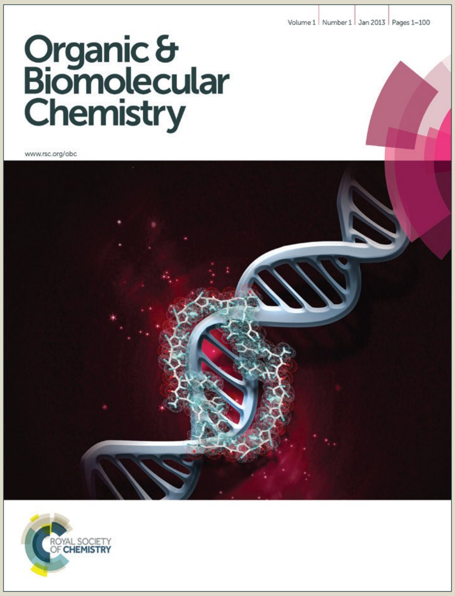
Organic & Biomolecular Chemistry

This article can be cited before page numbers have been issued, to do this please use: C. Yang, J. Han, J. Liu, M. Gu, Y. Li, J. Wen, H. Yu, S. Hu and X. Wang, *Org. Biomol. Chem.*, 2015, DOI:



Organic & Biomolecular Chemistry

Organic & Biomolecular Chemistry

Dynamic Article Links ►

View Article Online
DOI: 10.1039/C4OB02456G

COMMUNICATION

"One-pot" synthesis of amidoxime via Pd-catalyzed cyanation and amidoximation

Chu-Ting Yang,[a] Jun Han,[a] Jun Liu,[a] Mei Gu,[a] Yi Li,[a] Jun Wen,[a] Hai-Zhu Yu,[b] Sheng Hu,*[a] and Xiaolin Wang*[a]

A novel "one-pot" reaction was developed for the synthesis of aryl or heteroaryl-substituted amidoxime compounds containing various functional groups. Fluorescence titration experiments coupled with theoretical analysis revealed that the steric hindrance and electronic effects of substituents influence the binding ability of the amidoxime compounds to uranyl ions.

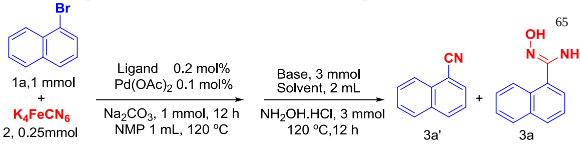
The oceans contain uranium resources 1000-fold that of the land.[1] Land extraction takes a heavy environmental toll, and the extraction of uranium from the oceans is an ideal alternative to maintain nuclear fuel reserves.[1b] Thus, the development of materials for adsorption of uranium from the ocean has attracted increasing attention.[2-6] Since the emergence of the first inorganic adsorbent in the 1960s,[1a] a variety of absorbent materials have been developed including functionalized polymers with small-molecule chelates,[2] a layered solid-state ion exchanger ($K_2MnSn_2S_6$),[3] metal–organic frameworks (MOFs),[4] and a super uranyl-binding protein with femtomolar (10^{-12} M) affinity and high selectivity.[5] Among these materials, the amidoxime-based absorbents are the most common and promising materials in the extraction of uranium.[1b,6]

So far, the main limitations of these materials are their low binding affinity and selectivity.[5] Better understanding on the complexation between amidoxime and uranyl ions may provide insights into future improvements of the materials. Nonetheless, previous reports have mainly focused on the binding motif,[7] while the substituent effects of amidoxime compounds are rarely studied.[8] For systematic studies on the interactions between amidoxime and uranyl, a general synthetic method for the necessary substrates is highly requisite.[9]

Herein, we report a novel "one-pot" reaction in which easily available aryl halides serve as the raw materials, and potassium hexacyanoferrate(II) ($K_4[Fe(CN)_6]$; less poisonous than cyanide) is the cyanating agent. With this method, a series of aryl-substituted amidoxime compounds were obtained with moderate to good yields. More importantly, fluorescence and UV-Vis spectroscopy indicated that steric hindrance and electronic effects of the substituents indeed had a significant impact on the binding ability of amidoxime compounds to uranyl ions. This proposal was also supported by theoretical calculations. Hence, this work not only provides a convenient method for the synthesis of amidoxime compounds, but also guides the development of new amidoxime-based adsorption materials with high binding affinity and selectivity.

