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Florian Luttringer, Nicolas Pétry, Eric Clot, Xavier Bantreil, Frédéric Lamaty. Mechanochemical Halogenations and Rearrangement of Sydnonones: Insight into Reaction Conditions and Mechanism. ChemistryEurope, 2024, pp.e202400054. 10.1002/ceur.202400054 . hal-04787289

HAL Id: hal-04787289

<https://hal.science/hal-04787289v1>

Submitted on 17 Nov 2024

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Mechanochemical Halogenations and Rearrangement of Sydrones: Insight into Reaction Conditions and Mechanism

Florian Luttringer,^[a] Nicolas Pétry,^[a] Eric Clot,^[b] Xavier Bantreil,^{*[a, c]} and Frédéric Lamaty^{*[a]}

New mechanochemical methods for sydnone halogenation and insights into an efficient ring rearrangement yielding 1,3,4-oxadiazolin-2-ones by heated ball-milling are reported herein. Using equimolar amounts of *N*-chlorosuccinimide (NCS), oxone and sodium chloride, 3-phenylsydnone was quantitatively chlorinated in short reaction time and high yields. Moreover, an efficient method for the bromination of sydnones was developed by mixing equimolar amount of *N*-bromosuccinimide

(NBS), Ac₂O and a sydnone in a vibratory ball-mill, in the absence of solvent, with excellent yields and a reduced environmental impact. When the reaction was heated while milling, a fast and efficient ring rearrangement into 1,3,4-oxadiazolin-2-ones was observed. Insights concerning the mechanism of the reaction under solvent-less conditions, supported by DFT calculations, are discussed. The scope of this reaction, including solid anhydrides, is presented.

Introduction

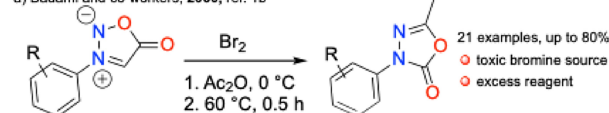
1,3,4-oxadiazolin-2-ones are 5-membered heterocycles highly patented for their antibacterial and antifungal properties.^[1] One of them, oxadiazon, is commercialized, acting as an inhibitor of the protoporphyrinogen oxidase enzyme for plant growth regulation.^[2] Other molecules are known to act as monoamine oxidase B (MAO B) inhibitors, but their synthesis and properties remain largely understudied.^[3] Several methods have been established to obtain oxadiazolinones, *i.e.* from hydrazonyl chloride, CO₂ and CsF/18-crown-6,^[1c,4] from *N*-aryl-*N*-bromocarbonylhydrazines and acyl chlorides^[5] or palladium-catalyzed oxidative carbonylation of substituted acylhydrazines with carbon monoxide.^[6] These methods are efficient for accessing the oxadiazolinone scaffold with a wide scope but the conditions may be less environmentally-friendly. Another method relies on the use of sydnones as precursors with bromine in acetic anhydride, used as solvent, at 60 °C.^[7]

Sydnones, 1,2,3-oxadiazolium-5-olates, are mesoionic compounds serving as useful synthons in cycloaddition reactions^[8] or other ring transformations leading to high-value heterocycles by loss of CO₂, as for instance reaction with alkynes to furnish pyrazoles,^[9] providing new tools for chemobiology.^[10] Usually, sydnones are chlorinated with Cl₂,^[11] KClO₃/HCl,^[12] PhICl₂,^[13] NCS

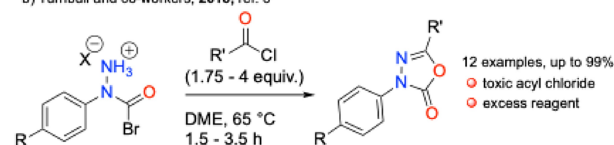
(*N*-chlorosuccinimide)/DMF,^[14] DABCO-Cl₂,^[15] or ICl/DCM^[16] and brominated with Br₂/NaHCO₃,^[17] Br₂/NaOAc^[18] or Br₂/Ac₂O,^[19] KBrO₃/HBr,^[2] NBS (*N*-bromosuccinimide, in DMF^[20] or in AcOH^[10]) or 1,3-dibromo-5,5-dimethylhydantoin (DBDMH).^[21] In 1958, a method for the bromination of sydnones with bromine in acetic anhydride at 0 °C was first described.^[22] However, upon heating the mixture over 40 °C, a gaseous evolution was observed, resulting from a clean sydnone-ring rearrangement (Schema 1). The same reaction with propanoic and succinic anhydrides furnished different products, that resulted from a rearrangement of the sydnones into 1,3,4-oxadiazolin-2-ones by loss of CO₂ and condensation of an anhydride moiety. In 2000, this methodology was applied to a series of sydnones that reacted with acetic anhydride at 60 °C, and the resulting molecules were tested for their antimicrobial properties.^[1b]

Previous work - oxadiazolinone formation in solution

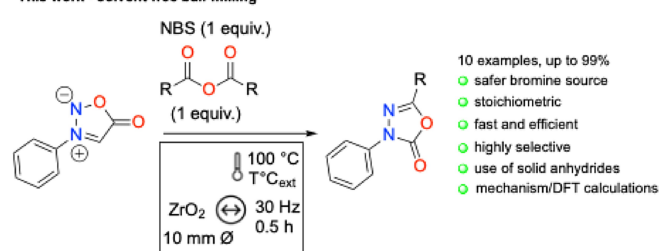
a) Badami and co-workers, 2000, ref. 1b



b) Turnbull and co-workers, 2018, ref. 5



This work - solvent-free ball-milling



Scheme 1. Previous and current approaches for the formation of an oxadiazolinone from a sydnone.

