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Synthesis and Reactivity of Benzothiazol-2-ylcarbonylhydroximoyl Chloride, a Versatile Synthon

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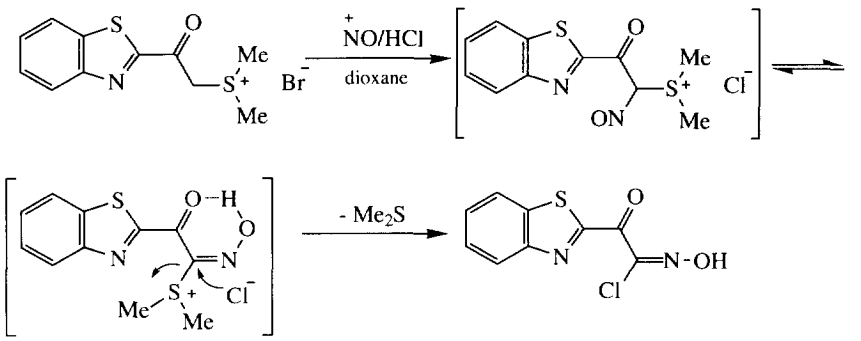
Abstract: The versatile, hitherto unreported benzothiazol-2-ylcarbonylhydroximoyl chloride (**2**) was prepared by treatment of the corresponding sulfonium bromide **1** with sodium nitrite and hydrochloric acid in dioxane. Compound **2** reacts with *o*-aminothiophenol and with o-phenylenediamine to afford the new ketones **3** and **4**, respectively. Oxidation of the latter with lead tetraacetate gave the benzotriazine derivative **7**. Reaction of **2** with heterocyclic amines furnished the novel fused heterocycles **8**, **9**, **12**, **14** and **16**. Compound **2** reacted also with 2-methylthiobenzimidazole and gave the new heterocyclic system **18**. Treatment of **2** with acrylonitrile, acrylamide and α-(benzothiazol-2-yl)cinnamonitrile (**25**) in the presence of triethylamine afforded the isoxazole derivatives **21**, **23** and **27**, respectively.

Extensive studies of the chemistry of hydroximoyl chlorides have established the value of these compounds as versatile precursors for the synthesis of a wide variety of heterocycles.[1-4] In continuation of our interest in the synthesis of heterocyclic systems containing a benzothiazole moiety,[5-11] we report here a facile synthesis of the highly reactive, hitherto unreported benzothiazol-2-ylcarbonylhydroximoyl chloride (**2**). The behaviour of the latter compound towards several aromatic and heterocyclic amines as well as some dipolarophiles are also investigated.

Thus, treatment of benzothiazol-2-yl-1-ethanonedimethylsulfonium bromide (**1**) with sodium nitrite in dioxane/water mixture, in the presence of hydrochloric acid, at room temperature furnished a single product which analysed correctly for $C_9H_5ClN_2O_2S$. The structure of the latter product was elucidated, on the basis of its elemental analyses and spectral data, as benzothiazol-2-ylcarbonylhydroximoyl chloride (**2**). The IR spectrum of the latter product revealed a broad band in the region 3300-3200 cm^{-1} due to a hydroxyl group and a strong band at 1665 cm^{-1} due to a carbonyl group. Its ^1H NMR spectrum displayed also a base-broad singlet at δ 13.74 and a multiplet at δ 7.42-8.11 assignable to hydroxyl and aromatic protons, respectively. A plausible mechanism for the formation of the hydroximoyl chloride **2** is depicted in scheme 1.

When the hydroximoyl chloride **2** was treated with o-aminothiophenol in ethanol at reflux, it afforded a yellow crystalline product identified as 3-(benzothiazol-2-yl)carbonyl-4H-1,2,4-benzothiadiazine (**3**). The IR spectrum of the latter product showed an NH stretching band at 3137 cm^{-1} and a carbonyl absorption band at 1670 cm^{-1}. The appearance of the latter band in the IR spectrum ruled out the other possible isomeric structure **5** for the reaction product.

