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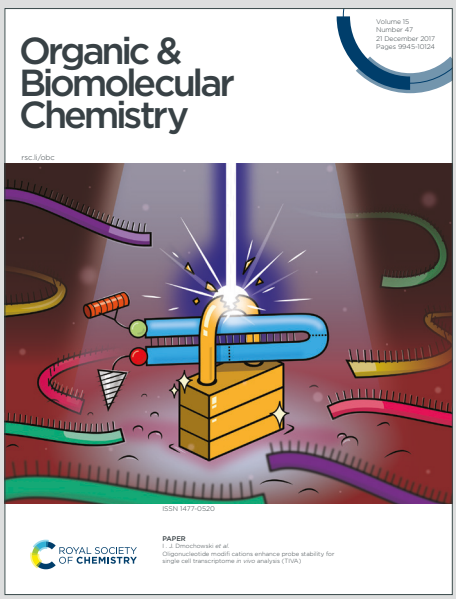

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ARTICLE

Metal-free C3-H acylation of quinoxalin-2(1*H*)-ones with α-oxo-carboxylic acids

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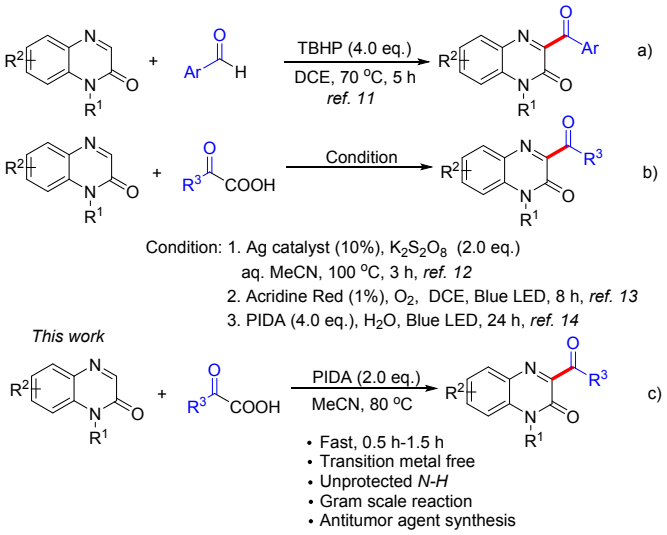
Direct C3-H acylation of quinoxalin-2(1*H*)-ones with α-oxocarboxylic acids under thermo conditions promoted by PIDA has been achieved in moderate to good yield in a very fast manner. Mechanistic study revealed that the reaction proceeds via radical process. In addition, this method could be applied to gram-scale reaction and antitumor agent synthesis. This work represents a simple, convenient and efficient synthesis of 3-acylated quinoxalin-2(1*H*)-ones.

Introduction

Among nitrogen-containing heterocycles, quinoxalin-2(1*H*)-one core is widely found in various pharmacologically compounds with biological and pharmaceutical applications.[1] A variety of bioactive compounds like benzodiazepine receptor panadiplon with this important pharmacophore have entered into clinical trials.[2] Hence, this privileged skeleton has caught considerable attention with respect to the development of new synthetic methodology for its functionalization.[3] In recent years, direct C3-H functionalization of quinoxalin-2(1*H*)-ones including alkylation,[4] arylation,[5] alkoxycarbonylation,[6] amidation,[7] amination[8] and phosphonation[9] have been well developed to access 3-substituted quinoxalin-2(1*H*)-ones.

With the development of radical reactions,[10] C3-H acylation via radical process are becoming a viable tool for the preparation of C3-acylated quinoxalin-2(1*H*)-ones. Generally, arylaldehydes and α-oxo-carboxylic acids are utilized as the radical precursors for the generation of acyl radical through hydrogen atom transfer (HAT) and oxidative decarboxylative process. In 2018, Qu and Yuan reported a TBHP promoted direct C3-H acylation of quinoxalin-2(1*H*)-ones with arylaldehydes as the radical precursors (Scheme 1a).[11] For α-oxo-carboxylic acids as radical precursors, oxidative decarboxylative strategy was employed with transition metal catalysts and photoredox catalysts. For example, Wang and Hu disclosed a Ag(I)-mediated decarboxylative acylation with $K_2S_2O_8$ as oxidant (Scheme 1b).[12] In 2020, Wei discovered a visible-light-catalyzed aerobic oxidative C3-H decarboxylative acylation with acridine red as the photocatalyst (Scheme 1b),[13] though N1 unprotected quinoxalin-2(1*H*)-ones were not tolerated. Recently, Xu and Xuan reported a visible-light-promoted C3-H decarboxylative acylation with α-oxo-carboxylic acids as radical precursors (Scheme 1b).[14] However, excess amount of α-oxo-carboxylic acids (4 equiv.) and phenyliodine (III) diacetate (PIDA, 4 equiv.) and long reaction time (24 h) were required for this reaction. Herein, we described a simple, efficient and convenient synthesis of 3-substituted quinoxalin-2(1*H*)-ones under thermo condition promoted by PIDA in a very fast manner (Scheme 1c).



