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Preparation of substituted semicarbazides from corresponding amines and hydrazines via phenyl carbamates

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ABSTRACT

A simple synthetic procedure for the conversion of amines and hydrazines into substituted semicarbazides was developed. The initial condensation between the desired amine and phenyl chloroformate into phenyl carbamate is followed by the addition of hydrazine under basic conditions. The reaction is tolerable to a variety of functional groups, with mild conditions and high percent yields.

Introduction

Semicarbazides[1] are a well known class of compounds with an extensive list of industrial and medicinal applications. Alkyl and aryl semicarbazides are good oxygen[2] and radical[3] scavengers as well as hardeners for epoxy resins.[4] Semicarbazides are also reported to be efficient catalysts for organometallic addition reactions[5] and metal delivery systems.[6]

Recently, there has been a renaissance of semicarbazide application in medicinal chemistry,[7] such as nitric oxide generators,[8] antioxidants,[9] kinase inhibitors,[10] and antivirals.[11] Their closely related analogues, semicarbazones, are also potent antimicrobials,[12] antivirals,[13] and anticonvulsants (epilepsy)[14] to name a few from the long list of biological activities.

There is a plethora of synthetic methods for the preparation of structurally diverse semicarbazides. Some of the oldest and simplest methods of preparation start from substituted ureas, hydrazine hydrates,[15] isocyanates,[16] and with carbamates.[17] In our search for antimicrobial agents with a variety of substituted semicarbazide moieties, our aim was to develop a large library of functionalized semicarbazide derivatives.

Results and discussion

Our goal was to develop a simple method for the preparation of semicarbazides that begins with readily available starting materials and can be carried out under mild reaction conditions while being highly efficient and economical. Since synthetic methods for the preparation of amines and hydrazines[18] are well studied, it is ideal to create an efficient methodology that combines these two building blocks into a structurally diverse library of semicarbazides (Fig. 1).

For our initial studies, we selected readily available ethyl chloroformate as a 'carbonyl source' to prepare carbamates from corresponding amines. Although the preparation of corresponding carbamates was straightforward, their transformation into semicarbazides was not as simple. While many semicarbazides can be prepared in this way, the reaction conditions are relatively harsh, requiring an elevated temperature for a long time period. This particular method is also limited to specific functional groups, which makes it ill-suited for developing a diverse library of multi-substituted semicarbazides. Using this method, the preparation of 4-pyridinyl, hydroxyphenyl, and alkyl semicarbazides gives mediocre results at the best (Scheme 1). In fact, in the reaction of ethyl hexylcarbamate with hydrazine at elevated temperatures, as well as with microwave heating, we were not able to detect the

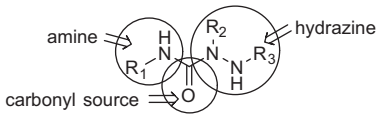

Figure 1. Semicarbazide building blocks.

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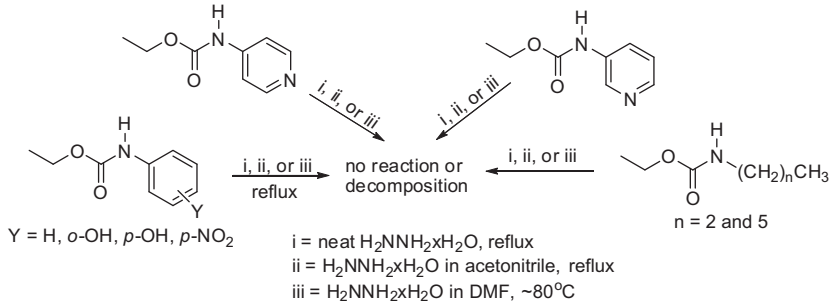


Scheme 1. Attempts to prepare semicarbazides under mild reaction conditions from ethyl carbamates.

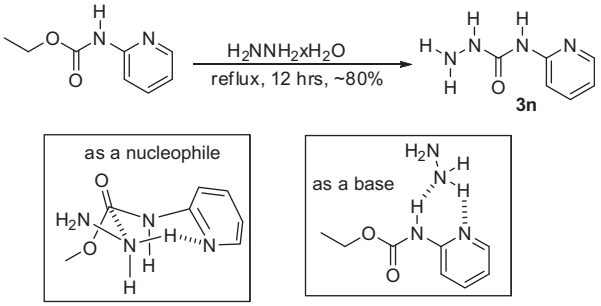


Figure 2. Possible explanation of higher reactivity *N*-2-pyridinylcarbamate.

formation of 4-hexylsemicarbazide. Reactions were performed in pure hydrazine hydrate, with hydrazine hydrate in acetonitrile and DMF as reaction media. In several cases studied, the only acceptable isolated yield was obtained for the preparation of 4-(2-pyridinyl)semicarbazide, which is shown in Figure 2. We believe this is due to the autocatalytic effect of the 2-pyridinyl group. The pyridine nitrogen can hydrogen bond with the hydrazine molecule, bringing it in close proximity to the carbonyl carbon. Here, it can react either as a nucleophile or more likely as a base to form 2-pyridinylisocyanate, which is followed by the addition of hydrazine to give 4-(2-pyridinyl)semicarbazide (**3n**). Therefore, the preparation of substituted semicarbazides from ethyl carbamates requires elevated temperature and the presence of a strong base. This approach is not applicable to prepare semicarbazides with temperature and strong base sensitive substituents. On the other hand, phenyl carbamates are more reactive, which makes them good substrates for the preparation of semicarbazides. However this also makes them harder to handle than ethyl carbamates.[19] However, our experience is that they can be prepared at room temperature or 0 °C and stored as pure solid material for months.