Similarly, compound **2** reacted with *o*-phenylenediamine and afforded a single product identified as 3-(benzothiazol-2-yl)carbonyl-1,4-dihydro-1,2,4-benzotriazine (**4**). Upon treatment of the latter product with lead



Scheme 1

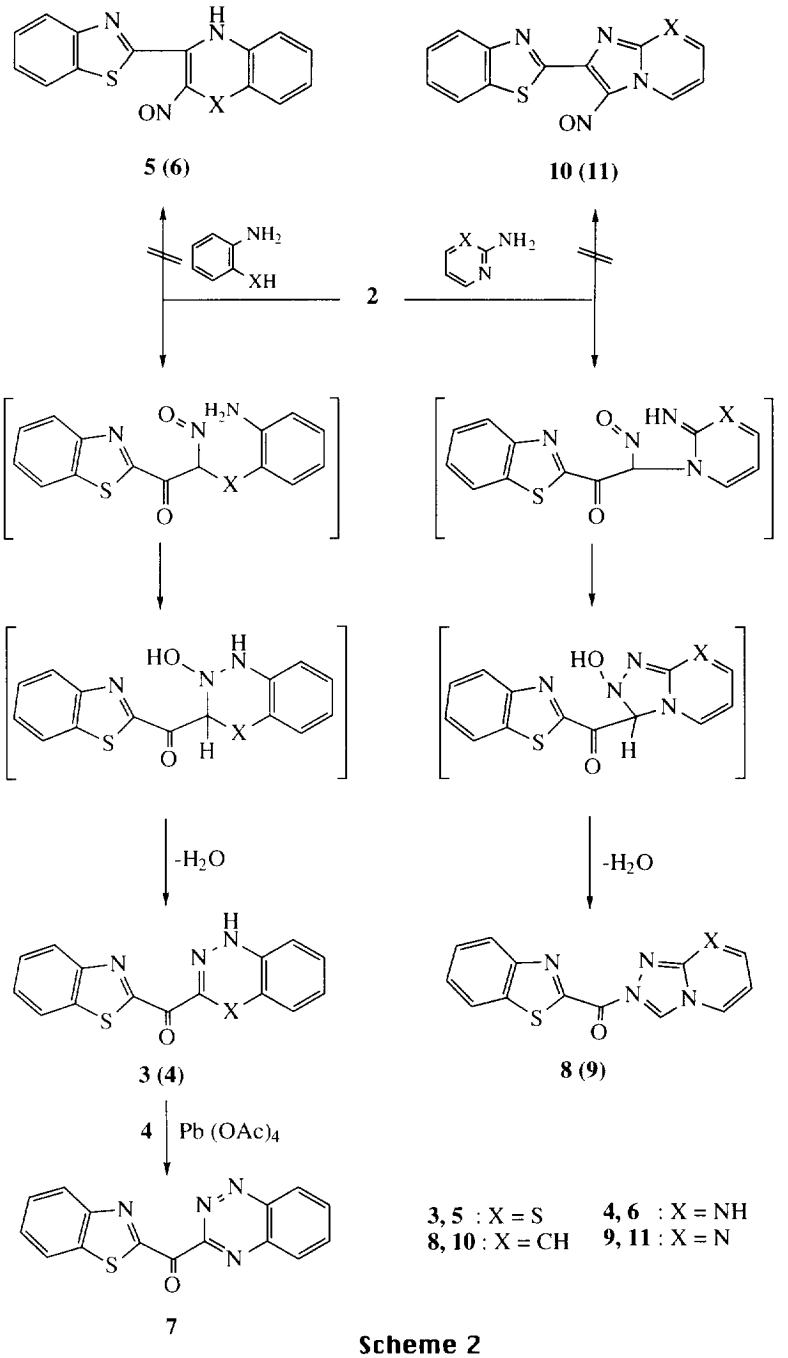
tetraacetate, in glacial acetic acid at room temperature, the corresponding oxidation product 3-(benzothiazol-2-yl)carbonyl-1,2,4-benzotriazine (**7**) was obtained. The structures of the products **4** and **7** were established from their elemental and spectral data. The IR spectrum of **4** revealed two NH stretching bands at 3229 and 3180 cm^{-1} and a strong carbonyl band at 1674 cm^{-1}, whereas the IR spectrum of **7** showed the absence of the NH bands in the region 3400-3100 cm^{-1} and revealed only a carbonyl absorption band at 1660 cm^{-1}. A reasonable mechanism for the formation of the products **3-7** is outlined in scheme 2.