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Supporting information for this article is available on the WWW under
<https://doi.org/10.1002/ceur.202400054>

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Relying on our expertise in mechanochemistry, on our previous study on the mechanochemical synthesis of sydrones,^[23] and on our preliminary results on their halogenation,^[24] we sought to investigate this methodology and elucidate its mechanism using this solvent-free innovative approach. Indeed, mechanochemistry has been widely used as a solvent-free (or solventless) technique for the development of organic methodologies and the synthesis of biologically active organic molecules, peptides and coordination complexes.^[25] Amongst other advantages, mechanochemistry generally leads to simplified procedures with shorter reaction times and selective syntheses, facilitating purifications.^[26] In this manuscript, mechanochemical reaction conditions descriptors proposed by Michalchuk *et al.* were used^[27] to describe at its best the type of mechanochemical conditions employed.

Results and Discussion

Halogenations of Sydrones

In our previous investigation, we reported two efficient iodination methods of sydrones, but bromination results were unsatisfactory, and chlorination was cumbersome.^[24] Thus, chlorination reagents which already proved efficient with other

substrates were tested.^[28] Using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) resulted in the degradation of the starting sydnone. In the case of trichloroisocyanuric acid (TCCA), an incomplete conversion (85%) with the formation of **2** along with degradation was observed. Based on the latest developments on mechanochemical halogenation methodologies of heterocyclic compounds,^[29] we further investigated bromination and chlorination using succinimide-derived halogenation reagents (NXS, X=Cl, Br). A chlorination method of sydnone **1** was developed in a vibratory ball-mill (vbm) with the use of both NCS (1 equiv.), oxone (0.5 equiv.) and NaCl as solid additive (5.2 equiv.). This combination of reagents allowed for a selective and efficient mechanochemical sydnone chlorination. The pure compound could be isolated in 71% yield after an extraction and aqueous NaOH washes (Table 1, entry 1). Such combination is rather unique: NaX salts have been used in solution as non-toxic halogen source with oxidizing agents such as oxone or K₂S₂O₈ for halogenations of imidazo-fused heterocycles,^[30] the regioselective halogenation of 2*H*-chromenones^[31] or the regioselective oxidative chlorination of arenol^[32] notably, while NaCl has already been used as a cheap and safe chloride source for chlorination processes in conjunction with NCS.^[33] In our case, control experiments in the absence of NCS (Table 1, entry 2), oxone (Table 1, entry 3) or NaCl (Table 1, entry 4) led to decomposition of the starting

Table 1. Optimization of the halogenation of sydnone **1**.

Entry ^[a]	NCS (equiv.)	Oxone (equiv.)	NaX (equiv.)	Selectivity 2/3/4	Conv (%) ^[b]	Yield (%)
1	1	0.5	NaCl (5.2)	100/0/0	100	71
2	0	1	NaCl (3)	– ^[c]	– ^[d]	–
3	1	0	NaCl (1)	100/0/0	traces	–
4	1	1	NaCl (0)	100/0/0	5	–
5	1	0.5	NaCl (8.6) ^[f]	100/0/0	100	76
6	1	0.5	NaCl (1)	100/0/0	100	78
7 ^[e]	1	0.5	NaCl (1)	100/0/0	100	83
8	0.1	0.5	NaCl (32.1) ^[g]	100/0/0	92	n.d.
9	1	0.5	NaBr (1)	(n.d.) ^[h]	100	–
10	1	0.5	NaBr (3)	0/100/0	100	86
11	1	0.5	NaBr (22.7) ^[i]	0/100/0	100	97
12	1	0.5	NaI (1)	33/0/66	100	–
13	1	0.5	NaI (3)	0/0/100	8	–
14	1	0.5	NaF (1)	100/0/0	15	–

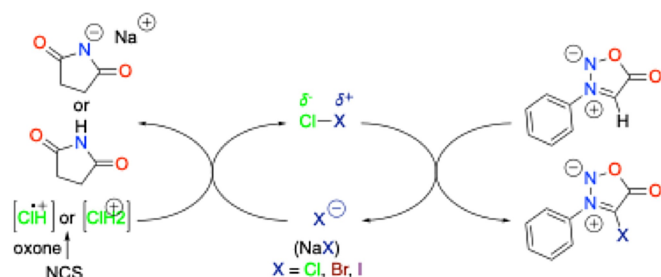
[a] Reaction conditions: **1** (0.302 mmol), *N*-chlorosuccinimide (0.302 mmol), oxone (triple salt, 0.151 mmol), NaX, vbm, 30 Hz, 1.5 h. [b] Conversion determined by HPLC. [c] Not evaluated. [d] Decomposition was observed. [e] Milling load = 80 mg.mL⁻¹. [f] 600 mg NaCl were used with 1.2 mmol of **1**. [g] 600 mg NaCl were used with 0.32 mmol of **1**. [h] **2** and **3** obtained as mixture but ratio could not be determined by ¹H NMR or HPLC. [i] 600 mg NaBr were used with 0.26 mmol of **1**.



material, with 5% conversion and the detection of traces of the expected compound. Raising the amount of NaCl to 600 mg (8.6 equiv.) did not impact much the yield of the reaction (Table 1, entry 5). The amount of NaCl used was thus reduced to 1 equiv., leading to an increase of the yield to 78% (Table 1, entry 6). Interestingly, increasing the milling load from 20 to 80 mg.mL⁻¹ furnished an even better yield of 83% (Table 1, entry 7). Intrigued by this combination of reagents, a catalytic experiment using 10 mol% NCS and 600 mg NaCl was setup and provided a good 92% conversion in 1.5 hours. However, these conditions gave rise to a by-product which could not be separated by simple basic washes and no attempt was made to recover the compound by chromatography techniques (Table 1, entry 8). This experiment supported the fact that the chlorine atom added to the sydnone was originating from NaCl.

