Solid state synthesis of 2-aroylbenzo[*b*]furans, 1,3-thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles from α-tosyloxyketones using microwave irradiation †

Rajender S. Varma,* Dalip Kumar and Per J. Liesen

Department of Chemistry and Texas Research Institute for Environmental Studies (TRIES), Sam Houston State University, Huntsville, TX 77341-2117, USA

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The expeditious solventless syntheses of 2-aroylbenzo[*b*]furans, 1,3-thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-*b*]-[1,3]thiazoles are described from readily accessible α-tosyloxyketones and mineral oxides in processes that are accelerated by exposure to microwaves. The 2-aroylbenzo[*b*]furans are readily obtained from salicylaldehydes and α-tosyloxyketones in the presence of solid potassium fluoride doped alumina ($KF–Al_2O_3$) whereas montmorillonite K-10 clay provides 1,3-thiazoles from thioamides and α-tosyloxyketones. Similarly, ethylenethiourea and α-tosyloxyketones provide bridgehead nitrogen heterocycles, 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles, in excellent yields which are not easily obtainable under classical heating conditions.

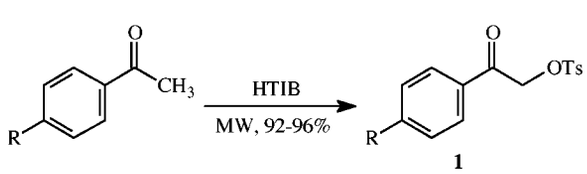
Introduction

The 2-aroylbenzo[*b*]furans,[1] 1,3-thiazoles[2] and 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles[3] are important classes of heterocyclic compounds that are known to possess important biological properties. 2-Aroylbenzo[*b*]furans, initially reported from the flower-heads of *Helichrysum arenarium* DC,[4] form a group of naturally occurring compounds which possesses a wide range of pharmacological activities.[3] In view of their cyclooxygenase-inhibitory activity, thiazoles find application in therapy as thromboembolic agents and are of significant importance being an integral structural component of vitamin B1 and coenzyme carboxylase.[5] The related bridgehead heterocyclic compounds, 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles, are known to possess a broad spectrum of anthelmintic and fungicidal activity.[3] Generally, synthesis of these heterocyclic compounds involves utilization of lachrymatory starting materials and hazardous reagents which requires a longer reaction time under drastic conditions and which results in the generation of aqueous or organic solvent waste.

Microwave (MW) heating has been used for the rapid synthesis of a variety of compounds[6a,7–10] wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules, non-polar molecules being inert to the MW dielectric loss. Heterogeneous reactions facilitated by supported reagents on various inorganic surfaces have received attention in recent years.[6] The coupling of MW irradiation with the use of catalysts or mineral supported reagents, under solvent-free conditions, provide unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and the ease of manipulation.[6a,10] In addition, the limitations of the MW-assisted reactions in solvents, namely, the development of high pressures and the need for specialized sealed vessels, are circumvented *via* this solid state strategy which enables organic reactions to occur rapidly at atmospheric pressure.[9,10] Consequently, these solvent-free MW-assisted reactions[6a,9,10] have gained popularity as they provide an opportunity to work with open vessels and an enhanced possibility of upscaling the reactions on a preparative scale. In view of the above mentioned limitations of the reported methods[11–18] and our continued interest in the development of environmentally benign protocols,[10] we now describe a microwave-accelerated solid state approach for the rapid assembly of 2-aroylbenzo[*b*]furans, 1,3-thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles.

Results and discussion

The key intermediates, α-tosyloxyketones, are important precursors for the synthesis of a variety of heterocyclic compounds.[19] Conventionally, the preparation of these tosylated carbonyl derivatives from aryl methyl ketones requires extended reaction time under refluxing conditions in acetonitrile.[20] Herein, we describe a high yield preparation of α-tosyloxyketones by simply admixing [hydroxy(tosyloxy)iodo]benzene (HTIB) with an appropriate aryl methyl ketone followed by MW heating (30 s) in an open vessel. Various electron-donating and electron-withdrawing substituents in the aryl ring influence neither the reaction time nor the yield of the α-tosylated ketones (Scheme 1).



