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Mn(III)-Promoted cyclization of substituted thioformanilides under microwave irradiation: a new reagent for 2-substituted benzothiazoles

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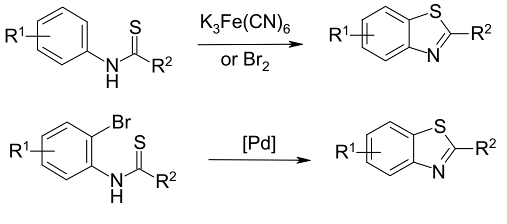
Abstract—Manganese triacetate is introduced as a new reagent to replace potassium ferricyanide or bromine for radical cyclization of substituted thioformanilides. 2-Substituted benzothiazoles are generated in 6 min under microwave irradiation.

Benzothiazole is a privileged bicyclic ring system.[1] Due to their potent antitumour activity[2–5] and other important pharmaceutical utilities,[6–9] the synthesis of these compounds is of considerable interests.[10] There are two major routes to benzothiazoles: (1) radical cyclization of phenylthioformamides promoted by potassium ferricyanide [11] or bromine;[12] (2) Pd-catalyzed cyclization of 2-bromophenylthioformamides[13] (Scheme 1). We report here our studies on using manganese(III) triacetate to replace potassium ferricyanide or bromine reagents for radical cyclization.[14]

Manganese(III) triacetate is an excellent one-electron oxidant, which has been widely employed to generate free radicals for cyclization reactions.[15] However, report on Mn(III)-induced thiyl radical reaction is very limited.[16] In this work we also discovered that the thiyl radical cyclization reaction can be dramatically accelerated by microwave irradiation.[17–20]



Scheme 1.

Initially we explored the reaction of thiobenzanilide (**1a**), which was prepared from commercially available benzanilide by sulfurization[21] with $Mn(OAc)_3 \cdot 2H_2O$[22] in glacial acetic acid in 1:1 molar ratio at 110 °C with mechanical stirring. Unfortunately, trace product was obtained even if the reaction time was extended to 6 h. Therefore, we tried to increase the amounts of $Mn(OAc)_3 \cdot 2H_2O$, the result showed that it was favourable, when the molar ratio of $Mn(OAc)_3 \cdot 2H_2O$ and **1a** reached 2:1, product was isolated in 32% yield. It was characterized to be 2-phenylbenzothiazole by its ^1H NMR, ^{13}C NMR and HRMS spectral data. Based on the results, the reaction conditions were optimized, the suitable molar ratio of $Mn(OAc)_3 \cdot 2H_2O$/**1a** and reaction time were 3:1 and 6 h (Table 1, entry 3), respectively. The yield cannot be increased even if using more $Mn(OAc)_3 \cdot 2H_2O$ and prolonging reaction time (Table 1).[23]

In order to shorten the reaction time and increase the yield, the microwave technology was applied in the above reaction. As expected, when the solution of **1a** and $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid was irradiated with microwave, the reaction was complete in 6 min higher than conventional heating (Table 1, entry 4). It is obvious that the microwave accelerates the reaction and improves the reaction yield.

Keywords: Benzothiazole; Manganese(III) triacetate; Thioformanilide; Microwave irradiation.

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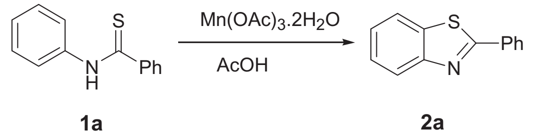
Table 1.



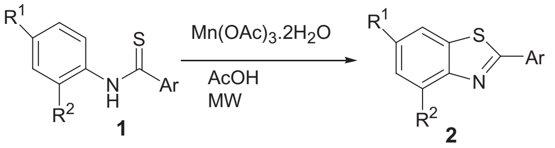
Entry	Solvent	Power (W)	Temp (°C)	Time (min)	Molar ratio[b]	Yield (%)[c]
1	AcOH	Conv.[a]	110	360	1:1	Trace
2	AcOH	Conv.[a]	110	360	1:2	32
3	AcOH	Conv.[a]	110	360	1:3	60
4	AcOH	300	110	6	1:3	80

[a] Conv. = conventional heating.

