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Efficient solvent-free synthesis of thiazolidin-4-ones from phenylhydrazine and 2,4-dinitrophenylhydrazine

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ABSTRACT

An efficient solvent-free synthesis of thiazolidinones from reaction of mercaptoacetic acid, aldehydes (benzaldehyde and valeraldehyde) or ketones (cyclopentanone and cyclohexanone), and hydrazines (phenylhydrazine and 2,4-dinitrophenylhydrazine) is reported. The compounds were generally characterized by spectroscopic techniques and specifically for 2-cyclohexanyl-3-(*N*-phenyl)-1,3-thiazolidin-4-one by X-ray crystallography.

In recent years, thiazolidinones and their derivatives have become among the most extensively investigated compounds. They constitute an important group of heterocyclic compounds, having valuable biological activities in the areas of medicine and agriculture. They have found uses, for example, as antimalarial,[1] antimicrobial[2,3] anti-inflammatory,[4,5] and antiviral agents, specially as anti-HIV agents.[6,7] The biological activity of thiazolidinones is reported to be associated with their ability to assume a 'butterfly-like' conformation. This provides a binding mode similar to that provided by others non-nucleosides reverse transcriptase inhibitors (NNRTIs).[8]

The main synthetic routes to 1,3-thiazolidin-4-ones involve three components (an aldehyde, an amine, and mercaptoacetic acid), either in a one- or two-step process.[9] The reactions proceed by initial formation of an imine, which undergoes attack by the sulfur nucleophile, followed by intramolecular cyclization on elimination of water. The most common protocol to remove the water is by azeotropic distillation. DCC, which is extensively used in peptide synthesis dehydration, strongly promotes the dehydration here too.[10]

Recently, we published some results on the formation of thiazolidinones by cyclocondensation reaction of arenealdehydes, mercaptoacetic acid and the aminoacid valine, as the amino fragment.[11,12] Such reactions have also been carried out using microwave irradiation with drastic reductions in reaction times.[13] In continuation of our research program, we have studied the solvent-free synthesis of five-membered heterocyclic thiazolidinones from phenylhydrazine and 2,4-dinitrophenylhydrazine as the amino cores.

The spirothiazolidinones **6a** and **6b** are know in the literature, however, their synthesis require long reaction times (20 h) high temperatures (110 °C) in either one- or two-step procedures.[14] Recently, the *N*-phenylhydrazone **5d** and the corresponding thiazolidinone **6d** were obtained using microwave irradiation with good yields in short reaction times.[15] To our knowledge, the 2-butyl-3-anilino-1,3-thiazolidin-4-one **6c** and thiazolidinones **8a–d** have not been previously reported in the literature.

In our study, we initially isolated the hydrazones intermediates **5a–d** and **7a–d**[16] in near quantitative yields (90–98%) on refluxing the hydrazines (**1,2**) with carbonyl compounds **4a–d** in toluene with water removal using a Dean–Stark apparatus. The same yields could also be obtained refluxing the precursors in methanol with Dean–Stark system. Subsequently, the thiazolidinones **6a–d** were synthesized from cyclocondensation reactions of the phenylhydrazones intermediates **5a–d** using a large excess of mercaptoacetic acid **3**, without any solvent at 60 °C (Scheme 1). To improve our studies, we applied the same methodology to synthesize the heterocycles **8a–d** from 2,4-dinitrophenylhydrazones **7a–d** and the mercaptoacetic acid as the solvent in good yields (Scheme 1).

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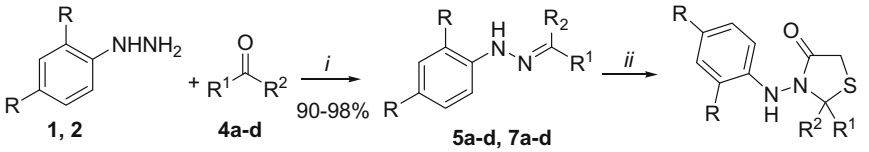


R = H (**1,5,6**)
R = NO_2 (**2,7,8**)

i: toluene or methanol, reflux, 3h
ii: $HSCH_2COOH$ **3**, 60ºC, 1-3h

entry	R	R^1	R^2	product	yields (%)[a]	melting point (ºC)[b]
1	H	-$CH_2CH_2CH_2CH_2$-		**6a**	89 (80)[c]	155-156 (157)[c]
2	H	-$CH_2CH_2CH_2CH_2CH_2$-		**6b**	81 (80)[c]	169-171 (171)[c]
3	H	H	*n*-Bu	**6c**	91	oil
4	H	H	Ph	**6d**	85 (76)[d]	166-168 (165)[d]
5	NO_2	-$CH_2CH_2CH_2CH_2$-		**8a**	84	184-186
6	NO_2	-$CH_2CH_2CH_2CH_2CH_2$-		**8b**	86	199-200
7	NO_2	H	*n*-Bu	**8c**	79	124-127
8	NO_2	H	Ph	**8d**	81	191-192

[a] – yields of purified compounds. [b] – melting points are uncorrected. [c] – data from literature ref. 14. [d] – data from literature ref. 15.

