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Mechanosynthesis of sydnone-containing coordination complexes[†]

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

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

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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



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

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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 sydnones *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 sydnones were not isolated and directly used in a cyclo-addition step.¹⁴ Under mechanochemical activation, ^{*t*}BuONO 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, ^{*t*}BuONO has to be prepared from *tert*-butanol using these reagents. We reasoned

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 Sydnones 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 sydnones 2d and 2h could be obtained in 91% and 81% yields, respectively. Sydnones 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 C_4 of the sydnone was next introduced to obtain a putative bidendate 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

 $\label{eq:constraint} \begin{array}{l} \mbox{Table 1} & \mbox{Optimization of the reaction conditions of sydnone mechanosynthesis}^a \end{array}$

Pr		D source m, 25 Hz = 5 min	N^{0} O N^{0} O N^{0} OH Ia' OH	yclization TFAA ⊝ om, 25 Hz Ph´ t₂ Ph´	N∽O N ⇒ ⊕ 2a
Entry	NO source (e	quiv.) T	FAA (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.



Scheme 2 Mechanochemical synthesis of N-arylsydnones 2a-i.



 $\label{eq:scheme3} \begin{array}{l} \mbox{Synthesis of coordination complexes with sydnone $\mathbf{3a}$ as the N,O-ligand.} \end{array}$

showed that this coupling could be performed using $Pd(OAc)_2/PPh_3$ (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 ($\nu = 1660-1726 \text{ cm}^{-1}$). The structures of the complexes $[Co(\mu-Cl)(3a)_2]_2 \cdot COCl_4$, $[CuCl_2(3a)_2]$, $[Cu(OTf)_2(3a)_2]$ 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) $[CuCl_2(3a)_2]$, (b) $[Co(\mu-Cl)(3a)_2]_2$. CoCl₄ and (c) $[ZnCl_2(3a)]$. H atoms and $CoCl_4^{2-}$ 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 $22-35^{\circ}$ 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.

Notes and references

- 1 E. Decuypère, L. Plougastel, D. Audisio and F. Taran, *Chem. Commun.*, 2017, **53**, 11515.
- 2 D. L. Browne and J. P. A. Harrity, Tetrahedron, 2010, 66, 553.
- 3 J. Applegate and K. Turnbull, Synthesis, 1988, 1011.
- 4 W. Baker, W. D. Ollis and V. D. Poole, J. Chem. Soc., 1950, 1542.
- 5 M.-H. Shih, J.-C. Chen, G.-L. Lin, T.-T. Lin and M.-H. Sun, *J. Pharm. Pharmacol.*, 2014, **66**, 73.
- 6 (a) S.-T. Lin, H.-S. Cheo, L.-S. Liu and J.-C. Wang, Organometallics, 1997, 16, 1803; (b) S.-T. Lin, H.-S. Choe, L.-S. Liu and J.-C. Wang, J. Organomet. Chem., 2000, 610, 1; (c) S. T. Lin, K. J. Peng, T. M. Barclay and A. W. Cordes, Inorg. Chim. Acta, 2001, 321, 89; (d) S. T. Lin, K. J. Peng, T. F. Hung and H. J. Tien, J. Chin. Chem. Soc., 2002, 49, 19.
- 7 (a) V. N. Kalinin and P. M. Se, J. Organomet. Chem., 1988, 352, C34;
 (b) V. N. Kalinin, P. M. Se and P. V. Petrovskii, J. Organomet. Chem., 1989, 379, 195; (c) L. N. Morozova, L. S. Isaeva, P. V. Petrovskii, D. N. Kravtsov, S. P. Minh and V. N. Kalinin, J. Organomet. Chem., 1990, 381, 281; (d) V. N. Kalinin, D. N. Pashchenko and M. S. Phan, Mendeleev Commun., 1992, 60; (e) V. N. Kalinin, F. M. She, V. N. Khandozhko and P. V. Petrovskii, Russ. Chem. Bull., 2001, 50, 525; (f) S. Wiechmann, T. Freese, M. H. H. Drafz, E. G. Hübner, J. C. Namyslo, M. Nieger and A. Schmidt, Chem. Commun., 2014, 50, 11822; (g) H. Liu, D. Audisio, L. Plougastel, E. Decuypere, D.-A. Buisson, O. Koniev, S. Kolodych, A. Wagner, M. Elhabiri, A. Krzyczmonik, S. Forsback, O. Solin, V. Gouverneur and F. Taran, Angew. Chem., Int. Ed., 2016, 55, 12073.
- 8 (a) S. M. Lee, US3549639A, 1970; (b) C. S. Lin, A. Yeh, T. Y. Liu, K. S. Kwan, D. J. Hodgson and H. J. Tien, *Inorg. Chim. Acta*, 1992, **192**, 81.
- 9 Contrary to the historical representation of sydnones with a negatively charged exocyclic oxygen, the mesomeric form having a negative charge on N_2 and an exocyclic carbon oxygen double bond