Scheme 1. Methods towards the synthesis of 3-acyl quinoxalin-2(1H)-ones.

Results and discussion

As shown in Table 1, reaction of unprotected quinoxalin-2(1*H*)-one **1a** with 2 equiv. of 2-oxo-2-phenylacetic acid **2a** in the presence of 2 equiv. of PIDA under nitrogen atmosphere at 80 °C for 16 h gave the desired 3-acylated product **3a** in 76% isolated yield (entry 1). Yield was slightly improved to 77% with 1.5 equiv. of PIDA while 1 equiv. gave the product in lower yield

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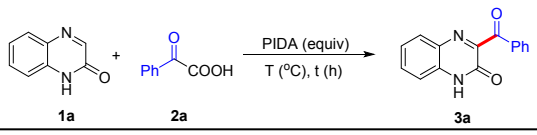
Table 1. Optimization of reaction conditions[a]



Entry	2 (equiv.)	PIDA (equiv.)	t (h)	Solvent	Yield (%)[b]
1	2.0	2.0	16 h	CH_3CN	76
2	2.0	1.5	16 h	CH_3CN	77
3	2.0	1.0	16 h	CH_3CN	68
4	1.5	1.5	16 h	CH_3CN	72
5	2.0	1.5	3 h	CH_3CN	85
6	2.0	1.5	30 min	CH_3CN	87
7	2.0	1.5	10 min	CH_3CN	52
8	2.0	1.5	30 min	DCE	84
9	2.0	1.5	30 min	toluene	86
10	2.0	1.5	30 min	DMF	66
11	2.0	1.5	30 min	H_2O	6
12[c]	2.0	1.5	30 min	CH_3CN	42
13[d]	2.0	1.5	30 min	CH_3CN	29

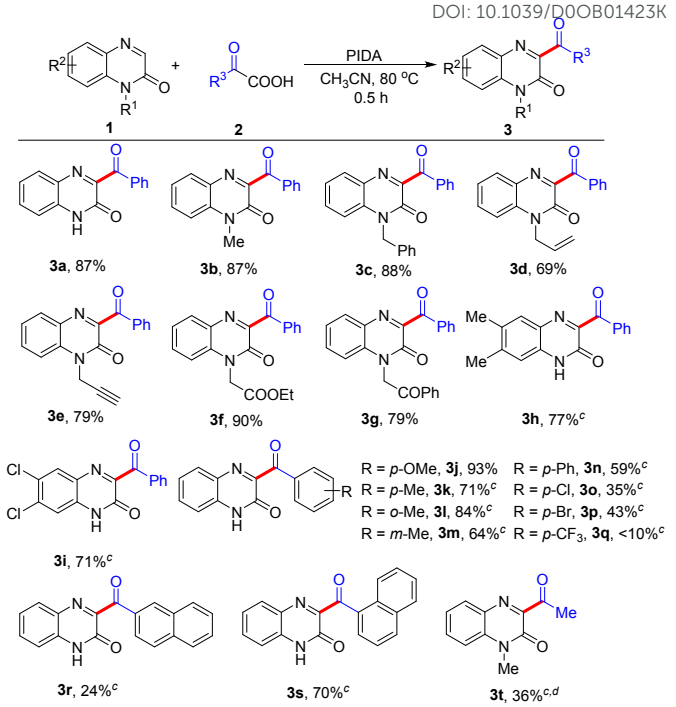
[a] All reactions were conducted at 0.3 mmol scale of **1** in 3.0 mL of acetonitrile in a closed flask under nitrogen atmosphere at 80 °C. [b] Isolated yield. [c] Reaction conducted under air. [d] Reaction conducted at 60 °C.

