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Catalyst-Free Synthesis of Quinoxalines

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Quinoxalines are a class of important heterocycles, so to explore a facile and practical new synthetic method is always demanded. We have developed a new catalyst-free domino synthesis of quinoxalines from phenacyl halides and 1,2-diaminoarenes. Phenacyl chlorides with lower activities are first used in synthesis of quinoxalines and afford up to 97 % yield with our protocol. Our process with sodium bicarbonate as deacid reagent is catalyst-free, simple, greener and practical.

Keywords: Quinoxalines, Domino synthesis, Phenacyl halides, 1,2-Diaminoarenes, Heterocycles.

INTRODUCTION

Quinoxalines are a privileged class of N-containing hetero-cycles and exhibit a wide range of biological activities, such as anti-inflammatory, kinase inhibitory, anticancer, antiviral, antibacterial and anthelmintic activities[1]. In addition to medicinal uses, quinoxaline derivatives have found applications in other fields, for example, organic ligands[2] and semiconductors[3].

Owing to their potential biological and other applications, a number of synthetic methods have been developed[4]. The most common method for their synthesis relies on the condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid[5]. The classical reaction process generally requires severe reaction conditions, such as strong acidic media.

Over the years, a number of synthetic approaches of quinoxalines have been reported, such as reaction of 1,2-keto hydroxyl compounds *via* Tandem oxidation procedure[6], various Brønsted acids-, Lewis acids-, or oxidants-promoted condensations[7], 1,4-addition of 1,2-diamines to diazenylbutenes[8], Bi(0)-catalyzed oxidative coupling of epoxides and ene-1,2-diamines[9], cyclization of α-arylimino oximes in Ac_2O[10], Cu-catalyzed synthesis of quinoxalines from *o*-phenylenediamines and nitroolefins[11], cascade synthesis from ketones and 1,2-diamines[12].

In addition, reaction of phenacyl bromides and 1,2-diaminoarenes is a good approach for synthesis of quinoxalines. Phenacyl bromides can be synthesized even in a green process[13].

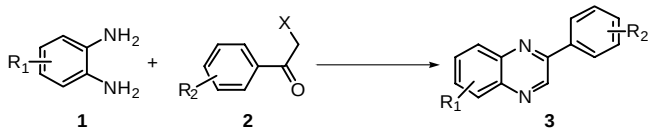
This reaction could be accomplished through a multistep and complex process in solid phase[14], which could be catalyzed by supported strong acid catalyst $HClO_4.SiO_2$[15], or by organic base catalyst DABCO[16] and pyridine[17], or by supported inorganic base catalyst KF-alumina[18], or by Amberlite resin supported hexafluorophosphate ion[19]. This reaction can also be performed under microwave-irradiation conditions[20]. A simple process without catalyst was also reported with equivalent β-cyclodextrin as an additive[21] or polyethylene glycol (PEG) as a medium[22]. However the catalysts and the additives not only increase the cost of the process and the trouble of workup, but also potentially pollute the environment.

Previous study revealed that the reaction between phenacyl bromides and 1,2-diamines yields quinoxalines as well as hydrogen bromide. So weak basic quinoxalines will form their HBr salts, unless certain deacid reagent, *e.g.* $NaHCO_3$ is added in the reaction to remove the HBr acid. Could $NaHCO_3$ be added in advance to the reaction? Perhaps it would promote the reaction of synthesis of quinoxalines. Our primary study convinced our idea.

As our ongoing research on synthesis of heterocycles[23], we developed a new catalyst free synthetic method for quinoxalines with sodium bicarbonate as a deacid reagent (**Scheme-I**).

EXPERIMENTAL

The chemicals and reagents were purchased from Aldrich, Acros, Alfa Aesar, Aladdin, or Kelong Chemicals Company and used without further purification.



Scheme-I: Catalyst-free synthesis of quinoxalines from 1,2-diaminoarenes and α-halo ketones

General procedure: To a dry test tube with a stir bar was added 1,2-diaminoarene (1 mmol), phenacyl bromide (1 mmol), $NaHCO_3$ and DMSO (5 mL). The test tube was transferred to a preheated oil bath pot for reaction. After a set period of time, the reaction was cooled to room temperature and quenched with water. The resulting mixture was extracted with ethyl acetate (15 mL) for three times. The combined organic layer was washed with water (5 mL) for twice and then dried over anhydrous sodium sulfate. The filtrate was condensed under reduced pressure on a rotator. The residual was purified on a silica gel column chromatography with a mixture of petroleum ether and ethyl acetate (volume ratio 5/1) as eluent to give the desired quinoxaline.

