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N-Chlorosuccinimide is a convenient oxidant for the synthesis of 2,4-disubstituted 1,2,4-thiadiazolidine-3,5-diones

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ABSTRACT

N-Chlorosuccinimide has been identified as a convenient and safe alternative oxidant for the oxidative condensation of isothiocyanates and isocyanates to afford 1,2,4-thiadiazolidine-3,5-diones.

The thiadiazolidinone (TDZD) ring system **1** (Fig. 1) possesses several interesting pharmacological properties.[1–5] In particular, 2,4-disubstituted TDZD derivatives inhibit the enzyme glycogen synthase kinase 3β (GSK3β).[2,3] GSK-3β has been shown to be involved in several important cellular functions, and inhibitors of this enzyme are believed to have therapeutic potential in the treatment of disorders such as type-II diabetes and manic depression.[1–4] Recently, it has also been reported that such derivatives possess potent antileukemic properties.[5] However, in spite of the therapeutic potential of TDZD analogs, the chemistry of this heterocycle remains relatively underexplored.

In the past, TDZD analogs have been prepared through two distinct synthetic approaches, that is, the acyl-sulfenation of ureas with chlorocarbonyl sulfenyl chloride,[6] and the oxidative condensation of isothiocyanates with isocyanates.[2,3] The latter method has been widely adopted since the nature of the 2- and 4-substituents can be controlled, which is seldom possible utilizing the former method.[7] Gaseous molecular chlorine[2] and sulfuryl chloride[6] are the only two oxidants used in the literature for the chlorination of isothiocyanates to afford *S*-chloroisothiocarbamoyl chlorides,[8] which can then undergo a cyclization cascade with isocyanates to give the appropriate iminium precursors for the preparation of TDZDs.[1]

During our ongoing effort at exploring the antileukemic potential of TDZDs through the preparation of large libraries of 2,4-disubstituted derivatives, a safer, stable, and more convenient oxidant was required. The use of a number of alternative reagents to chlorine gas was consequently attempted, employing benzyl isothiocyanate and ethyl isocyanate as test reactants. Pyridinium bromide perbromide, molecular bromine, and molecular iodine were found to be incapable of halogenating the isothiocyanate intermediate at various temperatures, ranging from ambient to reflux in either diethyl ether, hexanes, or CH_2Cl_2, as determined by visual inspection (i.e., no discoloration of bromine and iodine) as well as by GC–MS analysis. *N*-Bromosuccinimide, on the other hand, afforded α-bromo benzyl isothiocyanate, as previously reported by Jochims et al.,[9] suggesting that iodine, bromine, and their equivalents are incapable of mediating *S*-oxidation of isothiocyanates that in turn initiate the cyclization sequence leading to the TDZD ring system. It is possible that the oxidative potentials of bromine and iodine are not appreciably lower than that of the sulfur atom in the TDZD ring. In fact, this ring system has been demonstrated to be a strong biological oxidant.[5] We indeed found this to be true during our experiments with Mitsunobu and transition-state mediated coupling reactions with this heterocycle, wherein Ph_3P, as well as Pd^0 [as $Pd_2(dba)_3$], rapidly reduced TDZD **2**. In both cases, *p*-iodobenzyl isocyanate (**4**) was also observed as a byproduct. The presence of $Ph_3P{=}S$ in the GC–MS spectrum of the reaction product led us to postulate a mechanism for the reaction of Ph_3P with **2**, which is shown in Scheme 1. In the reaction of **2** with $Pd_2(dba)_3$, we observed the precipitation of a brown-black solid that was insoluble in water and organic solvents. This solid is most likely palladium monosulfide, since Pd^0 is known to be capable of functioning as a reductant, and its formation likely involves a single-electron transfer (SET) mechanism.[10,11]

Chlorine equivalents being the next obvious choice, *N*-chlorosuccinimide (NCS) and chloramine-T were employed as suspensions in diethylether, toluene, hexanes, and CH_2Cl_2 in separate reactions. While chloramine-T was ineffective, NCS (1.0 equiv)

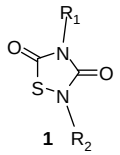

Figure 1. The thiadiazolidinone (TDZD) ring system.

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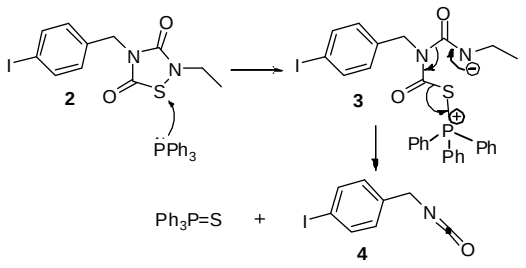


Scheme 1. Proposed mechanism for the reduction of TDZD with Ph_3P.

