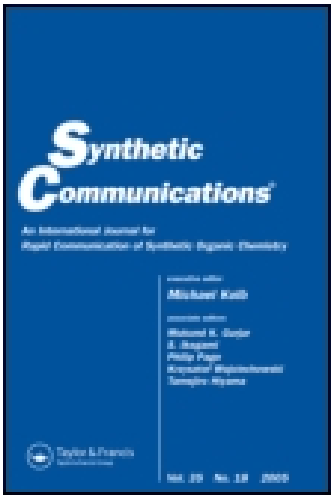

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Abstract: The synthesis of 2-amino-3-aryl-5-substituted thiophenes as anti-inflammatory agents catalyzed by KF-Al_2O_3 under microwave irradiation is reported.

Keywords: 2-Amino-3-aryl-5-substituted thiophenes; Anti-inflammatory agents; KF-Al_2O_3; Microwave irradiation

INTRODUCTION

The effort to develop novel drug-designing strategies has attracted great interest in the pharmaceutical industry and organic synthesis. Microwave-assisted solid-phase organic synthesis (MW-SPOS) has been regarded as one of the new important fields in synthetic organic chemistry. MW-SPOS techniques offer a powerful strategy for the discovery and generation of lead heterocyclic compounds. In addition, a solid-phase approach is interesting because the reaction can be driven to completion by using excess reagents, which are subsequently removed by simple filtration. On the other hand, the advantages of the microwave irradiation includes not only improving classical reactions but also shortening

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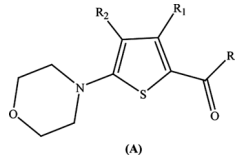
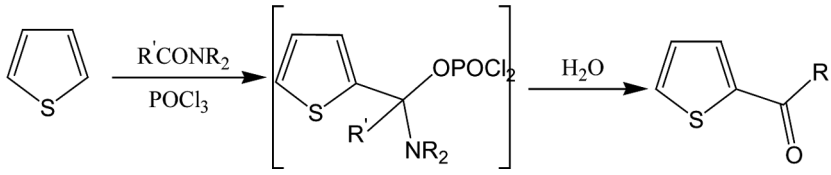
reaction times, improving the yields, and suppressing by-product formation as compared with conventional thermal heating.[1–6] There are many reports in the literatures about the synthesis of heterocyclic compounds by solid supports under microwave heating,[7] whereas the synthesis of thiophenes derivatives has received less attention under these conditions. Our interest in this class of compound was based on its use as novel nonsteroidal anti-inflammatory drugs (NSAIDs) having general formula (**A**).[8,9]



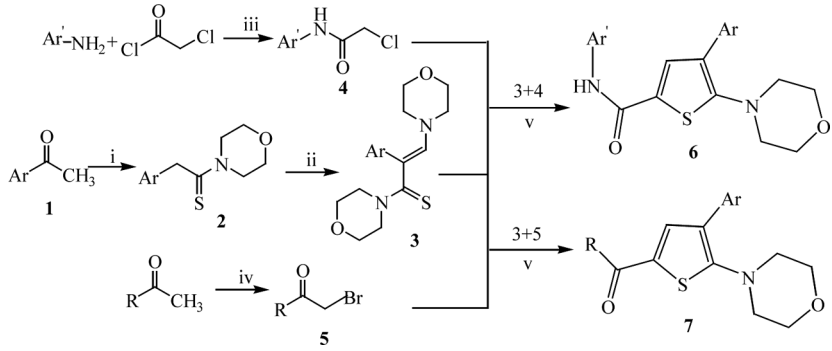
(A)

Several methods have been described for the synthesis of this framework. The reaction of organometallic derivatives of 2-H-substituted thiophenes with suitable carboxylating reagents afforded thiophene-2-carboxylic acids, which can be transformed into corresponding ketones by standard methods.[10] Another method for introducing acyl group on thiophene derivatives is the Vilsmeier–Haack reaction.[11] An N,N-dialkylamide reacts with phosphorus oxychloride or oxalyl chloride to give a chloroiminium ion, which is the reactive electrophile. This species acts as an electrophile in the absence of any added Lewis acid, but only rings with electron-releasing substituents are reactive (Scheme 1).

