Tetrahedron Letters 50 (2009) 3955–3958

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A convenient synthesis of di- and trisubstituted 2-aminoimidazoles from 1-amidino-3-trityl-thioureas

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ARTICLE INFO

Article history:
Received 18 March 2009
Revised 16 April 2009
Accepted 22 April 2009
Available online 3 May 2009

Keywords:
2-Aminoimidazoles
Amidinothioureas
Thiophile
Guanidines

ABSTRACT

Convenient synthesis of 2-amino-1,5-disubstituted and 2-amino-1,4,5-trisubstituted imidazoles has been reported using readily available starting materials and simple reagents under mild conditions. Guanylation of 1-amidino-3-trityl-thioureas **1** and **7** using mercury(II) chloride (Caution) as a thiophile resulted in corresponding guanidines **2** and **8** which on reaction with α-bromo ketones yielded 2-tritylaminoimidazoles. Deprotection of 2-tritylaminoimidazoles using trifluoroacetic acid at room temperature furnished desired 2-aminoimidazoles **4** and **10** in good to moderate yields.

Heterocyclic moieties often provide framework for pharmacophoric function and sometimes are part of pharmacophore itself.[1] The assembly of various structural fragments to the heterocyclic molecular scaffold can provide a facile framework as binding epitopes to macromolecular targets. Five-membered heterocycles in particular have proved to be productive and popular in the design of drugs. These rings can pack a relatively large number of polarized bonds in a relatively small molecular space and also can offer a convenient framework to which necessary side chains can be attached.[2] As representatives of these compounds, 2-aminoimidazoles have been identified as an important class of heterocycles due to their presence in many pharmacologically active substances and marine natural products.[3] Compounds incorporating 2-aminoimidazoles have been reported to possess potential *anti*-cancer,[4] *anti*-fungal,[5] and nitric oxide synthase inhibitory activities.[6] Therefore, development of simple and convenient synthetic procedures for such nitrogen-containing heterocycles represents an attractive and interesting area of research in synthetic organic and medicinal chemistry.

There are only a few approaches that describe the direct synthesis of 1-substituted 2-aminoimidazoles. The earliest method involves condensation of α-aminocarbonyl compounds with cyanamide or their synthetic equivalents.[7,8] This method is most commonly used for the direct construction of the 2-aminoimidazole ring. Other general applicable strategies are cyclocondensation of 2-aminopyrimidines with α-bromocarbonyl compounds followed by the cleavage of the intermediary imidazo[1,2-*a*]pyrimidin-1-ium salts with an excess of hydrazine,[9] iminophosphorane-mediated cyclization of α-azido esters,[10] ammonolysis of 2-amino-1,3-oxazol-3-ium salts,[11] sequential functionalization of 1,2-diprotected imidazole ring with different electrophiles.[12] Nevertheless, to match the increasingly scientific and practical demands for functionalized 2-aminoimidazoles, it is still of continued interest and of great importance to explore novel and efficient synthetic approaches for such heterocycles. The synthesis of 2-amino-5-aroyl/acyl imidazoles can be problematic, particularly using the Friedel–Crafts reaction, as deactivation occurs upon complexation of the basic imidazole with the Lewis acid.[13] Because of this limitation, a convenient method for the synthesis of 2-amino-1-aryl-4-substituted/unsubstituted-5-aroyl/acyl-imidazoles would find applications in medicinal chemistry.

Amidinothioureas have been studied by our group for the synthesis of biologically important 2-aminothiazoles.[14] We have recently explored amidinothioureas for the synthesis of highly substituted 2-arylamino imidazoles,[15] but this methodology was unable to give free amino group at the imidazole 2 position. We required a general method that would be amenable to preparation of analogues of different bioactive marine alkaloids possessing a 2-aminoimidazole skeleton. Therefore, we wish to report the development of a new method meeting these requirements. This method would result in medicinally useful compound library to study their biological activities and structure–activity relationships.

Reaction of trityl isothiocyanate with excess of amidines in diethyl ether furnished 1-amidino-3-trityl-thioureas **1** as white solids. As described in our previous communication, the corresponding guanidines **2** were obtained through the reaction of thioureas **1** with various anilines in presence of mercury(II) chloride[†] as thiophile (Scheme 1, Table 1, entries 1–4).[15] In comparison with *p*-substituted anilines, the reaction with *o*-substituted

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† Caution.

