S. Afr. J. Chem., 2013, **66**, 113–116,
<http://journals.sabinet.co.za/sajchem/>.

One-pot, Facile Synthesis of Quinoxaline Derivatives from Bis-aryl α-Hydroxyketones and *o*-Arenediamines using $KMnO_4/CuSO_4$

Ahmad Khorramabadi-zad*, Mohammad Azadmanesh and Somaye Mohammadi

Faculty of Chemistry, Bu-Ali Sina University, Hamedan 65174, Iran.

Received 31 December 2012, revised 25 February 2013, accepted 17 April 2013.

ABSTRACT

$KMnO_4/CuSO_4$, a readily available reagent combination, was found to be effective for the high-yield synthesis of quinoxaline derivatives from bis-aryl α-hydroxyketones and *o*-arenediamines in hot ethanol.

KEYWORDS

Quinoxalines, bis-aryl α-hydroxyketone, oxidation, Lewis acids, $KMnO_4$, $CuSO_4$.

1. Introduction

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles in medicinal chemistry.[1–3] For example, quinoxalines are a part of various antibiotics such as echinomycin, leromycin and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumours.[4] In addition, they are well known for their application in dyes,[5] efficient electroluminescent materials,[6] organic semiconductors,[7] building blocks for the synthesis of anion receptors,[8] cavitands,[9] dehydroannulenes[10] and DNA cleaving agents.[11] Different methods for the preparation of quinoxaline derivatives have been published in the literature.[12] The general method for the synthesis of quinoxalines is the condensation of *o*-arenediamines with 1,2-dicarbonyl compounds in refluxing ethanol in the presence of acetic acid.[13] Improved methods have been reported using different catalysts, including I_2,[14–15] sulfamic acid,[16] Montmorillonite K-10,[17] polyaniline-sulfate salt[18] $H_6P_2W_{18}O_{62}.24H_2O$,[19] $InCl_3$,[20] $MnCl_2$,[21] $CuSO_4.5H_2O$,[22] Zn[(L)proline],[23] $Ga(OTf)_3$,[24] PEG-400,[25] keggin heteropoly acid,[26] IBX[27] and SBA-Pr-SO_3H[28] have been explored.

The above cited references mostly use 1,2-diketones as starting materials, which are themselves prepared from α-hydroxyketones. Therefore, a more appropriate protocol for the synthesis of quinoxalines would be the *in situ* oxidation of the latter. However, a survey of the literature shows that there are few reports concerning this strategy, utilizing for example the reagents CAN,[29,30] $Pd(OAc)_2$[31] and MnO_2.[32] Notably, each of these reagents has its own drawback, namely, CAN contains a heavy metal cation which is not environmentally friendly, the reaction time in the presence of $Pd(OAc)_2$ is about 24 hours and, in the case of MnO_2, which is commercially available, it needs to be activated (e.g. with KOH in methanol).[32]

According to a recently published review,[33] iron-exchanged molybdophosphoric acid,[34] manganese octahedral molecular sieves[35] and ruthenium on charcoal[36] (in the presence of randomly methylated cyclodextrin) have also been used for the synthesis of quinoxalines from α-hydroxyketones. However, catalysts or co-catalysts used in cited references are either expensive or have to be prepared by sophisticated methods.

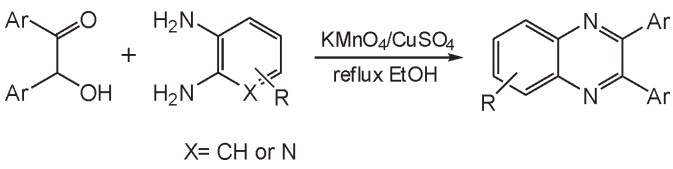
Hence, some of the synthesis protocols reported above suffer from one or more disadvantages, such as harsh reaction conditions, poor yields, prolonged reaction times, corrosive reagents, difficult work-ups and often expensive acid catalysts. On the other hand, a literature survey shows that $KMnO_4/CuSO_4$ mixture is a good choice for the oxidation of alcohols, oxidative coupling of primary aromatic amines, as well as conversion of aryl and alkyl sulfides into their corresponding sulfones.[37] Based on the above discussion therefore, it was decided to use $KMnO_4/CuSO_4$ for the preparation of substituted quinoxalines from bis-aryl α-hydroxyketones and *o*-arenediamines (Scheme 1).

