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SHORT COMMUNICATION

Selective synthesis of *E*-isomers of aldoximes via a domino aza-Michael/retro-Michael reaction

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A highly stereoselective synthesis of *E*-isomer of aldoximes was developed through a base-catalysed domino aza-Michael/retro-Michael reaction of hydroxylamine and 2-(R-benzylidene)malononitrile. This reaction generates (*E*)-aldoxime diastereomer in high yields (eight examples, isolated yields of 82–93 %), excellent diastereomeric purity (diastereomeric ratio higher than 95 : 5 by ^{1}H NMR), and proceeds under mild reaction conditions (aqueous NaOH, pH 12, room temperature, 4 h).

Keywords: isomer, aldoxime, hydroxylamine, 2-benzylidenemalononitrile

Oxime compounds frequently exhibit satisfactory insecticidal, fungicidal, or herbicidal activity. A recent study of molecular design, synthesis, and biological activity of oxime compounds has attracted a great deal of attention (Song et al., 2005). The addition of hydroxylamine to aromatic aldehyde to yield aldoximes is not only one of the best understood examples of a non-enzymatic addition-elimination reaction (Jencks, 1959), but also an important reaction in organic synthesis (Sandler & Karo, 1983). Two isomeric aldoximes (*Z* and *E*) are usually produced with different physical properties and biological activities and which should be separated by chromatography or recrystallisation. The classical methods of the synthesis of aldoximes usually give a mixture of the two geometric isomers (*Z* : *E* ratio of 85 : 15 to 1 : 1) (Sharghi & Hosseini, 2002; Sharghi & Sarvari, 2001; Guo et al., 2001).

Very few methods are available for the synthesis of exclusively *E*-isomer of aldoximes (Zvilichovsky & Heller, 1972; Uno et al., 1994). In many cases, *E*-isomers have been obtained from the *Z* forms by the hydrochloride method or by purification by column chromatography (Furniss et al., 1989). The reagents which have been used for the oximation of aldehydes also catalyse the inter-conversion of *Z*/*E*-isomers. The rate of equilibration of a mixture of *Z*/*E*-isomers and the position of the equilibrium is temperature-dependent (Smith & Antoniades, 1960). Recently, considerable attention has been paid to a selective synthesis of *E*- and *Z*-isomers of oximes (Sharghi & Sarvari, 2001). However, isolation of the (*E*)-oxime using the methodology described is not practical, as it must be carried out at 0 ℃ to prevent formation of the *Z*-diastereomer. These classical methods are dependent on temperature or acidic conditions hence are not practical for process-scale synthesis. Although our method requires an additional step, it effectively delivers the desired (*E*)-aldoximes under alkaline conditions at room temperature, providing a selective synthesis of (*E*)-aldoximes for acid-sensitive substrates.

Aldoxime formation proceeds through the formation of a tetrahedral intermediate followed by an acid-catalysed dehydration step (Uno et al., 1994). The formation of a mixture of isomers (*Z* and *E*) suggests an E1 elimination of water and a proton (Bruckner, 2002). We recently reported that the electron-deficient α,α-dicyanoalkenes could act as versatile direct viny-

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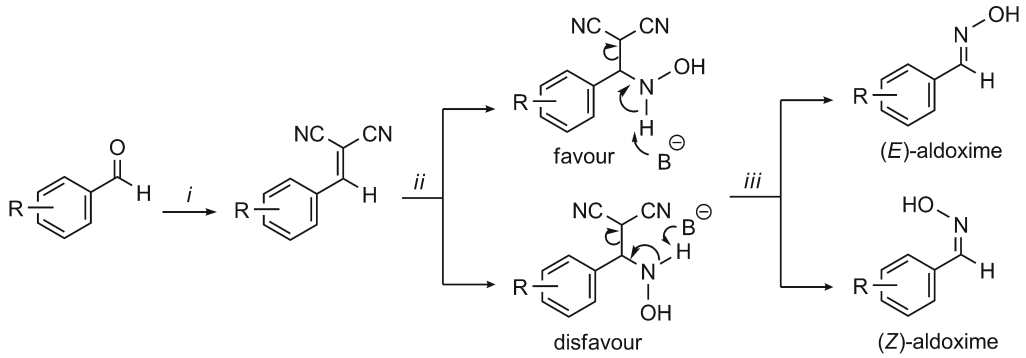
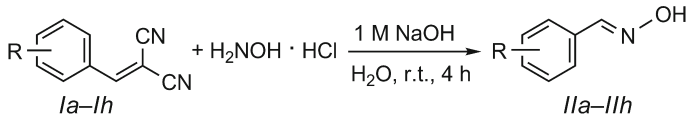


Fig. 1. Proposed formation of aldoximes via domino aza-Michael/retro-Michael addition reactions. Reaction conditions: *i*) $CH_2(CN)_2$; *ii*) $H_2NOH \cdot HCl$, aza-Michael addition; *iii*) splitting off $(CN)_2CH^-$ and HB, retro-Michael addition, E2 elimination.

