Revisiting the *Hinsberg* Reaction: Facile and Expeditious Synthesis of 3-Substituted Quinoxalin-2(1*H*)-ones under Catalyst-Free Conditions in Water

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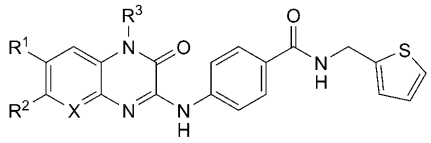
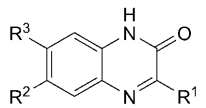
Substituted benzene-1,2-diamine reacted with various α-keto esters at 50° under mild conditions for 15 min using H_2O as reaction medium, providing a variety of 3-substituted quinoxalinone derivatives in excellent yields. The reaction was instantaneous, and products were isolated by simple filtration.

Introduction. – Heterocycles have been very important structural motifs in medicinal chemistry. The *Hinsberg* reaction [1] is a practical method to obtain 3-substituted quinoxalin-2(1*H*)-one derivatives. Quinoxalinones, a class of N-containing structural compounds, attracted the attention of many scientists [2]. These quinoxalinone derivatives are versatile scaffolds for drug-related molecules [3] (*Fig.*), and they possess a wide variety of biological activities such as anti-inflammatory, antimicrobial [4], antidiabetic [5], and antiviral against retroviruses including HIV [6]. Moreover, these quinoxalinones can be identified as platforms for diversity-oriented synthesis in solid phase [7], and they are established as inhibitors of aldose reductase [8], and agonists of γ-aminobutanoic acid (GABA)/benzodiazepine receptor complex [9].



X = CH, R^1 = H, R^2 = F, R^3 = Me
IC_{50} = 0.14 mM ± 10%
Quinoxalinone derivative with glycogen phosphorylase-inhibitory activity



R^1 = CH_2Br, R^2 = H, R^3 = CF_3
Quinoxalinone derivative with antitumor activity

Figure. *Biologically active quinoxalinone derivatives*

Fernandez and co-workers reported the kinetic study on *Hinsberg* reaction by reacting unsymmetrical benzene-1,2-diamines with pyruvate (2-oxopropanoate) derivatives and explained the positional isomerism [10]. To improve the regioselectivity in the positional isomerism, *Lumma et al.* synthesized the related compounds in acidic medium [11]. Recently, *Ballini et al.* developed a one-pot synthesis of polyfunctionalized dihydroquinoxalinone derivatives *via* anti-*Michael* reaction [12]. *Suschitzky et al.* described the reactions of benzene-1,2-diamine with different acetylenedi-

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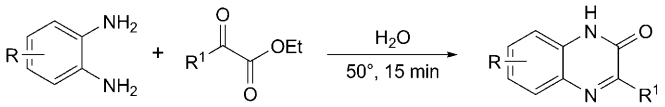
carboxylates [13], and *Mahaney et al.* reported the synthesis of quinoxalinone core moiety by nucleophilic aromatic substitution of *o*-halo nitrobenzene with chiral 2-aminobutanoic acid, followed by reduction and cyclization [14]. *Moglioni* and co-workers prepared several chemotherapeutic quinoxalinone derivatives by using *S. cerevisiae* as a biocatalyst and also by means of microwave-assisted organic synthesis [15]. In general, most of these methods involve use of toxic/volatile organic solvents with longer reaction times, poor yields, and tedious product-isolation procedures.

With 'green chemistry' becoming an important branch of chemistry, there is surge in environment-friendly and clean synthetic processes [16], which address the problem faced by conventional organic synthetics. H_2O is a cheap, nontoxic and environment-friendly solvent, which precludes environmental hazards associated with organic solvents. In continuation of our efforts towards developing 'green' synthetic protocols [17], we report the synthesis of 3-substituted quinoxalinones in H_2O under mild and catalyst-free conditions.

Results and Discussion. – In our initial study towards the development of cyclocondensation reaction, benzene-1,2-diamine (**1**) and ethyl pyruvate (=ethyl 2-oxopropanoate; **2**) were warmed in H_2O at 50° for 15 min to furnish 3-methylquinoxalin-2(1*H*)-one (**3**) in 89% yield (*Scheme 1*). The same reaction, when run at room temperature, was very slow, and in some cases, at room temperature the solubility of substituted benzene-1,2-diamine in H_2O was not sufficient. So, to circumvent this situation, we have carried out the reaction at optimal temperature (50°). The progress of the reaction could be simply monitored by naked eye, as solid separated out of the medium. Initially, benzene-1,2-diamine (**1**) was dissolved in H_2O at 50°. At this temperature, ethyl pyruvate (**2**) was added, and the mixture was stirred until precipitation of the product **3** from H_2O. The same protocol was extended by reacting different substituted benzene-1,2-diamines with various α-keto esters, and the corresponding products were characterized by ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectrometry, and the results were compiled in the *Table*.

