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Efficient synthesis of isoxazoles and isoxazolines from aldoximes using Magtrieve™ (CrO_2)

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ABSTRACT

Treatment of aldoximes **1** with Magtrieve™ (CrO_2) in presence of dipolarophile **3** or **4**, furnished a variety of isoxazolines **5a–u** and isoxazoles **6a–q** as 1,3-dipolar cycloaddition (1,3-DC) products (38 examples; 63–90% isolated yields). In situ formation of a nitrile oxide intermediate was confirmed through isolation of the dimerization product furoxane **2a** in absence of any dipolarophile. The methodology has been extended to intramolecular nitrile oxide cycloaddition (INOC) reactions to access highly useful chromane derivatives **7–8** (75–80% isolated yields). Magtrieve™, as a new reagent for 1,3-DC reactions, has offered excellent substrate generality and at the same time demonstrated tolerance toward sensitive protecting groups and electron-rich functional groups.

Isoxazoles and isoxazolines are very useful heterocycles[1] in organic and medicinal chemistry.[2a–e] Isoxazoline rings have been used by organic chemists for synthetic manipulation to access complex molecular architectures.[1b] Drugs such as Isocarboxazid, Valdecoxib, Oxacillin, Leflunomide, and Micafungin are the examples[2f] to substantiate the pharmaceutical acceptance of such heterocyclic systems. When suitably crafted within a small molecule, these scaffolds have been often conceived as stable amide surrogates.[3] Hence, new synthetic methodologies to construct these heterocycles with varieties of substitutions are highly desired.

The most convenient synthesis of isoxazoline and isoxazole ring systems has been executed in the literature via 1,3-dipolar cycloaddition (1,3-DC) reactions[4] of alkenes or alkynes with nitrile oxides,[5] generated in situ from aldoximes. Two different classes of reagents have been used in the literature for the conversion of aldoximes to nitrile oxides: (i) halogenating agents[6] or hypervalent iodine[7] to produce hydroximoyl halides or equivalent molecule as the reactive intermediates, and (ii) direct oxidizing agents[8] such as $K_3[Fe(CN)_6]$, Ceric ammonium nitrate (CAN), $Pb(OAc)_4$, and MnO_2. Use of MnO_2[8b] has offered advantages over many other choices mainly because of two reasons: (a) avoidance of additional base treatment that is required in the case of conventional halogenating agents and (b) mild reaction conditions compared to other direct oxidizing agents. However, the MnO_2 methodology has been essentially limited to aldoximes bearing strong electron-withdrawing groups such as carboxylate. In addition, only moderate yields of cycloaddition products along with the formation of significant amount of corresponding aldehydes have been reported for aromatic aldoximes. Moreover, aliphatic aldoximes were found to be very poor substrates for that matter.

Recently we discovered Magtrieve™ (CrO_2)[9] as a very efficient reagent for the oxidation of aldoximes to nitrile oxides. Subsequently, a structurally diverse set of isoxazoline and isoxazole ring systems were synthesized in high yields by reacting varieties of aldoximes and dipolarophiles in presence of Magtrieve™. A preliminary account of this methodology is being reported in this Letter.

Potential of CrO_2 for the oxidation of aldoximes to nitrile oxides was studied initially with 4-chlorobenzaldehyde oxime, **1a**, chosen as a model substrate. Using 10 mol equiv of CrO_2, several reaction conditions were scanned such as (a) dichloromethane at rt, (b) chloroform at 65 °C, (c) MeCN at 80 °C, and (d) toluene at 80 °C. It was found that the starting material **1a** disappeared after 2 h when heated at 80 °C in MeCN or toluene solvent, and it led to the formation of corresponding furoxane **2a** (dimerization product of in situ formed nitrile oxide) as a major product along with a trace amount (less than 10%) of 4-chlorobenzaldehyde as deoximation product (Scheme 1, Path-A). As reported in the literature, treatment of **1a** with excess MnO_2 (added in batches) led to a very sluggish reaction in dichloromethane at rt.[8bi] When the same reaction was carried out in chloroform at 65 °C, it resulted in almost equal distribution of **1a**, **2a**, and the deoximation product after 6 h. Interestingly, excess MnO_2 in toluene at 80 °C led to disappearance of the starting material within 2 h leading to the formation of 4-chlorobenzaldehyde as major product along with a minor amount of **2a** (Scheme 1, Path-B). The above observations prompted us to explore the potential use of Magtrieve™ for the synthesis of isoxazoline and isoxazole ring systems via 1,3-DC reactions.

