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Paper

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A facile and highly efficient one-step N-alkylation of thiazolidine-2,4-dione

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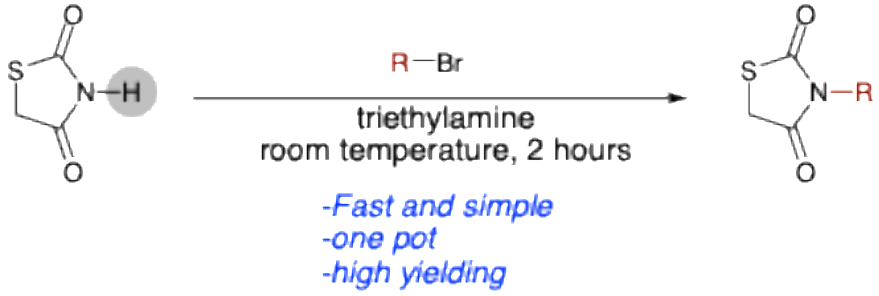
Abstract

N-Alkylation of thiazolidine-2,4-diones (TZDs) commonly employs the conversion of TZD to a salt with a strong base, which is then reacted with alkyl halides or alkyl tosylates. This two-step approach suffers from low overall yields, long reaction times, use of high temperatures, and generation of large amounts of waste. Herein, we describe a one-step N-alkylation of TZD with alkyl bromides at room temperature using a small amount of triethylamine as base and solvent. The reaction is fast and convenient, and it exclusively affords N-alkylated products in high yields.



Keywords: Thiazolidine-2,4-dione, N-alkylation, *N*-alkyl thiazolidine-2,4-dione, imide, glitazone

Introduction

Compounds containing a thiazolidine-2,4-dione (TZD) unit possess a wide variety of biological activities, such as anticancer[1-3], anti-oxidant[4,5], antiviral[6,7], anti-inflammatory[8,9], and antimicrobial properties.[10-12] This makes TZD a privileged heterocyclic structure in medicinal chemistry. A well-known group of biologically active TZD-containing molecules are the glitazones, a large class of compounds that exhibit anti-hyperglycemic activity. Among the glitazones, troglitazone, englitazone, rosiglitazone, and pioglitazone are commercially approved for the treatment of type-2 diabetes.[13,14] However, these glitazones, with the exception of pioglitazone, were withdrawn from the market due to serious side effects.[15-17] Modifying the structure of glitazones, such as functionalizing the imidic nitrogen, could reduce unwanted side effects and improve biological activity.[18] Hence, N-alkylated thiazolidine-2,4-diones would serve as a valuable precursors in structure-activity relationship studies, possibly leading to novel glitazones.[19,20]

Despite the potential pharmaceutical significance, routes for direct *N*-alkylation of TZDs remain scarce. A literature search revealed that most methods for N-alkylation involve converting TZD into its salt form using an appropriate base. The salt is then reacted with alkyl halides using large amounts of organic solvents, whereby the alkyl group is installed by N-alkylation via an S_N2 mechanism.[7,21] However, these methods suffer from low yields, require long reaction times, elevated temperature conditions, use of catalysts, and toxic solvents. Moreover, this two-step protocol for the N-alkylation of TZD generates considerable waste due to the required purification procedures in each step. Therefore, developing a mild, efficient, and more environmentally benign method of *N*-alkylation of TZD is still a challenge. In our attempt to synthesize different TZD derivatives through greener methods, we decided to explore simple methods for the N-alkylation of TZD.

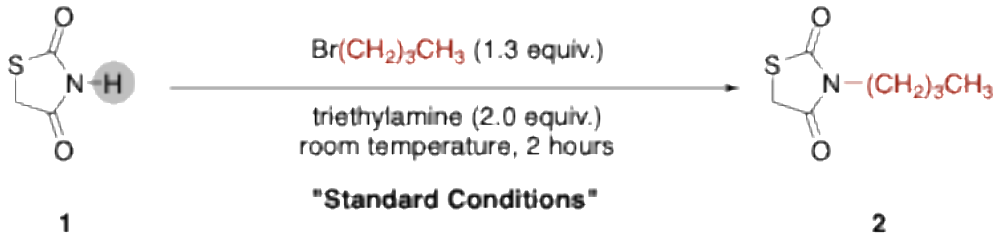
Herein, we report a simple, facile, and efficient N-alkylation of TZD at room temperature. Our protocol, which utilizes triethylamine, produces the N-alkylated products in high yield in a single step. To our knowledge, this is the first report on the use of triethylamine as both solvent and catalyst/base to realize the direct N-alkylation of TZD.