Scheme 1. *Synthesis of 3-Substituted Quinoxalinones in H_2O*

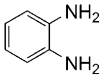
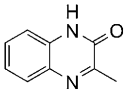
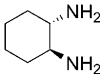
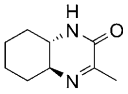
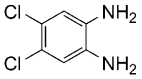
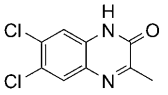
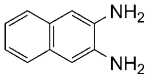
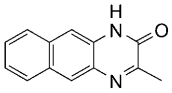
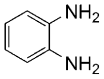
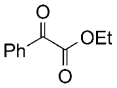
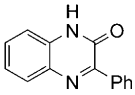
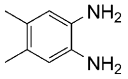
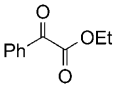
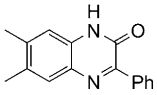
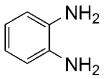
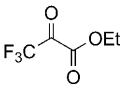
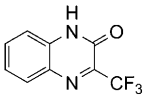
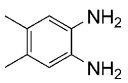
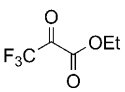
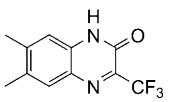
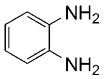
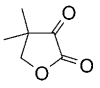
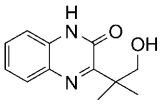
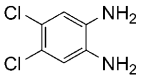
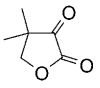
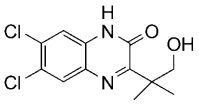
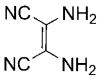
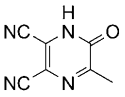


1 **2** **3**

The plausible mechanism involves the intermolecular condensation of benzene-1,2-diamine with the α-keto group of the ester to produce an intermediate ethyl 2-[(2-aminophenyl)imino]propanoate, which undergoes intramolecular cyclization to afford the corresponding 3-substituted quinoxalinone derivatives (*Scheme 2*).

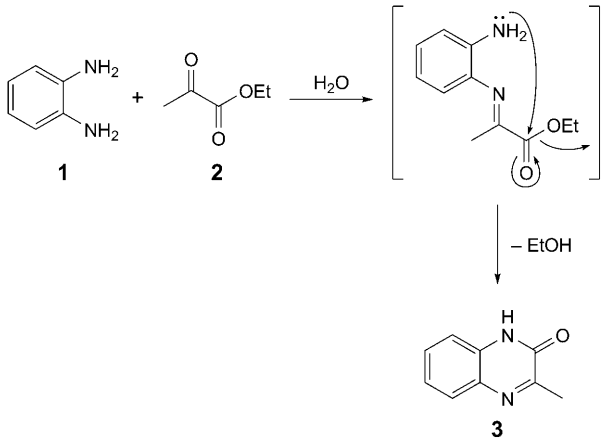
Conclusions. – We have developed a facile 'green' protocol for the synthesis of a wide variety of 3-substituted quinoxalinone derivatives. This methodology is advantageous over the existing methods in terms of rapid product isolation, operational simplicity, which precludes organic solvents.

Table. *Synthesis of 3-Substituted Quinoxalinones in H_2O under Mild Conditions*[a])

Entry	Diamine	Pyruvate	Product	Yield [%][b])
1				89
2				80[c])
3				85
4				75
5				81
6				83
7				82
8				85
9				84
10				72
11				68

[a]) Reaction conditions: benzene-1,2-diamine (1.0 mmol), pyruvate derivative (1.0 mmol), and H_2O (3 ml). [b]) Yields of isolated product after recrystallization. [c]) Yield of isolated product after column chromatography.

Scheme 2. *Mechanistic Pathway*



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Experimental Part

General. All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from *Fluka* and *S. D. Fine Chemicals.* TLC: Precoated silica-gel plates (*60 F_{254}*, 0.2-mm layer; *E. Merck*). M.p.: *Fischer–Johns* apparatus; uncorrected. ^{1}H-NMR Spectra: *Varian 200* or *Bruker 300* spectrometer; in $CDCl_3$; δ in ppm rel. to TMS as internal standard, *J* in Hz. MS: *VG Autospec*; in *m*/*z*.

General Procedure for the Synthesis of 3-Substituted Quinoxalinone Derivatives in H_2O. Benzene-1,2-diamine (1.0 mmol) was dissolved in H_2O at 50°, and under stirring α-keto ester (1.0 mmol) was added. After 15 min, the solid product precipitated from H_2O. This solid was filtered and recrystallized from EtOH to obtain the corresponding quinoxalinone derivative.

Recrystallization Procedure. After the reaction, the crude product was filtered and taken in hot EtOH (5 ml). The resulting supersaturated soln. was allowed to attain r.t. and was further cooled in refrigerator to obtain the pure product which was filtered, dried, and analyzed by spectroscopic techniques (^{1}H- and ^{13}C-NMR, and ESI-MS).