Our work was inspired by recent advances in Pd-catalyzed cyanation of aryl halides.[10,11] First 1-bromonaphthalene (1a) was used as the substrate, $K_4[Fe(CN)_6]$ (2) as the cyanation reagent, and ($Pd(OAc)_2$/dppf,[10a] $Pd(OAc)_2$/s-phos,[12] and $Pd(OAc)_2$/x-phos[13] as the tested catalyst. In all cases, cyanation products with yields >90% were obtained (3a', For details, see ESI). Next, $Pd(OAc)_2$/dppf was used as the standard system. After the cyanation reaction ended, the base, solvent, and hydroxylamine hydrochloride were added directly into the same pot for amidoximation (Table 1). N-Methyl-2-pyrrolidone (NMP) was used as the solvent, and a series of bases including carbonates (entries 1–3) and tert-butoxides (entries 4–6) were tested. Unfortunately the amidoxime product 3a was not detected in any of these reactions.

Table 1 One pot synthesis of amidoxime compound 3a[a]

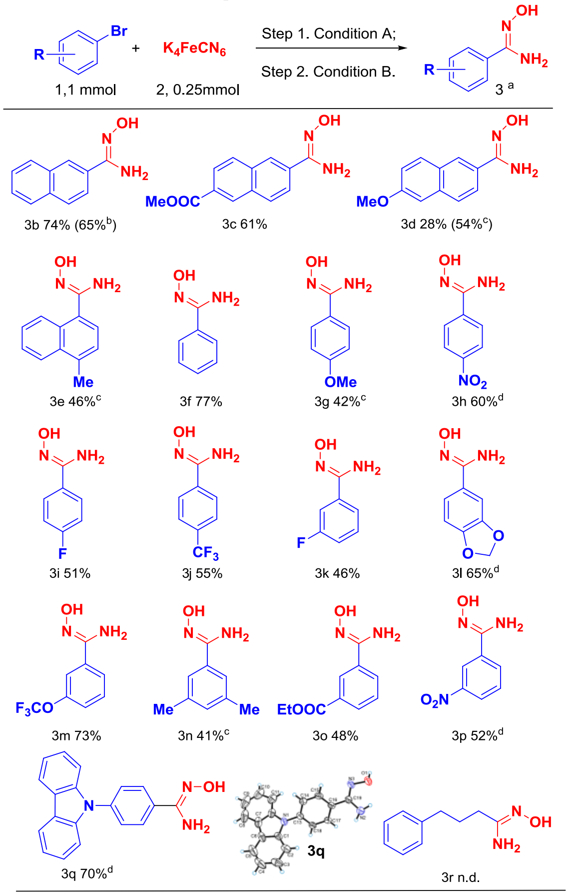


Entry	Cat. (0.1 mol%)	Ligand (0.2 mol%)	Base	Solvent	Yield 3a' (%)	Yield 3a (%)[b]
1	$Pd(OAc)_2$	dppf	Na_2CO_3	NMP	94	Trace
2	$Pd(OAc)_2$	dppf	K_2CO_3	NMP	92	Trace
3	$Pd(OAc)_2$	dppf	Cs_2CO_3	NMP	91	Trace
4	$Pd(OAc)_2$	dppf	KO^tBu	NMP	85	Trace
5	$Pd(OAc)_2$	dppf	NaO^tBu	NMP	88	Trace
6	$Pd(OAc)_2$	dppf	LiO^tBu	NMP	90	Trace
7	$Pd(OAc)_2$	dppf	Na_2CO_3	DMF	91	Trace
8	$Pd(OAc)_2$	dppf	Na_2CO_3	DMSO	89	Trace
9	$Pd(OAc)_2$	dppf	Na_2CO_3	Dioxane	93	Trace
10	$Pd(OAc)_2$	dppf	Na_2CO_3	PhMe	92	Trace
11	$Pd(OAc)_2$	dppf	Na_2CO_3	^tBuOH	76	21
12	$Pd(OAc)_2$	dppf	Na_2CO_3	EtOH	54	45
13	$Pd(OAc)_2$	dppf	Na_2CO_3	MeOH	12	74
14	**$Pd(OAc)_2$**	**dppf**	**Na_2CO_3**	**$MeOH:H_2O$ (9:1)**	**5**	**83**
15	$Pd_2(dba)_3$	dppf	Na_2CO_3	$MeOH:H_2O$ (9:1)	6	79
16	$Pd(OAc)_2$	x-phos	Na_2CO_3	$MeOH:H_2O$ (9:1)	10	73
17	$Pd(OAc)_2$	s-phos	Na_2CO_3	$MeOH:H_2O$ (9:1)	7	81
18[c]	$Pd(OAc)_2$	dppf	Na_2CO_3	$MeOH:H_2O$ (9:1)	11	76
19[d]	$Pd(OAc)_2$	dppf	Na_2CO_3	$MeOH:H_2O$ (9:1)	4	69

