International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 7 | Issue 4 | OCT-DEC| 2017 | 277-281
Research Article | Biological Sciences | Open Access | UGC Approved | MCI Approved Journal

ZIRCONIUM CHLORIDE ($ZrCl_4$): A SIMPLE AND EFFICIENT CATALYST FOR THE SYNTHESIS OF QUINOXALINES

J. Madhukar*

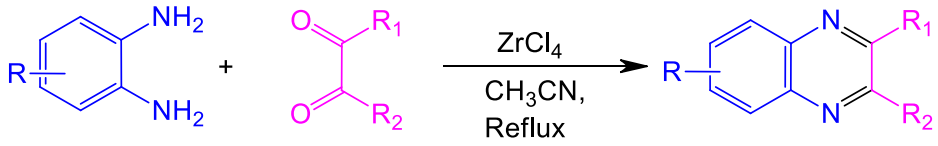
Department of Chemistry, Kakatiya University, Warangal-506001, Telangana, India.

***Corresponding Author Email:** madhukerj@gmail.com

ABSTRACT

An efficient and environmental benign process for the synthesis of quinoxalines has been developed. All the reactions were carried out in presence of a catalytic amount of ZrCl4 at acetonitrile reflux. This method is applicable to a variety of diketones and 1,2-phenylenediamines to afford the corresponding derivatives in excellent yields.

Graphical abstract

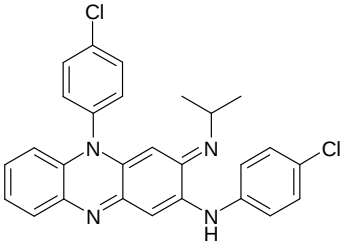


KEY WORDS

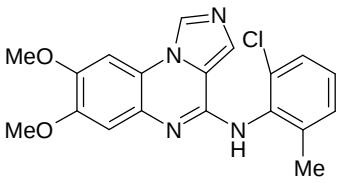
Diketones, ortho-phenylenediamines, $ZrCl_4$, CH_3CN, quinoxalines.

INTRODUCTION:

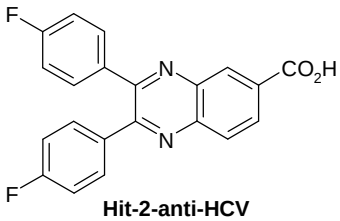
Quinoxalines are a versatile class of nitrogen containing heterocyclic compounds and they constitute useful intermediates in organic synthesis. Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including anti-bacterial, anti-viral, anti-inflammatory, anti-cancer, and kinase inhibitors.[1] In addition, quinoxaline derivatives have been evaluated as anthelmintic agents, semiconductors, dyes and biocides.[2] Therefore, a variety of synthetic strategies have been developed for the preparation of substituted quinoxalines.



Clofazimine-antileprosy



BMS-238497
T-cell proliferation



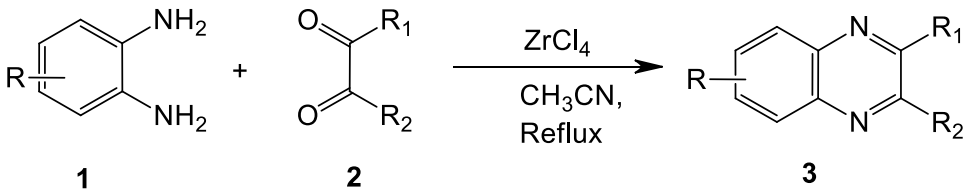
Hit-2-anti-HCV

Conventionally, quinoxalines synthesis can be achieved by the reaction of *ortho*-phenylenediamine with two-carbon synthones such as α-dicarbonyls,[3] α-halogeno carbonyls, α-hydroxycarbonyls, α-azocarbonyls, epoxides, and α, β-dihalides.[4] Among the reported procedures, the most common method is the condensation of an aryl 1, 2-di amine with 1,2-diketone compounds in refluxing ethanol or acetic acid[5] or using different catalysts and reaction conditions.[6] However, many of these methods suffer from several drawbacks, such as drastic reaction conditions, use of polar solvents (e.g. AcOH, EtOH, DMSO), expensive and toxic metal

catalyst (e.g. $Pd(OAc)_2$ and $RuCl_2(PPh_3)_3$-TEMPO), tedious work up procedures and unsatisfactory yields, which limit their use.[7] Therefore, the development of simple, convenient environmentally benign and improved method for the synthesis of quinoxalines derivatives would certainly be useful in generating combinatorial libraries for drug discovery.