Treatment of the hydroximoyl chloride **2** with 2-aminopyridine and with 2-aminopyrimidine in refluxing ethanol afforded, in each case, only one isolable product (as examined by TLC). The structure of the isolated products were identified as 1,2,4-triazolo[4,3-a]pyridine and 1,2,4-triazolo[4,3-a]pyrimidine derivatives **8** and **9**, respectively. The IR spectra of **8** and **9** showed a strong carbonyl absorption band at 1675 and 1684 cm^{-1}, respectively. The appearance of such bands excludes the other possible isomeric structures **10** and **11** for the reaction products (Scheme 2).

Further, treatment of **2** with 5-amino-3-phenyl-1*H*-pyrazole in refluxing ethanol afforded only one product for which structure **12** or **13** seemed possible (Scheme 3). Structure **12** was assigned for the reaction product on the basis of spectral data. Thus, the IR spectrum of the isolated product showed absorption bands at 3174 and 1667 cm^{-1} assignable to NH and carbonyl functions, respectively. These findings ruled out the other possible isomeric structure **13**.

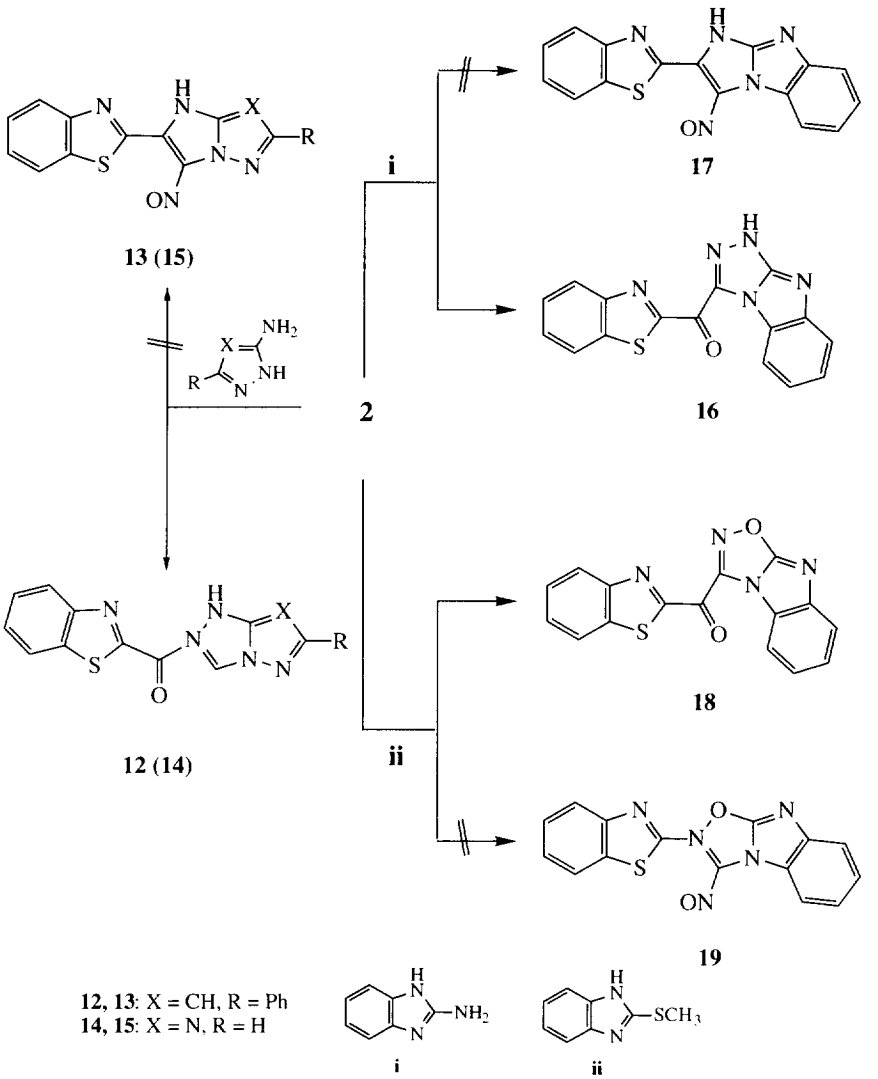
Similarly, compound **2** reacted with 3-amino-1H-1,2,4-triazole in refluxing ethanol and gave one isolable product which analysed correctly for $C_{11}H_6N_6OS$. The two isomeric structures **14** and **15** seemed possible for the reaction product (Scheme 3). However, the appearance of a strong carbonyl absorption band at 1696 cm^{-1} in addition to an NH band at 3178 cm^{-1}, in the IR spectrum of the reaction product provided a firm support for the structure **14** and ruled out the other possible isomeric structure **15**.