*3-Methylquinoxalin-2(1*H*)-one* (*Table*, *Entry 1*). Light yellow solid. M.p. 249–250°. ^{1}H-NMR (300 MHz, $CDCl_3 + (D_6)$DMSO): 6.72–6.64 (*m*, 1 H); 6.34–6.11 (*m*, 3 H); 1.50 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3 + (D_6)$DMSO): 158.2; 154.6; 133.5; 131.0; 128.2; 126.9; 122.1; 114.5; 19.6. ESI-MS: 161 ($[M+H]^+$).

*(4a*S*,8a*S*)-4a,5,6,7,8,8a-Hexahydro-3-methylquinoxalin-2(1*H*)-one* (*Table*, *Entry 2*). Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.69–6.63 (*m*, 1 H); 3.18–3.00 (*m*, 2 H); 2.22 (*s*, 3 H); 1.95–1.77 (*m*, 4 H); 1.44–1.25 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 163.0; 158.9; 62.5; 54.4; 31.7; 31.0; 25.1; 23.6; 20.8. ESI-MS: 167 ($[M+H]^+$).

*6,7-Dichloro-3-methylquinoxalin-2(1*H*)-one* (*Table*, *Entry 3*). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.64 (*s*, 1 H); 7.20 (*s*, 1 H); 1.53 (*s*, 3 H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 164.4; 154.4; 139.5; 131.1; 129.7; 127.9; 122.1; 19.9. ESI-MS: 246 ($[M+H]^+$).

*3-Phenylquinoxalin-2(1*H*)-one* (*Table*, *Entry 5*). Yellow solid. M.p. 237–239°. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.60 (*d*, $J = 7.6$, 1 H); 7.45–7.42 (*m*, 2 H); 7.00–6.96 (*m*, 2 H); 6.73–6.39 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$, TMS): 154.7; 154.0; 135.2; 132.0; 131.4; 129.3; 128.6; 128.3; 127.2; 123.5; 122.7; 114.7. ESI-MS: 223 ($[M+H]^+$).

*6,7-Dimethyl-3-phenylquinoxalin-2(1*H*)-one* (*Table*, *Entry 6*). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.64–7.60 (*m*, 2 H); 7.56 (*s*, 1 H); 7.45–7.37 (*m*, 3 H); 7.08 (*s*, 1 H); 3.81 (br. *s*, 1 H); 2.33 (*s*, 3 H); 2.29 (*s*,

3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.1; 144.1; 139.3; 132.5; 128.7; 128.0; 115.1; 19.3; 18.6. ESI-MS: 267 ($[M+H]^+$).

*3-(Trifluoromethyl)quinoxalin-2(1*H*)-one* (*Table*, *Entry 7*). Yellow solid. M.p. 232–235°. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.82 (*d*, $J=8.3$, 1 H); 7.52–7.57 (*m*, 1 H); 7.31–7.37 (*m*, 2 H); 3.74 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 151.4; 132.9; 132.4; 129.4; 129.7; 123.4; 121.2; 115.4. ESI-MS: 215 ($[M+H]^+$).

*6,7-Dimethyl-3-(trifluoromethyl)quinoxalin-2(1*H*)-one* (*Table*, *Entry 8*). Yellow solid. M.p. 268–270°. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.57 (*s*, 1 H); 7.11 (*s*, 1 H); 3.81 (br. *s*, 1 H); 2.33 (*s*, 3 H); 2.29 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 151.3; 143.0; 132.5; 128.7; 128.0; 115.1; 19.5; 18.4. ESI-MS: 243 ($[M+H]^+$).

*3-(2-Hydroxy-1,1-dimethylethyl)quinoxalin-2(1*H*)-one* (*Table*, *Entry 9*). Pale yellow solid. M.p. 176–178°. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.70–7.68 (*m*, 1 H); 7.46–7.42 (*m*, 1 H); 7.26–7.21 (*m*, 2 H); 3.82 (br. *s*, 1 H); 3.64 (*s*, 2 H); 1.31 (*s*, 6 H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 164.7; 154.1; 139.9; 131.1; 129.4; 128.4; 122.7; 114.7; 67.9; 44.5; 23.0. ESI-MS: 219 ($[M+H]^+$).

*6,7-Dichloro-3-(2-hydroxy-1,1-dimethylethyl)quinoxalin-2(1*H*)-one* (*Table*, *Entry 10*). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.67 (*s*, 1 H); 7.29 (*s*, 1 H); 3.82 (br. *s*, 1 H); 3.64 (*s*, 2 H); 1.31 (*s*, 6 H). ^{13}C-NMR (75 MHz, (D_6)DMSO): 164.9; 153.9; 139.5; 131.0; 129.6; 128.2; 122.9; 114.5; 67.9; 44.5; 23.2. ESI-MS: 304 ($[M+H]^+$).

1,6-Dihydro-5-methyl-6-oxopyrazine-2,3-dicarbonitrile (*Table*, *Entry 11*). ^{1}H-NMR (400 MHz, $CDCl_3$): 3.74 (br. *s*, 1 H); 2.57 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.6; 155.3; 123.4; 121.0; 115.4; 109.7; 19.4. ESI-MS: 177 ($[M+H]^+$).

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