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A novel and efficient synthesis of 2,5-substituted 1,2,4-triazol-3-ones

James Zhengwu Deng* and Christopher S. Burgey

Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA

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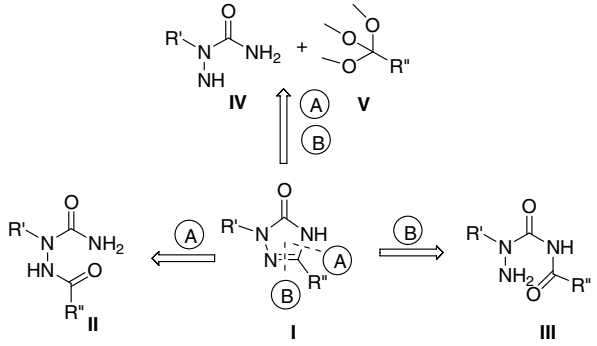
Abstract—A novel procedure for preparing 1,2,4-triazol-3-ones is described. Various alkyl, aryl, and heterocyclic groups were introduced successfully at both the N2 and C5 positions. The triazolone ring was constructed through an intramolecular cyclization of a novel acyclic precursor, which in turn was synthesized by treating a mono protected hydrazine with an acyl isocyanate. Under conditions that remove the hydrazine protecting group, the intramolecular cyclization occurs rapidly, to deliver the 2,5-substituted 1,2,4-triazol-3-ones in excellent yields (79–99%) without column purification.

1. Introduction

The triazolone ring structure is found in a number of biologically active compounds, including anti-fungals,[1] anti-inflammatories,[2] anti-tumor agents,[3] PPARs agonists,[4] and NK_1 antagonists.[5] In our efforts to discover novel therapeutic agents targeting G-protein coupled receptors, we have found that 1,2,4-triazolone is a potent structural scaffold. In order to explore structural diversity at the N2 and C5 positions, we sought to employ a general method to construct the core triazolone ring.

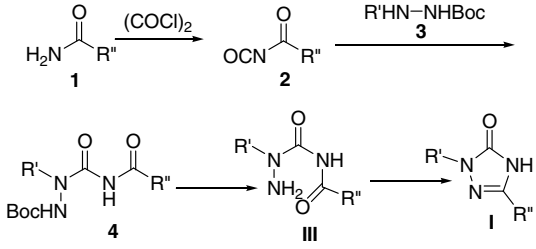
The most widely used strategy toward construction of the triazolone ring system is disconnection of bond A to give intermediate **II** (Scheme 1).[2,4,6] However, this route has limited application, since the harsh conditions (reflux in NaOH solution) required to cyclize intermediate **II** to the triazolone ring are not compatible with a wide array of functional groups. Simultaneous disconnection of both bond A and bond B is another strategy to generate this ring system. Intermediate **IV** and orthoester **V** could be cyclized under milder reaction conditions. Unfortunately, there are few orthoesters commercially available and methods for their preparation are not general.

Disconnection of bond B offers an alternative attractive route to the target (Scheme 1). Cyclization of intermediate **III** might be more facile and efficient than that of intermediate **II** because it would involve a more nucleophilic primary hydrazine attacking an electrophilic carbonyl group.



Scheme 1. Synthetic analysis of 2,5-substituted 1,2,4-triazol-3-one.

With this analysis, we proposed a synthetic route to 1,2,4-triazol-3-ones as shown in Scheme 2. A wide range



Scheme 2. Proposed synthetic route to 1,2,4-triazol-3-ones.

Keywords: Tiazolone; Heterocycles; Hydrazine; Acyl isocyanate.
* Corresponding author. Tel.: +1 215 652 1852; fax: +1 215 652 7310; e-mail: james_deng@merck.com

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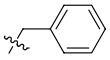
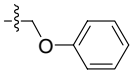
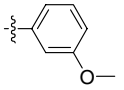
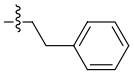
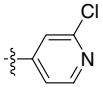
of primary amides **1** could be readily converted to the corresponding acyl isocyanate **2**, according to the reported procedure for preparation of benzoyl isocyanate.[7] Reaction of the mono protected hydrazine **3** with the acyl isocyanate **2** would construct intermediate **4**. Sub-target structure **III** could then be generated through removal of the Boc protection on its precursor **4** and subsequently be cyclized to the target triazolone **I**.

