Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6743–6746

Efficient one-pot formation of 4-N-substituted 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones from primary amines using *N*′-(ethoxymethylene)hydrazinecarboxylic acid methyl ester

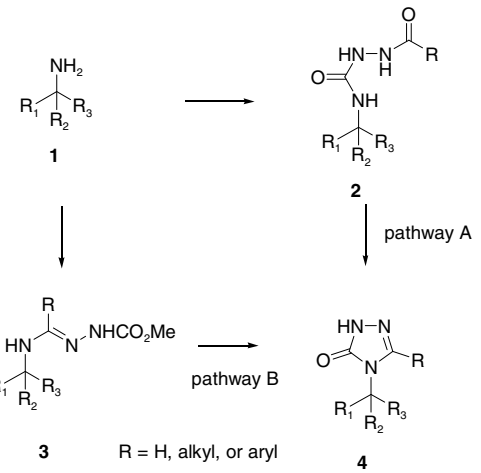
Ning Shao, Cheng Wang, Xianhai Huang,* Dong Xiao,* Anandan Palani, Robert Aslanian and Neng-Yang Shih

Department of Medicinal Chemistry, Schering-Plough Research Institute, Kenilworth, NJ 07033, USA

Received 5 July 2006; revised 14 July 2006; accepted 19 July 2006
Available online 8 August 2006

Abstract—(*E*)-*N*′-(Ethoxymethylene)hydrazinecarboxylic acid methyl ester was synthesized in one step in good yield. This reagent was successfully applied to the one-pot synthesis of 4-substituted 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones from readily available primary alkyl and aryl amines. This reaction process is relatively mild and easy to carry out. It is especially useful for the formation of sterically hindered triazolinones, which are otherwise difficult to obtain via existing literature procedures. A possible mechanistic pathway for the transformation is outlined.

2,4-Dihydro-3*H*-1,2,4-triazolin-3-ones (triazolinones) are 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] Among the reported synthetic methods for the construction of triazolinones, one of the most often used is nucleophilic substitution of an alkyl halide[5] or Mitsunobu reaction[7] of an alcohol with a triazolinone synthon. However, these reactions do not work well for sterically hindered substrates because of their S_N2 reaction character. Thus, alternative methods to construct hindered triazolinones are of increasing interest because of the growing demand for these moieties in the pharmaceutical industry. Two primary synthetic routes have been reported to synthesize non sterically hindered 2-hydro-4-substituted-3*H*-1,2,4-triazolin-3-ones **4** (R = aryl or alkyl): through intramolecular condensation of a 1-acyl semicarbazide **2** (pathway A),[8] and intramolecular condensation of an amidrazone **3** (aminoalkylidenehydrazine carboxylate) (pathway B)[9] (Scheme 1). However, the application of these two routes to the preparation of triazolinones **4** (R = H), which is the interest of our research is very limited. Herein, we report a general and efficient method to synthesize 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones **4** (R = H) (Scheme 1) from primary amines. We have recently



Scheme 1.

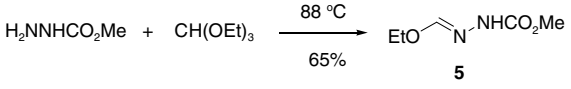
Keywords: (*E*)-*N*′-(Ethoxymethylene)hydrazinecarboxylic acid methyl ester; One pot; Sterically hindered triazolinones.
* Corresponding authors. Tel.: +1 908 740 3487; fax: +1 908 740 7664; e-mail addresses: xianhai.huang@spcorp.com; dong.xiao@spcorp.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.089

