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An improved synthesis of substituted benzo[*b*]thiophenes using microwave irradiation

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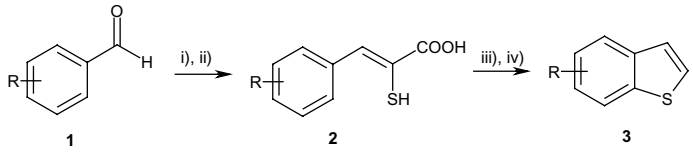
Abstract—An easy and high-yielding method for the synthesis of substituted benzo[*b*]thiophenes using microwave irradiation is described.

Benzo[*b*]thiophenes have always been of interest to medicinal chemists and can be found in a number of marketed drugs such as Sertaconazole (Ginedermofix™), Zileuton (Leutrol™) and Raloxifene (Evista™).

One of the classical syntheses of benzo[*b*]thiophenes starts from commercially available thiophenols, reacting with bromoacetaldehyde dimethyl acetal, followed by cyclisation using strong acid. The reaction steps are generally high yielding but when starting with 3-substituted thiophenols the route gives a mixture of 4- and 6-substituted benzo[*b*]thiophenes.[1] The regioisomers are generally difficult to separate so necessitating the application of an alternative route to access these substitution patterns. One such method has been described starting from commercially available benzaldehydes (Scheme 1).[2] Benzaldehydes **1** can be reacted with rhodanine and after hydrolysis with sodium hydroxide afford, in good yields, the corresponding β-aryl-α-mercaptoacrylic acids **2**. The acids **2** can then be cyclised and decarboxylated to give the corresponding benzo[*b*]thiophenes **3**. This route allows the preparation of 4- or 6-substituted benzo[*b*]thiophenes, but has the disadvantage that both reactions require high temperatures, moderate to long reaction times and are low yielding.

In this paper, we describe how both the cyclisation and the subsequent decarboxylation were improved using microwave technology.

Microwave technology has opened up new horizons for chemists. It enables chemical reactions to be performed very conveniently at high temperatures and, in most cases, under pressure. Using conventional heating, the energy must first be conducted through the walls of the vessel containing the reactants, whereas microwaves heat the contents directly, allowing the temperature to rise much faster, so boosting reaction rates. Another characteristic of microwaves is their ability to superheat solvents to temperatures well in excess of their normal boiling points; this is due to the even spread of heat



Scheme 1. (i) Rhodanine, AcOH; (ii) NaOH; (iii) cyclisation; (iv) decarboxylation.

Keywords: Benzothiophenes; Cyclisation; Decarboxylation; Microwave irradiation.
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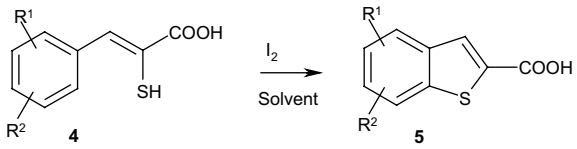
Table 1.



Entry	R^1	R^2	Solvent	Power (W)	Temp (°C)	Time (min)	Yield (%)[a]
1	4-OMe	5-F	DME	300	120	25	67
2	4-Me	H	Dioxane	400	180	8	80
3	4-Me	6-Br	DME	400	160	5	77
4	4-Me	7-OMe	DME	300	160	10	30[5]
5	4-F	7-OMe	DME	300	160	10	30[5]
6	6-Me	H	Dioxane	400	180	8	83

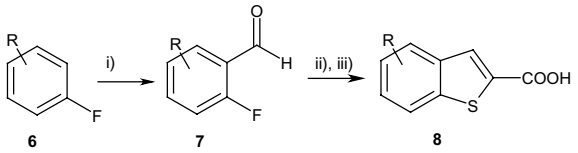
[a] Isolated yields.

through the liquid, allowing it to reach a higher temperature before bubbles form.[3] This led us to believe that microwave heating would improve both the cyclisation and decarboxylation reactions.

