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Synthesis of New 1,3,4-Thiadiazole Derivatives Based Hetrocyclics

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ABSTRACT:
A Facile route to some new 2-(3,5-diphenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene) derivatives via the reaction of 3-mercapto-1-(1-methylbenzimidazole-2-yl)-3-(phenylamino)-2(phenylsulfonyl)- propenone **(3)** with *N*-phenylbenzohydrazonyl chloride (**4**) is reported. Avariety of hydrazonoyl halides reacted with compound **3** affording 1,3,4-thiadiazole derivatives that incorporate a benzimidazole moiety.

المستخلص:

تحصلنا علي نتائج جديدة من مشتقات المركبات 2- (3،5-ثنائى فينيل-1،3،4-ثيادايازول-2-يليدين) عن طريق تفاعل 3-ميركابتو-1-(1-مثيل بنزواميدزول-2-يل)-3-(فينيل امينو)-2-فينيل سلفونيل-بروبينون [3] مع ن-فينيل بنزوكلوريد هيدروزنيل [4] . وأيضا عن طريق تفاعل أنواع مختلفة من هاليدات الهيدروزونيل مع المركب [3] ليعطي المشتقات الجديدة من 4,3,1- ثيادايزول المدمجة في حلقة بنزواميدزول.

***KEYWORDS*:** Hydrazonoyl halides; *N*-phenylbenzohydrazonyl chloride and 1,3,4-thiadiazoles .

INTRODUCTION

Benzimidazoles are very important classes of compounds due to their wide spectrum of biological activity. Their derivatives are used as antiviral,[1,2] antifungal,[3,4] antitumor[5,6] and antihe-lminthic agents[7] in veterinary medicin.[8] Some of the benzimidazole derivatives are now included in many of commercialized drugs.[9]

β-ketosulfone moiety is readily available from a variety of precursor functionalities and displays a broad range of synthetic versatility.[10,11] These are also important group of intermediates in *Michael* and *Knoevengel* reactions.[12] β-keto sulfones have attracted considerable attention from synthetic chemists in the past decade.[13]

Based on our current interest in the synthesis of heterocyclics containing benzimidazole moiety;[14,15] the present successful synthetic attempt was conducted.

Microwave irradiation has been recently demonstrated its utility as an energy source to improve yields and/or safe reaction conditions, especially in the field of heterocyclic synthesis.[16] Use of the pressurized microwave irradiation can be very advantageous to many chemists whereby the solvent can be heated up to temperatures that are 2 to 4 times their respective boiling points and thus providing an enhanced

reaction rate, in addition to keeping the atmosphere from moisture that may affect the sensitive reagents.

The present report involves the reaction of the versatile 1-(1-Methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-1-ethanone (**1**) with phenyl isothiocyanate and the uitillity of the product 3-mercapto-1-(1-methyl1*H*-benzimidazole-2-yl)-3-(phenylamino)-2-(phenylsulfonyl)propenone (**3**) and with hydrazonoyl halides, in the synthesis of the title compounds under microwave conditions as well as the adoption of conventional synthetic procedures.

MATERIALS and METHODS

All melting points were determined on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. 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 dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectr-ometer at 70 e.V. Elemental analyses (C, H, N, S) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

The β-ketosulfone **1**[17], and hydrazonyl halids **4** and **8a-f** [18-22] were prepared as reported in literature.

1-(1-Methylbenzoimidazol-2-yl)-3-mercapto-3-phenylamino-3-phenylsulphonylprop-2-en-1-one (3)

Compound **(1)** (3.14 g, l0 mmol) was added to a stirred solution of KOH (0.56 g, 10 mmol) in DMF (20 mL). After stirring for 30 min., phenyl isothiocyanate (1.35 g, 10 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then poured over crushed ice containing HCl. The solid product so formed was filtered off, washed with water, dried and finally recrystallized from EtOH/DMF to afford 3-mercapto-1-(1-methylbenzimidazole-2-yl)-3-(phenylamino)-2-(phenylsulfonyl)propenone (**3**); Yield: 60%, mp 115-116 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3346 (st.vib. NH), 1620 (b. vib. NH), 2570 (SH), 1680 (CO); 1H NMR, ($CDCl_3$) δ1.3 (s,1H,SH), 4.02 (s, 3H, NCH_3), 4.21 (s, 1H, NH), 6.39-7.93 (m, 14H, ArH's). MS (*m/z*): 449 (M^+, 77%). Anal. Calcd for $C_{23}H_{19}N_3O_3S_2$: C, 61.45; H, 4.26; N, 9.35; S, 14.27. Found: C, 61.43; H, 4.29; N, 9.31; S, 14.30.

