Dalton Transactions

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/dalton

Journal Name

COMMUNICATION

Thioiminium and thiaphospholanium derived from acetonitrile *via* nickel(II)–(2-mercaptophenyl)phosphine complexations†

Received 00th January 20xx,
Accepted 00th January 20xx

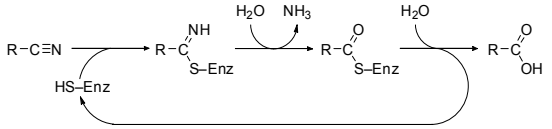
DOI: 10.1039/x0xx00000x

www.rsc.org/

Hao-Ching Chang,[a] Yu-Chen Hsu,[a] Chia-Hui Chen,[a] Ting-Shen Kuo[b] and Way-Zen Lee*[a]

$[Ni(P(o\text{-}C_6H_4S)(o\text{-}C_6H_4SC(CH_3)=NH_2)(C_6H_5))_2](ClO_4)_2$ (2) with two thioiminium functionalities is derived from CH_3CN solvent under anhydrous condition. Moreover, thiaphospholanium salts, $[(C_6H_5)P(C_6H_4SC(CH_3)(NHCOCH_3))(o\text{-}C_6H_4SH)](ClO_4)$ (3) and $[(C_6H_5)_2\text{-}P(C_6H_4SC(CH_3)(NH_3))](ClO_4)_2$ (5), can be obtained through a similar Pinner-type nitrile activation. These results demonstrate the possible intermediate of enzymatic nitrile transformation and also provide an approach to the preparation of 2-amino-1,3-benzothiaphospholanium derivatives.

Nitriles are important precursors in biosynthesis[1] as well as versatile reagents in chemical manufacturing. Meanwhile, contamination of nitriles in wastewater becomes a critical environmental issue.[1] Nitrilases (EC 3.5.5.1), which are competent for cyano–carboxyl transformation in nature,[2–5] have been introduced to address synthetic protocol and detoxification of nitrile.[4–7] Earlier studies of nitrilase have discovered that a Cys–Glu–Lys functional triad takes charge of the substrate derivatization.[4,8] In mechanistic aspect, the conserved glutamate and lysine residues act as general acid/base, which activate incoming substrate through a hydrogen bond network. Then the cysteine thiol nucleophilically attacks the cyano carbon within substrate, forming a thioimidate intermediate (Scheme 1); this intermediate is readily hydrolyzed to a thioacyl–enzyme complex, accompanied with ammonia releasing. Sequentially, a corresponding carboxylic product is produced while the catalytic site is regenerated by the second hydrolysis. By this cooperation, nitrilase hydrolyzes cyano compounds under physiological conditions, avoiding harsh reagents in conventional chemistry.



Scheme 1 Enzymatic nitrile degradation.

Interestingly in our recent studies, solvent acetonitrile is incorporated into thioiminium or ammonium functionalities in complexation reactions of nickel(II) ion with (2-mercaptophenyl)phosphines. At ambient temperature, $[Ni(CH_3CN)_6](ClO_4)_2$ reacted with two equivalents of $P(o\text{-}C_6H_4SH)_2(C_6H_5)$ (H_2PS2) in anhydrous CH_3CN giving a light-green supernatant along with grass green precipitate rapidly. The solid was isolated and then crystallized by vapor diffusion of Et_2O into its CH_2Cl_2 solution. The structure of the green product, determined by X-ray crystallography, is a square planar nickel(II) complex, $Ni(P(o\text{-}C_6H_4S)(o\text{-}C_6H_4SH)(C_6H_5))_2$ (**1**, Fig. 1a). Neutral complex **1** can be recognized as two mono-deprotonated $HPS2^-$ ligands coordinate to the nickel(II) ion. And two unreacted pendant thiols, one on each $HPS2^-$ ligand, reside above and below the coordination plane of **1**; the thiol proton points between the nickel center and the bonded sulfur atom of the ligand. The similar interaction was seen in $[PPN][Ni(ER)(P(o\text{-}C_6H_4S)_2(o\text{-}C_6H_4SH))]$ (ER = phenylselenide or 2-thienylthiolate).[9] If $[Ni(CH_3CN)_6](ClO_4)_2$ is slowly added into the H_2PS2 solution at above 55 °C, the same combination turned to an olive solution. From crystallization of the resulting crude, yellow-green crystals‡ were obtained and structurally analyzed as $[Ni(P(o\text{-}C_6H_4S)(o\text{-}C_6H_4SC(CH_3)=NH_2)(C_6H_5))_2](ClO_4)_2$

