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One-pot Four-component Reaction for Convenient Synthesis of New Quinoxaline Derivatives in the Presence of K_2CO_3

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Abstract

Convenient and simple procedures for the synthesis of functionalized Quinoxaline derivatives were developed via one-pot four-component reaction of o-aminoanilin, acetylenic ester, and malonyl dichloride in the presence of K_2CO_3 as effective base catalyst. These compounds widely are used in various industries like paint, pharmaceutical and medicine. Quinoxaline derivatives are also part of antibiotics structure such as Actinomycin, Lomacin. In other hand, using of K_2CO_3 as economically catalyst and the simplicity of the present procedure for synthesis of Quinoxaline derivatives makes it an interesting alternative to complex multistep approaches.. The structures of the newly synthesized compounds were confirmed by their elemental analysis and spectral data.

Keywords: *Quinoxaline derivatives, Multicomponent reactions, Activated acetylenes, o-Amino aniline, malonyl dichloride.*

Introduction

Heterocyclic chemistry is one of the most important disciplines in organic chemistry [1]. Among the various heterocyclic systems discovered and developed, nitrogen-containing ones play a fundamental role in the context of both chemistry and biology [2]. Quinoxaline derivatives are especially outstanding fused heterocyclic ring systems prevalent in natural and unnatural heterocyclic compounds possessing significant biological and pharmaceutical activities. Many of them possess anticancer [3,4], antiviral [5], antibacterial [6], anti inflammatory [7] properties and serve as inhibitor of enzymes by catalyzing the transport of the phosphate group

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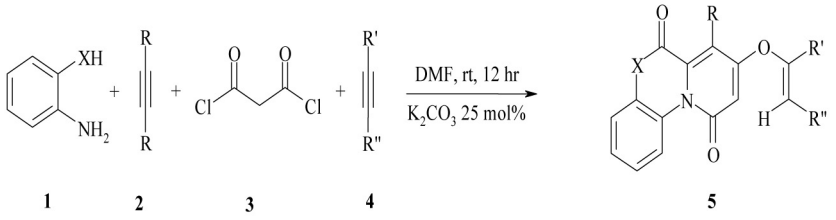
from ATP (kinase inhibitor) [8]. Quinoxalines are used as antibiotics [9,10], DNA-binding agents [11], building blocks in the synthesis of anion receptors [12].

Multicomponent reactions (MCRs) are able to combine multiple reagents into a single core in one step giving an easy access to millions of small organic molecules. These compounds are widely used in biological screening and materials science [13]. Therefore, these reactions are regarded as a powerful tool in parallel organic synthesis and combinatorial chemistry [14-15]. Modern planning strategies in organic chemistry such as diversity oriented synthesis aim at the development of short pathways (three- to five-step) leading to collections of small molecules having skeletal diversity [16]. As part of our continuing research [17-19], we now report the results of our studies involving the reactions 1,2-phenylendiamine (1), activated acetylenes (2, 4) Malonyl dichloride (3) in the presence of K_2CO_3 as effective catalyst which constitutes a synthesis of new class of Quinoxaline derivatives (5) (Scheme 1).



1 2 3 4 5

entry	X	R	R'	R"	Yield%
a	NH	CO_2Me	CO_2Me	CO_2Me	89
b	NH	CO_2Me	CO_2Et	CO_2Et	85
c	NH	CO_2Et	CO_2Me	CO_2Me	87
d	NH	CO_2Me	H	CO_2Me	80
e	NH	CO_2Me	H	CO_2Et	79
f	NH	CO_2Et	H	CO_2Et	80
j	O	CO_2Me	CO_2Me	CO_2Me	0

