Green Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c7gc01765k

Received 15th June 2017,
Accepted 6th July 2017

DOI: 10.1039/c7gc01765k

rsc.li/greenchem

Potassium isopropyl xanthate (PIX): an ultra-efficient palladium scavenger†

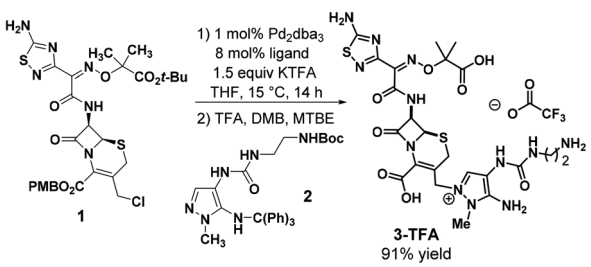
Hong Ren,* Christopher A. Strulson, Guy Humphrey, Rong Xiang, Guangtao Li, Donald R. Gauthier and Kevin M. Maloney *

The increasing employment of palladium-catalyzed reactions in the synthesis of active pharmaceutical ingredients (APIs) has created a pressing need for ultra-efficient palladium removal of the resulting metal contaminants. This communication discusses the identification and development of Potassium Isopropyl Xanthate (PIX) as a simple, readily available and ultra-efficient palladium scavenger capable of removing residual palladium from the API to levels less than 1 ppm. In addition, the discovery of a synergistic effect of iodine, in combination with PIX and other palladium scavengers, to enhance palladium removal has further increased the efficiency of the palladium removal process. The PIX and I_2 system has been successfully applied to the ceftolozane sulfate 2nd generation manufacturing chemistry to reduce palladium in the API resulting from a late stage palladium-catalyzed coupling reaction to only 0.1 ppm.

The emergence and broad substrate scope of palladium-catalyzed coupling reactions have revolutionized the number of bond disconnections available to synthetic chemists and allowed for the preparation of highly complex targets in the pharmaceutical industry. In addition to building molecular complexity, the use of catalytic processes is viewed as a green and sustainable approach to complex molecule synthesis.[1] While providing the noteworthy benefits described above, the deployment of palladium-catalyzed coupling reactions in the pharmaceutical industry has provided a new challenge related to palladium removal in Active Pharmaceutical Ingredients (APIs). In particular, palladium-catalyzed reactions conducted late in synthetic sequences often result in high levels of palladium entrained in the final compounds. The ICH guidelines for palladium list the daily permitted exposure at 100 mg day^{-1} for oral dosing and 10 mg day^{-1} for IV dosing, resulting in extremely low and challenging specifications for palladium in APIs, especially for high dose drugs. These important restrictions have presented the pharmaceutical industry with new scientific opportunities for innovation in palladium removal strategies to support the implementation of palladium-catalyzed reactions in API manufacturing and the development of green and sustainable manufacturing processes.

Ceftolozane, the cephalosporin antibiotic component in Zerbaxa™, was synthesized *via* a palladium-catalyzed C–N cross-coupling as shown in Scheme 1. This reaction forms the core structure of ceftolozane in a single, convergent step in excellent yield, resulting in a significantly more sustainable and green process. However, the ensuing reaction stream was shown to contain >2000 ppm of palladium-related species. The current ICH guidelines for palladium lead to a specification of <1 ppm of palladium in ceftolozane. Therefore, in order to implement the highly convergent and sustainable palladium-catalyzed C–N coupling, it became necessary to develop a highly efficient palladium removal process.

Initial attempts to apply conventional palladium removal options were met with limited success, confirming the challenges associated with palladium removal to the ppm level and reinforcing the need to develop a novel palladium removal strategy. Herein, we present the discovery and development of a new palladium removal strategy based on the solubilization of residual palladium with a novel xanthate scavenger and subsequent crystallization to afford ceftolozane in high recovery and with <1 ppm Pd.



Scheme 1 Zerbaxa ceftolozane manufacturing route.

