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Stereoselective synthesis of azepines through the conjugate addition of formamides to nitroalkenes and subsequent intramolecular nitrile oxide cycloaddition reaction

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ABSTRACT

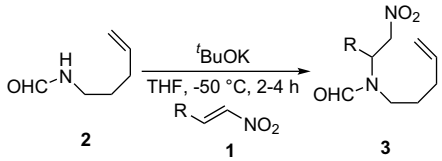
A concise and stereoselective formation of azepines is achieved through the conjugate addition of formamides to nitroalkenes and the subsequent intramolecular nitrile oxide cycloaddition (INOC) reaction. High cis-selectivity was observed. The one-pot modification of the two reactions provides direct preparation of azepines from nitroalkenes and formamides in moderate yields. The formyl group was readily removed by an acidic treatment without significant epimerization.

1. Introduction

The intramolecular nitrile oxide cycloaddition (INOC) reaction is a useful method to prepare heterocyclic compounds.[1,2] 4,5-Dihydroisoxazole, the cycloadduct of nitrile oxide, is regarded as a useful synthetic precursor for γ-amino alcohols and β-hydroxy ketones. There have been many examples applying the present methodology to the preparation of five- or six-membered carbo- and heterocyclic compounds[3] as well as the preparation of medium- or large-sized cyclic compounds.[4,5] On the other hand, the preparation of the precursor for the INOC reaction from commercially available starting material generally was not easy and required long steps. Primary aliphatic nitro compounds are readily prepared from the conjugate addition of a variety of nucleophiles to nitroalkenes.[6] The nitro group is converted into nitrile oxide by treatment with phenyl isocyanate,[7] the conjugate addition to the nitroalkenes and the following generation of nitrile oxide should be expected to be a facile and convenient strategy for INOC reaction. There have been several reports of such a methodology by Hassner,[8] Kurth,[9] and Yao.[10] They successfully prepared five- and six-membered carbo-, oxa-, and thio-cyclic compounds, and one-pot conversion to bicyclic isoxazoles from nitroalkenes was utilized in some of these protocols. If such nitro compounds include a nitrogen atom in a tether unit, these compounds are expected to be a good precursor for the aza-heterocyclic compounds through the INOC reaction.[11] However, nitrogen-nucleophiles have rarely been used through the conversion,[12] and the addition of amides to nitroalkene was limited only to cyclic lactams.[13] This is probably due to the instability of β-nitroamines that tends to cause the retro-Michael reaction during the INOC reaction under Mukaiyama conditions.[11] Recently, we found that formamides, the smallest amide of all the amide derivatives, underwent smooth conjugate addition to nitroalkenes to give β-nitroamides,[14] which worked as a useful precursor for the INOC reaction to prepare five- and six-membered aza-heterocyclic compounds in a stereoselective manner.[15] In this paper, we report that the present method is effective for the preparation of azepine derivatives. These medium-sized rings have been recognized relatively hard to be prepared through the INOC reaction thus far.[16] We have also succeeded in modifying these reactions in a one-pot manner that achieved direct preparation of azepines from nitroalkenes. The formyl group was readily removed under an acidic treatment to give N–H azepines without significant epimerization.

2. Results and discussion

The preparation of the INOC precursors **3** was smoothly carried out by the conjugate addition of secondary formamide **1** to nitroalkene **2** (Scheme 1). The results are summarized in Table 1.



2 1 3

Scheme 1. Conjugate addition of alkenyl amides to nitroalkene.

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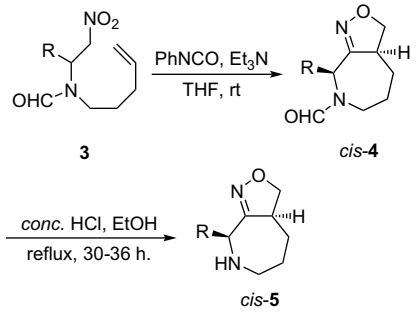
Table 1
Preparation of INOC precursor **3**

Entry	R	3	Yield (%)[a]
1	^{i}Pr	**3a**	85
2	$^{c}C_6H_{11}$	**3b**	80
3	Pr	**3c**	53
4	C_5H_{11}	**3d**	81
5	C_6H_{13}	**3e**	48

[a] Isolated yield.

