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Manipulation of N,O-Nucleophilicity: Efficient Formation of 4-N-Substituted 2,4-Dihydro-3*H*-1,2,4-Triazolin-3-ones

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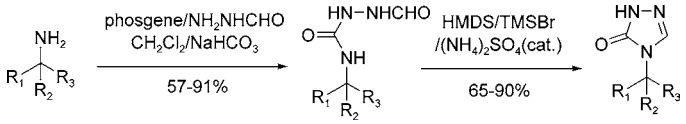
ABSTRACT



A new efficient two-step synthesis of 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones (triazolinones) from readily available amines is reported. Our novel conditions using hexamethyl disilazane, bromotrimethylsilane, and a catalytic amount of ammonium sulfate smoothly cyclize 1-formyl and 1-acetyl semicarbazides to the target triazolinones. This transformation features simultaneous manipulation of N- and O-nucleophilicity as well as differentiation of the nucleophilicity of a urea and an acyl carbonyl.

2,4-Dihydro-3*H*-1,2,4-triazolin-3-ones (triazolinones) have been very important pharmacophores in the drug discovery process. Their biological activity and diverse medicinal uses are exemplified by a range of therapeutic agents such as antiviral and antitumor agents,[1] antihistamines,[2] antibacterial agents,[3] cytidine aminohydrolase inhibitors,[4] antihypertensive agents,[5] and central nervous system drugs.[6] Recently, we have become interested in 4-N-substituted triazolinones **3** as part of our own research program. Among the synthetic methods for the construction of triazolinones, three are most often used: the first is nucleophilic substitution of an alkyl halide[5] or Mitsunobu reaction[7] of an alcohol with a triazolinone synthon, the second is intramolecular condensation of a 1-acyl semicarbazide,[8] and the third is intramolecular condensation of an amidrazone (aminoalkylidenehydrazine carboxylate).[9] In our synthetic efforts, however, we found that all existing methods proved to be fruitless for formation of the sterically hindered neopentyl triazolinones **3**. Our primary focus was on intramolecular condensation of formyl semicarbazides **1** (Scheme 1) since this is one of the most commonly used methods in the literature. However, with the typical literature procedures, hydrolytic base-induced condensation conditions (aqueous KOH or NaOH with heat),[4,10] our compounds simply decomposed. When we tried to activate the 1-formyl group by formation of an imidoyl

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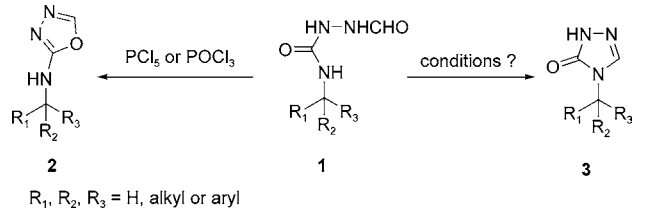
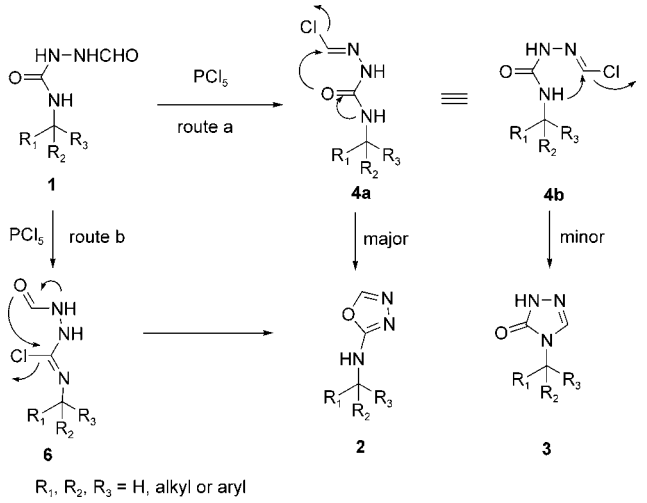
Scheme 1