Department of Process Research and Development, Merck & Co., Inc., Rahway, 07065 NJ, USA. E-mail: kevin_maloney@merck.com, hong.ren@merck.com

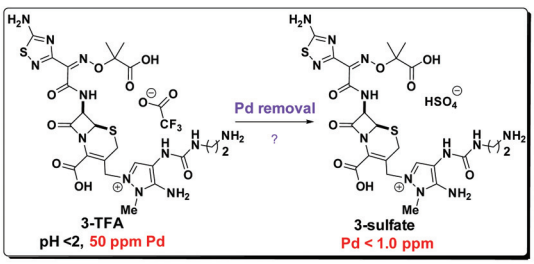
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c7gc01765k

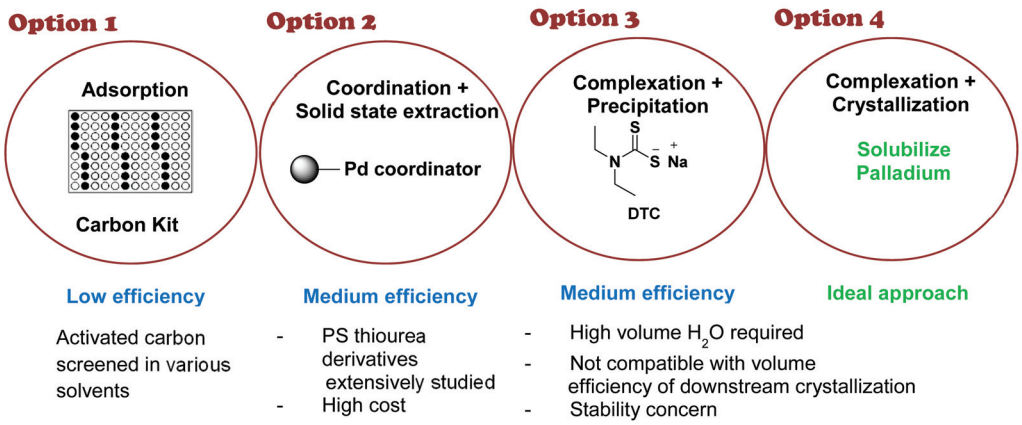
In our synthesis, the ceftolozane reaction stream after the palladium-catalyzed C–N coupling step contained ~2000 ppm of palladium-related species (Scheme 1). Following an aqueous work-up sequence utilizing thioglycerol as a palladium scavenger, a global deprotection and precipitation, the resulting intermediate **3-TFA** contained ~50 ppm of residual palladium species, representing a 20-fold reduction in palladium, but not close to our 1 ppm target. In order to further reduce the palladium content in the final API, several approaches were explored. Our initial efforts toward palladium removal, along with other impurities, involved crystallization of the API. Unfortunately, the highly efficient crystallization process developed to reject organic impurities provided minimal palladium rejection, typically resulting in palladium levels at ~40 ppm. Although disappointing, this result was unsurprising given the multiple binding sites for the metal on the highly polar ceftolozane structure.

After our unsuccessful preliminary effort using crystallization, we screened inexpensive and simple solid-phase adsorbents and activated carbons,[2] such as Norit, Nuchar, aquaguard, decolorizing charcoal and Darco (Scheme 2, option 1, see ESI† for more information), for palladium removal. In the best case, treatment of intermediate **3-TFA** with ~10 wt% of aquaguard for 1 h at 22 °C reduced the palladium from 50 ppm to 30 ppm (40% palladium removal). A variety of commercially available solid-state specialty scavengers,[3] such as polymer-bound thioureas and sulfur-containing compounds, were also screened in removing residual palladium (Scheme 2, option 2, see ESI† for more information). The best resin identified was the Silicycle thiourea resin that showed medium efficiency with 60–90% palladium removed to give ~10–20 ppm residual palladium in the final API and 95% recovery, but still failed to provide the requisite level of palladium removal.

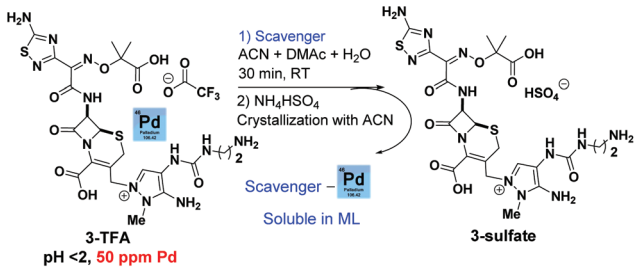
Having thoroughly screened solid phase palladium removal agents with minimal success, we shifted our attention to solutions based palladium chelating scavengers such as DEDTC (Scheme 2, option 3).[4] In this method, the palladium chelating scavenger was added to a solution of the intermediate **3-TFA** in water at pH < 2.0 resulting in precipitation of the palladium-DEDTC complex, which can subsequently be removed by filtration. In the case of DEDTC, residual palladium in **3-TFA** was reduced from 50 to 10 ppm (80% removal). Although this result served as a promising lead, this approach presented several challenges with respect to the development of an efficient process. First, this approach required a large amount of H_2O to precipitate the palladium DEDTC complex, leading to poor volume efficiency in the downstream crystallization and a correspondingly high Process Mass Intensity (PMI). Second, extended aging of **3-TFA** in H_2O led to its decomposition. Finally, DEDTC is not stable under acidic conditions, rapidly decomposing at pH < 7.0. These factors, in combination, rendered this approach less favourable for our ceftolozane process.