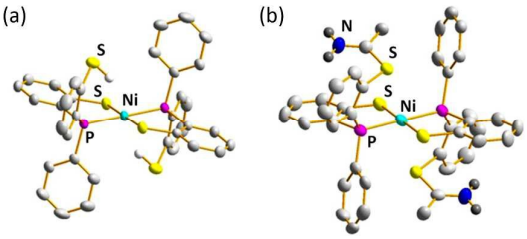


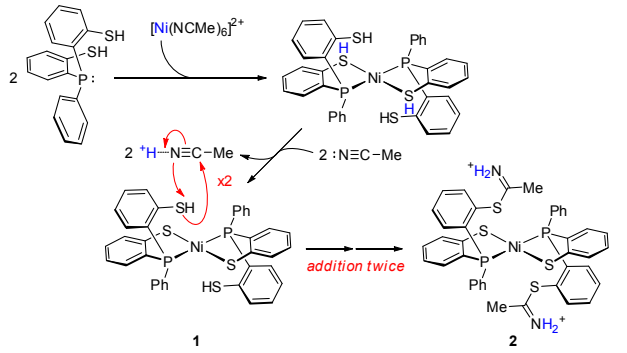
Fig. 1 Thermal ellipsoid representation of (a) $Ni(P(o\text{-}C_6H_4S)(o\text{-}C_6H_4SH)(C_6H_5))_2$ (**1**) and (b) $[Ni(P(o\text{-}C_6H_4S)(o\text{-}C_6H_4SC(CH_3)=NH_2)(C_6H_5))_2](ClO_4)_2$ (**2**) at 50% probability level. Aprotic hydrogens and anions of **1** and **2** are omitted for clarity.

[a] *Department of Chemistry, National Taiwan Normal University, Taipei 11677, Taiwan. E-mail: wzlee@ntnu.edu.tw*
[b] *Instrumentation Center, National Taiwan Normal University, Taipei 11677, Taiwan*

†Electronic Supplementary Information (ESI) available: Synthetic details and NMR, UV–vis, electrospray ionization mass spectra, X-ray crystallographic data for complexes **1**–**3**, **5**. CCDC: 14206690–14206694. See DOI: 10.1039/x0xx00000x

(**2**, Fig. 1b). Complex **2** shares the similar coordination geometry with **1**. Notably, the pendant thiols of ligands have been transformed into thioiminium groups. Finding of two perchlorate counter anions per nickel in the lattice and unambiguous C–N bond length (1.286-1.288 Å) of **2** confirm the assignment of thioiminium functionality, with a set of characteristic resonances at 8.28, 9.28, and 9.44 ppm in ^{1}H NMR spectrum.

Such a discrete inorganic complex bearing a thioiminium group is rare in literature. One report of a sulfide-bridged dimolybdenum compound performs nitrile cleavage, in which an iminiumthiolate-bridging species was determined by NMR and mass spectroscopy.[10] In that case, acetonitrile is attacked by bridging sulfur under H_2 atmosphere or by addition of triflic acid. To the best of our knowledge, complex **2** is the only structurally characterized complex possessing the thioiminium functionality. Formation of the thioiminium group is supposed to result from the reaction of the uncoordinated thiol with CH_3CN molecule. Stoichiometrically, as two equivalents of H_2PS2 coordinate to a nickel(II) ion forming complex **1** along with two residual protons, which are spontaneously solvated by surrounding CH_3CN molecules thus activating the C–N bond of the cyano group ($CH_3CN\cdots H^+$),[11] regarded as two equivalents of in situ generated $HClO_4$ in CH_3CN. In anhydrous condition, there is no water molecule to attract the proton interacting with the cyano group, enhancing the reactivity of $CH_3CN\cdots H^+$. Uncoordinated thiols in **1** therefore attack the charged cyano carbon forming a thioimino group.[12] Subsequent intramolecular proton transfer gives complex **2** (Scheme 2).



Scheme 2 Formation of complex **2** under anhydrous condition. The counter anions (ClO_4^-) are omitted for clarity.