Results and Discussion

During the course of our experiments (Table 1), we have identified the ideal reaction conditions for N-alkylation wherein TZD **1** (1 equivalent) and *n*-bromobutane (1.3 equivalents) were reacted in the presence of a small volume of triethylamine (two equivalents) serving both as base and solvent (entry 1). Carrying out the N-alkylation at room temperature gave a near quantitative yield of (99%) of N-butylated TZD **2** in just 2 hours.

Diluting the reaction by adding DCM as co-solvent (entry 2), resulted in a lower yield of 78%, even after extending the reaction time to 24 hours, suggesting the importance of high concentrations of both **1** and triethylamine. Typically, one would limit the amount of triethylamine in the alkylation reaction of **1** since triethylamine possesses enough nucleophilic character to compete against **1** which would result in lowering of yield of **2**. However, lowering the amount of triethylamine by diluting it with the DCM solvent (entry 3) lead to a much lower yield, even at reflux temperatures (entry 4). Replacing triethylamine with an inorganic base, K_2CO_3 (entries 5 and 6), commonly employed in preparing N-alkylated TZD, did not improve the yield of **2**, suggesting the importance of triethylamine in the reaction.

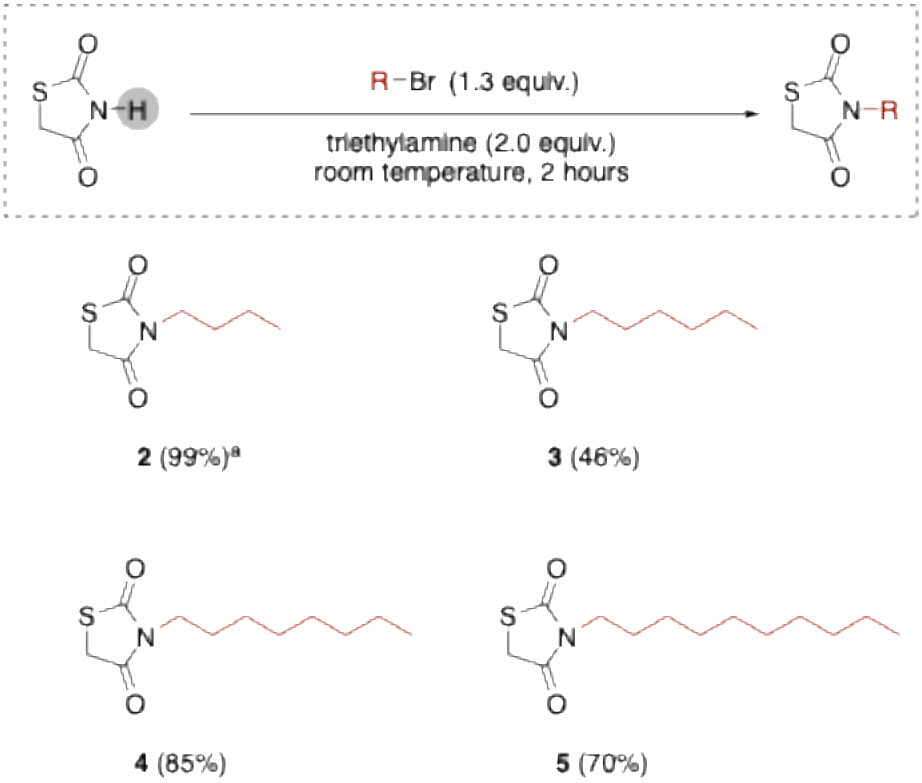
Table 1. Optimization of N-alkylation (alkyl = *n*-butyl) of TZD.