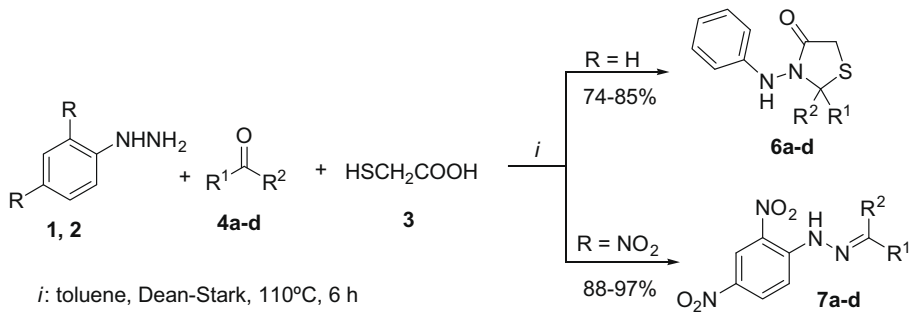
Scheme 1.

The crude products were purified by column chromatography using silica gel with hexane/ethyl acetate mixture (3:1) as the eluent.

We have investigated these reactions in more detail. The one-pot reaction of 1 equiv of phenylhydrazine **1**, 1 equiv of appropriated ketone (**4a,b**) or aldehyde (**4c,d**) with 3 equiv of mercaptoacetic acid **3** in toluene using a Dean–Stark trap for 6 h, gave the thiazolidinones **6a–d** in good yields after purification by column chromatography (Scheme 2). Unfortunately, the one-pot reaction using 2,4-dinitrophenylhydrazine **2** as the amino precursor, carbonyl compounds **4a–d** and mercaptoacetic acid **3** in toluene, did not produce the expected thiazolidinones **8a–d**, but rather the 2,4-dinitrophenylhydrazones intermediates **7a–d** in excellent yields (Scheme 2). The desired thiazolidinones **8a–d** could not be obtained even with very long reaction time (up to 96 h) or with large excesses of mercaptoacetic acid in toluene. We also attempted the synthesis of compounds **8a–d** in a two-step process from reaction of intermediates **7a–d** and excess of mercaptoacetic acid **3** in toluene reflux. However, we did not observe the formation of thiazolidinones **8a–d** even after long reaction time. In these reactions, the precursors **7a–d** were fully recovered.

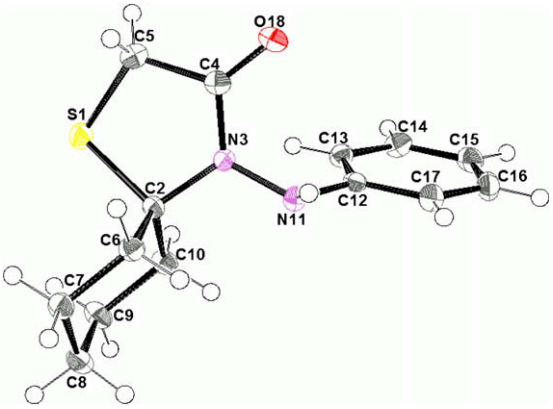
The compounds **6a–d** and **8a–d** have been characterized generally by NMR and mass spectrometry. The structure of compound **6b** was also confirmed by X-ray crystallography (Fig. 1). The atom arrangements of spirothiazolidinone 2-cyclohexanyl-3-(*N*-phenyl)-1,3-thiazolidin-4-one **6b** with selected geometric parameters are shown in Figure 1.[17] According to Cremer and Pople puckering analysis,[18] the conformation of the thiazolidin-4-one ring is best described as having a twisted conformation [on S1–C2] and the cyclohexanyl ring has the expected chair conformation. The thiazolidinone and phenyl rings are nearly orthogonal to each other, with a best plane between the rings of 79.39 (0.05)°.

