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Mechanosynthesis of sydnone-containing coordination complexes†

Nicolas Pétry,^a Thibaut Vanderbeeken,^a Astrid Malher,^a Yoan Bringer,^a Pascal Retailleau,^b Xavier Bantreil^a and Frédéric Lamaty^{b*}

***N*-Phenyl-4-(2-pyridinyl) sydnone was shown to act as a four-electron donor N,O-ligand in unprecedented coordination complexes featuring three different metallic centers (Co, Cu, and Zn). Starting with various anilines, the use of a ball-mill efficiently enabled the synthesis of *N*-arylglycines, subsequent nitrosylation and cyclization into sydnones, and further metalation.**

Sydnones, mesoionic heterocyclic compounds, are versatile building blocks in heterocyclic chemistry, for example in the formation of pyrazoles through copper-catalyzed 1,3-dipolar cycloaddition.¹ They also display interesting biological activities, *e.g.*, as antibacterial, antineoplastic and anti-inflammatory agents.² Sydnone synthesis from α -amino acids involves a nitrosylation step, using sodium nitrite in highly acidic media or isoamyl nitrite,³ and subsequent cyclization using acetic or trifluoroacetic anhydride (TFAA).⁴

In 2014, Shih *et al.* showed that palladium complexes featuring sydnone-4-carbaldehyde *N*(4)-phenylthiosemicarbazone ligands exhibited higher anticancer activities than 5-fluorouracil (Fig. 1).⁵ To date, this is the only reported example in which the exocyclic oxygen of the sydnone is shown to coordinate with a metal. Indeed, in the literature, sydnones have been modified as phosphine ligands for palladium complexation (Fig. 1),⁶ directly metalated at C₄,⁷ through deprotonation or carbon-halogen insertion, or modified at N₃ with a 3-pyridine for iron coordination.⁸ In this context, we wondered if the presence of a 2-pyridine at C₄ would enable access to unprecedented coordination structures featuring sydnones as N,O-ligands.⁹ Given our expertise in mechanochemistry for organic and organometallic synthesis,¹⁰

we envisioned a solvent-free mechanochemical approach¹¹ for efficient access to sydnones and to unprecedented coordination complexes.

During our study, we realized that accessing sydnone precursors could also benefit from mechanochemistry in terms of the reaction time and yield. *N*-Arylglycines were thus prepared *via* solvent-free mechanochemistry, using a 15 mL Teflon jar (filled with one stainless steel ball of 1 cm diameter) agitated at 25–30 Hz in a vibratory ball-mill (Scheme 1), through either alkylation of substituted anilines with ethylbromoacetate and subsequent saponification (one-pot two-step, method A) or reductive amination involving glyoxylic acid and sodium cyanoborohydride (method B).

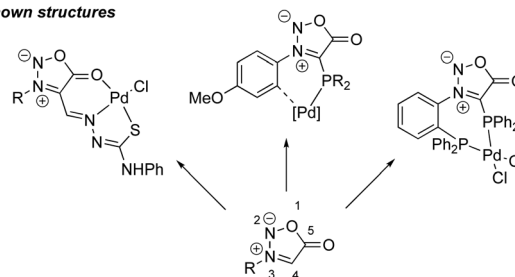
N-Arylglycines featuring electron-donating groups at the *para* position such as methyl (**1b**) and methoxy (**1c**) could be isolated in 95% and 80% yields over two steps, respectively, using method A. When a bromine atom was either at the *meta* or *para* position, method A was also found to be efficient, giving the corresponding glycines in 85% (**1h**) and 76% (**1d**) yields, respectively. Mesitylamine, even though extremely sterically

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Known structures



This work

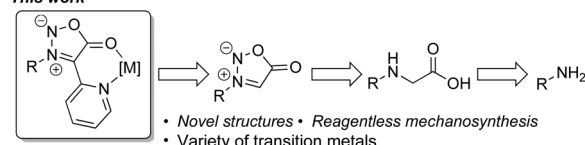
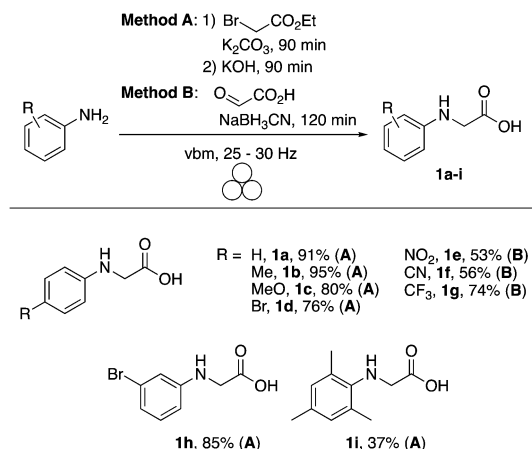


Fig. 1 Coordination complexes featuring sydnone-based polydentate ligands.



