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A convenient route for synthesis of new benzimidazole-based heterocycles

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Abstract: Reaction of 2-bromo-1-(1-methyl-1H-benzo[d]imidazole-2-yl) ethanone (**1**) with dimethylsulfide afforded the corresponding sulfonium bromide derivative **2.** Coupling of compound **2** with diazotized aromatic amines or with the corresponding N-nitrosoacetanilide derivatives afforded the corresponding hydrazonoyl bromides derivatives **5a-c** in good yields. Reaction of 2-bromo-1-(1-methyl-1H-benzo[d]imidazole-2-yl)ethanone (**1**) with potassium thiocyanate afforded the corresponding 1-(1-methyl-1H-benzo[d]imidazole-2-yl)-2-thiocyanatoethanone (**6**) that reacts with diazotized aromatic amines or with the corresponding N-nitrosoacetanilide derivatives to afford the corresponding iminothiadiazole derivatives **8a-c**. Compounds **8a-c** were converted into the corresponding N-acetylthiadiazole, N-nitrosothiadiazole, and thiadiazolone derivatives **9a-c ,10a-c and 11a-c** , respectively upon treatment with acetyl chloride , sodium nitirite in presence of acetic acid and refluxing in ethanolic HCl respectively. Reaction of compound **6** with aromatic amines afforded the corresponding arylaminothiazole derivatives **14a-c**. Coupling of compound **6** with diazotized anthranilic acid (or methyl antharanilate) and with diazotized anthranilonitrile afforded the corresponding thiadiazolo [3,2-a] quinazoline imine derivative **21a** and thiadiazolo [3,2-a] quinazolinone derivative **21b**, respectively.

Keywords: Benzimidazole, Thiadiazole, Thiazole, Thiadiazolo [3,2-a] quinazoline, Oxazole.

Introduction

In addition to, the potential biological activities reported for many compounds containing benzimidazole moiety that of considerable importance because of their uses as pharmaceuticals; they have been found to possess antimicrobial [1], antiviral [2], antifungal [3], antiparasitic [4], anthelmintic [5,6], pesticidal [7], herbicidal [8] and plant-growth regulating [9] properties. Benzimidazoles have also found wide medicinal applications as potent antihypertensive [10], an tihistaminic [11], anti-cancer [6,12], anti-inflammatory [13] agents, as gastric ulcer inhibitors [14] and for treatment of cardiovascular disease [15]. In addition, several benzimidazole derivatives are useful in the textile industry as dyeing agents [16,17], and as a potential treatment for tuberculosis via inhibition of H37Rv [18]. Also, it exhibited corrosion inhibition properties of benzimidazole derivatives [19-23]. Moreover, several benzimidazole derivatives were applied as fluorescent disperse dyes and a fluorescent whitener for polyester fibers [24]. ‹herefore , the reported potential biological activities of several benzimidazole derivatives have stimulated us to develop the chemistry of this class of compounds as useful precursors for the synthesis of many biologically interesting heterocycles. and in continuation of our interest in the synthesis of a variety of heterocyclic systems containing benzimidazole moiety from readily obtainable inexpensive starting materials we report in this study a useful route toward benzimidazole -based heterocycles via reaction of 2-bromo-1-(1-methyl-1H-benzo[d] imidazole-2-yl) ethanone (**1**). The products were elucidated on the basis of elemental analysis, spectral data and alternative chemical synthesis.

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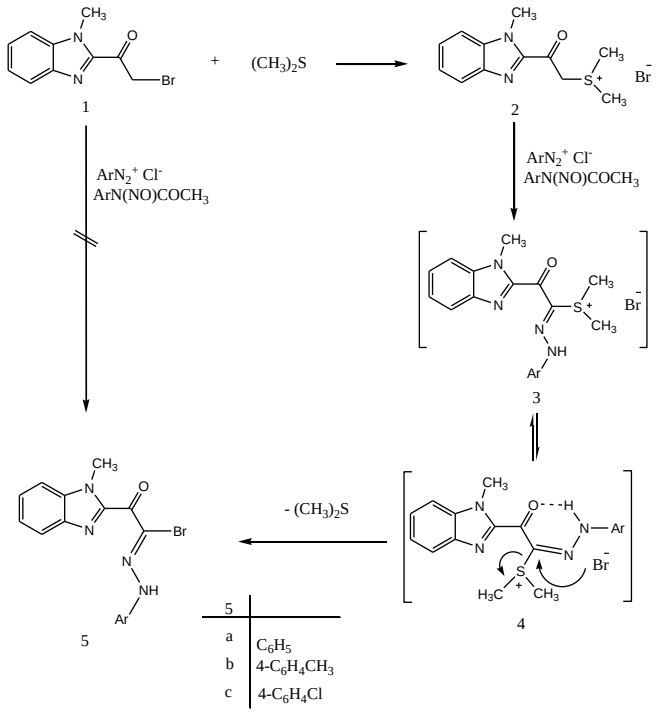
Results and discussion