(entry 2-3). 2.0 equiv. of **2a** was essential for this reaction as 1.5 equiv. of **2a** provided the product in lower yield (entry 4). Then, reaction time was investigated for this reaction (entry 5-7). Unexpectedly, the acylation reaction was completed in 30 min, and the desired product was obtained in 87% yield (entry 6). Results of solvent optimization indicated that acetonitrile was the best choice, though other solvents like 1,2-dichloroethane and toluene also gave the desired product in good yield (entry 8-11). This reaction was very sensitive to air, since the product was formed only in 42% yield under air (entry 12). In addition, yield decreased dramatically at lower temperature (60 °C) (entry 13).

Under the optimal reaction condition, the substrate scope was examined, and results were compiled in Table 2. Generally, the acylation reaction proceeded well to give the product in moderate to good yield. N-substituted quinoxalin-2(1*H*)-ones gave the product in 69%-90% yield (**3a**-**3g**). It was noteworthy that various important and active functional groups, such alkenyl, alkynyl, ketyl and esteryl groups were well tolerated in this reaction, though lower yield were obtained for substrates with alkenyl (**3d**) and alkynyl (**3e**) group, which might be due to the radical addition of the acyl radical to reactive unsaturated bonds.[10a] Unprotected quinoxalin-2(1*H*)-ones with methyl or chloride group on the benzene ring gave the desired product **3h** and **3i** in 77% and 71% yield, respectively.

Subsequently, various α-oxocarboxylic acids **2** were investigated under standard reaction condition. The electronic property of α-oxocarboxylic acids affected greatly on the efficiency of the acylation reaction. α-Oxocarboxylic acids **2** with electron-donating group (**3j**-**3n**) gave the desired products in higher yield than **2** with electron-withdrawing group (**3o**-**3q**).

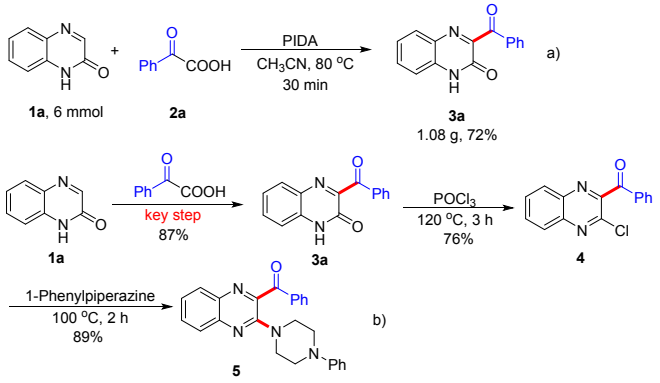
Table 2. Scope of quinoxalin-2(1H)-ones and α-oxocarboxylicacids[a,b]



[a] All reactions were conducted at 0.3 mmol scale of **1** in 3.0 mL of acetonitrile with 2 equiv. of **2** and 1.5 equiv. of PIDA in a closed flask under nitrogen atmosphere. [b] Isolated yield. [c] Reacting for 1.5 h. [d] With 4 equiv. of **2** and 3 equiv. of PIDA.

This might be attributed to that the reactivity of the nucleophilic acyl radical was reduced due to the attached electron-withdrawing group.[14] Naphthyl substituted α-oxo-carboxylic acids were well tolerated the acylation reaction to deliver the desired product (**3r** and **3s**), and higher yield was obtained with 2-(naphthalen-1-yl)-2-oxoacetic acid. Apart from the aromatic α-oxocarboxylic acids, C3 acylated product (**3t**) could be synthesized with aliphatic α-oxocarboxylic acid, though in lower yield.

To demonstrate the utility of the acylation reaction, a gram-scale reaction was carried out under the standard condition. To our delight, this scale-up acylation reaction provided the desired product **3a** in an acceptable 72% isolated yield (1.08 g) (Scheme 2a). In addition, potential antitumor agent[15] was synthesized in a total 59% yield in three steps using our method as a key step, which indicated the practicality of our decarboxylative acylation method (Scheme 2b).