Table 1. Characterisation data of prepared (*E*)-aldoximes



Compound	R	Yield[a]/%	M.p.[a]/°C	M.p.[b]/°C
IIa	H	92	33	32
IIb	4-Me	90	76–78	79–80
IIc	4-Cl	93	107–109	110
IId	3-Cl	91	72–73	71–72
IIe	2-Cl	84	75–76	75
IIf	3-Me	85	60–61	60
IIg	3-OMe	82	39–40	40
IIh	4-Br	92	114–115	115–116

a) Yields and m.p. of crystalline products obtained after chromatography; *b*) values reported in literature (Sharghi & Sarvari, 2001; Crawford & Woo, 1965; Dalton & Foley, 1973; Guo et al., 2001).

logous donors in asymmetric Michael addition reactions of nitroalkenes and α,β-unsaturated aldehydes with excellent chemical- and stereo-selectivity (Xue et al., 2005; Xie et al., 2006). Our report on the sequential Michael/retro-Michael addition reactions between α,α-dicyanoalkenes and α,β-unsaturated ketones (Xie et al., 2007) lead us to speculate that 2-benzylidenemalononitrile could be applied successively as Michael acceptor and retro-Michael donor in some domino sequences. In this respect, we envisaged that sequential aza-Michael/retro-Michael addition reactions between 2-benzylidenemalononitrile and hydroxylamine would be possible, as outlined in Fig. 1, to provide a straightforward protocol for the selective synthesis of (*E*)-aldoximes via E2 elimination.

All reagents were commercially available products (Sigma–Aldrich Co., China) and were used without further purification. 2-(R-benzylidene)malononitriles (*Ia–Ih*) were prepared as previously published (Chang et al., 2005). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker 400 spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. ESI-HRMS spectra (70 eV) were measured with a Finnigan LCQDECA ion trap mass spectrometer.

(*E*)-Aldoximes (*IIa–IIh*) were synthesised in accordance with the general method as follows: an aqueous solution of NaOH (1 M, 6 mL) was added to a solution of hydroxylamine hydrochloride (5 mmol) in H_2O (5 mL) under stirring at room temperature until the pH value reached 12. Next, 2-(R-benzylidene)malononitrile (*I*, 1 mmol) was added and the mixture was stirred for 4 h followed by extraction of the product with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with water (3 × 30 mL), dried with Na_2SO_4 and the solvent evaporated to give the crude (*E*)-aldoxime *II* in almost quantitative yield. The pure product was obtained by flash chromatography on silica gel using EtOAc/petroleum ether ($\varphi_r = 1 : 9$). The isolated yields and m.p. of all compounds *II* are given in Table 1 and the spectral data are summarised in Table 2.

In an initial investigation, we tested the reaction of 2-benzylidenemalononitrile with hydroxylamine hydrochloride in the presence of 1 M NaOH solution at room temperature. The desired crude (*E*)-aldoxime was isolated after 4 h in almost quanti-