Reaction of 3-mercapto-1-(1-methylbenzimidazole-2-yl)-3-(phenyl-amino)-2-(phenylsulfonyl)propenone (3) or its potassium salt intermediate 2, with hydrazonyl halide 4 and 8a-f

General procedure:

(A)-Thermal method:

Method 1. To a solution of compound **3** (0.45 g, 1 mmol) in EtOH (20 ml.), and an appropriate hydrazonoyl halide **4** and **8a-f** (1 mmol), triethylamine (0.5 ml.) was added. The reaction mixture was heated under reflux, where a colored precipitate started to take place within 5-20 min., heating was continued for further 2 h, the reaction mixture allowed to cool. The formed solid was filtered off, washed with EtOH and recrystallized from EtOH/DMF to afford the corresponding thiadiazole derivatives **5** and **10a-f** respectively in 75-81% yields.

Method 2. The appropriate hydrazonoyl halide **4** and **8a-f** (10 mmol) was added portion wise over a period of 30 min. to a solution of potassium salt intermediate **2**, and the reaction mixture was stirred for 12 h,

during which hydrazonyl halide dissolved and a yellowish-red colored product preciptated. The solid product was filtered off, washed with water, dried and recrystallized from EtOH/DMF to afford products identical in all respect (mp, mixed mp and spectra) with those obtained by method 1 above.

(B)-Microwave method:

To an ethanolic solution of 1-(1-methylbenzoimidazol-2-yl)-3-mercapto-3-phenylamino-3-phenylsulphonyl prop-2-en-1-one **(3)** (1 mmol) and the appropriate hydrazonyl halides **4** and **8a-f** (1 mmol) few drops of triethylamine were added in a process vial. The vial was capped properly and irradiated by microwave under pressurized conditions (17.2 bars, 150 ^{o}C) for 20 min. The yellowish-red colored products precipitated are formed. The solid product was filtered off, washed with water, dried and recrystallized from EtOH/*DMF* to afford the corresponding thiadiazole derivatives **5** and **10a-f**.

2-(3,5-Diphenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (5)

Yield 78% (Thermally) 89% (MW); mp. 188 ˚C; IR (KBr) υ_{max} /cm^{-1}: 1660 (CO), 1590 (C=N); ^{1}H NMR ($CDCL_3$): 4.02 (s, 3H, NCH_3), δ 6.80-7.92 (m, 19H, ArH's. MS (*m/z*): 550(M^+, 100%). Anal. Calcd for $C_{30}H_{22}N_4O_3S_2$: C, 65.44; H, 4.03; N, 10.17; S, 11.65. Found: C, 65.47; H, 4.01; N, 10.20; S, 11.69.

2-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2-(3*H*)-ylidene)1-(1-methylbenzoimidazol-2-yl-)-2-(phenylsulphonyl)ethanone (10a)

Yield 79%(Thermally) 84% (MW); mp. 202-203 ˚C; IR (KBr) υ_{max} /cm^{-1}: 1665 (CO), 1625 (CO), 1588 (C=N).^{1}H NMR ($CDCL_3$): δ 2.21 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 6.67- 7.79(m, 14H, ArH'. MS (*m/z*):516 (M^+, 100%).Anal. Calcd for $C_{26}H_{20}N_4O_4S_2$: C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found: C, 60.43; H, 3.92; N, 10.88; S, 12.41.