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Where **a** R = H; **b** R = Cl; **c** R = Me; **d** R = OMe

Scheme 1

The existing methods for the synthesis of 2-aroylbenzo[*b*]-furans normally use lachrymatory α-haloketones,[11] *N*-bromosuccinimide[12] or phase transfer catalysts.[13] We have explored a simplified approach for the rapid formation of 2-aroylbenzo[*b*]-furans **3**, which involves admixing salicylaldehydes with α-tosyloxyketones on mineral oxide supports such as basic alumina or alumina 'doped' with potassium fluoride followed by the exposure to microwaves for 2.5–3.5 min in an unmodified household microwave oven (Scheme 2). The basic reaction conditions using alumina impregnated with potassium fluoride are

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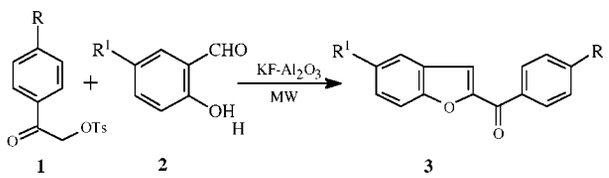
Table 1 Synthesis of 2-aroylbenzo[*b*]furans (**3a–h**) from α-tosyloxyketones **1**

Entry	R	R^1	Time/min	Yield (%)[a]	Mp/°C[b] Expt.	Ref.
3a	H	H	3.0	94	90–91	90–91[12]
3b	Cl	H	3.0	94	153–154	152–153[13]
3c	Me	H	2.5	91	95–96	95–96[14]
3d	OMe	H	3.5	89	97–98	97[1b]
3e	H	Cl	2.5	95	136–137	138[15]
3f	Cl	Cl	2.5	92	184–185	185[17]
3g	Me	Cl	2.5	96	167–168[c]	—
3h	OMe	Cl	3.5	89	136–137[c]	—

[a] Yields refer to pure isolated products. [b] Physical and chemical properties of all the compounds agreed with the assigned structures. [c] See Experimental section.

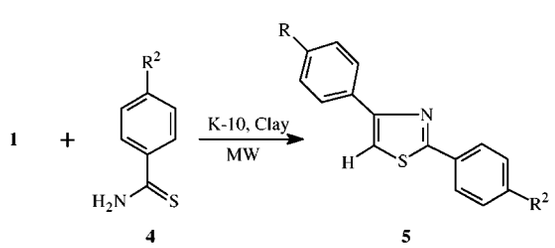


Scheme 2

ideally suited for obtaining optimum yields. The generality of this approach is established by utilising several substituted salicylaldehydes and α-tosyloxyketones in this reaction which tolerates a variety of functional groups (Table 1).

A plausible pathway for the formation of 2-aroylbenzo[*b*]-furans is the initial formation of an enolate anion under basic conditions followed by the nucleophilic displacement of the tosyloxy group and elimination of the water molecule to afford 2-aroyl[*b*]benzofuran **3**.

Thiazoles are conventionally prepared from α-haloketones and thioamides (or thioureas) *via* a method pioneered by Hantzsch.[16] In a cumbersome and time consuming preparation (25 h), King and Hlavacek[17] have synthesized 2-aminothiazoles by replacing α-haloketones with ketones and halogens. Subsequently, other methods[18] have been introduced in view of the pharmacological importance of the thiazole derivatives.[5b] The obvious limitations have been the use of strong mineral acids under drastic reaction conditions. We find that our earlier described solvent-free approach for the synthesis of 2-aroylbenzo[*b*]furans is equally applicable to thiazoles. The process simply requires mixing of thioamides with α-tosyloxyketones in the presence of acidic montmorillonite K-10 clay and brief exposure of the reaction mixture to 2–5 min of MW irradiation (Scheme 3). The scope of this reaction is defined by rapid



Scheme 3

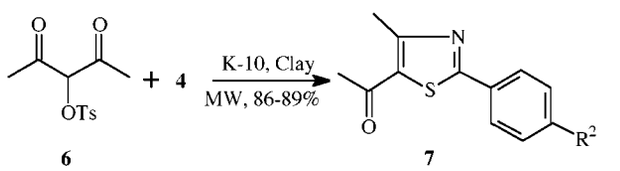
assembly of several thiazole derivatives starting from various substituted α-tosyloxyketones and thioamides (Table 2).

In the case of a diketone, exemplified by the reaction of 3-tosyloxypentane-2,4-dione **6**, with thioamides **4**, the formation of 5-acetyl-4-methyl-2-aryl-1,3-thiazole derivatives **7**, can be realised in excellent yields (Scheme 4). These 5-acetyl derivatives can be further elaborated to interesting thiazole derivatives.