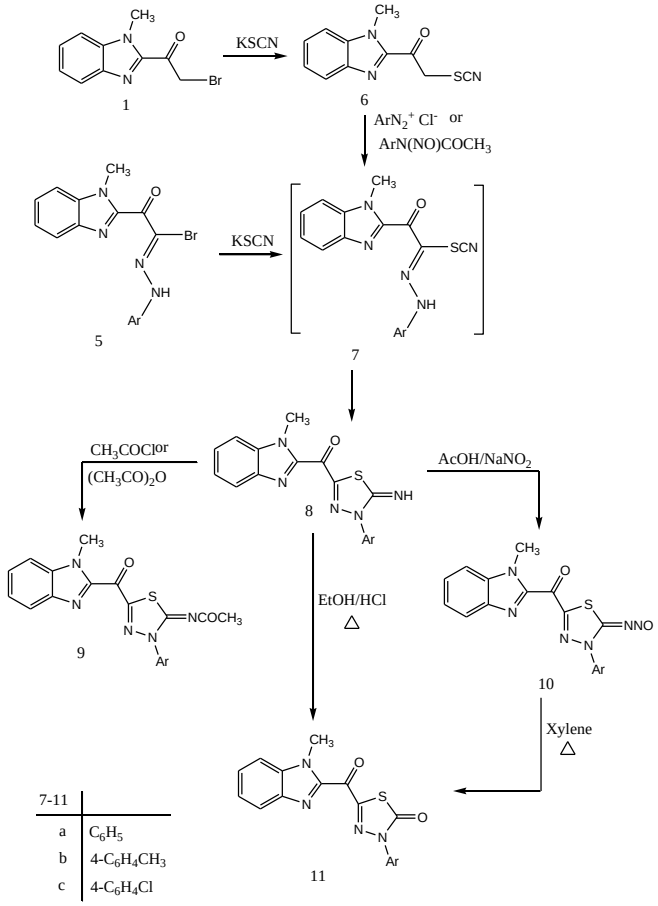
Treatment of 2-bromo-1-(1-methyl-1H-benzo[d] imidazole-2-yl)ethanone (**1**) with dimethylsulfide in refluxing methanol afforded 1-(1-methylbenzimidazol-

2-yl)-1-ethanone-2-dimethyl sulfoniumbromide (**2**). Coupling of sulfonium bromide **2** with the appropriate diazotized aromatic amines in ethanol, buffered with sodium acetate tri hydrate at 0-5°C or with the corresponding N-nitrosoacetanilide derivatives in ethanol, at room temperature, afforded the novel N-aryl-α-oxo-2-(1-methylbenzimidazole) ethane hydrazonoyl bromides **5**a-c All attempts to prepare hydrazonoyl bromides derivatives **5a-c** by direct coupling of compound **1** with diazotized aromatic amines or with N-nitrosoacetanilide derivatives were unsuccessful. The structure of the sulfonium bromide **2** and the hydrazonoyl bromides derivatives **5a-c** were established on the basis of their elemental analyses and spectral data. For example, the IR spectrum of compound **2** showed a strong carbonyl absorption band at 1702 cm-1, and those of compounds 5a-c revealed, in each case, a conjugated carbonyl absorption band near 1655 cm-^{1} and a hydrazone NH stretching band near 3170 cm$^{-1.}$ The ^{1}H NMR spectrum of **5a**, for example, displayed a singlet signal at δ 4.1 ppm due to methyl protons and a broad D_2O-exchangeable signal at δ 9.65 ppm due to NH proton in addition to a multiplet at 7.7-9.0 ppm corresponding to aromatic protons.



Scheme 1: Synthesis of *2-(2-Arylhydrazono)-2-bromo-1-(1-methyl-1H-benzo[d]imidazole-2-yl)ethanone* ***5a-c.***

Treatment of 2-bromo-1-(1-methyl-1H-benzo[d] imidazole-2-yl)ethanone (1) with potassium thiocyanate, in ethanol, at room temperature, afforded the corresponding 1-(1-methyl-1H-benzo[d]imidazole-2-yl)-2- thiocyanatoethanone (**6**).



Scheme 2: Synthesis the derivatives of iminothiadiazole N-acetylthiadiazole, N-nitrosothiadiazole, and thiadiazolone **8a-c**, **9a-c, 10a-c and 11a-c**, respectively.

The structure of compound **6** is inferred from its elemental analysis, IR and 1H NMR spectral data, in addition to its mass spectrum. Thus ,the IR spectrum of compound **6** revealed ,a band at 2170 cm^{-1} assignable to SCN group, in addition to carbonyl absorption band at 1638 cm^{-1}. Its ^{1}H NMR spectrum displayed two singlet signals at δ 3.35, 3.85 and a multiplet at 6.70-7.50 ppm corresponding to methyl, methylene and aromatic protons, respectively. Its mass spectrum exhibited a peak at m/z 231 corresponding to its molecular ion. Compound **6** couples readily with diazotized aromatic amines in ethanol, buffered with sodium acetate trihydrate at 0-5°C or with the corresponding N-nitrosoacetanilide derivatives in ethanol, at room temperature, afforded the novel (4,5-dihydro-5-imino-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl -1H-benzo[d] imidazole-2-yl)methanone **8a-c.** The

latter products were established from their IR and ^{1}H NMR spectral data as well as their elemental analyses (see experimental part). The IR spectra of **8a-c** showed, in each case, the absence of free SCN absorption band and revealed the appearance of an imine NH absorption band near 3273 cm^{-1}, in addition to a conjugated carbonyl absorption band near 1644 cm^{-1}. Reaction coupling of compound **6** with the appropriate diazotized aromatic amines in ethanol, buffered with sodium acetate trihydrate at 0-5°C or with the corresponding N-nitrosoacetanilide derivatives in ethanol, at room temperature, afforded 4,5-Dihydro-5-imino-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo [d]imidazole-2-yl)methanone **8a-c** on the basis of their elemental analyses and spectral data. Also, compounds **8a-c** were obtained by alternate chemical synthesis via treatment of compound **5** with potassium thiocyanate in refluxing ethanol via the reaction sequence.

All attempts to isolate the hydrazone intermediate **7a-c** were unsuccessful. Acetylation of compounds **8a-c** with acetyl chloride or acetic anhydride afforded the corresponding N-acetylimino derivatives **9a-c** in good yields. The structures of the reaction products 9a-c were confirmed by the disappearance of the imino NH absorption band and the appearance of two carbonyl bands around 1691 and 1649 cm^{-1} in their IR spectra.

