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A Novel One-Pot Synthesis of Quinoxaline Derivatives in Fluorinated Alcohols

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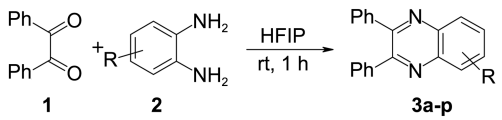
Hexafluoroisopropanol (HFIP) is explored as an effective medium for the synthesis of quinoxaline derivatives in high yields at room temperature. The solvent (HFIP) can be readily separated from reaction products and recovered in excellent purity for direct reuse.

Key Words : Quinoxaline, Hydrogen bonding, Heterocyclic, Fluorinated solvent

Introduction

Quinoxaline derivatives are an important class of fused heterocycles that display a wide range of biological, pharmacological, and medicinal properties involving antiviral, antibacterial, anti-inflammatory, and antiprotozoal and as kinase inhibitors.[1-5] Many quinoxaline derivatives have a wide application as dyes, electroluminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents.[6-11] Furthermore, the quinoxaline ring is a core structure of several drug molecules such as clofazimine, echinomycin, leromycin and actinomycin.[12-17] In view of the great importance of quinoxaline derivatives, in recent years efforts have been made in developing new methodologies for the synthesis of these compounds.[18] Among them, the condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid is a general approach.[19] In recent years, several new efficient methods have been developed including the use of I_2,[20,21] SA,[22] Montmorillonite K-10,[23] SSA,[24] $H_6P_2W_{18}O_{62}\cdot 24H_2O$,[25] $InCl_3$,[26] $MnCl_2$,[27] $CuSO_4\cdot 5H_2O$,[28] ionic liquid,[29] CAN,[30] $Ga(OTf)_3$[31] and TiO_2.[32] However, the reported methods still have drawbacks such as long reaction time, high reaction temperature, unsatisfactory yields, expensive and detrimental metal reagents, using toxic organic solvents, and so on. Recently, fluorinated alcohols have received much attention due to their unique properties such as low nucleophilicity, high polarity, strong hydrogen bond donating ability and ability to solvate water.[33] More recently, the ability of fluorinated alcohols to stabilize the helix conformation of proteins was highlighted by Povey.[34] The main advantage of fluorinated alcohols, for example hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE), is the possibility to carry out, in the absence of promoting agents, reactions that usually require the aid of Lewis acids or catalysts.[35-49] In addition, they can be easily separated from the reaction mixture for subsequent reuse. Due to the current challenges for developing environmentally benign synthetic processes and in continuation of our interest in the application of fluorinated solvents for various organic transformations[50-56] we report a new, convenient, mild and efficient procedure for the synthesis of quinoxaline derivatives by the reaction of aryl 1,2-diamines with 1,2-dicarbonyl compounds under mild reaction conditions in hexafluoroisopropanol (HFIP) (Scheme 1).



1 2 3a-p

Scheme 1. Synthesis of 2,3-disubstituted quinoxalines derivatives in HFIP.

Experimental

Typical Experimental Procedure. To a solution containing 1,2-dicarbonyl compounds (1 mmol), in HFIP (1 mL) was added the aryl 1,2-diamines (1 mmol) and the mixture was vigorously stirred at rt for appropriate reaction time. After completion of the reaction as indicated by TLC, the products were isolated by filtration (for solid products) or after selective evaporation of the HFIP (for liquid products) to yield the highly pure 2,3-disubstituted quinoxalines derivatives. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature. Spectroscopic data for selected examples are shown below.

2,3-Diphenylquinoxaline (Table 1, entry 1): White solid; mp 126-127 °C; IR (KBr): 3051, 1630, 1528, 1348, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.41 (m, 6H), 7.53-7.57 (m, 4H), 7.76-7.83 (m, 2H), 8.20-8.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.2, 128.9, 129.2, 129.8, 129.9, 139.1, 141.2, 153.4.

