Tetrahedron Letters 53 (2012) 1149–1152

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A chemoselective hydroxymethylation: new route for the synthesis of 6-aroyl-4-(4*H*-triazol-3-yl)thiomorpholin-3-ones

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ARTICLE INFO

Article history:
Received 28 October 2011
Revised 21 December 2011
Accepted 23 December 2011
Available online 30 December 2011

Keywords:
Chemoselective hydroxymethylation
Paraformaldehyde
6-Aroyl-4-(4*H*-triazol-3-yl)thiomorpholin-3-one
Boat conformation
Tandem cyclization

ABSTRACT

Treatment of 2-(2-oxo-2-arylethylthio)-*N*-(4*H*-1,2,4-triazol-3-yl)acetamides with paraformaldehyde in the presence of a base has led to a tandem chemoselective hydroxymethylation followed by cyclization yielding a set of novel 6-aroyl-4-(4*H*-triazol-3-yl)thiomorpholin-3-ones. The thiomorpholine ring has been found to have a boat like conformation in these compounds as evidenced by NOESY NMR spectrum.

Thiomorpholin-3-one is a well-known heterocycle that has been the subject of an intense research after its first preparation in 1950[1] because of its unique pharmacological properties. This nucleus is present in the 1,4-benzothiazine calcium antagonist Semotiadil[2] as well as in pyrimidothiazine derivatives[3] designed as an inhibitor of the glycinamide ribonucleotide transformylase with potent cell growth inhibition. Recently, thiomorpholine and its pyrrole derivatives have been found to exhibit antihypertensive[4] and antimycobacterial[5] activities. Chiral thiomorpholines have been used as a recyclable chiral catalyst for sulfur ylide mediated asymmetric epoxidation of aldehydes.[6] Various methods like Ugi reactions,[7] microwave assisted Smiles rearrangement,[8] and copper catalyzed cascade methods[9] are being employed for the synthesis of thiomorpholines.

1,2,4-Triazole[10] nucleus is an important structural motif present in a large number of functionalized molecules with a wide variety of uses, including applications in medicinal chemistry and materials science. Clubbed 1,2,4-triazoles are a new class of azole known for their promising antimicrobial activities both in vitro and in vivo.[11,12] The triazolyl–thiazoles are potent antimicrobial and antitubercular agents.[13] The activity of 1,2,4-triazole could be improved by the introduction of substituents in the triazole ring.[14]

Realizing the biological importance of triazole and other heterocycles, it is planned to generate several systems where the triazole ring and another heterocycle are linked or fused. In one such attempt, the reaction of 4*H*-3-amino-1,2,4-triazole (**1**) with thioglycolic acid (**2**) has yielded the mercaptan **3**, which was allowed to react with substituted phenacyl bromide to provide a host of compounds, 2-(2-oxo-2-phenylethylthio)-*N*-(1*H*-pyrrol-2-yl)acetamide **4a**–**4i** (Scheme 1).[15]

These compounds are allowed to react with paraformaldehyde in the presence of triethylamine. The expectation is that the hydroxylmethylation can take place at the 4 position of the triazole ring. If that happens, the lactam form of the side chain amide may involve in dehydration under acidic condition to yield [1,2,4]triazolo[1,3,5]oxadiazine (Scheme 2).

The compounds **4a**–**4i** are all new and have been well characterized. The ^{1}H NMR spectrum of **4b** has three broad one hydrogen singlets at 7.70, 11.64, and 13.40 ppm. The pair of doublets (J = 8.4 Hz) for the aromatic hydrogens appears at 7.60 and 7.98 ppm. Two hydrogen singlets are centered at 3.42 and 4.22 ppm. The triazole ring carbons appear with very poor intensity at 148.5 and 149.2 ppm, while the methylene carbons appear at 34.6 and 38.4 ppm.