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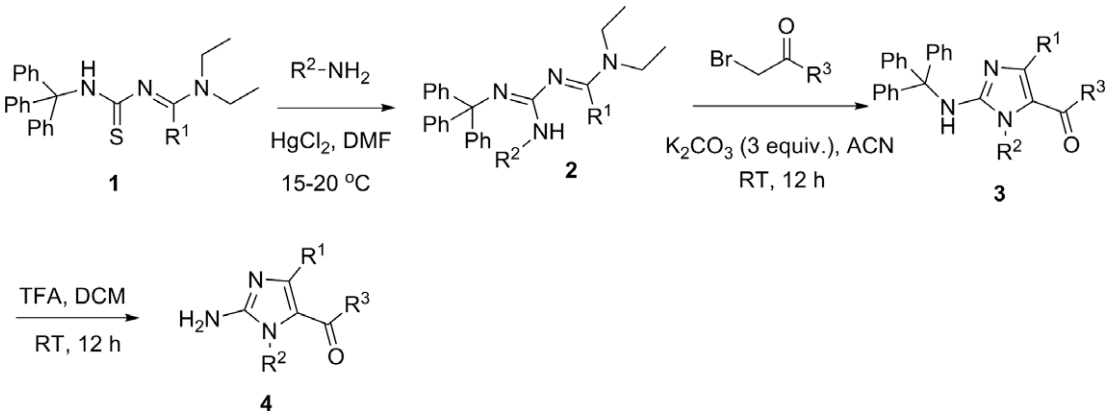
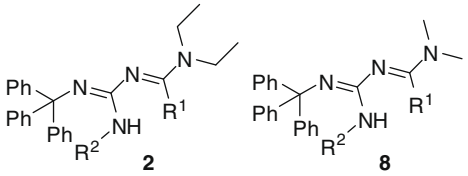
doi:10.1016/j.tetlet.2009.04.083



Scheme 1.