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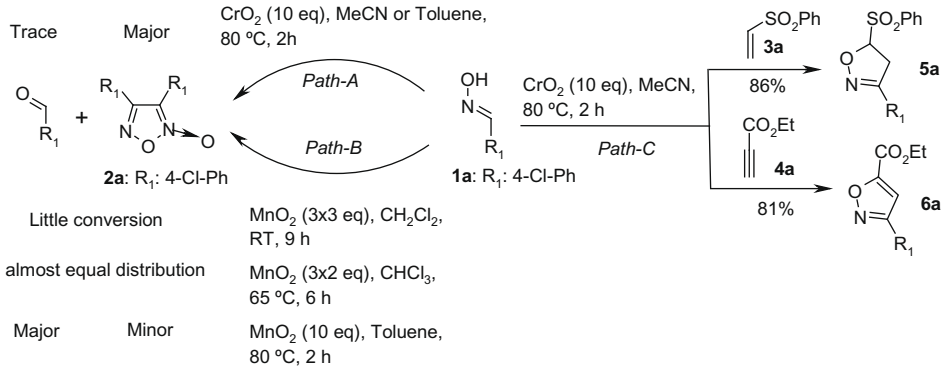
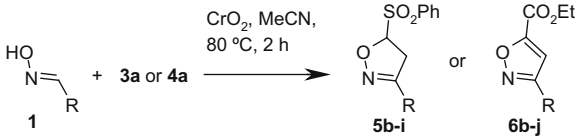


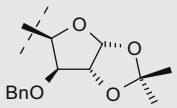
Scheme 1. Fate of aldoxime **1a** when treated with CrO_2 in presence or absence of dipolarophiles.

To execute 1,3-DC reactions, adoxime **1a** was treated with dipolarophiles **3a** and **4a** separately in presence of 10 mol equiv of CrO_2 in either toluene or MeCN at 80 °C for 2 h. The desired products **5a** and **6a** were obtained in high yields (Scheme 1, Path-C) along with minor amount of deoximation product in each case. An attempt to accomplish these reactions by using 5 mol equiv of CrO_2 led to incomplete reactions even after 6 h.

Following the typical procedure described for **5a** and **6a**, the present methodology was elaborated to a variety of aldoximes **1** and various choices of alkenes **3** or alkynes **4**. These reactions were carried out using stoichiometric amounts of aldoximes and dipolarophiles, except in the case of volatile substrates (3 equiv excess used). The corresponding cycloaddition products **5b–u** and **6b–q** were obtained in high yields after column or preparative thin layer chromatography (Table 1 and 2 and Fig. 1). While the aromatic and heteroaromatic aldoximes led to higher yields of cycloaddition products (80–90%), relatively less yields were obtained from the aliphatic aldoximes (e.g., **5g–i**, **5u** and **6g–j**: 63–78%) due to the formation of 15–25% of deoximation products. The regiochemistry of cycloaddition products **5** and **6** was established based on ^1H NMR analysis and literature precedence available for this class of compounds. Small amounts of other regioisomers (less than 10%) were also obtained in the case of **5e–i**, **5k**, **5q**, and **6g–i**.

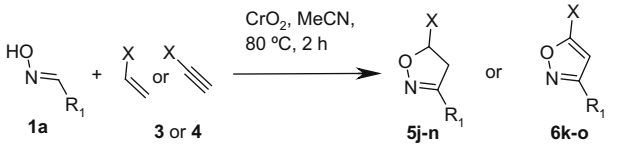
Table 1
Synthesis of isoxazolines **5b–i** and isoxazoles **6b–j** from various aldoximes **1** and respective 1,3-dipolarophile **3a** or **4a**



1	R	Description	5[a] (% yield)	6[a] (% yield)
1b	R_2	4-Br–Ph–	**5b** (85)	**6b** (83)
1c	R_3	Thiophen-2-yl–	**5c** (80)	**6c** (78)
1d	R_4	Pyridin-2-yl–	**5d** (83)	**6d** (85)
1e	R_5	4-(MeS)–Ph–	**5e** (82)	**6e** (87)
1f	R_6	4-(MeO)–Ph–	**5f** (84)	**6f** (80)
1g[b]	R_7	2-Phenylethyl–	**5g** (70)	**6g** (68)
1h[b]	R_8	2-Methylpropyl–	**5h** (67)	**6h** (65)
1i[b]	R_9	Cyclohexyl–	**5i** (65)	**6i** (63)
1j[b]	R_{10}			**6j** (75)

[a] Major regioisomer formed.
[b] ~60:40 mixture of *E* and *Z* isomers used.