Aiming at the construction of additional heterocyclic system with triazole, the reaction of **4** with paraformaldehyde has been carried out in 1,4-dioxan at 95 °C. Triethyl amine has been used as the catalyst and paraformaldehyde was used in equimolar ratio with **4**. It took nearly 20 h to get the reaction completed and even then the conversion was only to the extent of less than 50%.[16] Nevertheless, a new product has been formed. The reaction product **5** (Scheme 2) has been isolated, purified through flash column, and

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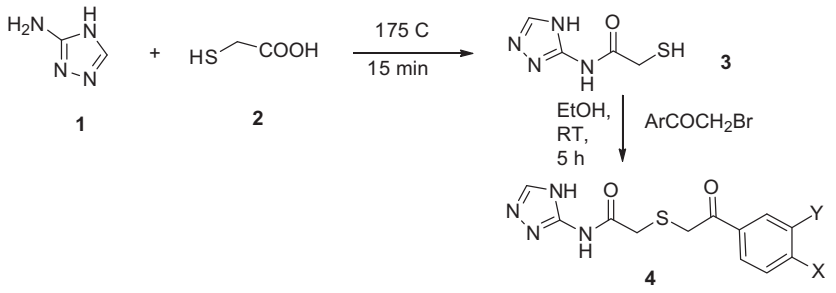
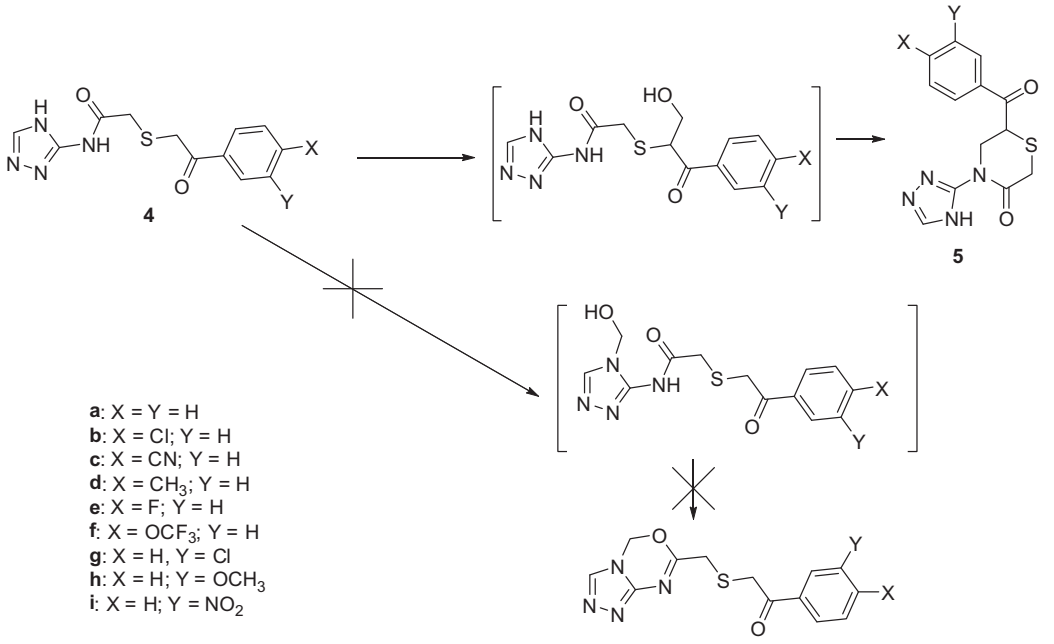
doi:10.1016/j.tetlet.2011.12.100



Scheme 1. Synthesis of **4**.



Scheme 2. Reaction of **4** with paraformaldehyde yielding **5**.

characterized for its structure. Compound **5b** has a set of mutually coupled doublets at 3.37 and 3.73 ppm with a large coupling constant of 14.8 Hz in its ^{1}H NMR spectrum. An AMX pattern at 4.56 (J = 14.8, 9.2 Hz), 4.87 (J = 9.2, 5.2 Hz), and 5.09 (J = 14.8, 5.2 Hz) ppm proves the presence of a CH_2–CH system. The aryl region has a pair of doublets for the *p*-chlorophenyl ring apart from a one hydrogen singlet. The presence of two CH_2 carbons and a CH carbon in the region below 100 ppm and a free carbonyl and an amide carbonyl, apart from the carbons due to the triazolyl ring and the *p*-chlorophenyl ring, is note worthy in the ^{13}C NMR spectrum. The HMBC connectivities are shown in the Figure 1. Thus from the one and two dimensional NMR data, the structure of compound **5** has been unambiguously assigned as 5-aroyl-*N*-triazolylthiomorpholin-3-one (Table 1). The expected [1,2,4]triazolo[1,3,5]oxadiazine has not been formed at all.

It is clear that the initial hydroxymethylation has occurred at the active methylene and not either at ring nitrogen or amide

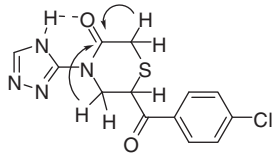


Figure 1. Hydrogen bonding and HMBC connectivities in **5**.