Initially, we focused on the cyclisation conditions. In our hands, when the cyclisation of the β-aryl-α-mercaptoacrylic acid **4** was performed under the literature conditions (iodine, dioxane, 110 °C),[2] the yields were poor, requiring long reaction times and giving complex reaction mixtures. The cyclisation under microwave irradiation in a sealed vessel in a CEM MARS microwave oven, at various continuous power and temperature settings, gave much improved yields with shorter reaction times and cleaner product mixtures (Table 1).[4,5] When a methoxy group was present in the 5-position of the β-aryl-α-mercaptoacrylic acid **4**, the cyclisation did not work as well but still afforded at least 30% of desired product (entries 4 and 5).

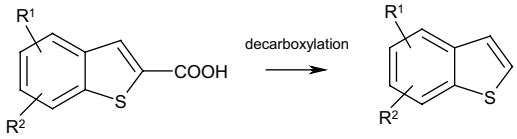
A more direct and amenable strategy to construct the thienyl ring has been described (Scheme 2).[6] This method is selective but depends on the commercial availability of the starting *o*-fluorobenzaldehyde, or on its synthesis via a fluorine directed *ortho*-lithiation. This route is slightly longer, does not scale up very well and still requires a decarboxylation.

The classical decarboxylation of benzo[*b*]thiophene-2-carboxylic acids involves a copper-mediated reaction in quinoline.[7] We have demonstrated that the reaction can be carried out directly on a 170 mmol scale in a 1 L round bottomed flask in a CEM MARS microwave oven at 200 °C (Table 2).[8]



Scheme 2. Reagents and conditions: (i) LDA, DMF, −78 °C; (ii) NEt_3, $HSCH_2COOCH_3$, DMSO; (iii) LiOH, THF, H_2O.

Table 2.



R^1	R^2	Solvent	Power (W)	Temp (°C)	Time (min)	Yield (%)[a]
6-Cyano	H	Quinoline	Conv.[b]	215	60	52
6-Cyano	H	Quinoline	600	200	45	93

[a] Isolated yields.
[b] Conv. = conventional heating (oil bath at 215 °C).

Although the reaction was successful, the reaction mixture was heterogenous and the work-up problematic. A new homogenous method was developed[9] and adapted using microwave heating, involving the use of an organic base (DBU) and a high boiling polar solvent (dimethylacetamide). The decarboxylation was carried out at 200 °C for 1 h in a sealed microwave vessel in a CEM MARS microwave reactor at 600 W continuous power.[10] Results are presented in Table 3. This method was very convenient as both base and solvent were easily washed out.

All this chemistry was performed in a CEM MARS microwave oven, which has a multimode cavity and is therefore non-focused. This implies that the reactions could be further optimised using a focused microwave oven, which maximises the microwave irradiation in the reaction mixture.

In conclusion, the chemistry described provides an easy and high-yielding method for the synthesis of substituted benzo[*b*]thiophenes using microwaves and in particular novel reaction conditions for the decarboxylation reaction. Studies are currently underway to assess the possibility that both the cyclisation and decarboxylation reactions can take place in a 'one-pot' reaction to further broaden the utility of this methodology. Our results will be reported in due course.

Table 3.

Entry	R^1	R^2	Yield (%)[a]
1	3-CF_3	H	75[11]
2	3-CF_3	5-Br	65[11]
3	3-CF_3	5-Cl	62[11]
4	3-CF_3	5-CN	78[11]
5	3-CF_3	6-Br	78[11]
6	4-F	H	87
7	4-Cl	H	100
8	4-Br	H	91
9	4-Me	H	100
10	4-CF_3	H	91
11	6-F	H	87
12	6-Cl	H	100
13	6-Br	H	95
14	7-F	H	92
15	4-F	6-F	54
16	4-F	6-Br	85
17	4-F	7-OMe	70
18	4-Cl	6-Br	49
19	4-Br	5-F	65
20	4-Br	6-F	83
21	4-Me	6-F	80
22	4-Me	6-Br	87
23	4-Me	7-OMe	70

[a] Isolated yields.

Acknowledgements

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