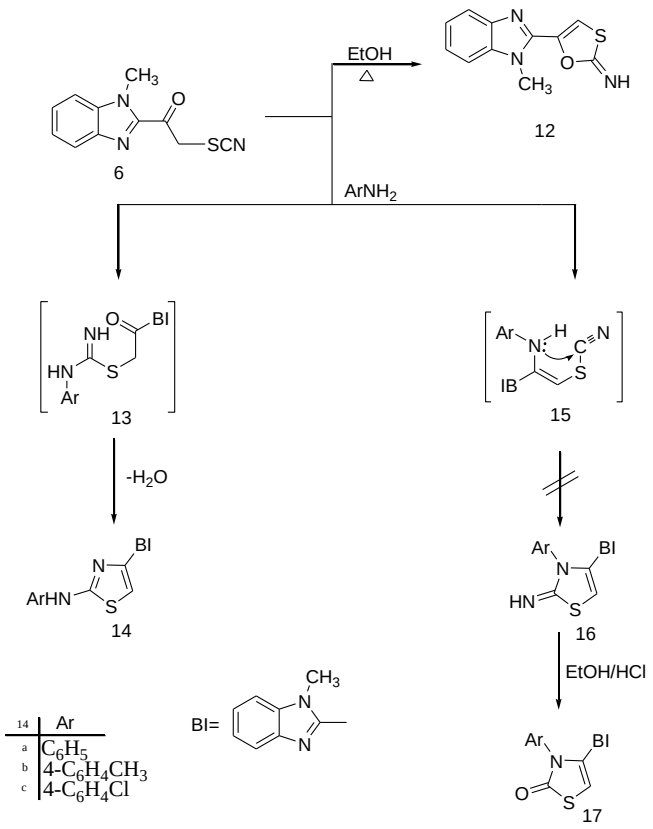
The ^{1}HNMR spectrum of **9c**, for example, exhibited singlet signals at δ 3.5 and 4.25 ppm corresponding to N-methyl protons and N-acetyl, respectively. Nitrosation of **8**a-c in a mixture of acetic acid and sodium nitrite, afforded products identified as (4,5-dihydro-5-nitrosoimino-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone**10a-c**.

The structures of the latter products were established on the basis of their elemental analyses and spectral data. For example, the IR spectra of **10a-c** showed, in each case, the lack of NH absorption band in the region 3100-3500 cm^{-1} and revealed a strong absorption band near 1660 cm^{-1} due to carbonyl group.

Refluxing of compounds **8a-c** in ethanolic hydrochloric acid solution, afforded the corresponding (4,5-dihydro-5-oxo-4-aryl-1,3,4- thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone **11a-c**.

The structures of the latter products were elucidated on the basis of their elemental analyses and spectral data. The lack of NH absorption and the appearance of two carbonyl absorptions in the region 1661-1705 cm^{-1}, respectively, supported the assigned structures **11**a-c. Compounds **7**a-c were confirmed chemically via alternative synthesis from **10a-c** by boiling in refluxing xylen.

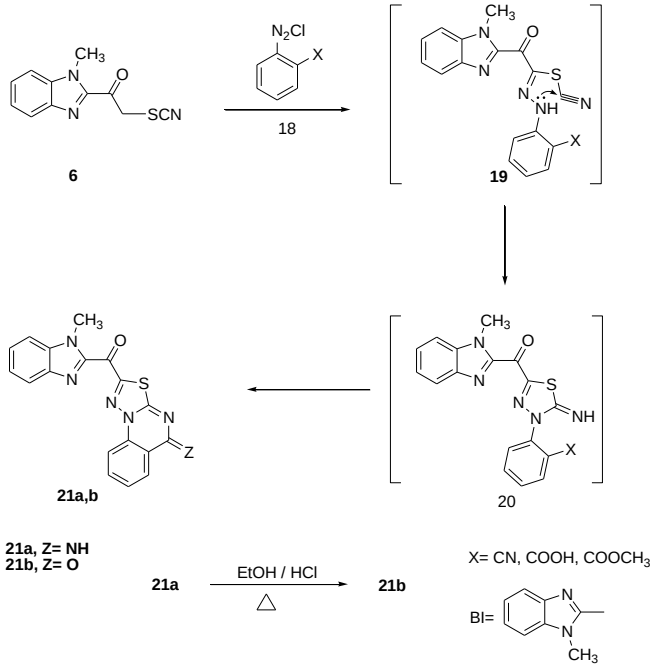
Heating of compound **6** in ethanol at reflux temperature afforded a single product which was analyzed correctly for $C_{11}H_9N_3OS$ and identified as 5-(1-Methrlbenzimidazol-2-y1)-2-inzino-1,3- oxathiole (**12**). The structure of the latter product was established on the basis of its elemental analysis and spectral data. The IR spectrum of compound **12** revealed the presence of NH absorption bond at 3342 cm^{-1} and the absence of SCN group absorption band near 2170 cm^{-1} and ,also the absence of C=O absorption in the region 1640-1700 cm^{-1}. Treatment of compound **6** with the hydrobromide of aromatic amines (aniline, p-toluidine or p-chloroaniline) in refluxing ethanol afforded, in each case, only one isolable product as evidenced by TLC analysis. The isolated products were identified as 4-(1-methyl-1H-benzo [d]midazol-2-y1)-N-arylthiazol-2-amine 10a-c on the basis of their elemental analyses and spectral data.



Scheme 3: Synthesis of arylaminothiazole derivative**14a-c**.