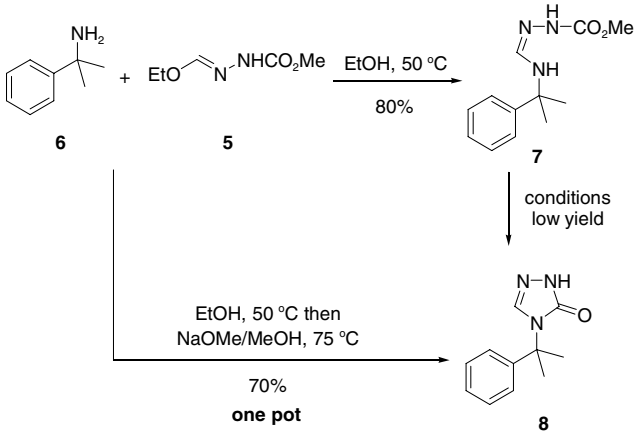
reported the application of pathway A to the synthesis of triazolinones **4** (R = H);[10] in this letter, we examine the feasibility of pathway B.

Many of the methods reported in the literature to prepare amidrazone **3** involve the reaction of a hydrazinocarboxylate with an iminoyl chloride, which often needs to be synthesized from an appropriate amine. Thus, this latter operation contributes an extra step to the synthetic sequence. Secondly, another disadvantage is potential sensitivity of other functional groups in the molecule to the iminoyl chloride moiety. Most importantly, none of the existing methods to convert **3** to **4** worked well for sterically hindered triazolinones such as those in which we were interested. Thus, new methods to prepare **3** and new conditions to transform **3** to **4** are of general interest. We surmised that **3** could be obtained in one step if a reagent could be prepared that would readily react with amines **1**. Thus, we turned our attention to the preparation of reagent *N′*-(ethoxymethylene)hydrazinecarboxylic acid methyl ester **5**, which should react with amines under very mild conditions.[11,12] Fortunately, when methyl hydrazinocarboxylate was heated in neat triethyl orthoformate at 88 °C for 64 h, compound **5** was obtained in good yield as a white solid (Scheme 2). This reagent is stable for months under ambient conditions and its shelf life can be extended by storage over an appropriate drying agent. ^{1}H-NOESY NMR spectroscopic studies showed the structure of **5** prepared under these reaction conditions to be the *E*-isomer.

With compound **5** in hand, we proceeded to explore the synthesis of intermediate **3** and its subsequent conversion to triazolinone **4**. Since we were interested particularly in the formation of hindered triazolinones, we chose *tert*-alkyl amine **6** as an initial starting material.



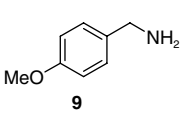
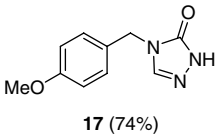
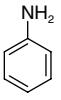
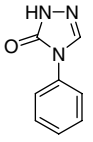
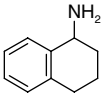
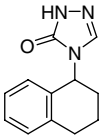
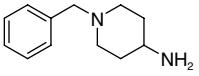
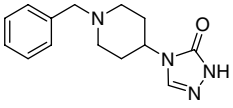
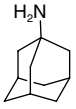
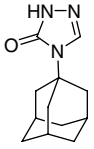
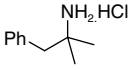
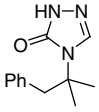
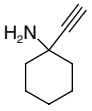
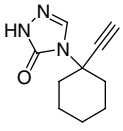
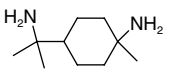
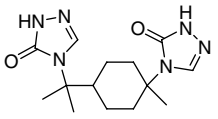
Scheme 2.



Scheme 3.