The addition reaction completed within 2–4 h and corresponding adducts **3** were isolated after the usual workup. For example, the treatment of *N*-(4-pentenyl)formamide **2** with ^{t}BuOK in THF with subsequent addition of 3-methyl-1-nitro-1-butene resulted in the smooth formation of adduct **3a** in 85% yield (entry 1). Compound **3** contained rotational isomers due to the tertiary amide unit. A variety of nitroalkenes were used in the reaction to give a series of precursors for the INOC reaction.

Exposure of the precursors **3** to phenyl isocyanate under basic conditions resulted in the smooth generation of nitrile oxide that immediately attacked the internal alkene unit to give bicyclic isoxazoles **4** in a moderate yield (Scheme 2). The results are summarized in Table 2.



Scheme 2. INOC reaction to prepare azepines **4** and **5**.

The yields of bicycloazepines **4** were in the range of 50–71% (entries 1–5), although the reaction was performed under the usual concentration (0.2 M); no high-dilution technique was required. For example, precursor **3a** underwent the INOC reaction to give azepine **4a** in 71% yield (entry 1). The NMR of **4a** looked somewhat complicated because of the existence of rotational isomers due to the tertiary formamide unit. Since VT NMR for compounds **4** never showed simple spectra, we checked GC analysis for their purities and diastereomeric ratios. To our surprise, one of the diastereomers of **4** was formed selectively through the reaction, because the GC analysis for the reaction mixture of **4** revealed that the diastereomeric ratio was generally high. In particular, the selectivity reached as high as 95:5 when the R group was a primary alkyl group (entries 3, 4, and 5). Thus, the present method provides a useful preparation of azepines from nitroalkenes in a stereoselective manner.

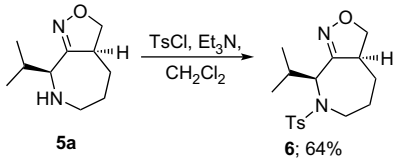
Table 2
INOC reaction of β-nitroamides **3**

Entry	R	4	Yield (%)[a]	cis/trans[b]	5	Yield (%)[a]	cis/trans[b]
1	^{i}Pr	**4a**	71	89/11	**5a**	74	87/13
2	$^{c}C_6H_{11}$	**4b**	65	90/10	**5b**	88	69/31
3	Pr	**4c**	50	95/5	**5c**	79	96/4
4	C_5H_{11}	**4d**	52	95/5	**5d**	89	90/10
5	C_6H_{13}	**4e**	59	96/4	**5e**	94	93/7

[a] Isolated yields.
[b] Determined by GC analysis.

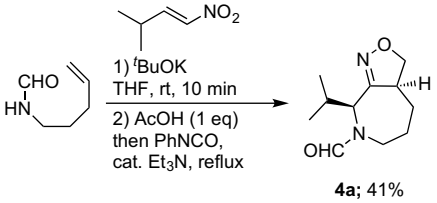
The *N*-formyl group was readily removed by the treatment of **4** under acidic conditions (Scheme 2). For example, treatment of **4a** with ethanolic diluted HCl solution at a gently refluxing temperature resulted in the smooth removal of the formyl group, giving *N*–H azepine **5a** in 74% yield (entry 1). The diastereomeric ratio of **5a** was found to be 87:13, which was close to the original diastereomeric ratio of **4a** (89:11). No significant epimerization was observed during the removal of the formyl group except for the deprotection of **4b** (entries 1 and 3–5). The reaction conditions for the removal were somewhat critical; the treatment of **4a** at room temperature resulted in no removal of the formyl group, while vigorous reflux of **4a** under the present conditions resulted in the complete removal of the formyl group but induced undesirable epimerization giving a 1:1 mixture of the two diastereomers of **5a**. It should be mentioned that the treatment of compound **5c** (cis/trans=96:4) underwent the conversion to **4c** in 87% yield by treatment with ethyl formate. This re-formylated **4c** showed an identical NMR spectrum to the original one and the diastereomeric ratio was found to be 96:4. Thus, the present deprotection of the formyl group occurred successfully with retaining the stereochemistry of **4** in the azepine ring.

