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SHORT COMMUNICATION

THE SYNTHESIS OF IMIDAZO[4',5':5,6]CYCLOOCTA[1,2-*B*]QUINOXALINE-2-ONES AND A – THIONE

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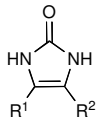
ABSTRACT. At present study, we synthesized the imidazo[4',5':5,6]cycloocta[1,2-*b*]quinoxaline-2-ones (-2-thione) with an additional double bond in the eight-membered ring via the reaction of a quinoxaline-fused cyclooctane-1,2-dione with urea (or thiourea) and *N,N'*-dimethylurea.

KEY WORDS: Quinoxaline, Imidazolone, Thioimidazolone, Cyclooctane-1,2-dione

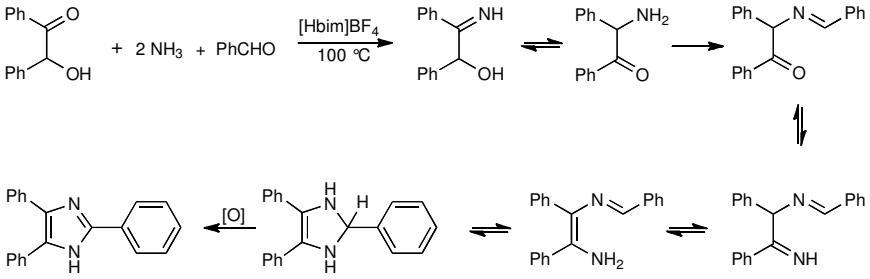
INTRODUCTION

The synthesis of some cyclooctane-based pyrazines and quinoxalines was reported from a cycloocta-quinoxaline-dione and 1,2-diamines [1]. As an extension of this, we considered using urea (thiourea) anticipating the formation of fused imidazolones. Imidazolones are of interest because they are found in natural products [2, 3] and have intermolecular proton transfer capability [4]. 1,3-Dihydroimidazol-2-ones derivatives show some biological activity [5, 6]. Enoximone posseses cardiotonic, vasodilative and contraceptive properties [7]. Niizato and coworkers reported piroximone for treatment of diabetes [8].

Enoximone: R^1 = Me, R^2 = 4-$MeSC_6H_4CO$
Piroximone: R^1 = Et, R^2 = isonicotinoyl



2-Hydroxyketones (α-ketols) cyclocondense with amines or ammonia generating imidazoles, for example as shown in Scheme 1, the sequence requiring an oxidative step at some stage, to achieve eventual aromatization [9].



Scheme 1

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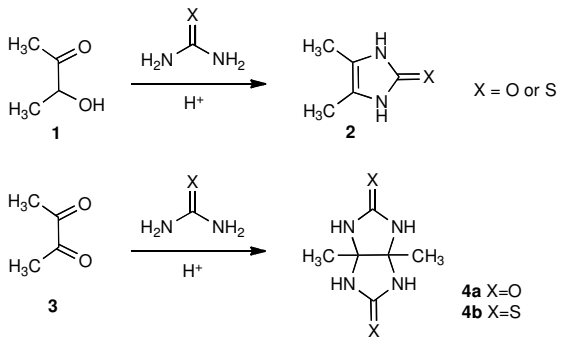
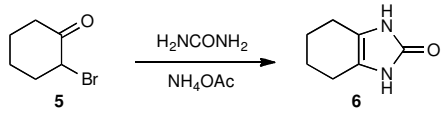
From the reaction of a α-ketol, e.g. **1** with urea (or thiurea), an imidazolone, e.g. **2** (or a thioimidazolone) is produced directly – no oxidative step is required – Scheme 1 suggests a reasonable sequence in this example. At a higher oxidation level, the reaction of a α-diketone, e.g. **3**, with urea and thiourea gives glycoluril **4a** or thioglycoluril **4b** (Scheme 2) [10].



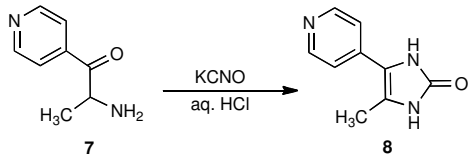
Scheme 2

An alternative pathway to imidazolones is the reaction of urea and an α-bromo-ketone, e.g. **6** from **5** (Scheme 3) [11].



Scheme 3

Imidazol-2-ones, e.g. **8** can also be produced by reaction of potassium cyanate with α-amino-ketones, e.g. **7** (Scheme 4) [12].