Table 2 Synthesis of 1,3-thiazole derivatives (**5a–h**) from α-tosyloxyketones **1**

Entry	R	R^2	Time/min	Yield (%)[a]	Mp/°C[b] Expt.	Ref.
5a	H	Cl	3	90	105	104–105[21]
5b	H	OMe	4	91	100	98–99[2]
5c	Cl	Cl	2	94	144	145[21]
5d	Cl	OMe	4	96	154[c]	—
5e	Me	Cl	5	92	169–170	170–171[21]
5f	Me	OMe	3	92	149–150[c]	—
5g	OMe	Cl	3	90	139–140[c]	—
5h	OMe	OMe	3.5	88	169–170[c]	—

[a] Yields refer to pure isolated products. [b] Physical and chemical properties of all the compounds agreed with the assigned structures. [c] See Experimental section.

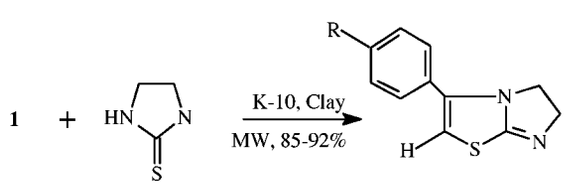


Where **a** R = Cl; **b** R = OMe

Scheme 4

The mechanistic pathway presumably involves a nucleophilic displacement of the tosylate group by the sulfur atom onto the α-carbon of the α-tosyloxyketones followed by intramolecular nucleophilic attack on the carbonyl carbon and elimination of a water molecule to afford thiazole derivatives.

The generalisation of this synthetic theme is extended to a concise preparation of bridgehead thiazoles, 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles **9**. These compounds are normally difficult to obtain and require a longer heating time in reactions that use α-haloketones[18a] or α-tosyloxyketones[18c] under strongly acidic conditions. Our solventless optimised reaction conditions for these bridgehead heterocycles merely require a mixing of α-tosyloxyketones with thioamides in the presence of montmorillonite K-10 clay. The mixture is then irradiated in MW for 3 min to afford substituted bridgehead thiazoles (Scheme 5).



Where **a** R = H; **b** R = Cl; **c** R = OMe; **d** R = Me

Scheme 5

The contribution of microwaves may not be purely a thermal one as is borne out by the fact that similar reaction rates are not attainable at the same bulk temperature in an oil bath. For example, the reaction of *p*-methyl-α-tosyloxyacetophenone and salicylaldehyde in an oil bath at 130 °C (the temperature in the microwave oven reached 130 °C after 1.5 min of irradiation) requires 95 min to deliver the 2-aroylbenzo[*b*]furan derivative **3c**, while the reaction of α-tosyloxyacetophenone and *p*-chlorothiobenzamide at the same temperature (bulk temperature of 130 °C) in an oil bath gets completed in 15 min to afford **5a**. The reaction of α-tosyloxyacetophenone with ethylenethiourea, however, remains incomplete even after heating at 130 °C (bulk temperature) for 24 h. Apparently, there is not a significant

difference between the reaction rates using MW irradiation and alternate heating mode for thiazoles (require 15 min) but it becomes more distinct in the formation of 2-aroylbenzo[*b*]-furans which requires a longer time (95 min). The case of the corresponding bridgehead heterocycles **9**, however, is a special one where the MW effect really becomes apparent since the reactions of α-tosyloxyketones with ethylenethioureas are incomplete in an oil bath. The formation of these heterocyclic compounds from the reaction intermediates involves the elimination of water molecules which couple very efficiently with microwaves. Consequently, the MW protocols are responsible for the faster formation of these heterocycles when compared to classical heating conditions.

In summary, we have developed efficient and clean syntheses of 2-aroylbenzo[*b*]furans, thiazoles and 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazoles from readily available α-tosyloxyketones under solvent-free conditions that utilise relatively benign inorganic oxides as catalysts and clean energy source microwaves.

Experimental

Melting points were determined on a Mel-Temp II hot stage apparatus using a Fluke 51 K/J digital thermometer and are uncorrected. A Sears Kenmore unmodified household microwave oven (900 W) equipped with a turntable was used for all experiments. The average bulk temperature at the end of the reaction was measured by inserting a thermometer in the alumina bath housing the reaction vessel. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL Eclipse$^+$300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer using tetramethylsilane as an internal standard.

General procedure for the synthesis of α-tosyloxyketones (1a–d)

A mixture of aryl methyl ketone (1 mmol) and [hydroxy(tosyloxy)iodo]benzene (1.2 mmol), taken in a glass tube, was placed in an alumina bath inside the MW oven and irradiated for 30 s at 50% power level. After completion of the reaction, as determined by TLC examination, the crude product was washed with hexane to afford pure tosyloxymethyl aryl ketone **1a**. Yield 96%; mp 91 °C (lit.,[20] mp 89–91 °C); **1b**: yield 93%; mp 122 °C (lit.,[22] 119–120 °C); **1c**: yield 94%; mp 82 °C (lit.,[22] 82–83 °C); **1d**: yield 92%; mp 115 °C (lit.,[22] mp 115–116 °C).