Table 2
Synthesis of isoxazolines **5j–n** and isoxazoles **6k–o** from **1a** and various alkenes **3** or alkynes **4**



3	X	5[a] (% yield)	4	X	6[a] (% yield)
3b	Ph–	**5j** (82)	**4b**	Ph–	**6k** (85)
3c	$-CO_2Et$	**5k** (80)	**4c**	$-CH_2-OTBS$	**6l** (80)
3d	–CN	**5l** (84)	**4d**	$-CH_2-OTHP$	**6m** (80)
3e	–Bn	**5m** (89)	**4e**	$-CH_2N(H)Boc$	**6n** (85)
3f	AcO–	**5n** (88)	**4f**	TMS–	**6o** (86)

[a] Major regioisomer formed.

Substrate generality of the present methodology was further established through the construction of trisubstituted ring systems (e.g., **5p–t** and **6p–q**). Chosen examples with commonly used protecting groups, for example, –OTBS, –OTHP, –N(H)Boc, –TMS, and acetonide (e.g., **6l–o**, **6j**, and **5u**), as well as cases with electron-rich

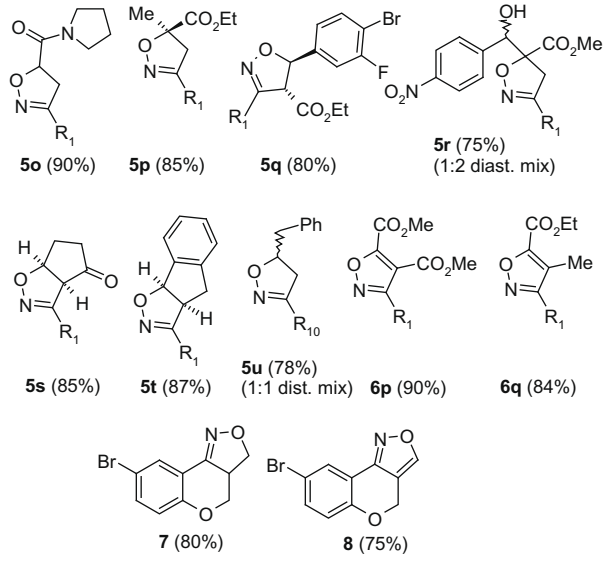


Figure 1. Additional examples of isoxazoles and isoxazolines synthesized using Magtrieve™ methodology.

groups, for example, **5c–e** and **6c–e** further proved the mildness of the method.

When compared to MnO_2, Magtrieve™ showed clear advantages in (i) overcoming the substrate limitation (ii) avoiding inconvenience that is caused by successive addition of reagent, and of course longer reaction time, (iii) controlling the formation of deoximation product. In addition to above advantages, CrO_2 did not lead to overoxidation of isoxazolines to isoxazoles which otherwise was reported[10] for MnO_2 at higher temperature. Therefore, it is evident that Magtrieve™ has clearly overcome the limitations of MnO_2 as reagent for 1,3-DC reactions.

In some instances, Magtrieve™ was found to be more efficient than previously known halogenating or equivalent reagents. For example, the synthesis of **5r** needed overnight reaction when NaOCl was used[11] as reagent whereas CrO_2 treatment required only 2 h. In addition, NaOCl was found to be a very poor reagent for S-containing substrates **1c** and **1e** leading to intractable reaction mixtures whereas CrO_2 led to smooth reactions. Similarly, use of *N*-chlorosuccinimide (NCS) and a recently reported hypervalent iodine reagent di-acetoxyiodobenzene (DIB) provided only modest yields of cycloaddition products from (*p*-thiomethyl)benzaldoxime **1e**. On the other hand, the examples with thiophene compounds **5c** and **6c** in the present study suggested that Magtrieve™ would be the choice for substrates that were reported to be sensitive for partial aromatic halogenation when Cl_2, NCS, or *N*-bromosuccinimide (NBS) was used as reagent.[6d]

Intramolecular nitrile oxide cycloaddition (INOC) is a powerful tool to construct often complex chemical structures.[12] Robustness of the current methodology was further established by accomplishing such reactions by treatment of oximes derived from 2-allyloxy-5-bromobenzaldehyde and 2-propargyloxy-5-bromobenzaldehyde with Magtrieve™. Corresponding chromane derivatives **7–8**[13] (Fig. 1) were obtained as intramolecular cycloaddition products in high yields (see the typical procedure for the synthesis of **7**).