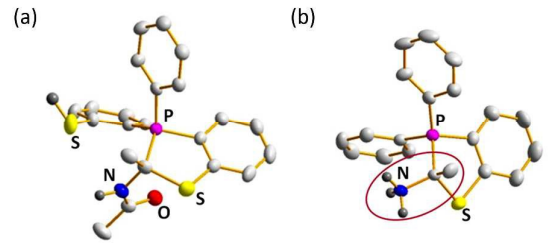


Fig. 2 Thermal ellipsoid representation of (a) $[(C_6H_5)P(C_6H_4SC(CH_3)(NHCOCH_3))(o\text{-}C_6H_4SH)](ClO_4)$ (**3**) and (b) $[(C_6H_5)_2P(C_6H_4SC(CH_3)(NH_3))](ClO_4)_2$ (**5**) at 50% probability level. Aprotic hydrogens and anions are omitted for clarity.

To testify the proposed Pinner-type mechanism, H_2PS2 ligand was treated with 70% $HClO_4$(aq) in CH_3CN overnight, and some colorless product was isolated from the resulting mixture. After crystallization *via* CH_3CN/Et_2O vapor diffusion, a clear crystal was analyzed as an amide-tethered phospho-lanium salt, $[(C_6H_5)P(C_6H_4SC(CH_3)(NHCOCH_3))(o\text{-}C_6H_4SH)](ClO_4)$ (**3**, Fig. 2a). The 1,3-benzothiaphospholane heterocycle of **3** is composed of one phosphine, one thiophenolate and one exogenous carbon derived from CH_3CN. In the presence of $HClO_4$, CH_3CN, the solvent molecule, is activated and converted into thioiminium once it is attacked by a thiol of H_2PS2. Without the coordination of nickel, the phosphine of the converted thioiminium is unrestricted to process intramolecular nucleophilic attack forming the heterocycle with a pendant amino group. The pendant amine performs further condensation to yield the acetamide in **3**. This result consists with the proposed acid-promoted nitrile activation, but the presence of water complicates the reaction. Afterwards, $P(o\text{-}C_6H_4SH)(C_6H_5)_2$ (HPS1) was selected for further investigation. Three equivalents of HPS1 were reacted with $[Ni(CH_3CN)_6](ClO_4)_2$ in anhydrous CH_3CN: two equivalents of the ligand coordinate the nickel(II) ion, which serves as Lewis acid, to generate protons for nitrile activation; the third equivalent of HPS1 can then proceed a similar tandem cyclization. $Ni(P(o\text{-}C_6H_4S)(C_6H_5)_2)_2$ (**4**), reported earlier by M. Y. Darensbourg,[13] was separated as precipitate in this condition while another metal-free product in supernatant was isolated and further crystallized by CH_3CN/Et_2O diffusion. X-ray analysis reveals that the organic product, $[(C_6H_5)_2P(C_6H_4SC(CH_3)(NH_3))](ClO_4)_2$ (**5**, Fig. 2b), possesses the same heterocycle as **3**. By performing the same reaction in CD_3CN, a deuterated product (**5D**) was isolated, of which the deuterated methyl group is validated by ^{1}H and ^{2}H NMR (Fig. 3) as well as by ESI-MS spectrum with an m/z shift of +3 (Fig. S4). These findings confirm the exogenous fragment in **5**, circled in Fig. 2b, comes from the solvent molecule, CH_3CN. The formation of **5** along with complex **4** shows the nitrile is intermolecularly activated by coordination-generated Brønsted acid. Wherein, nickel(II) ion serves as sacrificial Lewis acid. Remarkably, the yield of **5** *via* nickel complexation (56%)

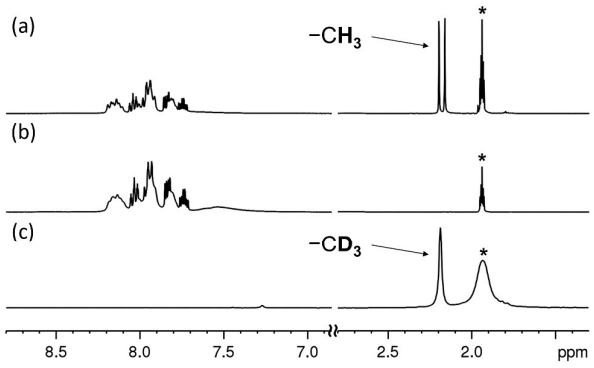
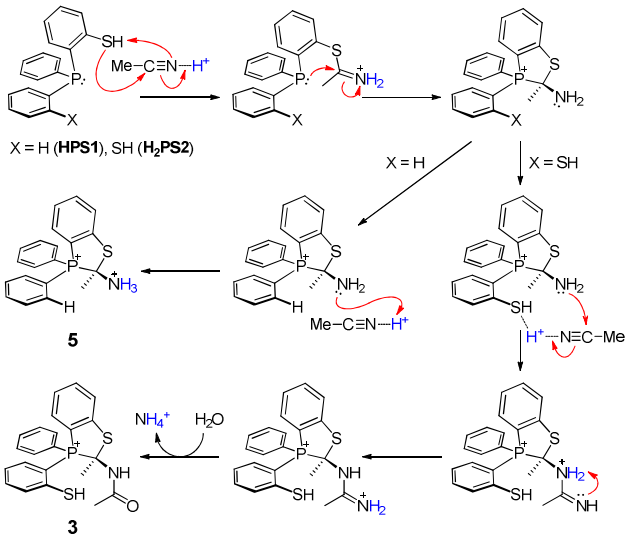