RESULTS AND DISCUSSIONS:

Zirconium tetrachloride ($ZrCl_4$) is a mild Lewis acid and known in the literature for various organic transformations.[8] Herein we report a simple and efficient protocol for the synthesis of quinoxalines derivatives using a catalytic amount of Zirconium Chloride at acetonitrile reflux.

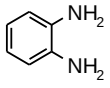
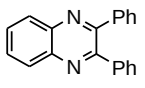
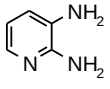
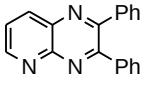
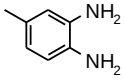
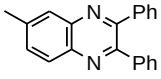
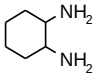
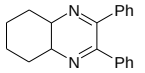


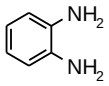
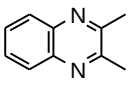
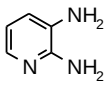
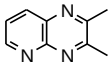
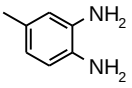
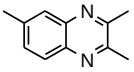
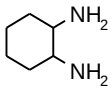
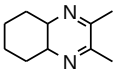
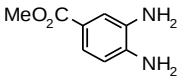
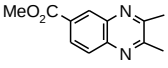
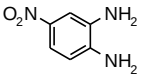
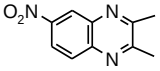
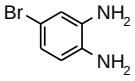
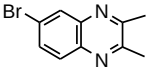
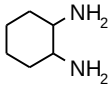
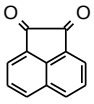
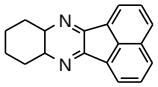
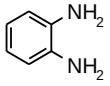
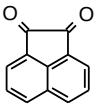
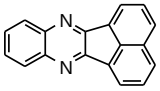
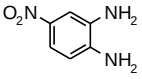
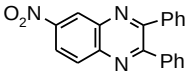
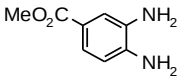
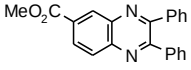
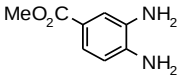
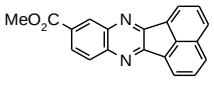
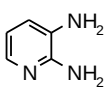
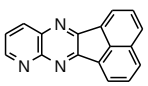
1 **2** **3**

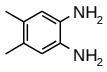
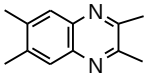
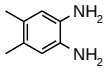
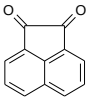
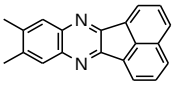
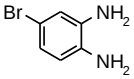
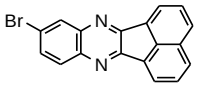
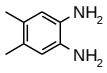
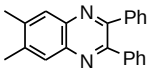
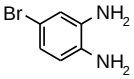
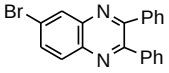
Scheme 1

