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Synthesis of novel silylated 1,2,4-triazin-5-ones

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Abstract—The reaction of various α-silyl-α-keto esters with thiosemicarbazide at 50 °C in ethyl acetate was found to give α-silyl-substituted thiosemicarbazone-acetic acid esters in good yield. These may then be converted to their corresponding silyl-substituted 1,2,4-triazin-5-ones by cyclization under basic conditions.

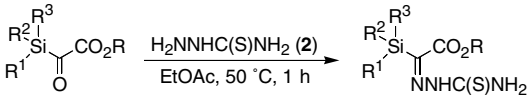
Our interest is focused on exploring the reactivity of α-silyldiazo carbonyl compounds, and we have recently used them to generate α-silyl amino acids and peptides,[1] α-silyl esters and their corresponding hydroxyacetic acids,[2] as well as α-silyl-substituted dioxolanones.[3] We now report the synthesis of novel 1,2,4-triazin-5-ones, utilizing a base-mediated intramolecular cyclization of α-silyl-substituted thiosemicarbazone-acetic acid esters. The latter compounds are obtained by condensation of α-silyl keto esters with thiosemicarbazide.[4]

1,2,4-Triazin-5-ones are attractive compounds, particularly because of their potent biological activities.[5] Synthetic contributions for the generation of these compounds include palladium-catalyzed polyhetero-Claisen rearrangements of 3-(allylthio)-1,2,4-triazin-5(4*H*)-ones,[6] the reaction of diethyl oxomalonate with thiosemicarbazide, followed by methylation,[7] and 1,5-electrocyclizations of nitrilimines.[8] Hence, we were interested in synthesizing analogous silyl-substituted 1,2,4-triazin-5-ones, which have potential biological activity, due to the presence of the hydrophobic and sterically-demanding triorganylsilyl substituent. For example, derivatives and analogues of natural amino acids that incorporate organosilanes have been developed since the 1950s, and it is known that peptides containing silyl alanine likewise show potent biological activity.[9] A similar concept was envisioned for silyl-substituted 1,2,4-triazin-5-ones.

As shown in Table 1, various α-silyl-substituted thiosemicarbazone-acetic acid esters **3** were obtained in good yields (up to 84% yield) by condensation of α-silyl-α-keto esters **1** with thiosemicarbazide (**2**).[10]

We found that the cyclization[11] of the α-triorganylsilyl-thiosemicarbazone-acetic acid esters **3** under basic

Table 1. Synthesis of silylated thiosemicarbazones **3** by condensation of α-silyl keto esters **1** with thiosemicarbazide (**2**)



1 **3**

Entry	R	$R^{1/2}$	R^3	Product	Yield[a] (%)
1	Me	Me	Me	**3a**	65
2	Me	Et	Et	**3b**	71
3	Me	Me	*t*-Bu	**3c**	76
4	Et	Me	Me	**3d**	69
5	Et	Et	Et	**3e**	78
6	Et	Me	*t*-Bu	**3f**	79
7	Bn	Me	Me	**3g**	74
8	Bn	Et	Et	**3h**	84
9	Bn	Me	*t*-Bu	**3i**	82
10	Bn	Me	Ph	**3j**	73
11	Bn	Ph	Me	**3k**	81
12	Bn	Ph	Ph	**3l**	79

[a] After column chromatography.

Keywords: α-Silyl-α-keto esters; Iminations; 1,2,4-Triazin-5-ones; Thiosemicarbazones; Intramolecular cyclization.
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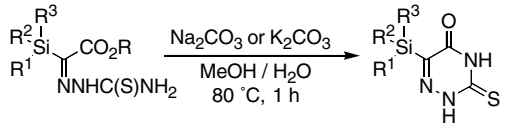
conditions is dependent on the size of the substituted silicon moiety present in the molecule. Hence, silyl-substituted thiosemicarbazones containing substituents larger than the trimethylsilyl group cyclized effectively to the desired 6-triorganylsilyl-3-thioxo-3,4-dihydro-2*H*-1,2,4-triazin-5-ones **4** in up to 88% yield, as shown in Table 2.[12]

In the case of the α-trimethylsilyl-substituted thiosemicarbazone derivatives **3a**, **3d**, and **3g**, however, the trimethylsilyl moiety is lost in the course of the reaction, generating 5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole-3-carboxylic acid esters **5** in up to 50% yield, as shown in Scheme 1.[13] The yields are low, since the cyclization did not go to completion, leaving unreacted starting material lacking the trimethylsilyl group in the reaction mixture. In the absence of Na_2CO_3, cyclization of TMS-substituted **3** to **5** also occurred in a solution of ethyl acetate at room temperature, although only after a few weeks. Compounds **3** also cyclized when they were left 3–4 months standing in air.