[a] Conditions: 1a (1 mmol), 2 (0.25 mmol), Pd catalyst (0.1 mol%), ligand (0.2 mol%), Na_2CO_3 (1 mmol), NMP (1 mL), 120 ℃, 12 h; then base (3 mmol), $NH_2OH{\cdot}HCl$ (3 mmol), solvent (2 mL), 120 ℃, 12 h. [b] Isolated yield. [c] 1-iodonaphthalene was used. [d] 1-chloronaphthalene was used.

We next studied the effect of the solvent including polar (entries 7 and 8) and non-polar solvents (entry 10), but still no amidoxime product was obtained. However, we were pleased to find that when the protic solvent tert-butanol was used, the consumption of cyanation products was notable, and 21% of target product 3a was isolated (entry 11). When ethanol or methanol was used as the solvent, the yield can be further increased to 74% (entries 12 and 13). In addition, doping with water could further facilitate the reaction. After further optimization (see ESI), we found that when the ratio of methanol to water is 9:1, the maximum yield of 83% (entry 14) was obtained. Meanwhile, the "one-pot" reaction could still achieve good yields even when other catalyst systems were used for the cyanation reaction, *e.g.*, different Pd catalyst (entry 15) or different ligands (entries 16 and 17). Finally, we noted that naphthyl iodide was also a good substrate (entry 18). Chlorides, which have lower activity than bromides, were suitable for this reaction although the yield was lower (entry 19).

Table 2 Substrate of the one pot reaction

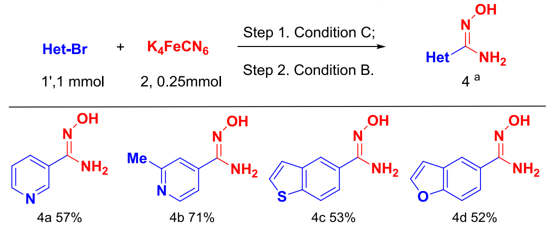


[a] Condition A: 1 (1 mmol), 2 (0.25 mmol), $Pd(OAc)_2$ (0.1 mol %), dppf (0.2 mol%), Na_2CO_3 (1 mmol), NMP (1 mL), 120 ℃, 12 h; Condition B: Na_2CO_3 (3 mmol), $NH_2OH\cdot HCl$ (3 mmol), MeOH (1.8 mL), H_2O (0.2 mL), 120 ℃, 12 h. For details, see ESI. Yields were determined through isolation of the desired products. [b] Aryl chloride was used. [c] Condition B: Na_2CO_3 (2 mmol), $NH_2OH\cdot HCl$ (2 mmol), MeOH (0.9 mL), H_2O (0.1 mL), 120 ℃, 8h; then Na_2CO_3 (2 mmol), $NH_2OH\cdot HCl$ (2 mmol), MeOH (0.9 mL), H_2O (0.1 mL), 120 ℃, 8 h. [d] 0.2 mol% catalyst was added.