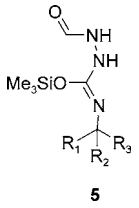
chloride using PCl_5[11] or $POCl_3$,[12] we did obtain some desired product **3**, but only in about 10% yield. The major product isolated under these conditions was 1,3,4-oxadiazole **2**. Two possible pathways could lead to formation of **2**. The first pathway (route a, Scheme 2) is activation of the formyl group

Scheme 2



of **1** to form a terminal imidoyl chloride **4**, followed by attack of the urea carbonyl oxygen (e.g., **4a**). Note that the imidoyl chloride **4** may also cyclize via attack of the urea nitrogen (e.g., **4b**) to give **3**. The second pathway to **2** (route b, Scheme 2) is activation of the urea moiety to form amino imidoyl chloride **6**, which is attacked by the formyl oxygen.

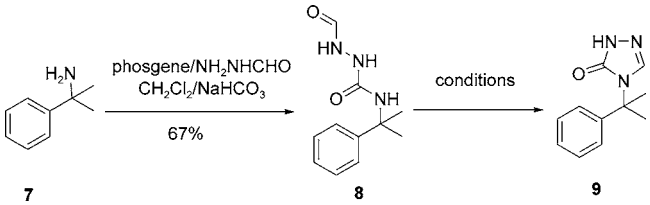
Although we could not rule out either route to **2**, to form the desired triazolinone **3** we had to either improve the nucleophilicity of the proximal urea nitrogen (**4b**, route a) or block reaction of the urea carbonyl (route b and **4a**, route a). To stop formation of **6**, we first tried to temporarily mask the urea carbonyl and simultaneously improve the nucleophilicity of the urea nitrogen by formation of an *O*-silylurea **5**.



However, no desired product **3** was obtained when **1** was treated with 1 equiv of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA)[13] or chlorotrimethylsilane (TMSCl) followed by 1 equiv of PCl_5 to activate the formyl group. These failures prompted us to wonder whether we could achieve activation of *both* the proximal urea nitrogen *and* the formyl group with silylation and thus realize the desired ring closure in one pot. This in fact turned out to be the case, and we eventually developed a new method to form hindered triazolinones as reported herein.

To test the idea of double activation, 1-formyl semicarbazide **8** was synthesized and subsequent cyclization conditions were investigated (Table 1). We chose the hindered

Table 1. Optimization of Reaction Conditions for the Synthesis of Triazolinone **9** from 1-Formyl Semicarbazide **8**



entry	conditions	yield
1	HMDS/TMSCl/py[a]	<5[c]
2	HMDS/$(NH_4)_2SO_4$ (catalyst)[b]	15[d]
3	HMDS/TMSCl/$(NH_4)_2SO_4$ (catalyst)[b]	45[d]
4	HMDS/TMSCl/$(NH_4)_2SO_4$ (catalyst) in DMF[a]	<5[c]
5	HMDS/TMSCl/Sc(OTf)$_3$[b]	<5[c]
6	HMDS/TMSCl[b]	<5[e]
7	HMDS/TMSBr/$(NH_4)_2SO_4$ (catalyst)[b]	65[d]

[a] Reaction was carried out at 100 °C. [b] Reaction was carried out at 140 °C with HMDS as a solvent. [c] Decomposition was observed. [d] Isolated yield. [e] No reaction.

neopentylamine **7** in this model so that the conditions would apply directly to our ongoing research program. Compound **8** was conveniently synthesized from amine **7** by treatment with phosgene to form an intermediate isocyanate followed by reaction with formyl hydrazide. With **8** in hand, we first tried the cyclization under basic conditions with hexamethyldisilazane (HMDS) and TMSCl in pyridine[1b] at 100 °C (entry 1); these conditions only resulted in the decomposition

