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Research Article

A NOVEL ONE POT SYNTHESIS OF PYRAZINES AND QUINOXALINES FROM ALDEHYDES

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An efficient benign coupling of Aldehydes and acetic anhydride followed by condensation with 1,2-diamines for a facile and one pot synthesis of pyrazines &quinoxalines was carried out with non- toxic and eco-friendly condition at ambient temperature. Easy work up and moderate to high yield are the special features of this method.

INTRODUCTION

Pyrazine contains two nitrogen atoms in its aromatic ring. Pyrazine and its derivatives are valuable compounds because of their application in the synthesis of perfumery, pharmaceutical and agricultural chemical industries.[1–3]

Quinoxaline is commonly called as 1,4-diazanaphthalene or benzopyrazine. Its derivative are mostly of synthetic origin. Quinoxaline derivatives are known as the important category of nitrogen-containing heterocyclic compounds which are indispensable structural units for both the chemist and the biochemist compounds. They have been considered as important compounds from both academic and industrial perspective because they are significant intermediates for the manufacturing of pharmaceuticals and advanced materials. Derivatives from Quinoxaline are well known in the pharmaceutical industry and possess a broad spectrum of biological activities including antiviral, anticancer, antimicrobial, antifungal, antidepressant activities. Besides, they are active against various transplantable tumors.[4-10] Considering their chemical and biological significance, numerous synthetic strategies have been developed for the preparation of quinoxaline derivatives. The most common and straightforward route to pyrazines &quinoxalines is the condensation of 1,2-dicarbonyl compounds with 1,2-diaminebenzenes under various conditions, including the employment of microwave irradiation,[11] different solventsand catalysts, such as polyaniline sulfate,[12] oxalic acid,[13]*o*-iodoxybenzoic acid (IBX),[14] polyethylene glycol (PEG),[15]montmorillonite K-10,[16]amberlyst-15,[17] molecular iodine,[18]silica gel,[19] ionic liquid,[20] NH4X,[21] Bi(OTf)3,[22] Ga(OTf)3,[23] NbCl5,[24]ZrCl4.[25]

But all these procedures have its drawbacks in terms of expensive reagents, difficult reaction conditions and low yields. In some cases, even the starting materials require a series of steps for their preparation.

From the synthesis standpoint, the traditional processes have its drawbacks in terms of expensive reagents, difficult reaction conditions and low yields. In some cases, even the starting materials require a series of steps for their preparation.

As a part of our research interest towards the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions at very short reaction times has been compared with other procedures. Herein, we report the one pot synthesis of quinoxaline derivatives by coupling aldehydes with acetic anhydride and condensation with 1,2-diamines in the presence of Cobalt (II) chloride at room temperature

Experimental

Summary of result in one pot synthesis of pyrazines & quinoxalines

Material and measurements

All chemicals are commercially available and used as received. Melting points were determined on Veego automatic melting point apparatus and are uncorrected.[1] H NMR spectra were recorded on varian 400 MHzVNMR spectrometer. Purification of product was done on Teledyne isco flash chromatography.

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Entry	Aldehyde	Moles of Acrtic anhydride	1,2-Diamines	Product	Yield (%)
1	Benzaldehyde	1.0	1,2-Diaminoethane	5,6-Diphenyl-2,3-dihydropyrazine	55%
2	Benzaldehyde	1.0	o-Phenylenediamine	2,3-Diphenyl-quinoxaline	57%
3	Benzaldehyde	3.0	o-Phenylenediamine	2-Methyl-3-phenyl-quinoxaline	65%
4	Heptaldehyde	3.0	o-Phenylenediamine	2-Hexyl-3-methylquinoxaline	58%
5	3-Bromobenzaldehyde	3.0	o-Phenylenediamine	2-(3-bromophenyl)-3-methylquinoxaline	61%

[a]The yields refer to isolated products

Synthesis of 5,6-Diphenyl-2,3-dihydropyrazine

1.94 g (0.0183 mole) of benzaldehyde was taken in 25 ml of acetonitrile and 0.24 g (10 mole %) Cobalt (II) chloride was added. 1.87 g (0.0183 mole) of Acetic anhydride was added and reaction mass was stirred for 12 hours at room temperature.

