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Synthesis and reactivity of benzoxa(thia)zol-2-thiones: new route to 2-alkylthiobenzoxa(thia)zoles

Abdallah Harizi, Anis Romdhane and Zine Mighri*

Laboratoire de chimie des substances naturelles et de synthèse organique, Département de chimie, Faculté des Sciences de Monastir, 5019 Monastir, Tunisie

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Abstract

The reaction of aromatic primary amines **1** with carbon disulfide in the presence of a catalytic amount of triethylamine followed by treatment with aqueous hydrogen peroxide leads to the corresponding benzoxa-(thia)zol-2-thiones **3a–c** which can be transformed with iminoethers into 2-alkylthiobenzoxa(thia)zoles **5a–h** in good yields (64–85%).

The 2-alkylthiobenzoxa(thia)zoles **5** are crucial heterocyclic substances which have been used intensively in medicinal chemistry and prepared by several ways.[1] In addition, benzoxazole- and benzothiazole-based compounds have shown diverse biological activities.[2–4] As a part of our ongoing work on the use of imidates in heterocyclic synthesis,[5] we report here a new and convenient synthesis of 2-alkylthiobenzoxa(thia)zoles **5** from reaction of phenylimidates with benzoxa(thia)zol-2-thiones **3**.

In order to prepare 2-hydroxy(or 2-mercapto)phenyl isothiocyanates **2** and study their reactivity with imidates, we used the method of Tajima and Li.[6] In fact, the reaction of 2-hydroxy or 2-mercaptophenol with carbon disulfide followed dehydrosulfurization with aqueous hydrogen peroxide but did not lead to the isothiocyanates **2**. These intermediates spontaneously cyclized and could not be isolated[6,7] even on changing the reaction conditions where temperature was less than 0°C and/or a double quantity of acid was used. In all cases the reaction led directly to the corresponding benzoxa(thia)zol-2-thiones **3a–c**[8] known as bactericides.[9]

It has already been proposed[10,11] that there was a tautomeric equilibrium between these structures and that the thione forms were predominant.

The reaction of benzoxa(thia)zol-2-thiones **3** with iminoethers[5] in refluxing THF provided the desired 2-alkylthiobenzoxa(thia)zoles **5** followed by elimination of benzamide. It is conceivable that the reaction starts by the addition of the SH group on the C=N double bond of the

* Corresponding author. Fax: 216 03 500 0278; e-mail: zine.mighri@fsm.rnu.tn

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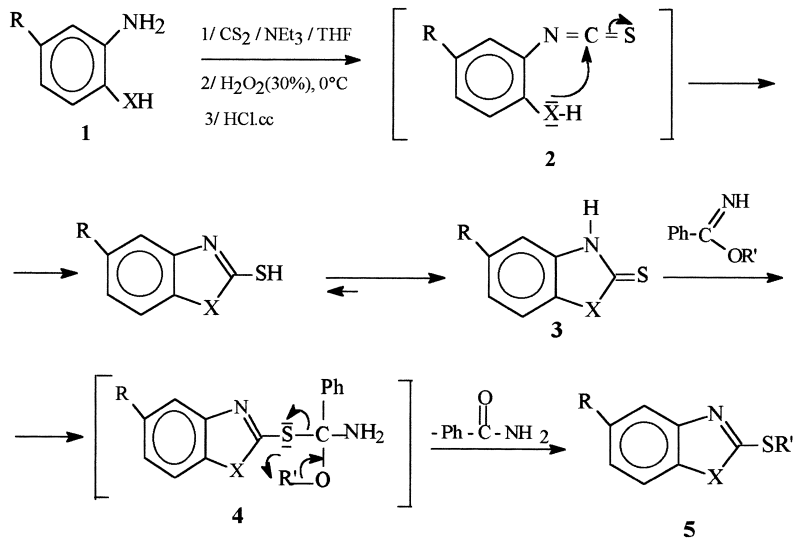
iminoether to give the intermediate **4**. These species rearranged by an intramolecular *s*-alkylation to yield compounds **5**. A possible mechanism of this reaction is shown in Scheme 1.



	3a	3b	3c	5a	5b	5c	5d	5e	5f	5g	5h
X	O	O	S	O	O	O	O	O	S	S	S
R	H	Cl	H	H	H	H	Cl	Cl	H	H	H
R'	-	-	-	Me	Pr	iPr	Et	iPr	Me	Pr	iPr
Yield (%)	67	72	78	64	67	72	75	64	85	63	67

Scheme 1.

In order to find out the best conditions for the synthesis of compounds **5**, we examined the reaction under various conditions by changing the temperature, the solvent and the catalyst; we found that the best yields were obtained when compounds **3** and phenyl imidate were heated under reflux of THF; we note that the use of a catalytic amount of acid or base did not give satisfactory results (less than 10%).