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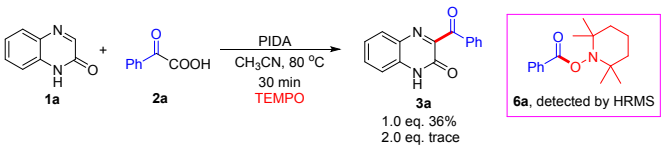
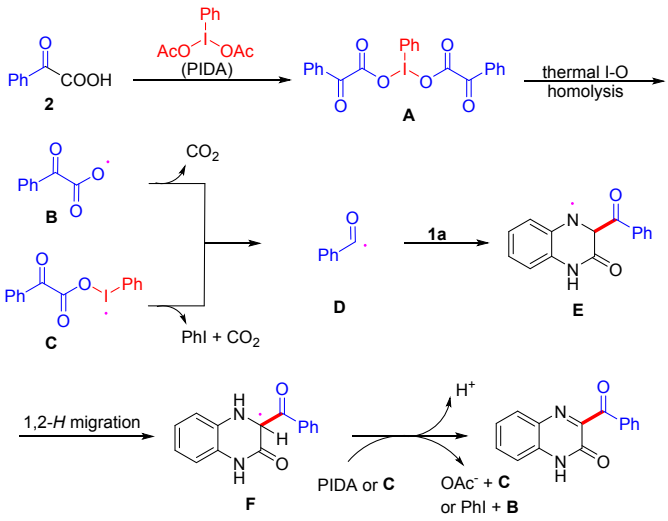
Scheme 2. Gram scale reaction and synthesis of the potential antitumor agent.



Scheme 3. Mechanistic study.



Scheme 4. Proposed mechanism.

In order to gain some insight into the reaction mechanism, radical trapping experiments were carried out with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as the radical scavenger (Scheme 3). Addition of 1 equiv of TEMPO into the standard reaction greatly decreased the yield to 36%, and the TEMPO adduct **6a** was detected by HRMS. The reaction was completely inhibited with 2 equiv of TEMPO. These experiments indicated that radical process was likely to be involved in this acylation reaction.

According to the preliminary mechanistic studies and literature,[10-14] a plausible mechanism is proposed in Scheme 4. Reaction of PIDA with α-oxocarboxylic acid gives the hypervalent iodine(III) reagent **A**, which undergoes thermo C-I bond homolysis to generate the oxygen-centered radical **B and C**. Fragment of **B** and **C** gives the acyl radical **D**, and addition of **D** to C=N bond of quinoxalin-2(1*H*)-one affords the nitrogen-centered radical **E**. 1,2-*H* migration of **E** and the following oxidative deprotonation of **F** forms the final product.

Conclusions

In summary, metal-free C3-H acylation of quinoxalin-2(1*H*)-ones with α-oxocarboxylic acid under thermo conditions promoted by PIDA has been achieved in a simple, convenient and efficient way. Under the standard condition, a variety of versatile functional groups were tolerated in this reaction to give the desired product in moderate to good yield. In addition, this method could be applied to gram-scale reaction and antitumor agent synthesis. These features including simplicity, high efficiency and excellent functional group tolerance make our protocol very attractive both in pharmaceutical chemistry and organic chemistry.

Experimental

General experimental method

^{1}H NMR spectra were recorded on a Bruker DPX600 spectrometer at 600 MHz or a Bruker DPX500 spectrometer at 500 MHz. ^{13}C NMR spectra were recorded on a Bruker DPX600 spectrometer at 600 MHz or a Bruker DPX500 spectrometer at 151 MHz or 125 MHz. All chemical shifts were reported in δ units with references to the residual solvent resonances of the deuterated solvents for proton and carbon chemical shifts. HRMS spectra were obtained on a Thermo Q Exactive spectrometer. Compounds **1b**-**1i** and **2b**-**2k** were prepared using literature methods.[15] All other chemicals were purchased from Chemical Co. and used as received unless otherwise specified.

General procedure for the synthesis of product (3a-3t)

A flame-dried Schlenk-tube equipped with a magnetic stir bar was charged with 1 (0.3 mmol), 2 (0.6 mmol, 2.0 equiv) and PIDA (0.45 mmol, 1.5 equiv). Then, the resulting mixture was evacuated and purged with nitrogen for 3 times. The reaction mixture was stirred at 80 °C for 0.5 h -1.5 h. After that, 20 mL sat. $NaHCO_3$ aq. was added to the reaction mixture, and the resulting solution was extracted with ethyl acetate (20 mL* 3). The combined organic solvent was dried over Na_2SO_4, and then removed under reduced pressure with a rotary evaporator. The crude residue was purified by silica gel column chromatography with ethyl acetate and petrol ether or dichloromethane and ethyl acetate to give the pure product **3**.