In conclusion, our methodology can be applied to the synthesis of thiazolidinones from hydrazines, in particular to thiazolidinones derived from 2,4-dinitrophenylhydrazine that cannot be synthesized by literature methods. This new methodology is easy, requires low temperatures, short reaction times, under solvent-free conditions with the potential of preparing a wide range of thiazolidinones



i: toluene, Dean-Stark, 110ºC, 6 h

Scheme 2.



C2-S1 = 1.8411(16)
S1-C5 = 1.8102(18)
C5-C4 = 1.508(2)
C4-N3 = 1.355(2)
N3-C2 = 1.475(2)
N3-N11 = 1.4052(18)
N11-C12 = 1.412(2)
C2-C10 = 1.528(2)
C2-C6 = 1.532(2)
N3-N11-C12 = 116.64(13)
S1-C5-C4 = 107.20(12)
C5-C4-N3 = 111.63(14)
C4-N3-C2 = 119.45(13)
N3-C2-S1 = 102.62(10)
C2-S1-C5 = 92.91(8)

Figure 1. Molecular structure and selected geometric parameters, (Å, °), for compound **6b**. Ellipsoids, for non-hydrogen atoms, are drawn at the 50% probability level: H atoms are drawn as arbitrary spheres.

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer (^{1}H at 400.14 MHz and ^{13}C at 100.61 MHz) in $CDCl_3$ containing TMS as an internal standard. Mass spectra were registered in a SHIMADZU QP 2010 spectrometer connected to a GC-SHIMADZU 2010. Melting points were determined using open capillaries on a Tecnopon PFM II apparatus and are uncorrected.

General procedure for the synthesis of thiazolidinones ***6a–d*** *and* ***8a–d***: A mixture of phenylhydrazone **5a–d** or **7a–d** (1 mmol) and excess of mercaptoacetic acid **3** (1 ml) was heated at 60°C until reaction was complete, as shown by TLC (about 3 h). Ethyl acetate (5 ml) was added, the organic layer was washed with saturated $NaHCO_3$ (3×20 ml) and water (1×10 ml), dried with $MgSO_4$, and concentrated to give an oil. The oil was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent (3:1).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.026.

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16. Selected ^{1}H NMR data for pentanal (2,4-dinitro)phenyl hydrazone **7c**: ^{1}H NMR (400 MHz, $CDCl_3$): 11.01 (s, 1H, NH); 9.11 (d, 1H, Ph, $J = 2.4$ Hz); 8.29 (dd, 1H, Ph, $J = 9.2$ Hz, $^{2}J = 2.4$ Hz); 7.92 (d, 1H, Ph, $J = 9.6$ Hz); 7.54 (t, 1H, CH, $J = 5.6$ Hz); 2.43 (m, 2H, CH_2); 1.60 (m, 2H, CH_2); 1.43 (sext, 2H, CH_2, $J = 7.4$ Hz); 0.97 (t, 3H, CH_3, $J = 7.4$ Hz).
17. X-ray crystal data for **6b**: CCDC 749873; empirical formula $C_{14}H_{18}N_2OS$; formula weight 262.36; $T = 120(2)$ K; $\lambda = 0.71073$ Å; crystal system = monocyclic; space group $P2_1/n$; unit cell dimensions $a = 9.4203(4)$ Å, $\alpha = 90°$, $b = 6.8798(3)$ Å, $\beta = 101.496(3)°$, $c = 20.8371(9)$ Å, $\delta = 90°$; $V = 1323.36(10)$ Å^3; z-4; $D = 1.317$ mg/m^{-3}; $\mu = 0.235$ mm^{-1}; $F(0\,0\,0) = 560$; crystal size = $0.28 \times 0.14 \times 0.10$ mm; θ range for data collection 3.12–27.56°; index ranges $-12 \leqslant h \leqslant 11$; $-8 \leqslant k \leqslant 8$; $-27 \leqslant l \leqslant 27$; reflections collected 16,344; independent reflections 3026 [R(int) = 0.0550]; reflections observed = 2402; data completeness = 0.994; absorption correction = none; refinement method = full-matrix least-squares on F^{-2}; goodness-of-fit on $F^2 = 1.059$; final R indices $R_1 = 0.0424$, $wR_2 = 0.0939$ [$I > 2\sigma(I)$]; R indices = $R_1 = 0.0580$, $wR_2 = 0.1018$; largest difference peak and hole = 0.360 and −0.275 e A^{-3}. Structure solution and refinement were achieved using SHELX97 and SHELXL97 (Sheldrick, G.M.) *SHELXS97* and *SHELXL97*, University of Göttingen, Germany, 1997.
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