It has been reported in the literature that only (*E*)-aldoximes could be oxidized to nitrile oxides when treated with $Pb(OAc)_4$.[8a] On the other hand, MnO_2 has been shown to produce nitrile oxides from both (*E*)-aldoximes and (*Z*)-aldoximes.[8bi] In the present work high yields of cycloaddition products, obtained from the mixture of (*E*)- and (*Z*)-aliphatic oximes **1g–j**, indicated that both the regioisomers were oxidized to nitrile oxides. Based on the above observation, a plausible mechanism can be invoked for CrO_2-mediated oxidation of aldoximes to nitrile oxides following Kiegiel's proposal.[8bi] Since the formation of aldehydes was found to be significantly less under CrO_2 treatment than under MnO_2, a separate mechanistic study of CrO_2-mediated oxidation of aldoximes has been undertaken in our laboratory and the results will be reported in due course.

In conclusion, Magtrieve™ (CrO_2) has been proven to be an efficient reagent for direct oxidation of variety of aldoximes to nitrile oxides in situ. Using Magtrieve™, this Letter has revealed a new procedure for 1,3-DC reactions, and also first time comprehensive methodology to access both isoxazoline and isoxazole heterocycles. Methodology offered excellent substrate generality and at the same time demonstrated tolerance toward various protecting groups and electron-rich functional groups. The methodology has been shown to be equally versatile for intramolecular nitrile oxide cycloaddition (INOC) reactions. Hence, the current method should be the choice for direct oxidation of oximes to nitrile oxides which are useful intermediates in the organic synthesis.

Typical synthesis of **5a**:[14a] Phenyl vinyl sulfone (100 mg, 0.59 mmol, 1.0 equiv) and 4-chlorobenzaldoxime (110 mg, 0.71 mmol, 1.2 equiv) were dissolved in 3 mL acetonitrile. Magtrieve™ (Aldrich cat. No. 480037; CAS No. 12018-01-8; 500 mg, 5.95 mmol, 10 equiv) was added and the reaction mixture was stirred under heating at 80 °C for 2 h. The reaction mixture was filtered through Celite bed. Magtrieve™ was washed with ethyl acetate (20 ml × 2). The combined filtrate was condensed to give the crude product, which was purified by silica gel prep. TLC (20% ethyl acetate in hexanes) to obtain **5a** (163 mg, 86%). R_f-value: 0.4 (20% ethyl acetate in hexanes). Mp: 142–144 °C. ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.81 (dd, J = 18.3, 10.8 Hz, 1H); 4.08 (dd, J = 18.3, 4.5 Hz, 1H); 5.59 (dd, J = 10.8, 4.5 Hz, 1H); 7.42 (d, J = 8.6 Hz, 2H); 7.58 (d, J = 8.6 Hz, 2H); 7.63 (t, J = 7.6 Hz, 2H); 7.73 (t, J = 7.5 Hz, 1H); 8.03 (d, J = 7.7 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 36.46, 93.13, 125.58, 128.12 (2C), 129.01(2C), 129.12(2C), 129.54(2C), 134.51, 134.86, 137.03, 155.88. LC–MS (*m/z*): 322 [M(^{35}Cl)+1], 339 [M(^{35}Cl)+18] base peak. HPLC purity: 98.4%.

Typical synthesis of **6a**:[14b] Using 4-chlorobenzaldoxime (100 mg, 0.64 mmol, 1 equiv), ethyl propiolate (190 mg, 1.93 mmol, 3.0 equiv), and 10 equiv of Magtrieve™ in 3.2 mL acetonitrile, the reaction was carried out as described for **5a** to obtain the desired product **6a** (130 mg, 81%). R_f-value: 0.7 (20% ethyl acetate in hexanes). Mp: 136–138 °C (lit.[14b] 136–138 °C). ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.47 (t, J = 7.1 Hz, 3H); 4.49 (q, J = 7.1 Hz, 2H); 7.25 (s, 1H); 7.49 (d, J = 8.4 Hz, 2H); 7.81 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 13.94, 62.23, 106.95, 126.24, 127.90 (2C), 129.18 (2C), 136.46, 156.44, 160.97, 161.77. LC–MS (*m/z*): 252 [M(^{35}Cl) +1] base peak, 269 [M(^{35}Cl)+18]. HPLC purity: 99%.

