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Convenient synthesis of 4*H*-1,2,4-triazole-3-thiols using di-2-pyridylthionocarbonate

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Abstract—We report here the convenient synthesis of 4*H*-1,2,4-triazole-3-thiols using di-2-pyridyl-thionocarbonate as the thiocarbonyl transfer reagent. This method is suitable for microplate parallel synthesis and produces samples in screening-ready condition. It uses two large sets of building-blocks: amines and hydrazides.

Five-membered rings are highly prevalent in the pharmacopoeia and more generally in collections of bioactive compounds. Since long we have been interested in the parallel synthesis of five-membered heterocycles.[1,2] Not only is ring closure usually entropically favoured, but also they are compact scaffold for the distribution of pharmacophore elements in space. Amongst five-membered rings, 1,2,4-triazole-3-thiols and derivatives (series A–E in Fig. 1) appear pharmacologically relevant since they are found in many bioactive compounds.

For example, D and E derivatives have been developed as memory enhancers, or sphingomyelinase inhibitors.[3,4] Recently CXCR2 antagonists displaying a triazolethiol moiety have been described.[5] Such heterocycles have also been developed as inhibitors of the large family of Matrix-MetalloProteinases (MMPs) and A Disintegrin and Metallo Domain (ADAMs) enzymes.[6] S-alkylated derivatives have been shown to antagonize Angiotensin II receptors (AT-1) or more recently to inhibit cyclo-oxygenase-2 (COX-2).[7,8] Other compounds in these series display anti-bacterial properties.[9,10]

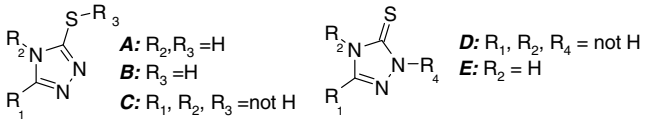

Figure 1. Markush formulas of 1,2,4-triazole-3-thiols derivatives.

More generally a survey in MDDR database[11] retrieves 245 molecules in series A–E, among which 63 are free-thiol derivatives (series A and B).

Suritozole and mitratapide (Fig. 2)[12] are two examples of bioactive 1,2,4-triazole-3-thiols.

Among the compounds presented in Figure 1, we were interested in type B compounds because they display structures complementary to those of linear carboxamides. Indeed, whereas the energetically favoured conformation of amide is the trans conformation, the substituents brought by the parent acid and amine in 4*H*-1,2,4-triazole-3-thiols are in a cis configuration rela-

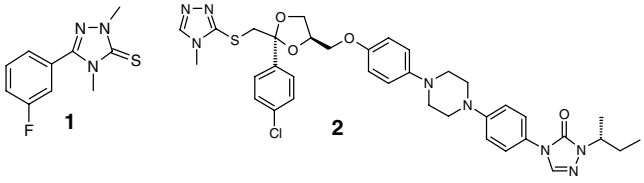

Figure 2. Structures of suritozole (**1**) and mitratapide (**2**).

Keywords: Triazol-3-thiols; Parallel synthesis; DPT; Solubility; *cis*-Amides.
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tive to the NC bond. Thus from a diversity viewpoint, using the same parent reagents, series B populates a region of space complementary to that of amides (Fig. 3).

4*H*-1,2,4-Triazole-3-thiols can be prepared from two reagent sets and in the end display three pharmacophore motives: two from the reagents and a thiol function. The general synthesis procedures of 4*H*-1,2,4-triazole-3-thiols proceed through the preparation of the corresponding acylthiosemicarbazides that are further cyclized under basic conditions (Fig. 3). Interestingly these intermediates can be used for the synthesis of other heterocycles.[13,14] Acylthiosemicarbazide intermediates are usually obtained by acylation of 2-substituted thiosemicarbazates with acid chlorides (Fig. 3, route 1), or by reaction of hydrazides with the corresponding thioisocyanate (Fig. 3, route 2).[15,16] Route 2 uses hydrazides that can easily be obtained from the corresponding carboxylic acid in two steps using *tert*-butylcarbazate, if they are not commercially available.[17] An analysis of commercially available reagents showed that amines and hydrazides were more represented in databases than acid chlorides or thiosemicarbazates.[18] We thus developed a procedure following Route 2 (Fig. 3).