The hydroximoyl chloride **2** reacts also with 2-aminobenzimidazole and with 2-methylthiobenzimidazole in refluxing ethanol to give, in each case, one isolable product identified as 3-(benzothiazol-2-yl)carbonyl-1H-1,2,4-triazolo[4,3-a]benzimidazole (**16**) and 3-(benzothiazol-2yl)carbonylbenzimidazo[1,2-d]-1,2,4-oxadiazole (**18**), respectively. Both microanalyses and spectral data were in complete agreement with the assigned structures. For example, the IR spectra of **16** and **18** showed a strong carbonyl absorption band at 1709 and 1671 cm^{-1}, respectively. These data exclude the other possible isomeric structures **17** and **19** (Scheme 3).



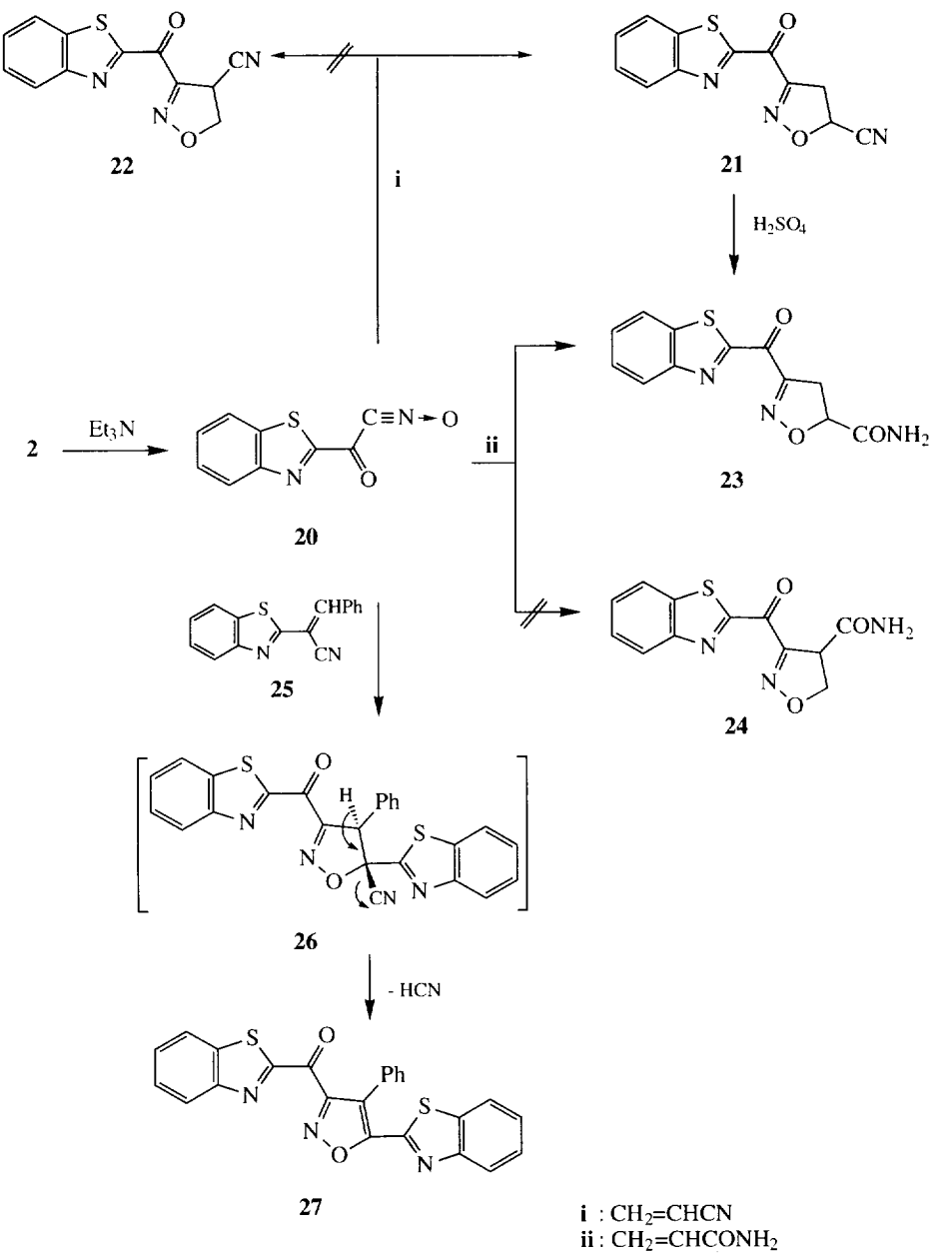
Scheme 2

The 1,3-dipolar cycloaddition reactions of the nitrile oxide **20** (generated in situ from the corresponding hydroximoyl chloride **2** by the action of triethylamine) with some dipolarophiles were also investigated.



Scheme 3

Thus, treatment of **20** with acrylonitrile, in toluene at room temperature afforded only one isolable product which analysed correctly for $C_{12}H_7N_3O_2S$. The two regioisomeric structures **21** and **22** seemed possible for the product isolated (Scheme 4). The IR spectrum of the isolated product showed only a carbonyl band at 1660 cm^{-1}. The absence of nitrile absorption band in the IR spectrum, as it is the case for aliphatic nitriles activated by a nitrogen or an oxygen atom in the α-position[7,12-14] provided