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Synthesis of Certain New Morpholine Derivatives Bearing a Thiazole Moiety

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Abstract

Morpholine is a synthetic simple heterocyclic organic compound having characteristic functional groups of amine and ether. Feasible physicochemical properties (polarity and solubility), low cost and wide availability make it a suitable candidate for the synthesis of many potent drugs. In our work, we synthesized a new series of thiazole substituted morpholine derivatives in two steps. In the first step, thiourea was synthesized in THF at 70-75°C for 24 h and then in the second step the formation of thiazole ring was ensured in EtOH-DMF (5:5 v/v) at 60°C for 24 hours.

Keywords: morpholine, thiourea, thiazole

INTRODUCTION

Morpholine is a synthetic simple heterocyclic organic compound having characteristic functional groups of amine and ether [1-3]. Feasible physicochemical properties (polarity and solubility), low cost and wide availability make it a suitable candidate for the synthesis of many potent drugs [4]. Some morpholine derivatives have been reported as anticancer, antifungal, antibacterial and antihypertensive agents. In addition, if the nucleus is linked to a lipophilic skeleton, it improves the bioavailability of bioactive compound in oral administration by enhancing its solubility in water [5-10]. Furthermore, thiazole-containing compounds possess significant interest coming from therapeutic point of view because of their utility as antibacterial and antifungal [11, 12], anti-inflammatory [13], antitubercular [14], central nervous system stimulate [15], anti-HIV [16] and antimalarial [17]. In this study, we report the synthesis of new thiazole substituted morpholine derivatives (5a-g).

MATERIALS AND METHODS

Chemistry

All starting materials and reagents were purchased from commercial suppliers. Reactions were monitored by TLC and TLC plates visualized with short wave UV fluorescence (k = 254 nm). Melting points were taken on a Yanagimoto micro-melting point apparatus and were corrected. IR spectra were measured on a SHIMADZU Prestige-21 (200 VCE)

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spectrometer. $^1$H and $^{13}$C NMR spectra were measured on spectrometer at VARIAN Infinity Plus 300 and at 75 MHz, respectively. $^1$H and $^{13}$C chemical shifts are referenced to the internal deuterated solvent. The elemental analysis was carried out with a Leco CHNS-932 (St. Joseph, Michigan) instrument. All chemicals were purchased from Merck (Darmstadt, Germany), Alfa Aesar (Ward Hill, MA) and Sigma-Aldrich (Taufkirchen, Germany).

**Synthesis of morpholine derivatives (5a-g)**

Thiourea derivatives (3) (1 mmol) and acetophenone derivatives (4) (1 mmol) in EtOH-DMF (5:5 v/v) were stirred and refluxed at 60°C for 24 h. After completion of the reaction, the mixture was allowed cooling to room temperature and poured into cold water (50 ml). The product (5a-g) was filtered, washed with water, and dried [19].

**Z(-4-(2-(morpholinoimino)-3-phenyl-2,3-dihydrothiazol-4-yl)benzonitrile (5a):**

Yield 70%, m.p.; 191-193 ˚C. $^1$H NMR (CDCl$_3$, 300 MHz, $\delta$, ppm): 7.50-6.60 (m, 9H, H-Ar); 6.20 (s, 1H, S-CH=C); 3.60 (m,4H, morpholine); 3.28 (m,4H, morpholine). $^{13}$C NMR (DMSO, 75 MHz, $\delta$, ppm): 154.5; 147.5; 147.3; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 129.2; 118.8; 116.3; 115.8; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 54.8 (2C, morpholine). IR (KBr, $\nu$, cm$^{-1}$): 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: C$_{20}$H$_{18}$N$_4$O$_4$S: C, 66.28; H, 5.01; N, 15.46; O, 4.41; S, 9.96. Found: C, 66.38; H, 4.99; N, 16.49; O, 4.93; S, 9.96.