Scheme 1. Synthesis of new quinoxaline derivatives **5.**

As a first step to optimize the reaction condition, we began our examination of the reaction of o-aminoanilin, acetylenic ester, and malonyl dichloride in the presence of different catalysts and solvents (**Table 1**). In order to establish the real effectiveness of the catalyst for the synthesis of other Quinoxaline derivatives, a test reaction was performed without catalyst using o-aminoanilin, dimetyl acetylene dicarboxylate, and malonyl dichloride in Toluene at reflux. It was found that no product was obtained in the absence of catalyst even after 24 h (Table 1, entry 1). In search of effective, eco-friendly, and efficient catalytic

system for this reaction, same test reaction was performed with different catalysts such as Me_3N, Et_3N, $P\Phi_3$, pipyridine, K_2CO_3 and pyridine. Among all screened catalysts, K_2CO_3 gave the best result in view of yield (Table 1, entry 10). In contrast all other catalysts did not afford the desired product (Table 1, entry 2-8). To assess the effect of solvents on this reaction, we screened different solvents such as Toluene, ACN and DMF. It was observed that DMF is the best solvent among tested solvents (Table 1, entry 10).

Table 1. Optimization of catalysts, solvents, and temperature in the synthesis of **5a.**

entry	Catalyst (25 mol %)	Solvent	Condition[a]	Time (h)	Yield[b] (%)
1	---------	Toluene	reflux	24	trace
2	$P\Phi_3$	Toluene	rt	48	0
3	$P\Phi_3$	Toluene	reflux	24	0
4	$P\Phi_3$	ACN	reflux	24	0
5	Me_3N	ACN	r.t.	48	0
6	Et_3N	ACN	r.t.	48	0
7	Pyridine	Toluene	reflux	24	0
8	Pipyridine	Toluene	reflux	24	0
9	K_2CO_3	ACN	r.t.	12	60
10	K_2CO_3	DMF	r.t.	12	89

[a] Reaction conditions: *o*-aminoanilin (1mmol), dimetyl acetylene dicarboxylate (2mmol), and malonyl dichloride (1mmol)
[b] Isolated yield.

Experimental

General procedure

All compounds were obtained from Fluka, Merck or Sigma Aldrich. m.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500, 125 MHz, respectively; δ in ppm. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

*Typical procedure for preparation of (***5***)*

To a stirred solution of 1,2-phenylendiamine (2 mmol), **2** (2 mmol), malonyl chloride **3** (2 mmol) and K_2CO_3 (0.5 mmol) in DMF (5 ml), a solution of **4** (2 mmol) in DMF (2 ml) was added drop wise. The reaction mixture was stirred for 12 h then it was extracted by ethyl acetate and dried over Na_2SO_4. The solvent was removed under reduced pressure and the precipitate was purified by ether to afford the pure title compounds **5**.

*Dimethyl (E)-2-{[7-methoxycarbonyl)-6,10-dioxo-6,10-dihydro-5H pyrido[1,2-a] quinoxaline -8-yl]oxy}-2-butenedioate (***5a***)*

Yellow powder; m.p 149–151 °C; Yield 89%; IR (KBr) (ν_{max}/cm^{-1}): 1742, 1733, 1425, 1260, 752; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 3.81 (3H, s, O-CH_3), 3.87 (3H, s, O-CH_3), 3.97 (3H, s, O-CH_3), 6.10 (1H, s, =CH), 6.39 (1H, s, =CH), 6.96-7.07 (2H, m, 2 CH), 7.87 (1H, d, ^3J= 5.4, CH), 9.05 (1H, d, ^3J= 8.4, CH), 10.12 (1H, br s, NH); ^{13}C NMR spectrum in $CDCl_3$

(δ, ppm): 50.6 (O-CH3), 51.3 (O-CH_3), 52.8 (O-CH_3), 101.5 (CH), 106.0 (CH), 115.7 (C), 123.9 (CH), 125.2 (CH), 126.8 (CH), 126.9 (CH), 128.4 (C), 128.9 (C), 132.0 (C), 142.8 (C), 149.4 (C), 152.7, 157.4, 161.0, 164.6, 166.6 (5 C=O); Anal. Calcd for $C_{20}H_{16}N_2O_9$ (428.35): C, 56.08; H, 3.76; N, 6.54%. Found: C, 56.00; H, 3.79; N, 6.63%; Mass spectrum, *m/z* (Irel , %): 428 (M+, 15), 337 (20), 297 (30), 269 (75), 173 (62), 145 (100), 90 (95), 77 (40), 59 (45).