3-Benzoylquinoxalin-2(1*H*)-one (3a):

Yellow solid. Yield: 87%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.87 (s, 1H) (N*H*), 7.97 (d, *J* = 7.7 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H) (aromatic *H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.49, 156.30 (*C*O), 153.42, 134.66, 134.59, 132.71, 131.79, 131.25, 129.69, 129.14, 129.06, 123.86, 115.94 (aromatic *C*). This is a known structure. These data are similar to the reported one.[14]

3-Benzoyl-1-methylquinoxalin-2(1*H*)-one (3b):

Pale yellow solid. Yield: 87%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.98 – 7.96 (m, 2H), 7.89 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 2H), 7.48 – 7.45 (m, 1H) (aromatic *H*), 3.67 (s, 3H) (C*H*$_3$). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.28, 154.82 (*C*O), 152.89, 134.67, 134.46, 133.94, 132.03, 131.72, 129.90, 129.72, 129.03, 123.98, 115.25 (aromatic *C*), 28.99 (*C*H$_3$). This is a known structure. These data are similar to the reported one.[14]

3-Benzoyl-1-benzylquinoxalin-2(1*H*)-one (3c):

Yellow solid. Yield: 88%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.04 (d, *J* = 7.9 Hz, 2H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.1 Hz, 1H), 7.59 (m, 3H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.37 – 7.33 (m, 4H), 7.28 (t, *J* = 6.6 Hz, 1H) (aromatic *H*), 5.54 (s, 2H) (C*H*$_2$). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.07, 154.86 (*C*O), 153.07, 135.47, 134.74, 134.45, 133.09, 132.09, 132.03, 130.24,

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129.81, 129.08, 128.80, 127.50, 126.89, 124.20, 115.53 (aromatic *C*), 45.00 (*C*H$_2$). This is a known structure. These data are similar to the reported one.[14]

1-Allyl-3-benzoylquinoxalin-2(1*H*)-one (3d):

Yellow solid. Yield: 69%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.99 (d, J = 7.8 Hz, 2H), 7.90 (d, J = 7.9 Hz, 1H), 7.76 – 7.73 (m, 2H), 7.63 (d, J = 8.5 Hz, 1H), 7.58 (t, J = 7.8 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H) (aromatic *H*), 6.01 – 5.95 (m, 1H), 5.24 – 5.16 (m, 2H) (olefinic *H*), 4.93 (d, J = 5.3 Hz, 2H) (CH_2). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.14, 154.79 (*C*O), 152.51, 134.72, 134.45, 133.04, 132.02, 131.91, 131.33, 130.11, 129.76, 129.06 (aromatic *C*), 124.08, 117.46, 115.54 (olefinic *C*), 43.90 (*C*H$_2$). This is a known structure. These data are similar to the reported one.[14]

3-Benzoyl-1-(2-propynyl)quinoxalin-2(1*H*)-one (3e):

Yellow solid. Yield: 79%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.07 – 7.94 (m, 2H), 7.92 (dd, J = 8.0, 1.3 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.77 – 7.70 (m, 2H), 7.58 (t, J = 7.8 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H) (aromatic *H*), 5.13 (d, J = 2.5 Hz, 2H) (CH_2), 3.43 (t, J = 2.5 Hz, 1H) (alkynyl *H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ 191.80, 154.58 (*C*O), 151.95, 134.81, 134.31, 132.31, 132.24, 131.86, 130.21, 129.81, 129.08, 124.47, 115.41 (aromatic *C*), 77.66, 75.64 (alkynyl *C*), 31.35 (*C*H$_2$). This is a known structure. These data are similar to the reported one.[14]

Ethyl 2-(3-benzoyl-2-oxoquinoxalin-1(2*H*)-yl)acetate (3f):

Yellow solid. Yield: 90%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.94 (d, J = 8.0 Hz, 3H), 7.81 – 7.71 (m, 2H), 7.69 (d, J = 8.5 Hz, 1H), 7.59 (t, J = 7.8 Hz, 2H), 7.49 (t, J = 7.6 Hz, 1H) (aromatic *H*), 5.18 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H) (CH_2), 1.22 (t, J = 7.1 Hz, 3H) (CH_3). ^{13}C NMR (151 MHz, DMSO-d_6): δ 191.72, 167.22, 154.39 (*C*O), 152.61, 134.85, 134.31, 133.17, 132.39, 131.68, 130.27, 129.64, 129.14, 124.45, 115.09 (aromatic *C*), 61.58 (*C*H$_2$), 43.67, 14.00 (*C*H$_3$). This is a known structure. These data are similar to the reported one.[14]