These results indicate that this "one-pot" reaction can synthesize amidoxime compounds. Next the range of the reaction substrates was explored. Naphthyl bromides and aryl bromides with different electron withdrawing/donating substituents were well tolerated to give the amidoxime products with moderate to good yields (Table 2). A relatively good yield could also be obtained with naphthyl chloride (3b). A series of functional groups including esters (3c, 3o), nitros (3h, 3p), CF_3 (3j), trifluoromethoxy (3m), fluorine (3i, 3k), ethers (3d, 3g), methylenedioxy (3l), and methyls (3e, 3n), were all compatible with this reaction. It is worth noting that when the aromatic ring contained electron-donating substituents, such as methoxy (3d), the efficiency of amidoximation was poor and most of the cyanation products were retained. By contrast, the yields of cyanation products are good to excellent (see ESI). Therefore, we suggest that the main reason of the low yields relates to the inefficient amidoximation.[9c] However, addition of hydroxylamine hydrochloride for another amidoximation could still improve the yield to a medium level (3d, 54% yield). The carbazole ring was also compatible with this reaction (3q) as shown by X-ray crystal analysis. Unfortunately, no corresponding cyanation or amidoximation product was obtained with alkyl bromides (3r).

Further experiments showed that this reaction was also compatible with heteroaryl bromides (Scheme 1). For example, amidoxime products could be obtained with the pyridine ring (4a, 4b), sulfur-containing heterocycles (4c), and oxygen-containing heterocycles (4d) although the amount of catalyst needed was high (0.2 mol%). Notably, it is possible that the introduction of heteroatom can provide new sites for the interaction with uranyl ions and increases the binding affinity of the molecules for uranyl ions. Preliminary fluorescence spectroscopy experiments show that the introduction of nitrogen-containing heterocyclic rings (4a) could indeed enhance binding affinity (see ESI).

Scheme 1 The reaction with heteroaryl bromides



[a] Condition C: 1 (1 mmol), 2 (0.25 mmol), $Pd(OAc)_2$ (0.2 mol %), dppf (0.4 mol %), Na_2CO_3 (1 mmol), NMP (1 mL), 120 ℃, 12h; Condition B: then Na_2CO_3 (3 mmol), $NH_2OH\cdot HCl$ (3 mmol), MeOH (1.8 mL), H_2O (0.2 mL), 120 ℃, 12h . Yields were determined through isolation of the desired products.

For the amidoxime compounds synthesized by the "one-pot" method, fluorescence titration experiments examined their interaction with uranyl ions. When 3a was used as the host molecule, adding uranyl ions (up to 5 equiv) had almost no effect on the fluorescence intensity at 350 nm (Fig. 1). Moreover, No significant change in UV-Vis absorption spectra was noted upon addition uranyl ions (Fig. 1, inset).

Interestingly, when 3b was used as the host molecule, adding uranyl ions substantially increased the fluorescence intensity at 370 nm with moderate redshift (380 nm, Fig. 2). Similar fluorescence enhancement was also observed with 3d (For details, see ESI). These results suggest that the 2-naphthalene substituted amidoxime compounds interact somewhat with uranyl ions. Therefore, we presume that the steric hindrance of the substituents in the amidoxime compounds have a significant

View Article Online
DOI: 10.1039/C4OB02456G

impact on the molecule's uranium adsorption.

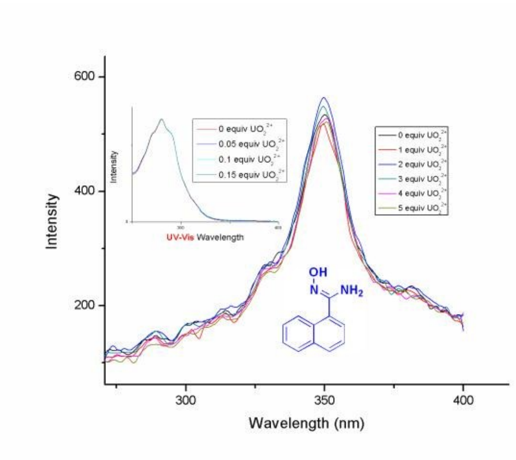


Fig. 1 Fluorescence and UV-Vis titration of 3a with $[UO_2](NO_3)_2$ (pH = 7.4, 25 ℃)