2(5-Acetyl-3-p-tolyl-1,3,4-thiadiazol2(3*H*)-ylidene)-1-(1-methylbenzimidazol-2-yl)2-(phenylsulfonyl)ethanone (10b)

Yield 75% (Thermally) 81% (MW); mp. 210-211 ˚C; IR (KBr) υ_{max} /cm^{-1}: 1665 (CO), 1625 (CO), 1606 (C=N); ^{1}H NMR ($CDCL_3$): δ 2.21 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 6.98-7.89(m, 13H, ArH's). MS (*m/z*): 530 (M^+, 100%). Anal. Calcd for $C_{27}H_{22}N_4O_4S_2$ (530.11): C, 61.12; H, 4.18; N, 10.56; S, 12.09. Found: C, 61.09; H, 4.22; N, 10.58; S, 12.13.

2-(5-Acetyl-3-(4-chlorophenyl)1,3,4thiadiazol-2(3*H*)-ylidene)-1-(1-methylbenzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (10c)

Yield 80% (Thermally) 89% (MW); mp. 297-298 ˚C; IR (KBr) υ_{max} /cm^{-1}: 1665 (CO), 1625 (CO), 1636 (C=N); ^{1}H NMR ($CDCL_3$): δ 2.21 (s, 3H, CH_3),4.02 (s, 3H, NCH_3), 7.11-7.99(m, 13H, ArH's); ^{13}C NMR (DMSO-d_6): δ24.74, 32.07, 106.62, 111.73, 114.32, 121.43, 123.95, 126.45, 127.94, 129.23,129.43, 134.02, 137.06, 139.41, 140.82, 142.31, 145.22, 146.31, 153.37, 182.34, 190.53. MS (*m/z*): 550 (M^+, 100%). Anal. Calcd for $C_{26}H_{19}ClN_4O_4S_2$: C, 56.67; H, 3.48; N, 10.17; S, 11.64. Found: C, 56.70; H, 3.46; N, 10.13; S, 11.71.

2-(5-Acetyl-3-(4-methoxyphenyl)1,3,4-thiadiazol-2(3*H*)-yli-dene)-1-(1-methylbenzimida-zol-2-yl)-2-(phenylsulfonyl)ethan- one (10d)

Yield 79% (Thermally) 86% (MW); mp. 183 ˚C; IR (KBr) υ_{max} /cm^{-1}: 1665 (CO), 1625 (CO), 1596 (C=N); ^{1}H NMR ($CDCL_3$): δ 2.21 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.02 (s, 3H, NCH_3), 6.84-7.99(m, 13H, ArH's). MS

(*m/z*): 546 (M^+, 100%). Anal. Calcd for $C_{27}H_{22}N_4O_5S_2$: C, 59.33; H, 4.06; N, 10.25; S, 11.73. Found: C, 59.30; H, 4.10; N, 10.28; S, 11.77.

2-(5-Benzoyl-3-phenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl) ethanone (10e)

Yield 78% (Thermally) 90% (MW); mp. 202-204 ˚C; IR (KBr) υ_{max} /cm^{-1}: 1660 (CO), 1642 (CO), 1590 (C=N). ^{1}H NMR ($CDCL_3$): δ 6.80-7.90 (m, 19H, ArH's). MS (*m/z*): 578 (M^+, 100%).

Anal. Calcd for $C_{31}H_{22}N_4O_4S_2$: C, 64.34; H, 3.83; N, 9.68; S, 11.08. Found: C, 64.38; H, 3.82; N, 9.64; S, 11.10.

5-(2-(1-Methyl-1*H*-benzimidazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*N*,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (10f)

Yield 79% (Thermally) 88% (MW); mp. 220-222˚C. IR (KBr) υ_{max} /cm^{-1}: 3395 (NH), 1677 (CO), 1665 (CO), 1600 (C=N); ^{1}H NMR ($CDCL_3$): δ 4.02 (s, 3H, NCH_3), 6.80-7.89 (m, 19H, ArH's), 10.60 (s, 1H, NH, D_2O-exchangable).^{13}C NMR (DMSO-d_6): δ 32.23, 104.31, 114.68, 115.32, 120,96, 122.75, 122.93, 124.11, 128.42, 128.61, 128.73, 129.29, 129.62, 133.68, 134.32, 137.69, 138.28, 141.18, 142.17, 147.09, 155.93, 162.71, 164.17, 182.35. MS (*m/z*): 593 (M^+, 100%), 77 (15.6%). Anal. Calcd for $C_{31}H_{23}N_5O_4S_2$: C, 62.72; H, 3.90; N, 11.80; S, 10.80. Found: C, 62.65; H, 3.93; N, 11.83; S, 10.81.