a firm support for the formation of 5-cyanoisoxazoline structure **21** and discarded the other possible regioisomer **22**. Moreover, the ^1H NMR spectrum of the product isolated displayed a doublet at δ 3.95 (J = 9.4 Hz), a triplet at 5.52 (J = 9.4 Hz) and a multiplet at δ 7.59-8.36 corresponding to methylene, methine and aromatic protons, respectively.



Scheme 4

Similarly, treatment of **20** with acrylamide under the same experimental conditions furnished a single product identified as 3-(benzothiazol-2-yl)carbonyl-4,5-dihydroisoxazole-5-carboxamide (**23**) (Scheme 4). Both microanalyses and spectral data were in complete agreement with the assigned structure. Thus, its IR spectrum showed bands at 3363 and 3179 cm^{-1} due to amino group and a broad band centered at 1655 cm^{-1} due

to two overlapped carbonyl groups. Its ^{1}H NMR spectrum revealed a doublet at δ 3.86 ppm (J = 8.8 Hz), a triplet at δ 5.29 (J = 8.8 Hz), a broad signal at δ 6.68 and a multiplet at δ 7.58-8.34 corresponding to methylene, methine, carboxamide and aromatic protons, respectively. Further evidence for the formation of structure **23** was its alternate synthesis from **21** as shown in scheme 4. Thus, treatment of **21** with concentrated sulphuric acid at room temperature followed by dilution with water afforded product identical in all respects (mp., mixed mp. and IR spectrum) with that obtained from the reaction of **20** with acrylamide.