Friedel–Crafts (FC) acylation has also been used for the preparation of acylthiophenes. The FC acylation of thiophenes fails if amino-substituted thiophenes are used as starting materials.[12] Therefore, 2-amino-3-aryl-5-substituted thiophenes (**A**) cannot be prepared by FC acylation. The most convenient method for preparing thiophene with a high degree of functionality is the Gewald method, in which elemental sulfur is reacted with an activated acetonitrile and an aldehyde, ketone, or 1,3-dicarbonyl compound in the presence of a base.[13] A modification of the Gewald method has been reported in which an alkoxyacetone is reacted with ethyl cyanoacetate, sulfur, and morpholine, producing most sources of alkoxy thiophene derivatives in poor yields (19–39%).[14]



Scheme 1. Vilsmeier–Haack reaction.



Scheme 2. Solvent-free synthesis of 2-amino-3-aryl-5-substituted thiophenes: i, $HN(CH_2\text{-}CH_2)_2O/S_g$; ii, $HN(CH_2\text{-}CH_2)O/HC(OCH_2\text{-}CH_3)_3$; iii, CH_2Cl_2; iv, Br_2/CH_3COOH; and v, $KF\text{-}Al_2O_3$/microwave irradiation.

Recently some methods for preparing 2-amino-3-aryl-5-substituted thiophenes were published.[9,15] Although the reported methods give high yield, these methods have not been used for synthesis of 2-amino-3-aryl-5-amido thiophenes. On the other hand, the toxic and volatile nature of many organic solvents, which are widely used in organic synthetic procedures, has posed a serious threat to the environment.

In continuation of our research in this area,[16–24] herein we report a new and efficient $KF\text{-}Al_2O_3$-catalyzed solvent-free protocol for the synthesis of 2-amino-3-aryl-5-substituted thiophenes as new anti-inflammatory drug candidates under microwave irradiation (Scheme 2). To the best of our knowledge, this is the first demonstration of the synthesis of 2-amino-3-aryl-5-amido thiophenes.

First experiments focused on the optimized of the amount of $KF\text{-}Al_2O_3$. The results are summarized in the Table 1. We found that 0.25 g of $KF\text{-}Al_2O_3$ could effectively catalyze the reaction for 1 mmol of **3** and 1 mmol **4** to produce the desired product (Table 1, entries 7, 8). While comparing the effect of catalysts for the reaction of **3** with **4**, we found that, $KF\text{-}Al_2O_3$ was more effective than $KOH\text{-}Al_2O_3$ or K_2CO_3 (Table 1, entries 3, 4).

Using more $KF\text{-}Al_2O_3$ has less effect on the yield and time of the reaction. As shown in Table 1, the use of $KF\text{-}Al_2O_3$ offers a convenient, environmentally friendly alternative to conventional reactions. Clearly, the reaction time by microwave irradiation has been reduced 60 times with higher yield than conventional heating (65% versus 50%, Table 1, entries 8, 11). Because the product of interest is not covalently bound to the solid support, monitoring of the reactions and analysis can be accomplished by using standard methods [thin-layer chromatography

Table 1. Reaction of **3** with **4** under different conditions

Entry	Catalyst (g)	Mode of heating	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	No catalyst	Δ	Solvent-free	80	420	Trace
2	No catalyst	MW	Solvent-free	80	7	Trace
3	K_2CO_3 (0.25)	MW	Solvent-free	80	7	50
4	KOH-Al_2O_3 (0.25)	MW	Solvent-free	80	7	55
5	KF-Al_2O_3(1)	MW	Solvent-free	80	7	70
6	KF-Al_2O_3(0.5)	MW	Solvent-free	80	7	66
7	KF-Al_2O_3(0.25)	MW	Solvent-free	60	7	63
8	KF-Al_2O_3(0.25)	MW	Solvent-free	80	7	65
9	KF-Al_2O_3(0.25)	MW	$C_6H_5CH_3$	80	7	55
10	KF-Al_2O_3(0.25)	MW	CH_2Cl_2	50	7	42
11	KF-Al_2O_3(0.25)	Δ	$C_6H_5CH_3$	80	420	50
12	KF-Al_2O_3(0.25)	Δ	CH_2Cl_2	50	420	40

