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ORIGINAL PAPER

An environmentally benign procedure for the synthesis of substituted 2-thiobenzothiazoles, 2-thiobenzoxazoles, 2-thiobenzimidazoles, and 1,3-oxazolopyridine-2-thiols

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Abstract An improved environmentally benign procedure for the synthesis of substituted 2-thio-benzothia(oxa)zoles, 2-thiobenzimidazoles, and 1,3-oxazolopyridine-2-thiols by cyclization of 2-aminophenols, 2-aminothiophenols, 1,2-phenylenediamines, or 2-amino-3-hydroxypyridines with potassium *O*-ethyldithiocarbonate in PEG 400 or glycerol under directed microwave irradiation is described. The method can be applied to the synthesis of a variety of derivatives.

Keywords 2-Thiobenzothiazoles · 2-Thiobenzoxazoles · 2-Thiobenzimidazoles · 1,3-Oxazolopyridine-2-thiols · Microwave synthesis · Green chemistry

Introduction

Heterocyclic 2-thiones are an important group of compounds with numerous applications as starting materials in the synthesis of various intermediates and final products [1, 2], many of which show a wide range of biological activities [3–6], e.g., as highly effective herbicides [7], fungicides, and bactericides [8, 9]. Furthermore, certain compounds that contain the benzothiazolyl structural moiety have in vitro antitumor properties [10].

One of the most important applications of heterocyclic 2-thiones, which are of particular interest to us, is their use as intermediates [11] in the synthesis of monomethine cyanine dyes. Their structural diversity and the ability to modify this type of structure can produce dyes superior to those currently used [12, 13]. Typically, the main part of the synthetic steps for obtaining dye structures involves the preparation of starting materials. The proposed procedure greatly facilitates the synthesis of such important intermediates.

The known synthetic procedures for obtaining 2-thiobenzoxazoles, 2-thiobenzothiazoles, and 2-thiobenzimidazoles from the corresponding 2-aminophenols, 2-aminothiophenols, and 1,2-phenylenediamines are based on the direct use of toxic and hazardous reagents such as carbon disulfide [1, 14–16]. A solvent-free synthetic methodology to obtain 2-mercaptobenzimidazoles is also known [17]; however, the experimental conditions in this case involve relatively long reaction times (4–24 h), high reaction temperatures, heating under an inert atmosphere, and laborious procedures are usually required for the isolation of the products, which are often obtained in 60–70% yields. The reported methods that involve the use of 2-amino-3-hydroxypyridine as the starting material include heating under reflux with carbon disulfide in the presence of base or direct reaction with potassium *O*-ethyldithiocarbonate in an appropriate solvent [16, 18]. The synthesis of 2-thiobenzoxazoles, 2-thiobenzothiazoles, 2-thiobenzimidazoles, and 1,3-oxazolopyridine-2-thiols from the corresponding 2-aminophenols, 2-aminothiophenols, 1,2-phenylenediamines, and 2-amino-3-hydroxypyridine under directed microwave irradiation has not been reported.

Dedicated to Professor Julio Álvarez-Builla on the occasion of his 65th birthday.

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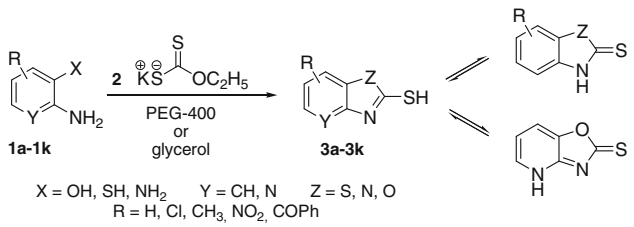
In recent years, a wide range of practical applications have been identified for microwave irradiation in organic synthesis. These applications are attractive as a result of considerable advantages such as the perceptible reduction of the reaction time and the reliable, simple, highly reproducible synthetic procedures that have, in most cases, reduced environmental impact and ensure higher yields of the desired products.

Results and discussion

It was of particular interest to us to study the application of directed microwave irradiation to the cyclization reaction of 1,2-phenylenediamine, 2-amino-3-hydroxypyridines, 2-aminophenols, or 2-aminothiophenols with potassium *O*-ethyldithiocarbonate (Scheme 1). The mechanism of this nucleophilic aromatic substitution reaction and subsequent cyclization has been reported [1, 19]. We envisaged that these processes could be carried out in green solvents, with simple equipment and an easy work-up to provide an environmentally benign approach.



