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STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED 2-(Z-STYRYLSULFONYL)-1*H*-IMIDAZOLES AND BENZOTHIAZOLE

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A novel method has been reported involving the synthesis of z-styryl sulfides by the reaction of phenylacetylene with 2-mercpto benzimidazoles and benzthiazole using NaOH as a base in absolute ethanol. On further oxidation with H_2O_2, these resulted in the formation of the desired styryl sulfones in good yields with retention of stereochemistry.

Keywords: 2-Mercaptoimidazoles; phenylacetylene; styryl sulfides; sulfones

INTRODUCTION

The use of styrylsulfones in organic chemistry and medicinal chemistry has increased dramatically.[1] Styrylsulfones have been employed in many synthetic methodologies as intermediates, enabling the preparation of great number of functionalized products, such as natural products and bioactive substances. The functional group is found in numerous biologically interesting compounds. These compounds include anticancer[2–4] and inhibitors for several enzymes such as cyclooxygenase-2(COX-2).[5] In contrast to different methods developed for Z,Z- and E,E-bis(styryl)sulfides and sulfones,[6] less attention was focused on stereoselective synthesis of styryl sulfones. In fact, the latter were reported earlier from our laboratories by condensation of sodium *E*-styrenesulfinates with α-halocarbonyl compounds[7] and 2-halomethyl benzimidazoles.[8] Our sustained interest in this field led us to develop a simple and elegant methodology for a new class of stereoselective styrylsulfones through a facile route. In the literature,[4] it has been reported that the synthesis of the title compounds requires a multistep synthesis (five steps). The first step involved in the preparation of 1H-benzo[d]imidazole-2-thiols is condensation of orthophenylene diamines with CS_2 in the presence of potassium hydroxide (KOH) in ethanol. On reaction with various phenacyl halides in the presence of K_2CO_3 in acetone, these gave 2-(1H-benzo[d]imidazol-2-ylthio)-1-phenylethanones. They were converted to 2-[{1H-bezo[d]imidazol-2-yl}sulfanyl]-1-phenyl-1-ehanols by reduction with sodium borohydride. These compounds were oxidized to get 2-[{1H-bezo [d]imidazol-2-yl}sulfonyl]-1-phenyl-1-ethanols. Ultimately, they were subjected to

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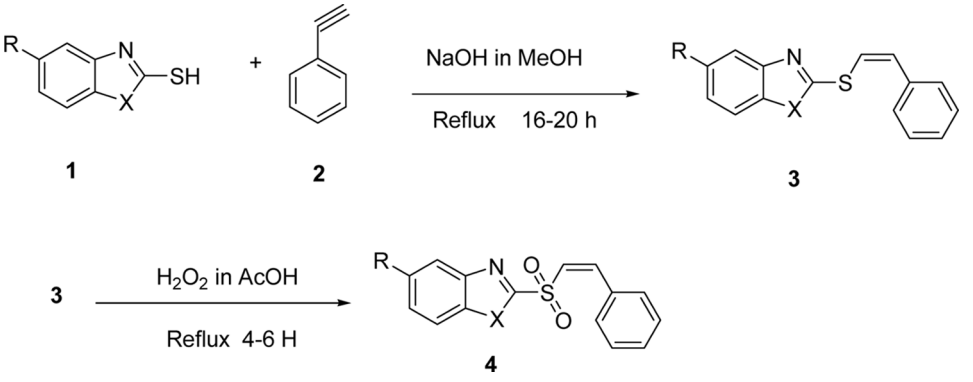
dehydration with methanesulfonyl chloride to afford 1-{sulfonyl}2-{([E)-2-phenyl-1-ethyl]sulfonyl} derivatives, which in turn were demesylated to 1H-benzo[d] imidazole-2-yl[(E)-2-phenyl-1-ehenyl]sulfones with 33% HBr in acetic acid. Recently, it was reported that certain styrylsulfone derivatives like FRI-20 inhibit tumor cell growth and viability by inhibiting the mitogen-activated protein kinase (MAPK) signal transduction pathway. The compounds regulate the extracellular signal-related kinase (ERK) and inhibit the proliferation of breast and prostate tumor cells in a dose-dependent manner without affecting normal cell growth. The cell growth inhibitory activity of this compound is dictated by the nature and position of the functional groups. In view of the wide range of biological activities exhibited by heteryl styrylsulfones, we report the stereoselective synthesis of some heteryl(*Z*)-styryl sulfones. These methodologies are quite useful, but they have some limitations, such as requiring the isolation of intermediates, longer reaction times, and lower overall yields. It is thus evident that there remains a scope for the development of clean and efficient methodologies for the preparation of the title compounds.