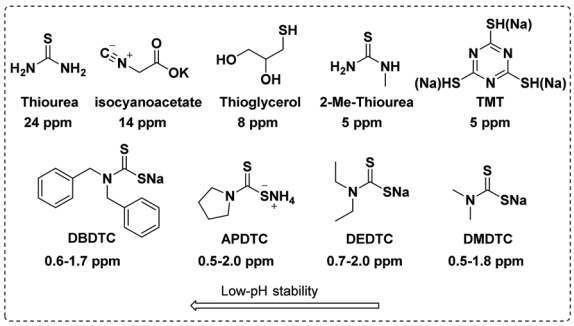
Having exhausted conventional approaches to achieve palladium rejection, we pursued a novel strategy by which we sought to identify a novel palladium scavenger that would efficiently and selectively bind palladium, while remaining in





Scheme 2 Zerbaxa ceftolozane palladium removal: unprecedented challenges.

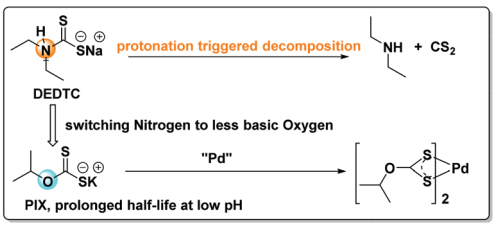




Scheme 3 Zerbaxa ceftolozane palladium removal with chelating agents. Reaction conditions: 5 mol% scavenger wrt **3-TFA** used in all the experiments. **3-TFA** and the scavenger were stirred in a mixture of MeCN, DMAc and H_2O (7 vol.) for 30 min at RT. 1 equiv. of NH_4HSO_4 was then added, followed by the addition of MeCN (14 vol.) over 10 h at 15 °C. The product was collected by filtration. Palladium assays from ICP-MS.

solution, prohibiting complexation of the palladium with **3-sulfate**. Utilization of the known crystallization of **3-sulfate** would afford the API with a suitable palladium level, with concomitant rejection of the palladium in the mother liquors (option 4, Scheme 2). In addition, the novel palladium scavenger would need to exhibit increased stability under acidic conditions. To explore this new strategy, we screened a broad range of soluble palladium chelating agents (Scheme 3). Among all scavengers tested, dithiocarbamates and their derivatives[5] showed the most promise in rejecting palladium, affording levels as low as 2 ppm when combined with the crystallization process. This green and sustainable approach provided an extremely promising starting point for palladium removal in the current crystallization, while avoiding introducing any additional steps or operations.

Despite this exciting result, the use of dithiocarbamates posed a significant robustness challenge for the crystallization process due to their extremely fast decomposition rates under strongly acidic conditions.[6] This competitive decomposition pathway, triggered by protonation of the thiocarbamate nitrogen, resulted in variable palladium rejection from 2 to 5 ppm in the final API.[7] We hypothesized that replacing the nitrogen with a less Lewis basic atom, such as oxygen or carbon, would lead to slower decomposition rates in related compounds (Scheme 4). Potassium isopropyl xanthate (PIX, **4**) proved optimal, both with respect to palladium rejection and commercial availability, among all xanthate derivatives tested, **4–7**