Table 1
Synthesis of *N*-amidino-*N′*-aryl-*N″*-trityl-guanidines

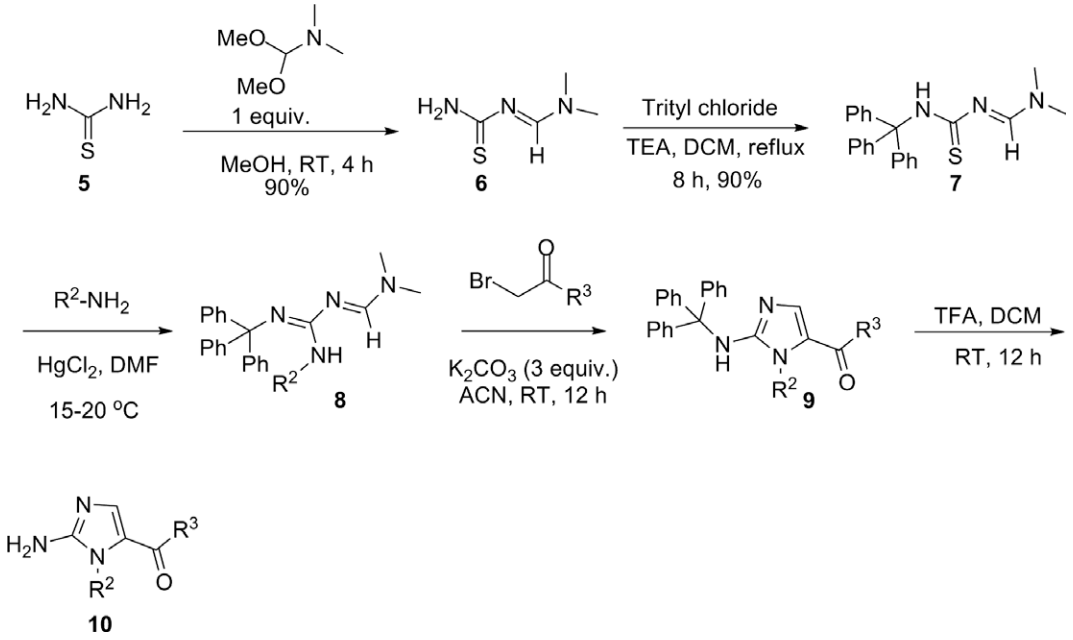


Entry	Product	R^1	R^2	Yield[a]
1	**2a**	CH_3	4-$OMeC_6H_4$	65
2	**2b**	CH_3	4-MeC_6H_4	67
3	**2c**	CH_3	2-ClC_6H_4	48
4	**2d**	CH_3	2-MeC_6H_4	50
5	**2e**	4-MeC_6H_4	4-ClC_6H_4	25
6	**8a**	H	4-FC_6H_4	78
7	**8b**	H	4-ClC_6H_4	70
8	**8c**	H	C_6H_5	65

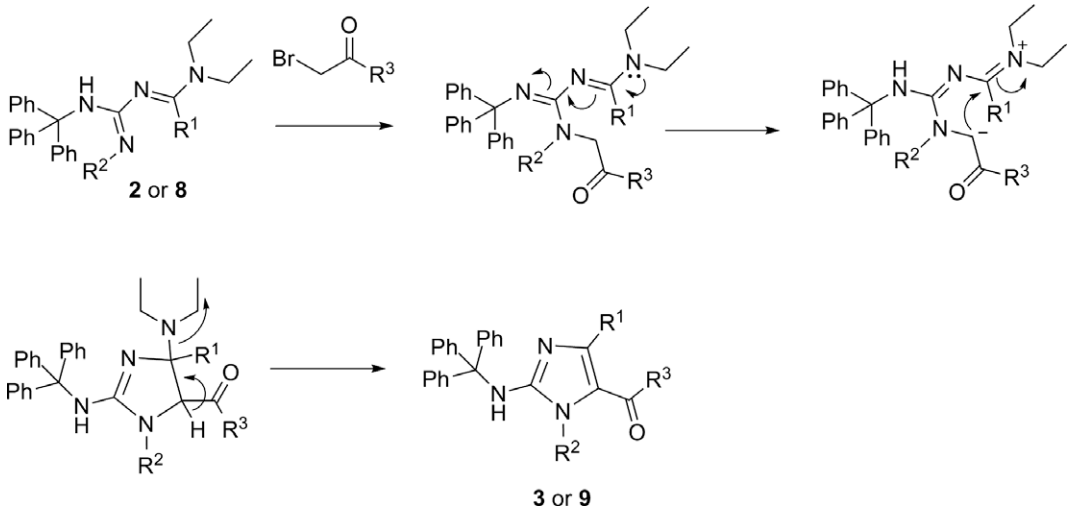
[a] Isolated yield.

anilines afforded the corresponding guanidines in slightly lower yield (Table 1, entries 3 and 4). Guanidine **2e** (R^1 = 4-MeC_6H_4) was obtained in lowest yield (Table 1, entry 5, 25%). Synthesis of guanidines **8a–c** was achieved starting from the thiourea (Scheme 2.). Monocondensation of thiourea with dimethylformamide dimethyl acetal (DMFDMA) was achieved to give thiourea **6** in 90% yield when methanol was employed as the solvent.[16] In agreement with the reported studies, our efforts failed to produce corresponding guanidines using N-monosubstituted (terminal) thiourea **6**.[17] Therefore, we protected the terminal amino group by reacting thiourea **6** with trityl chloride in dichloromethane using triethylamine as the base to give 1-amidino-3-trityl-thiourea **7**. Reaction of amidinothiourea **7** with anilines in presence of mercury(II) chloride† afforded guanidine **8a–c** in good yield (Scheme 2, Table 1, entries 6–8).

We performed several experiments for reaction of guanidines **2** or **8** with phenacyl bromides using different bases (NaH, KOBu-*t*, DBU, and K_2CO_3) and solvents (acetonitrile, THF, acetone, and 1,4-dioxane) at room temperature to obtain the desired imidazoles **3** or **9**. Our experiments failed to achieve imidazoles **3** through cyclization of guanidines **2** with phenacyl bromides using hindered base like *t*-KOBu in acetonitrile at room temperature. Due to the presence of bulky trityl group in the guanidines **2** or **8**, *t*-KOBu invariably failed to abstract the proton from nitrogen atom. we ob-



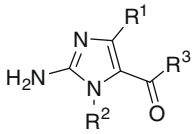
Scheme 2.