Table 2. Spectral data of newly prepared compounds

Compound	Spectral data[a]
IIa	^{1}H NMR ($CDCl_3$), δ: 9.18 (brs, 1H), 8.17 (s, 1H), 7.58–7.55 (m, 2H), 7.40–7.37 (m, 3H) ^{13}C NMR ($CDCl_3$), δ: 150.4, 131.9, 130.1, 128.8, 127.1 ESI-HRMS, m/z (found/calc.): 122.0599/122.0606 ($[M + H]^+$, C_7H_7NO + H)
IIb	^{1}H NMR ($CDCl_3$), δ: 9.03 (brs, 1H), 8.14 (s, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H) ^{13}C NMR ($CDCl_3$), δ: 150.2, 140.3, 129.5, 129.0, 126.9, 21.4 ESI-HRMS, m/z (found/calc.): 136.0757/136.0762 ($[M + H]^+$, C_8H_9NO + H)
IIc	^{1}H NMR ($CDCl_3$), δ: 8.74 (s, 1H), 8.13 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H) ^{13}C NMR ($CDCl_3$), δ: 149.3, 136.0, 130.3, 129.0, 128.2 ESI-HRMS, m/z (found/calc.): 156.0214/156.0216 ($[M + H]^+$, C_7H_6ClNO + H)
IId	^{1}H NMR ($CDCl_3$), δ: 9.06–8.77 (m, 1H), 8.12 (s, 1H), 7.58 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.43–7.30 (m, 2H) ^{13}C NMR ($CDCl_3$), δ: 149.2, 134.8, 133.5, 130.1, 130.0, 126.8, 125.2 ESI-HRMS, m/z (found/calc.): 156.0211/156.0216 ($[M + H]^+$, C_7H_6ClNO + H)
IIe	^{1}H NMR ($CDCl_3$), δ: 8.88–8.67 (m, 1H), 8.59 (s, 1H), 7.82 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.40 (dd, J = 7.9 Hz, J = 1.0 Hz, 1H), 7.36–7.24 (m, 2H) ^{13}C NMR ($CDCl_3$), δ: 147.6, 133.9, 131.1, 129.9, 129.6, 127.1, 127.0 ESI-HRMS, m/z (found/calc.): 156.0212/156.0216 ($[M + H]^+$, C_7H_6ClNO + H)
IIf	^{1}H NMR ($CDCl_3$), δ: 9.90 (s, 1H), 8.24 (s, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 2.41 (s, 3H) ^{13}C NMR ($CDCl_3$), δ: 150.5, 138.4, 131.6, 130.9, 128.6, 127.5, 124.2, 21.2 ESI-HRMS, m/z (found/calc.): 136.0759/136.0762 ($[M + H]^+$, C_8H_9NO + H)
IIg	^{1}H NMR ($CDCl_3$), δ: 9.80 (s, 1H), 8.15 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.20–7.08 (m, 2H), 6.93 (d, J = 8.2 Hz, 1H), 3.78 (s, 3H) ^{13}C NMR ($CDCl_3$), δ: 159.6, 150.4, 132.9, 129.7, 120.1, 116.4, 111.1, 55.1 ESI-HRMS, m/z (found/calc.): 152.0716/152.0712 ($[M + H]^+$, $C_8H_9NO_2$ + H)
IIg	^{1}H NMR ($CDCl_3$), δ: 8.56 (s, 1H), 8.11 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H) ^{13}C NMR ($CDCl_3$), δ: 149.4, 132.1, 130.8, 128.5, 124.3 ESI-HRMS, m/z (found/calc.): 199.9715/199.9711 ($[M + H]^+$, C_7H_6BrNO + H)

a) NMR data are in good agreement with the published data (Crandall & Reix, 1992; Gordon et al., 1984; Danoff et al., 1979; Edwards et al., 2007).

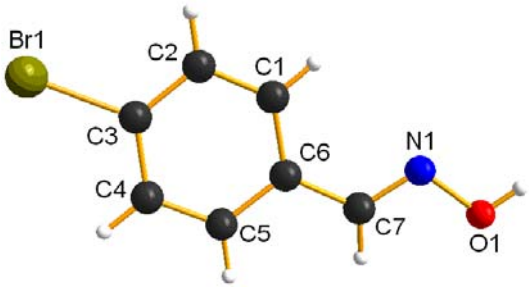


Fig. 2. A perspective drawing of *IIh* structure.

Table 3. Selected crystallographic data[a] and structure refinement for compound *IIh*

Empirical formula	C_7H_6BrNO
Formula mass	200.04
Temperature, T (K)	296(2)
Crystal system, space group	Monoclinic, $P2_1/c$
a (Å)	6.1929(4)
b (Å)	4.7875(3)
c (Å)	25.4600(13)
Unit-cell volume, V (Å^3)	752.75(8)
Formula per unit cell, Z	4
Absorption coefficient, μ (mm^{-1})	5.386
Crystal size (mm)	0.46 × 0.27 × 0.1
Diffractometer	Siemens P4
Reflections collected	5969
Independent reflections (R_{int})	1690 (0.0300)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1690/0/91
Goodness-of-fit on F^2	1.028
R indices [I > 2σ(l)]	R_1 = 0.0312, wR_2 = 0.0808
Largest difference peak and hole (e Å^{-3})	0.626 and −0.411

a) Standard deviations in parentheses.

tative yield. In further experiments, various 2-(R-benzylidene)malononitriles (possessing electron-donating or electron-withdrawing groups in the benzene ring) analogously underwent a condensation reaction with hydroxylamine at room temperature, giving the corresponding (*E*)-aldoximes in high yields (Table 1). The absence of *Z*-isomer was confirmed by ^{1}H NMR spectral data (Table 2). In addition, the *E* configuration was confirmed by a single-crystal X-ray diffraction of 2-(4-bromobenzylidene)malononitrile (*IIh*) (see Fig. 2 and Table 3).

In conclusion, the domino aza-Michael/retro-Michael addition reactions using 2-benzylidenemalononitrile strategy under alkaline conditions provides a straightforward protocol for the selective synthesis of (*E*)-aldoximes in high yields. Further work to extend

the synthetic utility of this reaction is in progress.

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