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RESEARCH ARTICLE

Efficient and solvent-free microwave-accelerated synthesis of isothiocyanates using Lawesson's reagent

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A new and practical procedure for the synthesis of isothiocyanates is described. A series of isothiocyanates (ITC) was readily obtained from the corresponding isocyanates (IC) using Lawesson's Reagent (LR) under microwave irradiation and solvent-free conditions.

Keywords: Isocyanates; Isothiocyanates; Lawesson's Reagent; Microwave; Solvent-free

1. Introduction

Isothiocyanates (ITC) are important molecules due to their outstanding role in many fields of organic chemistry. Their influence within the aroma of many edible plants (mustard, cabbage, radish, *etc.*) is well recognized [1–3]. Substantial quantities of isothiocyanates are released upon consumption of a number of cruciferous vegetables. Some of these naturally occurring isothiocyanates such as phenethyl isothiocyanate, benzyl isothiocyanate, and sulforaphane are effective inhibitors of cancer induction [4]. Naturally occurring isothiocyanates have many other interesting biological properties, such as antibacterial, antifungal, antimicrobial, and antioxidant activities [5, 6]. Moreover, they have been described as useful building blocks for the synthesis of many compounds such as thiourethanes [7] and heterocyclic derivatives [8]. Some isothiocyanates have also found applications in the synthesis of agrochemicals and pharmaceuticals [9].

The synthesis of ITC has been extensively studied over the past decades. They can be obtained from different starting materials, in particular isocyanides [10], alkenes [11], aldehydes [12], or organic halides [13]. They are mainly synthesized by acylation of amines using thiocarbonyl reagents like thiophosgene [14], or by condensation of a primary amine with an excess of carbon disulfide, in an organic solvent that is essentially miscible with water, followed by dehydrosulfurization with hydrogen peroxide [15]. Nevertheless, these procedures

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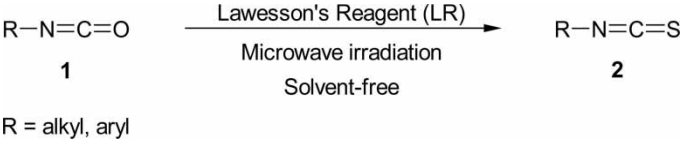
often require excessive amounts of reagents, and toxic reactants (thiophosgene or derivatives) sometimes need to be used. As an interesting alternative, the sulfurization of isocyanates (IC) **1** was considered by using 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, known as Lawesson's Reagent (LR) [16]. Aromatic ITC **2** have been obtained in moderate yields, between 54 and 60%, after reaction in boiling xylenes. Concurrent to this work, Lawesson's Reagent has been used for the efficient conversion of oxygen functionalities (amides [17], lactones [18], and esters, ketones, flavones, or isoflavones [19]) into their corresponding thio analogues, under microwave irradiation and solvent-free conditions. That procedure circumvents the need for an excess of reagent and the use of solvent during the conversion. Based on a recent study combining the advantages of LR and microwave-assisted synthesis [19], the current work deals with a simple and useful microwave procedure for the preparation of a wide variety of aromatic and aliphatic ITC **2**, in good yields (Scheme 1). This article, to the best of our knowledge, is the first involving LR in the synthesis of ITC under microwave irradiation.



SCHEME 1 Synthesis of isothiocyanates ITC using Lawesson's Reagent under microwave irradiation.

2. Results and discussion

In a previous work, we reported that ITC are abundant constituents in Brassicaceous vegetables [3]. We were interested in a simple and convenient procedure to prepare a wide variety of aromatic and aliphatic ITC. These molecules could be used as standard compounds and may allow the identification of unknown ITC in natural extracts.

Aromatic ITC have already been synthesized from IC in a standard procedure using 0.5 molar equivalent of LR, in refluxing anhydrous xylenes, under an inert atmosphere for 6 hours [16]. Since standard procedures require the use of dry aromatic hydrocarbon solvents, lengthy reaction times, harsh reaction conditions, and also have limitations for their applications, we focused on microwave-assisted synthesis. Microwave irradiation has been proven to provide significant rate enhancement in many reactions [20, 21]. Transformations of this kind also appealed to us as they may require only catalytic amounts of reagent, and may also circumvent or limit the formation of side-products, so that a higher product yield can frequently be observed.

