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Hypervalent iodine-mediated interaction of aldoximes with activated alkenes including Baylis–Hillman adducts: a new and efficient method for the preparation of nitrile oxides from aldoximes☆

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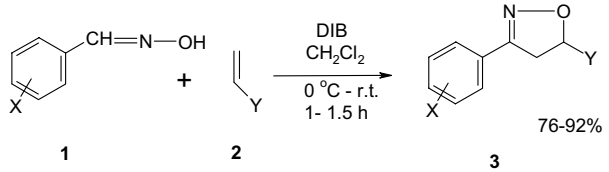
Abstract—Treatment of aldoximes with activated alkenes in the presence of diacetoxy iodobenzene (DIB) afforded isoxazolines in high yields. The method has been applied for the preparation of polyfunctional isoxazolines from Baylis–Hillman adducts.

Hypervalent iodine reagents have gained much importance in recent organic synthesis.[1] Different organoiodine(III) reagents have been applied for various organic transformations. One such reagent is diacetoxy iodobenzene (DIB), which is readily available and has been utilized in several oxidative conversions.[1,2] Here we report our work on the use of DIB for the preparation of isoxazolines by treatment of aldoximes with activated alkenes (Scheme 1).

Various aldoximes were reacted with different activated alkenes such as methyl acrylate and acrylonitrile in the presence of DIB to produce isoxazolines (Table 1). The reaction proceeded at 0 °C to room temperature.



Scheme 1.

The yields of the products were very high. The presence of an electron-donating or an electron-withdrawing group on the aromatic ring of the aldoximes did not affect the reaction. The reaction was completed within 1–1.5 h. The deoximation product was obtained in ~5% yield in each case. Ketoximes did not give isoxazolines and formed only deoximation products. Vinyl acetate also gave isoxazolines by reaction with aldoximes in the presence of DIB (Table 1, entries: **3h**, **3i**).

The probable mechanism of the reaction is shown in Scheme 2. The mechanism involves the formation of nitrile oxides from the aldoximes and subsequent 1,3-dipolar addition of this nitrile oxide to the alkene.

When the alkene was not added to the reaction mixture the dimerization product of the nitrile oxide could be isolated. This proves that the conversion proceeded through the reaction of the alkene with the intermediate nitrile oxide formed from the aldoxime.

Previously nitrile oxides have been prepared from aldoximes via halogenation using different reagents such as NBS,[3a] NCS,[3b] NaOCl[3c] and *t*-BuOCl.[3d] All of these methods involve two steps and some of the reagents[3a,b,d] work at high or low temperatures. The yields of isoxazolines using some reagents[3c] were also found to be highly variable.

Keywords: Aldoxime; Alkene; Baylis–Hillman adduct; DIB; Isoxazoline.
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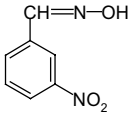
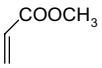
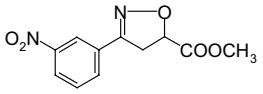
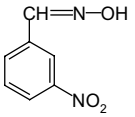
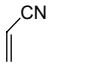
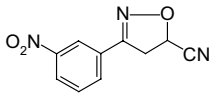
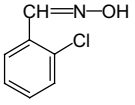
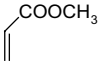
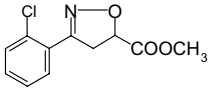
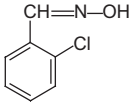
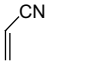
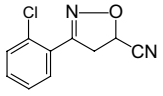
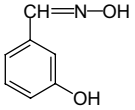
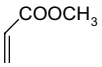
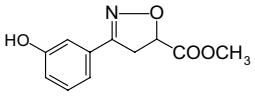
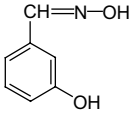
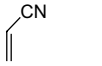
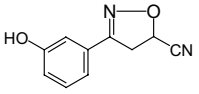
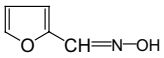
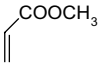
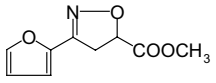
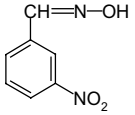
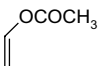
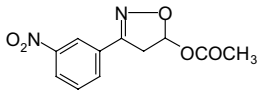
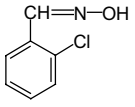
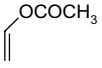
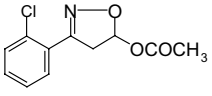
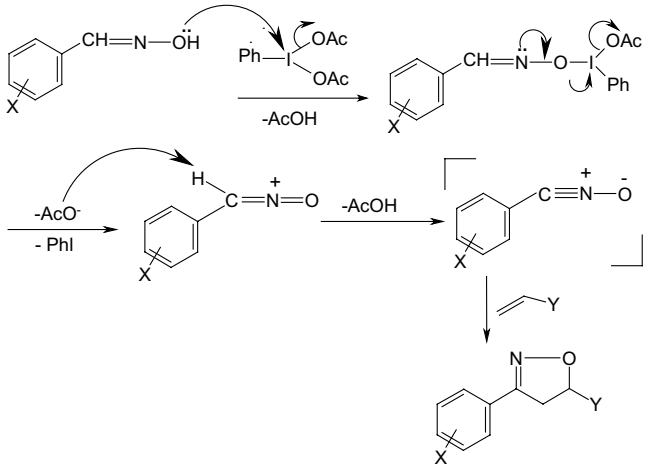
Table 1. DIB mediated reaction of aldoximes with alkenes[a]

