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Novel and Versatile Synthesis of Disubstituted 1,2-Dihydro-1,2,4-triazol-3-ones

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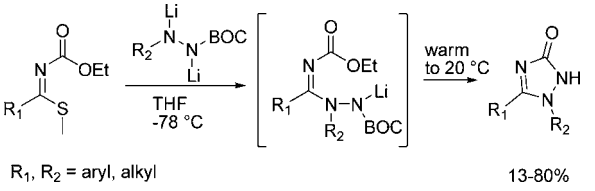
ABSTRACT



A novel method for the synthesis of a wide range of 1,5-disubstituted 1,2-dihydro-1,2,4-triazol-3-ones is described. The key step involves a reaction between a dilithiated BOC-hydrazine and a *N*-alkoxycarbonylcarboximidothioate. A broad range of aryl and alkyl functional groups are tolerated, providing a versatile route for the synthesis of triazolones.

Five-membered nitrogen containing heterocycles are commonplace in a wide range of natural products and pharmaceuticals.[1] In particular, the 1,2,4-triazol-3-one ring is present in compounds that have been evaluated for the treatment of cancer,[2−5] type 2 diabetes,[6] hepatitis C,[7] nausea,[8−10] and neurological disorders.[11,12] Compounds containing the 1,2,4-triazol-3-one ring have also demonstrated antifungal and antibacterial activity.[13]

As part of a medicinal chemistry program, we wanted to explore disubstitution around the 1,2-dihydro-1,2,4-triazol-3-one ring. We were interested in finding a versatile intermediate that would enable us to synthesize a range of synthetically challenging 1,5-disubstituted-1,2-dihydro-1,2,4-triazol-3-ones for biological evaluation.

Of particular interest in this respect was the *N*-alkoxycarbonylcarboximidothioate structural motif (Figure 1), which was first synthesized by Schoessler et al. in 1974.[14] This has been used as an intermediate to synthesize related heterocycles such as a monosubstituted 1,2-dihydro-1,2,4-triazol-3-one *via* a reaction with hydrazine,[15] and also 2,5-disubstituted 1,2-dihydro-1,2,4-triazol-3-ones.[16−18] However, there are no known examples where this intermediate has been used to synthesize 1,5-disubstituted 1,2-dihydro-1,2,4-triazol-3-ones which we were interested in synthesizing.

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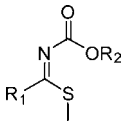


Figure 1. *N*-Alkoxycarbonylcarboximidothioate.

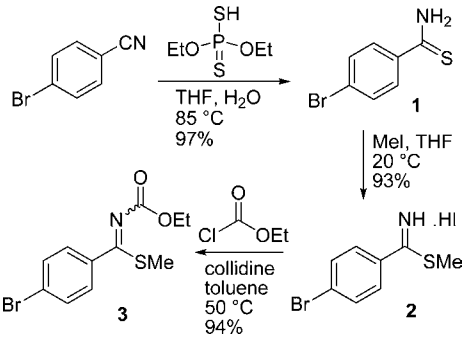
1,5-Disubstituted 1,2-dihydro-1,2,4-triazol-3-ones have proved to be challenging to synthesize, and there is limited literature precedent. Limitations of the current methodology include the use of unstable reactive intermediates such as isocyanates,[19] the use of highly toxic reagents such as sodium cyanide, and the use of multistage processes with low overall yield.[20] Herein we describe new methodology to utilize the *N*-alkoxycarbonylcarboximidothioate moiety to synthesize 1,5-disubstituted 1,2-dihydro-1,2,4-triazol-3-ones in three steps from a primary thioamide.

N-Alkoxycarbonylcarboximidothioate **3** was accessed *via* a primary thioamide, which was prepared by treating 4-bromobenzonitrile with diethyl dithiophosphate (Scheme 1).[21,22] There are several other methods for accessing primary thioamides such as the treatment of a primary carboxamide with a sulfurizing reagent such as Lawesson's reagent,[23] phosphorus pentasulfide,[24,25] or ammonium phosphorodithioate.[26]

The thioamide **1** was methylated using methyl iodide to afford carboximidothioate **2** and subsequently converted to the *N*-alkoxycarbonylcarboximidothioate **3** by reaction with ethyl chloroformate (Scheme 1). The methylation reaction was performed at ambient temperature using THF as solvent in the absence of base, resulting in the crystallization of carboximidothioate **2** as the HI salt in good yield and high purity, thus removing the need for chromatography. The reaction with ethyl chloroformate was performed in toluene using collidine as base, resulting in the precipitation of collidine hydrochloride, which was easily removed by filtration to afford **3** in high yield and purity after evaporation.

