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Studies on the reaction of unsymmetrical trifluoromethyl 1,2-phenylenediamine with various ketones leading to novel fluorinated heterocycles☆

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Abstract

Unsymmetrical 1,2-phenylenediamine on reaction with various ketones resulted in a number of fluorinated heterocycles such as benzimidazoles, quinoxalines and spiro benzimidazoles in high yields. The role of substituents in diamine in its reaction with various ketones and on the nature of product formation has been studied in detail.

Keywords: 1,2-Phenylenediamine; Benzimidazoles; Quinoxalines; Spirobenzimidazoles

1. Introduction

Synthesis of fluorinated heterocycles placing the fluorine or trifluoromethyl group at a strategic position enhances the activity of a molecule due to its lipophilic nature [1]. Benzimidazoles are known as an important class of compounds due to their wide range of activity as drugs [2], pesticides [3] and so on. In particular, trifluoromethyl benzimidazoles [4,5] are considered as pesticidal and antibacterial compounds. Benzimidazole compounds are generally synthesized from 1,2-phenylenediamines and carbonyl compounds [6,7]. In symmetrical diamines, the product will be same irrespective of which amine participates first in the reaction. In case of unsymmetrical diamines, the substituents influence initial participation of a particular amine group in reaction, resulting in regio-specific products. The electron withdrawing/donating nature of substituents in diamine influences the nucleophilicity of the amine group. In continuation of our work and interest on fluorinated heterocycles [8,9], we proposed to study the influence of powerful electron withdrawing groups such as trifluoromethyl and nitro groups which are meta to each other in 1,2-diamine on condensation reactions with ketones. The resulted novel fluorinated benzimidazoles, quinoxalines, spiro benzimidazoles are reported here for the first time.

2. Results and discussion

The 3-nitro-5-trifluoromethyl-1,2-phenylenediamine (**1**) has been reacted with various symmetric/unsymmetric 1,3-diketones, 1,2-diketones, aliphatic/aromatic monoketones and cyclic monoketones under acidic, thermal as well as microwave irradiation conditions. The results obtained under different conditions and the products formation are discussed.

2.1. Reaction of *1* with 1,3-diketones

The 1,3-diketones on reaction with diamine **1** in acetic acid at room temperature resulted a mono Schiff's base as uncyclised product **3**. Based on spectral data, it is presumed that the amine group meta to CF_3 and NO_2 groups participated in Schiff's base formation, while the other amine group could not participate because it is *ortho* to nitro and *para* to CF_3 group which are considered to be powerful electron withdrawing groups and may reduce the nucleophilicity of amine. Hence the formation of other regio

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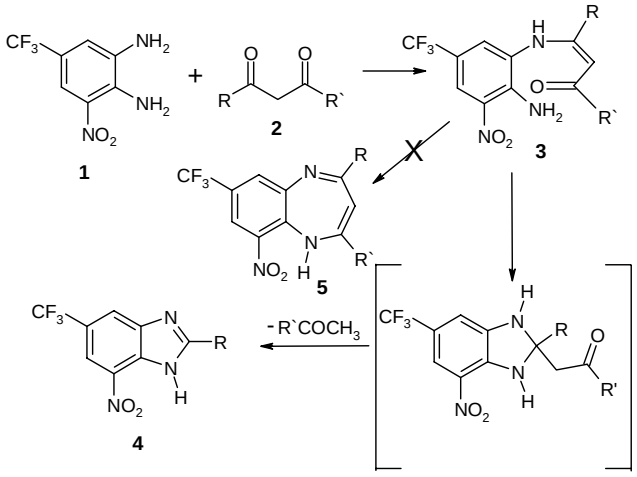
Table 1
4-[3-Nitro-5-trifluoromethyl-2-amino]anilino-3-alkene-2-one

