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NIS-promoted guanylation of amines

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ABSTRACT

An efficient NIS-promoted guanylation reaction is described. This procedure allows the guanylation of primary and secondary amines through the reaction with di-Boc-thiourea and di-Boc-*S*-methylisothiourea, respectively. We demonstrated that the use of NIS compares favorably with existing methods and is an attractive alternative to heavy metal or Mukayama's reagent activation.

Guanidine-containing molecules display a wide range of biologically important roles. Many natural metabolites exhibiting biological activities possess the guanidine functionality,[1] and a number of synthetic pharmaceuticals incorporate the guanidine framework as exemplified by the influenza inhibitor zanamivir.[2] In addition, in aqueous media, the protonated guanidine is highly stable and is at the heart of the formation of selective non-covalent associations with anionic complementary groups.[3] Considering the growing importance and applications of guanidine derivatives in the field of medicinal and supramolecular chemistry, a continuous synthetic interest has been shown for the conversion of amines to the corresponding guanidines.[4–6] The most commonly used reagents for this conversion include pyrazole-1-carboxamidine derivatives,[7] diprotected triflylguanidines,[8] and protected thioureas as well as *S*-methylisothioureas derivatives, which need to be activated by toxic mercury salts[9,10] or by Mukaiyama's reagent.[11] As most of these methodologies have pro and cons, the choice of a guanylating reagent usually depends on the synthetic strategy as well as on the reactivity of the starting amine. In this context, the development of additional methodologies is of primary importance as it can allow to increase the chemical flexibility of this usually challenging reaction.[12]

During our ongoing project that aimed at the synthesis and the evaluation of guanidino derivatives designed for their ability to complex polyanionic biomolecules,[13] we were interested in replacing the traditional promoters ($HgCl_2$ and Mukaiyama's reagent) used for the guanylation of thio- and *S*-methylisothioureas. The problems associated with the use of toxic metal salts are well documented and Mukaiyama's reagent that is rather insoluble in most standard organic solvents generates a side product commonly challenging to be removed by chromatography.[14] Here, we would like to report our findings on the conversion of amines into protected guanidines using *N*-iodosuccinimide as the promoter.

N-Iodosuccinimide (NIS) is a source of electrophilic iodine, which allows stereoselective and regioselective reactions on various functional groups. It is particularly mentioned in the literature for regioselective iodination of activated aromatic compounds,[15] iodolactonization,[16] iodohydroxylation,[17] and as a promoter of glycosylation reactions with thioglycosides.[18] In analogy to the $HgCl_2$-promoted guanylation, we reasoned that the thiophilic NIS should behave as a soft Lewis acid, and thus coordinate the protected thio- and *S*-methylisothioureas. Adding Et_3N would lead to a carbodiimide intermediate, which should be trapped by the amine to provide the desired protected guanidine. To test this hypothesis, we reacted the commercially available di-Boc-thiourea (1 equiv) with benzylamine (1.2 equiv) in the presence of NIS (1 equiv) and triethylamine (2 equiv) in dichloromethane. After 3 h at room temperature (TLC monitoring) the protected guanidine (Table 1, entry 1) was obtained in 85% yield without any noticeable undesirable side product. To investigate the scope and limitations of this original use of NIS, a series of structurally diverse amines were subjected to the reaction conditions.

The results are illustrated in Table 1. From these data, several conclusions can be reached. First, unhindered primary amines (entries 1–4) can generally be guanylated in high yields (>80%) demonstrating, therefore, the ability of NIS to act as an efficient carbodiimide promoter. Second, hindered or unreactive primary amines appeared to react somewhat slower, nevertheless good yields could still be obtained after longer reaction times and higher temperatures (entries 5 and 6). It should be noted that NIS worked solely for activation of the sulfur-leaving group as no iodinated by-products was formed during the process. Although