To better understand the mechanism of the reaction, other solid additives were used as reagents. When 1 equiv. NaBr was introduced in the milling jar instead of NaCl, a concomitant chlorination/bromination process occurred (Table 1, entry 9). Using 3 equiv. NaBr led to an exclusive bromination with a good yield of 86% (Table 1, entry 10) and when the amount of NaBr used was raised to 600 mg (22.7 equiv.), the yield of **3** increased to 97% (Table 1, entry 11). The same process happened when 1 equiv. of NaI was engaged, with a chlorination/iodination ratio of 33:66 (Table 1, entry 12) but when the amount of NaI was raised to 3 equiv., a dramatic loss of reactivity was observed with only 8% conversion into the iodosydnone **4** (Table 1, entry 13). When using NaF, chlorination only occurred at a very slow rate, leading to solely 15% conversion within 1.5 hours of milling (Table 1, entry 14). In view of the outcomes with different NaX sources, it seems that this reaction relies on the *in situ* production of halogen-halogen species, and further preferential attack of the sydnone on the most electrophilic halogen atom (Scheme 2).^[28b]

In parallel to the halogenation method using NCS/Oxone/NaX, we focused on the development of another efficient mechanochemical bromination approach, since the original method that we reported using NBS in a ZrO₂ vial resulted in a poor yield after a tedious purification procedure. By investigating further this reaction in the ball-mill, we found that **1** could be cleanly converted into the bromo compound **3** using 1 equiv. each of acetic anhydride and NBS. Gratifyingly, after an extraction and basic washes (NaOH, 1 M), the pure compound was recovered as a brown powder in an almost quantitative yield (99%). Pleased to observe such a selectivity, these



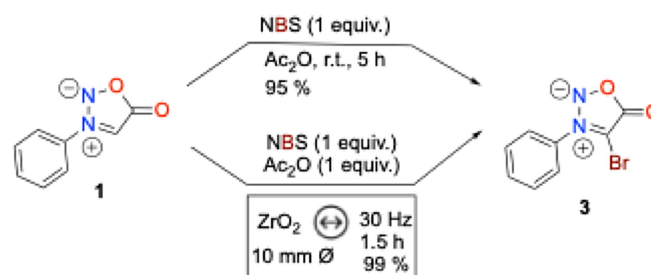
Scheme 2. Proposed mechanism for the halogenation of **1**.

conditions were used at room temperature in classical solution chemistry for comparison. With 1 equiv. of NBS and acetic anhydride as solvent (around 42 equiv.) a clean bromination occurred in few hours, giving **3** in 95% yield (Scheme 3). Both approaches, in solution, or in the ball-mill in stoichiometric conditions, were found to be much more efficient than using NBS in DMF^[20] or AcOH^[10] since the use of a toxic solvent was avoided and a higher yield was obtained due to a better selectivity.

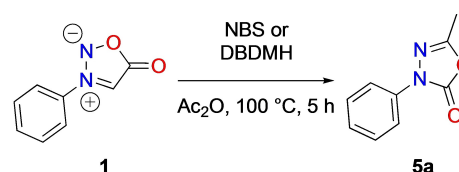
Rearrangement into Oxadiazolinone

Interestingly, in the literature, the reaction of a sydnone with a brominating agent (NBS^[34] or 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)^[35] in refluxing acetic anhydride furnished the acetylated sydnone in C⁴ position. However, in our hands, under the same reaction conditions, sydnone **1** cleanly converted into the corresponding 5-methyl-1,3,4-oxadiazolin-2-one **5a** within 5 hours (Scheme 4).

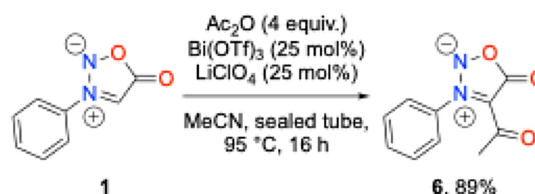
The pure heterocycle **5a** was recovered with an excellent yield of 98% using NBS after a quick filtration through a silica plug and fully characterized.^[1c] Moreover, at room temperature, the use of DBDMH resulted in the bromination of sydnone **1**, which rearranged into **5a** upon heating. To unambiguously characterize acetylated molecule **6**, another acetylation method developed in solution^[36] was employed (Scheme 5).



Scheme 3. Solution and mechanochemical sydnone bromination methods.



Scheme 4. Sydnone **1** rearrangement into 1,3,4-oxadiazolin-2-one **5a**.



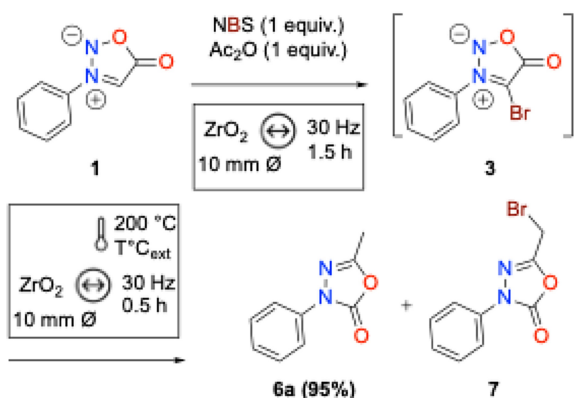
Scheme 5. Acetylation of **1** in solution.