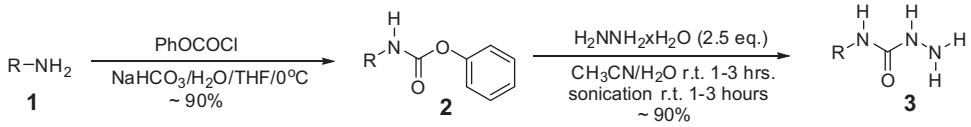
The synthesis of phenyl carbamates and their reactions are well documented in literature as a substitute for phosgene in the preparation of carbamate–urea derivatives.[20] Unfortunately, there is no general or economical method for the preparation of substituted

Table 1
Isolated yields for phenyl carbamates and 4-substituted semicarbazides

R	Carbamate **2**	Yield of **2** (%)	Semicarbazide **3**	Yield of **3** (%)
Ph	**2a**	98	**3a**	93
4-MeOPh	**2b**	97	**3b**	91
4-$EtCO_2$Ph	**2c**	97	**3c**	94
2-HOPh	**2d**	91	**3d**	96
3-HOPh	**2e**	91	**3e**	95
4-HOPh	**2f**	93	**3f**	97
4-PhOPh	**2g**	98	**3g**	98
4-PhPh	**2h**	98	**3h**	98
3,4,5-$(MeO)_3$Ph	**2i**	95	**3i**	91
2,5-$(MeO)_2$Ph	**2j**	94	**3j**	93
3,5-Me_2Ph	**2k**	91	**3k**	91
2,4-Cl_2Ph	**2l**	96	**3l**	95
3-BrPh	**2m**	92	**3m**	94
2-Pyridinyl	**2n**	91	**3n**	93
4-Pyridinyl	**2o**	93	**3o**	91
1-Naphthalenyl	**2p**	92	**3p**	95
2-Naphthalenyl	**2q**	97	**3q**	97
n-Propyl	**2r**	92	**3r**	91
n-Hexyl	**2s**	96	**3s**	92

phenyl carbamates. Our procedure utilizes readily available phenyl chloroformate and the corresponding amine as reactants in THF/water media with sodium bicarbonate as a base (Scheme 2). The reaction is done at 0 °C to prevent phenyl carbamate decomposition and is complete after all reagents are added. The product is isolated by simple extraction, with isolated yields greater than 90% (Table 1) and 96% purity or better, according to NMR analysis. Surprisingly, the solid phenyl carbamates are stable at room temperature for at least several months, making them an excellent intermediate.

To determine optimal reaction conditions for the preparation of 5-arylsemicarbazides, we performed NMR experiments with phenyl carbamate **2c** as a substrate with varying solvents, bases, temperature, and time. The NMR following the reaction under optimized conditions for the preparation of 5-arylsemicarbazides[21] is presented in Figure 3. The reaction is complete after one hour of sonication at room temperature.



a: R = C_6H_5; **b**: R = C_6H_4-*p*-OCH_3; **c**: R = C_6H_4-*p*-$CO_2C_2H_5$; **d**: R = C_6H_4-*o*-OH; **e**: R = C_6H_4-*m*-OH; **f**: R= C_6H_4-*p*-OH;
g: R = C_6H_4-*p*-OC_6H_5; **h**: R = C_6H_4-*p*-C_6H_5; **i**: R = C_6H_2-3,4,5-$(OCH_3)_3$; **j**: R = C_6H_3-2-CH_3-5-OCH_3;
k: R = C_6H_3-3,5-$(CH_3)_2$; **l**: R = C_6H_3-2,4-Cl_2; **m**: R = C_6H_4-*m*-Br; **n**: R = 2-pyridinyl; **o**: R = 4-pyridinyl;
p: R = 1-naphthalenyl; **r**: R = 2-naphthalenyl

Scheme 2. Synthetic routes for the preparation of phenyl carbamates and substituted semicarbazides.