1-Acetylphenyl-3-benzoylquinoxalin-2(1*H*)-one (3g):

Yellow solid. Yield: 79%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.17 – 8.15 (m, 2H), 7.97 – 7.95 (m, 3H), 7.78 – 7.74 (m, 2H), 7.72 – 7.70 (m, 1H), 7.66 – 7.58 (m, 5H), 7.47 – 7.50 (m, 1H) (aromatic *H*), 6.01 (s, 2H) (CH_2). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.03, 191.85, 154.37 (*C*O), 152.67, 134.81, 134.37, 134.29, 133.59, 132.30, 131.76, 130.20, 129.60, 129.15, 129.00, 128.40, 124.31, 115.39 (aromatic *C*), 49.08 (*C*H$_2$). This is a known structure. These data are similar to the reported one.[14]

3-Benzoyl-6,7-dimethylquinoxalin-2(1*H*)-one (3h):

White solid. Yield: 77%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.75 (s, 1H) (N*H*), 7.93 (d, J = 8.3 Hz, 2H), 7.73 (t, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.16 (s, 1H) (aromatic *H*), 2.36 (s, 3H), 2.30 (s, 3H) (CH_3). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.58, 154.80 (*C*O), 153.46, 141.80, 134.78, 134.50, 132.77, 130.77, 129.75, 129.62, 129.00, 128.83, 115.81 (aromatic *C*), 19.95, 18.87 (CH_3). This is a known structure. These data are similar to the reported one.[14]

3-Benzoyl-6,7-dichloroquinoxalin-2(1*H*)-one (3i):

Yellow solid. Yield: 71%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 13.00 (s, 1H) (N*H*), 8.17 (s, 1H), 8.00 (d, J = 7.3 Hz, 2H), 7.75 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.9 Hz, 2H), 7.55 (s, 1H) (aromatic *H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ 191.86, 157.66 (*C*O), 153.07, 134.87, 134.29, 133.81, 132.67, 130.72, 130.13, 129.79, 129.06, 125.61, 116.93 (aromatic *C*). This is a known structure. These data are similar to the reported one.[12]

3-(4-Methoxybenzoyl)-quinoxalin-2(1*H*)-one (3j):

White solid. Yield: 93%. MP: 242.7-243.5 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.81 (s, 1H) (N*H*), 7.93 (d, J = 8.9 Hz, 2H), 7.81 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.53 – 7.27 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H) (aromatic *H*), 3.87 (s, 3H) (CH_3).^{13}C NMR (151 MHz, DMSO-d6): δ 190.75, 164.27 (*C*O), 156.65, 153.39, 132.63, 132.19, 131.55, 131.21, 129.03, 127.59, 123.75, 115.85, 114.34 (aromatic *C*), 55.74 (O*C*H$_3$). HRMS (ESI): *m/z* calcd for $C_{16}H_{12}N_2O_3$ $[M+H]^+$: 281.0921. Found: 281.0914.

3-(4-Methylbenzoyl)-quinoxalin-2(1*H*)-one (3k):

Yellow solid. Yield: 71%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.84 (s, 1H) (N*H*), 7.85 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.44 – 7.30 (m, 4H) (aromatic *H*), 2.41 (s, 3H) (CH_3). ^{13}C NMR (151 MHz, DMSO-d_6): δ 191.99, 156.50 (*C*O), 153.39, 145.39, 132.67, 132.20, 131.67, 131.23, 129.80, 129.59, 129.09, 123.81, 115.91 (aromatic *C*), 21.37 (*C*H$_3$). This is a known structure. These data are similar to the reported one.[11]

3-(2-methylbenzoyl)-quinoxalin-2(1*H*)-one (3l):

White solid. Yield: 84%. MP: 202.1-204.6 °C. ^{1}H NMR (600 MHz, DMSO-d_6) : δ 12.84 (s, 1H) (N*H*), 7.81 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.32 (d, J = 7.5 Hz, 1H) (aromatic *H*), 2.57 (s, 3H) (CH_3). ^{13}C NMR (151 MHz, DMSO-d_6): δ 194.35, 156.99 (*C*O), 153.28, 139.43, 133.94, 133.23, 132.65, 132.43, 132.10, 131.70, 131.14, 129.09, 126.13, 123.82, 115.86 (aromatic *C*), 21.13 (*C*H$_3$). HRMS (ESI): m/z calcd for $C_{16}H_{12}N_2O_2$ $[M+H]^+$: 265.0972. Found: 265.0966.