*Diethyl (E)-2-{[7-methoxycarbonyl)-6,10-dioxo-6,10-dihydro-5H-pyrido[1,2-a] quinoxaline-8-yl]oxy}-2-butenedioate (***5b***)*

Yellow powder; m.p 154–156 °C; Yield 85%; IR (KBr) (ν_{max}/cm^{-1}): 1745, 1732, 1420, 1240, 763; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.12 (3H, t, ^3J= 7.2, CH3), 1.23 (3H, t, 3J= 7.1, CH_3), 3.79 (3H, s, O-CH_3), 4.22-4.40 (4H, m, 2 O-CH_2), 6.12 (1 H, s, =CH), 6.45 (1H, s, =CH), 7.00-7.11 (2H, m, 2 CH), 7.87 (1H, br s, CH), 8.55 (1H, d, ^3J= 8.0, CH), 10.25 (1H, br s, NH); ^{13}C NMR spectrum in $CDCl_3$ (δ, ppm): 13.4 (CH_3), 14.6 (CH_3), 51.6 (O-CH_3), 61.4 (O-CH_2), 62.3 (O-CH_2) 103.4 (CH), 106.7 (CH), 117.5 (C), 123.3 (CH), 125.4 (CH), 127.0 (CH), 127.2 (CH), 128.8 (C), 128.9 (C), 132.3 (C), 144.5 (C), 148.8 (C), 153.7, 158.2, 161.5, 164.8, 166.9 (5 C=O); Anal. Calcd for $C_{22}H_{20}N_2O_9$ (456.40): C, 57.90; H, 4.42; N, 6.14%. Found: C, 57.98; H, 4.71; N, 6.29%; Mass spectrum, *m/z* (Irel , %): 456 (M^+, 10), 356 (33), 297 (80), 173 (45), 145 (100), 90 (70), 77 (30).

*Dimethyl (E)-2-{[7-ethoxycarbonyl)-6,10-dioxo-6,10-dihydro-5H-pyrido[1,2-a] quinoxaline-8-yl]oxy}-2-butenedioate (***5c***)*

Yellow powder; m.p 150–153 °C; Yield 87%; IR (KBr) (ν_{max}/cm^{-1}): 1740, 1728, 1410, 1212, 750. 1H NMR spectrum in $CDCl_3$ (δ, ppm): 1.12 (3H, t, ^3J= 6.9, CH_3), 3.69 (3H, s, O-CH_3), 3.75 (3H, s, O-CH_3), 4.02 (2H, q, ^3J= 6.9, O-CH_2), 5.89 (1 H, s, =CH), 6.37 (1H, s, =CH), 7.00-7.11 (2H, m, 2 CH), 7.54 (1H, s, CH), 8.43 (1H, d, ^3J= 7.0, CH), 10.03 (1H, br s, NH); ^{13}C NMR spectrum in $CDCl_3$ (δ, ppm): 14.24 (CH_3), 51.3 (O-CH_3), 62.1 (O-CH_2), 102.1 (CH), 106.6 (CH), 117.7 (C), 123.9 (CH), 124.2 (CH), 126.6 (CH), 127.2 (CH), 127.8 (CH), 128.3 (C), 128.9 (C), 132.1 (C), 144.9 (C), 148.8 (C), 153.5, 158.1, 161.5, 164.8, 167.4 (5 C=O); Anal. Calcd for $C_{21}H_{18}N_2O_9$ (442.37): C, 57.02; H, 4.10; N, 6.33%. Found: C, 57.19; H, 4.32; N, 6.39%; Mass spectrum, *m/z* (Irel , %): 442 (M^+, 11), 351 (29), 311 (19), 145 (100), 90 (79), 77 (30).