Entry	Changes from the standard conditions	Yield (%)
1	none	99
2	Addition of DCM solvent (5 mL)	78[a]
3	1.5 eq. of triethylamine (instead of 2.0 equiv.) and addition of DCM solvent (5 mL)	58[a]
4	1.5 eq. of triethylamine (instead of 2.0 equiv.), addition of DCM solvent (5 mL), and reflux temperature (instead of room temperature)	72[b]
5	1.5 eq of K_2CO_3 (instead of 2.0 eq of triethylamine) and addition of acetone solvent (5 mL)	12[a]
6	1.5 eq of K_2CO_3 (instead of 2.0 equiv. of triethylamine), addition of acetone solvent (5 mL), and reflux temperature (instead of room temperature)	26[c]

Reaction times: [a]24 h, [b]5 h, [c]3 h,

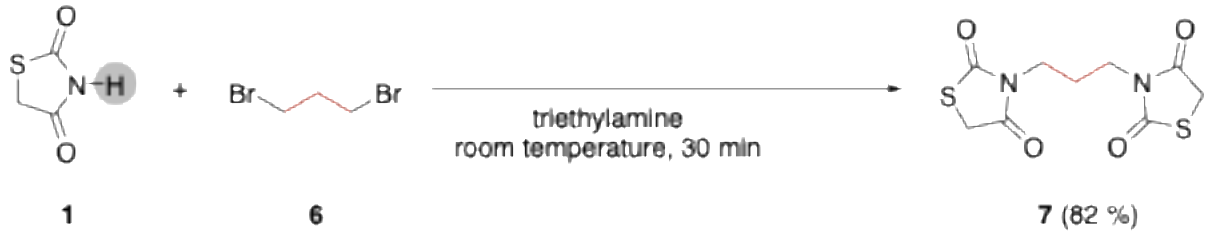
With the optimized method in hand, we then prepared a series of N-alkylated TZDs using different alkyl bromides (Scheme 1). The N-alkylated TZDs (**2 – 5**) were synthesized in moderate to high yields. To further test the efficiency of our method, we carried out the synthesis of **2** on a multigram scale which also gave an excellent yield. This shows that the developed N-alkylation protocol is applicable for large scale synthesis which would be beneficial for commercial scale production of N-alkylated TZDs as pharmaceutical precursors.



[a]Compound **2** is also produced with a yield of 99% on a 20.0 mmol scale.

Scheme 1. Synthesized *N*-alkylated thiazolidine-2,4-diones.

Finally, we carried out the synthesis of bis-thiazolidine-2,4-dione **7** via successive coupling of 1,3-dibromobutane **6** with two mole equivalents of TZD **1** using the developed *N*-alkylation protocol (Scheme 2). A high yield of **7** was obtained in 30 mins at room temperature. Bis-thiazolidine-2,4-diones, such as compound **7**, are interesting targets for structure activity relationship studies focused on assessing the effect of having two identical pharmacophores in a single molecule.[22]



Reaction conditions: 2.1 mmol of **1**, 1.0 mmol of **6**, and 3 mmol of triethylamine.

Scheme 2. Synthesis of alkyl-bridged bis(thiazolidine-2,4-dione).

Further experimental studies on the mechanism are still undergoing in our group, however, we surmise that the mechanism of the reaction involves the triethylamine-mediated deprotonation of the imidic N-H of **1** producing a nucleophilic anion which attacks the alkyl bromide via an S_N2 pathway.

Conclusions

In conclusion, a facile and highly efficient N-alkylation of TZD at room temperature has been accomplished. The developed protocol is faster, simpler, and generates lesser waste from excessive amounts of organic solvents compared to previous methods. Furthermore, this protocol can be used for gram scale synthesis of N-alkylated TZD.s

Experimental Section

General. All reactions were carried out under nitrogen atmosphere. Column chromatography was performed with silica gel 60 (70 – 230 mesh). TLC analysis was performed with plastic backed plates coated with silica gel F_{254} and the plates were visualized by UV light. IR spectra were recorded from KBr pellets for solid samples or neat for liquid samples on a Nicolet Magna 5700 FTIR spectrometer. ^{1}H-NMR spectra were acquired using a 300 MHzNMR Bruker spectrometer. Mass spectra were recorded on a Bruker LC-MS microTOF-Q III mass spectrometer.