The synthesis of isothiocyanates from amines requires the use of thiocarbonyl transfer reagents such as carbon disulfide. Nevertheless, toxicity of CS_2 to human and environment is a real problem.[19] Moreover, its physical properties make it unusable in automated chemistry.[20] *N*,*N*′-Thiocarbonyldiimidazole (TCDI) is a usual surrogate of CS_2.[21] More recently, di-2-pyridylthionocarbonate (DPT) and its equivalent 1,l′-thiocarbonyl-2,2′-pyridone were also used.[22,23] We were interested in evaluating the use of TCDI or DPT as thiocarbonyl transfer reagents in the synthesis of our target compounds. In particular our goal was to develop a protocol for both microplate synthesis (15 μmol) and larger scale synthesis, which would not require the purification of the intermediate isothiocyanate.[24,25]

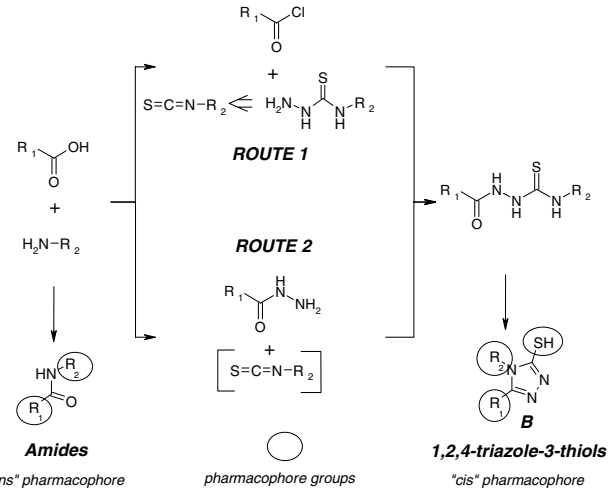


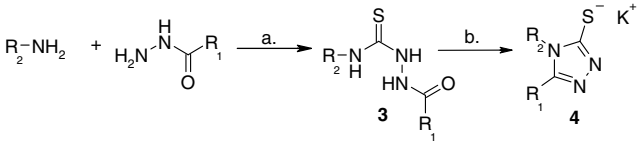
Figure 3. Routes to access 4*H*-1,2,4-triazole-3-thiols, mimicks of *cis*-amides.

The synthesis of 4*H*-1,2,4-triazole-3-thiols proceeds in two steps.[26] As shown in Scheme 1, the first step consists in the in situ formation of the isothiocyanate from the amine followed by reaction with the required hydrazide.[27]

Inversion of the sequence of introduction of reagents in the first step yielded 3*H*-1,3,4-oxadiazole-2-thione quantitatively (compound **5** in Fig. 4). Another frequent by-product is the symmetrical thiourea from the amine (compound **6**, Fig. 4).[28]

Table 1 compares results obtained using either TCDI or DPT. Under the same conditions, TCDI proved to be less efficient than DPT. Also, in our hands, the use of TCDI was hampered by a hardly preventable decomposition that makes difficult the measure of stoichiometric amounts. Furthermore, TCDI produces imidazole as a by-product (pK_a 6.95) whereas DPT produces 2-pyridone (pK_a 0.75). Thus conditions using DPT are milder and pyridone by-product can be more easily removed in water than imidazole.[22]

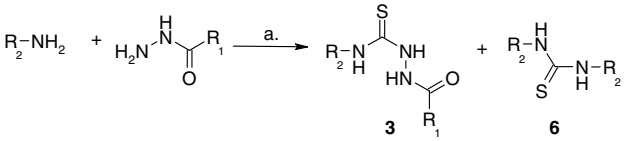
Cyclization of the acylthiosemicarbazide into 1,2,4-triazole-3-thiones proceeds under basic conditions. The use of bases such as carbonate, hydrogenocarbonate and hydroxide has been reported.[5,8,29] Solubility in DMSO



Scheme 1. Reaction and conditions: (a) (i) Thiocarbonyl transfer reagent 0.25 M in DMF (1.05 equiv), amine (free base) 0.1 M in DMF (1 equiv), 55 °C, 1.5 h (ii) hydrazide (free base), 0.1 M in DMF (1 equiv) 55 °C, 1.5 h, solvent evaporation; (b) KOH 0.1 M in H_2O/EtOH (40/60) 85 °C, 5 h.