For example, the IR spectra of **10**a-c, revealed, in each case, a stretching NH absorption band in the region 3311-3318 cm^{-1}. The isolated products were found to be stable towards hydrolysis in boiling ethanolic HC1 solution which excludes the other possible isomeric structure **17**. Treatment of compound **6** with diazotized anthranilonitrile in ethanol in the

presence of sodium acetate at 0-5°C afforded one product identified as **(**5-imino-5H-(1,3,4) thiazolo[3,2-a]quinazolin-2-yl)(1-methyl-1H-benzo[d] imidazole-2-yl)methanone ***(*21a)**.



Scheme 4: Synthesis of thiadiazolo [3,2-a] quinazoline imine derivative **21a** and thiadiazolo [3,2-a] quinazolinone derivative **21b**, respectively.

The structure of the latter product was supported by its elemental analysis and spectral data. The IR spectrum of compound **21**a showed a stretching NH band at 3275 cm^{-1} and a strong carbonyl band at 1660 cm^{-1}. In a similar manner, when compound **6** was treated with diazotized anthranilic acid or methyl anthranilate, it afforded one and same product identified as **(**5-oxo-5H-(1,3,4) thiazolo[3,2-a] quinazolin-2-yl)(1-methyl-1H -benzo [d]imidazole-2-yl)methanone ***(21b)***.

The structure of the latter product was established on the basis of its elemental analysis and spectral data. Its IR spectrum revealed two carbonyl absorption bands at 1730 and 1664 cm^{-1}. Compound **21b** was confirmed chemically via alternative preparation from compound **21a** by refluxing it in ethanolic hydrochloric acid solution where it afforded compound identical in all respects (mp. mixed mp. and spectra) with those obtained by first method.

Conclusion

In this review, we showed that over the past decades benzimidazole have achieved an important place in the arsenal of organic chemists involved in the construction of complex molecules and biologically active moleculesSynthesis of Substituted or unsubstituted benzimidazole has employed a great interest either by classical methods or by using palladium catalyzed reactions. Finally, one can reasonably anticipate that future studies will provide new applications to the preparations of complex molecules, particularly in the area of biologically active compounds.

Experimental

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethylsulphoxide (DMSO-d_6). Chemical shifts are quoted in δ and were related to that of the solvents. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical center of Cairo University.

2-Bromo-1-(1-Methyl-1H-benzo[d]imidazole-2-yl) ethanone (1):

A solution of 2-acety1-1-methylbenzimidazole (17.4 g, 100 mmol) in glacial acetic acid (100 ml) was heated to 80-90°C with vigorous stirring. To this hot solution, bromine (16g, 0.1mol) in glacial acetic acid (20 ml) was added drop wise over a period of 30 min .with stirring and maintaining temperature at 80-90°C. After the addition was complete, the reaction mixture was stirred for further1h till evolution of hydrogen bromide gas was ceased. The mixture was treated with a solution of sodium acetate trihydrate till complete precipitation of the product, the solid which formed was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded the corresponding 2-bromo-1-(1-methyl-1H-benzo[d] imidazole-2-yl) ethanone (**1**) in 85% yield, mp. 112 C; IR (KBr) ν max/cm^{-1}1695 (C=O), 1611 (C=N); ^{1}HNMR (DMSO-d6) δ 3.4 (s,3H,CH_3) 3.9, (s,2 H,CH_2), 6.4 -6.75 (m,4H,ArH) ppm.; MS: m/z (%), 254 (M^+ +1,100%), 252 (M^+ -1,60), 173 (28), 159.(30). For $C_{10}H_9BrN_2O$ (253.1). Calcd. : C, 47.46; H, 3.58; Br 31.57: N, 11.07; %. Found: C, 47.5; H, 3.6; Br, 31.57; N, 11.2; %.

1-(1-Methylbenzimidazol-2-yl)-1-ethanone-2-dimethyl sulfoniumbromide (2):

A mixture of 2-Bromo-1-(1-Methyl-1H-benzo[d] imidazole-2-yl)ethanone **(1)** (25.3 g, 100 mmol) and dimethylsulfide (12 ml) in absolute methanol (50 ml) was refluxed for 15 min., then cooled. The precipitated solid was filtered off, washed ether and finally recrystallized from ethanol to afford (80% yield) of **1** mp. 142 C; IR (KBr) ν_{max}/cm^{-1} 1695 (C=0), 1611 (C=N**).** For $C_{12}H_{15}BrN_2S0$: Calcd.: C, 45.71; H, 4.76; N,8.89; S, 10.16 %. Found: C, 45.8; H, 4.7; N, 8.9; S, 10.3 %.

2-(2-Arylhydrazono)-2-bromo-1-(1-methyl-1H-benzo [d]imidazole-2-yl)ethanone ***5a-c*****:**

Method A, General Procedure:

To a solution of the sulfoniumbromide **2** (9.45 g, 30 mmol) in ethanol (50 ml) and sodium acetate trihydrate (5 g) was added appropriate arene diazonium chloride (30 mmol) while stirring over a period of 30 min. After the addition was completed, the reaction mixture was stirred for further 3h at 0-5 °C and left to stand in an ice box for 12h., then diluted with water. The precipitated solid was filtered off, washed water, dried and finally recrystallized from acetic acid afforded the corresponding hydrazonoyl bromides **5a-c** in 80-85% yields. The compounds synthesized together with their physical data are listed below:

2-(2-Phenylhydrazono)-2-bromo-1-(1-methyl-1H-benzo[d]imidazole-2-yl)ethanone ***5a****:*