2. Results and Discussion

As was mentioned above, the $KMnO_4/CuSO_4$ system may be used for the oxidation of bis-aryl α-hydroxyketones to bis-aryl diketones. In fact, control tests confirmed that the co-presence of $KMnO_4$ and $CuSO_4$ is necessary for the reaction to proceed. In our hands, when use was made of this mixture in hot EtOH media, a black precipitate of MnO_2 was generated *in situ* by the action of $KMnO_4$ on hot EtOH during the reaction. Formation of black precipitate of MnO_2 could be proved by qualitative tests. This freshly prepared and active MnO_2 is a mild oxidant which can easily oxidize benzylic hydroxyls into the corresponding carbonyl groups, for which three routes have been proposed.[38]

In conclusion, this is the first report in which use is made of a $KMnO_4/CuSO_4$ mixture for the one-pot, direct synthesis of quinoxaline derivatives from bis-aryl α-hydroxyketones. The advantages of this procedure, in addition to its being a one-pot reaction, are the use of a green solvent, a cheap and readily available oxidizing agent, and high product yields when starting from bis-aryl α-hydroxyketones.

In order to show the efficiency of the present method, a



Scheme 1
Synthesis of quinoxalines from bis-aryl α-hydroxyketones and *o*-arenediamines.

* To whom correspondence should be addressed. E-mail: khoram@gmail.com

Table 1 Comparison of the present procedure with the previously reported ones for the reaction of 2-hydroxy-1,2-diphenylethanone with aryl 1,2-diamine.

Entry	Oxidant or catalyst (condition)	Time/min	Yield/%	Ref.
1	$KMnO_4/CuSO_4$	110	92	Present method
2	TiO_2/TEMPO/Incandescent lamp	180	25	39
3	TiO_2/TEMPO/UV light	180	10	39
4	TiO_2/TEMPO/Microwave	10	87	39
5	AcOH reflux	120	96	40

comparison of reaction times and yields is provided in Table 1 for the preparation of substituted quinoxalines from bis-aryl α-hydroxyketones and aryl 1,2-diamine. As is seen in this table, the present method (entry 1) is superior to that of the other ones in terms of both reaction times and yields, with the additional advantage of being less expensive.

3. Experimental

Melting point apparatus Stuart model SMP3 was used for measuring melting points. IR spectra were recorded on a PerkinElmer series II spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a Bruker DRX-300 spectrometer at 300 and 75 MHz, respectively. All chemicals and solvents were purchased from Aldrich, Merck and Fluka, and were used as received. Melting points and spectral data of all products are fully consistent with those of the reported ones.

3.1. Preparation of $KMnO_4/CuSO_4$ Mixture

The optimized amounts of $KMnO_4$ and $CuSO_4$ i.e. 5 mmol and 1 mmol, respectively, were ground together in a mortar to obtain a purple powder.

3.2. General Procedure for the Synthesis of Quinoxalines

Bis-aryl α-hydroxyketone (1.0 mmol), aromatic *o*-arenediamine (1.0 mmol) and the mixture of $KMnO_4/CuSO_4$ (0.35 mmol) were stirred and heated at reflux in ethanol. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured in cold water (50 mL), the precipitated solid was filtered, washed several times with water, dried and recrystallized from ethanol. The products were characterized by spectral and physical data. The experimental results are summarized in Table 2.

3.3. Spectral Data of Quinoxaline Derivatives

2,3-Diphenylquinoxaline (**1**): δ_H ($CDCl_3$, 300 MHz): 7.35–7.37 (m, 6H), 7.56–7.59 (m, 4H), 7.74–7.77 (m, 2H), 8.20–8.23 (m, 2H); δ_C ($CDCl_3$, 75 MHz): 128.3, 128.9, 129.2, 129.9, 130.0, 139.1, 141.2, 153.5; IR (KBr, cm^{-1}): 3056, 1478, 1442, 1396, 1347, 1142, 1058, 978, 770, 697, 598, 539.

6-Methyl-2,3-diphenylquinoxaline (**2**): δ_H ($CDCl_3$, 300 MHz): 2.63 (3H, s), 7.36 (m, 6H), 7.53–7.55 (m, 4H), 7.60–7.63 (d, 1H), 7.98 (s, 1H), 8.08–8.11 (d, 1H); δ_C ($CDCl_3$, 75 MHz): 22.0, 128.0, 128.3, 128.7, 128.7, 129.9, 132.4, 139.2, 139.7, 140.6, 141.3, 152.6, 153.3; IR (KBr, cm^{-1}): 3083, 3054, 3026, 1619, 1484, 1445, 1345, 1201, 1138, 1060, 1023, 979, 833, 775, 703, 695, 595, 545.