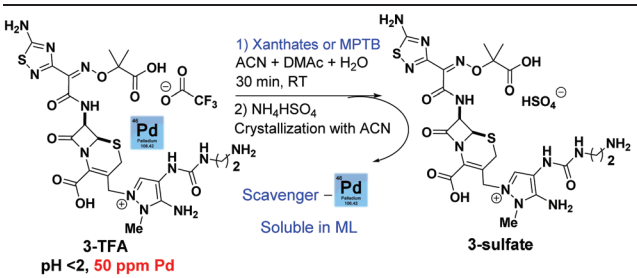


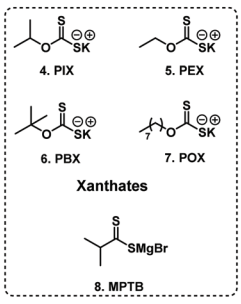
Scheme 4 Evolving from DTC to PIX.

and MTBP **8** (Table 1). We determined that stirring an aqueous acetonitrile/DMAc solution of intermediate **3-TFA** with xanthate **4** for 30 minutes was optimal for palladium removal. The resulting mixture was taken through the crystallization protocol to consistently yield **3-sulfate** with <1 ppm palladium. It is interesting to note that potassium isopropyl xanthate has been widely used in the recovery of heavy metals from ores in the mining industry as well as in the manufacture of fungicides, pesticides and polymers,[8] but, to the best of our knowledge, this example represents its first application to remove palladium in a pharmaceutical process.

To assess the pH stability of PIX under the processing conditions, **4** was dissolved in a model system consisting of the process solvents (DMAC, water, and ACN), and the pH was adjusted to specific values using TFA. The pH stability of **4** at pH 2 is of particular importance, since this is the measured pH of the crystallization process for ceftolozane **3-sulfate** from **3-TFA**. By omitting intermediate **3-TFA** in the measurement, we were able to directly determine the impact of pH on PIX stability. A direct-UV measurement method and a chromato-

Table 1 Screening of various PIX derivatives and MPTB





Entry[a]		Feed Pd (ppm)	Final Pd[b] (ppm)	Pd removed (%)
1	PIX	50	0.16	99.7
2	PEX	50	0.61	98.8
3	PBX	50	36	28
4	POX	50	32	36
5	MPTB	50	0.7	97

[a] 10 mol% scavengers used in experiments. [b] Palladium assays by ICP-MS.

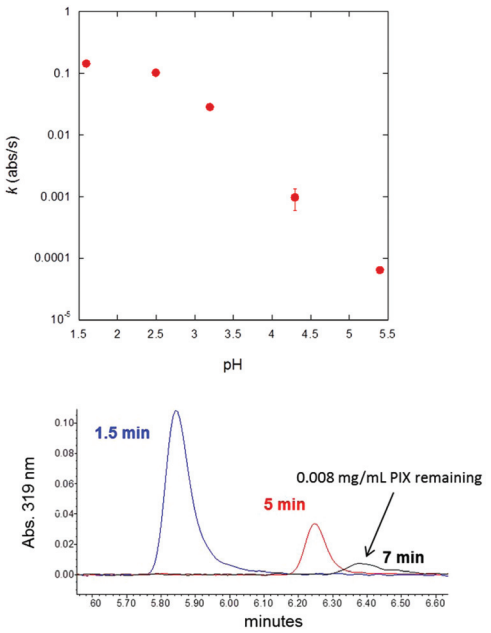
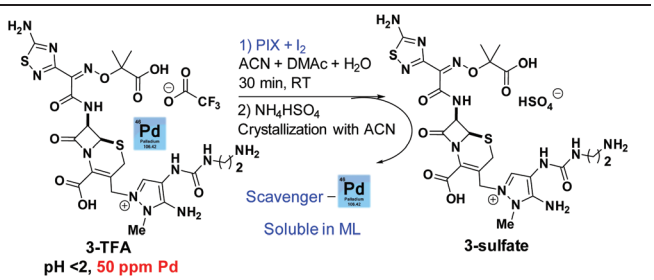


Fig. 1 Measuring palladium scavenger stability in acidic conditions (DEDTC was completely destroyed in <5 min under similar conditions).

graphic method monitoring the UV absorbance at 319 nm were employed to monitor degradation. The pH range from pH 1.7 to pH 5.4 was analyzed, and the results provided a clear trend for pH stability wherein **4** is increasingly unstable as the processing conditions become more acidic (Fig. 1). This trend is consistent with prior observations concerning xanthate stability.[9] It is important to note that, despite the increase in PIX degradation rate under acidic conditions, we were still able to observe an appreciable concentration (0.008 mg mL^{-1}) of **4** after 7 minutes in a pH 1.7 medium. Even at this low concentration, we observed robust and reproducible scavenging of the low levels of palladium (ppm range). In contrast, dithiocarbamates such as DEDTC were completely destroyed in <5 min under similar conditions.