General procedure for the synthesis of 2-aroylbenzo[*b*]furans (3a–h)

Salicylaldehyde (0.122 mg, 1 mmol), KF–alumina (0.620 g, 2 mmol of KF) and α-tosyloxyketone (1 mmol) were placed in a glass tube and mixed thoroughly on a vortex mixer. The glass tube was then placed in an alumina bath inside the MW oven and irradiated (intermittently at 1.5 min intervals; 130 °C) for a specified time (Table 1). On completion of the reaction, followed by TLC examination (hexane–EtOAc, 9:1), the product was extracted into methylene chloride (3 × 10 cm^3). The solvent was then removed under reduced pressure and the residue was crystallized from ethanol to afford a nearly quantitative yield of 2-aroylbenzo[*b*]furans (**3a**–**h**).

3g. (Found: C, 70.85; H, 4.10. Calc. for $C_{16}H_{11}ClO_2$ requires C, 71.11; H, 4.07%) δ_H ($CDCl_3$) 2.46 (3H, s, CH_3), 7.33 (2H, d, *J* 7.71, 3′-H, 5′-H), 7.42–7.45 (2H, m, 6-H, 3-H), 7.55 (1H, d, *J* 8.70, 7′-H), 7.68 (1H, d, *J* 2.19, 4-H), 7.95 (2H, d, *J* 8.52, 2′-H, 6′-H); δ_C ($CDCl_3$) 21.75, 113.63, 114.08, 122.55, 128.28, 129.34, 129.57, 129.69, 150.76, 154.17, 183.72 (CO).

3h. (Found: C, 66.82; H, 3.95. Calc. for $C_{16}H_{11}ClO_3$ requires C, 67.13; H, 3.84%) δ_H ($CDCl_3$) 3.91 (3H, s, OCH_3), 7.02 (2H, dd, *J* 2.46 and 6.87, 3′-H, 5′-H), 7.41–7.45 (2H, m, 3-H, 6-H), 7.56 (1H, d, *J* 8.79, 7-H), 7.69 (1H, d, *J* 2.82, 4-H), 8.10 (2H, dd, *J* 2.46 and 6.87, 2′-H, 6′-H); δ_C ($CDCl_3$) 55.63, 113.62, 114.00, 114.47, 122.52, 128.33, 129.56, 132.09, 153.96, 154.12, 163.88, 182.49 (CO).

General procedure for the synthesis of 2,4-disubstituted 1,3-thiazoles (5a–h)

α-Tosyloxyketone (1 mmol), the appropriate thioamide (1 mmol) and montmorillonite K-10 clay (125 mg) were mixed thoroughly using a pestle and mortar. The reaction mixture was transferred into a glass tube and exposed to microwave irradiation in an alumina bath for 2–5 min (intermittently with 1.5 min interval; 130 °C). The product was extracted into methylene chloride (2 × 10 cm^3) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallised from ethanol–hexane to afford the corresponding 1,3-thiazoles (**5a**–**h**).

5d. (Found: C, 63.50; H, 3.72; N, 4.58. Calc. for $C_{16}H_{12}ClNOS$ requires C, 63.79; H, 3.99; N, 4.65%) δ_H ($CDCl_3$) 3.87 (3H, s, OCH_3), 6.97 (2H, d, *J* 8.79, 3′-H, 5′-H), 7.38 (1H, s, 5-H), 7.40 (2H, d, *J* 7.98, 3″-H, 5″-H), 7.91 (2H, d, *J* 8.52, 2′-H, 6′-H), 7.97 (2H, d, *J* 8.64, 2″-H, 6″-H); δ_C ($CDCl_3$) 55.43, 112.05, 114.30, 126.40, 127.69, 128.15, 128.86, 132.95, 133.86, 154.67, 161.33, 168.11.

5f. (Found: C, 72.40; H, 5.26; N, 4.82. Calc. for $C_{17}H_{15}NOS$ requires C, 72.60; H, 5.34; N, 4.98%) δ_H ($CDCl_3$) 2.39 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 6.97 (2H, d, *J* 8.79, 3″-H, 5″-H), 7.23 (2H, d, *J* 8.25, 3′-H, 5′-H), 7.30 (1H, s, 5-H), 7.87 (2H, d, *J* 8.22, 2″-H, 6″-H), 7.97 (2H, d, *J* 8.52, 2′-H, 6′-H); δ_C ($CDCl_3$) 21.30, 55.42, 110.98, 114.22, 126.32, 126.87, 128.08, 129.38, 131.94, 137.89, 156.11, 161.11, 167.61.