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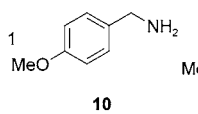
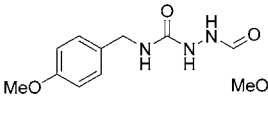
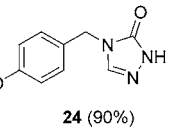
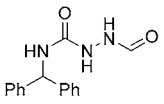
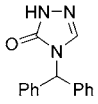
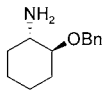
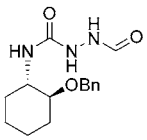
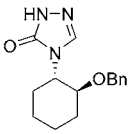
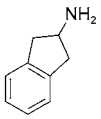
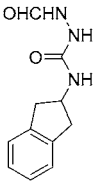
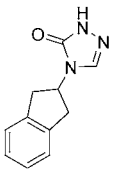
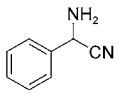
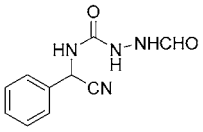
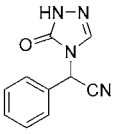
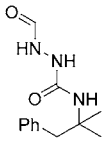
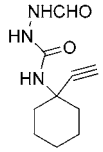
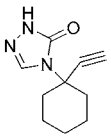
(13) (a) Xiang, G.; McLaughlin, L. W. *Tetrahedron* **1998**, *54*, 375. (b) Meng, G.; Chen, F.-E.; Clercq, E. D.; Balzarini, J.; Pannecouque, C. *Chem. Pharm. Bull.* **2003**, *51*, 779.

Table 2. Efficient Ring Closure of 1-Formyl Semicarbazides to Form Triazolinones Using HMDS/TMSBr/$(NH_4)_2SO_4$[a]

entry	amine	1-formyl semicarbazide (yield)[b]	triazolinone (yield)[b]
1	 **10**	 **17** (59%)	 **24** (90%)
2	 **11**	 **18** (91%)	 **25** (81%)
3	 **12**	 **19** (57%)	 **26** (68%)
4	 **13**	 **20** (89%)	 **27** (80%)
5	 **14**	 **21** (50%)	 **28** (60%)
6	 **15**	 **22** (76%)	 **29** (74%)
7	 **16**	 **23** (87%)	 **30** (77%)

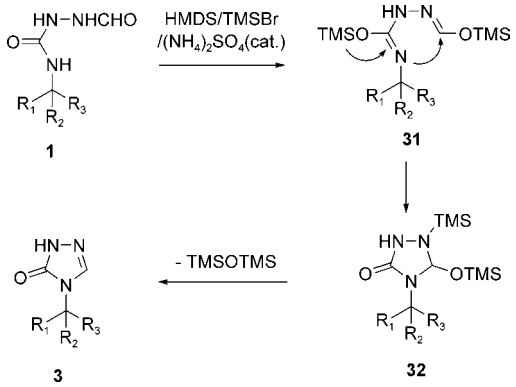
[a] See Supporting Information for a detailed procedure. [b] Isolated yield of spectroscopically pure product.

of the starting material. Since silylation with HMDS is most commonly carried out with acid catalysis,[14] we then tried the reaction with a catalytic amount of the weak acid ammonium sulfate $(NH_4)_2SO_4$ (entry 2, Table 1) in the presence of HMDS. These conditions did indeed provide compound **9**, although in only 15% isolated yield with most of the starting material being recovered. We attributed the low yield to a slow rate of silylation under the reaction conditions. To overcome this, TMSCl was used as an additive and HMDS was used as a solvent (entry 3, Table 1). To our delight, **9** was obtained in 45% yield under these conditions. To further improve the reaction, DMF was employed as a solvent, but this only resulted in decomposition of the starting material (entry 4, Table 1). Since the protic salt ammonium sulfate was a beneficial catalyst in this reaction, we investigated Lewis acid $Sc(OTf)_3$ as an alternative. To our disappointment, however, this Lewis acid only gave us a trace amount of **9** (entry 5, Table 1). When the reaction was carried out without any acid (entry 6, Table 1), the reaction did not proceed, and only the starting material was recovered. This suggested that the combination of HMDS, TMSCl, and a catalytic amount of ammonium sulfate is essential for the success of the one-pot silylation and triazolinone formation. Finally, the optimized conditions (entry 7, Table 1) were found by employing the more powerful co-silylating agent TMSBr, and **9** was obtained in 65% yield.