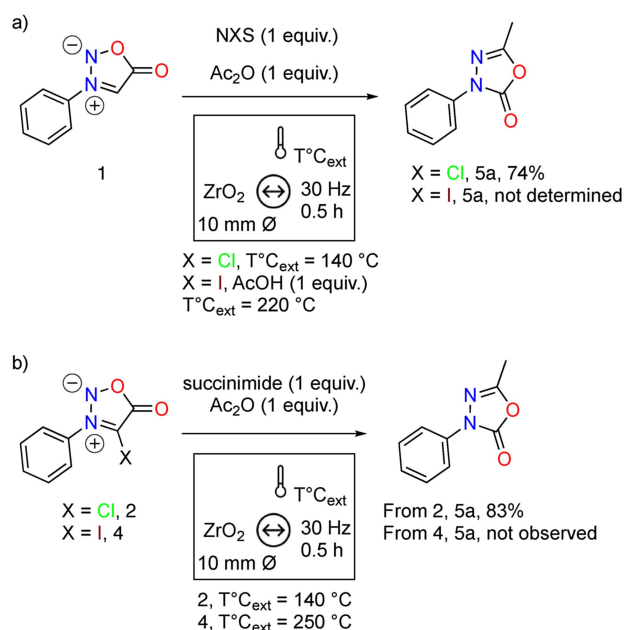
Reacting **1** with Ac₂O, a Lewis acid and LiClO₄ as co-catalyst in MeCN yielded 89% of 4-acetylsydnone **6**, which was fully characterized and differ in part from previously reported spectral data.^[34–35]

In order to improve the reaction conditions toward the oxadiazolinone synthesis, and notably reduce the quantity of acetic anhydride used, we tested this ring transformation in a heated vibratory ball-mill.^[24,37] First, sydnone **1** was brominated, using NBS and acetic anhydride in stoichiometric quantities, in the ball-mill for 90 minutes at room temperature and with a quantitative conversion as checked by HPLC. An external heating was then applied, using a heatgun with a set temperature of 200 °C (around 90 °C for the internal temperature), while milling for 1 h at 30 Hz. Quantitative conversion was obtained, and the pure oxadiazolinone **5a** was isolated with an excellent yield after filtration through a silica plug, to separate the small quantity of brominated by-product **7** that formed (Scheme 6).

After optimization of the different parameters, the bromination/rearrangement could be performed efficiently in a one-pot manner by milling sydnone **1** with stoichiometric quantities of NBS and Ac₂O for 30 min at 30 Hz upon gentle heating (heatgun with a set temperature of 100 °C). Additionally, as this rearrangement was only performed with bromosydnone in the literature, we wondered if other halogenated sydnones would give similar results. When NCS and Ac₂O were milled together with **1** at 140 °C, the reaction gave 74% yield of the oxadiazolinone **5a** after a quick filtration on a silica plug. When milling sydnone **1** with *N*-iodosuccinimide (NIS) and AcOH to generate **4** and then performing a heated milling in the presence of 1 equiv. Ac₂O, the ring formation occurred in 30 min, but only when the temperature was set to 220 °C. Moreover, the formation of many unidentified side products was observed in HPLC (Scheme 7, Eq. a) and in this case, **5a** was not further purified. Similarly, reacting directly chlorosydnone **2** with 1 equiv. of succinimide and Ac₂O at 140 °C furnished 83% of the oxadiazolinone after purification. Interestingly, when performing this rearrangement from the iodosydnone **4** with 1 equiv. succinimide and Ac₂O with heated milling, no formation of the oxadiazolinone occurred even at a preset temperature of 250 °C (Scheme 7, Eq. b).

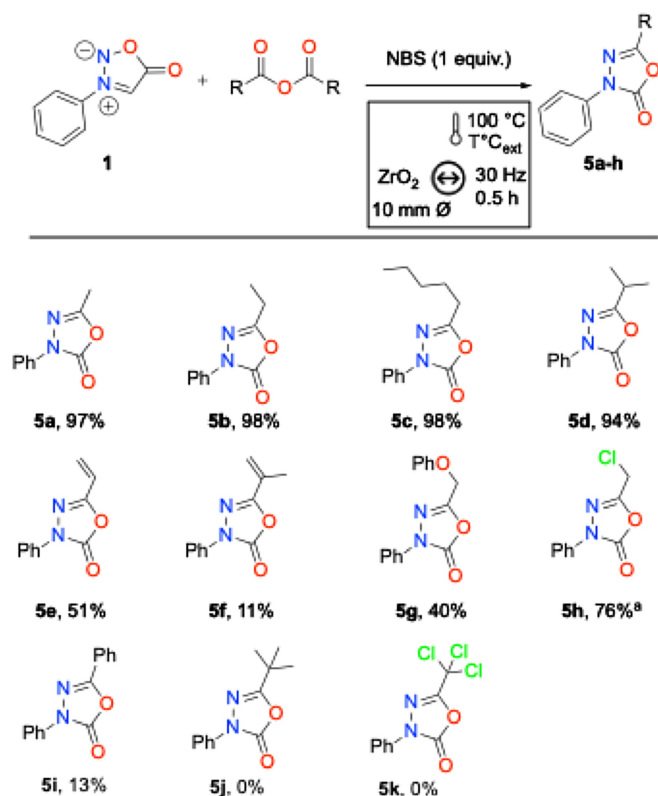


Scheme 6. Mechanochemical 1,3,4-oxadiazolin-2-one formation.