Yield: 80%; mp. 160-61 °C; IR (KBr) ν_{max}/cm^{-1} 3442 (NH), 1658 (C=O), 1602 (C=N); H^1 NMR ($CDC1_3$) δ 4.10 (s. 3H, CH,), 7.01 -7.90 (m, 9H, ArH) 9.65 (s, 1H, NH), ppm. For $C_{I6}H_{13}$ BrN_4O (357.2) : Calcd. : C, 53.80; H, 3.67; Br, 22.37; N, 15.68 % Found: C, 54.01; H, 3; Br, 22.37; N, 15.7%

(2- (4-Methylphenyl hydrazono)-2-bromo-1- (1-methyl-1H-benzo[d]imidazole-2-yl)ethanone ***5b****:*

Yield: 81%; mp. 165-671 °C; IR (KBr) ν_{max}/cm^{-1} 3153 (NH), 1656 (C=O), 1615 (C=N); H^1 NMR ($CDCl_3$) δ 2.37 (s. 3H, CH,), 4.10 (s. 3H, CH,), 7.01 - 7.90 (m, 8H, ArH) 9.65(s, 1H, NH), ; ^{13}CNMR ($CDC1_3$) δ *24.1,115.2,115.4 116.2,116.3,123,123.2, 128.3,129.7,129.6,134.2,,138.7,140.1,141.3,154.6,188. 2*ppm. For $C_{I7}H_{15}BrN_4O$(371.23): Calcd.: C, 54.99; H, 4.07; Br, 21.52; N, 15.09 % Found: C, 55.02; H, 4.11; Br, 21.53 ;N, 15.1 %

(2- (4- Chlorophenyl hydrazono)-2-bromo-1- (1-methyl-1H-benzo[d]imidazole-2-yl)ethanone ***5c****:*

Yield: 85%; mp. 198-200 °C; IR (KBr) ν_{max}/cm^{-1} 3274 (NH), 1655 (C=O), 1594 (C=N); H^1 NMR ($CDCl_3$) δ 4.05 (s. 3H, CH,), 7.0 -8.0 (m, 8H, ArH) 8.8 5 (s, 1H, NH), ppm. For $C_{I6}H_{12}$ $BrClN_4O$ (391.65): Calcd.: C,49.07; H, 3.09; Br, 20.42; Cl, 9.05; N, 14.31 %Found: C, 49.05; H, 3.1; Br, 20.44; Cl, 9.0; N, 14.4 %

Method B, General Procedure:

A mixture of of the sulfoniumbromide **2** (9.45g, 30 mmol) and the appropriate N-nitrosoacetanilide derivatives (30 mmol) in ethanol (50 ml) was stirred at room temperature for 12h, then diluted with water. The precipitated solid was filtered off, washed wirh water, dried and finally recrystallized from acetic acid afforded compounds identical in all respects (mp., mixed mp., and spectra) with those obtained by method A above.

*1-(1-Methyl-1H-benzo[d]imidazole-2-yl)-2-thio cyanatoethanone (****6****):*

To a solution of *2*-bromo-1-(1-methyl-1H-benzo [d]imidazole-2-yl)ethanone ***(1)*** (25.3 g, 100 mmol) in ethanol (20 ml) was added potassium thiocyanate (1 g, 10 mmol). The mixture was stirred for 3 h during which the reactants went into the solution and the products separated out as a solid which was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded the corresponding 1-(1-methyl-1H-benzo[d]imidazole-2-yl)-2-thiocyanatoethanone (**6**) in 97% yield, mp. 104-5°C; IR (KBr) ν_{max}/cm^{-1} 2170 (SCN), 1638 (C=O); ^{1}HNMR (DMSO-d6) δ 3.35 (s, 3H, CH_3), 3.85 (s, 2 H, CH_2), 6.70-7.50 (m, 4H, ArH); ^{13}CNMR ($CDC1_3$) δ 31.8, 37.4, 111.9, 115.3, 115.8, 123.0, 123.3, 134.3, 138.9, 141.5, 196.5. MS, m/z (%) 231(M^+, 100%) 232, 233 For $C_{11}H_9N_3OS$ (231.27): Calcd.: C, 57.13; H, 3.92; N, 18.17; S, 13.86%. Found: C, 57.23; H, 3.89; N, 18.17; S, 13.90%.

(4,5-Dihydro-5-imino-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone ***8a-c****:*

Method A, General Procedure:

A solution of the appropriate arene diazonium chloride (5 mmol) was added portion wise to a cold solution of 1-(1-methyl-1H-benzo[d]imidazole-2-yl)-2-thiocyanatoethanone (**6**) (5 mmol) in ethanol (50 ml), in the presence of sodium acetate trihydrate (5 g) with stirring. After the addition was complete, the mixture was stirred at 0-5°C for further 3h. The solid product was collected, washed with water and dried.

Recrystallization from dioxane afforded the corresponding 1,3,4- thiadiazole derivatives **8a-c** in 75-85% yields. The compounds synthesized together with their physical data are listed below:

Method B, General Procedure:

A mixture of compound **5** (9.45 g, 30 mmol) and potassium thiocyanate (1 g, 10 mmol) in ethanol (50 ml) was stirred at room temperature for 12h, then diluted with water. The precipitated solid was filtered off, washed water, dried and finally recrystallized from acetic acid afforded compounds identical in all respects (mp. mixed mp., and spectra) with those obtained by method A above.

*4,5-dihydro-5-imino-4-phenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (**8a**):*

Yield: 85%; mp. 147-9 °C; IR (KBr) ν_{max}/cm^{-1} 3274 (NH), 1644 (C=O), 1612 (C=N); ^{1}HNMR (DMSO-d6) δ, 3.5 (s. 3H, CH_3,), 7.3-8.0 (m, 9H, ArH) 8.3 (s, 1H, NH ,D_2O exchangeable) ; MS, m/z (%) 353 (M^+,100%) 337 (18%) 336(12),.For $C_{17}H_{13}N_5$ OS (335.38) : Calcd. : C, 60.88; H, 3.91; N, 20.88;S, 9.56% Found : C, 61.02;H, 3.90;N, 20.93; S, 9.53%.