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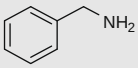
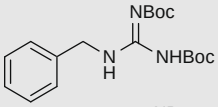
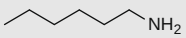
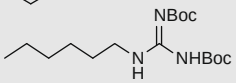
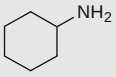
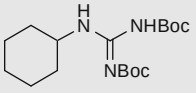
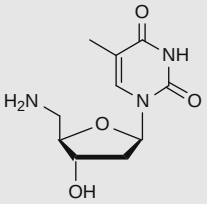
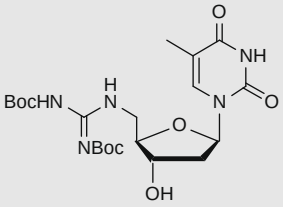
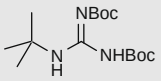
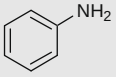
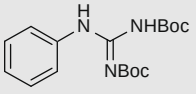
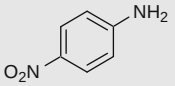
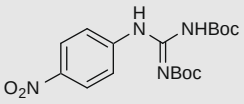
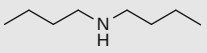
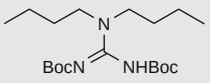
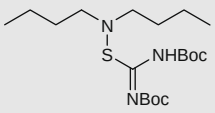
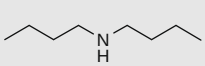
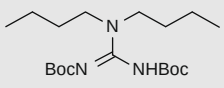
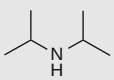
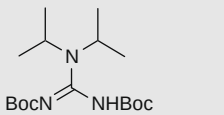
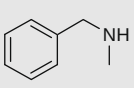
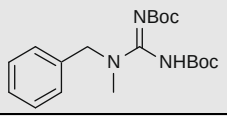
Table 1
Guanylation of amines using di-Boc-thiourea and NIS

Entry	Amine	Product	Yield (%)[a]	Time (h)
1			85	3
2			80	2
3			88	14
4			75	15
5			66	10[b]
6			71	16
7			15	22[b]
8			38	6
			25	

[a] Isolated yields.
[b] Refluxing dichloromethane.

it was not investigated, the reaction is, however, expected to produce iodinated by-products with substrates bearing reactive double bonds.[17] Interestingly, in the case of *N*,*N*-dibutylamine, we were able to isolate along with the expected guanidine a secondary product, which corresponds to the *S*-aminoisothiourea in 25% yield (entry 8, Supplementary data). This compound likely results from a competitive nucleophilic attack of the amine on the *S*-iodoisothiourea intermediate.[19] To circumvent this setback, we decided to evaluate the use of di-Boc-*S*-methylisothiourea in the presence of NIS. While these conditions could not be applied for the guanylation of primary amines as poor yields are obtained, they significantly facilitated the guanylation of secondary amines. In a typical reaction, NIS (1 equiv) and a slight excess of the *S*-methylisothiourea (1.5 equiv) were added to a solution of the amine (1 equiv) in DMF in the presence of 2 equiv of Et_3N. Under these reaction conditions, secondary amines were readily guanylated while no *S*-aminoisothiourea by-product could be detected (Table 2). As an example of a highly hindered secondary amine,

Table 2
Guanylation of secondary amines using di-Boc-*S*-methylisothiourea and NIS

Entry	Amine	Product	Yield[a] (%)
1			72
2			75
3			65

[a] Isolated yields.

diisopropylamine was guanylated in 75% yield, which compared favorably with all the other methods reported in the literature (entry 2).[4,8,11]

Although the precise reaction mechanism has not been clarified yet, we assume that a carbodiimide is the key intermediate, which is trapped by the amine affording the expected protected guanidine along with triethylamine iodide and succinimide derivatives.[20]

In conclusion, we demonstrated the ability of the thiophilic NIS to promote the conversion of amines into protected guanidines. This reaction was shown to easily tolerate a diversity of substitution patterns on the amines. Thioureas and *S*-methylisothioureas are common reagents for the synthesis of guanidines, and this conversion requires usually initial activation by heavy metal or the use of Mukaiyama's reagent. Guanylation with NIS eliminates without perceptible loss of yield the use of toxic heavy metals and the problem associated with their elimination. Moreover, it is an attractive alternative to Mukaiyama's reagent, especially when solubility and purification issues are encountered.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.073.

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