**Z(-N-(4-(4-fluorophenyl)-3-phenylthiazol-2(3H)-ylidene)morpholin-4-amine (5b):**

Yield 73%, m.p. 203-205 ˚C. $^1$H NMR (CDCl$_3$, 300 MHz, $\delta$, ppm): 7.50-7.00 (m, 9H, H-Ar); 6.40 (s, 1H, S-CH=C); 3.60 (m,4H, morpholine); 3.28 (m,4H, morpholine). $^{13}$C NMR (DMSO, 75 MHz, $\delta$, ppm): 154.5; 147.5; 147.4; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 129.2; 118.8; 116.3; 115.8; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 54.8 (2C, morpholine). IR (KBr, $\nu$, cm$^{-1}$): 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: C$_{19}$H$_{18}$FN$_3$O$_3$: C, 66.21; H, 5.10; F, 5.35; N, 11.82; O, 4.50; S, 9.02 Found: C, 66.18; H, 4.90; N, 13.01; O, 4.98; S, 9.96.

**Z(-N-(4-(2,4-dichlorophenyl)-3-phenylthiazol-2(3H)-ylidene)morpholin-4-amine (5c):**

Yield 76%, m.p. 200-202°C. $^1$H NMR (CDCl$_3$, 300 MHz, $\delta$, ppm): 7.50-6.90 (m, 8H, H-Ar); 6.40 (s, 1H, S-CH=C); 3.60 (m,4H, morpholine); 3.28 (m,4H, morpholine). $^{13}$C NMR (DMSO, 75 MHz,
RESULTS AND DISCUSSION

Thiourea derivatives were carried out by conventional synthesis, involves reaction of morpholine, with phenyl thioisocyanate in THF at 60°C for 24 h [18]. After thiourea synthesis, new thiazole substituted morpholine derivatives (5a-g) was synthesized using acetophenone derivatives in EtOH-DMF (Scheme 1) [19].

(Z)-N-(3-phenyl-4-p-tolylthiazol-2(3H)-ylidene)morpholin-4-amine (5g): Yield 85%, m.p. 175--177°C. \(^1\)H NMR (CDCl\(_3\), 300 MHz, \(\delta\), ppm): 7.50-6.68 (m, 9H, H-Ar); 6.45 (s, 1H, S-CH=C); 3.60 (m,4H, morpholine); 3.28 (m,4H, morpholine). \(^13\)C NMR (DMSO, 75 MHz, \(\delta\), ppm): 147.5; 147.3; 141.3; 138.3; 129.6 (2C); 118.8; 116.8; 115.8; 112.6; 106.6; 64.4 (2C, morpholine); 55.9; 54.8 (2C, morpholine). IR (KBr, \(\nu\), cm\(^{-1}\)): 3378 (OH); 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: C\(_{20}\)H\(_{21}\)N\(_3\)O\(_3\)S: C, 61.77; H, 5.18; N, 11.37; O, 12.99; S, 9.68. Found: C, 62.38; H, 6.15; N, 13.49; O, 13.90; S, 9.96.

In the first experiments, the reaction was only carried out in ethanol and the yield was observed.
to be rather low. In later experiments, the reaction was carried out in a mixture of EtOH-DMF (5: 5 v / v) to give product synthesis in yields ranging from 68% to 85%. Further, the compounds formed at the end of the reaction were poured into iced water, it was observed that hydroxyl group-containing compound (5e) was retained in water and obtained with lower yield.

Also, the structures of the compounds were deduced from their IR, $^1$HNMR, $^{13}$CNRMR spectra. In the infrared spectra of compounds (5a-g) around 3061(CH arom.); 1658(C=C); 1614(C=N) cm$^{-1}$ region. 5a and 5e characteristic absorption bands displayed 2257(C≡N) and 3378 (OH-) cm$^{-1}$ region. From the $^1$HNMR spectra of all the compounds showed (-S-CH=C) protons signal around 6.50 ppm; the (= CH proton) peaks on aromatic ring come between 6.68 and 8.00 ppm; and than the eight protons signal of morpholine also showed around 3.60-3.28 ppm. And also characteristic protons signals of 5e, 5f and 5g (-OH, -OMe and –CH$_3$) showed respectively around 6.20, 3.68 and 2.58 ppm. From the $^{13}$C NMR spectra, a sign can be seen about 160.0 ppm for thiazole ring (-N=C-S-).

In conclusion, we have reported the synthesis and characterization of new thiazole substituted morpholine derivatives (5a-g). All spectra and elemental analyses support the structure of the synthesized compounds.

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