Figure 4. Structures of potential by-products.

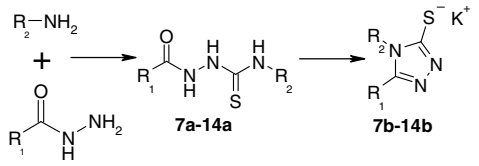
Table 1. Comparison of the use of TCDI or DPT at 5 μmol scale[a]



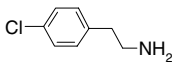
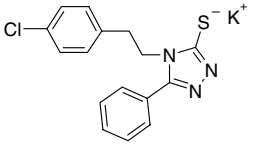
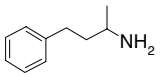
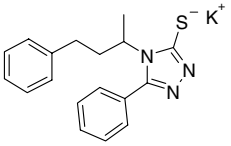
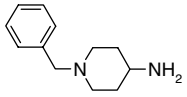
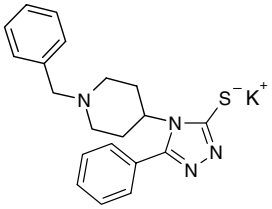
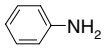
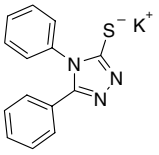
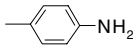
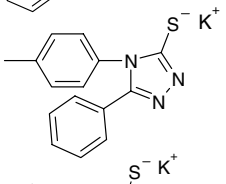
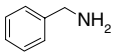
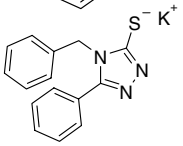
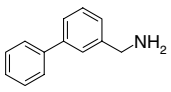
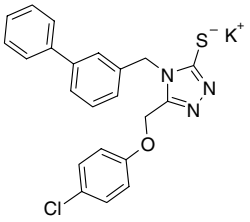
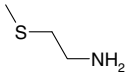
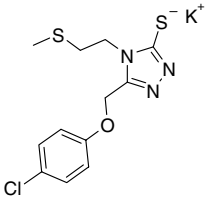
R_1	% **3** (% **6**)[b]	
	Ph	2-Thienyl
TCDI	74 (26)	72 (28)
DPT	91 (9)	99 (1)

[a] R_2-NH_2 used was 4-chloro-phenethylamine.
[b] Relative proportions of **3** and **6** evaluated in 215 nm HPLC-MS.

Table 2. Scope of the amine set[31]



7-12 : R_1 = C_6H_5-
13-14 : R_1 = pCl-C_6H_4-O-CH_2-

Amine R_2–NH_2	Yield (purity)[a] Acylthiosemi-carbazide		Yield (purity)[b] Product	
	**7a**	78 (100)		**7b** 72 (100)
	**8a**	45 (95)[c]		**8b** 40 (97)[d]
	**9a**	43 (100)[c]		**9b** 42 (97)[d]
	**10a**	45 (100)[c]		**10b** 50 (96)[d]
	**11a**	96 (96)		**11b** 72 (95)
	**12a**	94 (100)		**12b** 87 (95)
	**13a**	85 (100)		**13b** 80 (97)
	**14a**	74 (100)		**14b** 90 (99)

[a] 300 μmol scale; isolated yield of acyl-thiosemicarbazide; purity was assessed by HPLC at 215 nm.
[b] Isolated yield of the cyclization step; purity was assessed by HPLC at 215 nm.
[c] Purified by thick layer chromatography.
[d] Cyclized with 2 equiv of KOH and purified by extraction.

of final compounds is critical for high-throughput screening; we evaluated the solubility of sodium and potassium salts of our final thiols.[30] In this context, we found that potassium salts were more soluble than their sodium counterparts.[31] We thus decided to use potassium hydroxide for the cyclization step.