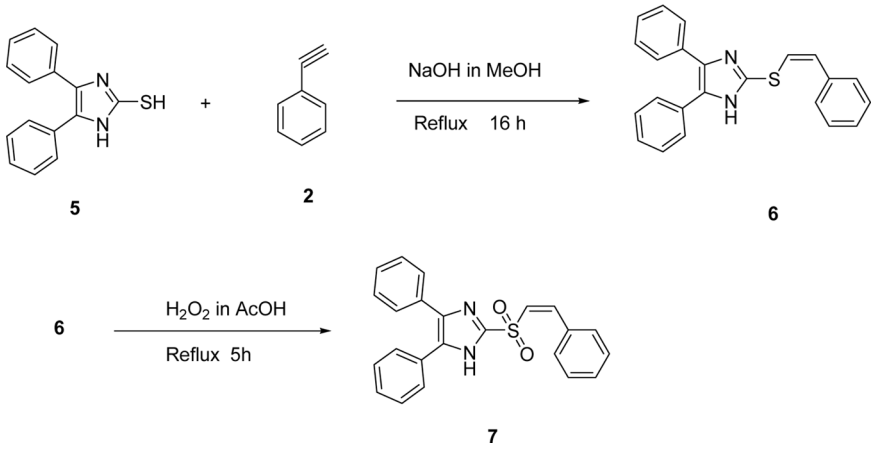
Herein, we report the synthesis of *Z*-styrylsulfones in a two-step reaction (Schemes 1 and 2). The first step involves the nucleophilic addition of the substituted 2-mercapto benzimidazoles, 2-mercapto benzthiazoles, and 4,5 diphenyl-2-mercapto imidazoles to phenyl acetylene in the presence of a base in ethanol. The reflux period varies from 12 to 16 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature, poured into crushed ice, and neutralized with conc. HCl to give 3-(1-phenyl-2-(Z-styrylthio)-1H-imidazol-4-yl)-2H-chromen-2-ones. Oxidation of these sulfides with hydrogen peroxides in acetic acid resulted in the formation of Z-styrylsulfones. The compounds were purified by column chromatography and fully characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and used without further purification unless otherwise stated. Reactions were monitored by



Scheme 1. R = OCH_3, X = NH; R = OCF_2H, X = NH; R = H, X = NH; R = H, X = s.



Scheme 2. Synthesis of 4,5-diphenyl-2-(styrylsulfonyl)-1H-imidazole.

TLC on precoated silica-gel plates (E. Merck, Mumbai, India) with an ultraviolet (UV) indicator. Column chromatography was performed with Merck 70- to 230-mesh silica gel, 60 Å. Yields were of purified products and were not optimized. Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India) and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained with Bruker AM 300- and 200-MHz spectrometers. The chemical shifts are reported in parts per million (δ) downfield using tetramethylsilane (Me_4Si) as internal standard and $CDCl_3$ and dimethylsulfoxide (DMSO-d_6) as the solvents, except where indicated. Spin multiplicities are given as s (singlet), d (doublet), br s (broad singlet), m (multiplet), and q (quartet). Coupling constants (*J* values) were measured in hertz (Hz). CHNS analysis was done using an Carlo Erba EA 1108 automatic elemental analyzer. Mass spectra (EI-MS) were determined on Perkin Elmer (Sciex API-2000, ESI) instrument at 12.5 eV. 4,5-Diphenyl-2-mercaptobenzimidazole was prepared according to the procedure reported in the literature.[9]

General Procedure for the Synthesis of 3-(1-Phenyl-2-(Z-styrylthio)-1H-imidazol-4-yl)-2H-chromen-2-ones

2-Mercaptobenzimidazoles (1 mmol) were added portionwise to a stirred solution of sodium hydroxide (2 mmol) in absolute ethanaol (20 mL) over a period of 0.30 h. On completion of the addition and when the reaction was no longer exothermic, phenylacetylene (1.25 mmol) was added, and the reaction mixture was refluxed for 12–16 h. The reaction mixture was then poured into crushed ice and neutralized with HCl solution. The solid was separated, filtered, washed with water, and dried, and the crude product was purified by column chromatography (ethylacetate/hexane 1:9) to afford the respective (Z)-styrylsulfides. All the other compounds were prepared similarly.