Typical synthesis of **7**:[14c] Using 2-allyloxy-5-bromobenzaldehyde oxime (400 mg, 1.56 mmol, 1.0 equiv) and Magtrieve™ (1.31 g, 15.6 mmol, 10 equiv) in MeCN (8 mL), the reaction was carried out as described for **5a** to obtain the desired product **7** (320 mg, 80%) after silica gel column chromatography (5–20% ethyl acetate in hexanes). R_f-value: 0.3 (20% ethyl acetate in hexanes). Mp: 108–109 °C. ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.88–4.02 (m, 2H); 4.07–4.14 (m, 1H); 4.71–4.78 (m, 2H); 6.88 (d, J = 8.8 Hz, 1H); 7.45 (dd, J = 8.8, 1.76 Hz, 1H); 7.95 (d, J = 1.76 Hz, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 45.10, 69.08, 70.63, 113.85, 114.48, 119.06, 127.69, 134.89, 151.51, 154.24. LC–MS (*m/z*): 254 [M(^{79}Br)+1] base peak., 256 [M(^{81}Br)+1]. HPLC purity: 98%.

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Supplementary data

Supplementary data (spectral characterization data of **5b–u**, **6b–q**, and **8**) associated with this paper can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.073.

References and notes

1. (a) Grűnanger, P.; Vita-Finzi, P. I.. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; John Wiley & Sons: New York, 1991; Vol. 49, (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410–416.
2. For examples of isoxazole- and isoxazoline-based compounds in medicinal chemistry, see: (a) Williams, M.; Kowaluk, E. A.; Arneric, S. P. *J. Med. Chem.* **1999**, *42*, 1481–1500; (b) Pitts, W. J.; Wityak, J.; Smallheer, J. M.; Tobin, A. E.; Jetter, J. W.; Buynitsky, J. S.; Harlow, P. P.; Solomon, K. A.; Corjay, M. H.; Mousa, S. A.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 27–40; (c) Sielecki, T. M.; Liu, J.; Mousa, S. A.; Racanelli, A. L.; Hausner, E. A.; Wexler, R. R.; Olson, R. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2201–2204; (d) Chambers, M. S.; Atack, J. R.; Carling, R. W.; Collinson, N.; Cook, S. M.; Dawson, G. R.; Ferris, P.; Hobbs, S. C.; O'Connor, D.; Marshall, G.; Rycroft, W.; MacLeod, A. M. *J. Med. Chem.* **2004**, *47*, 5829–5832; (e) Albrecht, B. K.; Berry, V.; Boezio, A. A.; Cao, L.; Clarkin, K.; Guo, W.; Harmange, J-C.; Hierl, M.; Huang, L.; Janosky, B.; Knop, J.; Malmberg, A.; McDermott, J. S.; Nguyen, H. Q.; Springer, S. K.; Waldon, D.; Woodin, K.; McDonough, S. I. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5209–5212; f To see first hand information about the approved drugs, Isocarboxazid, Valdecoxib, Oxacillin, Leflunomide, Micafungin, see free web site: www.wikipedia.org.