Scheme 7. Formation of oxadiazolinone **5a** using other N-halogenosuccinimides (a) or from sydnones **2** and **4** (b).

Driven by the ease of obtention of these compounds with our ball-milling method, we decided to expand the scope of the 1,3,4-oxadiazolinone formation by using different anhydrides (Scheme 8). Replacing acetic anhydride for propionic anhydride gave **5b** with an excellent 98% yield. Longer alkyl chains were also suitable for this method, as shown by using hexanoic anhydride, which provided **5c** with a 98% yield. A bulkier substrate such as isobutyric anhydride was also suitable giving **5d** (94%) but pivalic anhydride or trichloroacetic anhydride did not react and expected product **5j** and **5k** resp. were not obtained. Acrylic and methacrylic anhydrides respectively gave **5e** and **5f** with lower yields (51% and 11%), due to a more complicated purification step to separate the several by-products that formed. Interestingly, this mechanochemical method was highlighted by using solid anhydrides as new potential substrates. Phenoxyacetic anhydride gave **5g** with a 40% yield after filtration and using chloroacetic anhydride with our method led to a 54:46 mixture of **5h** and the corresponding bromo derivative as by-product, which could not be separated with classical separation techniques. Gratifyingly, replacing NBS with NCS with a set temperature of 140 °C gave selectively **5h** in 76% yield. Finally, reaction of benzoic anhydride provided **5i** albeit in low yield. This scope and limitations study showed that reactive and less hindered anhydrides react easily in ball-mill providing an eco-friendly method to prepare these molecules while for more demanding starting materials, the in-solution synthesis would be preferred.^[1c,4–6]

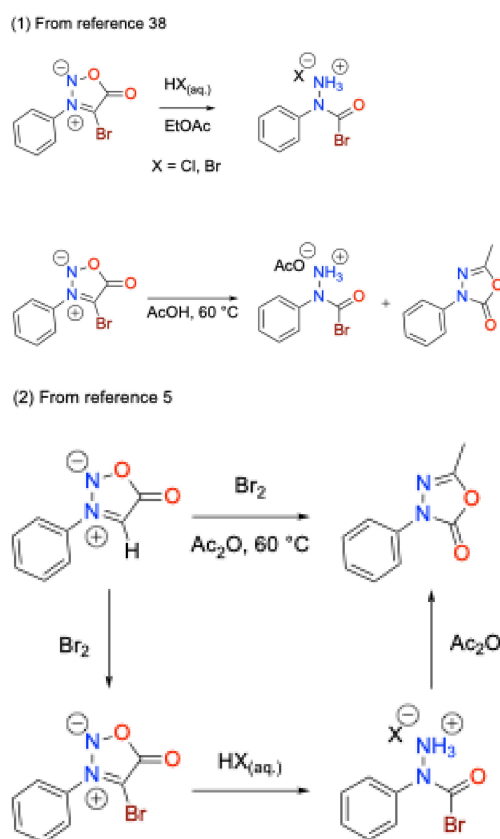


Scheme 8. Scope of the 3-Phenylsydnone **1** Rearrangement into 1,3,4-Oxadiazolin-2-ones with Anhydrides. [a] NCS was used instead of NBS at a preset temperature of 140 °C.

Mechanism and DFT Calculations

Mechanistically, the ring transformation using Br₂/Ac₂O was first thought to be a 1,3-dipolar cycloaddition as described in the literature.^[19,35] Other experiments suggest that HBr released in the mixture rather than a cycloaddition. Kuo *et al.*^[38] have shown that HX (X = Cl or Br) could hydrolyze the bromosydnone intermediate to yield a relatively stable bromocarbonylhydrazine salt. The authors also noted that acetic acid could convert the sydnone in the hydrazine salt with concomitant formation of the oxadiazolinone, but that amount was not quantified (Scheme 9, Eq. 1). Furthermore, it was shown that reaction of bromocarbonylhydrazine with acetic anhydride yielded the corresponding 1,3,4-oxadiazolin-2-one (Scheme 9, Eq. 2).^[5,39]

In the case of NBS/Ac₂O, HBr formation is rather improbable after total conversion of **1** into the bromo intermediate, and it is more likely that the resulting succinimide left in the media is involved in the mechanism. We thus tested the reaction of the 4-bromo-3-phenylsydnone **3** with succinimide and Ac₂O. When **3** was milled at 30 Hz with 1 equiv. of both succinimide and acetic anhydride, in a milling jar heated at 160 °C (set temperature) for 1 h, the ring transformation occurred smoothly, leading to **5a** with an excellent 98% yield. Interestingly, 8% conversion was observed by mechanochemistry when **3** was engaged with Ac₂O only, in the absence of succinimide, in a milling jar heated at 160 °C for 30 min. When 1 equiv. of



Scheme 9. Experiments in solution supporting the in-solution HBr-catalyzed sydnone ring rearrangement to oxadiazolinone.

succinimide was added to the mixture and the jar subjected to the same conditions, **5a** was obtained as the sole product. As succinimide could serve both as proton source (pK_a = 9.6)^[40] and weak nucleophile, control experiments, consisting in reacting **3** with Ac₂O and various reagents in place of succinimide (Table 2), were thus performed.