(TLC), column chromatography, ^{1}H NMR, etc.]. Finally, the products are isolated by column chromatography, eliminating the need for a cleavage step, which is required in solid-phase synthesis. To generalize this methodology, we subjected a series of substrates to the reaction to obtain the corresponding thiophenes under the optimized reaction conditions (Tables 2 and 3).

The variations in the yields were very little, and substituted aromatic amides such as 4-chloro and 3-methyl gave the substituted thiophenes in excellent yields.

The applicability of the present methodology is further extended by performing the reaction of **3** with **5** for the synthesis of 2-amino-3-aryl-5-acyl/carboxylate thiophenes. The reaction was performed well, and the reaction rates as well as the yields of products were satisfactory.

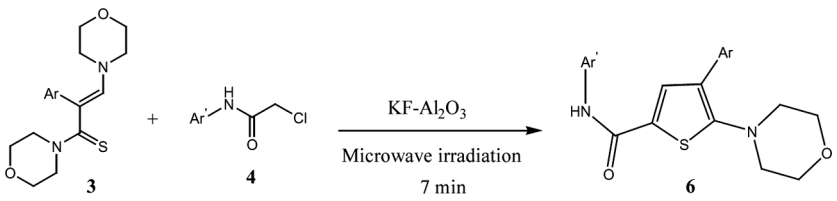
A proposed mechanism for the reaction course is shown in Scheme 3. Component **3** undergoes an S-alkylation with α-haloamide **4** or α-haloketone/ester **5**, affording the iminium ions **I**; then subsequent treatment with KF-Al_2O_3 leads to cyclization and formation of the thiophene ring with elimination of morpholine.

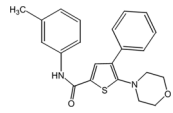
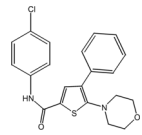
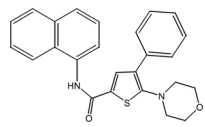
To confirm the proposed mechanism, the reaction of the benzyl bromide with **3** (Ar: phenyl) in the presence of H_2O was studied for trapping the iminium ion **I** (Scheme 4).

Indeed, the iminium ion **I** was hydrolyzed by the presence of water in the reaction medium to **8**, which was isolated and its structure confirmed (see Spectral Data section).

In conclusion, the alumina-supported potassium fluoride shows high catalytic activities for the synthesis of 2-amino-3-aryl-5-substituted

Table 2. Synthesis of 2-amino-3-aryl-5-substituted thiophenes under optimized conditions



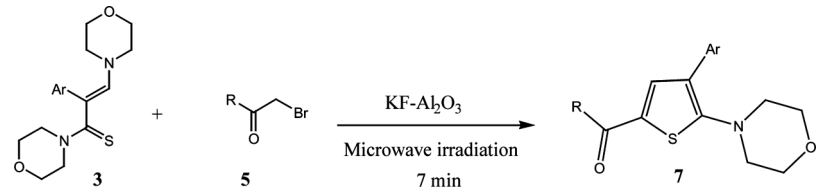
Entry	Ar	Ar'	Produce	Mp (°C)	Yield (%)
6a	Phenyl	3-Methylphenyl		171–173	65
6b	Phenyl	4-Chlorophenyl		239–241	60
6c	Phenyl	1-Naphthyl		181–183	55

thiophenes under solvent-free conditions by microwave irradiation. This procedure offers several advantages including low loading of catalyst, high yields, clean reaction, and use of various substrates, which make it a useful and attractive strategy for the synthesis of 2-amino-3-aryl-5-substituted thiophenes. These materials have the potential to be used as novel nonsteroidal anti-inflammatory drugs.