3-(3-Methylbenzoyl)-quinoxalin-2(1*H*)-one (3m):

Yellow solid. Yield: 64%. MP: 182.0-182.7 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.84 (s, 1H) (N*H*), 7.83 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.43 – 7.34 (m, 2H) (aromatic *H*), 2.37 (s, 3H) (CH_3). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.63, 156.49 (*C*O), 153.37, 138.58, 135.27, 134.65, 132.67, 131.66, 131.24, 129.87, 129.10, 128.89, 126.90, 123.79, 115.90 (aromatic *C*), 20.71 (*C*H$_3$). HRMS (ESI): m/z calcd for $C_{16}H_{12}N_2O_2$ $[M+H]^+$: 265.0972. Found: 265.0966. This is a known structure. These data are similar to the reported one.[16]

3-(1-Biphenylcarbonyl)quinoxalin-2(1*H*)-one (3n):

Yellow solid. Yield: 71%. MP: 287.3-290 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.88 (s, 1H) (N*H*), 8.05 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.7 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.48 – 7.36 (m, 3H) (aromatic *H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ 191.98, 156.27 (*C*O), 153.43, 145.93, 138.72, 133.43, 132.74, 131.79, 131.27, 130.41, 129.16, 128.69, 127.24, 127.16, 123.85, 115.94 (aromatic *C*). HRMS (ESI): m/z calcd for $C_{21}H_{14}N_2O_2$ $[M+H]^+$: 327.1128. Found: 327.1121.

3-(4-Chlorobenzoyl)-quinoxalin-2(1*H*)-one (3o):

Yellow solid. Yield: 35%. MP: 250.4-252.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.87 (s, 1H) (N*H*), 8.01 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.67 – 7.64 (m, 3H), 7.42 – 7.35 (m, 2H) (aromatic *H*). ^{13}C NMR (126 MHz, DMSO-d_6): δ 191.39, 155.66 (*C*O), 153.40, 139.66, 133.32, 132.82, 131.94, 131.58, 131.26, 129.23, 129.20, 123.87, 115.93 (aromatic *C*). HRMS (ESI): m/z calcd for

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$C_{15}H_9ClN_2O_2$ $[M+H]^+$: 285.0425. Found: 285.0424. This is a known structure without spectra.[17]

3-(4-Bromobenzoyl)-quinoxalin-2(1*H*)-one (3p):

Pale yellow solid. Yield: 43%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.88 (s, 1H) (N*H*), 7.93 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.81 – 7.72 (m, 2H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.45 – 7.32 (m, 2H) (aromatic *H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ 191.61, 155.62 (*C*O), 153.39, 133.64, 132.81, 132.17, 131.95, 131.71, 131.60, 131.25, 129.20, 128.99, 123.87, 115.93 (aromatic *C*). This is a known structure. These data are similar to the reported one.[11]

3-(β-naphthoyl)-quinoxalin-2(1*H*)-one (3r):

Yellow solid. Yield: 24%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.90 (s, 1H) (N*H*), 8.63 (s, 1H), 8.17 – 8.08 (m, 2H), 8.07 – 7.99 (m, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H) (aromatic *H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.60, 156.56 (*C*O), 153.54, 135.65, 133.32, 132.80, 132.12, 131.99, 131.72, 131.40, 129.84, 129.45, 129.19, 128.84, 127.84, 127.20, 123.82, 123.48, 115.93 (aromatic *C*). HRMS (ESI): m/z calcd for $C_9H_{12}N_2O_2$ $[M+H]^+$: 301.0965. Found: 301.0972.

3-(α-naphthoyl)-quinoxalin-2(1*H*)-one (3s):

Yellow solid. Yield: 70%. MP: decomposed. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.88 (s, 1H) (N*H*), 9.01 (d, *J* = 8.6 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.08 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.80 – 7.74 (m, 1H), 7.72 – 7.64 (m, 2H), 7.59 (t, *J* = 7.7 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.33 (m, 1H) (aromatic *H*).^{13}C NMR (151 MHz, DMSO-d_6): δ 194.45, 157.05 (*C*O), 153.47, 135.05, 134.13, 133.60, 132.77, 131.72, 131.24, 130.69, 130.10, 129.15, 129.02, 128.92, 126.89, 125.12, 124.94, 123.82, 115.87 (aromatic *C*). HRMS (ESI): m/z calcd for $C_9H_{12}N_2O_2$ $[M+H]^+$: 301.0965. Found: 301.0972.