5g. (Found: C, 63.58; H, 3.62; N, 4.54. Calc. for $C_{16}H_{12}ClNOS$ requires C, 63.79; H, 3.99; N, 4.65%) δ_H ($CDCl_3$) 3.85 (3H, s, OCH_3), 6.97 (2H, d, *J* 6.87, 3′-H, 5′-H), 7.35 (1H, s, 5-H), 7.42 (2H, d, *J* 8.49, 3″-H, 5″-H), 7.91 (2H, d, *J* 8.52, 2′-H, 6′-H), 7.97 (2H, d, *J* 8.25, 2″-H, 6″-H); δ_C ($CDCl_3$) 55.43, 111.19, 114.19, 127.39, 127.82, 129.19, 132.41, 135.93, 156.37, 159.83, 166.39.

5h. (Found: C, 68.38; H, 5.19; N, 4.76. Calc. for $C_{17}H_{15}NO_2S$ requires C, 68.69; H, 5.05; N, 4.71%) δ_H ($CDCl_3$) 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.86–6.97 (4H, m, 3′-H, 5′-H, 3″-H, 5″-H), 7.27 (1H, s, 5-H), 7.89–7.98 (4H, m, 2′-H, 6′-H, 2″-H, 6″-H); δ_C ($CDCl_3$) 55.34, 55.42, 110.04, 114.06, 114.23, 127.72, 128.07, 128.16, 129.88, 155.78, 159.60, 161.11.

General procedure for the synthesis of 5-acetyl-2-aryl-4-methyl-1,3-thiazoles (7a–b)

3-Tosyloxypentane-2,4-dione (0.270 mg, 1 mmol), the appropriate thioamide (1 mmol) and montmorillonite K-10 clay (125 mg) were mixed together using a pestle and mortar. The mixture was transferred to a glass tube and exposed to microwave irradiation in an alumina bath for 3 min (intermittently with 1.5 min interval; 130 °C). The product was extracted into methylene chloride (2 × 10 cm^3) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallised from hexane to afford corresponding 5-acetyl-2-aryl-4-methyl-1,3-thiazoles (**7a**–**b**).

7a. Yield 86%; mp 114 °C (Found: C, 57.70; H, 4.14; N, 5.41. Calc. for $C_{12}H_{10}ClNOS$ requires C, 57.37; H, 3.98; N, 5.58%) δ_H ($CDCl_3$) 2.55 (3H, s, 4-CH_3), 2.76 (3H, s, $COCH_3$), 7.41 (2H, d, *J* 8.22, 3′-H, 5′-H), 7.89 (2H, d, 2′-H, 6′-H); δ_C ($CDCl_3$) 18.49, 30.81, 128.14, 129.42, 131.37, 131.63, 137.34, 159.62, 168.01, 190.43.

7b. Yield 89%; mp 88–89 °C (Found: C, 63.51; H, 5.45; N, 5.56. Calc. for $C_{13}H_{13}NO_2S$ requires C, 63.16; H, 5.26; N, 5.67%) δ_H ($CDCl_3$) 2.55 (3H, s, 4-CH_3), 2.76 (3H, s, $COCH_3$), 3.86 (3H, s, OCH_3), 6.95 (2H, d, *J* 8.76, 3′-H, 5′-H), 7.92 (2H, d, *J* 8.79, 2′-H, 6′-H); δ_C ($CDCl_3$) 18.49, 30.74, 55.47, 114.44, 125.72, 128.56, 130.50, 159.49, 162.12, 169.43, 190.43.

General procedure for the synthesis of 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazole (9a–d)

α-Tosyloxyketone (1 mmol), ethylenethiourea (1 mmol) and montmorillonite K-10 clay (100 mg) were mixed thoroughly using a pestle and mortar. The mixture was transferred into a glass tube followed by microwave irradiation in an alumina bath for 3 min (intermittently). The thiazole salt so obtained was neutralised by the addition of a dilute solution of sodium hydroxide. The product was extracted into methylene chloride (2×10 cm^3) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallised from benzene–hexane to afford the corresponding 3-aryl-5,6-dihydroimidazo[2,1-*b*][1,3]thiazole (**9a**–**d**).

9a: Yield 85%; mp 111–112 °C (lit.,[18c] 112–113 °C); **9b**: yield 92%; mp 113–114 °C (lit.,[18c] 113–114 °C); **9c**: yield 89%; mp 87–88 °C (lit.,[18c] 85–88 °C); **9d**: yield 88%; gummy mass.[18c]

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Paper 8/07563H