EXPERIMENTAL

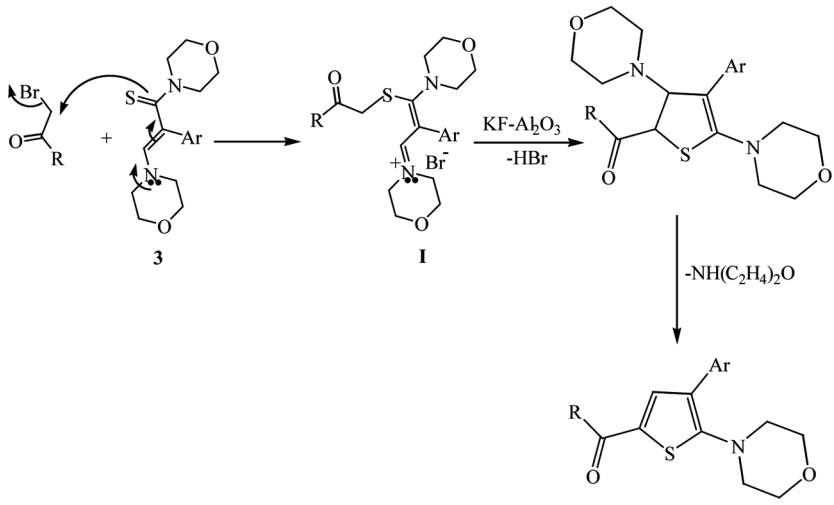
The compounds gave all satisfactory spectroscopic data. A Bruker (DRX-500 Avance) NMR instrument was used to record the ^{1}H NMR and ^{13}C NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Melting points were determined on a Buchi B540 apparatus. GC-MS (EI), 70 ev, HP6890 column: HP-5

Table 3. Synthesis of 2-amino-3-aryl-5-acyl/carb oxylate thiophenes under optimized conditions

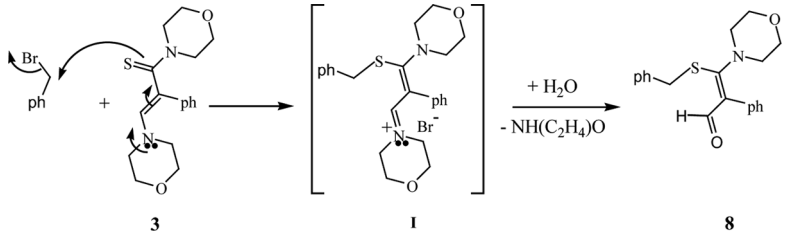


			This method		Reported method [Ref.]	
Entry	Ar	R	Time (min)	Yield (%)	Time (min)	Yield (%)
7a	Phenyl	Phenyl	7	89	180	98[12]
7b	Phenyl	4-Bromophenyl	7	84	180	56[12]
7c	Phenyl	4-Chlorophenyl	7	87	180	56[9]
7d	4-Chlorophenyl	4-Chlorophenyl	7	72	180	66[9]
7e	Phenyl	Ethoxy	7	65	30	82[15]
7f	4-Biphenyl	Ethoxy	7	62	—	—

(30 m × 0.25 mm × 0.2 μml MSD: HP5793) was used to record the mass spectra. The microwave-assisted reactions were performed in a microwave laboratory reactor (Ethos MR).



Scheme 3. Proposed mechanism.



Scheme 4. Trapping of iminium ion **I** with water.

Preparation of Catalyst

The KF-Al_2O_3 support was prepared according to previously reported procedure[25] with some modification. A mixture of potassium fluoride (45 g) and basic alumina (55 g, type T, Merck) in water (100 ml) was stirred at room temperature for 10 min. The resulting suspension was concentrated in vacuum and dried in a vacuum oven at 120 °C for 15 h. Use of basic alumina in the solid support gave better results relative to the neutral one.