*(4,5-dihydro-5-imino-4-methyl-phenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (**8b**):*

Yield: 77%; mp. 153-5 °C; IR (KBr) ν_{max}/cm^{-1} 3273 (NH), 1.645 (C=O), 1612 (C=N): ^{1}HNMR (DMSO-d6) δ, 2.4 5 (s. 3H, CH_3,), 3.5 (s. 3H, CH_3,), 7.30-7.80 (m, 8H, ArH) 8. 3.0 (s, 1H, NH, D_2O exchangeable): ^{13}CNMR (DMSO): δ 24.3, 31.8, 115.3, 115.8, 116.2, 116.5, 123, 123.2, 128.4, 129.9, 130.2, 134.3, 138.9, 141.5, 143.9, 152, 159.7, 175.6, MS, m/z(%) 349 (M, 100%) 350 (28%). For $C_{18}H_{15}N_5OS$ (349.41): Calcd.: C, 61.87; H, 4.33; N, 20.04;S, 9.18% Found: C, 61.78;H, 4.40;N, 20.02;S, 9.23%.

*(4,5-dihydro-5-imino-4-chlorophenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (**8c**) :*

Yield: 75%; 158-9 °C; IR (KBr) ν_{max}/cm^{-1} 3274 (NH), 1645 (C=O), 1612 (C=N) cm^{-1}: ^{1}HNMR (DMSO-d6) δ, 3.5 (s. 3H, CH_3,), 7.30-7.80 (m, 8H, ArH) 8. 3.5 (s, 1H, NH, D_2O exchangeable): MS, m/z (%) 369 (M, 80%), 370 (22%), 371. For $C_{17}H_{12}ClN_5OS$ (369.83): Calcd.: C, 55.21; H, 3.27; Cl, 9.59 , N, 18.94; S, 8.67%. Found: C, 55.16; H, 3.22; Cl, 9.58; N, 19.01; S, 8.70%.

*Acetylation of (4,5-dihydro-5-imino-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl) methanone **8a-c**:*

General Procedure:

A solution of the appropriate iminothiadiazole derivatives **8a-c** (2 mmol) in acetic anhydride or acetyl chloride (10 ml) was refluxed for 1 h, then cooled and poured onto crushed ice. The precipitated solid was filtered off, washed with water, dried and recrystallizated from dioxane to afford N-acetyliminothiadiazole derivatives, **5a-c** in 78-87% yield. The compounds synthesized together with their physical data are listed below:

*(4,5-dihydro-5-acetylimino-4-phenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl) methanone (**9a**):*

Yield: 87%; mp. 177-9 °C; IR (KBr) νmax/cm^{-1} 1691, 1666 (2C=O). ^{1}H NMR (DMSO-d6) δ; 2.20 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 7.42-8.0 (m, 8H, ArH) ^{13}CNMR (DMSO): δ 24.5, 31.8, 115.3, 115.8, 116.2, 116.5, 123, 123.2, 128.4, 129.9, 130.2, 134.3, 138.9, 141.5, 143.9, 152, 164.7, 173.6, 175.6 MS, m/z (%) 377 (M^+, 100%) 376 (28%). For $C_{19}H_{15}N_5O_2S$ (377.42): Caled.: C, 60.46.; H, 4.01; N, 18.56:S, 8.50%. Found: C, 60.39; H, 3.98; N, 18.60; S, 8.51 %.

*(4,5-dihydro-5-acetylimino-4-methyl-phenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (**9b**):*

Yield: 78%; mp. 182-3 °C; IR (KBr) ν_{max}/cm^{-1} 1682, 1656 (2C=O) 'H NMR (DMSO-d6) δ; 2.20 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 7.42-8.0 (m,8 H, ArH); MS, m/z (%) 391 (M^+,100%) 392 (28%). For $C_{20}H_{17}N_5O_2S$: Caled.: C, 61.37.; H, 4.38; N, 17.89; S, 8.19 % Found: C, 61.32; H, 4.40; N, 18.01; S, 8.20 %**.**

*(4,5-dihydro-5--acetylimino-4-chlorophenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (**9c**):*

Yield: 85%; mp. 191-2 °C; IR (KBr) νmax/cm^{-1} 1665, 1649 (2C=O). ^{1}H NMR (DMSO-d6) δ; 2.20 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 7.42-8.0 (m, 8H, ArH) ppm MS, m/z (%) 411 (M^+,92%) 413 (21%). For $C_{19}H_{14}C1N_5O_2S$ (411.86): Calcd. : C, 55.41; H, 3.43; Cl, 8.61; N, 17.02:S, 7.79 % Found: C, 55.42; H, 3.36; Cl, 8.63 ; N, 17.05; S, 7.79 %.

(4,5-dihydro-5-nitrosoimino-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone ***6a-c****:*

General Procedure:

To a solution of the appropriate iminothiadiazole derivatives **8a-c** (30 mmol) in acetic acid (20 ml) was added sodium nitrite (2.07 g, 30 mmol). The mixture was stirred for 15 min. during which the reactants dissolved and coloured products precipitated which were collected by filtration, washed with water and dried. Recrystallization from dioxane afforded the corresponding Nnitrosoiminothiadiazole derivatives **6a-c** in 65-75% yields. The compounds synthesized together with their physical data are listed below:

(4,5-dihydro-5-nitrosoimino-4-phenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone ***(10a)****:*

Yield: 69%; mp. 161-2 °C; IR (KBr) ν_{max}/cm^{-1} 1675 (C=O), 1593 (C=N); MS: m/z, (%) 364 (M^+ 60%), 233, 131. For $C_{17}H_{i2}N_6O_2S$(364.38): Calc.: C, 56.04; H, 3.32; N, 23.06; S, 8.80% Found: C, 56.01; H, 3.34; N, 23.03; S, 8.77%.