6-Nitro-2,3-diphenylquinoxaline (**3**): δ_H ($CDCl_3$, 300 MHz): 7.35–7.46 (m, 6H), 7.56–7.59 (m, 4H), 8.26–8.29 (d, 1H), 8.47–8.51 (dd, 1H), 9.04–9.05 (d, 1H); δ_C ($CDCl_3$, 75 MHz): 123.3, 125.6, 128.5, 129.7, 129.8, 129.8, 129.9, 130.7, 137.9, 138.0, 139.9, 143.5, 147.8, 155.6, 156.3; IR (KBr, cm^{-1}): 3056, 1618, 1521, 1399, 1346, 1338, 1055, 1025, 979, 768, 743, 699, 598.

2,3-Diphenylpyrido[2,3-b]pyrazine (**4**): δ_H ($CDCl_3$, 300 MHz): 7.28–7.32 (t, 6H), 7.50–7.53 (d, 2H), 7.59–7.66 (m, 3H), 8.44–8.46 (d, 1H), 9.11 (s, 1H); δ_C ($CDCl_3$, 75 MHz): 125.2, 128.1, 128.4, 129.2, 129.4, 129.8, 130.2, 136.1, 138.0, 138.1, 138.5, 149.7, 153.9, 154.6, 156.2; IR (KBr, cm^{-1}): 3057, 1593, 1548, 1432, 1389, 1241, 1190, 1021, 974, 800, 781, 698, 612, 543.

(2,3-Diphenylquinoxalin-6-yl)(phenyl)methanone (**5**): δ_H ($CDCl_3$, 300 MHz): 7.28–7.30 (m, 6H), 7.44–7.53 (m, 7H), 7.86–7.88 (d, 2H), 8.19–8.21 (d, 2H), 8.50 (s, 1H); δ_C ($CDCl_3$, 75 MHz): 128.3, 128.5, 129.1, 129.3, 129.6, 129.9, 130.0, 130.1, 132.3, 132.7, 137.1, 138.2, 138.6, 138.6, 140.1, 142.8, 154.4, 154.9, 191.4; IR (KBr, cm^{-1}): 3057, 3035, 1733, 1660, 1598, 1446, 1402, 1346, 1309, 1265, 1198, 1124, 1057, 1022, 980, 890, 846, 770, 715, 696, 600, 542.

2,3-Bis(4-chlorophenyl)quinoxaline (**6**): δ_H ($CDCl_3$, 300 MHz): 7.32–7.34 (d, 4H), 7.45–7.48 (d, 4H), 7.75–7.78 (dd, 2H), 8.13–8.16 (dd, 2H); δ_C ($CDCl_3$, 75 MHz): 128.7, 129.1, 130.4, 131.2, 135.3, 137.2, 141.2, 151.8; IR (KBr, cm^{-1}): 3062, 1592, 1555, 1490, 1394, 1343, 1219, 1089, 1012, 976, 844, 830, 761, 588, 539, 461.

2,3-Bis(4-chlorophenyl)-6-methylquinoxaline (**7**): δ_H ($CDCl_3$, 300 MHz): 2.62 (s, 3H), 7.32–7.35 (d, 4H), 7.45–7.47 (d, 4H), 7.60–7.63 (d, 1H), 7.93 (s, 1H), 8.03–8.06 (d, 1H); δ_C ($CDCl_3$, 75 MHz): 21.9, 128.0, 128.7, 131.2, 132.7, 135.2, 135.2, 137.4, 139.7, 141.0, 141.2; IR (KBr, cm^{-1}): 3070, 2948, 1620, 1594, 1484, 1343, 1089, 1013, 978, 833, 729, 547.