Fig. 3 NMR spectra of **5** (a) and deuterated **5D** (b, c), formed in CH_3CN and CD_3CN solvent, respectively. The characteristic methyl signal of **5** in ^{1}H NMR spectrum is a ^{31}P-coupled doublet at 2.18 ppm, $^2J_{HP}$ = 14.0 Hz. The signal vanished in ^{1}H spectrum of **5D** (b) and reappeared in its ^{2}H NMR (c). The asterisks denote internal reference of solvent.



Scheme 3 Proposed mechanism for benzothiaphospholanium products. Acidic protons are presented in blue and counter anions (ClO_4^-) are omitted.

is even better than that by applying concentrated $HClO_4$(aq) in CH_3CN (35%).† This result indicates the in situ generated $HClO_4$ is comparable to additive $HClO_4$(aq) and has no water interference.

The Proposed mechanism of the acid-promoted annulation between CH_3CN and (2-mercaptophenyl)phosphines is depicted in Scheme 3, whereby thioiminium species is rapidly cyclized due to the proximity of phosphine atom. In an intramolecular manner, cyclization producing phospholanium compounds is efficient;[14] yet there is no reported 1,3-benzothiaphospholanium but few fused benzothiaphospholanes derived from their benzothiadiphosphole precusor.[15] In both **3** and **5**, the incorporated cyano carbon is converted into a unique quaternary center, which bonds a phosphonium and an amidyl/amino group, exhibiting a large downfield shift in ^{13}C NMR (**3**: δ_C = 67.2 ppm, $^1J_{CP}$ = 59.2 Hz; **5**: δ_C = 69.5 ppm, $^1J_{CP}$ = 58.1 Hz). It is noteworthy that the reactivity of the amine of the cyclized intermediate is altered by an extra pendant thiol, which induces a sequential nucleophilic attack on second activated CH_3CN, eventually yielding the amide in **3**. Whereas, without the pendant thiol, no amide derived from HPS1 was observed. Activated CH_3CN is probably directed *via* hydrogen interaction and causes this differentiation.

In a way, nitrile is activated and reacted with (2-mercaptophenyl)phosphines to form thioiminium species. By employing template effect of d^8 nickel(II) ion, thioiminium functionalities are trapped as that in complex **2**. If the nucleophilicity of phosphine is not inhibited by the coordination, the imminent cycloaddition to the thioiminium occurs, similar to the first hydrolysis step carried out in the active site of nitrilase in which a water molecule is properly orientated for nucleophilic attack on the thioimidate intermediate. These isolated species can be regarded as snapshots of the enzymatic nitrile hydration. However, owing to the thermodynamic sink of the tandem cyclization, no catalysis has been achieved.

In summary, acid-triggered in situ acetonitrile incorporation is observed in the reactions of $[Ni(CH_3CN)_6](ClO_4)_2$ with (2-mercaptophenyl)phosphines. Several compounds possessing uncommon functionalities are isolated whereby proposed intermediates of nitrilase are consolidated. Besides the implication about how nitrilase functions, these results also provide a synthetic route to prepare 2-amino-1,3-benzothiaphospholanium derivatives which have not been studied yet.

Acknowledgements

We thank the Ministry of Science and Technology of Taiwan for financial supports (MOST 102-2113-M-003-007-My3 to W.-Z. L.).

