ether derivatives and related medium-ring systems, see: K. C. Nicolaou, C. V. C. Prasad, C.-K Hwang, M. E. Duggan, and C. A. Veale, *J. Am. Chem. Soc.*, 1989, **111**, 5321 and references cited therein.
17. A facile method for the formation of eight-membered rings involving one double bond has been reported, see: Y. Torisawa, T. Hosaka, K. Tanabe, N. Suzuki, Y. Motohashi, T. Hino, and M, Nakagawa, *Tetrahedron*, 1996, **52**, 10597 and references cited therein.

Received, 20th November, 1998