Compound no.	R	R′	Yield (%)	Melting point (°C)
3a	CH_3	CH_3	78	145
3b	CH_3	CF_3	75	139
3c	C_6H_5	CF_3	69	147
3d	CH_3	C_6H_5	72	151

isomer to compound **3** was not seen. It is further observed that the diamine **1** attacking the carbonyl carbon attached to either CH_3 or phenyl instead of CF_3. The carbonyl attached to CF_3 may be in enol form and is not available for nucleophilic attack. In order to cyclise mono Schiff's base **3**, it is heated in acetic acid thermally or under microwave conditions and obtained benzimidazole **4** instead of benzodiazepine **5**. The NMR spectrum of compound **3** showed two separate signals assignable to –NH– and =CH– groups suggesting the Schiff's base to be in the enamine form. The carbonyl carbon may be less electrophilic because of α,β-unsaturation. Thus, the cyclisation could be taking place by the attack of free amine onto β-carbon of α,β-unsaturated carbonyl group followed by elimination of trifluoroacetone or acetophenone leading to the formation of stable benzimidazoles **4**. Whereas in case of unsymmetrical 1,3-diketone having methyl and phenyl groups, the bulkier phenyl group is eliminated resulting in methyl benzimidazole. This is in agreement with our earlier report [10]. The results are tabulated in Table 1 (Scheme 1).

The reaction of **1** with 1,3-diketones is carried out as one pot synthesis under thermal conditions at (150 °C) using nitrobenzene as solvent and solvent free microwave irradiation conditions. The results revealed that the formation



Scheme 1.

of benzimidazole products are regio-specific in nature and the reaction times are less with high yields under microwave irradiation conditions (Table 2).

2.2. Reaction of diamine *1* with aliphatic/aromatic monoketones

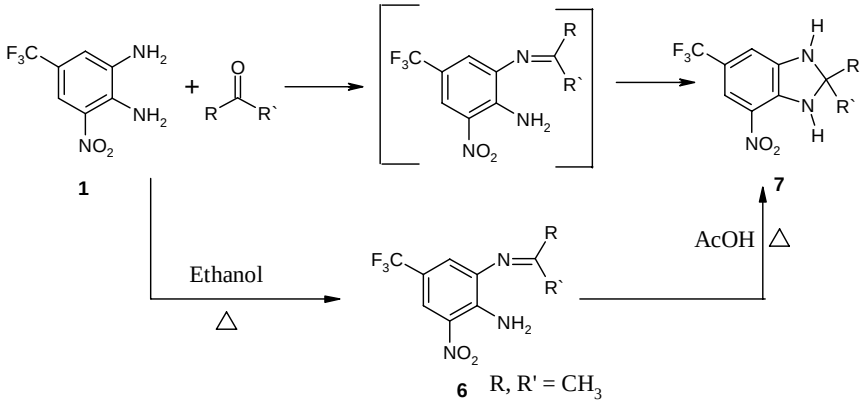
The diamine **1** is reacted with various aliphatic/aromatic ketones in acetic acid at reflux temperature and obtained 2,3-dihydro-2,2-alkyl/aryl benzimidazoles **7**. The reaction proceeds presumably through the formation of mono Schiff's base followed by cyclisation. The intermediate Schiff's base **6** is isolated from the reaction of diamine **1** with acetone in ethyl alcohol at 55 °C. The compound **6** in refluxing acetic acid gave the cyclised 2,3-dihydrobenzimidazole **7**. In all the

Table 2
7-Nitro-5-trifluoromethyl-2-alkyl/aryl benzimidazoles

1,3-Diketone (**2**)			Compound		Time (min)		Yield (%)		Melting point (°C)
	R	R′	No.	R	MW	Thermal	MW	Thermal	
a	CH_3	CH_3	**4a**	CH_3	5	110	87	74	228
b	CH_3	CF_3	**4a**	CH_3	4	90	85	70	228
c	CH_3	C_6H_5	**4a**	CH_3	4	100	83	73	228
d	C_6H_5	C_6H_5	**4b**	C_6H_5	4.5	90	82	70	217
e	C_6H_5	CF_3	**4b**	C_6H_5	5	90	80	71	217
f	CF_3	CF_3	**4c**	CF_3	4	120	75	65	96