3. (a) Kim, B. H.; Chung, Y. J.; Keum, G.; Kim, J.; Kim, K. *Tetrahedron Lett.* **1992**, *33*, 6811–6814; (b) Venkatesan, N.; Kim, B. H. *Curr. Med. Chem.* **2002**, *9*, 2243–2270; (c) Ahn, J-M.; Boyle, N. A.; MacDonald, M. T.; Janda, K. D. *Mini Rev.Med. Chem* **2002**, *2*, 463–473; (d) Renslo, A. R.; Luehr, G. W.; Gordeev, M. F. *Bioorg. Med. Chem.* **2006**, *14*, 4227–4240.
4. For 1,3-dipolar cycloaddition (1,3-DC) reactions, in general, see: (a) Padwa, A.. In *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. ; (b) Nguyen, M. T.; Chandra, A. K.; Sakai, S.; Morokuma, K. *J. Org. Chem.* **1999**, *64*, 65–69; (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909; (d) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887–2902.
5. For nitrile oxide and 1,3-DC reactions, see: (a) Grundmann, C. *Synthesis* **1970**, 344–359; (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988; (c) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719–736.
6. For aldoximes to nitrile oxides via hydroximoyl halides, see: (a) Larsen, K. E.; Torssell, K. B. G. *Tetrahedron* **1984**, *40*, 2985–2988; (b) Kim, J. N.; Ryu, E. K. *Synth. Commun.* **1990**, *20*, 1373–1377; (c) Syassi, B.; Bakkali, B. E.; Benabdellah, G. A.; Hassikou, A.; Dinia, M. N.; Rivière, M.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **1999**, *40*, 7205–7209; (d) Sammelson, R. E.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 2225–2228; (e) Rodrigues, R. C.; Aguiar, A. P. *Synth. Commun.* **2001**, *31*, 3075–3080; (f) Toker, J. D.; Tremblay, M. R.; Yli-Kauhaluoma, J.; Wentworth, A. D.; Zhou, B.; Wentworth, P. Jr.; Janda, K. D. *J. Org. Chem.* **2005**, *70*, 7810–7815; (g) Rai, K. M. L.; Hassner, A. *Synth. Commun* **1997**, *27*, 467–472. and references cited herein; (h) Kumar, V.; Kaushik, M. P. *Tetrahedron Lett.* **2006**, *47*, 1457–1460. and references cited herein.
7. For aldoximes to nitrile oxides using hypervalent iodine reagent diacetoxybenzene (DIB), see: (a) Das, B.; Holla, H.; Mahender, G.; Banerjee, J.; Reddy, M. R. *Tetrahedron Lett.* **2004**, *45*, 7347–7350; (b) Prakash, O.; Pannu, K. *ARKIVOC* **2007**, *xiii*, 28–33; (c) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539–1542.
8. For direct oxidation of aldoximes to nitrile oxides, see: Using $Pb(OAc)_4$: (a) Just, G.; Dahl, K. *Tetrahedron* **1968**, *24*, 5251–5269; Using MnO_2: (i) (b) Kiegiel, J.; Poplawska, M.; Jóźwik, J.; Kosior, M.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 5605–5608. and reference cited herein for other previously reported reagents for direct oxidation. (ii) Kudyba, I.; Jóźwik, J.; Romanski, J.; Raczko, J.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2257–2262.
9. For literature and synthetic applications of Magtrieve™ (CrO_2) see: (a) Liu, Y.-H. *Synlett* **2008**, 1103–1104. and references cited herein; (b) Liao, Y.; Shabany, H.; Spilling, C. D. *Tetrahedron Lett.* **1998**, *39*, 8389–8392; (c) Contour-Galcéra, M.-O.; Piotout, L.; Moinet, C.; Morgan, B.; Gordon, T.; Roubert, P.; Thurieau, C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 741–745; (d) Wan, H.; Peng, Y. *Monatsh Chem.* **2008**, *139*, 909–912.
10. Barco, A.; Benetti, S.; Pollini, G. P. *Synthesis* **1977**, 837.
11. This is in agreement with the literature report for **5r**-like compounds prepared in an overnight reaction using NaOCl procedure: Sammelson, R. E.; Gurusinghe, C. D.; Kurth, J. M.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 876–882.
12. (a) Beebe, X.; Chiappari, C. L.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1993**, *58*, 7320–7321; (b) Yip, C.; Handerson, S.; Jordan, R.; Tam, W. *Org. Lett.* **1999**, *1*, 791–794; (c) Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2001**, *3*, 2575–2578; (d) Shing, T. K. M.; Wong, W. F.; Cheng, H. M.; Kwok, W. S.; So, K. H. *Org. Lett.* **2007**, *9*, 753–756.
13. For similar compounds, see: (a) Lee, G. A. *Synthesis* **1982**, 508–509; (b) Vaidya, V. V.; Wankhede, K. S.; Salunkhe, M. M.; Trivedi, G. K. *Synth. Commun.* **2008**, *38*, 2392–2403; (c) Hassner, A.; Rai, K. M. L. *Synthesis* **1989**, 57–59.
14. (a) For des-Cl **5a**: see Ref. 6g.; (b) For **6a**, see: Wang, Y.-G.; Xu , W.-M.; Huang, X.; *Synthesis* **2007** 28–32; (c) For des-Br **7**: see Ref. 13c.