RESULTS AND DISCUSSION

When 1-(1-Methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-1-ethanone (1) was treated with phenyl isothiocyanate, in the presence of potassium hydroxide, it afforded the corresponding potassium salt **2**.

The latter product was converted into 3-mercapto-1-(1-methylbenzimidazole-2-yl)-3-(phenylamino)-2-(phenylsulfonyl) propenone (**3**) upon treatment with hydrochloric acid (Scheme 1).

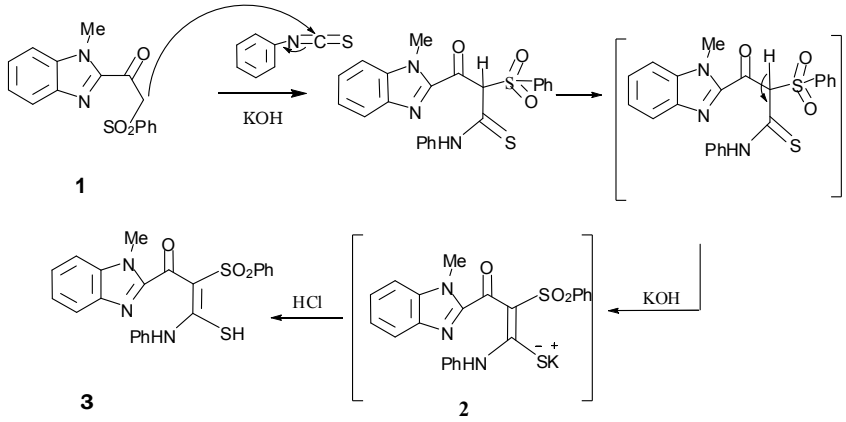


Figure 1 : Schematic Stepwise Synthesis of Compound **(3)**

The IR spectrum of compound **3** showed bands at 3346 and 1620 due stretching and bending vibration of NH group, respectively. And band at 1680 cm^{-1} due to carbonyl function, A plausible mechanism for the formation of compound **3** is outlined in (Scheme 1).

The potassium salt intermediate **2** reacts with *N*-phenylbenzohydrazonyl chloride (**4**) under reflux in ethanol and under microwave conditions in the presence of an equivalent amount of triethylamine to afford, a single product (as examined by TLC which was identified as 2-(3,5-diphenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-1-(1-

methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (**5**) according to elemental analysis and spectral data. The IR spectrum of compound (**5**) showed bands at 1590, 1660 cm^{-1} due to (C=N) and carbonyl function, respectively. The ^{1}H NMR spectra of isolated product (**5**) revealed multiplet signal in the range δ 6.80-7.92 characteristic for aromatic protons and also showed singlet signal at δ 4.02 due to NCH_3 protons. The mass spectrum of the same compound revealed a peak corresponding to its molecular ion at m/z 550 (Scheme **2**). Moreover, the structure Compound **5** was further supported by an independent synthesis from the reaction of compound **1** with carbon disulfide and methyl iodide, in the presence of potassium hydroxide to afford potassium salt intermediates **6** which upon treatment with HCl, gave **7**. The latter product reacted with the hydrazonyl chloride **4,** in refluxing ethanol and in the presence of catalytic amount of triethylamine (Scheme **2**).