Entry	Aldoxime	Alkene	Product	Time (h)	Isolated yield (%)[b]
3a				1.0	90
3b				1.0	86
3c				1.0	89
3d				1.0	86
3e				1.5	88
3f				1.5	85
3g				1.5	80
3h				1.0	82
3i				1.0	82

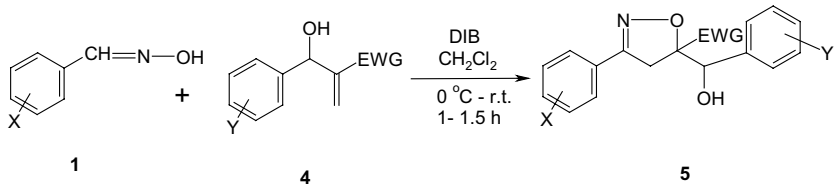
[a] The structures of the products were established from their spectral (^{1}H NMR and MS) data.
[b] Deoximation product (~5%) was obtained in each case.



Scheme 2.

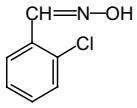
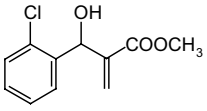
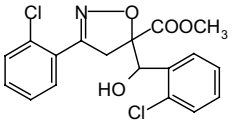
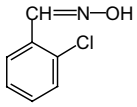
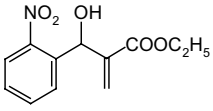
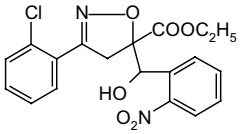
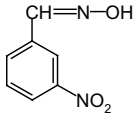
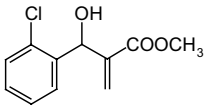
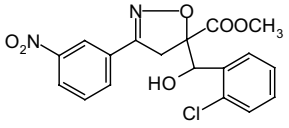
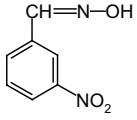
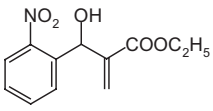
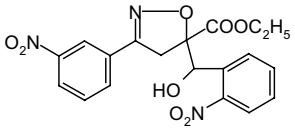
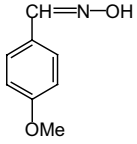
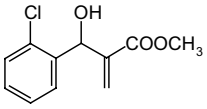
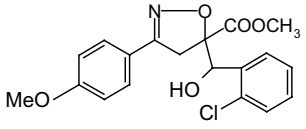
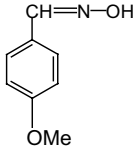
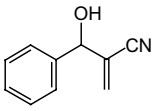
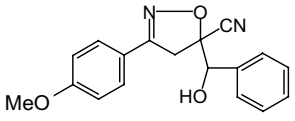
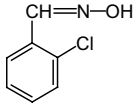
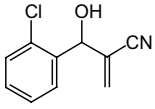
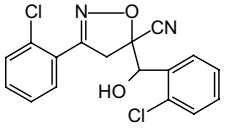
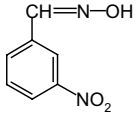
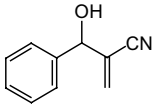
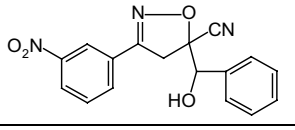
The present method offers an easy access to isoxazolines. The formation of nitrile oxide from aldoximes using DIB is a single-step process operating at temperatures between 0 °C and room temperature and the yields of isoxazolines are very high. Isoxazolines are important pharmacophores in several pharmaceutically important compounds.[4] They are also useful intermediate for synthesis of a wide variety of bioactive natural products.[4] The method has been extended for the synthesis of isoxazolines using Baylis–Hillman adducts, 3-hydroxy-2-methylene alkanoates and 3-hydroxy-2-methylene alkylenitriles[5] (Scheme 3).

Different aldoximes were treated with several Baylis–Hillman adducts with ester or nitrile substituents to form a series of isoxazolines (Table 2). Baylis–Hillman adducts are important precursors for the synthesis of various bioactive molecules.[6] Here we have utilized these adducts for the synthesis of isoxazolines containing different functional groups. Aldoximes containing an elec-



Scheme 3.

