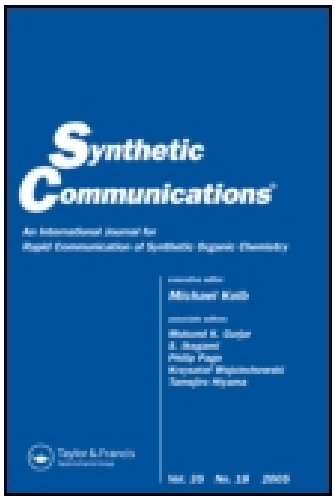

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Eco-Friendly Microwave-Assisted Scaleable Synthesis of 2-Cyanobenzothiazoles via N -Arylimino-1,2,3-dithiazoles

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Eco-Friendly Microwave-Assisted Scaleable Synthesis of 2-Cyanobenzothiazoles via *N*-Arylimino-1,2,3-dithiazoles†

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ABSTRACT

The cyclization procedure of *N*-aryl iminodithiazoles into 2-cyanobenzothiazoles was re-investigated with the aim to develop original and environmentally friendly procedures. In this article, the benefits associated with the microwave methodology are reported and the opportunity to use solvent-free procedures in order to scale

†Dedicated to Professor Charles W. Rees on the occasion of his 75th birthday.

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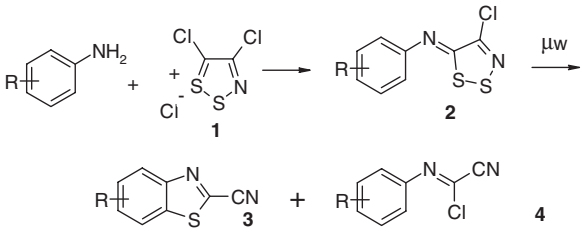
up organic synthesis is studied. The result obtained show that the strong thermal effects due to graphite/microwaves interaction can be efficiently used for the synthesis of heterocyclic molecules for which traditional methods failed or are less attractive.

Key Words: Microwave assisted organic chemistry; Benzothiazoles; Imino-1,2,3-dithiazoles

INTRODUCTION

It is well known that reaction of 4,5-dichoro-1,2,3-dithiazolium chloride **1** with primary aromatic amines in dichloromethane at room temperature allows access to stable *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazoles **2**.[1] These compounds have proved to be highly versatile intermediates in heterocyclic synthesis. Among the transformations studied we published that imino compounds **2** cyclized on vigorous heating to give sulphur, hydrogen chloride, and 2-cyanobenzothiazoles **3** (Sch. 1).[2]

In a search of new polyheterocyclic systems with potential pharmacological value, we showed that extension of the aromatic heterocyclic moiety of the starting imines allowed the preparation of original thiazole derivatives[3–7] which where inspired by natural marine alkaloids (e.g., Dercitine and Kuanoniamines) or by the terrestrial ellipticine. In all of these synthesis the crucial step was the fusion of the thiazole ring with various heterocyclic skeletons and the pharmaceutical development of such promising compounds was limited due to the difficulty to scale up the key step (this reaction was limited to 0.2 g of starting material). In connection with our recent work on the utility of microwaves in organic chemistry,[8–14] we decided to re-investigate the cyclization procedure of the *N*-aryl iminodithiazoles into 2-cyanobenzothiazoles with the aim to develop original and environmentally friendly procedures. In this article,



Scheme 1. Synthesis of benzothiazoles **3** via *N*-arylimino-1,2,3-dithiazoles **2** thermolysis.

we report the benefits associated with the microwave methodology and we study the opportunity to use solvent-free conditions in order to achieve better yields and cleaner reactions that for the purely thermal processes.

RESULTS AND DISCUSSION

Using a standard method applied for the preparation of various *N*-arylimino-1,2,3-dithiazoles, the starting anilines were condensed with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt) in dichloromethane at room temperature to give the desired imines **2** in good yields (1, 2). Studying the chemistry of Appel salt **1** and its derivatives, we previously showed that 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles **2**, which are stable crystalline solids, cyclized by vigorous heating to give sulfur, hydrogen chloride, and 2-cyanobenzothiazoles.[2] It was also published that electron releasing group favored formation of the benzothiazole **3** whilst a strongly electron withdrawing group reduced the yield of **3** dramatically in favor of the cyanoimidoyl chloride **4** which became the major product.

The traditional thermolysis procedure consisted of heating the neat imines **2** under argon at 200–250°C with a metal bath for 1 or 2 min.[2] The amount of starting material was limited to 0.2 g and the products were usually accompanied by complicated mixtures of carbonaceous compounds and impurities, which were difficult to eliminate.