Table 1
Yield and melting points of 6-aroyl-4-(4*H*-triazol-3-yl) thiomorpholin-3-one **5**

Entry	Compound	Yield (%)	Mp (°C)
1	**5a**	40	190–191
2	**5b**	43	171–172
3	**5c**	48	235–236
4	**5d**	40	Viscous liquid
5	**5e**	42	Viscous liquid
6	**5f**	38	Viscous liquid
7	**5g**	44	Viscous liquid
8	**5h**	42	Viscous liquid
9	**5i**	40	Viscous liquid

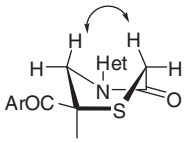
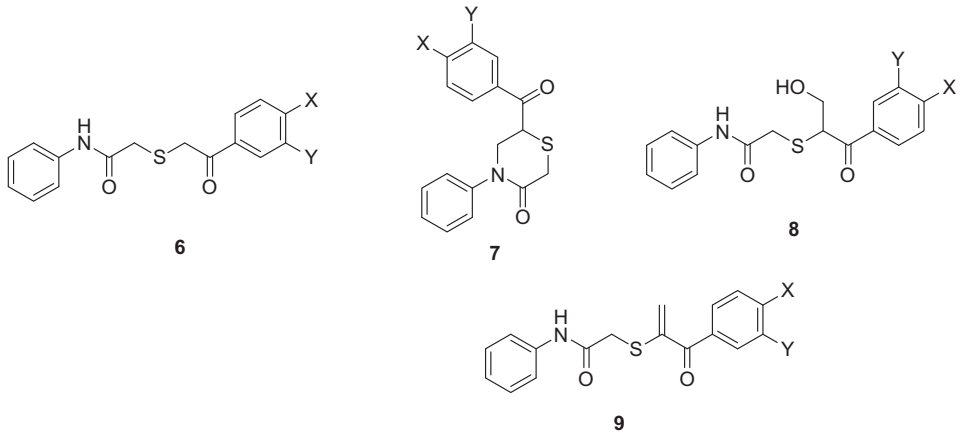


Figure 2. Conformation of **5** and the NOESY connectivity.

nitrogen. This is a chemoselective reaction, because there are also reports wherein the acidic NH of secondary amine can be hydroxymethylated with ease.[17] The hydrogen on the nitrogen of the triazole ring in **4** probably involves in a tautomeric 1,3 shift and



a: X = Y = H
b: X =Me; Y = H
c: X = Cl; Y = H
d: X = H; Y = OMe

Scheme 3. Reaction of **6** with paraformaldehyde yielding **7/8/9**.

hence hydroxymethylation would have not occurred there. The conformation of the resultant compound is also interesting. A single crystal could not be grown for this class of compounds, but still, the NOESY spectrum of **5b** has revealed some important spatial connections.

It is noticed that the deshielded methylene hydrogen of C-2 at 3.73 ppm has a NOESY contour with the shielded methylene hydrogen of C-5 at 4.56 ppm. If these two hydrogens are to be in spatial proximity, a chair like structure is totally ruled out for the thiomorpholinone ring. Probably a boat like arrangement can be visualized (Fig. 2), wherein the hydrogens showing NOESY connectivity may be the flag pole bowsprit type hydrogens. The shielding of the C-2 hydrogen could be ascribed to its position over the carbonyl and the deshielding of C-5 hydrogen may be due to its near planar arrangement with the triazole ring. The hydrogen bonding between NH and amide carbonyl can also be expected (Fig. 1). The signal due to NH hydrogen is not visible in the ^{1}H NMR spectra of some cases, probably due to this intramolecular hydrogen bonding.

The reaction when tried with other aldehydes, either alkyl or aryl aldehyde, has not gone in the expected direction. The reaction with formalin instead of paraformaldehyde was also tried, but the results were not encouraging. An acid catalyzed reaction avoiding triethylamine has also been attempted in the hope of noticing any other chemoselective reaction, but in vain. In all the above cases, the reaction has either not completed or resulted in a mixture of products, which could not be isolated.

