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ALUMINIUM NITRATE CATALYSED SYNTHESIS OF QUINOXALINE DERIVATIVES

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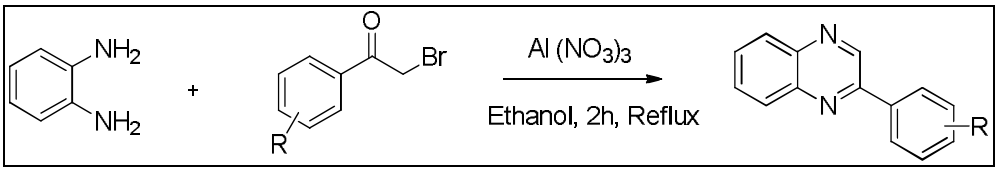
ABSTRACT

*A series of quinoxaline derivatives (**3a-h**) were efficiently synthesized with excellent yields by the reaction of 1,2-diamine (**1**) and substituted phenacyl bromides (**2a-h**) using a catalytic amount of aluminium nitride in ethanol as medium.Quinoxaline derivatives were synthesized in short-time periods and with excellent yields (78-92%). Compared with the classical synthetic methods, this present protocol advantages of easy reaction work up,easily separated from the reaction mixture.*

KEYWORDS: *Quinoxaline, Aluminium Nitrate, Synthesis, Methodology.*

Graphical Abtract:



INTRODUCTION:

Quinoxaline derivatives are an important class of heterocycle compoundsby the fusion of two aromatic rings, benzene and pyrazine.[1]Quinoxalinesand its derivatives are well known for their broad spectrum of pharmacological activities such as antimicrobial,[2] antitubercular,[3] anti-inflammatory, and antifungal.[4] Quinoxalines derivatives are having applications in dyes,efficient electrolu-minescent materials,[5]organic semiconductors,[6]building blocks for thesynthesis of anion receptor,[7] cavitands,[8] dehydroannulenes and DNA cleaving agents[9]have been reported. Aforementioned chemical and biological activities of quinoxalinesand their derivatives have attracted more attention on the synthesis of novel protocol for its synthesis.

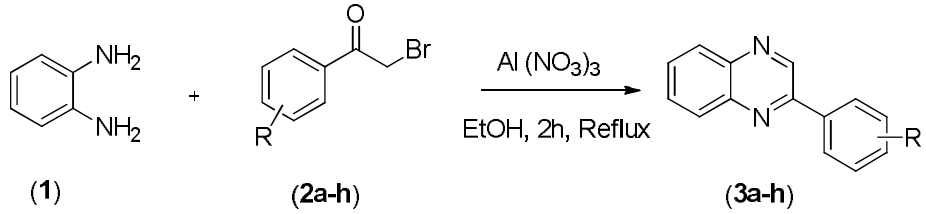
Therefore tremendous work was done for the synthesis of quinoxaline ring. Following are the some methods for the synthesis of quinoxaline such as condensation of O-phenylenediamine with 1,2-dicarbonyl compounds, 1,4-addition of O-phenylenediamine and 1,2-diazenylbutens[10]and oxidation trapping of α-hydroxyketones with O-phenylenediamine.[11]There are several catalysts have been reported for quinazolines such as- cellulose sulfuric acid,[12] PEG-400,[13]hypervalent iodine (III) sulfonate in PEG,[14]polyaniline-sulfate salt,[15]CAN,[16] MnO_2,[17] fluorinated alcohols and Amberlite IR-120H.[18] Among these synthetic methods we have adopted the reaction of O-phenylenediamine and phenacyl bromides. For this methods several protocols have been methods such as have been used heterogeneous catalysts like $HClO_4$-SiO_2,[19]TMSCl,[20] β-cyclodextrin,[21]and DABCO.[22]These methods are accompanying with several lacuna's such as long reaction time, prolonged heating, low yeild and expensive catalysts.

Lewis acids are excellent alternatives for conventional reagents and usually used in

various organic transformations. Aluminium Nitrate catalyst is lewis acid proven to be better than the conventional acid catalysts due to inexpensive cost, easy work up, simple operation, low toxicity and environmental compatibility. Herein we have developed novel efficient and synthetic route forquinoxalines from phenacyl bromide and O-phenylenediamine using Aluminium nitrate as a catalyst.