Table 2. DIB mediated reaction of aldoximes with Baylis–Hillman adducts[a]

Entry	Aldoxime	Baylis–Hillman adducts	Product	Time (h)	Isolated yield (%)[b]
5a				1.5	84
5b				1.0	82
5c				1.5	90
5d				1.0	88
5e				1.0	91
5f				1.0	89
5g				1.0	85
5h				2.0	78

[a] The structures of the products were established from their spectral (^{1}H NMR and MS) data.
[b] Deoximation product (~5%) was obtained in each case.

tron-donating as well as an electron-withdrawing group reacted similarly. The experimental procedure for the synthesis of isoxazolines using DIB is very simple.[7] The structures of all the isoxazolines were established from their spectral (^{1}H NMR and MS) data.[7]

Interestingly, in each case we obtained only one diastereoisomer of compounds **5** (as evident from TLC analysis and ^{1}H NMR data). This is possibly because attack by the nitrile oxide occuring from the side away from the hydroxyl group.

In conclusion, we have developed an easy and efficient method for the synthesis of isoxazolines employing DIB. The method has been shown to be applicable for the preparation of isoxazolines with various functionalities from different Baylis–Hillman adducts.

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7. General experimental procedure: An aldoxime (0.5 mmol) and an alkene (0.8 mmol) were dissolved in distilled CH_2Cl_2 (10 mL). The mixture was kept in an ice bath and stirred while DIB (0.8 mmol) was added in one portion. The mixture was allowed to stir at room temperature for 1–1.5 h. The reaction was monitored by TLC. After completion, water (15 mL) was added and the product was extracted with CH_2Cl_2 (3×15 mL). The extract was washed with water (2×10 mL), dried (Na_2SO_4), and concentrated. The residue was subjected to column chromatography over silica gel to obtain pure isoxazoline.
Spectral data of some representative isoxazolines are given below.
3a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.44 (1H, d, J = 2.0 Hz), 8.28 (1H, dd, J = 8.0, 2.0 Hz), 8.10 (1H, dd, J = 8.0, 2.0 Hz), 7.68 (1H, t, J = 8.0 Hz), 5.28 (1H, dd, J = 8.0, 6.0 Hz), 3.82 (3H, s), 3.78–3.62 (2H, m); EIMS: *m*/*z* 250 ($M^{+\cdot}$) (7%).
3b: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.46 (1H, d, J = 2.0 Hz), 8.35 (1H, dd, J = 8.0, 2.0 Hz), 8.09 (1H, dd, J = 8.0, 2.0 Hz), 7.69 (1H, t, J = 8.0 Hz), 5.48 (1H, dd, J = 8.0, 6.0 Hz), 3.84–3.75 (2H, m); EIMS: *m*/*z* 217 ($M^{+\cdot}$) (48%).
3g: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48 (1H, s), 6.78 (1H, d, J = 2.0 Hz), 6.47 (1H, d, J = 2.0 Hz), 5.29 (1H, dd, J = 8.0, 6.0 Hz), 3.82 (3H, s), 3.72–3.51 (2H, m); EIMS: *m*/*z* 195 ($M^{+\cdot}$) (16%).
3h: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.42 (1H, d, J = 2.0 Hz), 8.30 (1H, dd, J = 8.0, 2.0 Hz), 8.14 (1H, dd, J = 8.0, 2.0 Hz), 7.67 (1H, t, J = 8.0 Hz), 6.83 (1H, d, J = 4.0 Hz), 3.68 (1H, dd, J = 8.0, 4.0 Hz), 3.40 (1H, d, J = 10 Hz), 2.06 (3H, s) EIMS: *m*/*z* 250 ($M^{+\cdot}$) (9%).
5a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (2H, d, J = 8.0 Hz), 7.42–7.14 (6H, m), 5.72 (1H, d, J = 6.0 Hz), 3.85 (3H, s), 3.80–3.65 (2H, m), 3.12 (1H, d, J = 6.0 Hz), EIMS: *m*/*z* 379, 381, 383 ($M^{+\cdot}$) (15%, 9%, 2%, respectively).
5d: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.22 (8H, m), 6.08 (1H,br s), 4.20 (2H, q, J = 7.0 Hz), 3.83–3.68 (2H, m), 3.42 (1H, br s), 1.21 (3H, t, J = 7.0 Hz); EIMS: *m*/*z* 415 ($M^{+\cdot}$) (22%).
5e: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68–7.30 (6H, m), 6.96–6.78 (2H, m), 4.94 (1H, br s), 3.89 (3H, s), 3.85 (3H, s), 3.58 (2H, br s), 3.36 (1H, br s); EIMS: *m*/*z* 375, 377 ($M^{+\cdot}$) (18%, 6%, respectively).