Aryl hydrazines are a commonly used nucleophile, and it is well established that the most nucleophilic (terminal) nitrogen will react with a range of electrophiles. Examples include reaction with an alkyl halide[27,28] and condensation

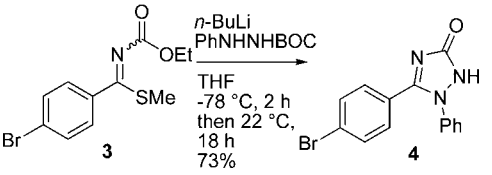
Scheme 1. Preparation of *N*-Alkoxycarbonylcarboximidothioate



with a carbonyl to afford hydrazones[29] or nitrogen containing heterocycles.[30,31] Maeorg et al. have demonstrated that protection of the terminal nitrogen of phenylhydrazine as BOC can be used to direct reactivity to the nitrogen adjacent to the aromatic ring.[32] Reaction of 1-BOC-phenylhydrazine with 2 equiv of *n*-butyllithium results in the formation of the dilithiated species. The nitrogen adjacent to the phenyl ring is the second nitrogen to be deprotonated and is consequently the most reactive species with electrophiles. This has been used to selectively prepare a range of alkylated hydrazine derivatives.[32] Using this knowledge, we predicted that a dilithiated BOC-phenylhydrazine would react with *N*-alkoxycarbonylcarboximidothioate **3** with high selectivity between the *N*-phenyl nitrogen and the imido carbon of **3**.

Our initial studies used *n*-butyllithium to generate the dilithiated BOC-phenylhydrazine, which was subsequently treated with a solution of *N*-alkoxycarbonylcarboximidothioate **3** in THF at −78 °C. Gratifyingly, the coupling partners reacted selectively in the predicted manner at −78 °C, and the resulting lithiated adduct cyclized to the 1,2-dihydro-1,2,4-triazol-3-one ring on warming to ambient temperature as a result of reaction between the BOC-protected nitrogen, and the ethyl carbamate moiety. In addition, spontaneous loss of BOC protection was observed after cyclization at ambient temperature to afford the unprotected 1,5-disubstituted 1,2-dihydro-1,2,4-triazol-3-one **4** (Scheme 2).

Scheme 2. Initial Studies Using *n*-Butyllithium[a]



[a] Conditions: PhNHNHBOC (0.66 mmol), *n*-BuLi (2.2 equiv), THF (6 mL), −78 °C, 15 min, then **3** (0.66 mmol) in THF (4 mL), −78 °C, 2 h, then 22 °C, 18 h.

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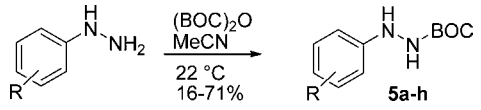
A limitation of our initial model system was the functional group tolerance to *n*-butyllithium which was used as a base to generate the dilithiated species. This issue was overcome by using lithium diisopropylamide (LDA) as a base, allowing us to use aryl hydrazines with a range of functional groups such as halogens and esters which could subsequently be elaborated to a wide range of substituted phenyl triazolones.

To investigate the scope of our chemistry, we prepared a range of BOC-phenylhydrazines **5a**–**h** by reaction of the relevant phenyl hydrazine with $(BOC)_2O$ in acetonitrile (Scheme 3).