Interestingly, using 1 equiv. of phthalimide instead of succinimide also gave a clean and selective rearrangement to the oxadiazolinone (Table 2, entry 3). However, the use of *N*-methylphthalimide or the potassium salt of phthalimide did not give any conversion into **5a** (Table 2, entries 4–5). Of note, in the former case, a total conversion of the reagent into an unidentified bromo-compound was observed. From these results, it seems that the proton of succinimide is necessary for the reaction to occur. An experiment with 10 mol% AcOH was thus investigated and in that case, a total conversion of **3** was obtained but this time alongside with by-products (Table 2, entry 6). Among them, traces of the bromocarbonylhydrazine previously observed in solution^[5] were detected in LC/MS. This led us to consider various proton sources. When using NaHCO₃, which has a pK_a value close to that of succinimide (pK_a = 10.3), the rearrangement did not occur (1% conversion, Table 2, entry 7). NaHSO₄, with a more acidic pK_a value (pK_a = 1.99), gave a total conversion in 30 min albeit the formation of by-products led to a reduced conversion into oxadiazolinone compared to succinimide (58% conv. into **5a**, Table 2, entry 8).



Table 2. Control experiments for the rearrangement of **3** into **5a**.

Entry	Reagent	Conv. into 5a (%) ^[a]
1	Succinimide	100
2	No reagent	8
3	Phthalimide	100
4	<i>N</i> -methylphthalimide	0
5	Potassium phthalimide	0
6	Acetic acid (10 mol%)	40
7	NaHCO ₃	1
8	NaHSO ₄	58
9	DMAP	0

[a] Determined by LC/MS.

Using DMAP, known for its nucleophilic assistance properties, afforded only traces of the expected compound along with some by-products and adding 1 equiv. of NaHSO₄ to the system did not impact much the conversion rate (Table 2, entry 9). All these experiments confirmed the crucial role of succinimide in the reaction in order to obtain a high selectivity.

To shed light on the reaction mechanism, DFT calculations (PBE0-D3, see ESI for computational details) have been carried

out. The reaction between succinimide and Ac₂O was assumed to form *N*-acetylsuccinimide and acetic acid (*vide infra*). The reaction between 4-bromo-3-phenylsydnone, **3** (**A** in Figure 1), and acetic acid was first considered.

Protonation of the sydnone **A** by acetic acid is effective through **TS-A-B** with a computed activation barrier of $\Delta G^\ddagger = 29.6$ kcal.mol⁻¹. The transition state is associated to a simultaneous formation of the N–H bond (1.150 Å) and of the C(4)–O bond (2.147 Å) with the acetate. The transformation is computed to be endoergic with $\Delta G = 14.4$ kcal.mol⁻¹. The product of the reaction, **B**, features a fully formed N–H bond (1.029 Å) and a fully formed C–O bond with the acetate (1.420 Å) at the 4-position. The N–H bond in **B** is orientated perpendicular to the 5-membered ring in order to create an H-bond interaction with the acetate (H...O = 2.194 Å). From **B**, the N(2)–O(1) bond is broken through **TS-B-C** with a low activation barrier of $\Delta G^\ddagger = 11.9$ kcal.mol⁻¹. The N–O bond elongates from 1.406 Å in **B** to 2.005 Å in **TS-B-C**, while the N–H...O H-bond interaction with the acetate shortens to 1.820 Å in **TS-B-C**. This transformation is computed to be endoergic with $\Delta G = 6.2$ kcal.mol⁻¹ and forms **C** featuring a CO₂ group bonded to C(4) with a C(4)–CO₂ bond distance of 1.793 Å. CO₂ dissociation from **C** to form **D** through **TS-C-D** is computed to be very easy ($\Delta G^\ddagger = 1$ kcal.mol⁻¹) and strongly favored thermodynamically ($\Delta G = -30.0$ kcal.mol⁻¹). The intermediate **D** does not feature anymore the N–H...O H-bond with the acetate group as a result of minimizing the π -repulsion between the planar Br–C–N–N moiety and the lone pair on the acetate oxygen. As a matter of fact, the all-planar geometry featuring an N–H...O H-bond, **D_{perp}** is computed to be a transition state associated to the rotation around the C–O bond and lies at $\Delta G^\ddagger = 13.4$ kcal.mol⁻¹ above **D**. The geometry of **D** allows nucleophilic attack from NH on the electrophilic

