Tetrahedron Letters 53 (2012) 4921–4924

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted Hantzsch thiazole synthesis of *N*-phenyl-4-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)thiazol-2-amines from the reaction of 2-chloro-1-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)ethanones and thioureas

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ARTICLE INFO

Article history:
Received 8 June 2012
Revised 24 June 2012
Accepted 26 June 2012
Available online 4 July 2012

Keywords:
Microwave irradiation
(6-Phenylimidazo[2,1-*b*]thiazol-5-yl)thiazol-2-amine 2-chloro-1-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)ethanones
6-Phenylimidazo[2,1-*b*]thiazoles

ABSTRACT

N-Phenyl-4-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)thiazol-2-amines (**6a–q**) have been synthesized by the Hantzsch thiazole reaction of 2-chloro-1-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)ethanones (**4a–e**) with suitably substituted thioureas using microwave heating. The ethanones (**4a–e**) were prepared by the reaction of 6-phenylimidazo[2,1-*b*]thiazoles (**3a–e**) with chloroacetylchloride in refluxing 1,4-dioxane whereas the thiazoles (**3a–e**) were synthesized by the reaction of 2-bromo-1-phenylethanones (**2a–e**) with thiazol-2-amine in refluxing acetone.

Introduction

Many natural products and biologically active compounds containing imidazo[2,1-*b*]thiazole moieties have been synthesized and shown to exhibit potent biological activity.[1] As shown in Figure 1, tetramisole (**A**) is a strong anthelmintic in the treatment of many nematodes.[2] Thieno[3,2-*d*]pyrimidinone (**B**)[3] and 5,6-diarylimidazo[2,1-*b*][1,3]thiazoles (**C**),[4] are excellent antibacterial agents and C-2 aryl-substituted pilicides [thiazole ring-fused 2-pyridones (**D**)][5] exhibit anti-coccidial behavior. ^{11}C-labeled imidazo[2,1-*b*]benzothiazole (**E**)[6] has been shown to be a superb fluoroprobe in PET analysis of Alzheimer's disease. Milne et al.[7] have prepared compound (**F**) which possesses an imidazo[2,1-*b*]benzothiazole ring. Compound **F**, although unrelated in structure to resveratrol, showed a 1000-fold greater affinity toward SIRT1 than resveratrol. These workers also demonstrated that compound **F** binds to the SIRT1 enzyme–peptide substrate complex at an allosteric amino terminal site to the catalytic domain resulting in lower Michaelis constant for acetylated substrates. Compound **G** (Fig. 1) inhibits binding of radio labeled TARC (Thymus and Activation Regulated Chemokine) and MDC (Macrophase-derived Chemokine) to CCR4 receptors on the surface of CEM[8] and also inhibits the in vitro migration of CEM cells mediated by TARC.[8] Subsequently another research group identified hydrazone derivatives of imidazo[2,1-*b*]benzothiazoles as a potent antitumor agent.[9] It has also been reported that imidazo[2,1-*b*]benzothiazole system acts as a scaffold endowing dihydropyridines with selective cardiodepressant activities.[10]

For the past few years, our group has, also, been preparing biologically important heterocycles using microwave irradiation[11a–g] Of particular importance to this report, is our preparation of novel bis(2-thioxothiazolidin-4-one) derivatives,[11a] several of which possess strong neuroprotecting activities against Alzheimer's and Parkinson's diseases. We have now extended our research to the microwave-assisted synthesis of potentially biologically active *N*-phenyl-4-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)thiazol-2 amine derivatives (**6a–p**) in which imidazo[2,1-*b*]thiazole core moieties are attached to a variety of 2-aminothiazoles, and report the results herein. We were attracted to the Hantzsch synthesis since it has been one of the methods of choice for preparing aminothiazoles.[12] Most of these syntheses involve extended conventional heating and give aminothiazoles in mediocre yields. For example, *N*-thiazoyl α-amino acids were prepared in yields generally ranging from 18% to 55% in a one-pot, two-step, 7–15 h Hantzsch reaction.[13] There are only a few reports on microwave-assisted Hantzsch reactions.[14a–d] Thus this study should add to the increasing importance of microwave-assisted reactions in heterocyclic chemistry.[15]

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http://dx.doi.org/10.1016/j.tetlet.2012.06.116