Initially, we chose the benzil and 1, 2-phenylenediamine as standard reactants to establish the best conditions for the reaction as shown in table 1. We examined the effect of temperature, amount of the $ZrCl_4$ and different solvents. It was found that catalytic amount (10% mol) of $ZrCl_4$ and acetonitrile reflux as suitable conditions for condensation reaction. Since the best conditions were established, this protocol was extended to various aromatic diketones including benzil and acenaphthylene-1, 2-dione and aliphatic carbonyls including biacetyl. In a similar manner, the aromatic diamines such as *ortho*-phenylenediamine (entries **3a**, **3e**, **3m**), 4-methylbenzene-1, 2-diamine (entries **3c**, **3g**), 4, 5-dimethylbenzene-1, 2-diamine (entries **3r**, **3s**, **3u**), 4-notrobenzene-1, 2-diamine (entries **3j**, **3n**), pyridine-2, 3-diamine (entries **3b**, **3f**, **3q**), 4-bromobenzene-1, 2-diamine (entries **3k**, **3t**, **3v**), methyl-3, 4-diaminobenzoate (entries **3i**, **3o**, **3p**) and alicyclic diamine such as cyclohexene-1, 2-diamine (entries **3d**, **3h**, **3l**) have been studied. The scope and generality of this procedure is illustrated with respect to various diketo carbonyls and 1, 2-diamines and the results are presented in table 1. In general, the condensation takes place faster, when the reaction was carried out between aromatic diketones and *ortho*-phenylenediamines. In a similar manner, the reaction between aliphatic diketones and alicyclic diamines was comparatively slower in terms of reaction rates as well as yields. All the reactions were completed within 4.0 to 6.0 hours of reaction time and the obtained products yields were in 75 to 95 %. The structures of the products were identified by their ^1H NMR, IR and mass spectral analysis.

Table 1: $ZrCl_4$ Catalyzed synthesis of quinoxalines:

S.No.	1,2-Diamine	1,2-Diketone	Product[a]	Reaction Time (h)	Yield[b] (%)
a				4.0	95
b				4.0	92
c				4.0	95
d				6.0	88

e				5.0	90
f				5.0	84
g				5.0	85
h				6.0	75
i				5.0	83
j				6.0	81
k				5.0	83
l				5.5	85
m				4.5	92
n				5.5	84
o				5.0	86
p				5.0	85
q				5.0	86

r				6.0	85
s				5.0	91
t				5.0	85
u				4.0	95
v				4.5	86

[a]All the products were identified by their ^{1}H NMR, IR and mass.
[b]Yields were isolated and unoptimized.

CONCLUSION:

In conclusion, we have demonstrated a simple and efficient protocol for the synthesis of quinoxalines using a catalytic amount of $ZrCl_4$ *via* the coupling of diketo carbonyls with 1, 2-diamines. The method is very simple, clean and generally applicable to a variety of reactants such as aromatic, hetero aromatic, aliphatic and alicyclic systems.

Experimental Section:

General methods: Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr disk. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for the synthesis of quinoxalines: To a stirred mixture of diketone (210mg, 1.0 mmol) and diamine (128mg, 1.1 mmol) in acetonitrile (5 mL) was added the catalyst $ZrCl_4$ (0.23mg, 0.1 mmol) and refluxed for a specific time (mentioned in the table). The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, as indicated by TLC, the reaction mixture was brought to room temperature, solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (2x10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude products, which were purified by column chromatography using silica-gel (60-120 mesh) by eluting with ethylacetate-hexane (3:7) mixture to afford pure products. All the pure products were identified by their IR, ^{1}H NMR and mass spectroscopy data.

Spectral data for selected compounds:

Compound (**3e**): IR (KBr): ν 3380, 2941, 2885, 1647, 1428, 1397, 1324, 1208, 1164, 1111, 1044, 989, 922, 856, 762, 671 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$): δ 2.72 (s, 6H), 7.60-7.70 (m, 2H), 7.90-8.01 (m, 2H). EIMS: *m/z* (%): 158 (m^+ 70), 143 (10), 130 (10), 118 (10), 117 (100), 102 (10), 90 (15), 89 (12), 77 (20), 76 (35), 75 (12), 61 (12), 50 (18), 41 (10). **Compound** (**3f**): IR (neat): ν 3376, 2994, 2947, 1641, 1599, 1560, 1461, 1395, 1313, 1238, 1191, 1151, 1108, 1041, 995, 918, 830, 796, 713, 680 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$): δ 2.78 (s, 3H), 2.83 (s, 3H), 7.58-7.68 (m, 1H), 8.35 (d, 1H, *J* = 5.0 Hz), 9.05 (d, 1H, *J* = 3.0 Hz). EIMS: *m/z* (%): 159 (m^+ 48), 144 (10), 118 (58), 105 (12), 91 (15), 77 (52), 61 (100), 50 (18), 41 (66). **Compound** (**3i**): IR (KBr): ν 3384, 2943, 2886, 1712, 1658, 1442, 1400, 1343, 1307, 1263, 1198, 1095, 1046, 992, 918, 854, 765, 695 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 6H), 3.99 (s, 3H), 7.98 (d, 1H, *J* = 6.5 Hz), 8.25 (d, 1H, *J* = 6.5 Hz), 8.68 (s, 1H). EIMS: *m/z* (%): 217 (m^+ 100), 191 (20), 177 (12), 102 (25). **Compound** (**3l**): ν 3387, 3064, 2938, 1661, 1592, 1449, 1323, 1211, 1172, 1110, 1045, 996, 927, 874, 794, 719, 681, 641 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$): δ 1.48-1.62 (m, 3H), 1.90-2.05 (m, 3H), 2.55 (d, 2H, *J* = 6.0 Hz), 3.08-3.18 (m, 2H), 7.68 (t, 2H, *J* = 6.0 Hz), 7.95 (d, 4H, *J* = 6.0 Hz). **Compound** (**3q**): ν 3383, 2940, 2850, 1620, 1563, 1494, 1442, 1399, 1367, 1325, 1255, 1200, 1158, 1113, 1095, 1044, 988, 907, 833, 769, 677 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.68-7.72 (m, 1H), 7.82-7.90 (m, 2H), 8.12-8.18 (m, 2H), 8.40 (d, 1H, *J* = 6.0 Hz), 8.01-8.10 (m, 2H), 9.12 (s, 1H).

EIMS: *m/z* (%): 255 (m^+ 25), 233 (56), 225 (18), 211 (33), 194 (15), 178 (30), 171 (65), 149 (20), 131 (25), 115 (15), 105 (100), 75 (28). **Compound** (**3s**): ν 3386, 2939, 2856, 1646, 1428, 1299, 1208, 1108, 1043, 992, 923, 857, 758 $cm.^{-1}$ ^1H NMR ($CDCl_3$): δ 2.52 (s, 6H), 7.81 (t, 2H, *J* = 6.0 Hz), 7.90 (s, 2H), 8.20 (d, 2H, *J* = 6.0 Hz), 8.39 (d, 2H, *J* = 6.0 Hz).

Acknowledgement:

The authors are thankful to Director CSIR-IICT-Hyderabad for providing analytical support (^1H NMR, ^{13}C NMR, IR and Mass).

REFERENCES:

[1] (a) A. Jaso, B. Zarranz, I. Aldana, A. Monge. *J. Med. Chem.* 2005, *48*, 2019; (b) J. Renault, M. Baron, P. Mailliet. *Eur. J. Med. Chem.* 1981, *16*, 545.

[2] (a) R. Sarges, H. R. Howard, R. G. Browne, L. A. Lebel, P. A. Seymour. *J. Med. Chem.* 1990, *33*, 2240; (b) S. Dailey, J. W. Feast, R. J. Peace, I. C. Sage, S. Till, E. L. Wood. *J. Mater. Chem.* 2001, *11*, 2238.

[3] (a) S. V. More, M. N. V. Sastry, C. C. Wang, C. F. Yao. *Tetrahedron Lett.* 2005, *46*, 6345; (b) K. M. Driller, S. Libnow, M. Hein, M. Harms, K. Wende, M. Lalk, D. Michalik, H. Reinke, P. Langer. *Org. Biomol. Chem.* 2008, *6*, 4218; (c) J. A.; Kowalski, S. F. Leonard, Jr. G. E. Lee. *J. Comb. Chem.* 2006, *8*, 774; (d) S. A. Kumar, A. Pandurangan. *Applied Catal A.* 2009, *357*, 184.