Spectral Data of the Compounds

5-Methoxy-2-(styrylthio)-1*H*-benzo[*d*]imidazole. Yield: 85%, mp 134–136°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1594 (C=C), 1625 (C=N), 3403 (NH), ^1H NMR ($CDCl_3 + DMSO\text{-}d_6$, δ ppm): 3.68 (s, 3H OCH_3), 6.61 (d, 1H, $J = 12$ Hz, styryl), 6.71 (d, 1H, $J = 2$ Hz, Ar-H), 6.74 (s, 1H, Ar-H), 7.02 (d, 1H, $J = 12$ Hz, styryl), 7.16 (m, 1H, Ar-H), 7.26–7.33 (m, 5H, Ar-H). EI-MS 282 (M+). ^{13}C NMR ($CDCl_3 + DMSO\text{-}d_6$, δ ppm) 54.9, 110.6, 119.5, 126.7, 127.3, 127.6, 127.8, 135.2, 146.1, 155.2. Anal. calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.00; H, 4.94; N, 9.95%.

5-(Difluoromethoxy)-2-(styrylthio)-1*H*-benzo[*d*]imidazole. Yield 88%, mp 108–110°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1596 (C=C), 1624 (C=N), 3426 (NH). ^1H NMR ($CDCl_3$, δ ppm): 6.85 (d, 1H, $J = 12$ Hz, styryl), 7.27 (d, 1H, $J = 12$ Hz, styryl), 7.31–7.39 (m, 7H, Ar-H), 7.44 (1, 1H, $OCF_2\underline{H}$), 7.53 (d, 1H, Ar-H, $J = 6$ Hz), 9.72 (s, 1H, NH), EI-MS 319 $(M+H)^+$. Anal. calcd. for $C_{16}H_{12}F_2N_2OS$: C, 60.37; H, 3.80; N, 8.80. Found: C, 60.33; H, 3.85; N, 8.85%.

2-(Styrylthio)-1*H*-benzo[*d*]imidazole. Yield 92%, mp 130–132°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1597 (C=C), 1616 (C=N), 3394 (NH). ^1H NMR ($CDCl_3$, δ ppm): 6.75 (d, 1H, $J = 12$ Hz, styryl), 6.85 (d, 1H, $J = 12$ Hz, styryl), 7.10 (d, 1H, $J = 8$ Hz Ar-H), 7.25–7.45 (m, 8H, Ar-H). Anal. calcd. for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.45; H, 4.83; N, 11.00%.

2-(Styrylthio)benzo[*d*]thiazole. Yield 80%, mp 114–116°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1598 (C=C), 1616 (C=N), 3348 (NH). ^1H NMR ($CDCl_3$, δ ppm): 6.65 (d, 1H, $J = 12$ Hz, styryl), 6.85 (d, 1H, $J = 12$ Hz, styryl), 7.20–7.49 (m, 9H, Ar-H). Anal. calcd. for $C_{15}H_{11}NS_2$: C, 66.88; H, 4.12; N, 5.20. Found: C, 66.84; H, 4.10; N, 5.24%.

4,5-Diphenyl-2-(styrylthio)-1*H*-imidazole. Yield 78%, mp 138–140°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1595 (C=C), 1623 (C=N), 3448 (NH). ^1H NMR ($CDCl_3$, δ ppm): 6.76 (d, 1H, $J = 12$ Hz, styryl), 7.01 (d, 1H, $J = 12$ Hz, styryl), 7.28–7.51 (m, 15H, Ar-H), 12.95 (s, 1H, NH). ^{13}C NMR ($CDCl_3$ δ ppm) 122.7, 127.2, 127.4, 127.6, 127.7, 128.2, 128.4, 128.6, 135.9, 138.7. EI-MS 355 $(M+H)^+$. Anal. calcd. for $C_{23}H_{18}N_2S$: C, 77.93; H, 5.12; N, 7.90. Found: C, 77.90; H, 5.10; N, 7.86%.