*Methyl 8-{[(E)-3-methoxy-3-oxo-1-proponyl]oxy}-6,10-dioxo-6,10-dihydro-5H-pyrido[1,2-a] quinoxaline-7-carboxylate (***5d***)*

Yellow powder; m.p 173–174 °C; Yield 80%; IR (KBr) (ν_{max}/cm^{-1}): 1718, 1463, 1254, 697. ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 3.64 (3H, s, O-CH_3), 3.79 (3H, s, O-CH_3), 5.90

(1H, d, ^3J= 9.1, =CH), 6.29 (1H, s, =CH), 7.06-7.18 (3H, m, 3 CH), 7.54 (1H, d, ^3J= 6.4, CH), 8.55 (1H, d, ^3J= 8.4, CH), 10.25 (1H, br s, NH); ^{13}C NMR spectrum in $CDCl_3$ (δ, ppm): 51.3 (O-CH_3), 53.4 (O-CH_3), 103.4 (CH), 107.5 (CH), 117.7 (C), 124.8 (CH), 126.1 (CH), 126.6 (CH), 126.9 (CH), 127.3 (CH), 128.4 (C), 131.6 (C), 142.8 (C), 148.7 (C), 152.3, 157.6, 161.4, 166.8 (4 C=O); Anal. Calcd for $C_{18}H_{14}N_2O_7$ (370.31): C, 58.38; H, 3.81; N, 7.56%. Found: C, 59.49; H, 3.88; N, 7.66%; Mass spectrum, *m/z* (Irel , %): 242 (3), 218 (75), 186 (100), 158 (40), 130 (30).

*Methyl 8-{[(E)-3-ethoxy-3-oxo-1-proponyl] oxy}-6,10-dioxo-6,10-dihydro-5H-pyrido[1,2-a] quinoxaline-7-carboxylate (***5e***)*
Yellow powder; m.p 178–181 °C; Yield 79%; IR (KBr) (ν_{max}/cm^{-1}): 1725, 1440, 1245, 755; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.18 (3H, t, ^3J= 6.8, CH_3), 3.75 (3H, s, O-CH_3), 4.11 (2H, q, ^3J= 6.8, O-CH_2), 5.97 (1H, d, ^3J= 10.2, =CH), 6.23 (1H, s, =CH), 7.06-7.20 (3H, m, 3 CH), 7.43 (1H, d, ^3J= 6.0, CH), 8.45 (1H, d, ^3J= 8.4, CH), 11.02 (1H, br s, NH); ^{13}C NMR spectrum in $CDCl_3$ (δ, ppm): 14.4 (CH3), 51.5 (O-CH_3), 63.3 (O-CH_2), 104.3 (CH), 108.8 (CH), 116.7 (C), 124.2 (CH), 126.5 (CH), 126.8 (CH), 126.9 (CH), 127.3 (CH), 128.3 (C), 131.5 (C), 143.4 (C), 145.1 (C), 148.9 (C), 153.5, 156.8, 161.2, 164.3 (4 C=O); Anal. Calcd for $C_{19}H_{16}N_2O_7$ (384.34): C, 59.38; H, 4.20; N, 7.29%. Found: C, 59.49; H, 4.38; N, 7.45%.

*Ethyl-8-{[(E)-3-ethoxy-3-oxo-1-proponyl] oxy}-6,10-dioxo-6,10-dihydro-5H-pyrido[1,2-a] quinoxaline-7-carboxylate (***5f***)*
Yellow powder; m.p 179–181 °C; Yield 80%; IR (KBr) (ν_{max}/cm^{-1}): 1718, 1440, 1235, 763; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): δ 1.09 (3H, t, ^3J= 7.1, CH3), 1.23 (3H, t, ^3J= 7.0, CH_3), 4.10-422 (4H, m, 2 O-CH_2), 5.85 (1H, d, ^3J= 9.2, =CH), 6.16 (1 H, s, =CH), 7.04-7.17 (3H, m, 3 CH), 7.35 (1H, d, ^3J= 6.0, CH), 8.33 (1H, d, ^3J= 8.0, CH), 10.52 (1H, br s, NH); ^{13}C NMR spectrum in $CDCl_3$ (δ, ppm): 13.1 (CH_3), 14.4 (CH_3), 61.2 (O-CH_2), 63.3 (O-CH_2), 105.3 (CH), 110.2 (CH), 113.7 (C), 124.1 (CH), 126.5 (CH), 126.5 (CH), 126.7 (CH), 127.3 (CH), 128.9 (C), 133.5 (C), 141.4 (C), 146.1 (C), 153.6, 156.7, 160.3, 165.4 (4 C=O); Anal. Calcd for $C_{20}H_{18}N_2O_7$ (398.36): C, 60.30; H, 4.55; N, 7.03%. Found: C, 60.19; H, 4.60; N, 7.18%.