[4] (a) S. Antoniotti, E. Dunach. *Tetrahedron Lett.* 2002, *43*, 3971; (b) B. Das, K. V. Lu, K. Suneel, A. Majhi. *Tetrahedron Lett.* 2007, *48*, 5371; (c) G. S. M. Sundaram, B. Singh, C. Venkatesh, H. Ila, H. Junjappa. *J. Org. Chem.* 2007, *72*, 5020; (d) S. Sithambaram, Y. Ding, W. Li, X. Shen, F. Gaenzler, S. L. Suib. *Green Chem.* 2008, *10*, 1029; (e) P. Haldar, B. Dutta, J. Guin, J. K. Ray. *Tetrahedron Lett.* 2007, *48*, 5855; (f) L. Yan, F. W. Liu, G. F. Dai, H. M. Liu. *Bioorg. Med. Chem. Lett.* 2007, *17*, 609; (g) C. S. Cho, S. G. Ohb. *J. Mol. Catal A.* 2007, *276*, 205; (h) J. S. Yadav, B. V. S. Reddy, Y. G. Rao, A. V. Narsaiah. *Chem. Lett.* 2008, 348.

[5] (a) M. M. Heravi, M. H. Tehrani, K. Bakhtiari, H. A. Oskooie. *Catal. Commun.*2007, *8*, 1341; (b) M. K. Nasar, R. R. Kumar, S. Perumal. *Tetrahedron Lett.* 2007, *48*, 2155; (c) A. Staszewska, P. Stefanowicz, Z. Szewezuk. *Tetrahedron Lett.* 2005, *46*, 5525; (d) R. S. Bhosale, S. R. Sarda, S. S.Ardhapure, W. N. Jadhav, S. R.Bhusare, R. P. Pawar. *Tetrahedron Lett.* 2005, *46*, 7183; (e) C. S. Cho, W. X. Ren, S. C. Shim, *Tetrahedron Lett.* 2007, *48*, 4665; (f) C.Neochoritis, J. S. Stephanatou, C. A. Tsoleridis. *Synlett.* 2009, 302.

[6] (a) J. J. Cai, J. P. Zou, X. Q. Pan, W. Zhang. *Tetrahedron Lett.* 2008, *49*, 7386; (b) C. Srinivas, C. N. S. S. P. Kumar, V. J. Rao, S. Palaniappan. *J. Mol. Catal A.* 2007, *265*, 227; (c) Z. Zhao, D. D. Wisnoski, S. E. Wolkenberg, W. H. Leister, Y. Wang, C. W. Lindsley. *Tetrahedron Lett.* 2004, *45*, 4873; (d) M. M. Heravi, B. Baghernejad,H. A. Oskooie. *Tetrahedron Lett.* 2009, *50*, 767; (e) M. Mateu, A. S. Capilla, Y. Harrak, M. D. Pujol. *Tetrahedron.* 2002, *58*, 5241; (f) J. S. Yadav, B. V. S. Reddy, K. Premalatha, K. S. Shankar. *Synthesis.* 2008, 3787.

[7] (a) X. Hui, J. Desrivot, C. Bories, P. M. Loiseau, X. Franck, R. Hocquemiller, B. Figade're. *Bioorg. Med. Chem. Lett.* 2006, *16*, 815; (b) F. Rong, S. Chow, S.Yan,G. Larson, Z. Hong, J. Wu. *Bioorg. Med. Chem. Lett.* 2007, *17*, 1663; (c) R. S.Robinson, R. J. K. Taylor. *Synlett.* 2005, 1003; (d) C. S. Cho, S. G. Oh. *J. Mol. Catal. A.* 2007, *276*, 205.

[8] G. V. M. Sharma, Ch. V. Reddy, P. R. Krishna. *J. Org. Chem.* 2003, *68*, 4574; G. Smitha, S. Chandrasekhar, Ch. S. Reddy. *Synthesis.* 2008, 829; Z. H. Zhang, T. S. Li. *Current Org. Chem.* 2009, *13*, 1.

***Corresponding Author:**
J. Madhukar*
Email: madhukerj@gmail.com