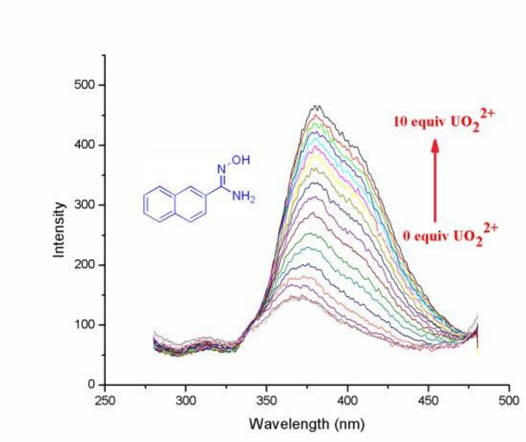
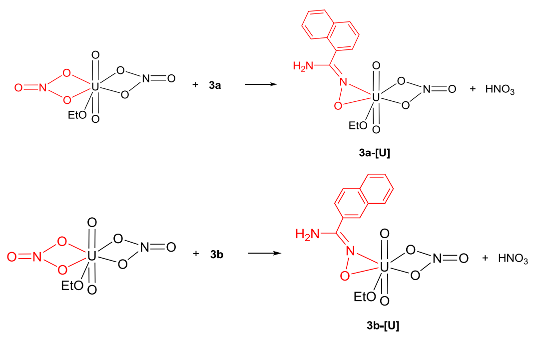


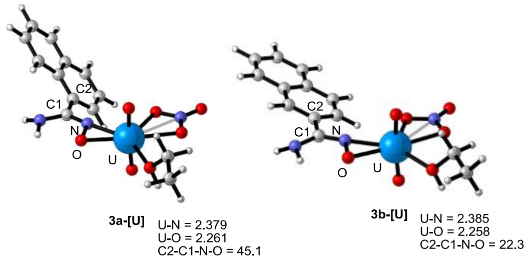
Fig. 2 Fluorescence titration of 3b with $[UO_2](NO_3)_2$ (pH = 7.4, 25 ℃)

DFT calculations have also been performed to analyze the relative binding ability of 3a and 3b (Scheme 2).[14] It's found that the binding ability of 3b is stronger than that of 3a. The adsorption of 3a with uranyl ion is endothermic by 4.7 kcal/mol, while the adsorption of 3b is thermodynamically significantly more feasible (exothermic by 2.7 kcal/mol). In other words, the binding of 3b is thermodynamically favourable.



Scheme 2 Ligand exchange reaction of 3a, 3b

In addition, the 3D structure of the uranyl complexes from 3a and 3b (Scheme 3) imply a significant larger C2-C1-N-O dihedral angle in the former case. In other words, the orbital conjugation is significantly damaged in 3a.[15] The reason for such observation might be related to the significant steric hindrance between the aromatic group on amidoxime and the other groups on the uranyl center (such as NO_3).



Scheme 3 Optimized structures of the uranyl complexes obtained via theoretical calculations.

Finally, using the Benesi-Hildebrand equation,[16] the association constants of the uranyl complexes with 3b and 3d were calculated to be K_{3b} ~0.91×10^4, K_{3d} ~3×10^4. This result suggests that compound 3d with electron-rich substituent has a stronger ability to bind uranyl ions consistent with theoretical data.[8]

To summarize, we have developed a novel "one-pot" reaction for the synthesis of amidoxime compounds. The "one-pot" procedure in our study presents several advantages, such as the readily available starting material, the less poisonous cyanating reagent, and the simple purification procedures. These functionalized aryl-substituted amidoxime compounds may have an ester group, trifluoromethyl group, nitro group, or methoxy and methyl group. Heteroaryl bromides can also be used in this reaction, and the introduction of N, S or O atoms may enhance the interaction between the resulting amidoxime compounds and uranyl ions. Finally, fluorescence, UV-Vis titration experiments and theoretical calculations suggest that the steric effect of the substituents in the amidoxime compound have a significant impact on its ability to bind uranyl ions. In addition, electron-rich substituents can enhance the binding affinity of uranyl ions. The results of this study contribute to the development of new amidoxime-based materials for extraction uranium from seawater. Follow-up studies are underway in our laboratory.

Acknowledgements

Our study was supported by the Natural Science Foundation of China (Nos. 21402179, 21401175, 91326110), the Science and Technology Development Foundation of China Academy of Engineering Physics (Grant No. 2011A0301003), the Originality Foundation of Institute of Nuclear Physics and Chemistry (Grant No. 2013cx01), and the Radiochemistry 909 Project in China Academy of Engineering Physics.