Detection method: The purities of all the synthesized compounds were checked by thin-layer chromatography (TLC) using suitable organic solvents. The IR spectra were recorded on a Bruker Tensor-27 FT-IR spectro-photometer in KBr discs. ^{1}H NMR spectra were recorded on a Bruker Advance 300 MHz NMR or 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 containing tetramethylsilane (TMS) as an internal standard. Melting points were determined on an X-4 melting-point apparatus with microscope and are uncorrected.

RESULTS AND DISCUSSION

It is noticed that some of the reported synthetic methods of quinoxalines with α-haloketones as substrates used acids as catalysts[15], while some used bases as catalysts[16-18], and some did not use any acid or base as catalyst. So first of all, we tried to synthesize 2-phenylquinoxaline from *o*-phenylenediamine and phenacyl bromide without addition of any base or acid and got the 2-phenylquinoxaline in 52 % yield at 120 °C in DMSO (Table-1, entry 1). Addition of an equivalent hydrogen bromide as catalyst resulted in an extremely complex mixture and no desired product could be isolated (entry 2).

It was reported that DABCO and pyridine could promote this reaction[16,17]. Perhaps pyridine acted as deacid reagent in the reported reaction. In view of this, sodium bicarbonate was used as a low-cost deacid reagent in this reaction system. Fortunately, the yield increased dramatically (entry 3). Increase of the amount of $NaHCO_3$ to 1.2 equivalents obviously raised the reaction yield to 99 % (entry 4). Lowering the amount of $NaHCO_3$ resulted in a decrease of the yield (entry 5). A stronger weak base K_2CO_3 even decreased the yield of the reaction (entries 6 *vs*. 5) and the reason perhaps is that the stronger basicity of K_2CO_3 promotes the hydrolysis of phenacyl bromide with the water produced during the condensation (**Scheme-II**). Shortening the reaction time resulted in decrease of the yields (entries 7-9 *vs*. 4) and lowering the temperature also disfavored the yield (entry 10). In the screened solvents, 95 % ethanol, ethyl acetate and 1,4-dioxane gave much lower yields of 2-phenylquinoxaline (entries 11-13) and perhaps the lower temperature was a partial reason of the lower yields. While DMA and DMF produced the desired product with comparative yields (entries 14-15). But considering DMSO is the greener solvent than DMA and DMF[24], we adopted DMSO as our solvent for this reaction. Besides, DMSO could be recovered by distillation after the reaction.

TABLE-1
OPTIMIZATION OF CONDITIONS OF REACTION OF *o*-PHENYLENEDIAMINE 1a AND 2-BROMOACETOBENZENE 2a[a]

Entry	Solvent	t (h)	$NaHCO_3$ (equiv.)	Yield (%)[b]
1	DMSO	24	0	52
2	DMSO	24	1.0[c]	0
3	DMSO	24	1.0	85
4	DMSO	24	1.2	99
5	DMSO	24	0.8	71
6	DMSO	24	1.2[d]	68
7	DMSO	12	1.2	76
8	DMSO	16	1.2	84
9	DMSO	20	1.2	92
10	DMSO	24	1.2	74
11[e]	95 % EtOH	24	1.2	49
12[e]	AcOEt	24	1.2	36
13[f]	1,4-Dioxane	24	1.2	60
14	DMA	24	1.2	94
15	DMF	24	1.2	96

[a]Reaction conditions: *o*-Phenylenediamine (1 mmol), 2-bromo-acetophenone (1 mmol), $NaHCO_3$, DMSO (5 mL), 24 h, 120 °C, under air, unless other mentioned. [b]Isolated yield; [c]HBr (1 mmol) was used as catalyst, but an extremely complex mixture was obtained; [d]K_2CO_3 (1.2 mmol) was added; [e]40 °C; [f]90 °C

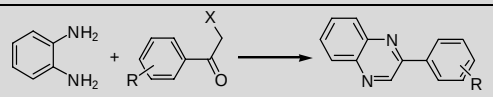
With the optimized conditions at hand, the reactions of α-halomethyl aryl ketones and *o*-phenylenediamine were next investigated (Table-2). Both electron-donating groups and electron-withdrawing groups on the aromatic ring of α-bromo-methyl aryl ketones could achieve excellent yields of quinoxa-lines (entries 2-5 *vs*. 1). For phenacyl bromides with nitro groups, the substituted positions on the phenyl groups hugely influenced the results, namely, *meta*-nitrophenacyl bromide yielded the highest yield of them and the *ortho*-nitrophenacyl bromide afforded the poorest yield (entry 7).

