Tetrahedron Letters 49 (2008) 7220–7222

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A facile synthesis of structurally novel 1-aryl-2-arylamino-4-alkyl/phenyl-5-aroyl-1*H*-imidazoles from amidinothioureas

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ARTICLE INFO

Article history:
Received 18 August 2008
Revised 30 September 2008
Accepted 3 October 2008
Available online 7 October 2008

Keywords:
2-Aminoimidazoles
Amidinothioureas
Thiophile
Desulfurization

ABSTRACT

We report here a convenient and efficient two-step synthesis of 1-aryl-2-arylamino-4-alkyl/phenyl-5-aroyl-1*H*-imidazoles from easily available amidinothioureas. Guanylation of amidinothioureas **1** using mercury(II) chloride as a thiophile yielded amidinoguanidines **2**, which reacted with various phenacyl bromides under mild conditions to afford the corresponding diversely functionalized imidazoles **3** in moderate to good yields.

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The imidazole moiety which incorporates both π-excessive and π-deficient characteristics[1] has proven to be a master key in a range of drug target families.[2] Compounds incorporating the imidazole scaffold are known as inhibitors of p38 MAPK,[3a] JNK3,[3b] B-Raf kinase,[3c] transforming growth factor β-1 (TGF-β1) type 1 activin receptor-like kinase,[3d] acyl-CoA: cholesterol *O*-acyl transferase (ACAT)[3e] and anti-amoebic agents.[3f] Imidazoles substituted with a 2-arylamino functionality have been reported to have potent and selective agonist activity at α_2-adrenoceptors.[4] Pharmacological evaluation of diversely functionalized imidazoles against a desired target can lead to meaningful structure—activity relationship (SAR) to facilitate the discovery and design of drug-like candidates. Due to this high level of importance and utility, an ever increasing amount of research has been focused on the preparation and functionalization of the imidazole moiety.[5]

Recently, several alkaloids possessing the 2-aminoimidazole moiety have been isolated and found to be biologically active.[6] Even though several methodologies for synthesis of 2-aminoimidazoles have been reported in the literature, only few describe the efficient synthesis of polysubstituted 2-aminoimidazoles, in particular, 4,5-disubstituted-2-aminoimidazoles.[7] A recent microwave-assisted protocol gives easy access to substituted 2-aminoimidazoles.[8] A convenient method for the synthesis of closely related 2-arylimidazoles might lead to a biologically important novel class of heterocycles. The synthesis of 5-aroyl imidazoles can be problematic, particularly using the Friedel–Crafts reaction as deactivation occurs upon complexation of the basic imidazole with the Lewis acid.[9] Therefore, a general synthetic methodology which would result in diversely functionalized 1-aryl-2-arylamino-4-alkyl/aryl-5-aroyl-1*H*-imidazoles could find applications in medicinal chemistry. Imidazoles possessing structural features of the title compound, to our knowledge, are unknown in the literature.

The synthesis of biologically active 2-aminothiazoles from amidinothioureas has been reported by our group.[10] In continuation of this work, we reasoned that the title compounds could be prepared from amidinothioureas via guanylation and cyclization with α-bromo carbonyl compounds. Herein, we report a general protocol for the synthesis of highly functionalized 2-aminoimidazoles.

Amidinothioureas can be obtained easily by reacting isothiocyanates with amidines. Amidinothioureas have been used as synthetic precursors to 2-aminothiazoles via reaction with various α-haloketones.[11] The corresponding amidinoguanidines can be synthesized through guanylation of amidinothioureas. Various mercury salts as well as other thiophiles have been used for the guanylation of thioureas.[12] Thus, we used various mercury salts for the guanylation of amidinothioureas and achieved the best results using mercury(II) chloride as a thiophile. $HgC1_2$ promotes desulfurization of thiourea to produce the corresponding carbodiimide intermediates; amines were then added to the carbodiimides to yield guanidine products.[13] The desulfurization of the substituted amidinothioureas was monitored visually based on the formation of the black precipitate of HgS. The use of $HgCl_2$ was limited to the guanylation of thiourea substrates having one hydrogen on each nitrogen. Here, we have efficiently demonstrated

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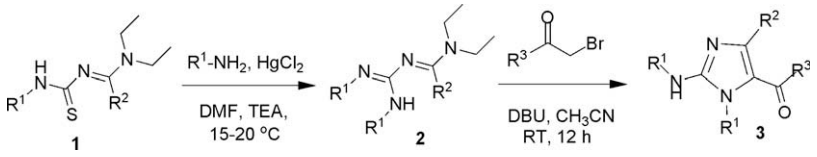
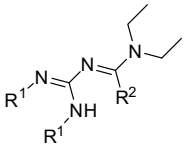
doi:10.1016/j.tetlet.2008.10.012



Scheme 1.

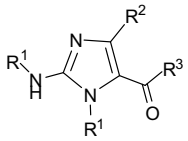
Table 1
Synthesis of amidinoguanidines **2** from amidinothioureas **1**



Entry	R^1	R^2	Product	Mp (°C)	Yield[a] (%)
1	C_6H_5	CH_3	**2a**	198–200	75
2	4-ClC_6H_4	CH_3	**2b**	215–217	70
3	4-MeC_6H_4	C_6H_5	**2c**	182–184	80
4	4-ClC_6H_4	C_6H_5	**2d**	185–187	68
5	C_6H_5	C_6H_5	**2e**	158–160	70
6	4-MeC_6H_4	CH_3	**2f**	167–169	70
7	4-ClC_6H_4	C_4H_9	**2g**	Oil	65

[a] Isolated yield.

