Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1008

www.rsc.org/obc

COMMUNICATION

Further investigations into the *N*-demethylation of oripavine using iron and stainless steel†‡

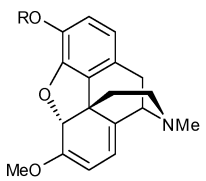
Gaik B. Kok and Peter J. Scammells*

Received 12th November 2010, Accepted 3rd December 2010
DOI: 10.1039/c0ob01021a

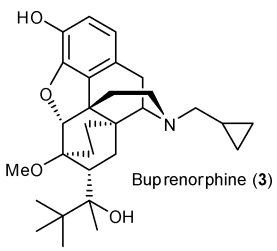
Further investigations into the direct synthesis of *N*-nororipavine from oripavine using iron powder under non-classical Polonovski conditions have been conducted. The stoichiometry, solvents and iron oxidation rates were found to have a dramatic effect on the rate of *N*-demethylation as well as product yield. Herein, we also present high-yield access to the *N*-demethylated product simply by employing stainless steel rather than iron powder as redox catalyst. To our knowledge, this is the first time stainless steel has been used to moderate the redox chemistry of iron in organic synthesis.

Oripavine (**1**) and thebaine (**2**) are naturally occurring opiate alkaloids isolated from the opium poppy, *Papaver Somniferum*. Oripavine is derived from the O-demethylation of thebaine, which in turn is biosynthesized from reticuline.[1] In former times, bulk supplies of oripavine were difficult to obtain due to its low natural abundance in the opium poppy. It has been isolated in amounts of 0.1% from the dried capsules of Tasmanian opium poppies.[1] Alternatively it can be synthesized in one step from thebaine, though this transformation has proven to be problematic[2–4] and the best reported yield is only 23%.[5] More recently, Sipos and coworkers reported an alternative synthesis in which thebaine was treated with DEAD to afford the corresponding *N*-nor-*N*-{[1,2-bis(ethoxycarbony)hydrazinyl]methyl} derivative.[6] Subsequent treatment of this intermediate with L-Selectride effected concomitant O- and N-dealkylations, giving *N*-nororipavine in an overall yield of 43%.

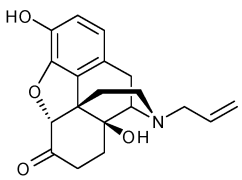
More recently, poppy strains have been developed which had a much higher content of thebaine and also produce substantial quantities of oripavine, which has opened the possibility of its use as a bulk raw material. Oripavine is a very attractive starting material for the preparation of a number of semi-synthetic opiate pharmaceuticals such as buprenorphine (**3**), naloxone (**4**) and naltrexone (**5**), which are used as analgesic agents and/or for the treatment of alcohol and opiate dependence. Both oripavine and thebaine possess a C-ring diene that can be elaborated to the "orvinol" class of opioid (such as buprenorphine) *via* a Diels–Alder approach, or to the "nal salts" (such as naloxone and naltrexone) by oxidation of the diene. Notably, oripavine lacks an O-3 methyl group (unlike thebaine) which obviates the need to perform an O-demethylation step *en route* to these semi-synthetic opiate targets.



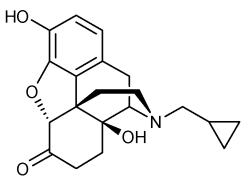
Oripavine (**1**, R = H)
Thebaine (**2**, R = Me)



Buprenorphine (**3**)



Naloxone (**4**)



Naltrexone (**5**)

All of the commonly used naturally occurring opiate substrates possess a *N*-methyl group and the cleavage of this group prior to the introduction of an *N*-allyl or *N*-cycloalkylmethyl group remains a problematic step in the synthesis of compounds **3**–**5** and related analogs. A number of general methods for *N*-demethylation of tertiary *N*-methylamines have been reported,[7] which include the use of cyanogen bromide (von Braun reaction),[8] chloroformates[9] and dialkyl azodicarboxylates.[10] These methods have drawbacks such as the requirement for toxic or expensive reagents and/or proceed in modest chemical yield. Photochemical[11] and biochemical[12,13] methods for *N*-demethylation have also been reported, but these approaches are typically low yielding. More recently, Hudlicky and co-workers have found that hydrocodone and certain tropane alkaloids can be *N*-demethylated and *N*-acylated using palladium acetate and acetic anhydride or solely *N*-demethylated with copper acetate and ammonium