Surprisingly, phenacyl chlorides could also achieve exce-llent yields up to 97 % (entries 8-9). In addi-tion, 3,4-difluoro substituted phenacyl chloride gave good yield (entry 10). How-ever, perhaps due to the instability of catechol in the conditions, 3,4-dihydroxyphenacyl chloride afforded much low yield (entry 11).

The amount of the reactants was scaled up to 10 mmol and the crude product was recrystallized once with hexane to afford 82 % yield (entry 12).

Next, we continued to study the reaction between substi-tuted 1,2-diaminoarenes and phenacyl bromide (Table-3). Elec-tron donating groups on the 1,2-diaminoarenes are beneficial to the reactions (entries 1-2) and the result is attributed to enhancement of the basicity and nucleophilic ability of amino groups of 1,2-diaminoarenes by electron-donating groups. Accordingly, electron-withdrawing groups cause decrease of the yields of quinazolines (entries 3-6). It seems that the stronger the electron-withdrawing ability of the substitutes, the lower the yield of the desired quinoxalines (entries 3-6).

TABLE-2
CATALYST-FREE SYNTHESIS OF QUINAZOLINES FROM α-HALOMETHYL ARYL KETONES AND *ortho*-PHENYLENEDIAMINE[a]

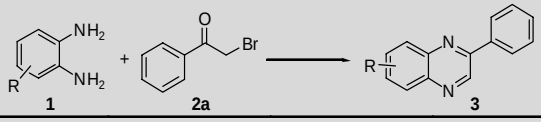


1a 2 3

Entry	R	X	Product	Yield (%)[b]
1	H	Br	3a	99
2	4-CH_3O	Br	3b	92
3	4-Ph	Br	3c	96
4	4-Br	Br	3d	83
5	3-NO_2	Br	3e	97
6	4-NO_2	Br	3f	73
7	2-NO_2	Br	3g	59
8	4-Cl	Cl	3h	97
9	2,4-Cl_2	Cl	3i	93
10	3,4-F_2	Cl	3j	76
11	3,4-$(OH)_2$	Cl	3k	41
12	H	Br	3a	82

[a]Reaction conditions: *o*-Phenylenediamine (1 mmol), α-halomethyl aryl ketones (1 mmol), $NaHCO_3$ (1.2 mmol), DMSO (5 mL), under air, 120 °C, 24 h. [b]Isolated yield

TABLE-3
CATALYST-FREE SYNTHESIS OF QUINAZOLINES FROM PHENACYL BROMIDE AND 1,2-DIAMINOARENES[a]



1 2a 3

Entry	R	Product	Yield (%)[b]
1	4,5-$(CH_3)_2$	3l	80
2[c]	4-CH_3O	3m	82
3[c]	4-Br	3n	76
4[c]	4-Cl	3o	72
5[c]	4-CF_3	3p	73
6[c]	4-NO_2	3q	51

[a]Reaction conditions: *o*-Phenylenediamine (1 mmol), α-halomethyl aryl ketones (1 mmol), $NaHCO_3$ (1.2 mmol), DMSO (5 mL), under air, 120 °C, 24 h. [b]Isolated yield

If non-symmetric 1,2-diaminoarenes are used as substrates, there exist two isomers in the resulting product quinazolines (entries 2-6), which are not isolatable on flash silica gel column chromatography due to the similarity of two isomers.

Conclusion

We have developed a new efficient, greener synthetic method of 2-arylquinoxalines from readily available 1,2-diaminoarenes and substituted phenacyl halides. The hard substrate substituted phenacyl chlorides are firstly used as efficient substrates for synthesis of quinoxalines. Our protocol with sodium bicarbonate as deacid reagent is facile, greener and practical.

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