In the course of our work on the synthesis of heterocyclic compounds which possess a thiazole ring,[3–8] various methodologies under conventional conditions or microwave (μw) irradiation where also developed in our group: heating the imines **2** at 200°C in the presence of biphenyl ether (oil bath or μw),[6] at 140°C (oil bath) for two or three days in sealed tube in the presence of toluene,[8] exposing the neat imines to microwaves in a glass vial with a screw-cap lid[8] or heating (oil bath or μw) the imines in pyridine at reflux in the presence of pyridinium tribromide.[5] Whatever method were used, the microwave procedures were more rapid than the purely thermal processes but the amount of the desired benzothiazoles **3** was constant (under 0.2 g of starting imine) and scaling up (up to 0.2 g) the quantity of starting material led to lowest yields of products, accompanied by complicated mixtures of carbonaceous compounds and impurities which were difficult to eliminate even by column chromatography or recrystallization.

Our previous experience in the use of microwave in organic synthesis,[8–14] and our ambition to improve the pharmaceutical development of our compounds, led us to check if there was any possibility for

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improvement in the thermolysis reaction of the imines **2**. Two routes were investigated: the first one involved the use of polar solvents that by themselves are good candidates for microwave heating. The second solvent-free approach includes the use of a support, which may allow a rapid a safe heating of the starting imines **2**.

Microwave Experiments in the Presence of Solvent

Although the use solvents are not recommended for Eco-friendly procedures and that hazards were associated with microwave heating of organic solutions, we have previously showed that the use of homogeneous starting mixtures, in polar solvent, may have a benefit effect on the scale up of various reactions under atmospheric pressure.[9] In order to avoid release of flammable and toxic vapours our strategy consisted to use a polar solvent which possess a high boiling point and may be rapidly heated under microwave irradiation. Among all the solvents tested (*N*,*N*-dimethylformamide: DMF, *N*,*N*-dimethylacetamide: DMA, sulfolane, and tetrahydrofuran), *N*-methylpyrrolidin-2-one (NMP, bp: 204°C) was defined as the best candidate: it is less toxic than DMF and DMA and, in comparison with sulfolane which is difficult to eliminate, it can be easily removed from the reaction mixture by washing with water. The purification of the crude product was then facilitated and it gave the attempted compound in good yields (Table 1).

We have shown that 1 g of the imino-1,2,3-dithiazoles may be heated in one step using this process. It allowed obtaining homogeneous solutions, which may avoid the presence of carbonaceous compounds,

Table 1. Microwave synthesis of benzothiazoles **3**.

Method A: **3** (1 g), *N*-methylpyrrolidin-2-one, μw (150°C, 90 W)[a]				
Starting imine **2** (*R*)		Reaction time (min)	Product **3** (*R*)	Yield of product (%)
a	(H)	1	(H)	49
b	(4-CH_3)	2	(6-CH_3)	55
c	(4-OCH_3)	1	(6-OCH_3)	48
d	(2,5-diCH_3)	1	(4,7-diCH_3)	58
e	(2,5-diOCH_3)	3	(4,7-diOCH_3)	64

[a]In these experiments the amount of **4** was very low and the product difficult to isolate.

and an interesting scaling up was expected. Unfortunately, enhancement (up to 1 g) of the quantity of starting material gave worse results (yields around 30%) and do not allowed to prepare the expected benzothiazoles in good yields.

Microwave Experiments in Solvent-Free Conditions

The solvent-free technique has been claimed to be particularly environmentally friendly, since it avoid the use of solvents, and an easier work-up can be claimed if the support can be removed from the reaction mixture simply by filtration. Graphite is one of the solids most efficiently heated by microwave[15] and is also known for its adsorbing properties of organic molecules. Inspired by a recent work on Friedel-Crafts acylation reactions[16] with carbon graphite as support, we recently showed that the strong thermal effect due to graphite/microwaves interaction can be efficiently use for the synthesis of various polyheterocyclic molecules for which traditional methods failed or are less attractive.[10,11]

Our first approach was to adsorb the starting material on an excess of graphite (3 equiv. by wt.) and to expose the powder obtained to microwaves at various times and power. The best conditions were performed at 150°C by a strict power control (150 W) of the focused microwave irradiation (Table 2).

We have observed that 1 g of the imino-1,2,3-dithiazoles may be heated in one step using this process. Although it may avoid the presence

Table 2. Microwave synthesis of benzothiazoles **3**.