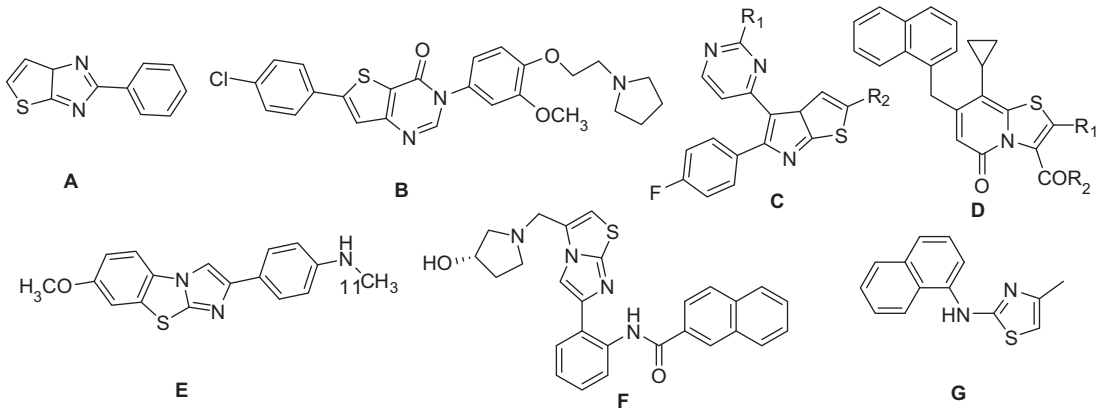
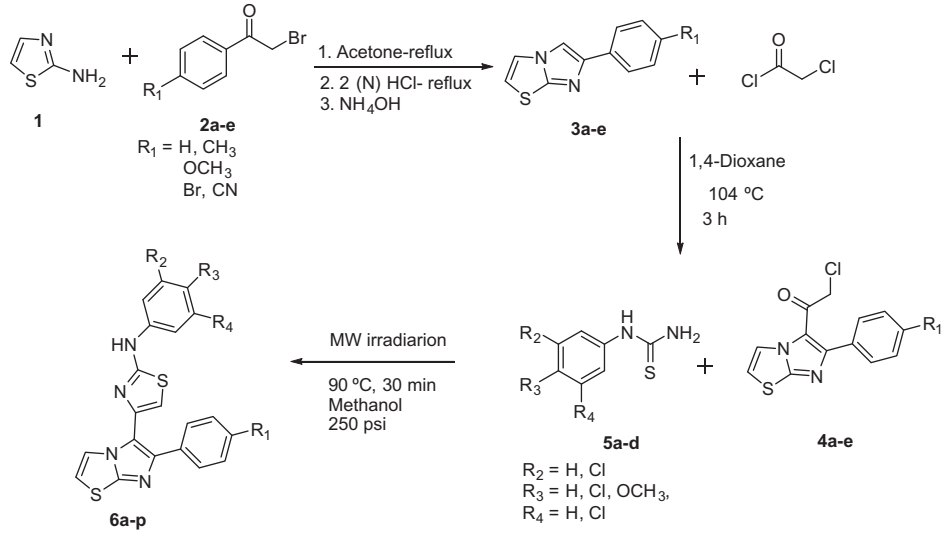


Figure 1. Imidazo[2,1-*b*]thiazoles and 2-aminothiazoles.



Scheme 1. Schematic representation for the synthesis of compounds **6a–p**.

Results and discussion

Scheme 1 outlines the synthesis of **6a–p**. Optimum conditions for carrying out the Hantzsch microwave-assisted reactions were ascertained by carrying out a series of reactions of 2-chloro-1-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)ethanones (**4a**) with *N*-phenylthiourea. The results, which are summarized in Table 1, showed that maximum yield of **6a** (95%) were obtained by heating at 90 °C for 30 min in methanol.

