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Solvent-free synthesis of 2-amino-4-arylthiazoles under microwave irradiation

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ABSTRACT

2-Amino-4-arylthiazoles were prepared in a one-pot solvent-free procedure by reaction of *p*-substituted acetophenones with thiourea and iodine under microwave irradiation.

It is well known that thiazole derivatives are important compounds in medicinal chemistry[1] due to their broad range of biological activities. This type of heterocycles have shown a wide variety of pharmacoactive properties as anti-inflammatory,[2] anti-tubercular,[3] anti-bacterial,[4] fungicidal,[5] local anaesthetic,[6] tranquilizers,[7] insecticidal,[8] anti-microbial,[9] anti-tumor[10] and diuretic.[11] Considerable efforts have been devoted to the synthesis of this type of compounds.[12] The Hantzsch thiazole synthesis is one of the most used methodologies to generate 2-aminothiazole ring system.[13] Although, there are several papers that report their preparation in good yields,[14] these methods frequently use an α-bromoketone prepared in a previous stage, a solvent and/or long reaction times.[15] Previously, we reported the synthesis of seven 2-amino-4-(4′-substituted phenyl)-1,3-thiazoles via a one-pot single-stage solid phase reaction.[9] Taking in consideration the advantages of microwave heating on solvent-free reactions,[16] in this Letter we report the rapid solventless synthesis of a series of 2-amino-4-aryl-1,3-thiazoles under microwave irradiation, prepared from the cyclocondensation of *p*-substituted acetophenones with thiourea and iodine.

The first part of the study was aimed at optimizing the reaction conditions. To do this, we started from the Hantzsch's modified method reported for the synthesis of 2-aminothiazoles.[9] In this sense and as depicted in Table 1 (entries 1–3), three reactions were performed under controlled temperature (140 °C, 10 W) to set the time for completion of the reaction. Subsequently, in an effort to obtain an improvement in yield with 10 min of reaction, a lower and higher temperature (Table 1, entries 4 and 5) were evaluated.

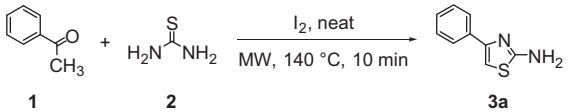
Through these experiments, a temperature of 140 °C at 50 W and a time of 10 min were the optimal conditions to complete the reaction. Under these conditions, 2-amino-4-phenylthiazole was obtained with good yields as shown in Scheme 1.

Following the reaction optimization, we decided to explore the influence of the proportion of thiourea and iodine in the reaction

Table 1
Optimization of reaction conditions for synthesis of 2-amino-4-phenylthiazole **3a**

Entry	Temp (°C)	Time (min)	Power (W)	Thiourea (equiv)	Iodine (equiv)	Yield[a] (%)
1	140	10	10	2	1	67
2	140	20	10	2	1	65
3	140	30	10	2	1	66
4	120	10	10	2	1	37
5	160	10	10	2	1	0
6	140	10	50	1	1	22
7	140	10	50	1.5	1	53
8	140	10	50	2	0.25	10
9	140	10	50	2	0.75	24
10	140	10	50	2	1	88

[a] Yield of the pure product.



Scheme 1. Microwave-assisted solvent-free synthesis of 2-amino-4-phenylthiazole.

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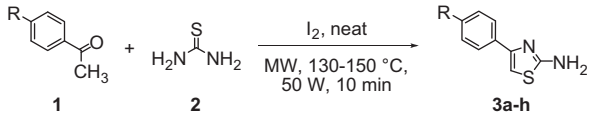
Table 2
Synthesis of 2-amino-4-arylthiazole from *p*-substituted acetophenones, thiourea and iodine



1 2 3a-h

R = H, Me, OMe, OH, NH_2, Cl, Br, NO_2

Entry	R	Product[a]	Temp (°C)	Microwave yield[b] (%)	Conventional yield[c] (%)
1	H	**3a**	140	88	65
2	Me	**3b**	150	80	64
3	OMe	**3c**	140	80	54
4	OH	**3d**	140	62	[d]
5	NH_2	**3e**	130	40	[d]
6	Cl	**3f**	150	91	81
7	Br	**3g**	150	99	85
8	NO_2	**3h**	145	99	91