Domestic microwave ovens produce regions of dissimilar energy intensity, which results in hot zones. Experiments run in this environment often suffer from poor reproducibility. Consequently all the reactions were conducted in the same vessel, in an optimal thermal area (most intense radiation zone), previously determined using $CoCl_2$ [22]. To study and optimize the process, we selected a suitable model compound: phenyl isocyanate. In our process, the isocyanate was simply mixed with Lawesson's Reagent and the mixture was stirred with a vortex mixer before reaction. The experiment was run by direct exposure of the reaction mixture to microwave irradiation, under solvent-free conditions and using an unmodified household microwave oven. Solvent-free conditions provide the opportunity to perform the reaction in an open vessel, which prevents the risk of high pressure development in reaction apparatus.

The yields were determined by gas chromatography and calculated using hexadecane as an internal standard. All the results are collected in table 1.

The use of a household microwave oven requires working at the maximum wattage in order to obtain continuous irradiation. Our system operates with a maximum delivered power of 850 W. The first experiment was performed during 3 min leading to a 50% yield (table 1, entry 1). When the reaction was repeated during 4 min, a 58% yield was obtained, but GC data showed the formation of a new product, identified by GC-MS as anisole. This could be attributed to the degradation of LR. In addition, a loss of starting material was measured by GC according to the internal standard (table 1, entry 2). In order to make the method milder and to homogenize the reaction mixture, we decided to use a sequential irradiation process: periods of 2 min duration each were selected. Thus, the reaction mixture could be stirred quickly with a vortex mixer between each irradiation period. In a set of experiments (table 1, entries 3–6), the effect of the wattage on the yield was investigated: the best yield was obtained for a lower wattage of 500 or 600 W. To make up for the problem of non-continuous irradiation, the open test tube was put in an alumina bath, which is known to strongly absorb

Table 1. Synthesis of isothiocyanates ITC **2a**–**h** under microwave irradiation (R-NCO 2 mmol, LR 1 mmol, hexadecane 0.44 mmol).

Entry	R	Reaction conditions	Wattage (W)	Time (t/min)	Yield (%)[c]	Yield (%)[d]
1	Phenyl, **2a**	Open vessel	850	1×3[a]	50	
2	Phenyl, **2a**	Open vessel	850	1×4[a]	58	
3	Phenyl, **2a**	Open vessel	850	2×2[a]	52	
4	Phenyl, **2a**	Open vessel	700	2×2[a]	56	
5	Phenyl, **2a**	Open vessel	600	3×2[a]	73	
6	Phenyl, **2a**	Open vessel	500	5×2[a]	70	
7	Phenyl, **2a**	Open vessel, Alumina	600	2×2[a]	78	
8	Phenyl, **2a**	Open vessel, Alumina	500	2×2[a]	77	62
9	Phenyl, **2a**	Closed vessel, Alumina	500	3×2[a]	74	
10	Phenyl, **2a**	Inert atmosphere, Alumina	500	3×2[a]	70	
11	Phenyl, **2a**	Open vessel, Alumina, LR 1.5 mmol	500	2×2[a]	73	
12	Cyclohexyl, **2b**	Open vessel, Alumina	500	2×2[a]	94	71
13	Hexyl, **2c**	Open vessel, Alumina	500	2×2[a]	97	70
14	Butyl, **2d**	Open vessel, Alumina	500	2×2[a]	83	43
15	Benzyl, **2e**	Open vessel, Alumina	500	2×2[a]	92	63
16	*p*-Tolyl, **2f**	Open vessel, Alumina	500	2×2[a]	71	62
17	2-Methoxyphenyl, **2g**	Open vessel, Alumina	500	2×2[a]	51	49
18	3-Chloropropyl, **2h**	Open vessel, Alumina	500	1×1[a]	78	44
19	Phenyl, **2a**	MW oven for organic synthesis, 140 °C	500	$2 + 2$[b]	3	
20	Phenyl, **2a**	MW oven for organic synthesis, 140 °C	500	$5 + 5$[b]	5	
21	Phenyl, **2a**	MW oven for organic synthesis, 140 °C	500	$5 + 10$[b]	14	
22	Phenyl, **2a**	MW oven for organic synthesis, 140 °C	800	$5 + 5$[b]	43	35
23	Phenyl, **2a**	MW oven for organic synthesis, 140 °C	800	$5 + 7$[b]	43	37
24	Phenyl, **2a**	MW oven for organic synthesis, 140 °C	800	$5 + 20$[b]	45	41