In a similar manner, when the nitrile oxide **20** was treated with α-(benzothiazol-2-yl)cinnamonitrile (**25**) in toluene, it afforded one product which analysed correctly for $C_{24}H_{13}N_3O_2S_2$. Spectral data (IR, ^{1}H NMR and MS) were in complete agreement with the 3-(benzothiazol-2-yl)carbonyl-5-(benzothiazol-2-yl)-4-phenyl-isoxazole structure (**27**) (Scheme 4). However, all attempts to isolate the isoxazoline intermediate **26** were unsuccessful. The IR spectrum of the reaction product was free of nitrile absorption band and revealed only carbonyl band at 1669 cm^{-1}. Its ^{1}H NMR spectrum displayed only a multiplet in the region δ 7.45-8.32 due to aromatic protons.

EXPERIMENTAL

Melting points were measured on a Gallenkamp electrothermal melting point apparatus. The infrared spectra were recorded in potassium bromide on a Pye-Unicam SP 3-300 infrared spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer at 70 eV. Microanalyses were carried out at the Microanalytical Center, University of Cairo, Giza, Egypt.

Benzothiazol-2-yl-1-ethanonedimethylsulfonium bromide[6] (**1**), 2-methylthiobenzimidazole[15] and α-(benzothiazol-2-yl)cinnamonitrile[16] (**25**) were prepared according to literature procedures.

Benzothiazol-2-ylcarbonylhydroximoyl chloride (2)

To a stirred solution of the sulfonium bromide **1** (6.36 g, 20 mmol) and sodium nitrite (1.4 g, 20 mmol) in dioxane (25 ml) and water (25 ml) was added concentrated hydrochloric acid (50 ml) portionwise over a period of 1h. The reaction mixture was stirred for further 2h at room temperature during which the sulfonium bromide **1** dissolved and a pale yellow product precipitated which was filtered off, washed with water and dried. Recrystallization from toluene afforded **2** in 3.75 g (78% yield); mp. 179-81°C; IR (KBr) ν 3300-3100 (br. OH), 1665 (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42-8.11 (m, 4H, ArH's), 13.74 (br.s, 1H, OH); (Calcd. for $C_9H_5ClN_2O_2S$: C, 44.91; H, 2.09; N, 11.64; S, 13.32. Found: C, 44.78; H, 2.17; N, 11.59; S, 13.28).

Reaction of 2 with o-aminothiophenol and o-phenylenediamine

General procedures. A mixture of the hydroximoyl chloride **2** (0.48 g, 2 mmol) and *o*-aminothiophenol or o-phenylenediamine (2 mmol) in ethanol (15 ml) was refluxed for 10 min, then cooled. The precipitated product was collected by filtration, washed with ethanol, dried and recrystallized from dimethylformamide to afford the benzothiadiazine **3** and benzotriazine **4** derivatives, respectively.

3: Yield (90%); mp. 258-60°C; IR (KBr) ν 3137 (NH), 1670 (C=O), 1595 (C=N) cm^{-1}; (Calcd. for $C_{15}H_9N_3OS_2$: C, 57.85; H, 2.91; N, 13.49; S, 20.59. Found: C, 57.67; H, 2.90; N, 13.28; S, 20.60).