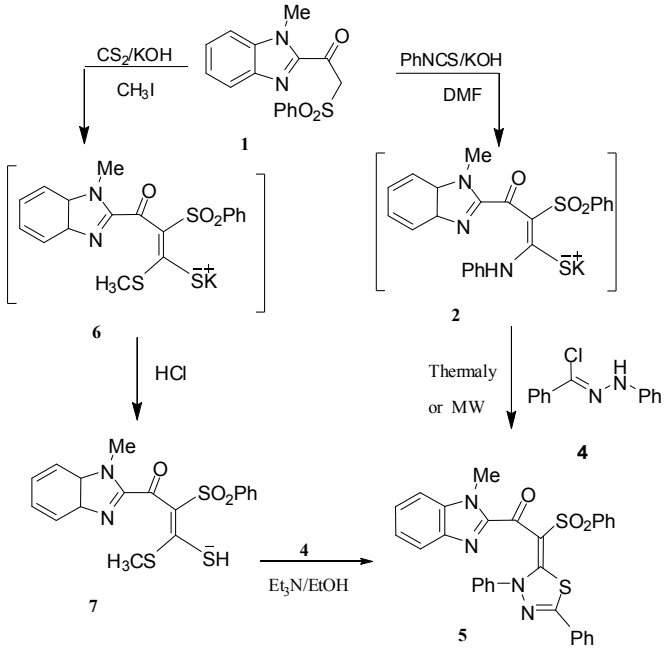
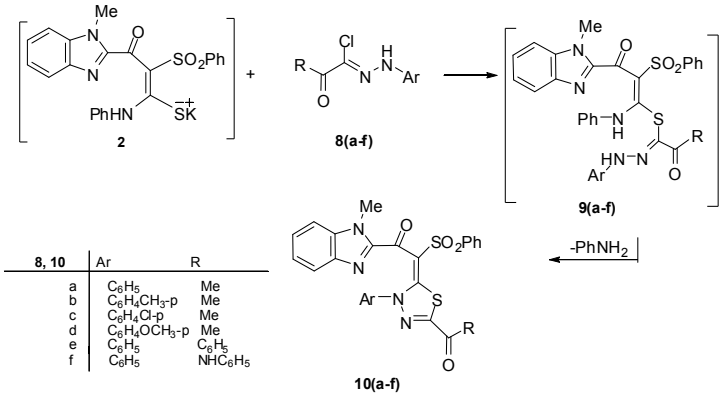


Figure 2 : Schematic Synthetic Steps of Compound **(5)** and **(7)**

In a similar manner, the hydrazonoyl halides **8a-f** react with the potassium salt intermediate **2**, to afford, the corresponding thiadiazole derivatives **10a-f** (Scheme **3**). The structure of thiadiazole derivatives **10a-f** were assigned on the basis of their elemental analysis and spectral data (*cf.* Materials and Methods Part). The IR spectra of the isolated products revealed, in each case, the appearance of two carbonyl absorption bands near 1665, 1645 cm^{-1} For example, The IR spectra of the compound **10f** revealed, bands near 3395 cm^{-1} due to NH protons absorption. The ^{1}H NMR spectrum of the isolated products **10a-f** revealed, in each case, multiplet signal in the range δ 6.60-7.99 characteristic for aromatic protons and also showed singlet signal at δ 4.02 due to NCH_3 protons . The ^{1}H NMR spectrums of **10 a-d** compounds showed singlet signal , in each case, at δ 2.21 due to CH_3 protons and spectrum of **10f** showed singlet signal at 10.60 ppm due to NH proton . The mass spectrum of the compounds **10a-f** revealed, in each case, a peak corresponding to its molecular ion at

m/z 516, 530, 550, 546, 578 and 593 respectively.



8, 10	Ar	R
a	C_6H_5	Me
b	$C_6H_4CH_3$-p	Me
c	C_6H_4Cl-p	Me
d	$C_6H_4OCH_3$-p	Me
e	C_6H_5	C_6H_5
f	C_6H_5	NHC_6H_5

Conventional method : 12h, EtOH/DMF,75-80% conversion yield
Microwave method : 20 min,ethanol, 81-90% conversion yield

Figure 3 : Schematic Synthesis of Thiazole Derivatives

CONCLUSIONS

A successful synthesis of a heterocyclic sulphone propenone was achieved, via treatment of a ketos-ulphone with phenyl isothiocynate. The sulphone propenone proved to be a versatile synthesis for a number of 1,3,4-thiadiazole based heterocyclic compounds.

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