Procedure for Preparation of 2-Amino-3-aryl-5-substituted Thiophenes under Microwave Heating

To an equimolar mixture of **3** (Ar: phenyl) and **4** (Ar: 3-methylphenyl), KF-Al_2O_3 (0.25 g) was added, and then the mixture was heated in a microwave oven for 7 min. After cooling, the residue was subjected to column chromatography (EtOAc/hexane 1:4) on silica gel to obtain pure products.

Spectra Data of the Selected Products

Compound **6a**: 5-Morpholin-4-yl-4-phenyl-thiophene-2-carboxylic Acid m-Tolylamide

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.70 (d, $J = 7.22$ Hz, 2H), 7.63 (s, 1H), 7.61 (s, 1H), 7.50 (m, 1H), 7.41–7.45 (m, 3H), 7.33 (d, $J = 7.4$ Hz, 1H), 7.26 (t, $J = 7.8$ Hz, 1H), 6.98 (d, $J = 7.4$ Hz, 1H), 3.80 (t, $J = 4.6$ Hz, 4H), 3.03 (t, $J = 4.6$ Hz, 4H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 160.42, 158.65, 139.41, 138.22, 135.92, 131.13, 129.30, 129.13, 128.06, 127.57, 127.38, 127.20, 125.51, 121.10, 117.50, 66.84, 52.81, 21.92; MS (EI) m/z: 378 (M^+).

Compound **6b**: 5-Morpholin-4-yl-4-phenyl-thiophene-2-carboxylic Acid (4-Chloro-phenyl)-amide

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.73 (s, 1H), 7.68 (d, $J = 7.53$ Hz, 2H), 7.58–7.61 (m, 3H), 7.43 (t, $J = 7.57$ Hz, 2H), 7.32–7.34 (m, 3H), 3.78 (t, $J = 4.6$ Hz, 4H), 3.02 (t, $J = 4.6$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 160.97, 158.85, 138.03, 136.10, 131.73, 128.96, 128.93, 128.57, 127.87, 127.69, 127.33, 126.85, 121.82, 66.68, 52.69; MS (EI) m/z: 398 (M^+).

Compound **6c**: 5-Morpholin-4-yl-4-phenyl-thiophene-2-carboxylic Acid Naphthalene-1-ylamide

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.21 (s, 1H), 7.88–7.95 (m, 3H), 7.70–7.74 (m, 4H), 7.42–7.53 (m, 5H), 7.33 (d, $J = 7.4$ Hz, 1H), 3.80 (t, $J = 4.6$ Hz, 4H), 3.02 (t, $J = 4.6$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 161.33, 158.75, 135.95, 134.57, 132.73, 131.73, 129.14, 129.12, 128.10, 128.03, 127.57, 127.39, 126.83, 126.72, 126.43, 126.41, 126.15, 121.93, 121.41, 66.85, 52.80; MS (EI) m/z: 414 (M^+).

Compound **7b**: (4-Bromo-phenyl)-(5-morpholin-4-yl-4-phenyl-thiophene-2-yl)-methanone

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.73 (d, $J = 8.26$ Hz, 2H), 7.65 (d, $J = 8.28$ Hz, 2H), 7.59 (d, $J = 7.54$ Hz, 2H), 7.53 (s, 1H), 7.43 (t, $J = 7.57$, 2H), 7.32 (t, $J = 8.34$ Hz, 1H), 3.80 (t, $J = 4.6$ Hz, 4H), 3.12 (t, $J = 4.6$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 186.42, 163.34, 139.22, 137.56, 135.97, 132.7, 130.81, 130.52, 129.23, 128.14, 127.78, 126.80, 126.68, 66.60, 52.24; MS (EI) m/z: 428 (M^+).