4: Yield (85%); mp. 229-31°C; IR (KBr) ν 3229, 3180 (2 NH), 1674 (C=O), 1598 (C=N) cm^{-1}; (Calcd. for $C_{15}H_{10}N_4OS$: C, 61.20; H, 3.42; N, 19.03; S, 10.89. Found: C, 60.98; H, 3.29; N, 18.91; S, 10.90).

Oxidation of 4.

To a stirred solution of **4** (0.294 g, 1 mmol) in glacial acetic acid (10 ml) was added lead tetraacetate (0.52 g, 1.2 mmol) portionwise. The reaction mixture was stirred at room temperature for 4h, then diluted with water. The solid that precipitated was filtered off, washed with water, dried and finally recrystallized from DMF to afford 3-(benzothiazol-2-yl)-1,2,4-benzotriazine (**7**) (0.23 g, 79 % yield), mp. 313-5°C; IR (KBr) ν 1660 (C=O), 1602 (C=N) cm^{-1}; (Calcd: for $C_{15}H_8N_4OS$: C, 61.63; H, 2.75; N, 19.16; S, 10.96. Found: C, 61.71; H, 2.68; N, 18.99; S, 10.73).

Reaction of 2 with heterocyclic amines

General procedure. A mixture of the hydroximoyl chloride **2** (0.48 g, 2 mmol) and the appropriate heterocyclic amine (2-aminopyridine, 2-aminopyrimidine, 5-amino-3-phenyl-1H-pyrazole, 3-amino-1,2,4-triazole or 2-aminobenzimidazole) (2 mmol) in ethanol (20 ml) was refluxed for 1h, then cooled. The solid so formed was collected by filtration, washed with water and dried. Recrystallization from the proper solvent afforded the compounds **8**, **9**, **12**, **14** and **16**, respectively.

8: Yield (68%); mp. 209-11°C (AcOH); IR (KBr) ν 1675 (C=O), 1626 (C=N) cm^{-1}; (Calcd. for $C_{14}H_8N_4OS$: C, 59.98; H, 2.87; N, 19.99; S, 11.43. Found: C, 59.85; H, 2.94; N, 19.83; S, 11.30).

9: Yield (65%); mp. 204-6°C (AcOH); IR (KBr) ν 1684 (C=O), 1606 (C=N) cm^{-1}; (Calcd. for $C_{13}H_7N_5OS$: C, 55.50, H, 2.50, N, 24.90; S, 11.39. Found: C, 55.56; H, 2.47; N, 24.80; S, 11.47).

12: Yield (55%); mp. 255-7°C (DMF); IR (KBr) ν 3174 (NH), 1667 (C=O), 1626 (C=N) cm^{-1}; (Calcd. for $C_{18}H_{11}N_5OS$: C, 62.59; H, 3.21; N, 20.27; S, 9.28. Found: C, 62.37; H, 3.10; N, 20.41; S, 9.30).

14: Yield (60%); mp. 285-7°C (DMF); IR (KBr) ν 3178 (NH), 1696 (C=O), 1636 (C=N) cm^{-1}; (Calcd. for $C_{11}H_6N_6OS$: C, 48.88; H, 2.23; N, 31.09; S, 11.86. Found: C, 48.76; H, 2.21; N, 31.22; S, 11.75).

16: Yield (58%); mp. 220-2°C (DMF/H_2O); IR (KBr) ν 3228 (NH), 1709 (C=O), 1659 (C=N) cm^{-1}; MS: m/z (%), 319 (M^+, 8.1), 303 (9.2), 287 (15.8), 266 (12.8), 210 (12.2), 154 (36.3), 102 (70); (Calcd. for $C_{16}H_9N_5OS$: C, 60.17; H, 2.84; N, 21.93; S, 10.04. Found: C, 60.09; H, 2.89; N, 21.71; S, 9.93).