The stereochemistry was determined by X-ray crystallographic analysis. Compound **5a** was converted to *N*-tosyl derivatives **6** by the treatment with tosyl chloride in 64% yield (Scheme 3). Compound **6** gave good crystals after recrystallization from CH_2Cl_2. Crystallographic data for **6** unambiguously revealed cis-configuration between the isopropyl group and the isoxazole ring.[17]



Scheme 3. Preparation of *N*-tosyl azepine **6**.

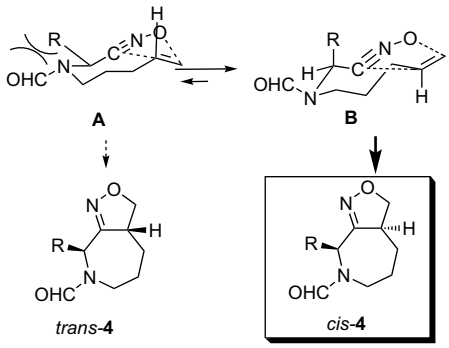
The present INOC reaction was performed in a one-pot manner in combination with conjugate addition of formamides to nitroalkenes (Scheme 4). For example, nitroalkene **1a** was added to a mixture of formamide **2** and ^{t}BuOK in THF. The addition was completed in 10 min and the reaction was quenched by the addition of AcOH. Then phenyl isocyanate and Et_3N were added to the reaction mixture, which was allowed to heat to the refluxing temperature. After the usual workup and purification through flash column chromatography, **4a** was isolated in 41% yield. Thus, the azepine ring was prepared in one step from nitroalkene and formamides. It should be noted that the addition of AcOH was essential to progress the INOC reaction. Without AcOH addition, no desired INOC adducts were observed in the reaction mixture.



Scheme 4. One-pot preparation of azepine **4a**.

We assume that the present azepine synthesis proceeded through a mechanism similar to the five- and six-membered ring formation.[15] Scheme 5 depicts a plausible mechanism in which two transition states **A** and **B** generate *trans*-**4** and *cis*-**4**, respectively.

Transition state **B** should be favorable because of less steric hindrance from the interaction between R and the formyl group.



Scheme 5. Plausible origin of stereoselectivity.

Thus, we have succeeded in forming stereoselective aza-heterocyclic compounds from the conjugate adducts of nitroalkene and formamides. High stereoselectivity was observed in the formation of bicyclic azepines. These two-step reactions were performed in one-pot to achieve facile stereoselective formation of azepine rings. The treatment of the adducts under acidic conditions resulted in the smooth removal of the formyl group with minimum loss of the diastereomeric ratio. As nitroalkenes and formamides are readily available, the present method can be a useful in the formation of aza-heterocyclic compounds in a stereoselective manner. Further studies on this issue are now under way in our laboratory.

3. Experimental section

3.1. General

All ^{1}H and ^{13}C NMR spectra were recorded on JEOL GSX-270 (270 MHz for ^{1}H and 67.5 MHz for ^{13}C) spectrometer. All the reactions in this paper were performed under nitrogen atmosphere unless otherwise mentioned. CH_2Cl_2 was dried over CaH_2, and distilled under nitrogen before use. High resolution mass spectra (HRMS) were measured at Integrated Center for Sciences, Ehime University, Matsuyama, Japan.