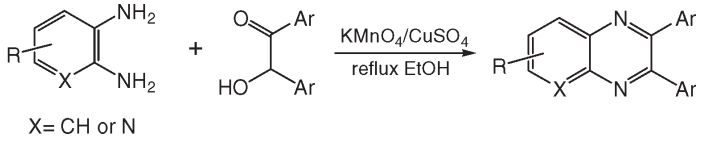
[2,3-Bis(4-chlorophenyl)quinoxalin-6-yl](phenyl)methanone (**8**): δ_H ($CDCl_3$, 300 MHz): 6.44–6.49 (m, 4H), 6.58–6.66 (m, 6H), 6.73–6.78 (m, 1H), 7.00–7.02 (d, 2H), 7.37 (s, 2H), 7.61 (s, 1H); δ_C ($CDCl_3$, 75 MHz): 123.8, 124.1, 124.9, 125.4, 125.5, 126.4, 126.5, 127.5, 128.2, 131.0, 131.1, 132.0, 132.2, 133.9, 135.4, 138.1, 148.3, 148.8, 190.8; IR (KBr, cm^{-1}): 3066, 1651, 1594, 1492, 1447, 1408, 1334, 1270, 1199, 1177, 1092, 1052, 978, 893, 833, 788, 594, 540, 483; MS (*m*/*z*): 454 (M^+).

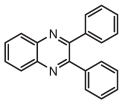
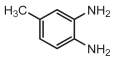
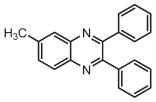
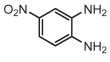
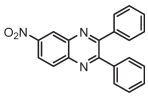
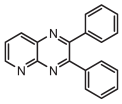
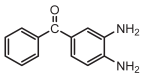
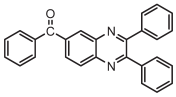
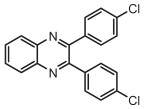
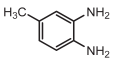
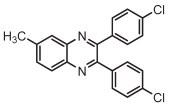
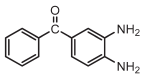
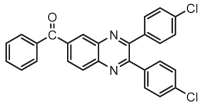
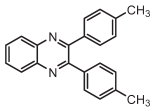
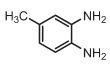
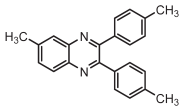
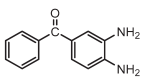
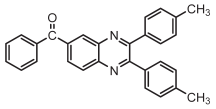
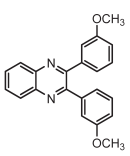
2,3-Di-p-tolylquinoxaline (**9**): δ_H ($CDCl_3$, 300 MHz): 2.39 (s, 6H), 7.16–7.18 (d, 4H), 7.45–7.47 (m, 4H), 7.76–7.77 (d, 2H), 8.19 (d, 2H); δ_C ($CDCl_3$, 75 MHz): 21.41, 129.0, 129.1, 129.8, 136.3, 138.8, 141.1, 153.5; IR (KBr, cm^{-1}): 3030, 2911, 1612, 1475, 1344, 1212, 1185, 1056, 1020, 977, 820, 762, 723, 595, 546,529.

6-Methyl-2,3-di-p-tolylquinoxaline (**10**): δ_H ($CDCl_3$, 300 MHz): 2.35 (s, 6H), 2.56 (s, 3H), 7.12–7.14 (d, 4H), 7.44–7.53 (m, 5H), 7.94 (s, 1H), 8.03–8.06 (d, 1H); δ_C ($CDCl_3$, 75 MHz): 21.4, 21.9, 127.9, 128.6, 129.0, 129.8, 129.8, 132.0, 136.5, 138.5, 138.6, 139.6, 140.1, 141.1, 152.5, 153.3; IR (KBr, cm^{-1}): 3026, 1610, 1512, 1484, 1394, 1342, 1203, 1055, 979, 818, 748, 588, 545, 505.

(2,3-Di-p-tolylquinoxalin-6-yl)(phenyl)methanone (**11**): δ_H ($CDCl_3$, 300 MHz): 7.10–7.15 (t, 4H), 7.43–7.48 (t, 6H), 7.56–7.61 (t, 1H), 7.89–7.91 (d, 2H), 8.23 (s, 2H), 8.51 (s, 1H); δ_C ($CDCl_3$, 75 MHz): 21.4, 21.5, 128.5, 129.1, 129.6, 129.7, 129.9, 130.2, 132.5, 132.7, 135.9, 135.9, 137.2, 137.9, 139.2, 139.4, 140.0, 142.9, 154.5, 155.1, 195.6; IR (KBr, cm^{-1}): 3033, 2917, 1665, 1610, 1579, 1454, 1398, 1305, 1182, 1053, 988, 882, 721, 704, 598, 548, 500.