[a] Spectroscopic data are consistent with those reported in the literature.[21]
[b] Yield after 10 min of irradiation time.
[c] Yield after 120 min under conventional heating.
[d] No product observed.

mixture. In accordance with the literature,[17] two moles of thiourea must be present for each mole of halogen. Varying the proportion of thiourea, it was found that at lower concentration the yield of thiazole was poor (Table 1, entries 6 and 7). King and Ryden reported that the formation of a thiazole from acetophenones and thiourea can be accomplished by an oxidative process. So, when the reaction is promoted by iodine it appears to proceed through a dimer of thiourea.[18] This fact explains partially the need of two equivalents of thiourea. In order to determine the most appropriate iodine concentration towards the synthesis of 2-aminothiazoles, different iodine amounts were examined. A significant reduction in yields was observed when using less than one equivalent of iodine (Table 1, entries 8 and 9). Thus, it was found that two equivalents of thiourea **2** and one equivalent of iodine afforded the corresponding 2-amino-4-phenylthiazole with the better yields (88%, see Table 1, entry 10).

With these results in hand, we extended our studies using different *p*-substituted acetophenones (Table 2).[19] It is possible to appreciate that both the temperature as well as the thiazole ring formation depend on the electronic effects of the *p*-phenyl substituent. Thus electro-releasing groups decrease the yield of the reaction (Table 2, entries 2–5) as they increase the electron density on the carbonyl group, hindering the cyclocondensation mechanism. Accordingly, acetophenones with *p*-substitution by slightly electron donors gave acceptable yields (Table 2, entries 1–3) and strong electron-releasing groups with protic hydrogens gave lower yields (entries 4 and 5). On the other hand excellent yields were obtained with *p*-substituted acetophenones with electron-withdrawing substituents (Table 2, entries 6–8).

For comparison purposes, the reactions were also carried out using a thermostated oil-bath under the same conditions but for a longer (optimized) period of time[20] to ascertain whether the microwave heating improves the yield. It was found that lower yields were obtained using oil-bath heating rather than the microwave activated method (Table 2). In addition the reaction time for microwave-assisted reactions was twelve times shorter than the same reactions in all of our studied substrates. As a result when the reaction time was shortened, thermal decomposition was also minimized, resulting in higher isolated yields.

In conclusion, there was an improvement in yields of the condensation of *p*-substituted acetophenones with thiourea and iodine to obtain 2-amino-4-(*p*-substituted-phenyl)-1,3-thiazoles using microwave heating under solvent-free conditions. Besides, the technique has the advantage of being simple and allows the synthesis of thiazole compounds in a minimum of time.

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19. General procedure for the synthesis of 2-amino-4-aryl-1,3-thiazoles (**3a**–**h**) Method A: A mixture of *p*-substituted acetophenone **1** (8.6 mmol), thiourea **2** (17.2 mmol, 1.3 g) and iodine (8.6 mmol, 2.2 g) was placed in an open vessel containing a Teflon coated stir bar. The vessel was placed in the microwave cavity (CEM, Discover) and subjected to MW irradiation (50 W) at indicated temperature for 10 min. After the completion of the reaction, the crude mixture was cooled to 70 °C and then it was triturated, filtered and washed with Et_2O. The crude product was dissolved in hot water and the pH was adjusted to 11–12 with NH_4OH. The precipitated was filtered and crystallized from EtOH–H_2O (1:4) to obtain the 2-amino-4-aryl-1,3-thiazole (**3a**–**h**).

Method B: Thiourea **2** (17.2 mmol, 1.3 g) and iodine (8.6 mmol, 2.2 g) were triturated and mixed with *p*-substituted acetophenone **1** (8.6 mmol). The reaction mixture was stirred and heated at 120 °C on a thermostated oil-bath for 120 min. After the completion of the reaction, the crude mixture was cooled to 70 °C and then it was triturated, filtered and washed with Et_2O. The crude product was dissolved in hot water and the pH was adjusted to 11–12 with NH_4OH. The precipitate was filtered and crystallized from EtOH–H_2O (1:4) to obtain the 2-amino-4-aryl-1,3-thiazole (**3a**–**h**).

20. For the control experiments thiazole derivatives were synthesized following the same one-pot protocol with the exception of using conventional heating in an oil-bath instead of microwave irradiation. The reaction time was the same as for the microwave activated procedure, however because the yields obtained were low, the reaction time was extended to 120 min.
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