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One-pot synthesis of quinoxalines from reductive coupling of 2-nitroanilines and 1,2-diketones using indium

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ABSTRACT

The one-pot reduction-cyclization of 2-nitroanilines and 1,2-diketones to give quinoxalines was investigated. Using indium and an appropriate acid such as acetic acid or indium(III) chloride, various quinoxaline derivatives including 2,3-dialkylquinoxalines, 2,3-diphenylquinoxalines, 2,3-di-2-thiophenylquinoxalines, 2,3-di(pyridin-2-yl)quinoxalines, and dibenzo[*a*,*c*]phenazines were synthesized in moderate to excellent yield.

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1. Introduction

Organic compounds containing the quinoxaline moiety have received considerable synthetic attention because of their interesting biological properties. Quinoxaline derivatives are not only widely distributed in nature, but they have been synthesized by many research groups and many of these compounds exhibit a broad spectrum of biological activity including antibacterial,[1–3] antifungal,[4,5] antiviral,[6] anticancer,[7] antituberculosis,[8] antimalarial,[9] and anti-inflammatory properties.[1,3] A typical approach to the quinoxaline ring is the condensation of 1,2-arylenediamines with 1,2-dicarbonyl compounds in ethanol or acetic acid.[10] Recently developed synthetic methods include the use of I_2,[11,12] sulfamic acid (SA),[13] Montmorillonite K-10,[14] silica-bonded S-sulfonic acid (SSA),[15] $H_6P_2W_{18}O_{62}\cdot 24H_2O$,[16] $InCl_3$,[17] $MnCl_2$,[11] $CuSO_4\cdot 5H_2O$,[18] ionic liquid,[19] ceric ammonium nitrate (CAN),[20] $Ga(OTf)_3$,[21] TiO_2,[22] and graphite.[23] In addition, the use of phenacyl bromides,[24] diazoketones,[25] and 2-(phenylethynyl)benzaldehydes in place of 1,2-dicarbonyl compounds has also appeared in the recent literature.[26]

Traditionally used reducing metal reagents such as iron, tin, and zinc metals are getting more unforgiving to use because of environmental issues. Since environmental issues are becoming increasingly important to human endeavors, the green chemistry characteristics of indium must be an attractive merit. Thus, the application of indium metal for various reductive organic transformations has been pursued by many synthetic groups recently.[27] Accordingly, we have developed various indium-mediated reductive reactions during the past decade focusing in particular on nitroarenes including reductive cyclization reactions to prepare nitrogen-containing heterocyclic compounds.[28] New and efficient one-pot indium-mediated syntheses of nitrogen containing heterocycles include 2,1-benzisoxazoles,[28a] benzimidazoles,[28b] quinolines,[28c] indazoles,[28d,e] oxazoles,[28f] indoles,[28g,h] and pyrroles.[28i] While 1,2-aryl diamines are the most commonly used starting substrates for the synthesis of quinoxalines, an extension of our indium-mediated reductive reaction to 2-nitroaryl amines would offer a more diverse one-pot synthetic approach to quinoxalines. Therefore, we examined the one-pot reductive heterocyclization using a 2-nitroaryl amine and 1,2-dicarbonyl compound in the presence of indium to accomplish a coupling reaction giving the quinoxaline. Herein, we report the simple and efficient transformation for preparation of quinoxalines from 2-nitroaryl amines, which have rarely been used as substrates for quinoxaline synthesis.

2. Results and discussion

Based on our previous efforts in indium-mediated heterocyclization reactions, trial experiments were carried out to

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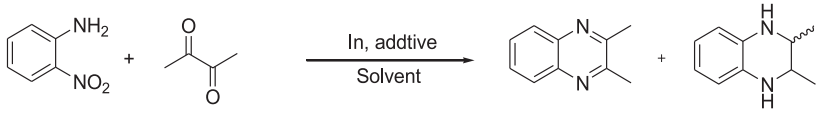
determine the optimum reaction conditions. Acetic acid or indium(III) chloride, $InCl_3$, was applied as an acid additive in various aprotic and protic solvents. Initial experiments of 2-nitroaniline (1 equiv) with 2,3-butanedione (1 equiv) in the presence of acetic acid produced a mixture of the desired 2,3-dimethylquinoxaline (**3**) and further reduced 2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (**4**) regardless of the solvent (entries 1–4), which was somewhat unexpected and disappointing. Formation of **4** may come from further in situ reduction of **3**, which implied that a moderation of the reaction conditions to prevent formation of **4** was necessary. Therefore, we tried the reaction with $InCl_3$, which was not as active as acetic acid in our previous indium-mediated heterocyclization reactions. As expected, application of $InCl_3$ led to a slower reaction, and consequently, formation of **4** was retarded and the yield of the quinoxaline was improved. However, the problem with the formation of **4** was not completely solved. If the amount of $InCl_3$ was doubled, the amount of **4** increased from a trace to 19% even with a shortened reaction time, as shown in entries 8 and 9 in Table 1. Therefore, another trial experiment was performed to suppress the formation of **4** by increasing the amount of 2,3-butanedione. Fortunately, the formation of **4** was effectively suppressed, and the desired product was obtained in high yield (entries 10, 11). After careful control experiments changing the molar ratio of substrates, indium, and $InCl_3$, we determined optimized reaction conditions (method A1); i.e., 2-nitroaniline (1 equiv)/2,3-butanedione (2 equiv)/indium (5 equiv)/$InCl_3$ (1.2 equiv) in methanol at reflux (entry 11, Table 1).