1.10 g (0.0183 mole) of 1,2-diaminoethane was added and stirring was continued for three hours at room temperature. Water (25 ml) is added and product is extracted in 2 x 25 ml MDC. MDC layer is dried over anhydrous sodium sulfate and distilled out the solvent. The residue obtained was purified by flash chromatography to afford 2.35 g (55%) off-white crystalline powder.

m.p.: 162-163°C; PMR ($CDCl_3$, δ): 3.9 (4H, 1t, $-CH_2$), 7.3-7.6 (10H, m, aromatic)

Synthesis of 2,3-Diphenyl-quinoxaline

1.94 g (0.0183 mole) of benzaldehyde was taken in 25 ml of acetonitrile and 0.24 g (10 mole %) Cobalt (II) chloride was added. 1.87 g (0.0183 mole) of Acetic anhydride was added and reaction mass was stirred for 12 hours at room temperature.

1.98 g (0.0183 mole) of o-phenylenediamine was added and stirring was continued for three hours at room temperature. Water (25 ml) is added and product is extracted in 2 x 25 ml MDC. MDC layer is dried over anhydrous sodium sulfate and distilled out the solvent. The residue obtained was purified by flash chromatography to afford 2.94 g (57%) off-white crystalline powder.

m.p.: 127-128°C; PMR ($CDCl_3$, δ):7.2-7.5 (10H, m, two phenyl substituents), 7.7 (2H, 1t, quinoxaline ring), 8.1 (2H. 1d, quinoxaline ring)

Synthesis of 2-Methyl-3-phenyl-quinoxaline

1.94 g (0.0183 mole) of benzaldehyde was taken in 25 ml of acetonitrile and 0.24 g (10 mole %) Cobalt (II) chloride was added. 5.61 g (0.0549 mole) of Acetic anhydride was added and reaction mass was stirred for 12 hours at room temperature.

1.98 g (0.0183 mole) of o-phenylenediamine was added and stirring was continued for overnight at room temperature.

Water (25 ml) is added and product is extracted in MDC. MDC layer is dried over anhydrous sodium sulfate and distilled out the solvent. The residue obtained was purified by flash chromatography to afford 2.62 g (65%) off-white crystalline powder.

m.p.: 55°C; PMR ($CDCl_3$, δ): 2.8 (3H, 1s, $-CH_3$), 7.4-7.6 (3H, 2t, phenyl substituent), 7.7 (2H, 1d, phenyl substituent), 8.1 (2H. 1t, quinoxaline ring), 8.2 (2H. 1d, quinoxaline ring);

Synthesis of 2-Hexyl-3-methylquinoxaline

2.0 g (0.0175 mole) of heptaldehyde was taken in 30 ml of acetonitrile and 0.23 g (10 mole %) Cobalt (II) chloride was added. 5.36 g (0.0525 mole) of Acetic anhydride was added and reaction mass was stirred for 12 hours at room temperature.

1.89 g (0.0175 mole) of o-phenylenediamine was added and stirring was continued for overnight at room temperature.

Water (20 ml) is added and product is extracted in 2 x 25 ml MDC. MDC layer is dried over anhydrous sodium sulfate and distilled out the solvent. The residue obtained was purified by flash chromatographyto afford 2.31 g (58%) off-white crystalline powder.

m.p.: 128-130°C; PMR ($CDCl_3$, δ): 0.9 (3H, 1t, $-CH_3$), 1.3 (6H, multiplet, $-CH_2$), 1.6(2H, multiplet, $-CH_2$), 2.4(2H, 1t, $-CH_2$), 2.7(3H, 1s, $-CH_3$), 7.7(2H, 1t, quinoxaline ring), 7.8(2H, 1d, quinoxaline ring)

Synthesis of 2-(3-bromophenyl)-3-methylquinoxaline

1.50 g (0.0081 mole) of 3-bromobenzaldehyde was taken in 20 ml of acetonitrile and 0.11 g (10 mole %) Cobalt (II) chloride was added. 2.48 g (0.0243 mole) of Acetic anhydride was added and reaction mass was stirred for 12 hours at room temperature.

0.87 g (0.0183 mole) of o-phenylenediamine was added and stirring was continued for overnight at room temperature.