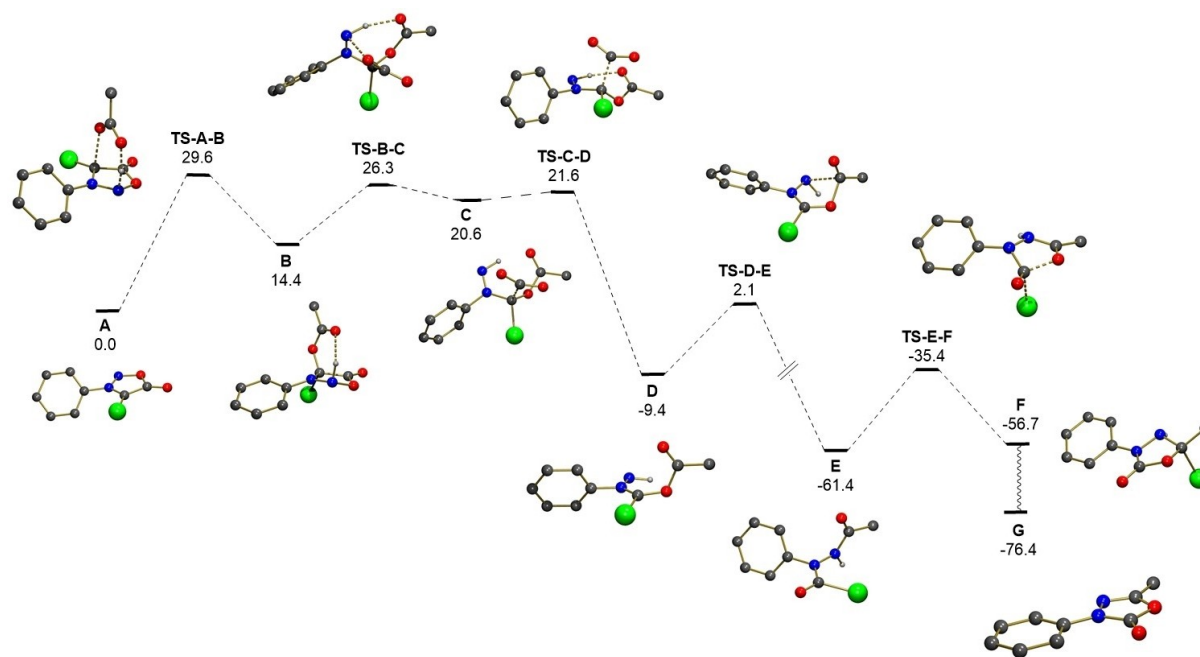


Figure 1. Computed reaction pathway (Gibbs free energy, kcal.mol⁻¹) obtained by DFT Calculations (PBE0-D3/Def2-QZVP//PBE0-D3/Def2-SVP, energy in kcal.mol⁻¹) for the formation of the oxadiazolinone **5a** from sydnone **3**.



carbon center on the acetate through **TS-D-E** to transfer the acetyl group from O to N. This reaction is computed to be very easy kinetically ($\Delta G^\ddagger = 11.5 \text{ kcal.mol}^{-1}$) and strongly favored thermodynamically ($\Delta G = -52.0 \text{ kcal.mol}^{-1}$). From **E**, the cyclization is effective through **TS-E-F** with $\Delta G^\ddagger = 26.0 \text{ kcal.mol}^{-1}$. The reaction is best described as a nucleophilic attack of the oxygen atom of the (NH)-acetyl group on the electrophilic bromo-substituted carbon atom. The O...C bond distance in **TS-E-F** is reduced to 1.610 Å compared to a value of 3.321 Å in **E**. Concomitantly, the C–Br bond distance elongates from 1.960 Å in **E** to 2.385 Å in **TS-E-F**. As the nucleophilic attack from O is perpendicular to the N–C–Br plane, the Br atom lies above the 5-membered ring in **TS-E-F** and migrates to the carbon atom of the acetyl in **F** (C–Br = 2.067 Å). The transformation from **E** to **F** is computed to be slightly endoergic ($\Delta G = 4.7 \text{ kcal.mol}^{-1}$), but elimination of HBr from **F** yields the final product **G** with $\Delta G = -19.7 \text{ kcal.mol}^{-1}$. As **D** features an imine group that reacts as a nucleophile toward the acetyl group in **TS-D-E**, we envisioned the reactivity of the imine group as a base toward external acetic acid. A transition state structure, **TS-D-D'** (Figure 2), was located on the potential energy surface with $\Delta G^\ddagger = 13.0 \text{ kcal.mol}^{-1}$ with respect to **D** + AcOH. In **TS-D-D'** the N–H bond is almost formed (N...H = 1.043 Å) and the O–H bond of the acetic acid is broken (O...H = 1.86 Å). The product of the reaction is the amine **D'** (Figure 2) and Ac₂O with a reaction energy of $\Delta G = -39.2 \text{ kcal.mol}^{-1}$. There is thus only a slight kinetic preference ($\Delta\Delta G^\ddagger = 1.5 \text{ kcal.mol}^{-1}$) for the intramolecular pathway **D**→**E** compared to the intermolecular one **D**→**D'** involving an extra acetic acid molecule. This is in agreement with the experimental observations where a mixture of the two resulting products is observed in reactions performed in solution.^[36] However, in the present case, the only source of acetic acid is from reaction between succinimide and Ac₂O. A transition state for such a reaction, **TS1** (Figure 2), was located with a very high activation barrier of $\Delta G^\ddagger = 43.2 \text{ kcal.mol}^{-1}$. This TS is best described as a nucleophilic attack of the nitrogen on the electrophilic carbon center (N...O = 2.042 Å) with a concomitant proton transfer to oxygen (N...H = 1.257 Å and H...O = 1.309 Å). The reaction is computed to be slightly endoergic with $\Delta G = 1.7 \text{ kcal.mol}^{-1}$. The calculations point thus to a very difficult formation of acetic acid when only succinimide and Ac₂O are reacted. The concentration of AcOH will thus be very low and the intramolecular pathway will be strongly favored over the intermolecular one requiring an extra acetic acid molecule. This explains the selectivity observed experimentally with only formation of **G**. To confirm this experimentally, an equimolar amount of Ac₂O and succinimide was ball-milled for 30 min (Scheme 8, Eq. 1, external temperature 100 °C, see