General Procedure for the Synthesis of Z-Styrylsulfones

To a solution containing Z-styrylsulfides (15 mmol) in 20 mL of glacial acetic acid, 30% hydrogen peroxide (8 mL) was added dropwise at room temperature. After the addition was complete, the reaction mixture was allowed to stir at room temperature for 24 h. The mixture was then poured into ice-cold water and stirred for 10 min. The solid was separated, filtered, and dried to give the required compound. All the other compounds were prepared similarly.

Spectral Data

5-Methoxy-2-(styrylsulfonyl)-1*H*-benzo[*d*]imidazole. Yield 90%, mp 220–222°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1155, 1356(SO_2), 1508 (C=C), 1601 (C=N), 3434 (NH). ^1H NMR ($CDCl_3$, δ ppm): 3.90 (s, 3H OCH_3), 7.05 (d, 1H, $J = 12$ Hz, styryl), 7.35 (d, 1H, $J = 12$ Hz, styryl), 7.60–7.81 (m, 8H, Ar-H). EI-MS 313 $(M\text{-}H)^+$. Anal. calcd. for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.00; H, 4.38; N, 8.96%.

5-(Difluoromethoxy)-2-(styrylsulfonyl)-1*H*-benzo[*d*]imidazole. Yield 89%, mp 198–200°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1148, 1341 (SO_2), 1594 (C=C), 1626 (C=N), 3588 (NH). ^1H NMR ($CDCl_3$, δ ppm): 7.0 (d, 1H, $J = 12$ Hz, styryl), 7.18 (d, 1H, $J = 12$ Hz, styryl), 7.20–7.40 (m, 9H, Ar-H). Anal. calcd. for $C_{16}H_{12}F_2N_2O_3S$: C, 54.85; H, 3.45; N, 8.00. Found: C, 54.80; H, 3.41; N, 8.10%.

2-(Styrylsulfonyl)-1*H*-benzo[*d*]imidazole. Yield 92%, mp 213–215°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1119, 1344 (SO_2), 1618 (C=N), 1606 (C=C), 3588 (NH). ^1H NMR ($CDCl_3$, δ ppm): 7.15 (d, 1H, $J = 12$ Hz, styryl), 7.45 (d, 1H, $J = 12$ Hz, styryl), 7.60–7.80 (m, 9H, Ar-H). Anal. calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.39; H, 4.28; N, 9.88%.

2-(Styrylsulfonyl)benzo[*d*]thiazole. Yield 88%, mp 208–210°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1141, 1315 (SO_2), 1626 (C=N), 1606 (C=C), 3392 (NH). ^1H NMR ($CDCl_3$, δ ppm): 7.10 (d, 1H, $J = 12$ Hz, styryl), 7.30 (d, 1H, $J = 12$ Hz, styryl), 7.4 (d, 1H, $J = 8$ Hz, Ar-H), 7.50–7.70 (m, 8H, Ar-H). Anal. calcd. for $C_{15}H_{11}NO_2S_2$. C, 59.78; H, 3.68; N, 4.65. Found: C, 59.81; H, 3.70; N, 4.69%.

4,5-Diphenyl-2-(styrylsulfonyl)-1*H*-imidazole. Yield 85%, mp 228–230°C. IR (KBr, $\gamma_{max}\,cm^{-1}$): 1173, 1395 (SO_2), 1509 (C=C), 1601 (C=N), 3430 (NH). ^1H NMR ($CDCl_3$, δ ppm): 7.15 (d, 1H, $J = 12$ Hz, styryl), 7.25 (d, 1H, $J = 12$ Hz, styryl), 7.30–7.45 (m, 15H, Ar-H). EI-MS 387 $(M + H)^+$. Anal. calcd. for $C_{23}H_{18}N_2SO_2$: C, 71.48; H, 4.69; N, 7.25. Found: C, 71.50; H, 4.72; N, 7.12%.

CONCLUSIONS

In conclusion, we have developed a simple, inexpensive, and efficient stereoselective synthesis of styrylsulfones without using any catalyst. The study of the biological activity of these new styrylsulfones is in progress and will be published elsewhere.

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