RESULTS AND DISCUSSIONS

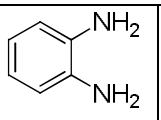
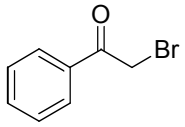
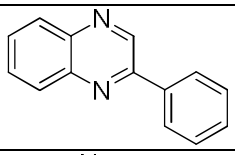
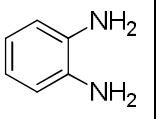
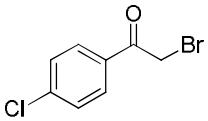
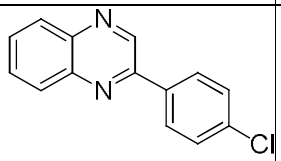
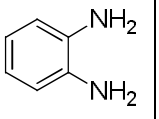
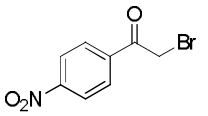
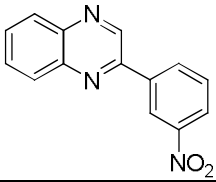
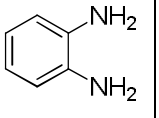
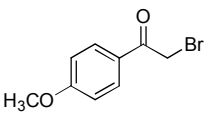
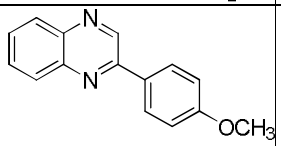
Herein we have developed excellent protocol for the synthesis of quinoxalines (**3a-h**) by reacting O-pheneylenediamine(**1**) and substituted phenacyl bromides (**2a-h**)in the presence of Al $(NO_3)_3$ (20mole%) as a catalyst. The reaction mixture was refluxed for 2h to affordquinoxalines (**3a-h**) with excellent yields and with high purity. The synthetic route is depicted in **Scheme 1.**

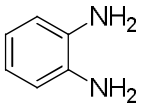
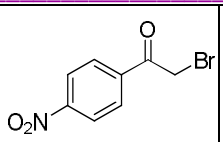
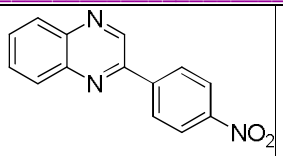
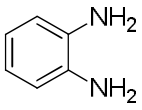
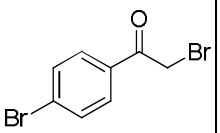
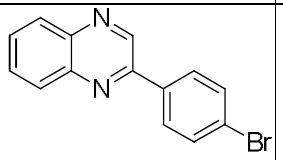
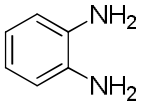
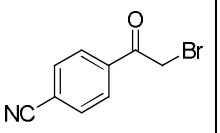
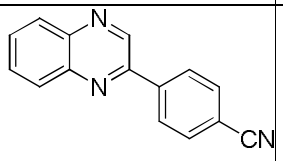
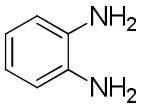
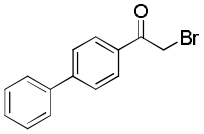
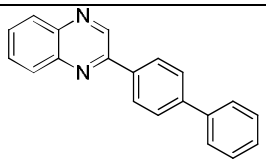


Scheme 1: Synthetic route for the Quinoxaline derivatives.

The physical data and isolated yields of the desired compounds (**3a-h**) are incorporated in **Table 1.**The compounds were characterised by ^{1}H NMR, ^{13}C NMR and Mass spectral techniques.

Table 1. Aluminium Nitratecatalyzed syntheses of Quinoxaline derivatives.