was chosen in agreement with the X-ray structures obtained herein and in literature.

- 10 (a) A. Beillard, E. Golliard, V. Gillet, X. Bantreil, T.-X. Métro, J. Martinez and F. Lamaty, Chem. Eur. J., 2015, 21, 17614;
 (b) A. Beillard, T.-X. Métro, X. Bantreil, J. Martinez and F. Lamaty, Chem. Sci., 2017, 8, 1086; (c) N. Pétry, H. Benakki, E. Clot, P. Retailleau, F. Guenoun, F. Asserar, C. Sekkat, T.-X. Métro, J. Martinez and F. Lamaty, Beilstein J. Org. Chem., 2017, 13, 2169;
 (d) A. Beillard, X. Bantreil, T.-X. Métro, J. Martinez and F. Lamaty, Green Chem., 2018, 20, 964.
- 11 (a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413; (b) G.-W. Wang, *Chem. Soc. Rev.*, 2013, **42**, 7668; (c) N. R. Rightmire and T. P. Hanusa, *Dalton Trans.*, 2016, **45**, 2352; (d) J. Andersen and J. Mack, *Green Chem.*, 2018, **20**, 1435; (e) J. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080; (f) D. Tan and T. Friščić, *Eur. J. Org. Chem.*, 2018,

18; (g) A. Beillard, X. Bantreil, T.-X. Métro, J. Martinez and F. Lamaty, *Chem. Rev.*, 2019, **119**, 7529.

- 12 S. Ikeda and S. Murata, J. Photochem. Photobiol., A, 2002, 149, 121.
- 13 See ESI[†] for details.
- 14 S. Specklin, E. Decuypere, L. Plougastel, S. Aliani and F. Taran, J. Org. Chem., 2014, 79, 7772.
- 15 K. Turnbull, J. Heterocycl. Chem., 1985, 22, 965.
- 16 (a) A. Rodriguez and W. J. Moran, Synthesis, 2009, 650;
 (b) A. W. Brown, J. Comas-Barceló and J. P. A. Harrity, Chem. Eur. J., 2017, 23, 5228.
- 17 (a) J. G. Hernández and T. Friščić, *Tetrahedron Lett.*, 2015, 56, 4253;
 (b) Q. Cao, J. L. Howard, E. Wheatley and D. L. Browne, *Angew. Chem., Int. Ed.*, 2018, 57, 11339;
 (c) Q.-L. Shao, Z.-J. Jiang and W.-K. Su, *Tetrahedron Lett.*, 2018, 59, 2277;
 (d) Q. Cao, W. I. Nicholson, A. C. Jones and D. L. Browne, *Org. Biomol. Chem.*, 2019, 17, 1722;
 (e) K. Kubota, T. Seo, K. Koide, Y. Hasegawa and H. Ito, *Nat. Commun.*, 2019, 10, 111.
- 18 V. T. Yilmaz, S. Hamamci and C. Thöne, Polyhedron, 2004, 23, 841.