Table 2 Synthesis of quinoxaline derivatives using bis-aryl α-hydroxyketones, different o-arenediamines and 35 mol% $KMnO_4/CuSO_4$ mixture.



Entry	Ar	Diamine	Product	Time/min	Yield/% [a]	M.p./°C (lit.)
1	phenyl			110	92	125–127 (128–129) [27]
2	phenyl			100	85	116–118 (117–118) [27]
3	phenyl			140	88	189–190 (193–194) [27]
4	phenyl			190	80	144–146 (141–142) [41]
5	phenyl			150	87	156–158 (139–140) [42]
6	4-chorophenyl			70	85	194–195 (195–196) [43]
7	4-chorophenyl			80	90	182–183 (180) [22]
8	4-chorophenyl			110	86	214–216
9	4-methylphenyl			130	91	148–149 (149–150)[40]
10	4-methylphenyl			90	86	132–133 (135–136) [42]
11	4-methylphenyl			150	83	190–192 [b]
12	3-methoxyphenyl			70	87	112–114 [c]

[a] Yields refer to isolated pure products.
[b,c] Melting points not reported (reference 14 and 44, respectively).

2,3-Bis(3-methoxyphenyl)quinoxaline (**12**): δ_H ($CDCl_3$, 300 MHz): 3.70 (s, 6H), 6.90–6.93 (dd, 2H), 7.10–7.13 (d, 4H), 7.21–7.27 (m, 2H), 7.73–7.76 (dd, 2H), 8.16–8.20 (dd, 2H); δ_C ($CDCl_3$, 75 MHz): 55.2, 114.8, 115.2, 122.4, 129.2, 129.4, 130.1, 140.3, 141.1, 153.2, 159.4; IR (KBr, cm^{-1}): 3053, 2945, 1608, 1579, 1452, 1430, 1291, 1234, 1042, 997, 868, 790, 755, 585.

Acknowledgements

We gratefully acknowledge the support of this work by the Research Council of Bu-Ali Sina University.