Encouraged by this result, the scope of this new synthetic method for the efficient construction of 4-substituted triazolinones was investigated. The 1-formyl semicarbazide precursors were again synthesized from the corresponding primary amines through isocynate formation followed by reaction with formyl hydrazides, in good to excellent yields (Table 2).

The ring closure reaction was carried out on semicarbazides **17**−**23** using the optimized combination of HMDS/TMSBr/$(NH_4)_2SO_4$ (catalyst) (Table 2). As shown in Table 2, starting from monoalkylamines (entry 1, Table 2) and disubstituted alkylamines (entries 2−5, Table 2), the corresponding triazolinones **24**−**28** were obtained in good to excellent yields. More importantly, sterically hindered neopentyl semicarbazides **22** and **23** cyclized smoothly to give desired triazolinones **29** and **30** in excellent yields (entries 6 and 7, Table 2). The phenolic methyl ether (entry 1, Table 2), benzyl ether (entry 3, Table 2), and alkyne group (entry 7, Table 2) are all stable under the reaction conditions. One interesting reaction worth mentioning is that of cyanoalkyl semicarbazide **21** (entry 5, Table 2). Under the same reaction conditions, a cyano group, which will not survive hydrolytic conditions such as aqueous NaOH or KOH in ethanol, is

Scheme 3

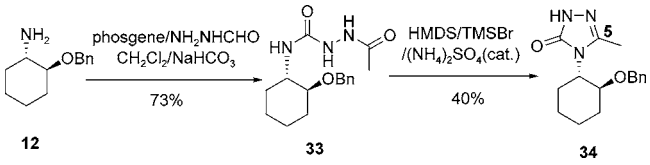


(14) Langer, S. H.; Connell, S.; Wender, I. *J. Org. Chem.* **1958**, *23*, 50.

stable and **21** smoothly cyclized to give **28** in good yield. This proves the mildness and usefulness of this reaction. To this end, all reaction results suggest that activation of both carbonyl groups in 1-formyl semicarbazides with silylation is in fact possible and supports our proposed mechanism for the formation of triazolinones (Scheme 3). Initial treatment of **1** with HMDS/TMSBr/$(NH_4)_2SO_4$ (catalyst) results in double silylation to give **31**. At this point, not only is the nucleophlicity of the proximal urea nitrogen improved but, in addition, only this nitrogen is available to attack the terminal silyloxy imine to give **32**. This ring-closed product then loses a molecule of TMSOTMS to give triazolinone **3**.

To further demonstrate the utility of this new reaction, 1-*acetyl* semicarbazide **33** was synthesized from amine **12** (Scheme 4). Compound **33** smoothly cyclized under the same

Scheme 4



12 **33** **34**

reaction conditions to give 4,5-disubtituted triazolinone **34** in 40% yield. This provides a route to incorporate other functionality at the 5-position of the triazolinones and thus paves the way for synthesis of other structurally diverse triazolinones.

In conclusion, we have developed new conditions using HMDS, TMSBr, and catalytic $(NH_4)_2SO_4$ to efficiently convert 1-formyl semicarbazides into 4-substituted 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones (triazolinones). A possible mechanism for this transformation is outlined that features manipulation of N- and O-nucleophilicity as well as differentiation of the nucleophilicity of a urea and an acyl carbonyl. Formation of 4,5-disubstituted triazolinones can also be realized under the same reaction conditions, providing a new route to structurally diversified triazolinones. Given the high efficiency and ease with both semicarbazide formation and ring closure starting from very readily available primary amines, this new method will be very useful in targeted SAR development and possibly parallel synthesis as well.

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Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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