When a mixture of **5** (5 equiv) and **6** in ethanol was heated at 50 °C for 72 h, intermediate **7** could be isolated

Table 1. Efficient one-pot formation of 4-N-substituted 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones from primary amines using *N′*-(ethoxymethylene)hydrazinecarboxylic acid methyl ester[a]

Entry	Amine	Triazolinone (yield)[b]
1	 **9**	 **17** (74%)
2	 **10**	 **18** (94%)
3	 **11**	 **19** (76%)
4	 **12**	 **20** (65%)
5	 **13**	 **21** (81%)
6	 **14**	 **22** (55%)
7	 **15**	 **23** (76%)
8	 **16**	 **24** (34%)

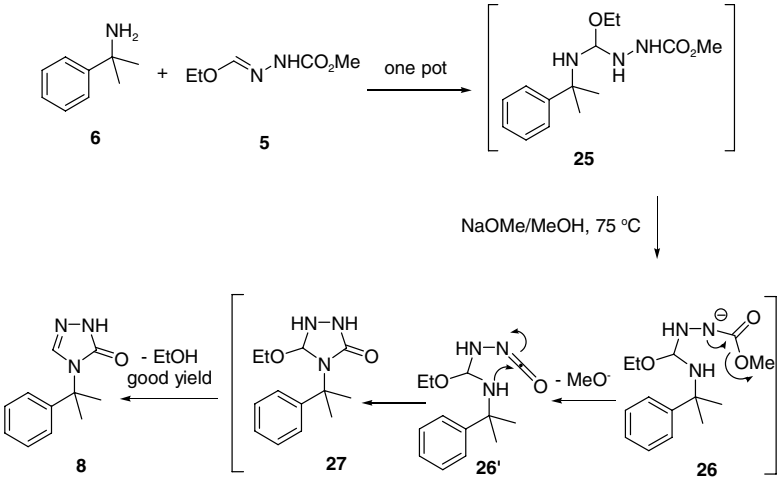
[a] See Supplementary data for detailed procedure.
[b] Isolated yield of spectroscopically pure product.

in good yield. We then attempted to convert **7** to **8**. However, to our disappointment, when **7** was subjected to literature methods for converting amidrazones to triazolinones, such as heating to high temperature[9a,b] or reacting under acidic conditions,[9c,d] **7** was reluctant to cyclize or gave only a low yield of **8**. We initially thought the failure might be due to the steric hindrance of the *tert*-alkyl group. After several failed attempts, we surprisingly discovered that compound **8** could be isolated in good yield when the reaction was carried out in a one-pot fashion by addition of NaOMe/methanol solution to the reaction mixture after the first step was complete (Scheme 3).

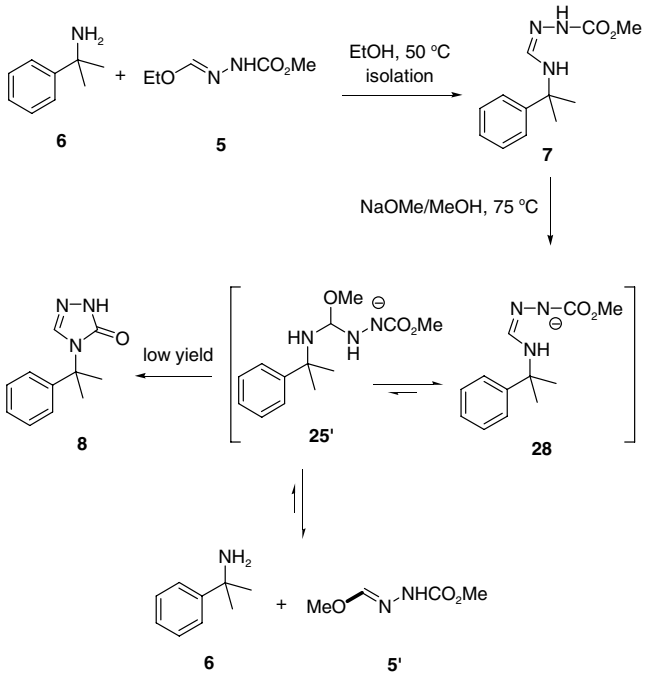
With the reaction conditions well established, the scope of this synthetic method was investigated. A variety of primary and aromatic amines react well to give the desired product in good to excellent yield, as shown in Table 1. *n*-Alkyl amines and aniline give excellent yields of the products (entries 1 and 2). *sec*-Alkyl amines work well as well (entries 3 and 4). More importantly, sterically hindered *tert*-alkyl amines cyclize smoothly to give desired triazolinones **21**, **22**, and **23** in moderate to good yield (entries 5, 6, and 7). Furthermore, when two hindered triazolinone units are present in the same substrate (entry 8), a 34% yield of product **24** could be obtained. The synthesis of such *tert*-alkyl triazolinones under literature reported standard conditions[9] is very difficult. It is noteworthy that when the starting material is an amine HCl salt, the reaction also proceeds smoothly to give the desired product, albeit in slightly lowered yield (entry 6). Since the reaction is carried out under mild basic conditions (NaOMe/MeOH), functional groups such as the phenolic methyl ether (entry 1), tertiary amine (entry 4), and alkyne (entry 7) are all stable under the reaction conditions. Compared to our previously reported route[10] (Pathway A, Scheme 1), the current method utilizes a novel and readily synthesized reagent **5** to form amidrazones, which are otherwise difficult to synthesize from primary amines, and which are subsequently converted to triazolinones under relatively mild basic conditions. The yields obtained under the current conditions are slightly lower than those obtained using pathway A; however, the yield of the cyclization step is comparable despite that the new conditions represent a two-step process performed in a one-pot fashion. Although it appears that this new method is only applicable to sterically hindered triazolones of generic structure **4** (Scheme 1, R = H), as reaction of an amine with a disubstituted hydrazone could be slow, further investigation is in progress for the efficient formation of 5-substituted triazolinones (**4**, R = alkyl).