Having identified PIX as the optimal palladium scavenger, we explored the synergistic impact of additives on palladium removal. Considering **4** is an ionic scavenger and is likely a better ligand for palladium(II)[10] (Scheme 4) than palladium(0) species, the presence of an oxidant may convert trace levels of residual palladium(0) to palladium(II) and provide a still more efficient removal of residual palladium. In an extensive screen of common oxidants (see ESI†) in combination with **4**, most proved incompatible with our system – either destroying the **3-TFA** intermediate or having little effect on palladium rejection. Iodine was the lone exception to these observations: the combination of PIX and I_2 resulted in a threefold reduction in palladium when compared to PIX alone (Table 2). In addition to PIX, the combination of I_2 with several additional palladium scavengers resulted in improved palladium rejection. A control experiment using I_2, but omitting treatment with **4**, resulted in no reduction of residual palladium, thus confirming the synergistic effect between PIX and I_2. To further demonstrate

Table 2 Enhancing palladium removal *via* I_2 oxidation[a]

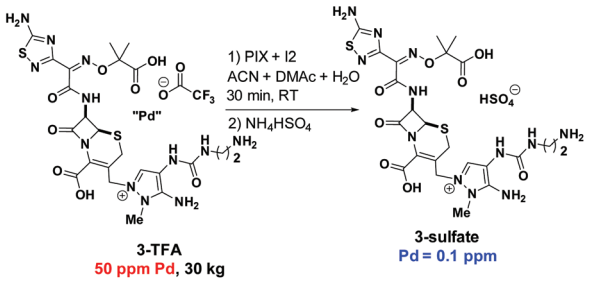


Palladium scavenger	Feed palladium (ppm)	Final palladium without I_2[b] (ppm)	Final palladium with I_2[b] (ppm)
PIX	75	0.9	0.3
PEX	42	2.0	0.68
DTC	65	8.5	1.8
MPTB	24	0.7	0.3
2-Methyl thiourea	65	1.2	0.8
TMT	25	5.0	2.2
Thioglycerol	120	8.0	4.4
Isocyanoacetate	25	14	5.5

[a] Reaction conditions: 5 wt% scavengers wrt **3-TFA** used in all the experiments. **3-TFA** and the scavenger were stirred in a mixture of MeCN, DMAc and H_2O (7 vol.) for 30 min at RT. 1 equiv. of NH_4HSO_4 was then added, followed by the addition of MeCN (14 vol.) over 10 h at 15 °C. The product was collected by filtration. [b] Palladium assays from ICP-MS.

the efficiency of the PIX–I_2 system, this protocol was performed on 30 kg scale to provide final API with a palladium level of a mere 0.1 ppm (Scheme 5).

In conclusion, we have developed a novel palladium removal approach utilizing PIX as a highly efficient scavenger to reduce palladium to ultra-low levels (<1 ppm). Our approach ensures that the palladium species remain soluble during the process, allowing for their rejection in the mother liquors. In this iteration, potassium isopropyl xanthate (PIX), a readily available and cheap reagent, proved optimal. The use of this method requires neither additional filtration steps nor use of specialized reagents, highlighting both its practicality and sustainability. The method features the first use of PIX as an ultra-efficient palladium scavenger in a pharmaceutical process and was demonstrated on 30 kg scale as part of the ceftolozane (**3-sulfate**) manufacturing process. We also discovered the synergistic effect of the addition of iodine to augment



Scheme 5 Zerbaxa ceftolozane palladium removal with PIX on pilot plant scale.

the palladium removal with PIX. We believe this hybrid treatment will be a broadly useful technique to apply when confronted with a problematic API-palladium separation and should be applicable to other metal species. Finally, the implementation of the PIX–I_2 process has enabled the incorporation of the palladium-catalyzed C–N cross-coupling leading to a significantly greener and more sustainable process to ceftolozane sulfate and, hence, Zerbaxa™.