Table 3
4-Nitro-6-trifluoromethyl-2,2-disubstituted-2,3-dihydro-1H-benzimidazole

Compound no.	Ketone		Time (min)		Yield (%)		Melting point (°C)
	R	R′	MW	Thermal	MW	Thermal	
7a	CH_3	CH_3	4.5	120	80	68	137
7b	CH_3	C_2H_5	4.0	120	82	74	140
7c	CH_3	Isobutyl	4.0	120	80	70	128
7d	CH_3	C_6H_5	4.5	120	80	69	151
7e	C_2H_5	C_2H_5	4.5	120	84	75	142

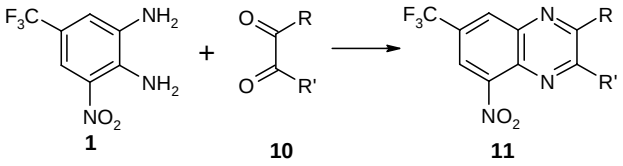


Scheme 2.

Table 4
4-Nitro-6-trifluoromethyl-2,2-spirocycloalkyl-1,2-dihydrobenzimidazole

Compound no.	*n*	Time (min)		Yield (%)		Melting point (°C)
		MW	Thermal	MW	Thermal	
9a	4	4.5	150	80	71	183
9b	5	4.0	120	85	70	198
9c	6	3.5	100	77	68	189
9d	7	4.5	120	72	65	168

cases, irrespective of the nature of substituents on carbonyl carbon, exclusive formation of 2,3-dihydro compound is observed and considered to be quite stable. This has been established by the fact that there is no change in **7** even after heating to high temperature. The condensation reactions are carried out under microwave irradiation, found to be shorter reaction times and the corresponding 2,2-disubstituted-2,3-dihydro benzimidazoles are isolated in enhanced yields. The results are given in Table 3 (Scheme 2).

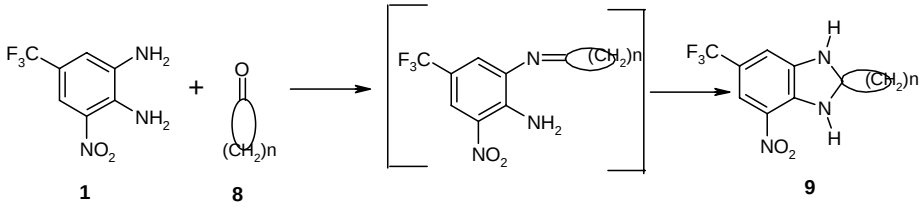


Scheme 4.

The reaction of diamine **1** with cyclic ketones under thermal conditions gave the corresponding spirobenzimidazole **9**. The intermediate Schiff's base could not be isolated as it is undergoing cyclisation and formed product due to poor thermal stability. The results are compiled in Table 4 (Scheme 3).

2.3. Reaction of *1* with 1,2-diketones

The reaction of diamine **1** with various 1,2-diketones in acetic acid yielded quinoxalines. Initially, the more



Scheme 3.

Table 5
5-Nitro-7-trifluoromethyl quinoxalines

Compound no.	R	R′	Time (min)		Yield (%)		Melting point (°C)
			MW	Thermal	MW	Thermal	
11a	C_6H_5	C_6H_5	4.5	120	88	75	141
11b	CH_3	CH_3	3.5	120	85	72	101
11c	H	H	–	300/RT	–	68	107
11d	CH_3	H	–	300/RT	–	75	109
11e	C_6H_5	H	4	90	82	66	135

nucleophilic amine attacks on 1,2-diketones as in 1,3-diketones followed by cyclisation with another amine to give product. The rate of reaction is comparatively faster than the monoketones. The reaction is depicted in Scheme 4 (Table 5).

3. Conclusion

Synthon 3-nitro-5-trifluoromethyl-1,2-phenylenediamine (**1**) is an important building block to synthesize unlimited number of fluorinated heterocycles of biological interest. Its utility in the simple one pot synthesis of various fluorinated benzimidazoles, dihydro- and spirobenzimidazoles as well as quinoxalines is amply demonstrated in this paper.