Medicinal Chemistry and Drug Action, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria, 3052, Australia. E-mail: peter.scammells@monash.edu; Fax: (+61) 3 9903 9582; Tel: (+61) 3 9903 9542

† This work is dedicated to the memory of Athel Beckwith, a teacher and scientist from whom we learned how to study chemistry by example. His pioneering advances in radical chemistry laid the foundation for much of the current radical clock methodology

‡ Electronic supplementary information (ESI) available: Representative experimental procedures and characterisation of reaction products. See DOI: 10.1039/c0ob01021a

peroxysulfate.[14] Whilst these methods proceed in good yield, they appear to be limited to these substrates.[13]

We were the first to investigate the use of the non-classical Polonovski reaction for the *N*-demethylation of opiate alkaloids.[15–18] In this approach the *N*-methylamine was oxidized to the corresponding amine-*N*-oxide prior to treatment with Fe(II) reagents such as $FeSO_4 \cdot 7H_2O$,[15] Fe(II)TPPS[16] and ferrocene.[17] Interestingly, it was also discovered that Fe(0) could also effect this transformation.[18] Whilst ferrocene was able to *N*-demethylate thebaine-*N*-oxide in good yield (84%), the results obtained with oripavine-*N*-oxide were poor (affording 38% *N*-nororipavine and 29% oripavine).[17] Similar results were obtained with Fe(0) whereby *N*-northebaine and *N*-nororipavine were obtained from the corresponding *N*-oxides in 86% and 40% yield, respectively.[18]

Herein we report our further investigations into the *N*-demethylation of oripavine using zero-valent iron. In our earlier studies, we found that the choice of solvent had a dramatic effect on the reaction outcome with respect to the yield of the *N*-nor product obtained. Therefore, we have carried out a more detailed solvent effect study on *N*-demethylation of oripavine, including a study on the effect of stoichiometry and/or temperature on the reaction. We have found that *N*-demethylation of oripavine is particularly sensitive to subtle changes in these experimental conditions. For the first time, we also report our findings on the use of stainless steel in Polonovski-type *N*-demethylations. Substituting stainless steel for iron powder has generally resulted in a higher yield of the *N*-nor product.

Our initial studies were focused upon the effect of stoichiometry and temperature on *N*-demethylation of oripavine with iron powder under non-classical Polonovski conditions (Scheme 1). Thus, oripavine was first oxidized to the corresponding *N*-oxide which was isolated as the corresponding hydrochloride salt **6**. All *N*-demethylation experiments on **6** were carried out using degassed solvents under an atmosphere of nitrogen. Initial reaction development and optimization were conducted in 2-propanol.

Results are summarized in Table 1; the result from our previous study,[18] using two equivalents of iron powder, has been included in the Table for reference (entry 1). Unlike the situation employing dextromethorphan as substrate,[18] for *N*-demethylation of oripavine, the amount of iron powder used has been found to have a dramatic effect on the yield of the reaction. Interestingly, at 40 °C, the yield of *N*-nororipavine improved as the amount of iron powder used was progressively reduced from 200 to 25 mol% (entries 1–3). In line with expectation, when the amount of iron powder used was reduced from 50 to 25 mol%, the reaction took three times longer to run to completion. On the other hand, increasing the amount of iron powder from 50 to 200 mol% did not have an effect on reaction time (entries 1 and 2), although the yield of *N*-nor product was appreciably reduced. Using 50 mol% of iron powder, increasing the temperature from 40 °C to 60 °C (entries 2 and 4) resulted in a significant reduction in reaction time with little consequence on the yield of the *N*-nor product. Again, at 60 °C, increasing the amount of iron powder used from 50 to 200 mol% resulted in lower yields (entries 4 and 5).