3.2. Conjugate addition of *N*-4-pentenylformamide to 3-methyl-1-nitro-1-butene 3a. General procedure

Under a nitrogen atmosphere, ^{t}BuOK (1.35 g, 12.0 mmol) was added to a solution of formamide (1.132 g, 10.0 mmol) in dry THF (30 mL) at 0 °C. The solution was stirred for an additional 1 h. After cooling to −50 °C, nitroalkene (1.38 g, 12.0 mmol) was added to the solution and the reaction mixture was stirred for 3 h at the same temperature. Saturated NH_4Cl(aq) (25 mL) was added to the reaction mixture and THF was removed using a rotary evaporator. Water (5 mL) was added to the mixture and the resulting aqueous solution was extracted with EtOAc (3×50 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, EtOAc was removed from the filtrate to give crude adduct **3a**, which was purified through flash chromatography (silica gel, hexane/EtOAc=7:1 then 3:1 in v/v) to give pure **3a** in oil in 85% yield (1.937 g, 8.49 mmol). The compound consisted of about 1:1 mixture of rotational isomers. Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.94–0.99 (m, 3H), 1.00–1.07 (m, 3H), 1.81–1.98 (m, 0.5H), 2.09 (m, 2H), 2.41–2.51 (m, 0.5H), 2.94–3.35 (m, 2H), 3.65 (dt, *J*=3.8, 9.7 Hz, 0.5H), 3.81 (dt, *J*=4.3, 10.1 Hz, 0.5H), 4.51–4.68 (m, 2H), 4.99–5.11 (m, 2H), 5.69–5.75 (m, 1H), 8.04 (s, 0.5H), 8.11 (s, 0.5H). ^{13}C NMR ($CDCl_3$) δ 19.6, 19.8, 19.9, 27.4, 28.6, 28.7, 28.8, 30.5, 31.3, 41.2, 49.0, 62.6, 63.5, 75.7, 115.5, 116.0, 137.0, 137.5, 163.7, 163.9. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.50; H, 8.75; N, 11.94.

3.2.1. 1-Cyclohexyl-2-nitro-1-[(N-formyl-N-4-pentenyl)amino]ethane [3b]

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.88–1.80 (m, 11H), 1.45–1.89 (m, 4H), 2.02–2.13 (m, 2H), 2.92–3.32 (m, 2H), 3.69 (dt, 0.5H, *J*=3.7, 10.0 Hz), 3.89 (dt, 0.5H, *J*=4.3, 10.6 Hz), 4.49–4.70 (m, 2H), 4.99–5.16 (m, 2H), 5.68–5.88 (m, 1H), 8.01 (s, 0.5H), 8.10 (s, 0.5H). ^{13}C NMR ($CDCl_3$) δ 25.5, 25.7, 25.8, 25.9, 27.5, 28.7, 30.1, 30.5, 30.6, 31.4, 37.7, 41.3, 49.4, 61.8, 62.4, 75.6, 75.7, 115.6, 116.1, 137.1, 137.6, 163.7, 163.9. Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found: C, 62.32; H, 9.02; N, 10.23.

3.2.2. 2-(N-Formyl-N-4-pentenyl)amino-1-nitropentane [3c]

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H, *J*=7.1 Hz), 1.26–1.94 (m, 4H), 2.04–2.10 (m, 2H), 3.00–3.31 (m, 2H), 4.01–4.29 (m, 1H), 4.39–4.59 (m, 2H), 4.98–5.15 (m, 2H), 5.69–5.88 (m, 1H), 8.07 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.6, 13.9, 19.3, 19.9, 28.0, 29.1, 30.7, 31.6, 32.3, 32.5, 40.7, 48.9, 56.2, 56.9, 76.5, 76.9, 116.0, 116.6, 137.1, 137.7, 163.6, 164.1. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.47; H, 8.74; N, 11.87.