[a]Number of irradiations for a given time: 3×2 indicates 3 irradiations of 2 minutes duration each (sequential irradiation process).
[b]$5 + 10$ indicates 5 minutes to reach 140 °C and 10 minutes of reaction at this temperature.
[c]Yield: the moles of ITC produced divided by the moles of starting IC initially introduced, expressed as a percentage. Determined by gas chromatography and calculated from hexadecane used as internal standard.
[d]Isolated yield, after purification on silica gel column.

microwave irradiation [19]. In this case, the reaction proceeded at almost constant temperature, even during the non-continuous irradiation periods. Thus, phenyl isocyanate **1a** was readily transformed into the corresponding ITC **2a** in a satisfying 78% yield (table 1, entries 7 and 8). As reaction conditions have to be compatible with the synthesis of volatile compounds, the mildest process was selected, and further experiments were carried out working at 500 W. To obtain more accurate information on the process, we also ran a set of experiments involving irradiation in a closed vessel (table 1, entry 9), under inert atmosphere (table 1, entry 10), or with 1.5 mmol of LR (table 1, entry 11). No appreciable difference in reaction performance related to these parameters was detected.

Thus, the best conditions are observed when the reaction proceeds in an open vessel, using an alumina bath, with 0.5 molar equiv. of LR, after 2 irradiation periods of 2 min duration each with a selected power of 500 W (table 1, entry 8). The same procedure was employed for the thionation of various aromatic and aliphatic isocyanates **1b–h** and the results are summarized in table 1. Each experiment was performed twice, first using internal standardization (hexadecane, 0.44 mmol) in order to calculate the overall yield, and was then repeated without this reference to isolate the target molecule and determine the isolated yield of each product. The corresponding isothiocyanates **2b–h** were obtained in a 43–71% yield range. The results were closely dependent on the volatility of the expected ITC: as a result, butyl isothiocyanate (the most volatile compound, table 1, entry 14) and cyclohexyl isothiocyanate (table 1, entry 12) were respectively isolated in 43 and 71% yield. The procedure could be extrapolated to the preparation of functionalised ITC such as 3-chloropropyl isothiocyanate **2h** (table 1, entry 18). This kind of building block can be of great interest for the synthesis of alkylthioalkyl ITC, commonly found in many foodstuffs [1–3]. All the reaction products were characterized by NMR and MS.

When working with the household microwave oven, the internal temperature of the mixture reached 135–145 °C at the end of the reaction, depending on the substrate. The reaction was thus repeated in a multimode microwave oven designed for organic synthesis (table 1, entries 19–24). In order to get a comparison with the results previously obtained in the household oven, the experiment was performed during 4 min, at 140 °C and 500 W (table 1, entry 19): the temperature of 140 °C was reached after 2 min of irradiation; this temperature was kept constant thanks to fluctuations of the wattage, and the reaction proceeded for another 2 min at that temperature. As indicated in table 1, only a 3% yield was observed. Taking into account this observation, a series of reactions was carried out with longer reaction times (table 1, entries 20 and 21) and/or higher wattage (table 1, entries 22–24). The results thus obtained showed that a satisfying yield was obtained only at 800 W. However, the isolated yield of phenyl isothiocyanate **2a** didn't exceed 41%. This low yield can be explained by considering the onset of degradation or side reactions. This assumption was confirmed with entry 24: variation in reaction time did not show any effect on the progress of the reaction. From this result, it appears that use of a domestic oven is more convenient to carry out our procedure. This difference is probably related to the alumina and the non-continuous irradiation in the household oven.

Another set of experiments was investigated in order to check the advantage of microwave irradiation on the process. The reaction was performed with conventional heating (table 2), in an oil-bath, at 140 °C, keeping all other parameters constant (isocyanate **1a–c** 2 mmol, LR 1 mmol, open vessel). As previously, yields were determined by gas chromatography including an internal standardization (hexadecane). After a reaction time similar to the irradiation period, *i.e.* 4 min, the reaction reached between 23 and 42% yield only (table 2, entries 1, 3, and 4). To observe the same yield as that obtained by the microwave procedure, a reaction time of more than 30 min was required (table 2, entries 2 and 5). As a result, we can assert that the reaction

Table 2. Synthesis of isothiocyanates ITC **2a–c** under conventional heating (temperature 140 °C).

Entry	R	Time (t/min)	Yield (%)[a]
1	Phenyl, **2a**	4	23
2	Phenyl, **2a**	30	70
3	Cyclohexyl, **2b**	4	42
4	Hexyl, **2c**	4	35
5	Hexyl, **2c**	30	80

[a]Determined by gas chromatography and calculated from hexadecane used as internal standard.

is clearly accelerated under microwave irradiation. Since thionation has been described as a polar transition-state reaction [23], it is supposed to be accelerated under microwave irradiation [24]. That could explain the significant rate enhancement observed in the strategy we have developed.