*(4,5-dihydro-5-nitrosoimino-4-methylphenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (****10b****):*

Yield: 75%; mp. 210-12 °C; IR (KBr) ν_{max}/cm^{-1} 1673 (C=O), 1578 (C=N) cm^{-1}; 'H NMR (DMSO-d6) δ 2.4 (s, 3H, CH_3), 3. 5 (s, 3H, CH_3), 7.2-8.4 (m, 9H, ArH) ^{13}CNMR (DMSO): δ 31.8, 115.3, 115.8, 116.2, 116.5, 123, 123.2, 128.4, 129.9, 130.2, 134.3, 138.9, 141.5, 143.9, 146.3, 152, 159.7,. MS: m/z, (%) 378 (M^+,65), 379 (26), 380 (25) ,131 (12). For $C_{18}H_{14}N_6O_2$ S (378.41): Calc.: C, 57.13; H, 3.73; N. 22.21; S, 8.46%. Found: C, 57.10; H, 3.70; N, 22.14; S, 8.50%.

*(4,5-dihydro-5-nitrosoimino-4-chlorophenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (****10c****):*

Yield: 65%; mp. 200-202 °C; IR (KBr) ν_{max}/cm^{-1} 1673 (C=O), 1612 (C=N) MS, m/z(%) 398 ($M^{+\cdot}$92%) 400 (21%). For $C_{17}H_{1l}CIN_6$ O_2S (398.83): Calcd.: C, 51.20; H, 2.78; Cl, 8.89 ; N, 21.07;S, 8.04% Found: C, 51.13;H, 2.69; Cl, 8.87;N, 21.10;S, 8.01%.

(4,5-dihydro-5-oxo-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone 11a-c:

Method A, General Procedure:

A solution of the appropriate N-nitroso iminothiadiazolone derivatives **6a-c** (3 mmol) was refluxed in xylene for lh, then cooled. The solid that formed was collected by filtration, washed with water and dried. Recrystallization from dioxane afforded the corresponding thiadiazolinone derivatives **11a-c** in 80--85% yields. The compounds synthesized together with their physical data are listed below:

*(4,5-dihydro-5-oxo-4-phenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (****11a****):*

Yield: 83%; mp. 198-9 °C; IR (KBr) ν_{max}/cm^{-1} u 1692, 1667 (2C=O) MS, m/z (%) 336 (M,92%) 337 (21%) 338 (22). For $C_{17}H_{12}N_4O_2S$ (336.37): Calcd.: C, 60.70; H, 3.60; N, 16.66; S, 9.53%. Found: C, 60.71; H, 3.57; N, 16.68; S. 9.57%.

*(4,5-dihydro-5-oxo-4-methylphenyl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (****11b****):*

Yield: 80%; mp. 206-207 °C; IR (KBr) ν_{max}/cm^{-1} 1661, 1680 (2C=O); MS, m/z(%) 350 (M^+,92%) 351 (21%). For $C_{18}H_{14}N_4O_2S$ (350.39): Calcd. C. 61.70; H, 4.03; N, 15.99; S. 9.15 %. Found: C, 61.65; H, 4.01;N, 16.01; S, 9.14%.

*(4,5-dihydro-5-oxo-4-chlorophenyl1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (****11c****):*

Yield: 85%; mp. 215-6 °C; IR (KBr) ν_{max}/cm^{-1} 1705, 1667 (2C=O); MS: m/z(%), 371(M^+ +1, 62%), 370 (M^+, 92%), 239, 131. For $C_{17}H_{11}ClN_4O_2S$ (370.81): Calcd.: C, 55.06; H, 2.99; Cl, 9.56; N, 15.11; S, 8.65 % Found: C, 55.10; H, 2.98 Cl, 9.55; N, 15.10; S, 8.62%.

Method B:

To a solution of the appropriate ***(***4,5-dihydro-5-imino-4-aryl-1,3,4-thiadiazol-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone ***8a-c*** (10 mmol) in ethanol (20 ml), was added hydrochloric acid (37%, 5 m1). The reaction mixture was relluxed for 4 h. The reaction mixture left to cool and the precipitate so formed was collected by filtration, washed with water and dried. Recrystallization from dioxane afforded compounds identical in all respects (mp,, mixed mp. and spectra) with those obtained by method A above.

*5-(1-Methrlbenzimidazol-2-y1)-2-inzino-.1,3-oxathiole (****12****):*

A solution of 1-(1-methyl-1H-benzo[d]imidazole-2-yl)-2-thiocyanatoethanone (**2**) (30 mmol) in ethanol (20 ml) was refluxed for 2h, and then cooled. The

precipitated product was collected by filtration, washed with water and dried. Acetic acid Recrystallization from acetic acid afforded the iminooxathiole **12** in 80% yield; mp. 228-30 °C. IR (KBr) ν_{max}/cm^{-1} 3342 (NH), 1620 (C=N) For $C_{11}H_9N_3OS$ (231.27): Calcd.: C, 57.13; H, 3.92; N, 18.17; S, 13.86%. Found: C, 57.13; H, 3.89;N, 18.17; S, 13.90%.