3.2.3. 2-(N-Formyl-N-4-pentenyl)amino-1-nitroheptane [3d]

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 3H), 1.20–1.40 (m, 6H), 1.52–1.74 (m, 2H), 2.05–2.13 (m, 2H), 3.00–3.31 (m, 2H), 4.00–4.27 (m, 1H), 4.40–4.60 (m, 2H), 5.00–5.18 (m, 2H), 5.70–5.88 (m, 1H), 8.08 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 25.5, 26.1, 27.8, 28.9, 30.0, 30.1, 30.5, 31.1, 31.4, 40.4, 48.4, 55.9, 57.0, 76.3, 77.2, 115.6, 116.2, 137.0, 137.5, 163.5, 163.9. Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 61.01; H, 9.45; N, 10.69.

3.2.4. 2-(N-Formyl-N-4-pentenyl)amino-1-nitrooctane [3e]

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.81–0.96 (m, 5H), 1.16–1.42 (m, 8H), 1.64–1.98 (m, 2H), 2.07–2.13 (m, 2H), 2.99–3.31 (m, 2H), 4.01–4.27 (m, 1H), 4.39–4.59 (m, 1H), 5.00–5.15 (m, 2H), 5.69–5.88 (m, 1H), 8.07 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.9, 26.6, 27.9, 28.8, 29.0, 29.1, 30.2, 30.4, 30.6, 31.5, 31.6, 31.7, 40.6, 48.8, 56.3, 57.1, 76.5, 77.4, 115.9, 116.5, 137.1, 137.6, 163.6, 164.0. HRMS (EI$^+$ M) *m*/*z* 270.1942. Calcd for $C_{14}H_{26}N_2O_3$ 270.1943.

3.3. INOC reaction of 3, preparation of *cis*-7-formyl-8-isopropyl-3a,4,5,6-tetrahydro-3*H*,8*H*-isoxazolo[3,4-*c*] azepine 4a. General procedure

Under a nitrogen atmosphere, phenyl isocyanate (0.609 mL, 5.62 mmol) was added to a solution of **3a** (0.5129 g, 2.25 mmol) and Et_3N (0.946 mL, 6.74 mmol) in dry THF (15 mL) and the resulting solution was heated at the refluxing temperature for 1.5 h. Diphenyl urea precipitated gradually. After disappearance of **3a** in TLC detection, the reaction mixture was cooled and filtered. The filtrate was then concentrated in vacuo and the residue was subjected to flash chromatography (silica gel, hexane/EtOAc=5:1, 3:1, 1:1 then 1:2 in v/v) to give **4a** in 71% yield (0.3342 g, 1.59 mmol). The compound consisted of about 1:1 mixture of rotational isomers. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, *J*=7.0 Hz), 1.18 (d, 3H, *J*=6.7 Hz), 1.44–1.79 (m, 4H), 2.37–2.63 (m, 2H), 2.91–3.08 (m, 1H), 4.05 (d, 1H, *J*=6.3 Hz), 4.07–4.15 (m, 1H), 4.19–4.37 (m, 2H), 8.12 (s, 0.5H), 8.28 (s, 0.5H). ^{13}C NMR ($CDCl_3$) δ 18.7, 18.8, 19.0, 19.3, 20.7, 24.1, 26.2, 26.6, 27.1, 29.4, 30.1, 31.5, 38.5, 42.2, 44.7, 45.9, 49.8, 50.0, 54.3, 54.9, 62.1, 62.4, 74.5, 75.0, 75.6, 75.8, 160.2, 162.2, 162.3, 163.1. HRMS (EI$^+$ M$^+$) *m*/*z* 210.1369. Calcd for $C_{11}H_{18}N_2O_2$ 210.1368.