Reaction of 2 with 2-methylthiobenzimidazole

A mixture of **2** (0.48 g, 2 mmol) and 2-methylthiobenzimidazole (0.33 g, 2 mmol) in ethanol (20 ml) was refluxed for 2h, then cooled. The yellow coloured precipitate was filtered off, washed with water and dried. Recrystallization from dimethylformamide/water gave 3-(benzothiazol-2-yl)carbonylbenzimidazo[1,2-d]-1,2,4-oxadiazole (**18**) in 63% yield; mp. 181-3°C; IR (KBr) ν 1671 (C=O), 1624, 1602 (2 C=N) cm^{-1}; MS: m/z 320 (M^+, 6.7), 278 (13.4), 188 (29.7), 162 (80.4), 134 (100), 108 (35). (Calcd. for $C_{16}H_8N_4O_2S$: C, 59.99; H, 2.51; N, 17.49; S, 10.00. Found: C, 59.83; H, 2.39; N, 17.35; S, 9.96).

Reaction of 2 with acrylic acid derivatives

To a solution of **2** (0.48 g, 2 mmol) and acrylonitrile or acrylamide (2 mmol) in dry toluene (20 ml) was added triethylamine (0.2 ml) dropwise over a period of 30 min while stirring. The mixture was stirred for 8h, (TLC control). The solvent was evaporated under reduced pressure and the residue was triturated with methanol, filtered off and recrystallized from ethanol to afford the dihydroisoxazoles **21** and **23**, respectively.

21: Yield (73%); mp. 144-6°C; IR (KBr) ν 1660 (C=O), 1597 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (d, J = 9.4 Hz, 2H, CH_2), 5.52 (t, J = 9.4 Hz, 1H, CH), 7.59-8.36 (m, 4H, ArH's); (Calcd. for $C_{12}H_7N_3O_2S$: C, 56.02; H, 2.73; N, 16.33; S, 12.46. Found: C, 55.82; H, 2.64; N, 16.37; S, 12.50).

23: Yield (65%); mp. 203-5°C; IR (KBr) ν 3363, 3179 (NH_2), 1655 (broad two overlapped (C=O), 1590 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (d, J = 8.8 Hz, 2H, CH_2), 5.3 (t, J = 8.8 Hz, 1H, CH), 6.68 (br. s, 2H amide-NH_2), 7.58-8.34 (m, 4H, ArH's); (Calcd. for $C_{12}H_9N_3O_3S$: C, 52.35; H, 3.29; N, 15.26; S, 11.64. Found: C, 52.21; H, 3.36; N, 15.03; S, 11.71).

Partial hydrolysis of 21

The dihydroisoxazole-5-carbonitrile **21** (0.257 g, 1 mmol) was added to concentrated sulphuric acid (10 ml) and the mixture was left to stand at room temperature for 12h, then diluted with water. The solid that precipitated was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded product identical in all respects (mp., mixed mp. and IR spectrum) with compound **23** obtained from the reaction of hydroximoyl chloride **2** with acrylamide.

Reaction of 2 with α-(benzothiazol-2-yl)cinnamonitrile (25)

A mixture of the hydroximoyl chloride **2** (0.48 g, 2 mmol) and α-(benzothiazol-2-yl)cinnamonitrile (**25**) (0.52 g, 2 mmol) in dry toluene (15 ml) and triethylamine (0.2 ml) was stirred for 6h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol. The solid so formed was collected by filtration, washed with ethanol, dried and finally recrystallized from DMF to afford 3-(benzothiazol-2-yl)carbonyl-5-(benzothiazol-2-yl)-4-phenylisoxazole (**27**) in 0.58 g (66% yield), mp. 185-7°C; IR (KBr) ν 1669 (C=O), 1596 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45-8.32 (m, ArH's); MS: m/z, 440 (M^++1,11), 439 (M, 18.6), 278 (3.0), 277 (5.7), 162 (100), 134 (50.7); (Calcd. for $C_{24}H_{13}N_3O_2S_2$: C, 65.58; H, 2.98, N, 9.56; S, 14.58. Found: 65.61; H, 2.94; N, 9.31; S, 14.67).

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