Scheme 1 Mechanosynthesis of *N*-arylglycines **1a-i**.

hindered, reacted upon using method A to furnish the expected glycine **1i** in 37% yield. Even if modest, this yield is four-fold higher than the 10% yield reported in the literature.¹² When using anilines bearing electron-withdrawing groups such as NO₂, CF₃ and CN, method B was found to be more efficient, giving the corresponding products in 53–74% yields (**1e-g**). In all the cases, yields obtained using mechanochemical approaches were similar if not better compared to those obtained with literature conditions in solution.¹³ In addition, the reaction time was limited to 2–3 h, and a simple extraction/precipitation procedure was required to isolate pure compounds.

Using *N*-phenylglycine **1a** as the model substrate, the synthesis of corresponding sydnone *via* a mechanochemical one-pot two-step approach was next investigated. Recently, the Taran group developed a one-pot procedure using *tert*-butyl nitrite and TFAA under solvent-free conditions and magnetic stirring, but sydnone were not isolated and directly used in a cycloaddition step.¹⁴ Under mechanochemical activation, ^tBuONO was found to be efficient and nitrosylation was completed within 5 min, as confirmed by HPLC analysis (Table 1, entry 1). Addition of trifluoroacetic anhydride (2.5 equiv.) to the reaction mixture in the same jar furnished sydnone **2a** in 51% yield. Even though this method is sodium nitrite and acid free, ^tBuONO has to be prepared from *tert*-butanol using these reagents. We reasoned

Table 1 Optimization of the reaction conditions of sydnone mechano-synthesis^a

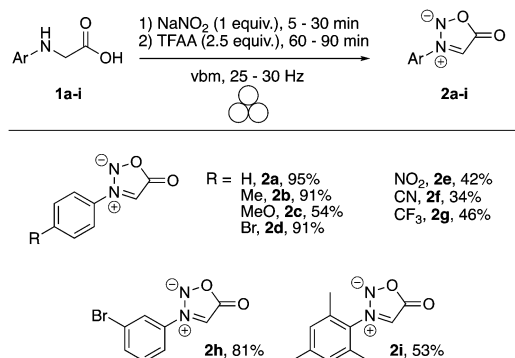
Entry	NO source (equiv.)	TFAA (equiv.)	t ₂ (min)	Yield 2a (%)
1	^t BuONO (1.2)	2.5	30	51
2	NaNO ₂ (1.0)	2.5	30	54
3	NaNO ₂ (1.0)	2.5	60	95
4	NaNO ₂ (1.0)	2	60	77
5	NaNO ₂ (1.0)	3	60	92

^a Total mass of the reagents was calculated to obtain a milling load (ML) of 20 mg mL⁻¹. Reactions were performed in a vbm at 25 Hz.

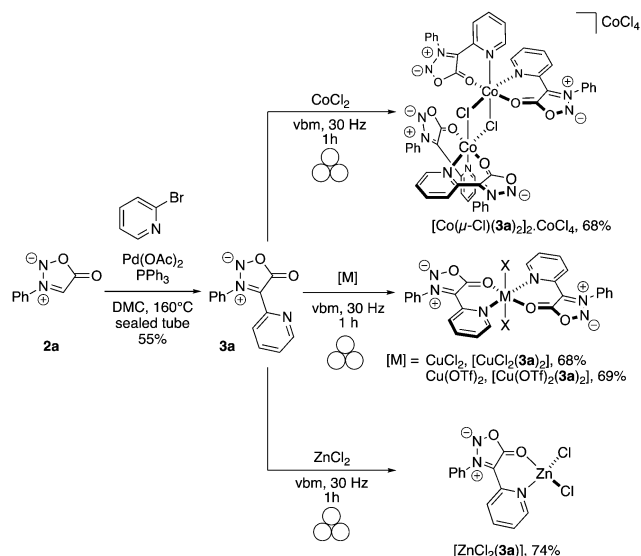
that sodium nitrite, without the addition of concentrated HCl, could furnish the nitrosylated intermediate. Indeed, the two hydrogen atoms necessary for water release in the nitrosylation mechanism would in this case come from the amine and acid functions of **1a**. Gratifyingly, milling **1a** and NaNO₂ in stoichiometric quantities for 5 min resulted in full conversion of **1a** into *N*-nitroso-*N*-phenylglycinate. Subsequent addition of TFAA to the crude mixture and milling for 30 min yielded sydnone **2a** in 54% yield (Table 1, entry 2). Increasing the milling time of the second step to 1 h enabled an excellent yield of 95% (Table 1, entry 3). Notably, changing the stoichiometry of TFAA did not improve the final yield (Table 1, entries 4 and 5).