Finally, methylation of 6-triorganylsilyl-3-thioxo-3,4-dihydro-2*H*-1,2,4-triazin-5-ones **4** was successfully carried out with iodomethane[14] to afford pharmaceutically relevant 6-triorganylsilyl-3-methyl-sulfanyl-2*H*-1,2,4-triazin-5-ones **6** in up to 89% yield, as shown in Scheme 2. When an excess of MeI (3:1) was used, the N–H bond of **6** was also methylated. Examples of 2-methyl-3-methylsulfanyl-2*H*-1,2,4-triazin-5-ones are well known in the literature.[8,15]

In summary, we have shown that silylated thiosemicarbazones are easily obtained by condensation of α-silyl-α-keto esters with thiosemicarbazide in up to 84% yield. Cyclization of these precursors under basic conditions allows for the ready synthesis of the corresponding silylated 1,2,4-triazin-5-ones in up to 88% yield. Future work toward the synthesis of silylated nitrogen-containing heterocycles will be reported in due course.

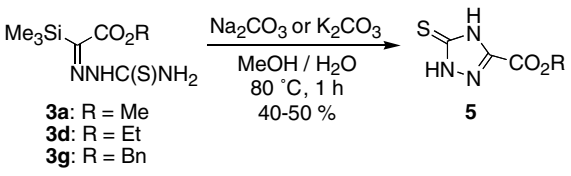
Table 2. Cyclization of silylated thiosemicarbazone-acetic acid esters **3** to their corresponding 1,2,4-triazin-5-ones **4**



3 **4**

Entry	R	$R^{1/2}$	R^3	Product	Yield[a] (%)
1	Et, Bn	Et	Et	**4a**	81
2	Et	Me	*t*-Bu	**4b**	84
3	Bn	Me	*t*-Bu	**4b**	77
4	Bn	Me	Ph	**4c**	72
5	Bn	Ph	Me	**4d**	88
6	Bn	Ph	Ph	**4e**	79

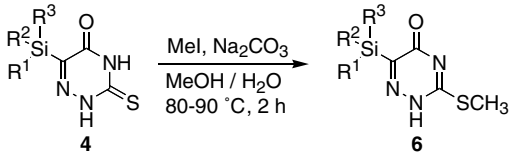
[a] After column chromatography.



3a: R = Me
3d: R = Et
3g: R = Bn

5

Scheme 1. Cyclization of α-trimethylsilyl-thiosemicarbazone-acetic acid esters **3** to give novel 1,2,4-triazole carboxylic acid ester derivatives **5**.



4 **6**

Scheme 2. Methylation of silyl-substituted 1,2,4-triazin-5-ones **4**.

Acknowledgements

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10. General procedure of the condensation reaction: To a solution of the corresponding α-silyl keto ester **1** (10 mmol) in ethyl acetate (100 mL) was added thiosemicarbazide (**2**) (1.82 g, 20 mmol). The suspension was stirred for 1 h at 50 °C, after which unreacted **2** was filtered off. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate, 10:1 up to 3:1, R_f 0.15–0.25). All products were obtained

as slightly yellow solids upon evaporation of the solvents and dried in high vacuum.

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12. General procedure for the cyclization of **3** to give silylated 1,2,4-triazin-5-ones **4**: A solution of the corresponding α-triorganylsilylthiosemicarbazone-acetic acid esters **3** (3 mmol) in methanol (20 mL) was added to a solution of 1 g of Na_2CO_3 or K_2CO_3 in water (20 mL). This mixture was stirred for 1 h at 80 °C under reflux, cooled to ambient temperature, and the product was extracted twice with ethyl acetate (2×30 mL). The combined organic layers were dried over $MgSO_4$, and removal of the solvent afforded the crude silylated 1,2,4-triazin-5-one. The product was then purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate, 10:1 up to 3:1, R_f values 0.15–0.25), to afford **4** as a slightly yellow solid.
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