4. Experimental

4.1. General

All the reagents were obtained from commercial sources and the diamine **1** was prepared by a known method in literature [11]. Melting points were determined in open glass capillaries using Fisher-Johns melting point instrument. IR spectra were recorded on FT-IR, Perkin-Elmer 1310 infrared spectrometer. ^{1}H NMR spectra were recorded on Varian Gemini (200 MHz) in $CDCl_3$/DMSO-d_6 with tetramethyl silane as internal standard. The mass spectra were measured on a VG micro mass 7070-H mass spectrometer. Elemental analysis were carried on vario EL, Elemental instrument. Microwave irradiations were carried out using sealed tube (Aldrich, Ace pressure tube, 10.2 cm, 15 ml) in a domestic microwave oven (BPL BMO 700T 600 W).

4.2. Typical procedure for the preparation of open chain Schiff's base *3*

A mixture of diamine **1** (10 mmol) and 1,3-diketone (**2**) (10 mmol) is taken in acetic acid (15 g) and stirred at room temperature for 5 h. The progress of the reaction was monitored by TLC. After 5 h, the reaction mixture was poured on to crushed ice and neutralized with ammonia solution. The separated solid is filtered, washed with water and dried. The latter is purified through column using hexane–chloroform [1:1] as eluent to give the uncyclised mono Schiff's base **3**.

4.2.1. 4-[3-Nitro-5-trifluoromethyl-2-amino-phenylamino]-3-penten-2-one (*3a*)

IR (KBr) ν: 3454, 3292, 1639, 1541, 1345 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.8 (s, 3H, –CH_3); 2.2 (s, 3H, –CH_3); 5.4 (s, 1H, =CH); 6.8 (s, 2H, NH_2); 7.4 (s, 1H, Ar–H); 8.4 (s, 1H, Ar–H); 12.0 (s, 1H, NH). MS (*m*/*z*): 303 (M^+), 288, 242. Anal. Calcd. for $C_{12}H_{12}F_3N_3O_3$: C, 47.52%; H, 3.98%; N, 13.85%. Found: C, 47.59%; H, 3.95%; N, 13.81%.

4.2.2. 4-[3-Nitro-5-trifluoromethyl-2-amino-phenylamino]-1,1,1-trifluoro-3-penten-2-one (*3b*)

IR (KBr) ν: 3460, 3300, 1652, 1560, 1351 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.0 (s, 3H, –CH_3); 5.6 (s, 1H, =CH); 6.9 (s, 2H, NH_2); 7.5 (s, 1H, Ar–H); 8.5 (s, 1H, Ar–H); 11.9 (s, 1H, NH). MS (*m*/*z*): 357 (M^+), 342, 246. Anal. Calcd. for $C_{12}H_9F_6N_3O_3$: C, 40.34%; H, 2.53%; N, 11.76%. Found: C, 40.38%; H, 2.53%; N, 11.74%.

4.2.3. 4-[3-Nitro-5-trifluoromethyl-2-amino-phenylamino]-1,1,1-trifluoro-4-phenyl-but-3-en-2-one (*3c*)

IR (KBr) ν: 3472, 3310, 1663, 1570, 1345 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.9 (s, 1H, =CH); 6.8 (s, 2H, NH_2); 6.9 (m, 3H, Ar–H); 7.2 (m, 2H, Ar–H); 7.3 (s, 1H, Ar–H); 8.2 (s, 1H, Ar–H); 11.9 (s, 1H, NH). MS (*m*/*z*): 419 (M^+), 400. Anal. Calcd. for $C_{17}H_{11}F_6N_3O_3$: C, 48.69%; H, 2.64%; N, 10.02%. Found: C, 48.65%; H, 2.62%; N, 10.02%.

4.2.4. 4-[3-Nitro-5-trifluoromethyl-2-amino-phenylamino]-1-phenyl-but-2-en-1-one (*3d*)

IR (KBr) ν: 3450, 3310, 1655, 1560, 1349 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.0 (s, 3H, –CH_3); 6.0 (s, 1H, =CH); 6.8 (s, 2H, NH_2); 7.6 (m, 4H, Ar–H); 7.9 (m, 2H, Ar–H); 8.4 (s, 1H, Ar–H);12.6 (s, 1H, NH). MS (*m*/*z*): 365 (M^+), 350, 245. Anal. Calcd. for $C_{17}H_{14}F_3N_3O_3$: C, 55.89%; H, 3.86%; N, 11.50%. Found: C, 55.83%; H, 3.82%; N, 11.52%.