2. Results and discussion

Our initial experiments demonstrated that the proposed route was a viable and efficient way to prepare 1,2,4-triazol-3-ones. The mono Boc protected hydrazine **5**[8] reacted with an acyl isocyanate **6** to afford key intermediate **7** (Scheme 3). The excess isocyanate **6** was trapped by polymer-supported trisamine. Upon removal of the Boc protecting group in TFA/CH_2Cl_2 1:2 solution, clean cyclization to the desired triazolone **9** was observed. The cyclization reaction proceeded very fast (<2 h), while the presumed acyclic intermediate **8** was never detected by LC/MS. In most cases, the pure triazolones **9** were obtained in good yields, without column purification (Table 1).[9] A wide range of acyl isocyanates, including aryl (entries a and d), benzyl (entry b), functionalized alkyl (entries c and e), hindered alkyl (entry k), and heterocyclic (entries f, g, h, i, and j) groups can be employed to give triazolone products in excellent overall yields. Steric hindrance and substitution on the aryl ring or alkyl chain of the acyl isocyanate, did not markedly affect the reaction efficiency. Attempts to convert unsubstituted pyridyl amides, such as nicotinic amide, to acyl isocyanates were unsuccessful. The reaction gave insoluble species, which did not react well with **5**.

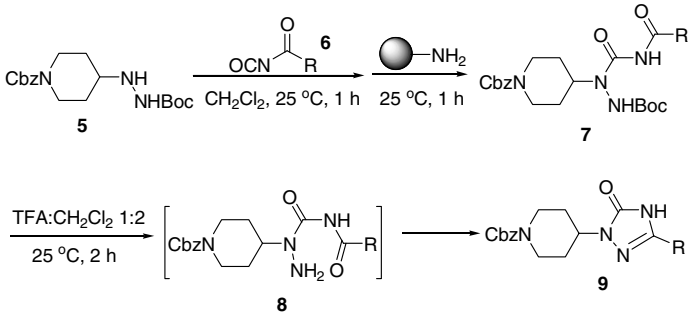
Table 1. Variation of the C5 substituent

Entry	R	Yield (%)
1		97
2		79[a]
3		80[a]
4		99
5		87
6		95
7		98
8		91[b]
9		79[a,b]
10		82[b]
11		90

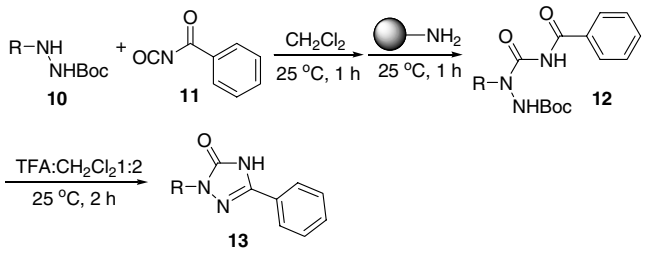
[a] For these entries, yields were calculated based on purified products from silica column (MeOH/CH_2Cl_2 gradient) to remove small amount of amide degraded from acyl isocyanate **6**.

[b] For these entries, three equivalents of polymer-supported *i*-$PrEt_2N$ were added into the reaction of protected hydrazine with acyl isocyanate, to scavenge the HCl left from the reaction to form acyl isocyanate.

Following the method above, we investigated the scope of substituents at the N2 position of triazolone (Scheme 4). A wide range of hydrazines **10** could be subjected to the developed reaction conditions to give triazolones **13** in good yield with high purity (Table 2). We have been able to successfully employ aryl (entries a and g), alkyl (entries b–d), branched alkyl (entry e) and 2-pyridyl (entry f) groups in the synthesis. Hydrazinecarboxylates **10** can be synthesized through direct mono protection of a primary hydrazine,[10,11] or reduction of a hydrazone formed by reaction of the *tert*-butyl carbazate with an aldehyde or a ketone.[12] The aryl or heterocyclic hydrazine species could also be constructed through a direct SN_{Ar} displacement, an addition of arylmetallics to an azodicarboxylate,[13] or through a Buchwald–Hartwig-type aryl amination reaction catalyzed by copper or palladium.[14]

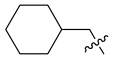
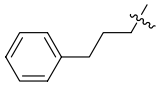
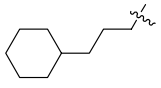
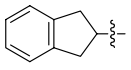


Scheme 3. Exploration of C5 substitutions of 1,2,4-triazol-3-one.