Notes and references

[a] *Institute of Nuclear Physics and Chemistry, China Academy of Engineering Physics, Mianyang, Sichuan, 621900, P. R. China. E-mail: xlwang@caep.cn; husheng@126.com.*
[b] *Department of Polymer Science and Engineering, University of Science and Technology Beijing, Beijing 100083, China. Fax: (+86)-10-6233-4516; Tel: (+86)-10-6233-4748.*

View Article Online
DOI: 10.1039/C4OB02456G

† Electronic Supplementary Information (ESI) available: Experimental details, NMR data, Crystallographic data, calculation details are provided. CCDC 1035363. For ESI and crystallographic data in CIF see DOI: 10.1039/b000000x/.

1 (a) R. V. Davies, J. Kennedy, R. W. McIlroy, R. Spence and K. M. Hill, *Nature*,1964, **203**, 1110–1115; (b) OECD, Uranium 2009: Resources, Production and Demand, OECD NEA Publication 6891, 2010, 29–32.

2 (a) H. J. Schenk, L. Astheimer, E. G. Witte and K. Schwochau, *Sep. Sci. Technol.*, 1982, *17*, 1293–1308; (b) L. Astheimer, H. J. Schenk, E. G. Witte and K. Schwochau, *Sep. Sci. Technol.*, 1983, **18**, 307–339; (c) N. Seko, A. Katakai, S. Hasegawa, M. Tamada, N. Kasai, H. Takeda, T. Sugo and K. Saito, *Am. Nuc. Soc.*, 2003, **144**, 274–278; (d) N. Seko, M. Tamada, N. Kasai, F. Yoshii and T. Simizu, *Proc. Civil Eng. Ocean*, 2004, **20**, 611-616; (e) J. Kim, C. Tsouris, R. T. Mayes, Y. Oyola, T. Saito, C. J. Janke, S. Dai, E. Schneider and D. Sachde, *Sep. Sci. Technol.*, 2013, *48*, 367–387.

3 M. J. Manos and M. G. Kanatzidis, *J. Am. Chem. Soc.*, 2012, **134**, 16441–16446.

4 M. Carboni, C. W. Abney, S. Liu and W. Lin, *Chem. Sci.*, 2013, **4**, 2396–2402.

5 L. Zhou, M. Bosscher, C. Zhang, S. Özçubukçu, L. Zhang, W. Zhan, C. J. Li, J. Liu, M. P. Jensen, L. Lai and C. He, *Nat. Chem.*, 2014, **6**, 236–241.

6 (a) I. Tabushi,Y. Kobuke and T. Nishiya, *Nature*,1979, **280**, 665–666; (b) T. Hirotsu, N. Takagi, S. Katoh, K. Sugasaka, N. Takai, M. Seno and T. Tiagaki, *Sep. Sci. Technol.*, 1987, **22**, 2217–2227; (c) T. Kago, A. Goto, K. Kusakabe and S. Morooka, *Ind. Eng. Chem. Res.*, 1992, **31**, 204–209; (d) A. Zhang, T. Asakura, G. Uchiyama, *React. Funct. Polym.*, 2003, **57**, 67–76; (e) P. A. Kavakli, N. Seko, M. Tamada and O. Güven, *Sep. Sci. Technol.*, 2004, *39*, 1631–1643; (f) S. Das, A. K. Pandey, A. Athavale, V. Kumar, Y. K. Bhardawaj, S. Sabharwal and V. K. Manchanda, *Desalination*, 2008, **232**, 243–253; (g) T. L. Prasad, P. K.Tewari and D. Sathiyamoorthy, *Ind. Eng.Chem. Res.*, 2010, **49**, 6559–6565; (h) Y. Yue, R. T. Mayes, J. Kim, P. F. Fulvio, X.-G. Sun, C. Tsouris, J. Chen, S. Brown and S. Dai, *Angew. Chem. Int. Ed.*, 2013, **52**, 13458–13462; (i) Y. Lu, *Nat Chem.*, 2014, **6**, 175–177.