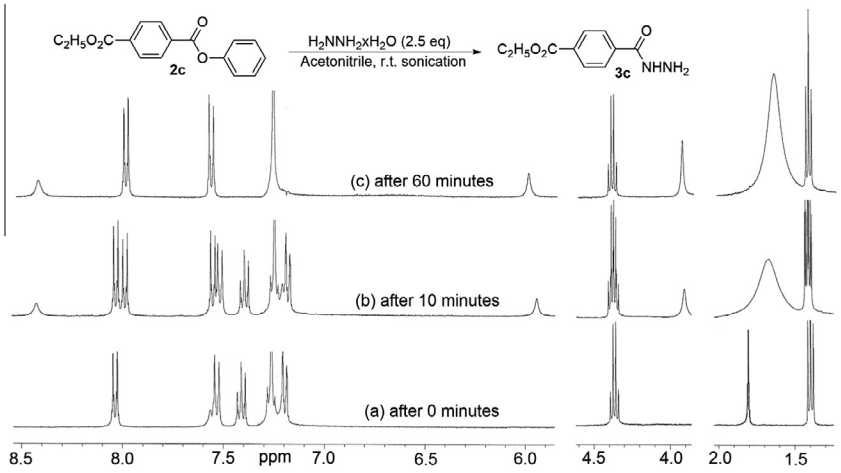
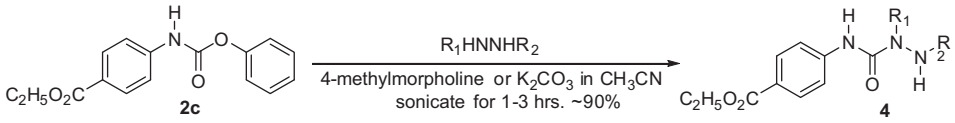


Figure 3. NMR experiment showing reaction progress under optimized conditions for the preparation of semicarbazide **3c**.



4a: $R_1 = CH_3$, $R_2 = H$; **4b**: $R_1 = H$, $R_2 = C_6H_5$; **4c**: $R_1 = H$, $R_2 = 2,4\text{-}(O_2N)_2C_6H_3$; **4d**: $R_1 = H$, $R_2 = COC_6H_5$; **4e**: $R_1 = H$, $R_2 = COC_6H_4\text{-}p\text{-}NO_2$; **4f**: $R_1 = H$, $R_2 = O_2SC_6H_4\text{-}p\text{-}CH_3$; **4g**: $R_1 = H$, $R_2 =$ COO-cholesteryl

Scheme 3. Preparation of multi-substituted semicarbazides.

The preparation of substituted semicarbazides is almost as simple and straightforward as the preparation of phenyl carbamates. However, the general procedure varies depending on the nature of the particular phenyl carbamate and hydrazine. Simple reaction conditions outlined in Figure 3 are applicable for the preparation of a wide variety of arylsemicarbazides from corresponding arylcarbamates **2a**–**2r** (Table 1). The reaction is complete after sonication for one hour at room temperature. It is important to note that hydrazine hydrate must be present in excess (2.5 equiv) because it serves as both a base and a nucleophile. Hydrazine hydrate is not fully soluble in acetonitrile, so in order to make the reaction mixture homogenous, a few drops of water can be added. Alternatively, DMF and THF can also be used as reaction solvents; however, acetonitrile is preferred due to the simplicity of isolation and purification of the product. The presence of functional groups such as hydroxyl, carbethoxy, carboxy, nitro, or halogens does not alter the reaction.

When the same reaction conditions were applied to phenyl 4-alkylcarbamates, there was no detectable product. However, the reaction can be completed by minimal heating in all three studied solvents. Again, the best isolated yields were obtained when the acetonitrile solution was sonicated at 60 °C overnight (12 h). In this way, this approach can be used to selectively transform arylcarbamates into arylsemicarbazide in the presence of alkylcarbamate moiety.

For mono-substituted hydrazines, the reaction can be performed under identical conditions but with equivalent amounts of hydrazine and either *N*-methylmorpholine or anhydrous potassium carbonate as a base (Scheme 3). Although both bases gave excellent isolated yields, we prefer potassium carbonate over *N*-methylmorpholine because it is easier to handle in larger amounts. For larger molecules that are known to entrap water, such as steroids,[22] partial hydrolysis of ester groups may occur. In this case, *N*-methylmorpholine is the favored base over potassium carbonate.

Table 2
Isolated yields of semicarbazides **4** with potassium carbonate as base

R_1	R_2	Semicarbazide **4**	Yield of **4** (%)
Me	H	**4a**	91
H	Ph	**4b**	98
H	2,4-$(NO_2)_2$Ph	**4c**	92
H	CHOPh	**4d**	97
H	4-NO_2CHOPh	**4e**	91
H	4-$MeSO_2$Ph	**4f**	93
H	CO_2-cholesteryl	**4g**	90

In theory, it is possible to form two different products in the reaction with mono-substituted hydrazines. However, under the conditions shown in Scheme 3, we obtained almost quantitative yields of only one product (Table 2). We propose that this is due to the mild reaction conditions, which favor the formation of one product. This is because the product which is formed has a nitrogen attached to the carbonyl group with the higher electron density in the starting hydrazine or hydrazide.

In conclusion, we have developed an exceptionally simple, high yield, and economical procedure for the preparation of substituted semicarbazides from readily available amines and hydrazines via phenyl carbamates. This condensation reaction can even be performed with hydroxyl, carboxylic, nitro, or heterocyclic groups. Not only is this approach applicable to large scale industrial syntheses, but also to the synthesis of semicarbazides with a variety of functional groups, with the exception of amines.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.052.

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