Table 1 *N*-Demethylation of oripavine *N*-oxide hydrochloride with iron powder in 2-propanol[a,b]

Entry	Iron powder (equiv)	T (°C)	Time (h)	Nororipavine (%)[d]	Oripavine (%)[d]
1[c]	2	40	48	40	24
2	0.5	40	48	53	25
3	0.25	40	144	65	25
4	0.5	60	16	52	29
5	2	60	16	48	21

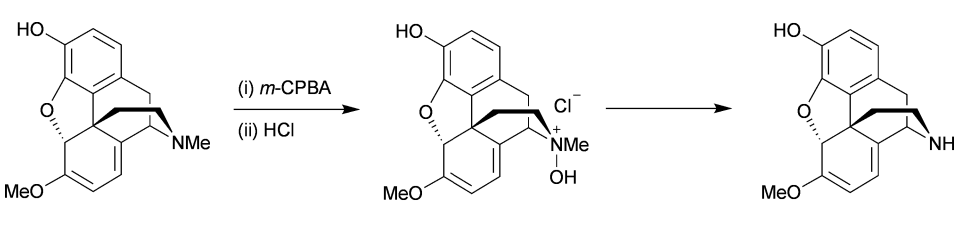
[a] Reactions were conducted under nitrogen with degassed solvents. [b] Concentration: 10 mL of solvent per 100 mg of substrate. [c] Reference 18. [d] Isolated *via* column chromatography.

We have previously found that, for these Polonovski-type reactions, chloroform is generally a better medium than 2-propanol.[18] However, due to solubility issues, *N*-demethylation of certain substrates including oripavine has not been conducted in chloroform. We have therefore undertaken the solvent effect study by conducting the reaction using a mixture of chloroform and 2-propanol, choosing to vary the proportion of the solvents in the mixture. Results are summarized in Table 2. Where direct comparisons can be made, the reaction in the binary solvent

Table 2 *N*-Demethylation of oripavine *N*-oxide hydrochloride with iron powder in $CHCl_3$/*i*-PrOH[a,b]

Entry	$CHCl_3$/*i*-PrOH	Fe (equiv)	T (°C)	Time (h)	Nororipavine (%)[c]	Oripavine (%)[c]
1[d]	1 : 1	2	40	48	57	20
2[d]	3 : 1	2	40	44	70	25
3	1 : 1	0.5	40	3.5	71	25
4	3 : 1	0.5	40	5.5	70	25
5	9 : 1	0.5	40	168	58	23
6	3 : 1	0.5	RT	5.5	75	23
7	3 : 1	0.5	60	4	65	25
8	3 : 1	0.25	RT	24	76	20

[a] Reactions were conducted under nitrogen with degassed solvents. [b] Unless otherwise indicated, concentration: 10 mL of solvent per 100 mg of substrate. [c] Isolated *via* column chromatography. [d] Concentration: 20 mL of solvent per 100 mg of substrate.



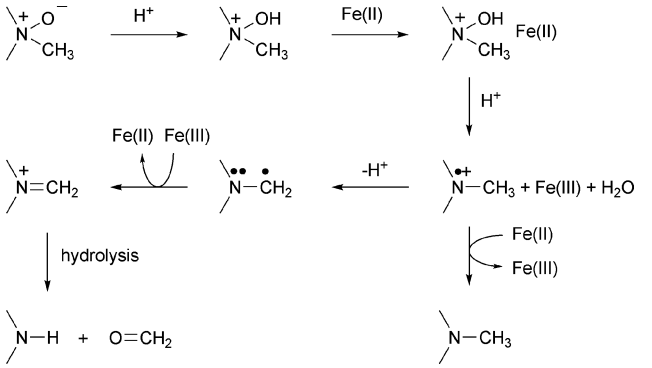
Oripavine (**1**) Oripavine-*N*-oxide HCl (**6**) *N*-Nororipavine (**7**)

Scheme 1 *N*-Demethylation of oripavine.