[b] Molar ratios = the molar ratios of thiobenzanilide and $Mn(OAc)_3{\cdot}2H_2O$.

[c] Isolated yields.

Table 2. Reaction of arylthioformanilides (**1a–f**) with $Mn(OAc)_3{\cdot}2H_2O$ under microwave irradiation



Product[a]	Ar	R^1	R^2	Yield (%)[b]
2a	Ph	H	H	80
2b	Ph	OCH_3	H	75
2c	*p*-F–C_6H_4	H	H	62
2d	*o*-Cl–C_6H_4	H	H	76
2e	*p*-$C_8H_{17}O$–C_6H_4	OCH_3	H	83
2f	*p*-$C_8H_{17}O$–C_6H_4	Cl	H	79
2g	*p*-$C_8H_{17}O$–C_6H_4	Br	H	86
2h	*p*-$C_{10}H_{21}O$–C_6H_4	Cl	H	88

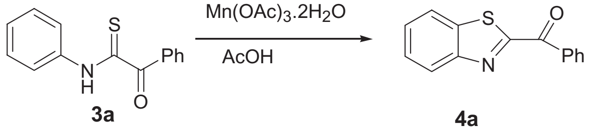
[a] All products were characterized by their NMR and MS spectra.

[b] All products were purified by flash column chromatography.

Furthermore, the reactions of arylthioformanilides **1b–h** and $Mn(OAc)_3{\cdot}2H_2O$ in acetic acid were performed under microwave irradiation to afford 2-arylbenzothiazoles **2b–h** (Table 2).[24] The reactions were finished in 6 min. Their structures were confirmed by ^1H NMR, ^{13}C NMR and HRMS spectral data.

To further evaluate the scope of Mn(III)-promoted cyclizations, the reaction of α-benzoylthioformanilide (**3a**)[25] and $Mn(OAc)_3{\cdot}2H_2O$ was carried out in glacial acetic acid in 1:3 molar ratio at 110 °C with mechanical stirring. The results showed that the reaction was slow (Table 3). Therefore, the same reaction was done under microwave irradiation, the expected product 2-benzoylbenzothiazole (**4a**) in 60% yield.[26] Compounds **3b–f**[25] instead of **3a** the expected products 2-benzoylbenzothiazoles (**4b–f**) in good yields (Table 4).

Table 3.



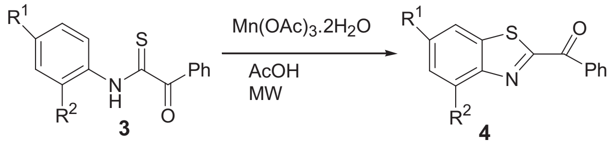
Entry	Solvent	Power (W)	Temp (°C)	Time (min)	Molar ratio[b]	Yield (%)[c]
1	AcOH	Conv.[a]	100	120	1:3	Trace
2	AcOH	Conv.[a]	110	60	1:3	Trace
3	AcOH	Conv.[a]	110	600	1:3	50
4	AcOH	300	110	6	1:3	60

[a] Conv. = conventional heating.

[b] Molar ratios = the molar ratios of α-benzoylthioformanilide (**3a**) and $Mn(OAc)_3{\cdot}2H_2O$.

[c] Isolated yields.

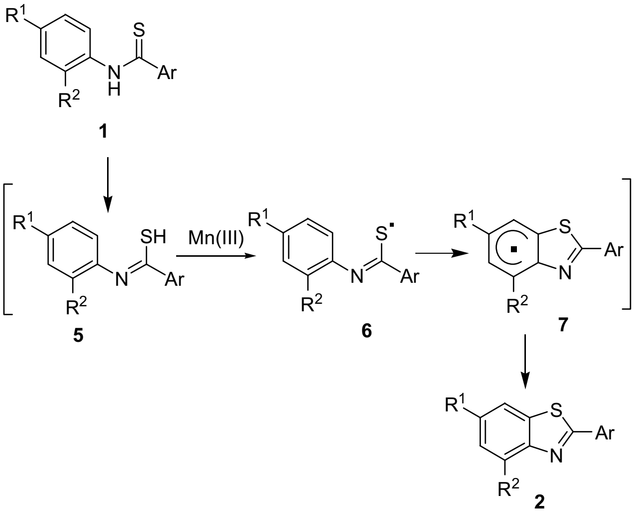
Table 4. Reaction of α-benzoylthioformanilides (**3a–f**) with $Mn(OAc)_3{\cdot}2H_2O$ under microwave irradiation