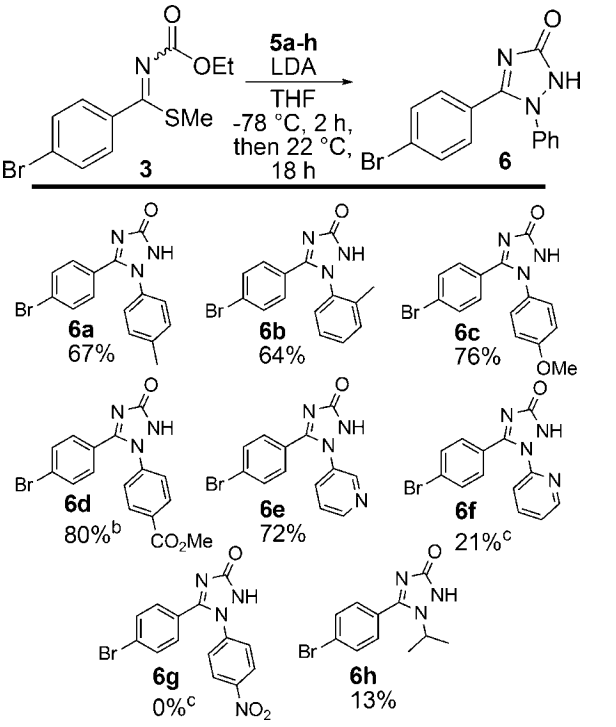
Scheme 3. Preparation of BOC-phenylhydrazines



The BOC-hydrazines **5a**–**h** were dilithiated using LDA and then reacted with *N*-alkoxycarbonylcarboximidothioate **3** to yield 1,2-dihydro-1,2,4-triazol-3-ones **6** (Scheme 4). A range of aryl hydrazines are tolerated to yield 1,2-dihydro-1,2,4-triazol-3-ones in moderate to very good yields, often without the need for chromatography. Electron-rich phenyl hydrazines yielded products such as **6a** (4-Me) and **6c** (4-OMe). Ortho substitution (2-Me) is tolerated to yield **6b**. The electron-deficient phenyl hydrazine **5d** (4-CO_2Me) afforded 1,2-dihydro-1,2,4-triazol-3-one **6d**, along with a small amount of thioester due to nucleophilic attack by the methanethiolate anion that is produced as the reaction progresses. The *para*-nitro hydrazine **5g** failed to yield triazolone **6g** and afforded unreacted starting material, presumably due to the strongly electron-withdrawing nitro group reducing the nucleophilicity of the dianion to a significant extent. The 2-pyridyl product **6f** is formed in lower yield, but the 3-pyridyl product (**6e**) is formed efficiently. This can be rationalized if we consider the electronic effect of the *o*-pyridinyl hydrazine resulting in a stabilized and less nucleophilic dianion species. Extension of this methodology to give 1-alkyl-5-aryl product **6h** was achieved by reacting **3** with 1-BOC-2-isopropylhydrazine. The lower yield can be rationalized by considering the lower stability of the dilithiated BOC-alkylhydrazine intermediate, which is consistent with the observations of Maeorg et al.[33]

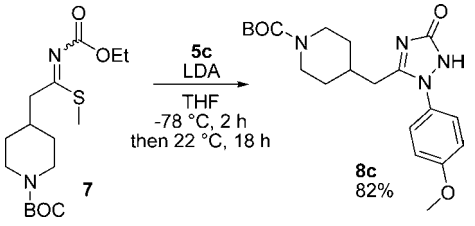
The aliphatic *N*-alkoxycarbonylcarboximidothioate **7** can also be prepared from the corresponding nitrile in an analogous method to intermediate **3**. Reaction of **7** with aryl hydrazine **5c** confirmed that this methodology can also be used to synthesize 1-aryl-5-alkyl-1,2-dihydro-1,2,4-triazol-3-one **8c** in good yield (Scheme 5).

Scheme 4. Scope of 1,5-Disubstituted 1,2-Dihydro-1,2,4-triazol-3-ones[a]



[a] Conditions: **5** (0.66 mmol), LDA (2.2 equiv), THF (6 mL), −78 °C, 15 min, then **3** (0.66 mmol) in THF (4 mL), −78 °C, 2 h, then 22 °C, 16 h. [b] A 5:1 mixture of ester and thioester was isolated. [c] Unreacted starting materials isolated.

Scheme 5. Synthesis of 3-Alkyl-1,2-dihydro-1,2,4-triazol-3-ones[a]



[a] Conditions: **5c** (0.66 mmol), LDA (2.2 equiv), THF (6 mL), −78 °C, 15 min, then **7** (0.66 mmol) in THF (4 mL), −78 °C, 2 h, then 22 °C, 18 h.