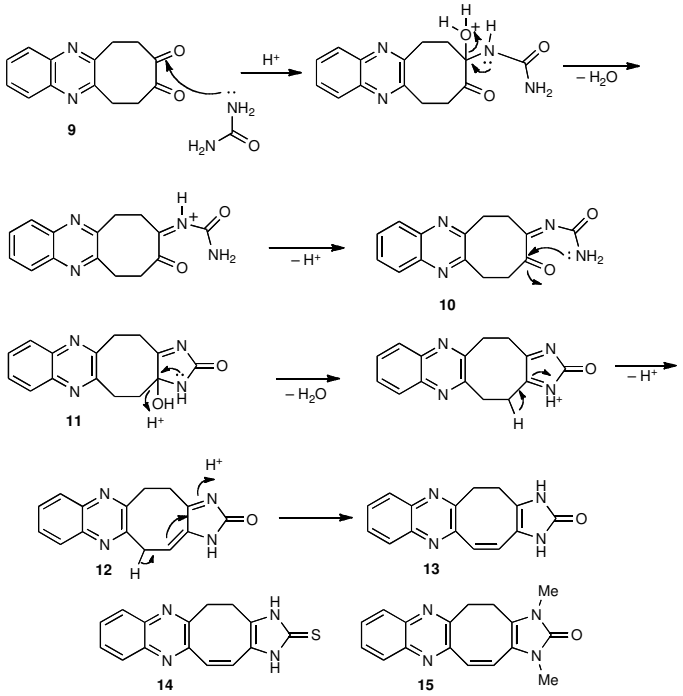


Scheme 4

RESULTS AND DISCUSSION

We anticipated that α-diketone **9** would react with a urea/thiourea to produce a glycouril/thioglycuril type of structure. However, we found that in the reaction of **9** with urea/thiourea, the higher oxidation level was accommodated, not by formation of a glycoluril, but by loss of water, generating an additional double bond in the eight-membered ring. Scheme 5 shows how the sequence can be envisaged for the reaction of **9** with urea, generating **10**. Thus addition of urea amino group to one carbonyl and loss of water would produce **10**. Now, an intramolecular addition of the second amino group to the other carbonyl group would generate

11 from which loss of one water molecule, then a proton from the eight-membered ring, would form **12**, which produces the aromatic imidazolone by tautomerism, finally forming **13**. The order in which the two molecules of water are lost could be different from that shown. From reaction with thiourea, product **14** was obtained and from *N,N'*-dimethylurea, we produced compound **15**. The structures follow from the spectroscopic data discussed below.



Scheme 5

In the ^{1}H NMR spectrum of the new products, the resonances of the introduced double bond protons appeared as doublets at δ 6.98 and 7.12 ppm for **13**, 7.09 and 7.20 for **14**, and 7.02 and 7.15 for **15**, with coupling constants of 12.9, 13.2, and 12.6 Hz, respectively, consistent with the necessary *cis* orientation of the eight-ring endocyclic double bonds. In addition each compound had signals for four protons of the two methylene groups of the cyclooctene rings, for **13** two triplets at δ = 3.44 and δ = 3.76 (J = 6.3 Hz), for **14** two triplets at δ = 3.55 and δ = 3.78 (J = 6.3 Hz), and for **15** δ = 3.42 and δ = 3.81 (J = 5.4 Hz). The four quinoxaline benzene ring signals were in the range δ = 8.16-8.41 in each case. For **13** and **14** there were two broad singlet signals for the N-hydrogens at 8.60, 8.80 and 9.8, 10.1 ppm. The two N-methyl groups of product **15** showed at δ = 3.35 and 3.36. The IR spectra of compounds **13** and **14** showed two absorption bands: one at 3403 cm^{-1} and the other at 3392 cm^{-1} for (N-H) and 1720 cm^{-1} for (C=O) and 1632 cm^{-1} for (C=S), respectively. The IR spectrum of compound **15** showed an absorption band at 1676 cm^{-1} for (C=O).

CONCLUSION

The synthesis of the novel eight-membered ring-containing quinoxaline and imidazolone or thioimidazolone is described in this paper. The subject of study, specially reaction with other N-substituted urea or thiourea and various 1,3-diamines is ongoing.

EXPERIMENTAL

General procedure. All substrates were purchased from Merck and used without further purification. Melting points were determined on a digital melting point apparatus (electrothermal) and are uncorrected. Infrared spectra were recorded on a Thermonicolet (Nexus 670) FT-infrared spectrometer and measured as KBr discs. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in $CDCl_3$ using TMS as the internal reference. High resolution mass spectra were recorded on an Agilent Technology (HP), MS Model: 5973 Network Mass, Selective Detector Ion Source: Electron Impact (EI) 70 eV, Ion source temperature: 230 ºC, Analyzer: quadrupole, Analyzer temperature: 150 ºC and relative abundances of fragments are quoted in parentheses after the m/z values.

6,7,8,9,10,11-Hexahydrocycloocta[b]quinoxaline-8,9-dione ***9***. To a mixture of $KMnO_4$ (4.0 g), $CuSO_4.5H_2O$ (2.0 g), and water (300 mL) in dichloromethane (15 mL) was added solid $Cu(OAc)_2.H_2O$ (1.0 g) and **9** (0.276 g, 2 mmol) in dichloromethane (5 mL), and tert-butyl alcohol (1 mL). After 12 h, the reaction mixture was filtered, and solvent was removed to yield dione. M.p. 182-185 ^{o}C; ^{1}H NMR ($CDCl_3$) δ = 3.02 ppm (t, J = 6.45 Hz, 4H), 3.45 (t, J = 6.45 Hz, 4H), 7.76 (dd, J_1 = 6.3 Hz, J_2 = 3.6 Hz, 2H), 8.02 (dd, J_1 = 6.3 Hz, J_2 = 3.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 31.57ppm, 39.56, 128.69, 130.20, 141.73, 153.04, 206.37; FT-IR (KBr) ν_{max}/cm^{-1}: 2923, 1703; MS (EI, 70 ev): *m/z* (%) 240 (M^+, 60), 212 (30), 183 (100), 169 (86). Found: M^+; 240.0900, $C_{14}H_{12}N_2O_2$ requires M^+ 240.0899.