3.3.1. cis-7-Formyl-8-cyclohexyl-3b,4,5,6-tetrahydro-3H, 8H-isoxazolo[3,4-c]azepine [4b]

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.84–1.95 (m, 10H), 2.00–2.27 (m, 1H), 2.54 (t, 1H, *J*=8.2 Hz), 2.87–3.11 (m, 1H), 3.99–4.17 (m, 2H),

4.17–4.59 (m, 2H), 8.09 (s, 0.5H), 8.27 (s, 0.5H). ^{13}C NMR ($CDCl_3$) δ 23.9, 25.1, 25.2, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.6, 27.2, 28.0, 28.4, 28.7, 29.1, 29.3, 29.7, 30.4, 31.3, 32.3, 35.1, 35.6, 38.3, 39.4, 42.2, 46.0, 46.8, 49.7, 50.0, 52.7, 54.2, 60.8, 61.3, 74.4, 74.8, 75.4, 75.5, 159.7, 162.0, 162.1, 162.9, 163.5. HRMS (EI$^+$ M) m/z 250.1682. Calcd for $C_{14}H_{22}N_2O_2$ 250.1681.

*3.3.2. cis-7-Formyl-8-propyl-3c,4,5,6-tetrahydro-3H, 8H-isoxazolo[3,4-c]azepine [**4c**]*

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=6.7 Hz), 1.16–1.97 (m, 6H), 2.10–2.27 (m, 2H), 2.53 (t, 1H, J=11. 4 Hz), 2.89–3.15 (m, 2H), 4.00–4.12 (m, 2H), 4.20–4.42 (m, 2H), 8.12 (s, 0.5H), 8.26 (s, 0.5H). ^{13}C NMR ($CDCl_3$) δ 13.1, 13.3, 18.4, 18.5, 24.1, 26.3, 27.9, 29.2, 30.2, 31.8, 32.2, 32.3, 32.4, 32.8, 38.6, 39.9, 43.9, 46.9, 47.0, 48.8, 49.3, 49.5, 55.5, 56.9, 56.0, 74.5, 74.8, 75.6, 75.8, 161.0, 162.4, 163.3, 163.4, 163.6. HRMS (EI$^+$ M) m/z 210.1369. Calcd for $C_{11}H_{18}N_2O_2$ 210.1368.

*3.3.3. cis-7-Formyl-8-pentyl-3d,4,5,6-tetrahydro-3H, 8H-isoxazolo[3,4-c]azepine [**4d**]*

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.81–0.95 (m, 3H), 1.14–1.97 (m, 10H), 2.12–2.28 (m, 2H), 2.52 (t, 1H, J=11. 4 Hz), 2.89–3.15 (m, 2H), 4.04–4.20 (m, 2H), 4.20–4.40 (m, 2H), 8.12 (s, 0.5H), 8.26 (s, 0.5H). ^{13}C NMR ($CDCl_3$) δ 13.6, 13.7, 22.1, 24.1, 24.9, 25.0, 26.4, 28.0, 29.3, 30.2, 30.3, 30.4, 30.9, 31.1, 31.9, 32.9, 38.6, 40.0, 43.9, 47.1, 49.2, 49.4, 49.5, 55.8, 56.4, 74.6, 74.8, 75.7, 75.9, 161.0, 162.5, 163.3, 163.4, 163.6. HRMS (EI$^+$ M) m/z 238.1682. Calcd for $C_{13}H_{22}N_2O_2$ 238.1681.

*3.3.4. cis-7-Formyl-8-hexyl-3e,4,5,6-tetrahydro-3H, 8H-isoxazolo[3,4-c]azepine [**4e**]*

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.76–0.97 (m, 3H), 1.15–2.01 (m, 12H), 2.16–2.25 (m, 2H), 2.52 (t, 1H, J=11. 3 Hz), 2.91–3.13 (m, 2H), 4.05–4.20 (m, 2H), 4.20–4.39 (m, 2H), 8.12 (s, 0.5H), 8.26 (s, 0.5H). ^{13}C NMR ($CDCl_3$) δ 13.6, 13.7, 22.2, 22.3, 24.2, 25.2, 25.3, 26.4, 28.0, 28.3, 28.4, 28.6, 29.4, 30.3, 30.4, 31.2, 31.3, 31.4, 31.9, 32.9, 38.7, 40.0, 44.0, 47.1, 49.2, 49.4, 49.6, 55.9, 56.4, 74.8, 75.7, 75.9, 161.1, 162.5, 163.3, 163.4, 163.7. HRMS (EI$^+$ M) m/z 252.1837. Calcd for $C_{14}H_{24}N_2O_2$ 252.1838.