Water (25 ml) is added and product is extracted in 2 x 25 ml MDC. MDC layer is dried over anhydrous sodium sulfate and distilled out the solvent. The residue obtained was purified by flash chromatography to afford 1.47 g (61%) off-white crystalline powder.

m.p.: 230-232°C; PMR ($CDCl_3$, δ): 2.7 (3H, 1s, $-CH_3$), 7.5 (1H, m, phenyl substituent),7.4-7.7 (3H, m, phenyl substituent), 7.6(2H, 1t, quinoxaline ring), 7.8 (2H. 1d, quinoxaline ring)

RESULTS AND DISCUSSION

Several experiments were carried out to optimize the newly developed general protocol for synthesis of pyrazines and quinoxalines. In deciding the best solvent for the above transformation, a series of polar protic and polar aprotic solvents were tried in the model reaction and acetonitrile was found to be the best. Mole of acetic anhydride was optimised to 1 equivalent to 3 equivalent mole depending upon the product of interest.[26] The effect of mole % of Cobalt (II) Chloride on the yield of quinoxalines reaction in acetonitrile was also studied during the course of table work and it was observed that 10 mole % of Cobalt (II) chloride in acetonitrile is suitable choice for the general reaction.

Typical procedure for preparation of pyrazines &quinoxalines

To astirred solution of aldehyde (10mmol) in acetonitrile (25 ml), was added Cobalt (II) chloride (10 mol%) followed by acetic anhydride (required mol) (Table 1). The mixture was stirred for 12 hours at room temperature.

1,2-diamine (10mmol) was added and stirring was continued for three hours at room temperature.

Water (25 ml) is added and product is extracted in 2 x 25 ml MDC. MDC layer is dried over anhydrous sodium sulfate and distilled out the solvent. The residue obtained was purified by flash chromatography.

5,6-Diphenyl-2,3-dihydropyrazine

Off-white crystalline powder, Yield: 55%, m.p.: 162-163°C PMR ($CDCl_3$, δ): 3.9 (4H, 1t, $-CH_2$), 7.3-7.6 (10H, m, aromatic).

2,3-Diphenyl-quinoxaline

Off-white crystalline powder, Yield: 57%, m.p.: 127-128°C; PMR ($CDCl_3$, δ): 7.2-7.5 (10H, m, two phenyl substituents)**,** 7.7 (2H, 1t, quinoxaline ring)**,** 8.1 (2H. 1d, quinoxaline ring).

2-Methyl-3-phenyl-quinoxaline

Off-white crystalline powder, Yield: 65%, m.p.: 55°C; PMR ($CDCl_3$, δ): 2.8 (3H, 1s, $-CH_3$), 7.4-7.6 (3H, 2t, phenyl substituent), 7.7 (2H, 1d, phenyl substituent), 8.1 (2H. 1t, quinoxaline ring), 8.2 (2H. 1d, quinoxaline ring).

2-Hexyl-3-methylquinoxaline

Off-white crystalline powder, Yield: 58%, m.p.: 128-130°C; PMR ($CDCl_3$, δ): 0.9 (3H, 1t, $-CH_3$), 1.3 (6H, multiplet, $-CH_2$), 1.6(2H, multiplet, $-CH_2$), 2.4(2H, 1t, $-CH_2$), 2.7(3H, 1s, $-CH_3$), 7.7(2H, 1t, quinoxaline ring), 7.8(2H,1d, quinoxaline ring).

2-(3-bromophenyl)-3-methylquinoxaline

Off-white crystalline powder, Yield: 61%, m.p.: 230-232°C; PMR ($CDCl_3$, δ): 2.7 (3H, 1s, $-CH_3$), 7.5 (1H, m, phenyl substituent)**,** 7.4-7.7 (3H, m, phenyl substituent)**,** 7.6(2H, 1t, quinoxaline ring)**,** 7.8 (2H. 1d, quinoxaline ring).

CONCLUSIONS

In summary, a new application of cobalt chloride catalysed coupling and condensation as an effective, very cheap and non-toxic catalyst for the synthesis of pyrazines and quinoxalines respectively, based on coupling of aldehydes with acetic anhydride and later condensation with 1,2-diamines under mild reaction conditions is presented.

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