1-Methyl-3-methoxyquinoxalin-2(1*H*)-one (3t):

Yellow solid. Yield: 36%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.89 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.80 – 7.68 (m, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.52 – 7.32 (m, 1H) (aromatic *H*), 3.64 (s, 3H), 2.58 (s, 3H) (C*H*$_3$). ^{13}C NMR (151 MHz, DMSO-d_6): δ 198.67, 152.93 (*C*O), 152.24, 134.18, 132.48, 131.22, 130.23, 123.94, 115.08 (aromatic *C*), 28.90, 28.55 (*C*H$_3$). This is a known structure. These data are similar to the reported one.[12]

Synthesis of potential antitumor agent.[17]

A mixture of **3a** (0.5 mmol) and an excess of $POCl_3$ (1.25 mmol) was stirred under heating at 120 °C for 3 h. On cooling, the mixture was taken up with ice, and the aqueous solution was extracted with ethyl acetate for 3 times. The combined organic solvent was dried over Na_2SO_4, and then removed under reduced pressure with a rotary evaporator. The crude residue was purified by silica gel column chromatography with ethyl acetate and petrol ether to give the pure product **4a** as a yellow solid.

3-Benzoyl-2-chloroquinoxaline (4a):

Yellow solid. Yield: 76%. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 8.17 – 8.10 (m, 2H), 8.93 – 7.88 (m, 3H), 7.86 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H). (aromatic *H*). ^{13}C NMR (151 MHz, DMSO-d_6): δ 191.32 (*C*O), 149.89, 142.89, 141.67, 139.30, 135.16, 134.26, 132.81, 131.65, 130.38, 129.21, 129.16, 128.21 (aromatic *C*). This is a known structure. These data are similar to the reported one.[17]

A mixture of chloroquinoxaline (**4a**, 0.3 mmol) and 1-phenylpiperazine (1.5mmol) was stirred under heating at 100 °C for 2 h. On cooling, the mixture was taken up with water, and the aqueous solution was extracted with ethyl acetate for 3 times. The combined organic solvent was dried over Na_2SO_4, and then removed under reduced pressure with a rotary evaporator. The crude residue was purified by silica gel column chromatography with ethyl acetate and petrol ether to give the pure product **5a** as a yellow solid.

3-Benzoyl-2-(4-phenylpiperazine)quinoxaline (5a):

Yellow solid. Yield: 89%. ^{1}H NMR (600 MHz, Chloroform-*d*): δ 8.05 (d, *J* = 7.9 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.74 – 7.61 (m, 2H), 7.59 – 7.42 (m, 3H), 7.35 – 7.13 (m, 2H), 7.03 – 6.76 (m, 3H) (aromatic *H*), 3.70 (t, *J* = 5.1 Hz, 4H), 3.18 (t, *J* = 5.1 Hz, 4H) (C*H*$_2$). ^{13}C NMR (151 MHz, DMSO-d_6): δ 192.76 (*C*O), 151.40, 150.57, 144.14, 140.97, 135.28, 134.88, 134.48, 131.58, 130.47, 129.00, 128.95, 128.74, 126.31, 126.06, 119.06, 115.42 (aromatic *C*), 47.49, 47.29 (C*H*$_2$). This is a known structure. These data are similar to the reported one.[17]

Conflicts of interest

There are no conflicts to declare.

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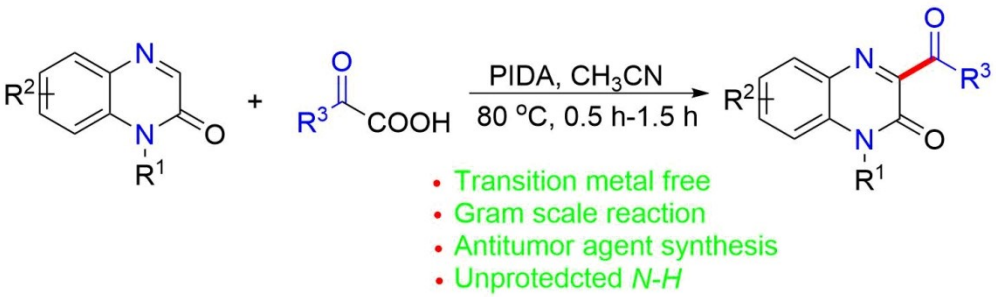

- Transition metal free
- Gram scale reaction
- Antitumor agent synthesis
- Unprotedcted *N-H*