*4-(1-Methyl -1H-benzo [d]midazol-2-y1)-N-aryl thiazol-2- amine **14a-c**:*

To a solution of 1-(1methyl-1H-benzo[d]imidazole-2-yl)-2-thiocyanatoethanone ***(2)*** (2.31 g, 1.0 mmol) in ethanol (20 ml) was added the appropriate aromatic aminehydrobromide (aniline, p-toluidine or p-chloroanitine) (10 mmol) and the mixture was refluxed for 2h, then cooled. The solid that formed was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded the corresponding thiazole derivatives **10a-c** in 75-78% yields. The compounds synthesized together with their physical data are listed below:

*4-(1-Methyl -1H-benzo [d]midazol-2-y1)-N-phenyl thiazol-2- amine **(14a)**:*

Yield: 75%; mp. 139-41 °C; IR (KBr) ν_{max}/cm^{-1} 3313 (NH), 1593 (C=N); ^{1}H NMR (DMSO-d6) δ 3.5 (s, 3H, CH_3), 7.0-7.2 (m, 9H, ArH), 7.3 (s,1H, thiazole-5-CH), 8.2 (brs, 1H, NH ,D_2O exchangeable); MS: m/z(%), 305, 306 (M^+ 52%), 307 (M^+ +1,62%). For $C_{17}H_{14}N_4S$ (306.38): Calcd.: C, 66.64; H, 4.61; N, 18.29; S, 10.47% Found : C, 66.59; H, 4.64; N, 18.25; S, 10.45%.

*4-(1-Methyl -1H-benzo [d]midazol-2-y1)-N-p-tolylthiazol-2- amine (**14b**):*

Yield: 78%; mp. 146-8 °C; IR (KBr) ν_{max}/cm^{-1} 3311 (NH), 1593 (C=N) MS: m/z(%), 320 (M^+ 51%), 321 (23), 222 (21), 131(11) ^{1}H NMR (DMSO-d6) δ 2.5 (s, 3H ,CH_3), 3.5 (s, 3H ,CH_3), 7.0-7.2 (m, 8H, Ar H), 7.3 (s, 1H, thiazole-5-CH), 8.2 (brs, H, NH, D_2O exchangeable). For $C_{18}H_{16}N_4S$ (320.41) Calcd.: C, 67.47; H, 5.03; N, 17.49;S, 10.01 %. Found: C, 67.46; H, 5.02; N, 17.46; S, 10.09%.

*4-(1-Methyl -1H-benzo [d]midazol-2-y1)-N-p-chloro phenylthiazol-2- amine (**14c**):*

Yield: 77%; mp. 162-4 °C; IR (KBr) ν_{max}/cm^{-1} 3318 (NH), 1609 (C=N) MS: m/(%)z, 340, (63) 342 (32), 131 (21). For $C_{17}H_{13}ClN_4S$ (340.83): Calcd.: C, 59.91; H, 3.84; Cl, 10.40; N, 16.44; S, 9.41% Found: C, 60.01; H, 3.90; Cl, 10.35; N, 16.50; S, 9.46%

*Reactions of 1-(1-Methyl-1H-benzo[d]imidazole-2-yl) -2-thiocyanatoethanone (**6**) with ortho-substituted arene diazonium salts:*

General Procedure:

To a cold solution of 1-(1-methyl-1H-benzo[d] imidazole-2-yl)-2-thiocyanatoethanone (**6**) (6.93 g, 30 mmol) in ethanol (50 ml) and sodium acetate trihydrate (5 g) was added the appropriate diazonium salt solution of anthranilonitrile, anthranilic acid or methyl anthranilate (30 mmol), while stirring over a period of 30 min. After the addition was complete, the reaction mixture was stirred for further 3 h at 0-5°C and left to stand in an ice box for 12hrs then diluted with water. The solid that formed was filtered off, washed with water and dried. Recrystallization from dimethyl formamide afforded (5-oxo-5H-(1,3,4) thiazolo[3,2-a]quinazolin-2-yl)(1-methyl-1H-benzo[d] imidazole-2-yl)methanone ***(21b)*** and **(**5-imino-5H-(1,3,4) thiazolo[3,2-a]quinazolin-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone **(21a)** in 78% and 80% yield, respectively. The compounds synthesized together with their physical data are listed below:

*(5-imino-5H-(1,3,4)thiazolo[3,2-a]quinazolin-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (**21a**):*

Yield: 80%; mp. >300 °C; IR (KBr)i) ν_{max}/cm^{-1} 3275 (NH), 1660 (C=O), 1599 (C=N) MS: m/z, (%) 360 (M^+,33), 361 (M^++1,43), 362 (M^+ 2,43), 131(22) For $C_{18}H_{12}N_6OS$ (360.08): Caled.: C, 59.99; H, 3.36; N, 23.32; S, 8.90%. Found: C, 59.98; H, 3.31; N, 23.29; S, 8.97%.

*(5-oxo-5H-(1,3,4)thiazolo[3,2-a]quinazolin-2-yl)(1-methyl-1H-benzo[d]imidazole-2-yl)methanone (**21b**):*

Yield: 78%; mp. > 300°C; IR (KBr)1. ν_{max}/cm^{-1}1730, 1664 (2C=O), 1587 (C=N) MS: m/z (%), 361(M^+,43), 360 (M^+-1,43), 239 (32), 131 (51). For $C_{18}H_{11}N_5O_2S$ (361.38): Calcd.: C, 59.82 ; H, 3.07; N, 19.38; S, 8.87%. Found: C, 59.81; H, 3.04; N, 19.40: S, 8.83%

*Conversion o**f 21a i**nto **21b**:*

To solution of the quinazolin imine **1**7a (10 mmol) in ethanol (20 ml) was added hydrochloric acid (37%, 5 ml). The reaction mixture was refluxed for 4 h then left to cool. The precipitate so formed was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded compounds identical in all respects (mp., mixed mp. and spectra) with that obtained from reaction of **6** with diazotized anthranilic acid.

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