3. Conclusions

We have shown that the combination of LR and microwave irradiation is a practical and mild synthetic methodology for obtaining aliphatic or aromatic isothiocyanates in good yields. The strategy is simple, rapid, solvent free, and the work-up is clean and not time-consuming. This procedure can be employed for a 'multistandard synthesis', as part of the identification of new target molecules in natural extracts or as part of the preparation of a series of standard compounds. It can be used also as a convenient tool in total synthesis.

4. Experimental

Solvents were dried by conventional methods [25]. Chromatographic separations were performed using 40–63 mesh (VWR) silica gel, and eluted with distilled solvents. TLC was carried out on SDS precoated silica plates (60/15 μm layer thickness). Reactions under microwave irradiation were performed in a Samsung M181DN domestic microwave oven. Some experiments were achieved in a Milestone MW Laboratory System multimode microwave oven for organic synthesis. The temperatures of the reactions performed with the domestic microwave oven or conventional heating were measured by direct introduction of a thermometer into the reaction mixture. For the domestic oven, the measurement was recorded immediately at the end of the irradiation period, with a thermometer previously heated to 120 °C in order to minimize heat losses. The Milestone microwave oven was equipped with an optical fibre for the internal control of the temperature of the mixture during the experiments. In each case, at the end of the reaction, the mixture was a homogeneous liquid solution, so the temperature was easily determined. Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 200 FT spectrometer at room temperature. The ^{1}H chemical shifts are reported as ppm downfield from tetramethylsilane (TMS), and the ^{13}C chemical shifts are referenced to the solvent peak $CDCl_3$ (δ_C 77.7 ppm). Each compound was analysed by GC and GC-MS using Hewlett-Packard 5890/5970A systems, with an HP5 column (30 m × 0.32 mm fused silica capillary column; film thickness 0.25 μm). Mass spectra were obtained by electron ionization at 70 eV of the mass range 35–400 Da.

4.1 *Microwave-assisted synthesis. General procedure*

An isocyanate **1a**–**h** (2 mmol) and Lawesson's Reagent (0.404 g, 1 mmol) were mixed in an open test tube placed in an alumina bath. The reaction mixture was exposed to microwave irradiation, in an unmodified household microwave oven, with 2 irradiation periods of 2 min duration each, at 500 W. The mixture was stirred for 5 seconds with a vortex mixer between each irradiation period. After cooling to room temperature, the mixture was dissolved in dichloromethane (5 mL) and adsorbed on silica gel. ITC **2a**–**h** were purified by column chromatography with light petroleum (40–60 °C) as the eluent (70 mL), and isolated with at least 98% of purity (GC analysis). All the ITC **2a**–**h** are already known and commercially available.

4.2 *Data for compounds 2a–h*

Phenyl isothiocyanate 2a. Colourless oil, yield 62%. ^{1}H NMR ($CDCl_3$) δ 7.08–7.30 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$) δ_C 126.18 (C^3), 127.76 (C^5), 129.99 (C^4), 131.65 (C^2), 135.72 (C^1). MS (EI, 70 eV) m/z (%) 137 ($M^+ + 2$, 5.1), 136 ($M^+ + 1$, 9.0), 135 (M^+, 100), 77 (46.8), 76 (5.5), 75 (4.9), 74 (5.9), 64 (5.6), 63 (5.5), 51 (23.7), 50 (14.3), 39 (5.2).

Cyclohexyl isothiocyanate 2b. Colourless oil, yield 71%. ^{1}H NMR ($CDCl_3$) δ 1.37–1.91 (m, 10H, H^{3-5}), 3.65–3.77 (m, 1H, H^2). ^{13}C NMR ($CDCl_3$) δ_C 23.64 (C^4), 25.46 (C^5), 33.62 (C^3), 55.83 (C^2), 130.10 (C^1). MS (EI, 70 eV) m/z (%) 143 ($M^+ + 2$, 4.8), 142 ($M^+ + 1$, 8.9), 141 (M^+, 100), 83 (53.4), 82 (24.8), 72 (15.9), 67 (26.2), 58 (12.8), 55 (85.8), 53 (14.3), 41 (43.8), 39 (39.7).