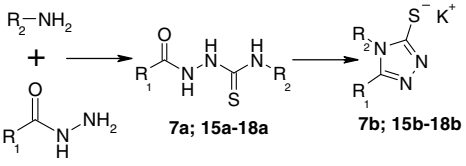
Using this optimized protocol, we evaluated the scopes of both reagent sets at a larger scale.[32] Various amines were evaluated for their ability to form the acylthiosemicarbazide and the ability of the latter to undergo cyclization (Table 2).[33] Benzylamines and phenethylamines were converted quantitatively and the resulting acylthiosemicarbazides were obtained in very good yields (compounds **12a**, **13a**, **7a**). Interestingly anilines gave heterogenous results depending on the substituents (compounds **10a** or **11a**). Unexpectedly, α-substituted primary amines gave acylthiosemicarbazides in only moderate yields and the symmetrical thiourea by-product was produced in high proportions.

Cyclization efficiency was also a function of the amine precursor. Steric hindrance at the amine function seems critical at this step. Good to excellent yields were obtained for compounds **7b**, **11b**–**14b** (72–90%).

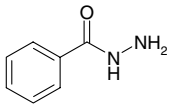
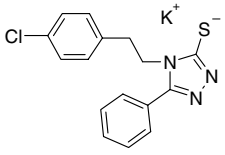
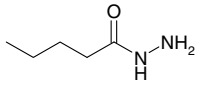
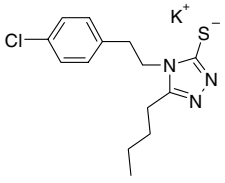
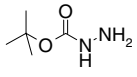
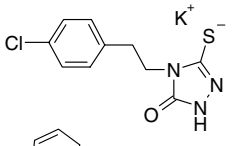
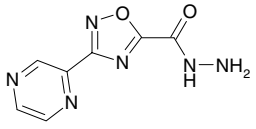
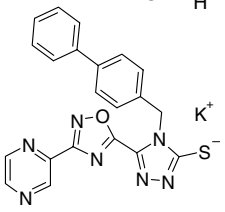
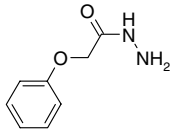
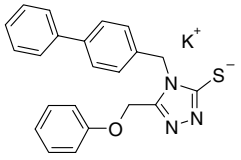
Cyclization of **8a**–**10a** into **8b**–**10b** was slower than for other acylthiosemicarbazides and addition of higher amounts of KOH was required to complete the reaction.

Various hydrazides such as aliphatic, benzylic or heteroaromatic were also tested (Table 3). They all gave target

Table 3. Scope of the hydrazide set[31]



7; 15-16 : R_2 = pCl-C_6H_4-CH_2-CH_2-
17-18 : R_2 = pC_6H_5-C_6H_4-CH_2-

Hydrazide R_1-$CONHNH_2$	Yield (purity)[a] Acylthiosemi-carbazide		Yield (purity)[b] Product	
	**7a**	78 (100)		**7b** 72 (100)
	**15a**	73 (100)		**15b** 70 (97)
	**16a**	64 (100)[c]		**16b** 60 (98)
	**17a**	65 (100)		**17b** 80 (95)
	**18a**	58 (100)		**18b** 71 (100)

[a] 300 μmol scale; isolated yield of acyl-thiosemicarbazide; purity was assessed by HPLC at 215 nm.
[b] Isolated yield of the cyclization step; purity was assessed by HPLC at 215 nm.
[c] Purified by thick layer chromatography.

products in good yield. Interestingly, *tert*-butylcarbazate gave good results and allows the synthesis of 5-thioxo-1,2,4-triazolidin-3-one **16b**. Synthesis of such compounds is only poorly described and uses either semicarbazide and thioisocyanate or thiobisureas and carbamoylthiosemicarbazide.[34,35]

At last, compound **12b**, a prototypal example of these series, was found to have a measured pK_a of 7.95.[36] This value is in the range of published pK_as.[37]

In conclusion, we developed a facile synthesis of 4*H*-1,2,4-triazole-3-thiols in two steps that is suitable for both one-pot parallel synthesis in microplates and larger scale synthesis. This method can be used for various sets of hydrazides including *tert*-butylcarbazate. The most reactive amines are benzylamines, phenethylamines and linear alkylamines but this method can also be used with anilines and α-substituted amines.