The milling conditions were then applied to *N*-arylglycines **1a-i** (Scheme 2). The reaction time and the milling frequency were modulated to achieve in each case fast and full conversion, which enabled the avoidance of chromatography on silica gel. In all the cases, the total reaction time did not exceed 120 min with yields comparable to those obtained in solution.¹³ Sydnone featuring methyl (**2b**) and methoxy (**2c**) groups at the *para* position of the phenyl moiety were produced in 91% and 54% yields, respectively. With a bromine atom either at the *para* or *meta* position, the corresponding sydnone **2d** and **2h** could be obtained in 91% and 81% yields, respectively. Sydnone **2e-g**, featuring NO₂, CN and CF₃ electron-withdrawing groups were isolated in lower yields of 34–46%. Even though full conversion was achieved, a recrystallization step (for **2e-f**) or chromatography on silica gel (only for **2g**) which reduced the final yield was required to furnish pure compounds. The same conditions apply to sydnone **2i**, featuring the sterically hindered mesityl group, which was obtained in 53% yield. To the best of our knowledge, it is the first time that sydnone **2i** is synthesized and fully characterized.^{7f,15}

A pyridine at C₄ of the sydnone was next introduced to obtain a putative bidentate ligand. *N*-Phenylsydnone **2a** was reacted with 2-bromopyridine in the presence of Pd(OAc)₂/PPh₃ or Pd(OAc)₂/XPhos as catalytic systems according to literature methods.¹⁶ However, the yields obtained were not reproducible and separation of the XPhos ligand was complicated. Although other palladium-catalysed cross-couplings were successful in the ball-mill,¹⁷ attempts to perform the coupling reaction with **2a** under mechanochemical conditions failed. A quick study



Scheme 2 Mechanochemical synthesis of *N*-arylsydnone **2a-i**.



Scheme 3 Synthesis of coordination complexes with sydnone **3a** as the N,O-ligand.

showed that this coupling could be performed using Pd(OAc)₂/PPh₃ (1:2) in DMC (dimethylcarbonate), an environmentally friendly solvent, giving the corresponding 3-phenyl-4-(2-pyridine)-sydnone **3a** in 55% yield, with a facilitated purification (Scheme 3).

Bidentate compound **3a** was then reacted, using a vibratory ball-mill, with various metallic salts (CoCl₂, CuCl₂, Cu(OTf)₂ and ZnCl₂) under solvent-free conditions. We were pleased to observe that after 1 h of milling the corresponding complexes were obtained in 66–74% yields. Conversion was observed in the solid state by IR spectroscopy, as the C=O stretching band in **3a** ($\nu = 1757 \text{ cm}^{-1}$) shifted to lower wave numbers upon coordination ($\nu = 1660\text{--}1726 \text{ cm}^{-1}$). The structures of the complexes [Co(μ -Cl)(**3a**)₂]₂·CoCl₄, [CuCl₂(**3a**)₂], [Cu(OTf)₂(**3a**)₂] and [ZnCl₂(**3a**)] were confirmed by single crystal X-ray diffraction after crystallisation (Fig. 2).¹³ Interestingly, the cobalt complex possesses a dimeric structure with two sydnone ligands at each metallic center, and bridging chloride atoms. This kind of arrangement was rarely observed in the literature with bidentate N,O ligands.¹⁸ For copper containing species, an octahedral geometry with two sydnone ligands and with a *trans*-arrangement between

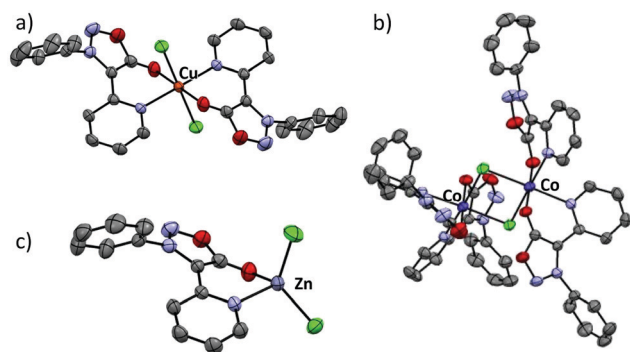


Fig. 2 X-ray diffraction of complexes (a) [CuCl₂(**3a**)₂], (b) [Co(μ -Cl)(**3a**)₂]₂·CoCl₄ and (c) [ZnCl₂(**3a**)]. H atoms and CoCl₄²⁻ are omitted for clarity.

the two chloride (or triflate) ligands was observed. On the other hand, the reaction with zinc(II) chloride provided the complex with only one sydnone ligand and a tetrahedral geometry. In all the X-ray structures, the pyridine and sydnone rings were not found in the same plane and a twist of 22–35° was observed in the complexes. This non-planarity was also witnessed in the X-ray structure of **3a**.¹³ Such observation tends to indicate that pyridine and sydnone rings may not be conjugated. Additionally, the exocyclic C–O bond was measured to be 1.21–1.24 Å, which is consistent with a double bond character. Bidentate sydnone **3a** may thus act as a four-electron rather than a three-electron donor ligand.

In conclusion, the use of a ball mill enabled the efficient reagentless preparation of a series of *N*-aryl glycines and the corresponding sydnones. *N*-Phenyl-4-(2-pyridinyl) sydnone **3a** was used for the first time as a ligand to coordinate with metals, leading to unprecedented compounds *via* a mechanochemical solvent-free approach. These results pave the way for the development of novel families of coordination complexes.

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Conflicts of interest

There are no conflicts to declare.

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