Method B: **3** (5 g), graphite (0.5 g, 10% by wt.), μw (150°C, 150 W)						
Starting imine **2** (*R*)		Time[a] (min)	Product **3** (*R*)	Yield of **3** (%)	Product **4** (*R*)	Yield of **4**
a	(H)	3	(H)	42	(H)	2
b	(4-CH_3)	5	(6-CH_3)	50	(6-CH_3)	4
c	(4-OCH_3)	5	(6-OCH_3)	50[b,c]	(6-OCH_3)	3
d	(2,5-diCH_3)	2	(4,7-diCH_3)	49	(4,7-diCH_3)	6
e	(2,5-diOCH_3)	5	(4,7-diOCH_3)	52	(4,7-diOCH_3)	—

[a]Reaction time.
[b]The yield decreased (35%) in the presence of an excess of graphite (3 equiv. by wt.), in 5 min with 1 g of starting material.
[c]No modification of the yield (50–54%) with longer reaction times (20 or 30 min).

of carbonaceous compounds, the scale up of such a procedure was rapidly limited. As described in the use of NMP, enhancement of the quantity of starting material (up to 1 g) gave worse results and do not allowed to prepare the expected benzothiazoles: the yields became low and various impurities were detected in the final mixture. These results may be linked with the difficulty to obtain a good temperature control at the surface of the solid phase. In some of our experiments, we observed that large quantity of graphite may lead to technical problems (hazardous electric arcs and important local elevation of temperature) regarding controllability and reproductibility (an other problem concern the sublimation of one of the reactants which may be observed in some experiments).

Following the strategy which consist to vary the ratio between the quantity of the reactant and the support (graphite) and in connection with our recent work on heterocyclic reactions with carbon graphite as support[10,11] we discovered that a short (2–5 min) microwave irradiation (150 W) of the starting imino-1,2,3-dithiazoles at 150°C in the presence of a small amount of graphite (10% by weight) afforded the attempted 2-cyanobenzothiazoles. Under similar experimental conditions (with same quantity of starting material, graphite, and same reaction time), a conventional heating allowed the products in very long time.

To our knowledge the use of graphite as fusion accelerator (which assists the initial heating but does not react with other reactants) under microwave irradiation was very rarely described. The yields calculated are quite good, the process is reproducible and mutigrams quantity (5–10 g) of the *N*-arylimino-1,2,3-dithiazoles can be heated in good conditions.

The main interest to use small quantities of graphite is to facilitate the work up procedures, avoiding filtration step (which avoid also the use of solvents). The crude products obtained can be directly purified by column chromatography, or, in some favorable cases, recrystallized in the appropriate solvent.

N-Arylcyanoimidoyl Chlorides **4**

In all the experiments performed, the yield of cyanoimidoyl chlorides **4** was quite constant (2–6%, see table). Working with highest quantity (5 g) of the starting material allowed us to isolate and characterize these by-products, a strategy that is particularly useful in research and development activities.

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CONCLUSION

In conclusion we have described a novel and productive eco-friendly methodology of the synthesis of 2-cyanobenzothiazoles via the starting *N*-arylimino-1,2,3-dithiazoles. In connection with our previous results, we show that the strong thermal effect due to graphite/microwaves interaction can be efficiently use for the synthesis of heterocyclic molecules for which traditional methods failed or are less attractive. This work also confirm that working under focused microwave irradiation need a special attention: (a) the ratio between the quantity of the material and the support (e.g., graphite) may be very important, (b) the use of adapted reactants offer operational, economical, and environmental benefits over conventional methods.

The strategy described in this article is actually developed in our group. Scale-up and technical transposition to various multi-step synthesis are actually in course and will be published later.

EXPERIMENTAL SECTION

General

Commercial reagents were used as received without additional purification. Melting points were determinate on a Köfler melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Paragon 1000PC FT-IR. ^{1}H and ^{13}C NMR were recorded on a JEOL JNM LA 400 (400 MHz) spectrometer (*Centre Commun d'Analyses, Université de La Rochelle*). The mass spectra (HRMS) were recorded on a Varian MAT 311 in the *Centre Régional de Mesures Physiques de l'Ouest* (*CRMPO, Université de Rennes*). Analytical thin layer chromatography (tlc) was performed on Merck 60F-254 silica gel plates. Column chromatography was performed by using Merck silica gel (70–230 mesh).

Focused microwave irradiations were carried out with *Synthewave*™ S402 (Prolabo) or CEM *Discover*™ focused microwave reactor (300W, 2450 MHz, monomode system) which has in situ magnetic variable speed rotation, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control. Experiments may be performed at atmospheric pressure or under pressure in pressure-rated reaction tubes with continuous pressure measurement.