As shown above, the one-pot reaction proceeds well to give the desired product. However, as described earlier, the intermediate *tert*-alkyl amidrazone **7** does not cyclize or gives only a low yield of **8** under a variety of conditions when **7** is isolated in pure form. This apparently contradictory result prompted us to formulate a possible mechanistic pathway by which this reaction could take place. Although it has been reported in the literature[9] that **7** is a precursor for the formation of less sterically hindered triazolinones, we propose that **25** could be an alternative reaction intermediate in the formation of more sterically hindered triazolinones. As outlined in Scheme 4, in the one-pot reaction, we believe that compound **6** first reacts with reagent **5** to give intermediate **25**. Upon treatment with NaOMe, deprotonation of the nitrogen proton alpha to the carboxylate in **25** gives anion **26**, which collapses to isocyanate **26′**. This reactive isocyanate undergoes ring closure to give **27**, which then loses a molecule of EtOH to give the desired product.

In the case of the stepwise process in which **7** is isolated and then resubjected to cyclization conditions, extensive NMR spectroscopic studies have shown that the configuration of the C=N bond of **7** is predominantly cis, which should enable the closure of the ring. However, steric hindrance and the ring strain caused by the double bond may increase the difficulty to form the desired product under traditional heating or acidic conditions. Under the currently investigated basic conditions, two



Scheme 4.



Scheme 5.

possible intermediates, **25′** and **28**, can be formed (Scheme 5) when **7** is treated with NaOMe/MeOH. Intermediate **25′** can either undergo the same process as intermediate **25** (Scheme 4) to give the desired product, or alternatively dissociate to starting material **6** and compound **5′**, which is unlikely to revert to **25′** under the reaction conditions because the formation of **25′** requires an excess of reagent **5′** (5 equiv) as well as prolonged reaction time. For intermediate **28**, the anion formed is a more stabilized one than that in **26** and it may not follow the same reaction pathway as intermediate **26**. So either way (through intermediate **25′** or **28**) will give low yield of compound **8** for sterically hindered cases. However, we are not ruling out **7** as the intermediate for less sterically hindered substrates because **7** is the observed intermediate by both mass spectroscopy and after isolation in all cases. Further investigation into the reaction pathway is underway, and will be reported in due course.