References

1 A. Jaso, B. Zarranz, I. Aldana and A. Monge, *J. Med. Chem.*, 2005, **48**, 2019–2025.
2 A. Dell, D.H. William, H.R. Morris, G.A. Smith, J. Feeney and G.C.K. Roberts, *J. Am. Chem. Soc.*, 1975, **97**, 2497–2502.
3 C. Bailly, S. Echepare, F. Gago and M.J. Waring, *Anti-Cancer Drug Des.*, 1999, **14**, 291.
4 S. Sato, O. Shiratori and K. Katagiri, *J. Antibiot.*, 1967, **20**, 270.
5 N.D. Sonawane and D.W. Rangnekar, *J. Heterocycl. Chem.*, 2002, **39**, 303–308.
6 K.R. Justin Thomas, V. Marappan, T.L. Jiann, C. Chang-Hao and T. Yu-ai, *Chem. Mater.*, 2005, **17**, 1860–1866.
7 S. Dailey, J.W. Feast, R.J. Peace, R.C. Saga, S. Till and E.L. Wood, *J. Mater. Chem.*, 2001, **11**, 2238–2243.
8 L.S. Jonathan, M. Hiromitsu, M. Toshihisa, M.L. Vincent and F. Hiroyuki, *Chem. Commun.*, 2002, 862–863.
9 P.C. Peter, Z. Gang, A.M. Grace, H. Carlos and M.G.T. Linda, *Org. Lett.*, 2004, **6**, 333–336.
10 O. Sascha and F. Rudiger, *Synlett*, 2004, 1509–1512.
11 L.S. Hegedus, M.G. Marc, J.W. Jory and P.B. Joseph, *J. Org. Chem.*, 2003, **68**, 4179–4188.
12 A.E.A. Porter, A.R. Katritsky and C.W. Rees, in *Comprehensive Heterocyclic Chemistry*, Pergamon, Oxford, 1984.
13 J.D. Brown, in *The Chemistry of Heterocyclic Compounds: Quinoxalines, Supplement II,* (C.E. Taylor and P. Wipf), John Wiley and Sons, New Jersey, 2004.
14 R.S. Bhosale, S.R. Sarda, S.S. Ardhapure, W.N. Jadhav, S.R. Bhusare and R.P. Pawar, *Tetrahedron Lett.*, 2005, **46**, 7183–7186.
15 S.V. More, M.N.V. Sastry, C.C. Wang and C.F. Yao, *Tetrahedron Lett.*, 2005, **46**, 6345–6348.
16 H.R. Darabi, S. Mohandessi, K. Aghapoor and F. Mohsenzadeh, *Catal. Commun.*, 2007, **8**, 389–392.
17 T.K. Huang, R. Wang, L. Shi and X.X. Lu, *Catal. Commun.*, 2008, **9**, 1143–1147.
18 C. Srinivas, C.N.S.S.P. Kumar, V. Jayathirtha Rao and S. Palaniappan, *J. Mol. Catal. A: Chem.*, 2007, **265**, 227–230.
19 M.M. Heravi, K. Bakhtiari, F.F. Bamoharram and M.H. Tehrani, *Monatsh. Chem.*, 2007, **138**, 465–467.
20 P. Hazarika, P. Gogoi and D. Konwar, *Synth. Commun.*, 2007, **37**, 3447–3454.
21 M.M. Heravi, K. Bakhtiari, H.A. Oskooie and S. Taheri, *Heteroat. Chem.*, 2008, **19**, 218–220.
22 M.M. Heravi, S. Taheri, K. Bakhtiari and H.A. Oskooie, *Catal. Commun.*, 2007, **8**, 211–214.
23 M.M. Heravi, M.H. Tehrani, K. Bakhtiari and H.A. Oskooie, *Catal. Commun.*, 2007, **8**, 1341–1344.
24 J.-J. Cai, J.-P. Zou, X.-Q. Pan and W. Zhang, *Tetrahedron Lett.*, 2008, **49**, 7386–7390.
25 X.Z. Zhang, J.X. Wang, Y.J. Sun and H.W. Zhan, *Chin. Chem. Lett.*, 2010, **21**, 395–398.
26 T.-K. Huang, L. Shi, R. Wang, X.-Z. Guo and X.-X. Lu, *Chin. Chem. Lett.*, 2009, **20**, 161–164.
27 M.M. Heravi, K. Bakhtiari, M.H. Tehrani, N.M. Javadi and H.A. Oskooie, *ARKIVOC*, 2006, **xvi**, 16–22.
28 G. Mohammadi Ziarani, A. Badiei and M. Haddadpour, *Int. J. Chem.*, 2011, **3**, 87–94.
29 S.V. More, M.N.V. Sastry and C.F. Yao, *Green Chem.*, 2006, **8**, 91–95.
30 A. Shaabani and A. Maleki, *Chem. Pharm. Bull.*, 2008, **56**, 79–81.
31 R.S. Robinson and R.J.K. Taylor, *Synlett*, 2005, 1003–1005
32 S.A. Raw, C.D. Wilfred and R.J.K. Taylor, *Chem. Commun.*, 2003, 2286–2287.
33 Y.V.D. Nageswar, K. Harsha Vardhan Reddy, K. Ramesh and S. Narayana Murthy, *Org. Prep. Proced. Int.*, 2013, **45**, 1–27.
34 K.T.V. Rao, P.S.S. Prasad and N. Lingaiah, *J. Mol. Catal A: Chem.*, 2009, **312**, 65–69.
35 S. Sithambaram, Y. Ding, W. Li, X. Shen, F. Gaenzler and S.L. Suiib, *Green Chem.*, 2008, **10**, 1029–1032.
36 A.V. Kumar, V.P. Reddy and K.R. Rao, *Synlett*, 2010, **17**, 2571–2574.
37 A. Shaabani and D.G. Lee, *Tetrahedron Lett.*, 2001, **42**, 5833–5836.
38 G. Tojo, M.I. Fernàndez and M. Fernàndez, *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice* (*Basic Reactions in Organic Synthesis*), 2005.
39 V. Jeena and R.S. Robinson, *Beilstein J. Org. Chem.*, 2009, **5**, 1–4.
40 M.R. Islami and Z. Hassani, *ARKIVOC*, 2008, **15**, 280–287.
41 H.I.X. Mager and W. Berends, *Rec. Trav. Chim.*, 1965, **84**, 314.
42 W.X. Guo, H.L. Jin, J.-X. Chen, F. Chen, J.-C. Ding and H.-Y. Wu, *J. Braz. Chem. Soc.*, 2009, **20**, 1674–1679.
43 K. Niknam, D. Saberi and M. Mohagheghnejad, *Mol. Cells*, 2009, **14**, 1915–1926.
44 J. Ji and K.-I. Lee, *J. Korean Chem. Soc.*, 2005, **49**, 150–154.