4.3. Typical procedure for the preparation of benzimidazoles *4* from Shiff's base *3*

4.3.1. Method A (microwave conditions)

The Schiff's base **3** (10 mmol) is adsorbed on silica gel and irradiated in microwave oven for 3 min. The reaction mixture is cooled and purified by column chromatography on silica gel using hexane–chloroform [1:1] as eluent. The solid product obtained is 7-nitro-5-trifluoromethyl-2-aryl/alkylbenzimidazole (**4**).

4.3.2. Method B (thermal conditions)

The Schiff's base **3** (10 mmol) is dissolved in acetic acid and refluxed for 1 h while monitoring the reaction by TLC. After 1 h, the reaction mixture is cooled and poured on to crushed ice. The separated solid is filtered, washed with water, dried, and purified by column using hexane–chloroform [1:1] as eluent. The compound is characterized as benzimidazole **4**.

4.4. Typical procedure for the preparation of benzimidazoles *4* from diamine *1* and 1,3-diketones

4.4.1. Method A (microwave conditions)

A mixture of diamine **1** (10 mmol) and 1,3-diketone (10 mmol) is adsorbed on silica gel and irradiated by microwave radiation for 5 min. The reaction mixture is cooled and purified by column using hexane–chloroform [1:1] as eluent to give benzimidazole **4a**–**4c**.

4.4.2. Method B (thermal conditions)

Diamine **1** (10 mmol) and 1,3-diketone (10 mmol) are taken in nitrobenzene (10 ml) and refluxed for 2 h monitoring the reaction by TLC. The reaction mixture is cooled and nitrobenzene is removed under vacuum. To the residue hexane is added as a result product is separated. The latter is filtered, washed with hexane and dried. The solid is purified through a column of silica gel using hexane–chloroform [1:1] as eluent to give the benzimidazoles **4a**–**4c**.

*4.4.2.1. 2-Methyl-7-nitro-5-trifluoromethyl benzimidazole (**4a**).* IR (KBr) *v*: 3250, 1615, 1524, 1338 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.7 (s, 3H, $–CH_3$); 8.2 (s, 1H, Ar–H); 8.4 (s, 1H, Ar–H); 10.5 (s, 1H, –NH). MS (*m/z*): 245 (M^+), 226, 199. Anal. Calcd. for $C_9H_6F_3N_3O_2$: C, 44.09%; H, 2.46%; N, 17.14%. Found: C, 44.05%; H, 2.47%; N, 17.14%.

*4.4.2.2. 2-Phenyl-7-nitro-5-trifluoromethyl benzimidazole (**4b**).* IR (KBr) *v*: 3384, 1645, 1524, 1338, 1290 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.6 (m, 3H, Ar); 8.2 (m, 2H, Ar); 8.4 (s, 1H, Ar); 8.5 (s, 1H, Ar); 10.9 (s, 1H, NH). MS (*m/z*) M^+ 307 (M^+), 261, 105, 77. Anal. Calcd. for $C_{14}H_8F_3N_3O_2$: C, 54.73%; H, 2.62%; N, 13.67%. Found: C, 54.71%; H, 2.60%; N, 13.59%.

*4.4.2.3. 7-Nitro-2,5-bis trifluoromethyl benzimidazole (**4c**).* IR (KBr) *v*: 3300, 1615, 1524, 1338 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 8.5 (s, 1H, Ar–H); 8.6 (s, 1H, Ar–H); 11.3 (s, 1H, –NH). MS (*m/z*): 299 (M^+), 270, 254. Anal. Calcd. for $C_9H_3F_6N_3O_2$: C, 36.13%; H, 1.01%; N 14.04%. Found: C, 36.12%; H, 1.03%; N 14.14%.