Hexyl isothiocyanate 2c. Colourless oil, yield 70%. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, H^7), 1.27–1.49 (m, 6H, H^{4-6}), 1.70 (quint, 2H, H^3), 3.52 (t, 2H, H^2). ^{13}C NMR ($CDCl_3$) δ_C 13.95 (C^7), 22.46 (C^6), 26.25 (C^5), 29.96 (C^4), 30.99 (C^3), 45.10 (C^2), 129.51 (C^1). MS (EI, 70 eV) m/z (%) 143 (M^+, 4.3), 142 (6.0), 128 (7.0), 115 (100), 114 (23.2), 110 (24.9), 100 (20.5), 82 (8.2), 72 (58.4), 55 (17.5), 43 (33.8), 41 (42.8), 39 (26.8).

Butyl isothiocyanate 2d. Colourless oil, yield 43%. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H, H^5), 1.46 (qt, 2H, H^4), 1.69 (tt, 2H, H^3), 3.53 (t, 2H, H^2). ^{13}C NMR ($CDCl_3$) δ_C 13.28 (C^5), 19.80 (C^4), 31.94 (C^3), 44.79 (C^2), 129.78 (C^1). MS (EI, 70 eV) m/z (%) 117 ($M^+ + 2$, 4.8), 116 ($M^+ + 1$, 7.8), 115 (M^+, 100), 114 (27.1), 100 (12.1), 72 (86.4), 60 (18.5), 59 (24.4), 57 (31.1), 56 (22.0), 45 (24.8), 41 (92.1), 39 (44.8).

Benzyl isothiocyanate 2e. Colourless oil, yield 63%. ^{1}H NMR ($CDCl_3$) δ 4.71 (s, 2H, H^2), 7.29–7.40 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$) δ_C 48.64 (C^2), 126.81 (C^4), 128.34 (C^6), 128.94 (C^5), 132.14 (C^1), 134.21 (C^3). MS (EI, 70 eV) m/z (%) 151 ($M^+ + 2$, 0.8), 150 ($M^+ + 1$, 1.7), 149 ($M^{\bullet+}$, 17.4), 121 (2.7), 92 (7.7), 91 (100), 89 (7.0), 72 (1.5), 65 (18.1), 63 (7.5), 51 (7.0), 50 (4.7), 39 (9.1).

***p*-Tolyl isothiocyanate 2f.** White solid, mp 25 °C (Lit[26]: 25–26 °C), yield 62%. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, H^6), 7.08–7.18 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$) δ_C 21.20 (C^6), 125.50 (C_3), 128.36 (C^2), 130.12 (C^4), 134.49 (C^1), 137.50 (C^5). MS (EI, 70 eV) m/z (%) 151 ($M^+ + 2$, 4.8), 150 ($M^+ + 1$, 11.2), 149 (M^+, 100), 148 (35.3), 121 (6.5), 117 (6.5), 91 (86.5), 89 (13.5), 65 (15.1), 63 (14.1), 51 (8.9), 39 (12.8).

2-Methoxyphenyl isothiocyanate 2g. Colourless oil, yield 49%. ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H, H^8), 6.86 (td, 1H, H^6), 6.91 (dd, 1H, H^4), 7.11 (dd, 1H, H^7), 7.22 (td, 1H, H^5). ^{13}C NMR ($CDCl_3$) δ_C 55.94 (C^8), 111.47 (C^4), 120.65 (C^2, C^6), 125.45 (C^7), 128.23 (C^5), 139.69 (C^1), 155.98 (C^3). MS (EI, 70 eV) m/z (%) 167 ($M^{\bullet+}$ + 2, 5.1), 166 ($M^{\bullet+}$ + 1, 10.2), 165 ($M^{\bullet+}$, 100), 150 (30.5), 132 (31.0), 122 (81.4), 120 (7.9), 78 (10.2), 64 (10.1), 63 (17.3), 51 (11.3), 50 (8.6), 39 (9.2).

3-Chloropropyl isothiocyanate 2h. Colourless oil, yield 44%. ^{1}H NMR ($CDCl_3$) δ 2.07 (q, 2H, H^3), 3.62 (t, 2H, H^2), 3.70 (t, 2H, H^4). ^{13}C NMR ($CDCl_3$) δ_C 32.81 (C^3), 41.53 (C^2), 42.56 (C^4), 131.60 (C^1). MS (EI, 70 eV) m/z (%) 137 (M^+ + 2, 28.9), 135 (M^+, 77.9), 100 (19.9), 86 (12.4), 76 (27.8), 72 (100), 59 (10.7), 49 (12.8), 45 (13.7), 41 (76.1), 39 (30.8).

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