Entry	Reactants		Products	M. P. (°C)	Yields[a]	Time (h)
3a				73-75	88	2
3b				128-130	92	2
3c				160-162	89	2.3
3d				95-97	90	2.5

3e				171-174	92	2
3f				116-120	82	2.1
3g				194-195	78	2.5
3h				135-140	89	3

[a]Isolated yields of the products

Initially we have screened the solvent parameterand studied the reaction in different solvents like water, methanol and ethanol as protic solvents aswell as THF, dichloromethane, acetonitrile, dimethyl sulphoxide and dimethylformamide as aprotic solvent. It has been also cleared that the quinoxaline formation in ethanol solvent proceeds with excellent yield (**Table 2, entry 7**). Whereas reaction in methanol, dichloromethane and acetonitrile solventafforded low yield of the product (**Table 2, entries 2-6**). No product formation was observedwhen water was used as a solvent (**Table 2, entry 1**). From **Table 2** it is concluded that in absence of catalyst there is negligible conversion of products solvent (**Table 2, entry 10**).

Table 2. Screening of reaction condition with respect to solvent and catalyst[a]

Sr. No.	Solvent	Catalyst	Yeild[b]
1	Water	20% Al $(NO_3)_3$	N.R.
2	Methanol	20% Al $(NO_3)_3$	56
3	Dimethyl sulphoxide	20% Al $(NO_3)_3$	72
4	Dimethylformamide	20% Al $(NO_3)_3$	68
5	THF	20% Al $(NO_3)_3$	66
6	Dichloromethane	20% Al $(NO_3)_3$	71
7	Ethanol	20% Al $(NO_3)_3$	88
8	Ethanol	25% Al $(NO_3)_3$	88
9	Ethanol	30% Al $(NO_3)_3$	87
10	Ethanol	Without catalyst	05

[a]**Reaction conditions:**Phenacyl bromide (0.001mole),o-phenylenediamine (0.001mmol), 20% Al $(NO_3)_3$, in 8 ml Ethanol, refluxed, [b]Isolated yields of the products.

EXPERIMENTAL

Chemicals and solvents were procured from Merck and S. D. fine chem. Melting points were determined in open capillary and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (GF 254) using UV light to visualize the course of the reactions. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded BrukerAvance 300-500 (FT-NMR) andBruker DRX-300 instruments, respectively, using $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts are reported in δ ppm with TMS as internal standard. High-resolution massspectra (HRMS) were obtained using the Agilent 6520 (Q-TOF) ESI-HRMS instrument.Routine monitoring of reaction was performed by TLC using 0.25 mm E. Merck precoated silica gel TLC plates (60 F254)hexane:ethyl acetate as eluent.

General experimental procedure for synthesis of quinoxalines

Phenacyl bromide (**2a**) (0.001 mole) and Al $(NO_3)_3$ (20 mole %) were stirred in 8 ml ethanol were stirred for 5 min. After 5 minutes, O-phenylenediamine(**1**) (0.001 mole) wasadded to reaction mass and then resultant mixture was refluxed for 2 h (**Table1**). The progress of the reaction was monitored by TLC. Aftercompletion of reaction, reaction mixture was diluted with ethyl acetate (10 ml). The filtrate was washed with aqueous $NaHCO_3$ and then with waterfollowed by separation of aqueous layer and organic layer. The crude product was purified by crystalisation using ethanol to afford the pure Quinoxoline.

Similarly other derivatives (**3b-j**) were prepared.

2-(Phenyl)quinoxaline (3a)

^{1}H NMR (400 MHz, DMSO *d6*): δ ppm = 9.20 (s, 1H), 7.81 (m, *J*=10 Hz, 2H), 7.71 (m, *J*=14 Hz, 2H), 7.58 (m, *J*=14 Hz, 5H); ^{13}C NMR (300 MHz, $CDCl_3$): δ= 146.7, 143.74, 140.82, 132.47, 130.12, 129.75, 128.60, 127.68, 126.6; MS (ESI): m/z 206 (M^+).

CONCLUSIONS

We have developed a green and efficient protocol for one-pot synthesis of quinoxaline derivatives from readily available o-phenylenediamineand substituted phenacyl bromides using aluminium nitrateas catalyst. The conditions are mild and a wide range of functional groups can be tolerated in the building blocks for the synthesized quinoxalines. This catalyst offered advantages including simplicity of operation, easy workup, time saving and excellent purity and high yields of products

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