system compared to 2-propanol alone, has resulted in significant improvements in both the completion time as well as in the yield of *N*-nororipavine obtained, and in the total product recovery. Interestingly, of the different $CHCl_3$/*i*-PrOH mixtures tested, we have found that, in general, the yield of the *N*-nor product was essentially invariant to the amount of catalyst used when a 3 : 1 $CHCl_3$/*i*-PrOH mixture was employed. For example, identical yields were obtained when the reactions were conducted at 40 °C with either sub-stoichiometric or excess catalyst (entries 2 and 4), unlike the situation where a 1 : 1 mixture was employed (entries 1 and 3) or, as previously alluded to, when 2-propanol alone was used. With either binary mixture, employing sub-stoichiometric amounts of catalyst dramatically accelerated the reaction (entries 1–4), reducing the reaction times from about 2 days to only a few hours. Having now established conditions where the reaction could be completed in a reasonable time of only a few hours, we decided to investigate the reaction at ambient temperature. As the results illustrated by using 50 mol% iron powder in the 3 : 1 $CHCl_3$/*i*-PrOH mixture (entries 4 and 6) show, there appears to be no advantage with respect to completion time in conducting the reaction at a higher temperature. Indeed, after standard workup and subsequent column chromatography, the reaction at ambient temperature gave a slightly improved yield of the *N*-nor product of 75% and near quantitative total product recovery. Increasing the temperature to 60 °C did, however, accelerate the reaction, albeit the yield of *N*-nororipavine obtained was also slightly compromised (entries 4 and 7). At ambient temperature using a lower catalyst loading of 25 mol% (entry 8), the reaction also complete in reasonable time (24 h), delivering a 76% yield of **7**.

Interestingly, using 50 mol% of iron powder at 40 °C, we have found that the reaction time increases with increasing proportion of chloroform in the binary mixture (entries 3–5). For example, increasing the proportion of chloroform from 75% to 90% greatly decelerates the reaction and has resulted in a diminished yield of *N*-nororipavine. Hence, for reasons still unknown, for the $CHCl_3$/*i*-PrOH binary solvent system, there appears to be a narrow window around the ratio of chloroform and 2-propanol for optimum catalytic turnover.

In summary, the best yields of *N*-nororipavine were obtained with sub-stoichiometric amounts of iron powder (25 or 50 mol%) at room temperature in a mixed chloroform/2-propanol solvent system. The iron(II) salt-mediated version of the Polonovski reaction is believed to be a radical mechanism involving two successive one-electron transfers, based on Fe(II)/Fe(III) redox reactions (Scheme 2).[19] In this proposed mechanism, iron(II) initially coordinates to the protonated *N*-oxide and subsequently undergoes a one-electron reduction, which results in cleavage of the N–O bond and formation of an aminium radical cation. This radical cation loses a α-proton and undergoes an electron reorganization to form a more stable carbon-centered radical (whilst still bound to iron). Oxidation of the carbon-centered radical by iron(III) forms an iminium ion and subsequent hydrolysis affords the desired secondary amine. The major by-product is the parent tertiary *N*-methylamine, which is believed to form when the intermediate aminium radical cation dissociates from the oxidized iron complex and undergoes further reduction by iron(II). Zero-valent iron has only recently been reported to catalyze the *N*-demethylation of amine-*N*-oxides[18] and the mechanism of this reaction has not been explored in detail. However, it is



Scheme 2 Proposed mechanism for non-classical Polonovski reaction.

plausible that a mechanism similar to that described above could be involved, with trace amounts of iron(II) present in the iron powder or formed *in situ* during the course of the reaction effecting the *N*-demethylation. Zero-valent iron in the form of iron powder has previously been used as a source of iron(II) in Fenton reactions following the *in situ* oxidation of the iron.[20–24] Other mechanisms involving the Fe(0)/Fe(II)/Fe(III) redox system are also plausible and this matter clearly requires further investigation.

Iron speciation is strongly influenced by the presence of other chemical elements. In particular, by virtue of the resistance of stainless steel to various forms of oxidation, we envisage that a lesser or controlled amounts of Fe(0)/Fe(II)/Fe(III) in the reaction may conveniently be accommodated for by the use of stainless steel as catalyst. Indeed, stainless steel is a group of iron-based alloys with additions of elements such as chromium and molybdenum to control oxidation of zero-valent iron to the higher oxidized species. This group of iron alloys also exists commercially in various well-characterized forms, and may provide some insight into the effects of other added elements on these reactions.

Two common stainless steel powders have been used for this study: 303-L (% Fe : Cr : Ni = 70 : 17 : 13; 140 mesh) and 316-L (% Fe : Cr : Ni : Mo = 67.5 : 17 : 13 : 2.5; 100 mesh). Since our earlier studies with iron powder have been conducted in various $CHCl_3$/*i*-PrOH solvent systems, we have chosen the same binary media for these stainless steel studies so that a direct comparison with the reaction using iron powder can be made. Results have been summarized in Table 3.