Method A. The mixture of α-diketone **13** (0.41 mmol) and urea (1 mmol) in ethanol (3 mL) and some concentrate hydrochloric acid was refluxed for 6 h. The product of reaction was precipitated. The mixture of reaction was filtered and dried.

Method B. The mixture of α-diketone **13** (0.41 mmol) and urea (1 mmol) in benzene (15 mL) and some trifloroacetic acid was heated at refluxed in a Dean-Stark apparatus for 6 h. The product of reaction precipitated and was filtered of and dried.

1,3,4,5-Tetrahydro-2H-imidazo[4′,5′:5,6]cycloocta[1,2-b]quinoxaline-2-one ***13***. 60% yield, m.p. > 300 ^{o}C. ^{1}H NMR ($CDCl_3$ + CF_3COOH) ppm δ: 3.44 (t, J = 6.3 Hz , 2H), 3.76 (t, J = 6.3 Hz , 2H), 6.98 (d, J = 12.9 Hz , 1H), 7.12 (d, J = 12.9 Hz, 1H), 8.16-8.20 (m, 2H), 8.32-8.41 (m, 2H), 8.6 (bs, 1H), 8.8 (bs, 1H). ^{13}C NMR ($CDCl_3$ + CF_3COOH) ppm δ: 26.73, 29.68, 115.63, 119.98, 121.10, 123.89, 124.91, 125.68, 128.41, 135.64, 135.25, 137.95, 147.96, 153.27, 153.88. FT-IR (KBr) ν_{max}/cm^{-1}: 3403, 3137, 3020, 2848, 1720. MS (EI, 70 eV): m/z (%) 264 (M^+, 100), 249 (13), 237 (13), 220 (12). Found: M^+; 264.1012, $C_{15}H_{12}N_4O$ requires M^+; 264.1011.

1,3,4,5-Tetrahydro-2H-imidazo[4′,5′:5,6]cycloocta[1,2-b]quinoxaline-2-thione ***14***. 60% yield, m.p. > 300 ^{o}C. ^{1}H NMR ($CDCl_3$ + CF_3COOH) ppm δ: 3.55 (t, J = 6.6, 2H), 3.78 (t, J = 6.6 Hz, 2H), 7.09 (d, J = 13.2 Hz, 1H), 7.20 (d, J = 13.2 Hz, 1H), 8.178-8.20 (m, 2H), 8.38-8.32 (m, 2H). 9.8 (bs, 1H), 10.1 (bs, 1H). ^{13}C NMR ($CDCl_3$ + CF_3COOH) ppm δ: 26.128, 29.27, 123.05,

123.36, 125.27, 125.41, 126.75, 130.18, 135.40, 135.42, 135.76, 137.63, 147.65, 149.93, 153.13. FT-IR (KBr) ν_{max}/cm^{-1}: 3428, 3022, 3853, 1632, 1600, 1485, 1226, 759. MS (EI, 70 eV): m/z (%) 280 (M^+, 100), 265 (12), 243 (28), 220 (19). Found: M^+; 280.0783, $C_{15}H_{12}N_4S$ requires M^+; 280.0783.

1,3-Dimethyl-1,3,4,5-tetrahydro-2-H-imidazo[4',5':5,6]cycloocta[1,2-b] quinoxaline-2-one ***15***. 55% yield, m.p. > 300 ^oC. ^1H NMR ($CDCl_3$) ppm δ: 3.35, (s, 3H), 3.36 (s, 3H), 3.415 (t, overlaping with CH_3, 2H), 3.81 (t, *J* = 5.4 Hz, 2H), 7.02 (d, *J* = 12.6 Hz, 1H), 7.15 (d, *J* = 12.6 Hz, 1H), 8.09-8.21 (m, 2H), 8.27-8.40 (m, 2H). ^{13}C NMR ($CDCl_3$) ppm δ: 24.31, 27.07, 27.73, 31.25, 114.73, 121.47, 122.43, 126.84, 128.43, 129.11, 129.32, 129.82, 130.14, 140.75, 141.65, 151.18, 154.80. FT-IR (KBr) ν_{max}/cm^{-1}: 3421, 1676, 764, 592. MS (EI, 70 eV): m/z (%) 292 (M^+, 100), 277 (44), 265 (23), 234 (14). Found: M^+; 292.1323, $C_{17}H_{16}N_4O$ requires M^+ ; 292.1324.

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