Scheme 4. Exploring the substitutions at N2 position.

Table 2. Variation of the N2 substituents

Entry	R	Yield (%)
1		90[a]
2		95
3		96
4		99
5		86[a]
6		98
7		96[a]

[a] Products in these entries were obtained as pure TFA salts, which are not soluble in CH_2Cl_2.

Finally, in an attempt to avoid the acidic conditions in the cyclization step, we explore the use of benzyl carbamate as the hydrazine protecting group (Scheme 5). Following the same reaction sequence (Scheme 3), intermediate **15** was obtained. Hydrogenation of **15** under a balloon atmosphere of hydrogen, in 1:1:1 mixture of C_2H_5OH/EtOAc/CH_2Cl_2, gave cyclized triazolone **17** in high yield (92%), presumably through its acyclic precursor **16**. The acyclic intermediate **16** was not detected in the reaction, which indicates that the cyclization process is also fast under neutral conditions. This serves to further expand the scope of this methodology.

In summary, we have developed an efficient synthetic route toward 1,2,4-triazol-3-ones. Without column purification, 2,5-substituted 1,2,4-triazol-3-ones can be obtained in good yield and high purity. We have shown that various alkyl, aryl, and heterocyclic groups can be tolerated with this method. Cyclization of the triazolone ring occurs rapidly, under both neutral and mild acidic conditions, with high efficiency.

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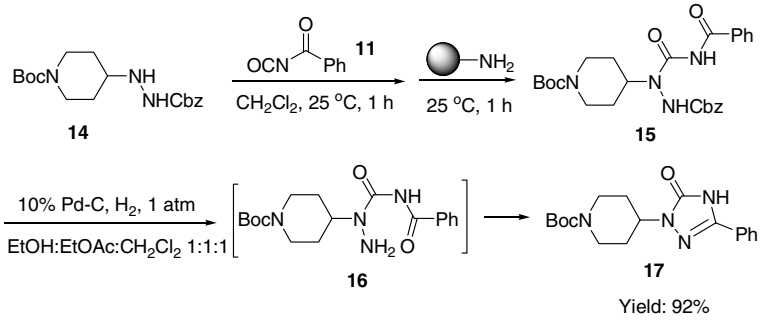
8. The mono Boc protected hydrazine **5** was obtained through a reductive amination reaction of *N*-benzyloxycarbonyl-4-piperidone with *tert*-butyl carbazate (3 equiv $NaBH(OAc)_3$, dichloroethane).
9. Representative experimental procedure: Mono Boc protected hydrazine **10** (1 mmol) was dissolved in 7 mL of CH_2Cl_2, to which acyl isocyanate **11** (1.5 mmol) in 3 mL of CH_2Cl_2 was added. The reaction mixture was stirred at room temperature for one hour, after which polymer-supported trisamine (3 mmol) was added to the reaction. After 1 h, the reaction was filtered, washed with CH_2Cl_2 (2×10 mL) and MeOH (2×10 mL). The filtrate was



Scheme 5. Cyclization of triazolone ring under neutral condition.

concentrated and dissolved in 10 mL of CH_2Cl_2, to which 5 mL of TFA was added. After 2 h, the reaction mixture was concentrated and rediluted with CH_2Cl_2 (100 mL). CH_2Cl_2 solution was washed with saturated sodium bicarbonate solution (100 mL) and concentrated. Most of the time, the residue was pure (>95%); in cases where the purity was <95%, additionally rinsing the solid with ethyl ether (2×5 mL) gave pure (>95%) triazolone product. All compounds listed were characterized by NMR and LC/MS.

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