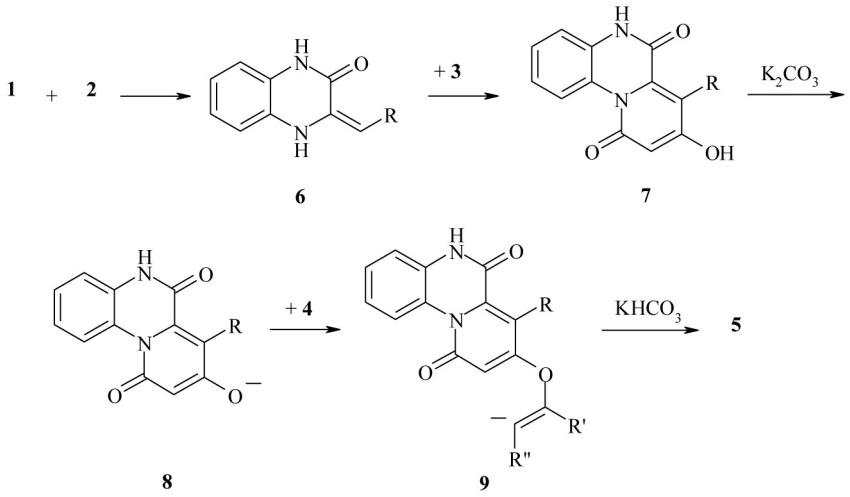
Results and discussion

The structures of compounds **5a–f** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. For example, the 1H NMR spectrum of **5a** exhibited six singlets identified as O-methyl (*δ* 3.81 and 3.87, 3.97 ppm), CH (*δ* 6.10, 6.39 ppm), and broad NH (*δ* 10.12 ppm) protons, along with multiplets for the aromatic region. The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** showed 20 distinct resonances, which

confirmed the proposed structure. The IR spectrum of **5a** displayed characteristic NH, C=O and aromatic bands. The ^{1}H NMR and ^{13}C NMR spectra of **5b-f** were similar to those for **5a** except for the ester moieties, which exhibited characteristic resonances in appropriate regions of the spectrum. Thus, the ^{1}H NMR spectrum of each isolated product **5a–c** exhibited a vinylic proton signal at about 5.89–6.45 ppm, which is in agreement with the (E) configuration [19] in the vinyl moiety of other products **5d–f** the coupling constants also was in agreement with the (E) configuration.

To extend our knowledge of this reaction, we performed the reaction between o-hydroxy anilin, acetylenic ester, and malonyl dichloride in the presence of K_2CO_3, but we could not get any product.

A tentative mechanism for this transformation is proposed in **scheme 2**. It is conceivable that the initial event is the formation of alkylidene quinoxaline (**6**), this compound is subsequently attacked by malonyl dichloride to produce (**7**) [21]. Compound (**7**) undergoes hydrogen elimination in the presence of K_2CO_3 and converted to enolate (**8**), this intermediate attack activated acetylenic ester to furnish intermediate (**9**), which is protonated by $KHCO_3$ to produce final product 5.



Scheme 2. Proposed mechanism for the formation of products.

Conclusion

To sum up, we have reported a new pseudo four component procedure for the synthesis of biologically active Quinoxaline derivatives via four component reaction of o-Amino aniline, activated acetylens and malonyl dichloride in the presence of potassium carbonate in moderate to good yield. The functionalized N-Heterocycles reported in this research may be considered as potentially useful intermediates because they possess atoms with different oxidation states. The

present procedure has the advantage that not only is the reaction performed under simple conditions, but also the reactants can be mixed without any prior activation or modification.

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