Table 3 *N*-Demethylation of oripavine *N*-oxide hydrochloride with iron alloys/stainless steel[a,b]

Entry	Iron alloy (equiv)	$CHCl_3$/*i*-PrOH	T (°C)	Time (h)	**7** (%)[c]	**1** (%)[c]
1	303-L (0.5)	1 : 1	40	27	79	11
2	303-L (0.5)	3 : 1	40	96	79	17
3	303-L (0.5)	9 : 1	40	96	70	18
4	303-L (0.5)	3 : 1	60	40	81	17
5	303-L (0.5)	3 : 1	RT	480	82	16
6	303-L (10)	3 : 1	40	96	77	22
7	316-L (0.5)	3 : 1	60	144	74	25
8	316-L (10)	3 : 1	60	96	67	30
9	paper clips (d)	*i*-PrOH	50	120	73	17

[a] Reactions were conducted under nitrogen with degassed solvents. [b] Concentration: 10 mL of solvent per 100 mg of substrate. [c] Isolated *via* column chromatography. [d] Four steel clips, each weighing 1.1 g, were used for 100 mg of substrate.

For a given concentration of 50 mol% of stainless steel 303-L powder at 40 °C, we have found the yield of *N*-nororipavine obtained was essentially invariant when the reaction was conducted in either 1 : 1 or 3 : 1 $CHCl_3$/*i*-PrOH (entries 1 and 2). Interestingly, in an outcome reminiscent of the previous situation employing iron powder, when the proportion of chloroform in the binary mixture was increased to 90% (entry 3), the yield of *N*-nororipavine obtained was somewhat compromised. Again, we have no definitive explanation for this apparent dependency of the reaction outcome on the proportion of one solvent in the binary solvent system except to point out that, at least in the case of stainless steel, our results corroborate with previous studies[25] on the corrosion of stainless steel by organic solvent mixtures. Thus, it has been reported that certain organic solvents, although non-corrosive individually, are unstable when in prolonged contact with stainless steel materials. Halogenated solvents were found to be particularly sensitive to corrosion. Our results therefore suggest that, when employing a binary solvent mixture, it is imperative that studies on the effect of the components in a range of mixtures be conducted.

When the reaction was conducted using stainless steel 303-L powder in 3 : 1 $CHCl_3$/*i*-PrOH, we have found that either reducing the temperature to ~24 °C or increasing the temperature to 60 °C did not alter the yield of *N*-nororipavine or product yield ratio, although the higher temperature did accelerate the reaction (*cf.* entries 4 and 5 with entry 2). Additionally, unlike the situation employing iron powder as catalyst, the reaction using stainless steel appears to tolerate excess catalyst loading, albeit with no apparent added advantage (*cf.* entry 2 with 6).

Reactions conducted with added molybdenum in the form of stainless steel 316-L (entries 7 and 8) appear to offer no advantage with respect to yield of *N*-nororipavine obtained. For this catalyst, increasing the amount of catalyst twentyfold was beneficial with respect to completion time although the yield of *N*-nor product obtained was slightly lower (*cf.* entries 7 and 8).

With the two grades of stainless steel employed in these studies available in different mesh sizes, it is difficult to ascertain the relative reaction rates of the two stainless steels. It is not unreasonable in these heterogeneous reactions to expect a dependency of the reaction rates on mesh sizes. We have found that reactions using stainless steel 304-L wires (0.127 mm diameter), for example, were significantly slower than the same reaction employing powdered material (data not shown).

We have also investigated the *N*-demethylation of oripavine-*N*-oxide using standard office paper clips (entry 9). Four paper clips per 100 mg of substrate in 2-propanol afforded a 73% isolated yield of *N*-oripavine.

In conclusion, we have found that *N*-demethylation of oripavine using iron powder under Polonovski-type conditions is highly sensitive to a range of conditions including stoichiometry, temperature and the solvents used. In general, a lower level of iron is favourable with respect to the yield of *N*-nororipavine obtained. The reaction, when conducted in a binary solvent system consisting of chloroform and 2-propanol, also gave better yield of *N*-nororipavine compared to that employing 2-propanol alone as solvent. We have employed, for the first time, stainless steel as redox catalyst in *N*-demethylation. For a given set of reaction conditions, substituting stainless steel for iron powder has generally led to an improved yield of *N*-nororipavine obtained. Employing 50 mol% stainless steel 303-L powder in a 3 : 1 $CHCl_3$/*i*-PrOH solvent system under a range of temperatures (RT, 40 °C or 60 °C), we have consistently been able to achieve the synthesis of *N*-nororipavine from oripavine in about 80% yield. Under the same reaction conditions, more variable reaction outcomes of 65–76% of *N*-nororipavine were obtained when iron powder was employed as redox catalyst, with the best result achieved when the reaction was conducted at room temperature.