6-Methyl-2,3-diphenyl-quinoxaline (Table 1, entry 2): White solid; mp 118-120 °C; IR (KBr): 3052, 1640, 1532, 1344, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.6 (s, 3H); 7.32 (m, 6H); 7.52 (m, 4H); 7.57 (d, J = 8.75 Hz, 1H); 7.96 (s, 1H); 8.05 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 127.1, 128.2, 128.6, 128.7, 129.8, 132.3, 139.2, 139.7, 140.4, 141.3, 152.5, 153.3.

2,3-Diphenylpyrido[2,3-*b*]pyrazine (Table 1, entry 6): Yellow crystals; mp 135-137 °C; IR (KBr): 3055, 1640,

1530, 1340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.45 (m, 5H), 7.59-7.66 (m, 4H), 7.73-7.76 (m, 2H), 8.54-8.56 (m, 1H), 9.20 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.6, 128.5, 128.8, 129.7, 129.8, 130.2, 130.6, 136.6, 138.5, 138.9, 150.2, 154.4, 155.1, 156.7.

2-Furan-3-yl-3-furan-2-yl-quinoxaline (Table 1, entry 8): Light yellow solid; mp 134-136 °C; IR (KBr): 3427, 2983, 1605, 1567, 1442, 879, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68-6.53 (m, 4H), 7.68-7.63 (m, 2H), 7.80-7.73 (dd, J = 3.1 Hz, J = 6.8 Hz, 2H), 8.18-8.11 (dd, J = 3.5 Hz, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.1, 113.5, 128.1, 133.6, 142.2, 143.4, 145.1, 150.1.

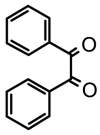
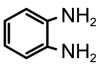
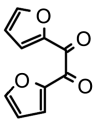
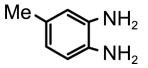
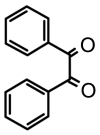
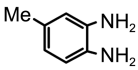
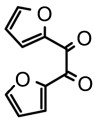
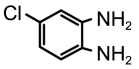
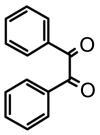
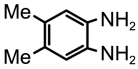
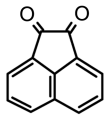
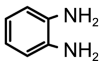
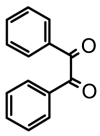
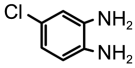
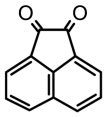
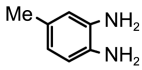
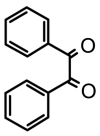
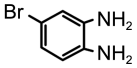
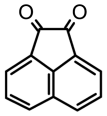
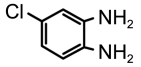
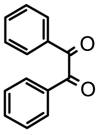
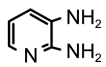
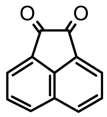
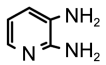
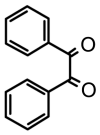
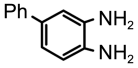
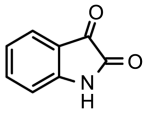
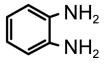
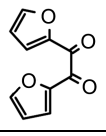
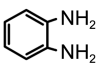
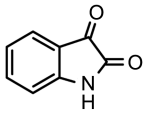
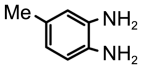
2-Furan-3-yl-3-furan-2-yl-6-methyl-quinoxaline (Table 1, entry 9): Light yellow solid; mp 116-118 °C; IR (KBr): 3422, 2980, 1600, 1567, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 6.68-6.65 (m, 4H), 7.59-7.54 (dd, J = 1.8 Hz, J = 8.6 Hz, 1H), 7.64-7.60 (m, 2H), 7.93-7.88 (s, 1H), 8.04-7.99 (d, J = 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.9, 111.9, 112.6, 112.8, 117.2, 118.9, 124.6, 127.9, 128.6, 132.8, 141.2, 150.9.

Acenaphtho[1,2-*b*]quinoxaline (Table 1, entry 11): White solid; mp 242-245 °C. IR (KBr): 3443, 3047, 2922, 2361, 1614, 1481 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.75 (m, 2H), 7.98 (t, J = 7.7 Hz, 2H), 8.15 (d, J = 7.7 Hz, 2H), 8.18-8.22 (m, 2H), 8.42 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.7, 126.8, 127.2, 128.2, 128.9, 129.6, 130.1, 133.2, 142.5, 145.3.