Table 2
Synthesis of 1-aryl-2-arylamino-4-alkyl/phenyl-5-aroyl-1*H*-imidazoles



Entry	R^1	R^2	R^3	Product	Mp (°C)	Yield[a] (%)
1	C_6H_5	CH_3	4-ClC_6H_4	**3a**	128–130	55
2	C_6H_5	CH_3	4-MeC_6H_4	**3b**	172–174	60
3	4-ClC_6H_4	CH_3	4-ClC_6H_4	**3c**	190–192	58
4	4-ClC_6H_4	CH_3	4-MeC_6H_4	**3d**	117–119	65
5	4-MeC_6H_4	CH_3	4-ClC_6H_4	**3e**	215–217	68
6	C_6H_5	C_6H_5	4-MeC_6H_4	**3f**	204–206	68
7	4-ClC_6H_4	C_6H_5	4-ClC_6H_4	**3g**	207–209	55
8	4-ClC_6H_4	C_6H_5	4-MeC_6H_4	**3h**	186–188	58
9	4-MeC_6H_4	C_6H_5	4-ClC_6H_4	**3i**	239–241	65
10	4-MeC_6H_4	C_6H_5	4-MeC_6H_4	**3j**	221–223	60
11	4-ClC_6H_4	C_4H_9	4-ClC_6H_4	**3k**	133–135	58

[a] Isolated yield.

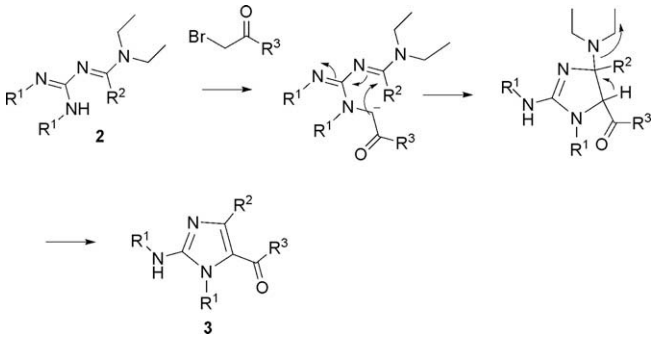
the $HgCl_2$-promoted guanylation of amidinothioureas **1** to generate a wide range of amidinoguanidines **2** (Scheme 1).

The scope of the guanylation reaction was explored for a variety of amidinothioureas and the results are summarized in Table 1. The reaction conditions were consistent and the yields ranged from 65% to 80%.

Our ultimate aim was to synthesize diversely functionalized imidazoles using cheap and readily available reagents under mild conditions. Initially, we performed the reaction of symmetrical amidinoguanidines **2** with phenacyl bromide at room temperature in the presence of KOBu-*t*. The formation of the imidazole moiety was apparent from the dark yellow spot on the TLC and after column purification, it was identified as the desired compound by LCMS. On confirmation of the feasibility of the cyclization reactions of phenacyl bromides with substrate **2** to give imidazoles **3,** we undertook further investigations using different bases (DBU, NaH, K_2CO_3, and KOBu-*t*) and solvents (THF, DMF, and acetonitrile) at room temperature to optimize the conditions. In the reaction of **2** with phenacyl bromides, the best results were obtained when DBU was used as the base in acetonitrile which is used as solvent at room temperature for 12 h. (Scheme 1, Table 2).

The generality of this new synthetic method for the efficient construction of 1,2,4,5-tetrasubstituted imidazoles was investigated by employing these optimized conditions. The results are summarized in Table 2. The reaction presumably proceeds through N-alkylation of the phenacyl bromide followed by attack of the carbanion on the amidino carbon and elimination of diethylamine (Scheme 2). A variety of substrates, including functionalized aromatic for variation of the substituents at the imidazole one and two positions, methyl/phenyl at the imidazole 4 position, and different aroyl groups at the 5 position were demonstrated. However, our efforts to cyclize the corresponding amidinoguanidines for the synthesis of imidazoles with alkyl substituents at positions 1 and 2 failed. The generality of this method for alkyl substituents at position 4 was studied by synthesizing an imidazole with an *n*-butyl group at this position (Table 2, entry 11).

In conclusion, we have reported a convenient two-step synthesis of biologically important 1-aryl-2-arylamino-4-alkyl/aryl-5-aroyl-1*H*-imidazole derivatives from easily available amidinothioureas under mild conditions. The reaction is applicable to a wide range of substituted anilines, phenacyl bromides, and amidines. Work is underway in our laboratory to further explore the scope of this reaction.



Scheme 2.

Acknowledgments

J.C.K. and A.B.B. thanks B. V. Patel PERD centre for the award of research fellowship. We thank Prof. Harish Padh, Director, B.V. Patel PERD centre, for constant encouragement and support.

Supplementary data

General experimental procedures and spectral data for new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.012.

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