Acknowledgements

We gratefully acknowledge the ARC Centre for Free Radical Chemistry and Biotechnology for financial support.

References

1 B. Nielsen, J. Roe and E. Brochmann-Hanssen, *Planta Med.*, 1983, **48**, 205–206.
2 J. D. Andre, J. R. Dormoy and A. Heymes, *Synth. Commun.*, 1992, **22**, 2313–2173.
3 J. A. Lawson and J. I. Degraw, *J. Med. Chem.*, 1977, **20**, 165–166.
4 M. Hori, T. Kataoka, H. Shimizu, E. Imai, T. Iwamura, M. Nozaki, M. Niwa and H. Fujimura, *Chem. Pharm. Bull.*, 1984, **32**, 1268–1271.
5 A. Coop, J. W. Lewis and K. C. Rice, *J. Org. Chem.*, 1996, **61**, 6774.
6 A. Sipos, S. Berényi and S. Antus, *Helv. Chim. Acta*, 2009, **92**, 1359–1365.
7 S. Thavaneswaran, K. McCamley and P. J. Scammells, *Nat. Prod. Commun.*, 2006, **1**, 885–897.
8 J. von Braun, *Ber. Dtsch. Chem. Ges.*, 1900, **33**, 1438–1452.
9 J. H. Cooley and J. E. Evain, *Synthesis*, 1989, 1–7.
10 For example see: L. S. Schwab, *J. Med. Chem.*, 1980, **23**, 698–702.
11 J. A. Ripper, E. R. T. Tiekink and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 443–445.
12 K. Kieslich, Thieme: Suttgart, *Microbial Transformations of Non-Steroid Cyclic Compounds*, 1976, 213–215.
13 V. Chaudhary, A. Moudra, B. Allen, V. De Luca, D. P. Cox and T. Hudlicky, *Collect. Czech. Chem. Commun.*, 2009, **74**, 1179–1193.
14 R. J. Carroll, H. Leisch, E. Scocchera, T. Hudlicky and D. P. Cox, *Adv. Synth. Catal.*, 2008, **350**, 2984–2992.
15 (*a*) K. McCamley, J. A. Ripper, R. D. Singer and P. J. Scammells, *J. Org. Chem.*, 2003, **68**, 9847–9850; (*b*) S. Thavaneswaran and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2868–2871.
16 (*a*) Z. Dong and P. J. Scammells, *J. Org. Chem.*, 2007, **72**, 9881–9885; (*b*) G. B. Kok, T. D. Ashton and P. J. Scammells, *Adv. Synth. Catal.*, 2009, **351**, 283–286.
17 G. B. Kok and P. J. Scammells, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4499–4502.
18 G. B. Kok, C. C. Pye, R. D. Singer and P. J. Scammells, *J. Org. Chem.*, 2010, **75**, 4806–4811.
19 D. Grierson, *Org. React.*, 1990, **39**, 85–295.
20 C. R. Keenan and D. L. Sedlak, *Environ. Sci. Technol.*, 2008, **42**, 1262–1267.
21 M. Kallel, C. Belaid, T. Mechichi, M. Ksibi and B. Elleuch, *Chem. Eng. J.*, 2009, **150**, 391–395.
22 R. Boussahel, D. Harik, M. Mammar and S. Lamara-Mohamed, *Desalination*, 2007, **206**, 369–372.
23 J. A. Bergendahl and T. P. Thies, *Water Res.*, 2004, **38**, 327–334.
24 W. Wang, M. Zhou, Q. Mao, J. Yue and X. Wang, *Catal. Commun.*, 2010, **11**, 937–941.
25 A. Y. Ku and D. H. Freeman, *Anal. Chem.*, 1977, **49**, 1637–1638.