To increase our understanding of the mechanism of the 1,2-dihydro-1,2,4-triazol-3-one formation, we investigated the progression toward **6e** as the temperature increased from −78 to 20 °C. By quenching an aliquot of the reaction at −78 °C, the formation of adduct **9** could be observed by LC-MS, but no 1,2-dihydro-1,2,4-triazol-3-one **6e** was present (Scheme 6).

When the reaction mixture was warmed to −30 °C over 30 min, a small amount (3%) of **6e** was observed. Subsequent warming to 0 °C over an additional 30 min period resulted in 15% of **6e**, and at 20 °C the major observed component of the reaction was **6e**. When the reaction was

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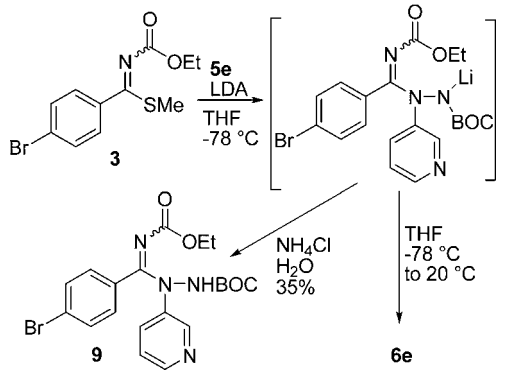
quenched at −78 °C using an aqueous ammonium chloride solution, we were able to isolate **8** in 35% yield (Scheme 6).

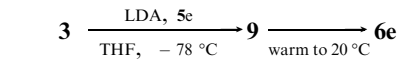
Scheme 6. Reaction Progression



We were intrigued to discover that performing this reaction with less than 2 equiv of base afforded product **6e** (Table 1). An investigation of base stoichiometry demonstrated that the use of 1 equiv of LDA afforded **6e** in a low yield (11%). In addition, only a small amount of intermediate **9** was observed after 2 h at −78 °C (13%). This can be rationalized if the methanethiolate or ethoxide anions which are generated as the reaction proceeds act as the base and drive the reaction to completion. It was notable that the intermediate **9** could not be observed with 0.9 equiv of base at −78 °C, which suggests that as the reaction warms up, a small amount of lithiation and subsequent reaction on the adjacent hydrazine nitrogen occurs at higher temperatures. This is consistent with the observations of Maeorg et al. when performing the alkylation of 1-BOC-2-phenylhydrazines with only 1 equiv of base at higher temperatures.[32]

To further investigate the scope of *N*-alkoxycarbonylcarboximidothioate **3** as a useful intermediate for the synthesis of 1,2-dihydro-1,2,4-triazol-3-ones, we decided to investigate reactivity with unprotected hydrazines. The synthesis of 2,5-disubstituted 1,2-dihydro-1,2,4-triazol-3-ones had previously been reported by Clark et al.,[16−18] but there were no reported examples with aryl substitution in the 5-position. As expected, the unprotected hydrazines reacted with *N*-alkoxycarbonylcarboximidothioate **3** selectively to yield 2-substituted-5-aryl 1,2-dihydro-1,2,4-triazol-3-ones **10** selectively (Scheme 7). This selectivity

Table 1. Investigation of Base Stoichiometry

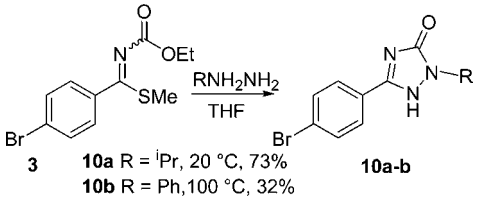


entry	equiv of LDA	conversion to **9** at −78 °C (%)[a]	isolated yield of **6e** (%)
1	2.2	53	73
2	1.0	13	11
3	0.9	0	7

[a] Determined by LC-MS, after 2 h.

can be rationalized by initial nucleophilic attack of the imido carbon by the terminal hydrazine NH_2, followed by cyclization to the triazolone.

Scheme 7. Synthesis of 2,5-Disubstituted 1,2-Dihydro-1,2,4-triazol-3-ones



In summary, we have developed a novel and versatile synthesis of 1,5-disubstituted-1,2-dihydro-1,2,4-triazol-3-ones, with high selectivity and functional group tolerance. The methodology enables the synthesis of a broad range of 1,2-dihydro-1,2,4-triazol-3-ones in good yield with aryl or alkyl substitution.

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Supporting Information Available. Experimental details, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.