Having observed a selective hydroxymethylation with **4**, it is planned to generalize this reaction and accordingly, the reaction was tried with simple 2-(2-oxo-2-phenylethylthio-*N*-phenylacetamide, **6a** (Scheme 3), which has been prepared following the method adopted for **4**. Under identical reaction conditions, a product with relatively poor yield (16%) was obtained. The EI mass spectrum has a signal at *m*/*e* 297, which corresponds to the molecular mass of the related thiomorpholine, **7a**. The proton NMR signals in $CDCl_3$ not only exhibited the expected signals for thiomorpholine, but showed an additional one hydrogen singlet at 8.30 ppm. As the compound was not sufficiently soluble in $CDCl_3$, the ^{13}C NMR spectrum of the compound could not be recorded. When the proton and carbon-^{13} NMR spectra were recorded in DMSO-d_6, it was realized that the compound formed is not **7**, but **8**. The additional signals at 5.08 ppm and 10.10 ppm for OH and NH and the observed coupling pattern for the methylene and methine hydrogens, different from AMX, clearly suggested that the compound is **8a**. The observed mass is not that of the molecular ion but that of the M-18. It is obvious that the cyclization has not been realized here. The nucleophilicity of PhNH seems to be less than that of Het-NH.

In the case of **6b**, the reaction has yielded not only **8b** (18%), but also the dehydrated product **9b** (21%). Two sharp singlets at 2.43 and 3.64 ppm and a pair of doublets (J = 2.0 Hz) in the olefinic region, at 5.93 and 6.01 ppm, confirm the structure of **9b**. With **6c**, interestingly, **8c** was not formed. **9c** was obtained in 15% and surprisingly a trace of **7c** has been obtained in this case. **7c** has three pairs of doublet of doublets at 4.14 (J = 14.0 Hz, 4.8 Hz), 4.43 (J = 14.0 Hz, 8.8 Hz), and 4.75 (J = 8.8 Hz, 4.8 Hz). A pair of doublets for the geminal hydrogens appears at 3.34 and 3.65 ppm with a coupling constant of 14.8 Hz. However with **6d**, only **8d** (20%) could be isolated with no trace of **7d** or **9d**.

The formation of **8** clearly proves that the mechanism of the formation of **5** from **4** involves the intermediate shown in Scheme 2, involving initial hydroxymethylation at active methylene between carbonyl and sulfur followed by cyclization. The presence of acid in the medium could be the driving force for the dehydration of **8** to form **9** in some cases, conjugation adding support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.100.

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15. *General procedure as exemplified for 2-((2-oxo-2-phenylethyl)thio)-N-(4H-1,2,4-triazol-3-yl)acetamide (**4**)*: The thiol **3** was treated with substituted phenacyl bromides and potassium carbonate in equimolar amount taken in ethanol. The mixture was left at room temperature for 5 h and the resultant was worked out to give **4**, which was purified by crystallization. The characterization data for **4a**: 87% yield as a white solid; mp 220 °C; δ_H (400 MHz, DMSO-d_6) 3.44 (s, 2H), 4.25 (s, 2H), 7.54 (t, J = 7.2 Hz, 2H), 7.66 (t, J = 7.2 Hz, 1H), 7.71 (s, 1H), 7.98 (d, J = 7.2 Hz, 2H), 11.67 (bs, 1H), 13.4 (bs, 1H), δ_C (100 MHz, DMSO-d_6) 34.5, 38.5, 128.5, 129.4, 133.9, 135.7, 148.5, 149.1, 168.4, 195.0; ESI-m/z calcd for $[C_{12}H_{12}N_4O_2S]^+$ 276.07, found 276.6.
16. *General procedure as exemplified for 6-benzoyl-4-(4H-1,2,4-triazol-3-yl)thiomorpholin-3-one (**5**)*: Compound **4** was treated with paraformaldehyde in equimolar ratio along with a catalytic amount of triethylamine taken in dioxane. The mixture was heated to 95 °C and maintained at that temperature for 20 h. The product obtained was purified through silica column using a mixture of chloroform and methanol (9:1) as eluent. The characterization data for **5a**: 40% yield as a white solid; mp 190–191 °C; δ_H (400 MHz, $CDCl_3$) 3.38 (d, J = 15.0 Hz, 1H), 3.76 (d, J = 15.0 Hz, 1H), 4.56 (dd, J = 14.6 Hz, 9.0 Hz, 1H), 4.87 (dd, J = 9.0 Hz, 5.0 Hz, 1H), 5.09 (dd, J = 14.6 Hz, 5.0 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.78 (s, 1H), 7.90 (d, J = 7.2 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 30.6, 46.1, 128.5, 129.0, 134.2, 134.5, 148.7, 168.3, 193.7; ESI-m/z calcd for $[C_{13}H_{12}N_4O_2S+H]^+$ 289.07, found 289.0.
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