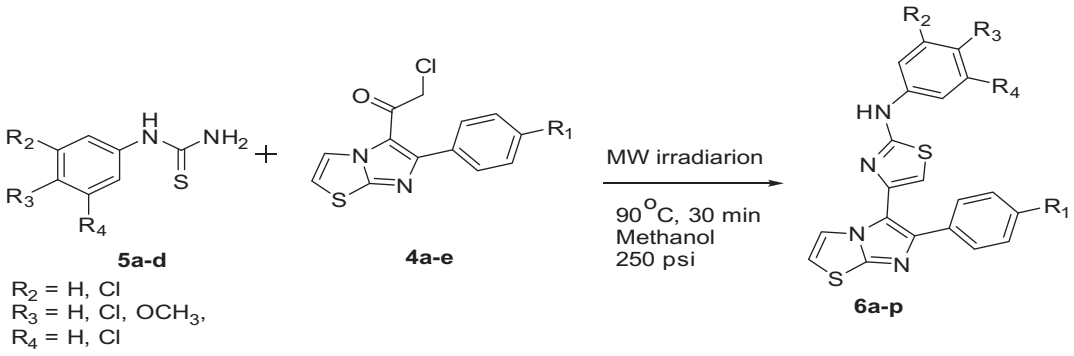
The results for the reactions of **6a–p** are shown in Table 2. Compounds **6a**–**p** were obtained in 89–95% yields and most of them are powder-like solids. They are insoluble in usual organic solvents such as, dichloromethane, ethyl acetate, THF, ethanol, or methanol but soluble in DMF or DMSO. The proposed structures of **6a–p** were confirmed, in part, by the presence of C=N signals around δ 164 ppm (indicative of an 2-aminothiazole ring) in the ^{13}C NMR spectra. The ^{1}H NMR spectra of these compounds showed a broad singlet (equivalent to 1H) around δ 11 ppm which corresponds to NH functionality. The starting 2-chloro-1-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)ethanones (**4a–e**) were prepared by refluxing 2.5 equiv of chloroacetylchloride and 1 equiv of 6-phenylimidazo[2,1-*b*]thiazoles (**3a–e**) in refluxing 1,4-dioxane. Although we tried other solvents, 1,4-dioxane proved to be superior. The structures of **4a**–**e** were confirmed by the presence of C=O signals around δ 180 ppm and the CH_2 signal around δ 47 ppm. The ^{1}H NMR spectra of **4a**–**e** showed characteristic singlets (equivalent to 2H) around δ 4 ppm which corresponds to $-CH_2$ functionality.

Table 1
Screening of solvents, reaction time, and temperature for synthesis of **6a**

Condition	Temp (°C)	Time (min)	Yield (%)
No solvent	90–120	15	Trace
Ethanol	90–120	15	79
Ethanol	90–120	30	85
Methanol	90	15	71
Methanol	90	30	95
Acetonitrile	90–100	15–30	55
Water	90–120	30–45	Trace
THF	70–100	30–45	Trace
n-Butanol	90–110	30–45	Trace
DME	90–110	30–45	Trace
Sulfonale	90–130	30–45	Trace
Benzene/toluene	90–110	30–45	Trace
DMF	90–110	30–45	Trace

Reaction condition: microwave irradiation using **4a**:**5a** (1:1 equiv) and 1 mmol of **4a**, solvent (2 mL) under 250 psi pressure in a capped specially designed microwave test tube.

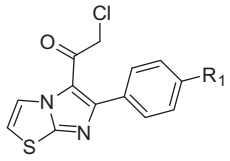
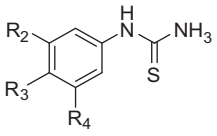
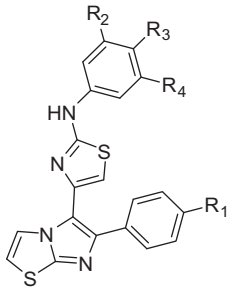
Table 2
The synthesis of *N*-phenyl-4-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)thiazol-2-amines (**6a–p**) by the microwave-assisted Hantzsch reaction of ethanone derivatives (**4a–e**) with substituted thioureas (**5a–d**)