Synthesis of *N*-(4-Chloro-*5H*-1,2,3-dithiazol-5-ylidene) derivatives 2: General Procedure

Appel salt **1** (1.1 equiv.) was added to a solution of aniline derivative (1 g) in dichloromethane (20 mL). The mixture was stirred at room temperature for 2h and then washed twice with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuum. Purification by column chromatography with light petroleum-dichloromethane as the eluent afforded the title compounds **2a–e** as stable yellow solids.

Synthesis of 2-Cyanobenzothiazoles: General Procedures

Method A: in the presence of solvent (NMP). *N*-Arylimino-1,2,3-dithiazole **2** (1 g) was irradiated with *N*-methylpyrrolidin-2-one (10 mL) as the solvent. The irradiation was programmed to maintain a constant temperature (150°C) with a maximal power output of 90 W. After cooling, dichloromethane was added, the organic layer washed with water, dried over $MgSO_4$, and the crude product was purified by column chromatography (silica gel) with light petroleum-dichloromethane as the eluent.

Method B: with carbon graphite as fusion accelerator. Benzothiazoles (5 g) were irradiated in the presence of graphite (0.5 g, 10 wt% to the reactants). The irradiation was programmed to obtain a constant temperature (150°C) with a maximal power output of 150 W. After cooling, the mixture was dissolved in dichloromethane and purified by column chromatography (silica gel). Elution with light petroleum-ethyl acetate gave the corresponding cyanoimidoyle chloride **4** followed by the attempted benzothiazole **3**.

Spectral data for *N*-(4-chloro-*5H*-1,2,3-dithiazol-5-ylidene) derivatives **2** and benzothiazoles **3** and *N*-arylcyanoimidoyl chlorides **4** were consistent with the assigned and previously published structures.[8,17]

Benzothiazole-2-carbonitrile (3a). White needles. M.p.: 80°C (Lit.[1b] 78°C). ν/cm^{-1} 3080, 2230, 1684, 1550, 1460, 1318, 874, 763. ^{1}H NMR ($CDCl_3$): δ 8.24 (dd, 1H, $J = 7.0$, 2.2 Hz), 8.00 (dd, 1H, $J = 7.0$, 2.2 Hz), 7.65 (m, 2H). HRMS (EI): calcd. for $C_8H_4N_2S$ (M^+): 160.0095. Found: 160.0091.

6-Methylbenzothiazole-2-carbonitrile (3b). Yellow needles. M.p.: 92°C (Lit.[1b] 88°C). ν /cm^{-1} 2940, 2228, 1607, 1560, 1474, 1316, 1244, 816. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H, $J = 8.6$ Hz), 7.76 (d, 1H, $J = 1.6$ Hz), 7.46 (dd, 1H, $J = 8.6$, 1.6 Hz). HRMS (EI): calcd. for $C_9H_6N_2S$ (M^+): 174.0251. Found: 174.0252.

6-Methoxybenzothiazole-2-carbonitrile (3c). Yellow needles. M.p.: 126°C (Lit.[8] 130°C). ν/cm^{-1} 3063, 3026, 2983, 2949, 2228, 1600, 1268, 833. ^{1}H NMR ($CDCl_3$): δ 8.08 (d, 1H, $J = 9.2$ Hz), 7.36 (d, 1H, $J = 2.4$ Hz), 7.24 (dd, 1H, $J = 9.2$, 2.4 Hz). HRMS (EI): calcd for $C_9H_6N_2OS$ (M^+): 190.0201. Found: 190.0198.

4,7-Dimethylbenzothiazole-2-carbonitrile (3d). Yellow needles. M.p.: 90°C. ν/cm^{-1} 3018–2928, 2236, 1904, 1476, 1146, 836. ^{1}H NMR ($CDCl_3$): δ 7.35 (d, 1H, $J = 8.0$ Hz), 7.30 (d, 1H, $J = 8.0$ Hz), 2.75 (s, 3H). HRMS (EI): calcd for $C_8H_{10}N_2S$ (M^+): 188.0408. Found: 188.0414.

4,7-Dimethoxybenzothiazole-2-carbonitrile (3e). Yellow needles. M.p.: 174°C (Lit.[4] 174°C). ν/cm^{-1} 2229, 1595, 1501, 1454, 1280, 1140, 1094, 1046, 969. ^{1}H NMR ($CDCl_3$): δ 6.93 (s, 2H), 4.05 (s, 3H), 3.98 (s, 3H). HRMS (EI): calcd for $C_{10}H_8N_2OS$ (M^+): 220.0306. Found: 220.0303.

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