*4.5. Synthesis of 3-N-propylidene-4-amino-5-nitrobenzotrifluoride (**6**)*

5-Trifluoromethyl-3-nitro-1,2-phenylenediamine (**1**) (5 mmol) and acetone (5 mmol) are dissolved in ethanol (5 ml), catalytic amount of acetic acid is added to it and heated at 55 °C for 1.5 h. The reaction mixture is cooled to room temperature. The solvent was removed from the reaction mixture and the residual solid was washed with water and recrystallised with dichloromethane to obtain the title compound (mp: 107 °C, yield: 75%).

IR (KBr) *v*: 3451, 3348, 1541, 1380 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.6 (s, 6H, $–CH_3$); 6.5 (s, 1H, Ar–H); 7.0 (s, 2H, $–NH_2$); 7.6 (s, 1H, Ar–H). MS (*m/z*): 261 (M^+), 246, 202.

*4.6. Typical procedure for the preparation of 1,3-dihydro benzimidazoles (**7a–7e**, **9a–9d**)*

4.6.1. Method A (microwave conditions)

The diamine **1** (10 mmol) and monoketone (10 mmol) (aliphatic/aromatic/cyclic) is adsorbed on silica gel and irradiated by microwave radiation 4.5 min at regular intervals of 1.5 min each. The reaction mixture is allowed to cool, and purified by column using hexane–chloroform [1:1] as eluent to give the title compounds.

4.6.2. Method B (thermal conditions)

An equimolar mixture of diamine **1** (10 mmol) and monoketone (10 mmol) (aliphatic/aromatic/cyclic) is taken in acetic acid (10 ml) and refluxed for 2 h. After the reaction mixture is cooled and poured on to crushed ice, neutralized by ammonia solution. The separated solid is filtered, washed with water, dried and purified through column on silica gel using chloroform as eluent to result the title compounds.

*4.6.2.1. 4-Nitro-6-trifluoromethyl-2,2-dimethyl-2,3-dihydro-1H- benzimidazole (**7a**).* IR (KBr) *v*: 3420, 3320, 1570, 1330 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 7.0 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.2 (s, 1H, –NH); 1.6 (s, 6H, $–CH_3$). MS (*m/z*): 261 (M^+), 246, 202. Anal. Calcd. for $C_{10}H_{10}F_3N_3O_2$: C, 45.98%; H, 3.86%; N, 16.08%. Found: C, 45.92%; H, 3.84%; N, 16.3%.

*4.6.2.2. 4-Nitro-6-trifluoromethyl-2,-methyl-2-ethyl-2,3-dihydro-1H- benzimidazole (**7b**).* IR (KBr) *v*: 3420, 3325, 1570, 1330 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 6.9 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.1 (s, 1H, –NH); 1.8 (q, 2H, $–CH_2$); 1.6 (s, 3H, $–CH_3$); 1.1 (t, 3H, $–CH_3$). MS (*m/z*): 275 (M^+), 260, 246, 200. Anal. Calcd. for $C_{11}H_{12}F_3N_3O_2$: C, 48.00%; H, 4.39%; N, 15.26%. Found: C, 48.3%; H, 4.44%; N, 15.24%.

*4.6.2.3. 4-Nitro-6-trifluoromethyl-2-methyl-2-isobutyl-2,3-dihydro-1H-benzimidazole (**7c**).* IR (KBr) *v*: 3410, 3320, 1570, 1330 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 6.9 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.2 (s, 1H, –NH); 1.9 (m, 1H, –CH); 1.8 (d, 2H, $–CH_2$); 1.6 (s, 3H, $–CH_3$);1.0 (m, 6H, $–CH_3$). MS (*m/z*): 303 (M^+), 288, 246. Anal. Calcd. for $C_{13}H_{16}F_3N_3O_2$: C, 51.48%; H, 5.31%; N, 13.85%. Found: C, 51.43%; H, 5.37%; N, 13.85%.