Scheme 1

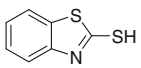
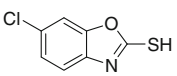
The improved synthetic procedure to obtain substituted hetaryl thiols involves the use of a Biotage microwave system (Initiator 2.5) with directed microwave irradiation.

The cyclization was carried out at low microwave power without a catalyst and in glycerol or PEG 400, which have been confirmed as eco-friendly solvents [20, 21]. In this way the use of toxic solvents was avoided. The application of PEGs and glycerol [22] in synthetic organic chemistry as eco-friendly reaction media represents both an opportunity and a challenge, and the wide availability of these solvents at low cost may give such processes a promising future in green chemistry [21, 23].

On the basis of previously reported results [18] as well as our own experimental data, optimization of the reaction conditions was investigated (Table 1). The best yields for shorter reaction times were obtained when 2.2–2.5 molar equivalents of potassium *O*-ethyldithiocarbonate was used.

The best yields of **3b** and **3e** were obtained on irradiating the reaction mixture for 5 min at 30 W (Table 1, entry 1) or for 2 min at 45 W (Table 1, entry 13) in the presence of glycerol or PEG 400. Complete consumption of the starting materials (i.e., they were no longer detected by TLC) was considered to represent the end of the

Table 1 Optimization of reaction conditions for compounds **3b** and **3e** in the Biotage microwave system

Entry	Compound	Solvent	Power/W	Irradiation time/min	Final temperature reached/°C	Isolated yield/%
1	**3b** 	Glycerol	30	5	140	94
2	**3b**	PEG 400	30	5	127	78
3	**3b**	Glycerol	40	3	155	81
4	**3b**	Glycerol	40	4	185	90
5	**3b**	Glycerol	45	2	163	79
6	**3b**	PEG 400	45	2	165	86
7	**3b**	Glycerol	50	2	170	64
8	**3b**	Glycerol	60	1.5	175	92
9	**3b**	Glycerol	70	1	185	93
10	**3b**	Glycerol	80	1	230	89
11	**3b**	Glycerol	90	1	277	–[a]
12	**3e** 	PEG 400	30	5	130	80
13	**3e**	PEG 400	45	2	165	92
14	**3e**	Glycerol	45	2	167	89
15	**3e**	PEG 400	70	1	200	85
16	**3e**	PEG 400	80	1	228	83

[a] Reaction overheated

Table 2 Starting compounds, reaction conditions, and isolated yields for products **3a–3 k**

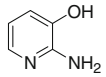
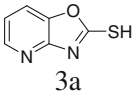
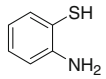
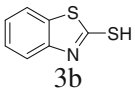
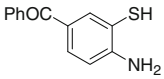
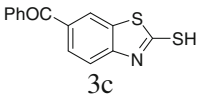
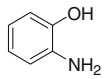
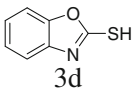
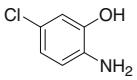
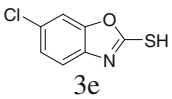
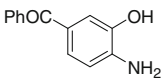
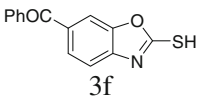
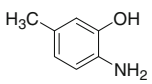
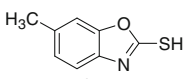
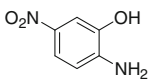
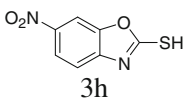
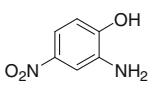
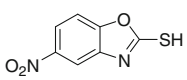
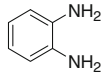
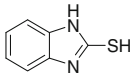
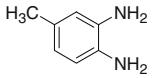
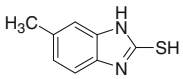
Starting compound	Product	Biotage microwave system					m.p./°C
		Irradiation Time/min	Power/W	Final reached temperature/°C	Yield/%	Solvent	m.p. reported/°C
 1a	 3a	5	30	142	81	Glycerol	241–243 243 [25]
 1b	 3b	5	30	140	94	Glycerol	174–176 167 [26]
 1c	 3c	3	40	152	83	PEG 400	204–205
 1d	 3d	3	40	155	91	Glycerol	193–195 191 [26]
 1e	 3e	2	45	165	92	PEG 400	222–225 224–225 [27]
 1f	 3f	3	40	153	87	PEG 400	208–210/ 210–212 [28]
 1g	 3g	3	40	155	89	Glycerol	207–209/ 209 [29]
 1h	 3h	3	40	152	75	PEG 400	215–216/ 216–217 [30]
 1i	 3i	3	40	153	78	PEG 400	242–244/ 244–245 [31]

