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Synthesis of Certain New Morpholine Derivatives Bearing a Thiazole Moiety

Nurcan Berber *[1]

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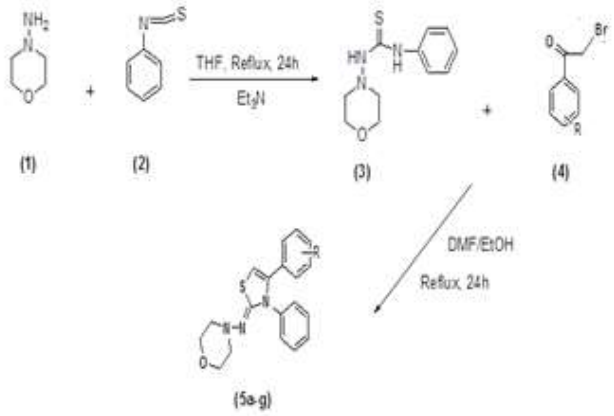
spectrometer.^{1}H and ^{13}C NMR spectra were measured on spectrometer at VARIAN Infinity Plus 300 and at 75 MHz, respectively. ^{1}H and ^{13}C chemical shifts are referenced to the internal deuterated solvent. The elemental analysis was carried out with a Leco CHNS-932 (St. Joseph, Michigan) instrument.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



	R		R
5a	-CN	**5e**	2,3-di-OH
5b	-F	**5f**	4-OMe
5c	2,4-di-Cl	**5g**	4-CH_3
5d	2-NO_2		

Figure 1. Synthesis of new thiazole substituted morpholine derivatives (5a-g)

Synthesis of thiourea derivatives (3)

1 mmol morpholine-4-amine **(1)** and 1 mmol isothiocyanates **(2)** was stirred in THF. After 10 minutes, 2-3 drops of triethylamine were added and stirred in THF at 70-75^{O}C for 24 h. The reaction mixture was stirred for 24 h at room temperature and then the solvent was evaporated. The obtained product was washed with cold water and dried [18].

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 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, 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, δ, 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, υ, cm^{-1}): 3061 (CH arom.); 2257 (C≡N); 1658(C=C); 1614(C=N); Anal. Calcd. For: $C_{20}H_{18}N_4OS$: C, 66.28; H, 5.01; N, 15.46; O, 4.41; S, 8.85. 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 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, 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, δ, ppm): 154.5; 147.5; 147.4; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 129.2; 118.8; 116.3; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 54.8 (2C, morpholine). IR (KBr, υ, cm^{-1}): 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: $C_{19}H_{18}FN_3OS$: C, 64.21; 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. 200-202ºC. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, 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,

δ, ppm): 154.5; 147.5; 147.4; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 118.8; 116.3; 115.8; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 54.8 (2C, morpholine). IR (KBr, υ, cm^{-1}): 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: $C_{19}H_{17}Cl_2N_3OS$: C, 56.16; H, 4.22; Cl, 17.45; N, 10.34; O, 3.94; S, 7.89. Found: C, 58.12; H, 4.99; N, 18.49; O, 4.93; S, 8.96.

(Z)-N-(4-(2-nitrophenyl)-3-phenylthiazol-2(3H)-ylidene)morpholin-4-amine (5d): Yield 72%, m.p. 187--189ºC; ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 8.00-7.00 (m, 9H, H-Ar); 6.50 (s, 1H, S-CH=C); 3,60 (m,4H, morpholine); 3,28 (m,4H, morpholine). ^{13}C NMR (DMSO, 75 MHz, δ, ppm): 154.5; 147.5; 147.4; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 118.8; 116.3; 115.8; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 54.8 (2C, morpholine). IR (KBr, υ, cm^{-1}): 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N, 14.65; O, 12.55; S, 8.38. Found: C, 61.38; H, 4.99; N, 15.49; O, 13.08; S, 9.96.

(Z)-3-(2-(morpholinoimino)-3-phenyl-2, 3-dihydrothiazol-4-yl)benzene-1,2-diol (5e): Yield 68%, m.p. 178--180ºC. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 8.00-7.00 (m, 8H, H-Ar); 6.50 (s, 1H, S-CH=C); 6.20 (2H,OH-) 3,60 (m,4H, morpholine); 3,28 (m,4H, morpholine). ^{13}C NMR (DMSO, 75 MHz, δ, ppm): 154.5; 147.5; 147.3; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 118.8; 116.3; 115.8; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 54.8 (2C, morpholine). IR (KBr, υ, cm^{-1}): 3378 (OH); 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37; O, 12.99; S, 8.68. Found: C, 62.38; H, 6.15; N, 13.49; O, 13.90; S, 9.96.

(Z)-N-(4-(4-methoxyphenyl)-3-phenylthiazol-2(3H)-ylidene)morpholin-4-amine (5f): Yield 75%, m.p. 182--184ºC. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 7.80-7.00 (m, 9H, H-Ar); 6.50 (s, 1H, S-CH=C); 3.68 (3H,-OCH3) 3,60 (m,4H, morpholine); 3,28 (m,4H, morpholine). ^{13}C NMR (DMSO, 75 MHz, δ, ppm): 154.5; 147.5; 147.4; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 118.8; 116.3; 115.8; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 55.9; 54.8 (2C, morpholine). IR (KBr, υ, cm^{-1}): 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.44; O, 8.71; S, 8.73. Found: C, 66.38; H, 4.99; N, 12.89; O, 9.93; S, 10.96.

(Z)-N-(3-phenyl-4-p-tolylthiazol-2(3H)-ylidene)morpholin-4-amine (5g): Yield 85%, m.p. 175--177ºC. ^{1}H NMR ($CDCl_3$, 300 MHz, δ, 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); 2.58 (3H,-CH_3). ^{13}C NMR (DMSO, 75 MHz, δ, ppm): 154.5; 147.5; 147.3; 141.3; 138.6; 132.1 (2C); 129.6 (2C); 118.8; 116.3; 115.8; 112.6; 111.8; 106.6; 64.4 (2C, morpholine); 55.9; 54.8 (2C, morpholine). IR (KBr, υ, cm^{-1}): 3061 (CH arom.); 1658(C=C); 1614(C=N); Anal. Calcd. For: $C_{20}H_{21}N_3OS$: C, 68.35; H, 6.02; N, 11.96; O, 4.55; S, 9.12. Found: C, 69.98; H, 7.99; N, 13.49; O, 4.93; S, 10.03.

RESULTS AND DISCUSSION

Thiourea derivatives were carried out by conventional synthesis, involves reaction of morpholine, with phenyl thioisocyanate in THF at 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].

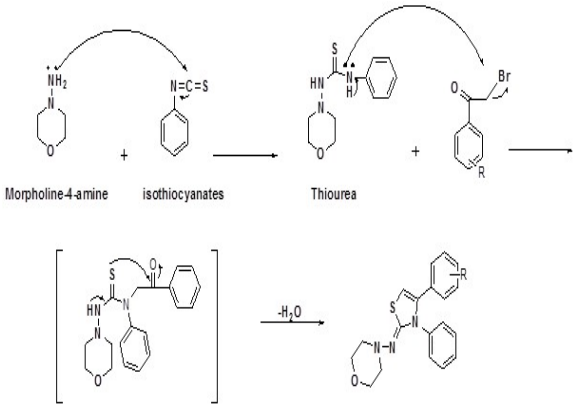


Figure 2. Reaction mechanism of new thiazole substituted morpholine derivatives (5a-g)

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}CNMR 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}NMR 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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