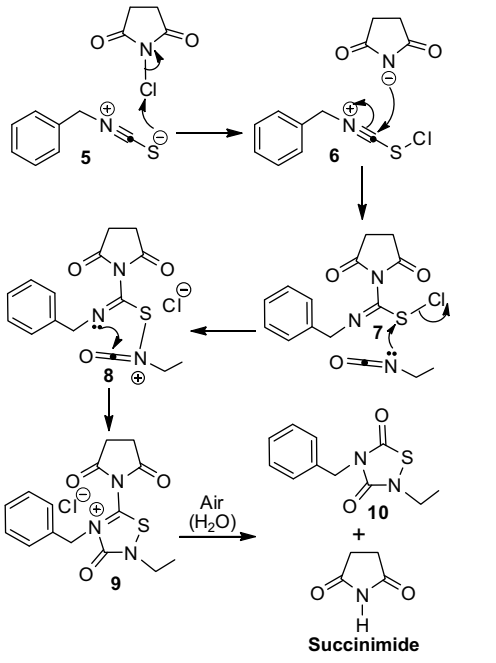
afforded ca. 10% mass conversion of benzyl isothiocyanate to TDZD **10** (Scheme 2) after workup. A slew of optimizations in reaction conditions were then attempted in order to improve the efficiency of this reaction. As a result, it was observed that the use of $CHCl_3$ afforded a more homogenous reaction mixture and a higher conversion rate than all other solvents that were employed. Refluxing of the reaction mixture, however, led to the appearance of numerous decomposition products that could not be characterized. Increasing the number of equivalents of NCS led to an increase in reaction yield after a period of 16 h, with the yield tapering off at ca. 60% at 4 equiv or more, indicating that more than 5–6 equiv of NCS are ineffectual in improving the reaction yield.[12] Quantitative recovery of the excess amounts of NCS from the above reactions suggests that the requirement for excessive equivalents of NCS seems to arise simply from a lower rate of reaction. In order to increase the reaction rate, we attempted chemical initiation by the addition of azobisisobutyronitrile (AIBN). However, this resulted in the appearance of numerous decomposition products with no appreciable increase in the reaction yield. Photochemical acceleration by irradiating the reaction with a 400 W Hg-lamp also did not lead to an increase in the reaction rate.

Attempts were then made to gain insights into the nature of the reaction intermediates involved. The lack of an accelerating effect of radical initiators on the reaction rate suggested that SET mechanisms were not significant kinetic components of the reaction pathway. This was corroborated in another experiment, where the addition of the free radical inhibitor, *m*-dinitrobenzene, to the reaction mixture did not cause a decrease in reaction rate. These experiments suggested that NCS oxidizes the isothiocyanate functional group in a classical ionic manner, involving an initial oxidative reaction of NCS with isothiocyanate, as shown in Scheme 2, which illustrates a postulated mechanism for the reaction of NCS with benzyl isothiocyanate (**5**) and ethyl isocyanate. The initial electrophilic attack of the sulfur of **5** on the chlorine of NCS affords **6**, which is immediately converted into **7**. Sulfenyl chloride **7** would then be capable of undergoing an electrophilic attack by the nitrogen of ethyl isocyanate, forming the highly electrophilic species **8**, followed by cyclization to **9**. Iminium chloride **9** would then undergo hydrolysis when exposed to air, yielding **10** and succinimide. The mechanism proposed for the condensation of **7** with ethyl isocyanate is conceptually similar to that suggested by Martinez et al. for the oxidative condensation of isothiocyanates with isocyanates,[2] The initial reaction of NCS with isothiocyanates could also proceed via an alternative reaction mechanism (Scheme 3) involving a 6-membered concerted process to yield **11** as the sulfenyl chloride intermediate which then undergoes condensation with ethyl isocyanate in a manner similar to the mechanism shown in Scheme 2.