*4.6.2.4. 4-Nitro-6-trifluoromethyl-2,-methyl-2-phenyl-2,3-dihydro-1H-benzimidazole (**7d**).* IR (KBr) *v*: 3420, 3370, 1590, 1350 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.7 (s, 1H, Ar–H); 7.4 (m, 2H, Ar–H); 7.2 (m, 3H, Ar–H); 7.1 (s, 1H, –NH); 6.6 (s, 1H, Ar–H); 4.5 (s, 1H, –NH); 2.0 (s, 3H, $–CH_3$). MS (*m/z*): 323 (M^+), 308, 262, 246. Anal. Calcd. for $C_{15}H_{12}F_3N_3O_2$: C, 55.73%; H, 3.74%; N, 12.99%. Found: C, 55.70%; H, 3.71%; N 12.94%.

*4.6.2.5. 4-Nitro-6-trifluoromethyl-2,2-diethyl-2,3-dihydro-1H-benzimidazole (**7e**).* IR (KBr) *v*: 3410, 3320, 1575, 1340 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 6.8 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.1 (s, 1H, –NH); 1.8 (q, 4H, $–CH_2$); 1.0 (t, 6H, $–CH_3$). MS (*m/z*): 289 (M^+), 260, 214. Anal. Calcd. for $C_{12}H_{14}F_3N_3O_2$: C, 49.82%; H, 4.87%; N, 14.53%. Found: C, 49.87%; H, 4.82%; N, 14.21%.

*4.6.2.6. 4-Nitro-6-trifluoromethyl-1,3-dihydro-spiro-[benzimidazole-2,1′-cyclopentane] (**9a**).* IR (KBr) *v*: 3450, 3340, 1570, 1310 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 7.1 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.4 (s, 1H, –NH); 1.8–1.2 (m, 8H, $–CH_2–$). MS (*m*/*z*): 287 (M^+), 258, 212. Anal. Calcd. for $C_{12}H_{12}F_3N_3O_2$: C, 50.17%; H, 4.21%; N, 14.62%. Found: C, 50.18%; H, 4.20%; N, 14.63%.

*4.6.2.7. 4-Nitro-6-trifluoromethyl-1,3-dihydro-spiro-[benzimidazole-2,1′-cyclohexane] (**9b**).* IR (KBr) *v*: 3410, 3330, 1570, 1320 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 7.1 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.4 (s, 1H, –NH); 2.0–1.4 (m, 10H, $–CH_2–$). MS (*m*/*z*): 301 (M^+), 282, 258, 245. Anal. Calcd. for $C_{13}H_{14}F_3N_3O_2$: C, 51.82%; H, 4.68%; N, 13.94%. Found: C, 51.80%; H, 4.63%; N, 13.97%.

*4.6.2.8. 4-Nitro-6-trifluoromethyl-1,3-dihydro-spiro-[benzimidazole-2,1′-cycloheptane] (**9c**).* IR (KBr) *v*: 3430, 3320, 1550, 1330 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 7.1 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.4 (s, 1H, –NH); 2.0 (m, 4H, $–CH_2–$); 1.6 (m, 8H, $–CH_2–$). MS (*m*/*z*): 315 (M^+), 272, 258, 212. Anal. Calcd. for $C_{14}H_{16}F_3N_3O_2$: C, 53.37%; H, 5.11%; N, 13.32%. Found: C, 53.31%; H, 5.14%; N, 13.37%.

*4.6.2.9. 4-Nitro-6-trifluoromethyl-1,3-dihydro-spiro-[benzimidazole-2,1′-cyclooctane] (**9d**).* IR (KBr) *v*: 3410, 3310, 1570, 1350 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.6 (s, 1H, Ar–H); 7.1 (s, 1H, –NH); 6.5 (s, 1H, Ar–H); 4.3 (s, 1H, –NH); 2.0 (m, 4H, $–CH_2–$); 1.6 (m, 6H, $–CH_2–$); 1.4 (m, 6H, $–CH_2–$). MS (*m*/*z*): 329 (M^+), 310, 272, 258. Anal. Calcd. for $C_{15}H_{18}F_3N_3O_2$: C, 54.70%; H, 5.50%; N, 12.75%. Found: C, 54.7%; H, 5.59%; N, 12.79%.