Table 2 continued

Starting compound	Product	Biotage microwave system					m.p./°C
		Irradiation Time/min	Power/W	Final reached temperature/°C	Yield/%	Solvent	m.p. reported/°C
 1j	 3j	2	45	163	84	PEG 400	298–301/ 301–303 [32]
 1k	 3k	3	40	155	81	PEG 400	289–291/ 290–92 [17]

reaction. Irradiation at power levels below 30 W did not lead to a sufficiently high temperature for the starting compounds to react and in these cases longer irradiation times were needed. Irradiation at power levels higher than 80 W led to overheating of the reaction mixture (entry 11—temperature in the reaction mixture reached about 260 °C) and a decrease in the yield (Table 1, entry 10). Furthermore, a high pressure resulted when the reaction was carried out in a closed vial at higher power.

The experiments carried out for the optimization of the reaction conditions did not highlight which solvent—glycerol or PEG 400—was better in terms of the product yield or the rate of the reaction. Both solvents are suitable for obtaining the products in good to excellent yields. Glycerol has more advantages from an economical and environmental point of view [22–24].

These conditions were extended to the synthesis of different hetaryl thiols with various substituents (Table 2). The reaction was found to be generally applicable to various 2-aminophenols, 2-aminothiophenols, 1,2-phenylenediamines, and 2-amino-3-hydroxypyridines, regardless of the substituents in the aromatic nucleus (products **3a**–**3k**).

In conclusion, we have demonstrated that heterocyclic 2-thioles can be synthesized from various 2-amino-3-hydroxypyridines, 2-aminophenols, 1,2-phenylene-diamine, or 2-aminothiophenols under green mild reaction conditions with directed microwave irradiation (Table 2) ensuring energy efficiency. The demonstrated approach is highly reproducible and can be applied to the synthesis of a variety of 2-thiohetaryl derivatives with different substituents in the aromatic nucleus and gives products with high purity and in short reaction times. Green solvents were used and the reaction procedure ensures the easy isolation of the products and solvent recyclability.

Experimental

All products were characterized and/or compared with reported data. Melting points were obtained on a Gallenkamp apparatus and are corrected. ^{1}H NMR and ^{13}C NMR spectra of the compounds not reported previously were recorded on a Varian 200 MHz spectrometer in DMSO-d_6 as solvent. Elemental analyses were performed on a Vario III instrument. The reactions were carried out in a Biotage microwave system (Initiator 2.5). Experiments were performed in power-control mode and the temperature was monitored using the built-in calibrated IR sensor. The progress of the reactions was monitored by TLC (Merck F 254 silica gel; dichloromethane/*n*-heptane 4:1). All starting materials and solvents were commercial products from Sigma-Aldrich, except for compounds **1c**, **1f**, and **1g** which were synthesized by known procedures [29, 33, 34]. Analytical samples of the reaction products were obtained by recrystallization from methanol or ethanol.

General procedure for preparation of compounds in the Biotage microwave system

The starting compounds **1a**–**1k** (0.001 mol) and potassium *O*-ethyldithiocarbonate (**2**, 0.0025 mol) were mixed in a 2- to 5-cm^3 microwave vial with 2–3 cm^3 of the appropriate solvent (PEG 400 or glycerol). The reaction mixture was homogenized and pre-stirred for 4 min and irradiated at 30–45 W for a time ranging between 2 and 5 min (Table 2). The product (**3a**–**3k**) was dissolved in 1–2 cm^3 of ethanol and precipitated by dilution with water (50 cm^3), acidified to pH 3–4 with CH_3COOH, filtered, and air-dried.

6-Benzoylbenzothiazole-2-thiol (**3c**, $C_{14}H_9NOS_2$)
M.p.: 204–205 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 14.42$ (s, 1H, SH), 8.52 (s, 1H, ArH), 7.82 (d, 2H, ArH), 7.71 (d, 2H, ArH), 7.43–7.59 (m, 3H, ArH) ppm; ^{13}C NMR (200 MHz, DMSO-d_6): $\delta = 194.92$, 192.35, 144.87, 137.62, 133.03, 130.16, 130.02, 129.76, 129.05, 124.51, 112.59 ppm.

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