Scheme 3.

tained the best results for the cyclization of substituted guanidines **2** or **8** with various phenacyl bromides to give imidazoles **3** or **9** when K_2CO_3 (3 equiv) was used as the base in acetonitrile as solvent at room temperature (Schemes 1 and 2). Due to the presence of bulky trityl group, the reaction presumably proceeds through selective N-alkylation of the phenacyl bromides at the nitrogen atom directly attached to the aryl ring. The formation of the heterocycle takes place by the attack of carbanion on amidino carbon and elimination of diethylamine (Scheme 3). Deprotection of 2-tritylamino imidazoles using trifluoroacetic acid at room temperature resulted in desired 1,4,5-trisubstituted 2-aminoimidazoles **4** (Table 2). All the reactions between guanidines and phenacyl bromides, with systematic variation of R^1, R^2, and R^3 proceeded smoothly to afford the corresponding imidazole **3** or **9**, which were detritylated to give desired imidazoles **4a–d**, **4f**, **10a–d**, and **10f** in good to moderate yields (Table 2, entries 1–4, 6, 9–12, and 14). Reaction of guanidines **2b** and **8b** with α-bromo-4-acetyl pyridine hydrobromide, when subjected to the identical reaction conditions mentioned previously, furnished 2-aminoimidazole **4e** and **10e** as novel entries (Table 2, entries 5 and 13).

Table 2
Synthesis of 2-amino-1,5-disubstituted imidazoles and 2-amino-1,4,5-trisubstituted imidazoles



Entry	Product	R^1	R^2	R^3	Yield[a]
1	**4a**	CH_3	4-$OMeC_6H_4$	4-ClC_6H_4	65
2	**4b**	CH_3	4-MeC_6H_4	4-$OMeC_6H_4$	60
3	**4c**	CH_3	2-ClC_6H_4	4-MeC_6H_4	52
4	**4d**	CH_3	2-MeC_6H_4	4-ClC_6H_4	50
5	**4e**	CH_3	4-MeC_6H_4	4-Pyridyl	60
6	**4f**	CH_3	4-MeC_6H_4	4-SO_2Me	62
7	**4g**	CH_3	4-MeC_6H_4	C=N(O*n*Pr)COOEt	55
8	**4h**	4-MeC_6H_4	4-ClC_6H_4	4-MeC_6H_4	60
9	**10a**	H	4-FC_6H_4	4-MeC_6H_4	75
10	**10b**	H	4-FC_6H_4	4-ClC_6H_4	71
11	**10c**	H	4-FC_6H_4	4-$OMeC_6H_4$	68
12	**10d**	H	4-ClC_6H_4	4-MeC_6H_4	63
13	**10e**	H	4-ClC_6H_4	4-Pyridyl	55
14	**10f**	H	C_6H_5	4-SO_2Me	54
15	**10g**	H	4-FC_6H_4	C=N(OMe)COOEt	65

[a] Isolated yield.

Previously we had reported that the oxime moiety plays an important role in modulating *anti*-inflammatory activity.[18] It is noteworthy that the alkoxyimino feature is also present in many cephalosporin side chains and has given rise to cephalosporin drugs with not only better therapeutic index but also much better and broader spectrum of activity. Therefore, in the present work we were interested in studying the reaction of 4-bromo-2-alkoxyimiono-3-oxo-butyric acid ethyl ester side chain with substituted guanidines using general reaction conditions. This reaction resulted in biologically interesting imidazoles **4g** and **10g** in 55% and 65% yields, respectively (Table 2, entries 7 and 15).

In summary, we have developed a convenient method for synthesis of biologically interesting 1,5- and 1,4,5-substituted 2-aminoimidazoles. This reaction is applicable to a wide range of substituted anilines, α-bromo ketones, and amidines. Synthesis of 1,5-disubstituted 2-aminoimidazoles was achieved starting from inexpensive and readily available reagents. The total synthesis of marine alkaloids using this strategy is under investigation in our laboratory.

Acknowledgments

We thank Professor Harish Padh and Professor C. J. Shisoo, Directors, B.V. Patel PERD centre, for their constant encouragement and support. Reviewers' useful comments are gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.083.

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