Experimental section

Typical procedure for palladium removal with PIX: Ceftolozane **3-TFA** (14.3 g at 56 wt%) and 48 mL of a 2.5 : 1 : 2 water : DMAc : acetonitrile v : v : v (50 : 19 : 31 w/w) were combined and stirred at 22 °C to give a slurry. Isopropylxanthic acid potassium salt (PIX) **4** (0.104 g, 5 mol%) was added in one portion and the resulting reaction slurry was stirred at 22 °C for 30 min. A second portion of isopropylxanthic acid potassium salt **4** (0.104 g, 5 mol%) was added and the reaction mixture was stirred at 22 °C for 30 min. Iodine (0.076 g, 2.5 mol%) was then added and the reaction slurry was stirred at 22 °C for 1 h. The slurry was then filtered and the resulting waste cake was washed with 8 mL of a 2.5 : 1 : 2 water : DMAc : acetonitrile. The filtrate and wash were combined and cooled to 15 °C. Ammonium bisulfate (ammonium hydrogen sulfate) (1.449 g, 1.05 equiv.) was added and stirred at 15 °C for 15 min. Acetonitrile (12 mL) was added, followed by ceftolozane **3-sulfate** (0.08 g). The resulting slurry was aged at 15 °C for 3 h. Acetonitrile (100 mL) was then charged over 10 h and the resulting slurry was aged at 15 °C for 1 h. Solids were filtered, washed with water : DMAc : acetonitrile (2.5 : 1 : 13) followed by acetonitrile, and then dried under vacuum with a nitrogen sweep at 25 °C for 17 h to afford ceftolozane **3-sulfate** (9.51 g, 89% yield) with 0.1 ppm palladium.

Acknowledgements

We thank the following for their help with and suggestions for the work presented in this paper: LC Campeau, Rebecca Ruck, Kevin Campos, and David Tschaen.

References

1 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998, p. 30.
2 M. Prashad, H. Bin, D. Har, O. Repicoe and T. J. Blacklock, *Adv. Synth. Catal.*, 2001, **343**, 461–472.
3 (*a*) R. L. Dorow, P. M. Herrinton, R. A. Hohler, M. T. Maloney, M. A. Mauragis, W. E. McGhee, J. A. Moeslein, J. W. Strohbach and M. F. Veley, *Org. Process Res. Dev.*, 2006, **10**, 493–499; (*b*) P. Ryberg, *Org. Process Res. Dev.*, 2008, **12**, 540–543; (*c*) M. M. Ravn, S. H. Wagaw, K. M. Engstrom, J. Mei, B. Kotecki, A. J. Souers, P. R. Kym, A. S. Judd and G. Zhao, *Org. Process Res. Dev.*, 2010, **14**, 417–424; (*d*) I. N. Houpis, D. Shilds, U. Nettekoven, A. Schnyder, E. Bappert, K. Weerts, M. Canters and W. Vermuelen, *Org. Process Res. Dev.*, 2009, **13**, 598–606; (*e*) L. Wang, L. Green, Z. Li, J. M. Dunn, X. Bu, C. J. Welch, C. Li, T. Wang, Q. Tu, E. Bekos, D. Richardson, J. Eckert and J. Cui, *Org. Process Res. Dev.*, 2011, **15**, 1371–1376.
4 V. W. Rosso, D. A. Lust, P. J. Bernot, J. A. Grosso, S. P. Modi, A. Rusowicz, T. C. Sedergran, J. H. Simpson, S. K. Srivastava, M. J. Humora and N. G. Anderson, *Org. Process Res. Dev.*, 1997, **1**, 311–314.
5 W. P. Gallagher and A. Vo, *Org. Process Res. Dev.*, 2015, **19**, 1369–1373.
6 K. I. Aspila, V. S. Sastri and C. L. Krabarti, *Talanta*, 1969, **16**, 1099–1102.
7 E. Humeres, N. A. Debacher and M. Sierra, *J. Org. Chem.*, 1999, **64**, 1807–1813.
8 (*a*) D. E. Barnes and C. Pohlandt-Watson, *Fresenius' J. Anal. Chem.*, 1993, **345**, 26–42; (*b*) K. Roy, *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim, Wiley-VCH, 2005, DOI: 10.1002/14356007.a28_423.
9 (*a*) I. Iwasaki and S. R. Cooke, *J. Am. Chem. Soc.*, 1958, **80**, 285–288; (*b*) Z. Sun and W. Forsling, *Miner. Eng.*, 1997, **10**, 389–400.
10 I. Ara, F. E. Bahij, M. Lachkar and N. B. Larbi, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2003, **59**, m199–m200.