Compound **7f**: 4-Biphenyl-4-yl-5-morpholin-4-yl-thiophene-2-carboxylic Acid Ethyl Ester

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.84 (s, 1H), 7.78 (d, $J = 8.14$ Hz, 2H), 7.65–7.67 (m, 4H), 7.48 (t, $J = 7.55$ Hz, 2H), 7.38 (t, $J = 7.29$ Hz, 1H), 4.38 (q, $J = 7.1$ Hz, 2H), 3.81 (t, $J = 4.6$ Hz, 4H), 3.07 (t, $J = 4.6$ Hz, 4H), 1.43 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 162.58, 159.91, 140.92, 140.21, 136.04, 134.90, 129.23, 128.31, 127.81, 127.67, 127.34, 126.78, 121.88, 66.78, 61.15, 52.74, 14.95; MS (EI) m/z: 393 (M^+).

Compound **8**: 4-(1-Benzylsulfanyl-2-phenyl-buta-1,3-dienyl)-morpholine

^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 9.96 (s, 1H), 7.36–7.32 (m, 5H), 7.28 (d, $J = 9.8$ Hz, 2H), 7.23 (t, $J = 7.41$ Hz, 1H), 7.01 (d, $J = 7.33$ Hz, 2H), 3.96 (s, 2H), 3.56 (t, $J = 4.68$ Hz, 4H), 3.13 (t, $J = 4.68$ Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 189.91, 167.39, 137.04, 136.93, 130.73, 129.25, 129.16 128.71, 128.22, 127.17, 122.14, 66.77, 52.71, 40.36; MS (EI) m/z: 339 (M^+).

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REFERENCES

1. Loupy, A. *Microwaves in Organic Synthesis*; John Wiley-VCH: New York, 2002.
2. Habibi, D.; Marvi, O. Montmorillonite KSF clay as an efficient catalyst for the synthesis of 1,4-dioxo-3,4-dihydrophthalazine-2(1*H*)-carboxamides and -carbothioamides under solvent-free conditions using microwave irradiation. *Catal. Commun.* **2007**, *8*, 127.
3. Bengtson, A.; Hallberg, A.; Larhed, M. Fast synthesis of aryl triflates with controlled microwave heating. *Org. Lett.* **2002**, *4*, 1231.
4. Xu, L. W.; Xia, C. G.; Li, J. W.; Li, F. W.; Zhou, S. L. Efficient palladium/copper cocatalyzed C-N coupling reaction of unactivated aryl bromide or iodide with amino acid under microwave heating. *Catal. Commun.* **2004**, *5*, 121.
5. Gold, H.; Ax, A.; Vrang, L.; Samuelsson, B.; Karlen, A.; Hallberg, A.; Larhed, K. M.; Anders, H.; Mats, L. Fast and selective synthesis of novel cyclic sulfamide HIV-1 protease inhibitors under controlled microwave heating. *Tetrahedron* **2006**, *62*, 4671.
6. Yadav, G. D.; Desai, N. M. Novelties of low energy microwave irradiation in tri-phase vis-à-vis bi-liquid phase-transfer catalysis in selective etherification of aromatic phenols. *Catal. Commun.* **2006**, *7*, 325.
7. Bougrin, K.; Loupy, A.; Soufiaoui, M. Microwave-assisted solvent-free heterocyclic synthesis. *J. Photochem. Photobio. C.* **2005**, *6*, 139.
8. Moghaddam, M. F.; Zali- Boinee, H. An efficient and facile one-step synthesis of highly substituted thiophenes. *Tetrahedron* **2004**, *60*, 6085.
9. Pillai, A. D.; Rathod, P. D.; Xavier, F. P.; Vasu, K. K.; Padh, H.; Sudarsanam, V. Design synthesis and pharmacological evaluation of some