which was the de-iodinated product, 2,3-dimethylquinoxaline as well as the over-reduced product, 6-iodo-2,3-dimethyltetrahydroquinoxaline. De-iodination presumably involved electron transfer processes in the reductive cyclization, which was similar to our previous reports on other indium-mediated heterocyclization reactions.[28]

To extend our newly designed synthetic method to various quinoxaline derivatives from 2-nitroanilines and other 1,2-diketones, cyclizations of substituted 2-nitroanilines with 1,2-diphenyl-1,2-ethanedione (benzil) were carried out under the optimized reaction conditions that had been used for heterocyclization of substituted 2-nitroanilines with 2,3-butanedione. Cyclization of 2-nitroaniline and benzil (2 equiv) with indium (5 equiv)/$InCl_3$ (1.2 equiv) in methanol at reflux was completed within 20 min in quantitative NMR yield. Unfortunately, there was a problem in the isolation of pure product; i.e., the diphenyl-substituted quinoxaline product and starting substrate, benzil had the same TLC R_f value (R_f=0.40, 30% ethyl acetate/hexane solution), and consequently, flash column chromatography was not practical for product purification. Therefore, as an excess of benzil should be avoided, control experiments using a 1 to 1 M ratio of 2-nitroaniline and benzil with varying molar amounts and/or kinds of reagents were performed. After several control experiments, modified reaction conditions were identified, which solved the separation issue; i.e., 2-nitroaniline (1 equiv)/benzil (1 equiv)/indium (5 equiv)/$InCl_3$ (1 equiv) in methanol at reflux (method A2). In addition to these modified conditions, use of an appropriate amount of acetic

Table 1
Formation of 2,3-dimethylquinoxalines in the presence of In/AcOH or $InCl_3$ under various reaction conditions



1 2 3 4

Entry	Molar equiv (eq)				Solvent (mL)/ Temp (°C)	Time (h)	Yield[a] (%)	
	1	**2**	In	Additive			**3**	**4**
1	1	1	4	AcOH(10)	EA(5)/reflux	0.5	58	37
2	1	1	4	AcOH(10)	Toluene(5)/80	0.5	55	28
3	1	1	4	AcOH(10)	ACN(5)/50	17	39[b]	34
4	1	1	4	AcOH(10)	MeOH(5)/reflux	0.5	77[b]	13
5	1	1	4	$InCl_3$(1)	EA(5)/reflux	16	21	7
6	1	1	4	$InCl_3$(1)	THF:H_2O(3:3)/50	18	28	31
7	1	1	4	$InCl_3$(1)	MeOH(5)/reflux	2.5	72[b]	Trace
8	1	1	5	$InCl_3$(1)	MeOH(5)/reflux	1	73[b]	Trace
9	1	1	5	$InCl_3$(2)	MeOH(5)/reflux	0.5	55[b]	19
10	1	2	5	$InCl_3$(1)	MeOH(5)/reflux	2.5	90	—
11	1	2	5	$InCl_3$(1.2)	MeOH(5)/reflux	1.5	91 (87[c])	—
12	1	4	5	$InCl_3$(1)	MeOH(5)/reflux	7	88	—

[a] GC yield with an internal standard (octane).
[b] 1–8% of 1,2-diaminobenzene was observed.
[c] Isolated yield.

Using the optimized reaction conditions, method A1, heterocyclizations of various substituted 2-nitroaniline derivatives with 2,3-butanedione (2 equiv) were initially examined in the presence of indium (5 equiv)/$InCl_3$ (1.2 equiv) in methanol at reflux to test the synthetic scope of the reaction (Table 2). In most cases, cyclization reactions delivered the quinoxalines from the 2-nitroanilines in excellent yield, 68–95%, within 50–140 min. Electronic effects of substituents appeared to have little effect on the yield; however, an alkyl substituent (entries 2–4, Table 2) prolonged the reaction time regardless of its position compared to electron-withdrawing substituents such as halo, trifluoromethyl, or cyano groups (entries 7–14). In the case of the iodo-substituted 2-nitroaniline (entry 11), traces of by-products were observed, one of

acid in toluene solvent was equally effective as the above-mentioned method A2; i.e., 2-nitroaniline (1 equiv)/benzil (1 equiv)/indium (5 equiv)/AcOH (5 equiv) in toluene at 80 °C (method B1). With use of excess AcOH (10 equiv), the 2,3-diphenyl-1,2,3,4-tetrahydroquinoxaline byproduct was encountered. Since method B1 was as productive as method A2, both conditions were applied to the synthesis of 2,3-diphenylquinoxaline derivatives, and the results are summarized in Table 3. In most cases, both methods worked equally well, and moderate to good yields of the desired 2,3-diphenylquinoxaline derivatives were obtained regardless of the nature and position of substituents, although the reaction time was somewhat longer with method B1 compared to method A2.

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