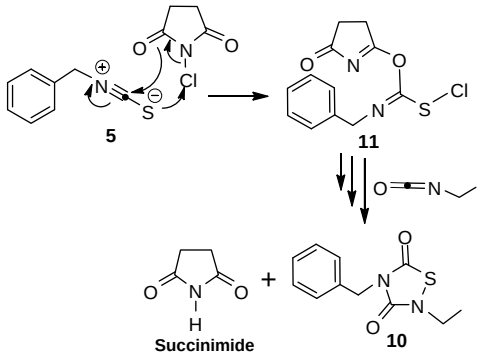
We next examined the scope and limitations of this reaction (Table 1). The yields obtained in cases where the isothiocyanates and isocyanates are alkyl or benzylic (entries 1–4, and 6) are comparable to those obtained utilizing the classical chlorine gas method.[2]

Phenyl isothiocyanate (entry 5) also afforded the expected product in good yields when the reactant was an alkyl isocyanate, however, the use of a phenyl isocyanate (entry 11) resulted in a very sluggish reaction. Increasing the equivalents of NCS to 10 did not improve the reaction yield, indicating that this method in its current form is limited in use to the synthesis of non-aryl substituted TDZDs. Entries 7–9 indicate that olefin, ester, and acrylyl functionalities remain intact under the reaction conditions. Interestingly, it was noted that *m*-anisyl isothiocyanate afforded the required TDZD analog without concomitant chlorination of the aromatic ring, which is not the case when the classical chlorination methodology is employed, since we have noted extensive aromatic chlorination during our experiments with anisyl isothiocyanates using molecular chlorine.

In conclusion, out of a variety of halogen equivalents examined, NCS was found to be the only halogenating agent that initiates the reaction pathway for the oxidative condensation of isothiocyanates with isocyanates to yield 1,2,4-thiadiazolidine-3,5-dione. Compared to the classically used reagents for this transformation (i.e., chlorine gas or SO_2Cl_2), NCS is a safer and a more convenient alternative reagent for the preparation of 1,2,4-thiadiazolidine-3,5-diones.

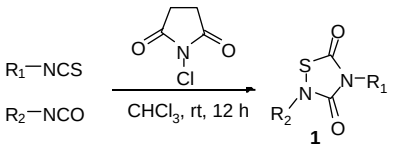


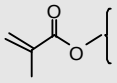
Scheme 2. Postulated mechanism for NCS-mediated TDZD formation.



Scheme 3. Alternative mechanism for NCS-mediated TDZD formation.

Table 1
Scope of NCS-induced TDZDs formation



No	R_1	R_2	Equiv. of NCS	Yield (%)
1	Bn	Et	4	45
2	Bn	Bn	4	50
3[13]	Hexyl	Bn	4	52
4[14]	Bn	2-Cl–Et	4	39
5	Ph	Et	4	45
6	Cyclohexyl	Et	4	40
7	Bn	Allyl	4	34
8	Bn	2-(Carboxyethyl)-ethyl	4	52
9	Bn		4	50
10	*m*-Anisyl	Allyl	4	21
11[15]	Bn	Ph	3–10	10

Acknowledgment

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12. *General experimental procedure*: The appropriate isothiocyanate (1 mmol) and isocyanate (1 mmol) were each dissolved in anhydrous $CHCl_3$ (10 mL/mmol) and NCS (4 mmol) was added in one portion. After stirring at rt for 12 h under argon and subsequently for 10 min in air, the reaction mixture was diluted with diethylether and filtered through a sintered glass funnel to remove unreacted NCS and the precipitated succinimide. The filtrate was concentrated under reduced pressure and subjected to column chromatography over silica gel, eluted with 15–20% diethylether–hexanes to isolate the pure product.
13. *2-Benzyl-4-hexyl-1,2,4-thiadiazolidine-3,5-dione*: yellow oil; yield: 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.75 (s, 2H), 3.67 (t, J = 7.5 Hz, 2H), 1.66 (m, 2H), 1.30 (m, 6H), 0.87 (t, J = 5.7 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.0, 153.4, 134.8, 129.1, 128.9, 128.6, 48.8, 43.1, 31.6, 28.1, 26.6, 22.8, 14.3. GC–MS m/z 292. Anal. ($C_{15}H_{20}N_2O_2S$) C, H, N.
14. *2-Chloroethyl-benzyl-1,2,4-thiadiazolidine-3,5-dione*: clear viscous oil; yield: 39%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.32 (m, 5H), 4.83 (s, 2H), 3.92 (t, J = 5.7 Hz, 2H), 3.69 (t, J = 5.7 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.8, 153.2, 135.0, 128.9, 128.8, 128.4, 46.9, 46.2, 42.1. GC–MS m/z 270. Anal. ($C_{11}H_{11}ClN_2O_2S$) C, H, N.
15. *2-Phenyl-4-benzyl-1,2,4-thiadiazolidine-3,5-dione*: white solid; mp 90 °C; yield: 10%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.25 (m, 10H), 4.91 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.1, 151.1, 135.9, 135.1, 129.6, 129.3, 128.9, 128.6, 127.1, 123.5, 46.4. GC–MS m/z 284. Anal. ($C_{15}H_{12}N_2O_2S$) C, H, N.