3.4. Removal of the formyl group. Preparation of *cis*-8-isopropyl-3a,4,5,6,7,8-hexahydro-3*H*-isoxazolo[3,4-*c*] azepine 5a. General procedure

A solution of **4a** (0.1435 g, 0.637 mmol) in ethanol (6 mL) and concd. HCl (1 mL) was heated gently at the refluxing temperature (bath temperature was 90 °C) for 30 h. The reaction was monitored by GC analysis. After completion of the reaction, $NaHCO_3$(aq) (5 mL) was added to neutralized the solution, and the mixture was extracted with EtOAc (3×50 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, the solvent was removed using a rotary evaporator to give crude product, which was purified through flash column chromatography (silica gel/hexane/EtOAc, 3:1 then 1:2 v/v) to give **5a** in 74% yield (0.0859 g, 0.472 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 3H, J=7.1 Hz), 1.23 (d, 3H, J=7.0 Hz), 1.44–1.73 (m, 5H), 2.15–2.30 (m, 1H), 2.73–2.86 (m, 1H), 2.99 (d, 1H, J=7.2 Hz), 3.09 (ddd, 1H, J=9.7, 10.7, 13.1 Hz), 3.36–3.49 (m, 1H), 3.83 (dd, 1H, J=8.0, 10.3 Hz), 4.46 (dd, 1H, J=8.0, 10.2 Hz). ^{13}C NMR ($CDCl_3$) δ 18.6, 19.0, 28.4, 28.8, 30.7, 48.8, 51.2, 61.8, 74.2, 164.6. HRMS (EI$^+$ M) m/z 182.1417. Calcd for $C_{10}H_{18}N_2O$ 182.1419.

*3.4.1. cis-8-Cyclohexyl-3b,4,5,6,7,8-hexahydro-3H-isoxazolo-[3,4-c]azepine [**5b**]*

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.07–1.39 (m, 4H), 1.50–1.80 (m, 11H), 2.05 (m, 1H), 2.71–2.80 (m, 1H), 3.05 (d, 1H, J=7.0 Hz), 3.04–3.10 (m, 1H), 3.37–3.47 (m, 1H), 3.83 (dd, 1H, J=8.0, 10.2 Hz), 4.45 (dd, 1H, J=8.0, 10.2 Hz). ^{13}C NMR ($CDCl_3$) δ 26.2, 26.5, 28.7, 28.9, 30.9, 40.1, 48.4, 51.0, 60.6, 74.0, 164.3. HRMS (EI$^+$ M) m/z 222.1731. Calcd for $C_{13}H_{22}N_2O$ 222.1732.

*3.4.2. cis-8-Propyl-3c,4,5,6,7,8-hexahydro-3H-isoxazolo-[3,4-c]azepine [**5c**]*

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=6.3 Hz), 1.46–2.00 (m, 9H), 2.79–2.92 (m, 2H), 3.41 (dt, 1H, J=6.6, 17.8 Hz), 3.49 (dd, 1H, J=5.4, 8.7 Hz), 3.92 (t, 1H, J=8.2 Hz), 4.41 (dd, 1H, J=8.1, 9.9 Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 19.5, 29.7, 30.1, 34.5, 45.7, 50.6, 55.0, 74.8, 166.2. HRMS (FAB$^+$ M+1) m/z 183.1499. Calcd for $C_{10}H_{19}N_2O$ 183.1497.