2-[4-morpholino]-5-substituted thiophenes as novel anti-inflammtory agents; generation of a novel anti-inflammatory pharmacophore. *Bio. Med. Chem.* **2004**, *12*, 4667.
10. Leban, J.; Kralik, M.; Mies, J.; Baumgartner, R.; Gassen, M.; Tasler, S. Biphenyl-4-ylcarbamoyl thiophene carboxylic acids as potent DHODH inhibitors. *Bio. Med. Chem.* **2006**, *16*, 267.
11. Rothemunt, P. A new Porphyrin synthesis. The synthesis of Porphin. *J. Am. Chem. Soc.* **1936**, *58*, 625.
12. Noack, A.; Hartman, H. Synthesis and characterisation of *N,N*-disubstituted 2-amino-5-acylthiophenes and 2-amino-5-acylthiazoles. *Tetrahedron* **2002**, *58*, 2137.
13. Gewald, K.; Schinke, E.; Bottcher, H. Heterocyclen aus CH-aciden Nitrilen, VIII. 2-Amino-thiophene aus methylenaktiven Nitrilen, Carbonyl-verbindungen und Schewefel. *Chem. Ber.* **1966**, *99*, 94.
14. Pinto, I. L.; Jarvest, R. L.; Serafinowska, H. T. The synthesis of 5-alkoxy and 5-amino substituted thiophenes. *Tetrahedron Lett.* **2000**, *41*, 1597.
15. Heyde, C.; Zug, I.; Hartmann, H. A simple route to *N,N*-dialkyl derivatives of 2-amino-5-thiophenecarboxylates. *Eur. J. Org. Chem.* **2000**, 3273.
16. Moghaddam, M. F.; Saeidian, H. Controlled microwave-assisted synthesis of ZnO nanopowder and its catalytic activity for *O*-acylation of alcohol and phenol. *Mater. Sci. Eng. B.* **2007**, *139*, 265.
17. Mirjafary, Z.; Saeidian, H.; Sadeghi, A.; Moghaddam, M. F. ZnO nano-particles: An efficient nanocatalyst for the synthesis of β-acetamido ketones/esters via a multi-component reaction. *Catal. Commun.* **2008**, *9*, 299.
18. Moghaddam, M. F.; Zali-Boinee, H. Oxidative cyclization of thiobenzanilides to benzothiazoles using *N*-benzyl-DABCO tribromide under mild conditions. *Synlett* **2005**, 1612.
19. Moghaddam, M. F.; Zali-Boinee, H. A versatile one-pot synthesis of 2,3,5-tri-substituted thiohenes from thiomorpholides. *Tetrahedron Lett.* **2003**, *44*, 6253.
20. Moghaddam, M. F.; Dekamin, M. G. Thia-Fries rearrangement of aryl sulfonates in dry media under microwave activation. *Tetrahedron Lett.* **2000**, *41*, 3479.
21. Moghaddam, M. F.; Porkaleh, H.; Zali-Boinee, H. Facile Double fries rearrangement of diesters under microwave irradiation; application to the synthesis of a biogenetically rare type of natural phenol. *Lett. Org. Chem.* **2006**, *3*, 123.
22. Moghaddam, M. F.; Ghafarzadeh, H. Microwave- assisted rapid hydrolysis and preparation of thioamides by Wilgerodt-Kindler reaction. *Synth. Commun.* **2001**, *31*, 317.
23. Moghaddam, M. F.; Saeidian, H.; Mirjafary, Z.; Sadeghi, A. KF-Al203 promoted synthesis of fully substituted new indeno- and naphtho-fused thiophenes under solvent-free conditions by controlled microwave heating. *Lett. Org. Chem.* **2007**, *4*, 576.
24. Moghaddam, M. F.; Oskoui, A. A.; Zali-Boinee, H. Rapid and selective acetalization of aldeheydes using anhydrous copper sulfate supported on

silica gel ($CuSO_4/SiO_2$) under microwave irradiation in solvent-free conditions. *Lett. Org. Chem.* **2005**, *2*, 151.
25. Schmittiling, A. E.; Sawyer, J. S. Selective desilylation of tert-butyldimethylsilyl ethers of phenols using potassium fluoride-alumina and ultrasound. *Tetrahedron Lett.* **1991**, *32*, 7207.