5a-d
R_2 = H, Cl
R_3 = H, Cl, OCH_3,
R_4 = H, Cl

4a-e

6a-p

Entry	 **4**	 **5**	 **6**	Yield[a,b]	Yield[a,c]
1	**4a**, R_1 = H	**5a**, $R_2 = R_3 = R_4$ = H	**6a**, $R_1 = R_2 = R_3 = R_4$ = H	98	65
2	**4b**, R_1 = OCH_3	**5a**, $R_2 = R_3 = R_4$ = H	**6b**, R_1 = OCH_3, $R_2 = R_3 = R_4$ = H	96	45
3	**4c**, R_1 = CH_3	**5a**, $R_2 = R_3 = R_4$ = H	**6c**, R_1 = CH_3, $R_2 = R_3 = R_4$ = H	92	69
4	**4d**, R_1 = CN	**5a**, $R_2 = R_3 = R_4$ = H	**6d**, R_1 = CN, $R_2 = R_3 = R_4$ = H	90	60
5	**4e**, R_1 = Br	**5a**, $R_2 = R_3 = R_4$ = H	**6e**, R_1 = Br, $R_2 = R_3 = R_4$ = H	95	78
6	**4a**, R_1 = H	**5b**, $R_2 = R_4$ = H, R_3 = Cl	**6f**, R_1 = H, $R_2 = R_4$ = H, R_3 = Cl	93	74
7	**4a**, R_1 = H	**5c**, $R_2 = R_4$ = Cl, R_3 = H	**6g**, R_1 = H, $R_2 = R_4$ = Cl, R_3 = H	99	88
8	**4a**, R_1 = H	**5d**, $R_2 = R_4$ = H, R_3 = OCH_3	**6h**, R_1 = H, $R_2 = R_4$ = H, R_3 = OCH_3	90	53
9	**4c**, R_1 = CH_3	**5d**, $R_2 = R_4$ = H, R_3 = OCH_3	**6i**, R_1 = CH_3, $R_2 = R_4$ = H, R_3 = OCH_3	89	47
10	**4e**, R_1 = Br	**5c**, $R_2 = R_4$ = Cl, R_3 = H	**6j**, R_1 = Br, $R_2 = R_4$ = Cl, R_3 =	98	67
11	**4c**, R_1 = CH_3	**5b**, $R_2 = R_4$ = H, R_3 = Cl	**6k**, R_1 = CH_3, $R_2 = R_4$ = H, R_3 = Cl	93	81
12	**4c**, R_1 = CH_3	**5c**, $R_2 = R_4$ = Cl, R_3 = H	**6l**, R_1 = CH_3, $R_2 = R_4$ = Cl, R_3 = H	96	80
13	**4e**, R_1 = Br	**5b**, $R_2 = R_4$ = H, R_3 = Cl	**6m**, R_1 = Br, $R_2 = R_4$ = H, R_3 Cl	89	55
14	**4e**, R_1 = Br	**5d**, $R_2 = R_4$ = H, R_3 = OCH_3	**6n**, R_1 = Br, $R_2 = R_4$ = H, R_3 = OCH_3	91	58
15	**4d**, R_1 = CN	**5c**, $R_2 = R_4$ = Cl, R_3 = H	**6o**, R_1 = CN, $R_2 = R_4$ = Cl, R_3 = H	98	67
16	**4b**, R_1 = OCH_3	**5c**, $R_2 = R_4$ = Cl, R_3 = H	**6p**, R_1 = OCH_3, $R_2 = R_4$ = Cl, R_3 = H	96	70

[d] 3.6 mmol:23.4 mmol/10 mL MeOH.
[a] Isolated yield, all compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS analysis.
[b] MW, 30 min, 90 °C.1 mmol:06 mmol **4**:**5**/2 mL MeOH.
[c] Conventional heating for 8 h at 90 °C; 0.1 mmol:06 mmol **4**:**5**/2 mL MeOH.

The starting 6-phenylimidazo[2,1-*b*]thiazoles (**3a–e**) were synthesized according to a literature[16] procedure. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, DEPT-135, and HRMS analysis.

Interestingly, the same reactions carried out under conventional reflux conditions using methanol as a solvent gave **6a–p** in lower yields (Table 2), required longer reaction time (8 h), and/or the products required rigorous purification. However, the microwave reactions provided **6a–p** in higher yields in faster reaction times (usually less than 30 min) and the pure products were obtained by simple washing of the crude products with cold ethanol. Our method compares favorably to that reported for the microwave-assisted synthesis of functionalized simple 2-aminothiazoles[14a] with respect to yield and reaction time. However a higher temperature was needed in our procedure presumably due to the more complex nature of the phenylimidazo[2,1-*b*]thiazol-5-yl)thiazol-2-amine products.

In conclusion, we have successfully developed an easy practical access to a novel series of *N*-phenyl-4-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)thiazol-2-amine derivatives. Thus, the mild reaction condition, easy work up procedure, good to excellent yields, and readily available starting materials make this reaction an attractive method for the preparation of title compounds. To the best of our knowledge, there has been no reported example of synthesis of this type of biologically important molecule. Efforts directed toward the synthesis of other important drug molecules with imidazo[2,1-*b*]thiazol-5-yl)thiazole moieties by microwave irradiation are ongoing in our laboratory. Also work is in progress to obtain biological activity (antibacterial, antifungal, anticancer, antitumor, and neuroprotective kinase inhibitory activity) of these important compounds. Results in these studies will be presented in due course.

Acknowledgments

The authors are grateful to NIH (IRC2NS064950) for generous financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.116.

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