General procedure for the N-alkylation, producing thiazolidine-2,4-diones (2-5) and 7. To a round bottomed flask containing a stirred mixture of thiazolidine-2,4-dione (586 mg, 5 mmol, 1 eq.) and triethylamine (10 mmol, 2.0 eq.), *n*-alkylbromide (6.5 mmol, 1.3 eq.) was added. The resulting mixture was stirred for 2 h at rt. The reaction mixture was quenched by adding 10 mL of water. The product was extracted with EtOAc (10 mL, 3x) and the extract was washed with water (10 mL, 3x) and brine (20 mL). The organic layer was collected and dried with anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified using column chromatography with gradient elution using *n*-hexane, 5% EtOAc in *n*-hexane, and 10% EtOAc in *n*-hexane solvent systems.

3-n-Butylthiazolidine-2,4-dione (2). Yellowish oil; IR ν_{max}: (neat) 2960, 2872, 1738, 1684 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 2H, CH_2), 3.60 (t, 2H, *J* 7.38 Hz, CH_2), 1.55 (m, 2H, CH_2), 1.29 (sext, 2H, *J* 6.76 Hz, CH_2), 0.92 (t, 3H, *J* 7.31 Hz, CH_3). NMR result agrees well with that of literature data[23]; ESI-MS *m/z* calculated for $C_7H_{11}NO_2S$ [(M-H)$^-$]: 172.04377, found: 172.04770.

3-n-Hexylthiazoldine-2,4-dione (3). Yellowish oil; IR $\nu_{max:}$ (neat) 2960, 2856, 1752, 1682 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.19 (2H, s, CH_2), 3.47 (t, 2H, *J* 7.17 Hz, CH_2), 1.48 (m, 2H, CH_2), 1.24 (br. s, 6H, 3xCH_2), 0.85 (t, 3H, *J* 6.42 Hz, CH_3); ESI-MS *m/z* calculated for $C_9H_{15}NO_2S$ [(M+Na)$^+$]: 224.07157, found: 224.08684.

3-n-Octylthiazolidine-2,4-dione (4). Yellowish oil; IR ν_{max}: (neat) 2926, 2856, 1752, 1682 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.16 (s, 2H, CH_2), 3.52 (t, 2H, *J* 6.74 Hz, CH_2), 1.77 (m, 2H, CH_2), 1.25 (m, 10H, 5xCH_2), 0.86 (t, 3H, *J* 6.05, CH_3); ESI-MS *m/z* calculated for $C_{11}H_{19}NO_2S$ [(M+Na)$^+$]: 252.10287, found: 252.12346.

3-n-Decylthiazolidine-2,4-dione (5). Yellowish oil; IR ν_{max}: (neat) 2926, 2854, 1753, 1694 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.18 (s, 2H, CH_2), 3.46 (t, 2H, *J* = 7.16 Hz, CH_2), 1.47 (m, 2H, CH_2), 1.23 (m, 10H, 5xCH_2), 0.85 (t, 3H, *J* = 6.33 Hz, CH_3); ESI-MS m/z calculated for $C_{13}H_{23}NO_2S$ [(M+Na)$^+$]: 280.13417, found: 279.90668.

Synthesis of 3,3'-(propane-1,3-diyl)bis(thiazolidine-2,4-dione) (7). 1,3-Dibromopropane (1 mmol, 1.0 eq.) was added to a stirred solution of thiazolidine-2,4-dione (2.1 mmol, 2.1 eq.) and triethylamine (3 mmol, 3.0 eq.) in a 25 mL round bottomed for 30 mins at rt. The reaction was quenched by adding 10 mL of water. The mixture was filtered and the residue was washed with EtOAc (5 mL, 3x) resulting to a yellowish solid. IR ν_{max}: (KBr disc) 2972, 2930, 1710, 1665; ^{1}H-NMR (300 MHz, DMSO-d_6): 4.17 (s, 4H, 2xCH_2), 3.48 (t, 4H, *J* 3.08 Hz, 2xCH_2), 1.75 (quin, 2H, *J* 7.31 Hz, CH_2). NMR result agrees well with that of literature data[24]; ESI-MS *m/z* calculated for $C_9H_{10}N_2O_4S_2$ [$(M+Na)^+$]: 297.30592, found: 296.99966.

Acknowledgements

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Supplementary Material

The ^{1}H NMR data are given in the Supplementary Material file associated with this manuscript.

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