In conclusion, we have synthesized (*E*)-*N′*-(ethoxymethylene)hydrazinecarboxylic acid methyl ester in good yield. This reagent was successfully applied to the one-pot synthesis of 4-substituted 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones from readily available aromatic and primary amines. This reaction process is relatively mild and easy to carry out. It is especially useful for the formation of sterically hindered triazolinones, which are otherwise difficult to synthesize using existing literature procedures. A possible mechanistic pathway for the transformation was outlined and further studies of the reaction pathway are ongoing.

Acknowledgements

We thank Drs. T.-M. Chan and Ross Yang for NMR spectrometry and mass spectrometry assistance, respectively; Dr. Michael Wong for helpful discussions and proof-reading of the manuscript; and Drs. Catherine Strader, John Piwinski, and Satwant Narula for their strong support of the postdoctoral program.

Supplementary data

Experimental details and spectral data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.089.

References and notes

1. (a) Michael, J.; Larson, S. B.; Vaghefi, M. M.; Robins, R. K. *J. Heterocycl. Chem.* **1990**, *27*, 1063; (b) Haines, D. R.; Leonard, N. J.; Wiemer, D. F. *J. Org. Chem.* **1982**, *47*, 474.
2. Loev, B.; Musser, J. H.; Brown, R. E.; Jones, H.; Kahen, R.; Huang, F.-C.; Khandwala, A.; Sonnino-Goldman, P.; Leibowitz, M. *J. Med. Chem.* **1985**, *28*, 363.
3. Malbec, F.; Milcent, R.; Vicart, P. *J. Heterocycl. Chem.* **1984**, *21*, 1769.
4. Hrebabecky, H.; Beranek, J. *Collect. Czech. Chem. Commun.* **1985**, *50*, 779.
5. Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Chen, T.-B.; O'Malley, S. S.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S.; Lotti, V. J.; Chang, R. S. L.; Greenlee, W. *J. Med. Chem.* **1995**, *38*, 3758, and references cited therein.
6. Cowden, C. J.; Wilson, R. D.; Bishop, B. C.; Cottrel, I. F.; Davies, A. J.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 8661.
7. Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Rivero, R. A.; Chen, T.-B.; O'Malley, S. S.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S.; Lotti, V. J.; Chang, R. S. L.; Greenlee, W. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2787.
8. Madding, G. D.; Smith, D. W.; Sheldon, R. I.; Lee, B. *J. Heterocycl. Chem.* **1985**, *22*, 1121.
9. (a) Uneyama, K.; Yamashita, F.; Sugimoto, K.; Morimoto, O. *Tetrahedron Lett.* **1990**, *31*, 2717; (b) Moffett, R. B.; Kamdar, B. V. *J. Heterocycl. Chem.* **1979**, *16*, 793; (c) Bartsch, H.; Erker, T. *J. Heterocycl. Chem.* **1988**, *25*, 1151; (d) Bartsch, H.; Erker, T. *J. Heterocycl. Chem.* **1990**, *27*, 991; (e) Grandolini, G.; Ambrogi, V.; Perioli, L. *Farmaco* **1996**, *51*, 203; (f) Shapiro, R.; DiCosimo, R.; Hennessey, S. M.; Stieglitz, B.; Campopiano, O.; Chiang, G. C. *Org. Proc. Res. Dev.* **2001**, *5*, 593.
10. Huang, X.; Palani, A.; Xiao, D.; Aslanian, R.; Shih, N.-Y. *Org. Lett.* **2004**, *6*, 4795.
11. Pathak, U. S.; Rathod, I. S.; Patel, M. B.; Shirsath, V. S.; Jain, K. S. *Indian J. Chem., Sect. B* **1995**, *34*, 617.
12. (*Z*)-*N′*-(Ethoxymethylene)hydrazinecarboxylic acid ethyl ester was prepared over two decades ago, but few synthetic applications of this reagent have been reported. See: Milcent, R.; Vicart, P.; Bure, A.-M. *Eur. J. Med. Chem. Chim. Ther.* **1983**, *18*, 215.