*4.7. Typical procedure for the preparation of 5-nitro-7-trifluoro methyl quinoxalines (**11**)*

4.7.1. Method A (microwave conditions)

A mixture of diamine **1** (10 mmol) and 1,2-diketone (10 mmol) (aliphatic/aromatic) is dissolved in minimum amount of acetic acid (5 ml) and transferred into a sealed tube tightened with a cap and irradiated by microwave radiation for 4.5 min at regular intervals of 1.5 each. The reaction mixture is allowed to cool, poured on to crushed ice and the separated solid is filtered, washed with water and dried. The latter is purified by column using dichloromethane as eluent to give corresponding quinoxalines.

4.7.2. Method B (thermal conditions)

A mixture of diamine **1** (10 mmol) and diketone (10 mmol) is taken in acetic acid and refluxed for 2 h. The reaction mixture is cooled and poured on to crushed ice the resulted solid is filtered, washed with water and dried. The dried solid is purified by column chromatography on silica gel using dichloromethane as eluent.

*4.7.2.1. 5-Nitro-7-trifluoromethyl-2,3-diphenyl quinoxaline (**11a**).* IR (KBr) *v*: 1590, 1340 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 8.6 (s, ^1H, Ar–H); 8.2 (s, ^1H, Ar–H); 7.6 (m, 4H, phenyl); 7.3 (m, 6H, phenyl). MS (*m*/*z*): 395 (M^+), 349, 199. Anal. Calcd. for $C_{21}H_{12}F_3N_3O_2$: C, 63.8%; H, 3.05%; N, 10.62%. Found: C, 63.78%; H, 3.09%; N, 10.60%.

*4.7.2.2. 5-Nitro-7-trifluoromethyl-2,3-dimethyl quinoxaline (**11b**).* IR (KBr) *v*: 1540, 1340 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 8.5 (s, 1H, Ar–H); 8.2 (s, 1H, Ar–H); 2.85 (s, 3H, $–CH_3$); 2.8 (s, 3H, $–CH_3$). MS (*m*/*z*): 271 (M^+), 225, 199. Anal. Calcd. for $C_{11}H_8F_3N_3O_2$: C, 48.71%; H, 2.97%; N, 15.49%. Found: C, 48.78%; H, 2.92%; N, 15.49%.

*4.7.2.3. 5-Nitro-7-trifluoromethyl quinoxaline (**11c**).* IR (KBr) *v*: 1530, 1320 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 9.1 (d, 1H, Qui-H); 8.6 (s, 1H, Ar–H); 8.3 (s, 1H, Ar–H). MS (*m*/*z*): 243 (M^+), 224, 197. Anal. Calcd. for $C_9H_4F_3N_3O_2$: C, 44.45%; H, 1.65%; N, 17.28%. Found: C, 44.40%; H, 1.68%; N, 17.21%.

*4.7.2.4. 5-Nitro-7-trifluoromethyl-2-methyl quinoxaline (**11d**).* IR (KBr) *v*: 1540, 1340 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.9 (s, 3H, $–CH_3$); 8.2 (s, 1H, Ar–H); 8.5 (s, 1H, Ar–H); 8.9 (s, 1H, Ar–H). MS (*m*/*z*): 257 (M^+), 211, 185. Anal. Calcd. for $C_{10}H_6F_3N_3O_2$: C, 46.70%; H, 2.95%; N, 16.33%. Found: C, 46.62%; H, 2.88%; N, 16.27%.

*4.7.2.5. 5-Nitro-7-trifluoromethyl-2-phenyl quinoxaline (**11e**).* IR (KBr) *v*: 1590, 1340 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.4 (m, 3H, phenyl); 8.0 (m, 2H, phenyl); 8.3 (s, 1H, Ar–H); 8.4 (s, 1H, Ar–H); 10.9 (s, 1H, Qui-H). MS (*m*/*z*): 319 (M^+), 289, 273. Anal. Calcd. for $C_{15}H_8F_3N_3O_2$: C, 56.43%; H, 2.52%; N, 13.16%. Found: C, 56.40%; H, 2.58%; N, 13.21%.

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