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Supplementary data

Full characterizations of compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.094.

References and notes

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18. We performed an analysis of.sdf files from different providers using PipelinePilot™ from Scitegic®. Initial files contained reagents from Sigma–Aldrich–Fluka; Acros; Matrix; Maybridge; Fischer and Enamine, available at the gram scale for a price lower than 80 €. The search retrieves, respectively, 30 thiosemicarbazides (NH–CO–NH–NH_2); 214 hydrazides (C–CO–NH–NH_2); 236 acid chlorides (C–CO–Cl) and 832 primary amines (not[O,S]–C–NH_2). Similar results were obtained using the whole MDL™ Available Chemical Directory.
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26. *Protocol for the synthesis at 15 μmol scale using DPT in Matrix™ 1.5 mL PP-tubes*: To 63 μL of a solution of 0.25 M di-pyridyl-thiocarbonate in DMF (1.05 equiv) was added 150 μL of 0.1 M amine (free base) in DMF (1 equiv). The reaction mixture was heated at 55 °C for 1.5 h. Then 150 μL of a solution of 0.1 M hydrazide (free base) in DMF (1 equiv) was added. The reaction mixture was heated at 55 °C for 1.5 h to allow the synthesis of the thiosemicarbazide. Solvent was removed under reduced pressure; 300 μL of 0.1 M KOH in H_2O/EtOH (40/60) was added. Acyl-thiosemicarbazide may poorly dissolve in 0.1 M KOH in H_2O/EtOH (40/60). Each hour, it is required to sonicate the product to dissolve the intermediate and to complete the reaction. The reaction mixture was heated at 85 °C for 5 h until complete cyclization. Solvents were removed under reduced pressure.
27. Hydrazides used were commercially available or synthesized using classical methods from *t*-butylcarbazate. See Supplementary data for details.
28. It was observed that old DMF containing dimethylamine (characteristic fishy smell) yielded mainly the symmetrical

thiourea instead of the desired acyl-thiosemicarbazide. It is thus essential that DMF be stored on 4 Å molecular sieves.
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31. Compound **7a** was cyclized using KOH to give **7b** or NaOH to give the corresponding Na salt. Both compounds were solubilized at 10^{-2} M in DMSO. DMSO solutions were centrifuged. A 10 μL aliquot was diluted in MeOH and analyzed by HPLC at 215 nm. The potassium salt was more soluble than its sodium salt counter part (Area: 2,549,782 versus 1,588,948).
32. *Protocol for the synthesis at 300 μmol scale using DPT*. In this case, the reactions are performed 20 times under the same conditions (15 μmol scale) and acylthiosemicarbazides pooled in CH_2Cl_2 or AcOEt. The organic layer is washed three times with water to remove pyridone, dried over $MgSO_4$ and evaporated under reduced pressure. If necessary, acylthiosemicarbazides are recrystallized from petroleum ether or purified on silica gel (thick layer chromatography on silica gel:using DCM/MeOH (9/1) or chloroform–diethylic ether (7/3) as eluent) to remove by-products **5** and **6** (1,3,4-oxadiazol-2-thione and symmetrical thiourea). Pure acylthiosemicarbazides are then cyclized in a 0.1 M in H_2O/EtOH (40/60) of KOH (1 equiv or 2 equiv). The reaction mixture was heated at 85 °C for 2–8 h until complete cyclization. Solvents were removed under reduced pressure.
33. Unfortunately, reaction with ammonia or precursors of ammonia yielded the corresponding 3*H*-1,3,4-oxadiazole-2-thione by-product (Fig. 4, compound **5**) quantitatively. The desired product can be obtained by reaction of hydrazide with thiocyanic acid, potassium salt (Yehya, E.; Korany, A.; Ahmad, F. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 2037– 2049) or by reaction of activated carboxylic acid with thiosemicarbazide, followed by cyclization.
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