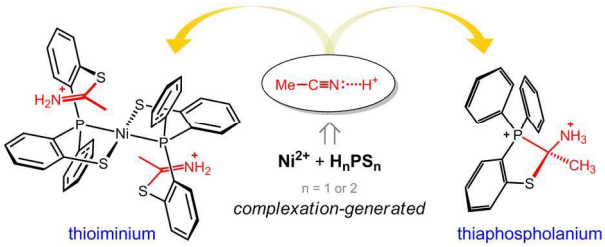
Notes and references

‡Crystals of **2** were obtained with different colors, from green to olive. X-ray crystallography revealed the same nickel complex but different solvent-packing modes: {**2**·4CH_3CN} in $P\bar{1}$ (Z = 1), a = 9.5352(3) Å, b = 11.8573(5) Å, c = 13.0288(6) Å, α = 80.481(2)°, β = 73.240(2)°, γ = 76.247(2)°, V = 1362.60(10) Å^3 and R = 0.0651 and {**2**·3CH_3CN·Et_2O} in $P2_1$ (Z = 2), a = 8.99760(10) Å, b = 31.5617(5) Å, c = 9.9610(2) Å, α = γ = 90°, β = 90.7300(10)°, V = 2828.49(8) Å^3 and R = 0.0568.

1 T. C. Bhalla, N. Sharma and R. K. Bhatia, in *Microorganisms in Environmental Management: Microbes and Environment*, ed. T. Satyanarayana, B. N. Johri and A. Prakash, Springer, New York, 2012, ch. 25, pp 569–587.
2 (*a*) K. V. Thimann and S. Mahadevan, *Arch. Biochem. Biophys.*, 1964, **105**, 133–141; (*b*) S. Mahadevan and K. V. Thimann, *Arch. Biochem. Biophys.*, 1964, **107**, 62–68.
3 (*a*) H. C. Pace and C. Brenner, *Genome Biol.*, 2001, **2**, reviews0001.1–0001.9; (*b*) C. Brenner, *Curr. Opin. Struct. Biol.*, 2002, **12**, 775–782.
4 R. N. Thuku, D. Brady, M. J. Benedik and B. T. Sewell, *J. Appl. Microbiol.*, 2009, **106**, 703–727.
5 J.-S. Gong, Z.-M. Lu, H. Li, J.-S. Shi, Z.-M. Zhou and Z.-H. Xu, *Microb. Cell Fact.*, 2012, **11**, No. 142.
6 C. Vergne-Vaxelaire, F. Bordier, A. Fossey, M. Besnard-Gonnet, A. Debard, A. Mariage, V. Pellouin, A. Perret, J.-L. Petit, M. Stam, M. Salanoubat, J. Weissenbach, V. De Berardinis and A. Zaparucha, *Adv. Synth. Catal.*, 2013, **355**, 1763–1779.
7 Y. P. Xue, C.-C. Shi, Z. Xu, B. Jiao, Z.-Q. Liu, J.-F. Huang, Y.-G. Zheng and Y.-C. Shen, *Adv. Synth. Catal.*, 2015, **357**, 1741–1750.
8 (*a*) J. E. Raczynska, C. E. Vorgias, G. Antranikian and R. Wojciech, *J. Struct. Biol.*, 2011, **173**, 294–302; (*b*) L. Zhang, B. Yin, C. Wang, S. Jiang, H. Wang, Y. A. Yuan and D. Wei, *J. Struct. Biol.*, 2014, **188**, 93–101.
9 C.-M. Lee, C.-H. Chen, S.-C. Ke, G.-H. Lee and W.-F. Liaw, *J. Am. Chem. Soc.*, 2004, **126**, 8406–8412.
10 P. Bernatis, J. C. V. Laurie and M. R. DuBois, *Organometallics*, 1990, **9**, 1607–1617.
11 J. F. Coetzee and I. M. Kolthoff, *J. Am. Chem. Soc.*, 1957, **79**, 6110–6115.
12 (*a*) É. Dufour, A. C. Storer and R. Ménard, *Biochemistry*, 1995, **34**, 16382–16388; (*b*) S. Y. Reddy, K. Kahn, Y.-J. Zheng and T. C. Bruice, *J. Am. Chem. Soc.*, 2002, **124**, 12979–12990.
13 J. S. Kim, J. H. Reibenspies and M. Y. Darensbourg, *J. Am. Chem. Soc.*, 1996, **118**, 4115–4123.

14 W. R. Purdum and K. D. Berlin, *J. Org. Chem.*, 1975, **40**, 2801−2806.
15 G. Baccolini and E. Mezzina, *J. Chem. Soc., Perkin Trans. 1*, 1990, 19−22.

Graphical Abstract



Acid produced by nickel complexation drives incorporation of acetonitrile to yield uncommon thioiminium/phospholanium species.