The reaction was conducted until TLC indicated that the starting materials have been completely converted. The purification was performed by silica-gel column chromatography (chloroform:ethyl acetate, 80:20) to give, after elimination of the benzamide, a light oil identified as the product **5**.

The structures of compounds **3** and **5** have been assigned from their analytical data, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.[8,12] In fact, the ^{1}H NMR spectra of product **5** showed: (i) the absence of any D_2O exchangeable signals; and (ii) the presence of the signals corresponding to the introduced R′ groups. The IR spectra also revealed the absence of absorbance due to NH or SH bands. The mass spectra showed essentially the molecular peak ($M^{+\cdot}$) and the ^{13}C NMR spectra of these compounds were also in agreement with the proposed structures.

In conclusion, we present an efficient method for the preparation of benzoxa(thia)zol-2-thiones **3** which react with phenylimidates to give 2-alkylthiobenzoxa(thia)zoles **5** with good yields. The reaction of compounds **3** with other *N*-substituted imidates is actually under progress.

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8. Benzoxa(thia)zol-2-thiones: compound **3** are synthesized according to Tajima's porcedure;[6] compound **3a**: mp 191°C; IR ($CHCl_3$) 1200, 3220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 4H), 8.2 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121, 123.5, 125.4, 128.0, 135.5, 138.2, 176.2; compound **3b**: mp 148°C; IR ($CHCl_3$) 1180, 3180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 3H), 8.8 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.3, 123.2, 125.1, 127.8, 135.2, 138.4, 168.7; compound **3c**: mp 167°C; IR ($CHCl_3$) 1200, 3170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (m, 4H), 10.3 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.2, 123.2, 124.8, 128.2, 135.3, 138.4, 175.6.
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12. Synthesis of 2-alkylthiobenzoxa(thia)zoles **5**. Compound **5a**: oil; IR ($CHCl_3$) 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.9 (s, 3H), 7.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 120.6, 123.3, 125.1, 128.5, 135.3, 138.4, 175.2; MS (70 eV) *m*/*z* (%) 165 (100), 150 (20), 132 (90), 122 (82), 63 (21); compound **5b**: oil; IR ($CHCl_3$) 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, J = 6.9, 3H), 1.9 (m, 2H), 3.3 (t, J = 6.9, 2H), 7.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 22.6, 35.4, 120.3, 123.5, 125.2, 128.4, 135.0, 138.2, 174.8; MS (70 eV) *m*/*z* (%) 193 (8), 151 (100), 122 (7); compound **5c**: oil; IR ($CHCl_3$) 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, J = 7, 6H), 2.2 (m, 1H), 7.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 70.1, 120.5, 123.2, 125.6, 128.3, 135.0, 138.2, 175.2; MS (70 eV) *m*/*z* (%) 193 (5), 151 (100), 122 (8), 41 (10); compound **5d**: oil; IR ($CHCl_3$) 1640 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 1.1 (t, J = 7, 3H), 3.2 (q, J = 7, 2H), 7.5 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 43.0, 119.8, 123.0, 125.6, 128.2, 135.7, 138.2, 174.7; MS (70 eV) *m*/*z* (%) 213 (65), 185 (100), 156 (36), 63 (12); compound **5e**: oil; IR ($CHCl_3$) 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, J = 7, 6H), 2.2 (m, 1H), 7.5 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 70.1, 120.5, 123.0, 125.3, 127.8, 134.9, 138.2, 175.2; MS (70 eV) *m*/*z* (%) 227 (4), 185 (100), 156 (8), 41 (12); compound **5f**: oil; IR ($CHCl_3$) 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 3H), 7.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 121.2, 123.7, 125.6, 128.1, 135.5, 138.2, 174.3; MS (70 eV) *m*/*z* (%) 181 (100); compound **5g**: oil; IR ($CHCl_3$) 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, J = 6.9, 3H), 1.9 (m, 2H), 3.3 (t, J = 6.9, 2H), 7.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 22.6, 35.4, 120.4, 123.4, 125.5, 128.4, 135.6, 138.6, 174.0; MS (70 eV) *m*/*z* (%) 209 (22), 194 (14), 167 (100), 108 (15); compound **5h**: oil; IR ($CHCl_3$) 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.1 (d, J = 7, 6H), 2.2 (m, 1H), 7.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 70.1, 120.5, 123.5, 125.3, 128.5, 135.7, 138.3, 173.7; MS (70 eV) *m*/*z* (%) 209 (2), 123 (68), 105 (100), 77 (38), 56 (12).