7 (a) E. G. Witte, K. S. Schwochau, G. Henkel and B. Krebs, *Inorg. Chim. Acta*, 1984, **94**, 323–331; (b) A. Zhang, T. Asakura and G. Uchiyama, *React. Funct. Polym.*, 2003, **57**, 67–76; (c) T. Hirotsu, S. Katoh and K. Sugasaka, *J. Chem. Soc., Dalton Trans.* 1986, 1609–1611; (d) Y. Y. Park, S. Y. Kim, J. S. Kim, M. Harada, H. Tomiyasu, M. Nogami and Y. Ikeda, *J. Nucl. Sci. Technol.*, 2000, **37**, 344–348; (e) S. Vukovic, L. A. Watson, S. O. Kang, R. Custelcean and B. P. Hay, *Inorg. Chem.*, 2012, **51**, 3855–3859; (f) G. Tian, S. Teat, Z. Zhang and L. Rao, *Dalton. Trans.*, 2012, **41**, 11579–11586; (g) L. Rao, G. Tian, X. Sun, and F. Endrizz, *Coordination of* UO_2^{2+} *with amidoxime-related ligands: thermodynamics, kinetics, and structure*, Oak Ridge National Laboratory, Oak Ridge, TN, 2013; pp. 20−33; (h) *Cambridge Structural Database*, Version 5.32; November 2010; (i) S. P. Kelley, P. S. Barber, P. H. K. Mullins and R. D. Rogers, *Chem. Commun.*, 2014, **50**, 12504–12507.

8 DFT study investigates the electronic effects of amidoximate ligands bound to the uranyl cation: C. W. Abney, S. Liu and W. Lin, *J. Phys. Chem. A*, 2013, **117**, 11558–11565.

9 (a) N. Sahiner, N. Pekel and O. Guven, *React. Funct. Polym.*, 1999, **39**, 139–146; (b) X. Yang, G. Liu, H. Li, Y. Zhang, D. Song, C. Li, R. Wang, B. Liu, W. Liang, Y. Jing and G. Zhao, *J. Med. Chem.*, 2010, **53**, 1015–1022; (c) A. Vörös, Z. Baán, P. Mizsey, and Z. Finta, *Org. Process Res. Dev.*, 2012, **16**, 1717−1726.

10 Examples: (a) T. Schareina, A. Zapf and M. Beller, *Chem. Commun.*, 2004, 1388–1389; (b) T. Schareina, A. Zapf and M. Beller, *J. Organomet. Chem.*, 2004, **689**, 4576–4583; (c) O. Grossman and D. Gelman, *Org. Lett.*, 2006, **8**, 1189–1191; (d) T. Schareina, R. Jackstell, T. Schulz, A. Zapf, A. Cotté, M. Gotta and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 643–648; (e) P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2010, **49**, 8918–8922; (f) P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 648–651; (g) T. D. Senecal, W. Shu and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2013, **52**, 10035–10039.

11 Reviews: (a) L. H. Jones, N. W. Summerhill, N. A. Swain and J. E. Mills, *Med. Chem. Commun.*, 2010, **1**, 309–318; (b) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177–2250; (c) P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011,**40**, 5049–5067.

12 T. E. Barder, S. D.Walker, J. R. Marinelliand and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685–4696.

13 H. N. Nguyen, X. Huangand and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11818–11819.

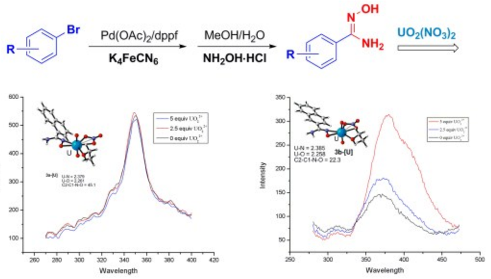
14 All species were fully optimized with B3LYP/(SDD-MWB60: 6-311G(d,p)) method on Gaussian 09 suit of program. Frequency calculation were performed at the same level of theory to ensure all these structures are local minima. Solution phase single point calculations were performed with EtOH solvent and SMD model. More details are given in the supporting information.

15 CYLview, 1.0b; C. Y. Legault, Université de Sherbrooke, 2009

16 H. Benesi and J. Hildebrand, *J. Am. Chem. Soc.*, 1949, **71**, 2703–2707.

View Article Online
DOI: 10.1039/C4OB02456G

TOC



“One-pot” synthesis of amidoxime was developed for studies on the interactions between amidoxime and uranyl.