Product[a]	R^1	R^2	Yield (%)[b]
4a	H	H	60
4b	CH_3	H	62
4c	CH_3O	H	67
4d	Cl	H	50
4e	Br	H	57
4f	H	Cl	63

[a] All products were characterized by NMR and MS spectra.

[b] All products were purified by flash column chromatography.



Scheme 2.

A rational mechanism is proposed for manganese(III) triacetate-promoted cyclization reactions (Scheme 2). Arylthioformanilide **1** can exist as thioimidol **5**, the later one reacts with $Mn(OAc)_3$ to produce thiyl radical **6**, while Mn(III) is reduced to Mn(II) at the same time. Then, 1,5-homolitic radical cyclization of **6** followed by aromatization of radical **7** gives 2-arylbenzothiazole **2**.

In summary, we have developed a highly efficient method for preparation of 2-arylbenzothiazoles **2** and 2-benzoyl-benzothiazoles **4** using manganese(III)-promoted radical cyclizations of arylthioformanilides **1** and α-benzoylthio-formanilides **3** under microwave irradiation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.090.

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23. General procedure for the preparation of 2-phenylbenzothiazole (**2a**) using conventional heating: To a solution of thiobenzanilide (**1a**) (0.21 g, 1 mmol) dissolved in 15 mL acetic acid, was added $Mn(OAc)_3 \cdot 2H_2O$ (0.81 g, 3 mmol, 3 equiv), the mixture was stirred at 110 °C for 6 h. Then the mixture was allowed to cool to room temperature, poured into water and extracted with chloroform for three times (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography on silica-gel using petroleum ether/acetone = 4:1 as eluent to give 2-phenylbenzothiazole (**2a**), yield 60%.
24. General procedure for preparation of 2-phenylbenzothiazole (**2a**) under microwave irradiation: Into 100 mL three-necked flask thiobenzanilide (**1a**) (0.21 g, 1 mmol) and acetic acid (15 mL) were added. The flask was placed into a microwave vessel, $Mn(OAc)_3 \cdot 2H_2O$ (0.81 g, 3 mmol, 3 equiv) was added. The mixture was heated to 110 °C for 6 min at 300 W in a kitchen-type microwave oven. The treatment and purification procedure of the mixture was same as Ref. 23. Compound **2a**, Yield 80%, mp 115–116 °C. ^1H NMR($CDCl_3$): δ 7.37–8.12 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR ($CDCl_3$): δ 168.5, 154.5, 135.4, 134.0, 131.4, 129.4, 128.0, 126.7, 125.6, 123.6, 122.0; HRMS: *m*/*z* (%, elemental composition), calcd for $C_{13}H_9NS$ (M^+) 211.0456, found 211.0462 (M^+, 100.0).
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26. General procedure for preparation of 2-benzoylbenzothiazole (**4a**) under microwave irradiation: The experimental procedure was same as Ref. 24. Compound **4a**, yield 60%, mp 98–99 °C. ^1H NMR ($CDCl_3$): δ 7.54–8.57 (m, 9H, $C_6 H_5$, C_6H_4); ^{13}C NMR ($CDCl_3$): δ 185.9, 167.5, 154.3, 137.4, 135.4, 134.4, 131.7, 129.0, 128.1, 127.4, 126.2, 122.6; HRMS: *m*/*z* (%, elemental composition), calcd for $C_{14}H_9NOS$ (M^+) 239.0405, found 239.0408 (M^+, 45.13).