Results and Discussion

In preliminary experiments, benzil (1 mmol) in 1 mL TFE was allowed to stir at room temperature with *o*-phenylenediamine. After 10 h, only 10% of expected 2,3-diphenylquinoxaline **3a** was obtained. Our efforts were then focused

Table 1. Synthesis of quinoxalines derivatives in HFIP

Entry	Dicarbonyls	Diamines	Product[a]	Yield	Entry	Dicarbonyls	Diamines	Product[a]	Yield %
1			**3a**	95	9			**3i**	96
2			**3b**	97	10			**3j**	90
3			**3c**	97	11			**3k**	95
4			**3d**	85	12			**3l**	95
5			**3e**	90	13			**3m**	85
6			**3f**	90	14			**3n**	85
7			**3g**	92	15			**3o**	80
8			**3h**	95	16			**3p**	85

[a]Reaction conditions: 1,2-dicarbonyl compounds (1 mmol), aryl 1,2-diamines (1 mmol), HFIP (1 mL) at rt.

on HFIP. As a strong H-bond donor (α = 1.96, pK_a = 9.3), with high ionizing power (Y_{OTs} = 3.79), and polarity (P_s = 11.08), it could activate the 1,2-dicarbonyl compounds towards the nucleophilic attack of amine groups. The reaction was then investigated in HFIP: where a solution of benzil (1 mmol), *o*-phenylenediamine (1 mmol) in HFIP (Table 1, entry 1) was stirred at room temperature. The reaction was remarkably fast (1 h) and, after distilling off the HFIP, the 2,3-diphenylquinoxaline **3a** was isolated in 95% yield. Further experiments revealed that a similar procedure is applicable for the preparation of a wide range of compounds analogous to adduct **3** (Table 1). In order to evaluate the efficiency of this methodology, various arene-1,2-diamines, such as mono- and disubstituted amines, reacted efficiently with 1,2-dicarbonyl compounds to give the corresponding 2,3-disubstituted quinoxalines (Table 1). Results in Table 1 show that electron-donating groups at the phenyl ring of 1,2-diamine favored the formation of product (Table 1, entries 2 and 3) to give quantitative yields.

In contrast, electron-withdrawing groups such as chloro, and bromo gave slightly lower yields (85-90%) (Table 1, entries 4, 5). Interestingly, 2,3-diaminopyridine underwent smooth coupling with benzil to afford the corresponding pyrido[2,3-*b*]pyrazine **3f** in 90% yield (Table 1, entry 6). Similarly, several 1,2-dicarbonyl compounds such as furil, isatin, and acenaphthene-1,2-quinone also reacted rapidly with 1,2-diamines to produce a variety quinoxaline derivatives (Table 1, entries 8-16). In all cases, the reactions proceeded rapidly at room temperature with high efficiency. The products were characterized by ^{1}H and ^{13}C NMR, IR spectroscopic data and also by comparison with authentic samples. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. One of the major advantages of this protocol is the isolation and purification of the products, which have been achieved by simple filtration and crystallization of the crude products. Interestingly, the reaction did not proceed to completion when either ethanol or water alone was used as solvent. After the reaction, HFIP can be easily separated (by distillation) and reused without decrease in its activity. For example, the reaction of benzil and *o*-phenylenediamine afforded the corresponding 2,3-diphenylquinoxaline derivative in 95%, 95%, 93%, 92% and 92% isolated yield over five cycles. We believe that the procedure is simple, convenient and does not require any aqueous work-up, thereby avoiding the generation of waste, and may contribute to the area of green chemistry.

Conclusion

In conclusion, we have developed an efficient methodology for the synthesis of quinoxaline derivatives through the reaction of aryl 1,2-diamines with 1,2-dicarbonyl compounds at room temperature. It also has a good aspect of green chemistry since the HFIP can be easily recovered and reused for at least 5 times without significant change of activity. This protocol may also be applicable for large-scale preparation of quinoxalines. Further studies and efforts to extend the scope of this method for other useful reactions are currently underway.

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