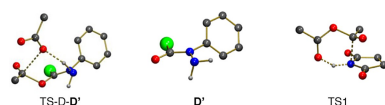


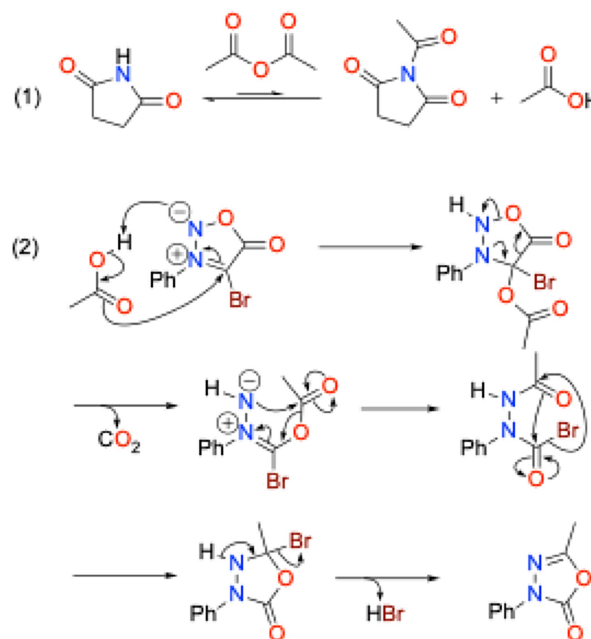
Figure 2. Optimized geometries of **TS-D-D'**, **D'** and **TS1** (most H atoms omitted for clarity) obtained by DFT Calculations (PBE0-D3/Def2-QZVP//PBE0-D3/Def2-SVP, energy in kcal.mol⁻¹).

Supporting Information) resulting in the conversion into 11 % of *N*-acetylsuccinimide and acetic acid.

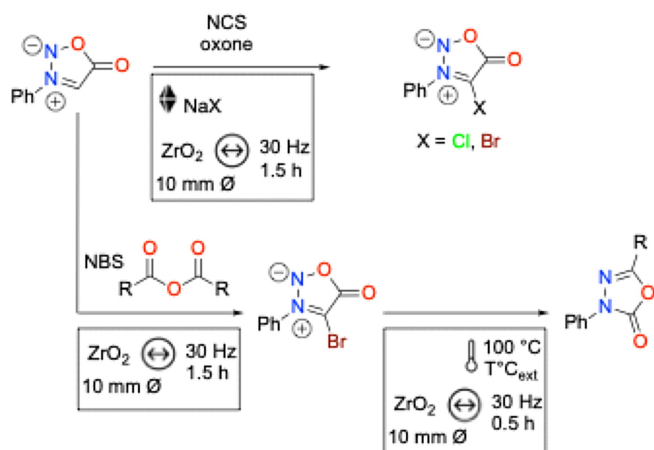
From the experimental results and the DFT calculations, a possible mechanism for the solvent-free formation of oxadiazolinone from sydnone **3** can be proposed (Scheme 10). Reaction of the succinimide on acetic anhydride will generate *N*-acetylsuccinimide and acetic acid. Attack of acetic acid on the bromo sydnone **3**, followed by release of CO₂ provides a reactive iminium derivative, which rearranges in the corresponding acyl hydrazine. Cyclization followed by elimination of HBr results in the formation of oxadiazolinone **5a**.

Conclusions

A solventless, convenient, eco- and user-friendly method for the mechanochemical chlorination and bromination of sydnones has been developed resulting in good yields of the expected products. For the chlorination, the use of solid-only reagents in equimolar amounts with NCS, oxone and NaCl has been found to be critical for a successful process. On the other hand, an efficient and quantitative bromination of sydnones was performed using only stoichiometric quantities of NBS and Ac₂O in the ball-mill. Heating this same mechanochemical reaction triggered a rearrangement into 1,3-oxadiazolin-2-one (Scheme 11). When varying the anhydride, unprecedented heterocycles were synthesized with modest to excellent yields, with some limitations compared to solution with hindered anhydrides. Of note, this method brings the first examples of solid anhydrides used for oxadiazolinone formation. Moreover, DFT calculations and mechanochemical experiments were performed to provide insight into the rearrangement mechanism in the solid state.



Scheme 10. Proposed mechanism for the formation of oxadiazolinone **5a** with succinimide and Ac₂O.



Scheme 11. Summary of the reaction conditions for the halogenation of sydrones and rearrangement.

Acknowledgements

We gratefully acknowledge financial support from the CNRS, the University of Montpellier and Institut Universitaire de France.

Conflict of Interests

The authors declare no conflict of interest.

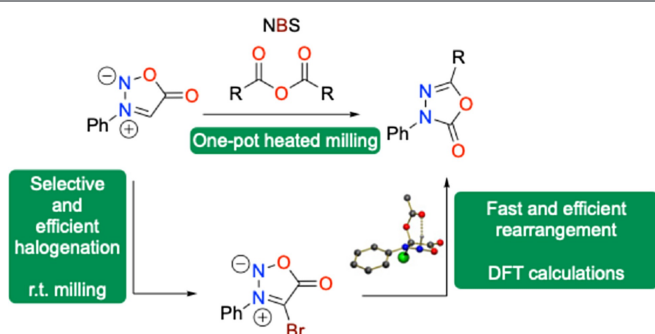
Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: sydrones · mechanochemistry · ball-milling · rearrangement · DFT calculations

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Straightforward halogenation of sydnes was enabled by ball-milling at room temperature. By rising the temperature in the same conditions, a

rearrangement into oxadiazolinones occurred. Experimental data and DFT calculations shed light on the mechanism.

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Prof. Dr. X. Bantreil*, Dr. F. Lamaty*

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**Mechanochemical Halogenations
and Rearrangement of Sydnes:
Insight into Reaction Conditions and
Mechanism**