*3.4.3. cis-8-Pentyl-3d,4,5,6,7,8-hexahydro-3H-isoxazolo-[3,4-c]azepine [**5d**]*

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=6.8 Hz), 1.25–1.99 (m, 13H), 2.81–2.91 (m, 2H), 3.38–3.44 (m, 1H), 3.47 (dd, 1H, J=5.4, 8.7 Hz), 3.91 (t, 1H, J=8.2 Hz), 4.41 (dd, 1H, J=8.0, 9.9 Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 22.5, 26.0, 29.5, 30.0, 31.3, 32.3, 45.6, 50.5, 55.3, 74.8, 166.0. HRMS (EI$^+$ M) m/z 210.1733. Calcd for $C_{12}H_{22}N_2O$ 210.1732.

*3.4.4. cis-8-Hexyl-3e,4,5,6,7,8-hexahydro-3H-isoxazolo-[3,4-c]azepine [**5e**]*

Yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=6.0 Hz), 1.25–2.00 (m, 15H), 2.81–2.92 (m, 2H), 3.38–3.43 (m, 1H), 3.47 (dd, 1H, J=5.4, 8.7 Hz), 3.91 (t, 1H, J=8.2 Hz), 4.41 (dd, 1H, J=8.1, 9.9 Hz). ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 26.3, 29.2, 29.6, 30.1, 32.4, 32.8, 45.7, 50.6, 55.4, 74.8, 166.1. HRMS (EI$^+$ M) m/z 224.1890. Calcd for $C_{13}H_{24}N_2O$ 224.1889.

3.5. One-pot procedure for the preparation of 4a

Under a nitrogen atmosphere, ^{t}BuOK (0.155 g, 1.38 mmol) was added to a solution of formamide (0.1409 g, 0.1.25 mmol) in dry THF (7 mL) at 0 °C. The solution was stirred for an additional 1 h. After cooling to −50 °C, nitroalkene (0.173 g, 1.50 mmol) was added to the solution and the reaction mixture was stirred for 2 h at the same temperature. AcOH (0.079 mL, 1.38 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature. Et_3N (0.53 mL, 3.75 mmol) and phenyl isocyanate (0.339 mL, 3.13 mmol) were added to the mixture and the reaction mixture was heated at the refluxing temperature for 15 h. After cooling to room temperature, the precipitate was removed by filtration. The filtrate was concentrated and the residue was subjected to flash chromatography (silica gel/hexane/EtOAc, 3:1 then 1:2 v/v) to give **4a** in 41% yield (0.1062 g). GC and NMR data were identical to the authentic sample of **4a**.

3.6. Reformylation of 5c

A solution of **5c** (ds ratio was 94:6, 0.0206 mg, 0.113 mmol) in ethyl formate (6 mL) was heated to refluxing temperature for 6 h. The reaction mixture was concentrated by rotary evaporator and the residue was purified by flash chromatography (silica gel/hexane/EtOAc, 3:1 then 1:2 v/v) to give **4c** in 87% yield (0.0207 g). The NMR data were identical to the authentic sample of **4c** and GC analysis showed the diastereomeric ratio was 94:6.

3.7. Preparation of *cis*-8-isopropyl-7-(*p*-toluenesulfonyl)-3a,4,5,6,7,8-hexahydro-3*H*-isoxazolo[3,4-*c*]azepine 6

To a solution of **5a** (0.1071 g, 0.588 mmol) in CH_2Cl_2 (10 mL) Et_3N (0.164 mL, 1.175 mmol) and DMAP (0.05 g) were added. Then TsCl (0.168 g, 0.880 mmol) was added to the solution and the reaction mixture was stirred for 10 h at 0 °C. Water (20 mL) was added to the reaction mixture, which was extracted with CH_2Cl_2 (3×30 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, the filtrate was concentrated in vacuo and

the residue was subjected to flash chromatography (silica gel/hexane–EtOAc 10:1 then 5:1 v/v) to give **6** in 64% yield (0.126 g). White solid. Mp 133 °C. ^{1}H NMR ($CDCl_3$) δ 0.73 (d, 3H, J=6.7 Hz), 1.10 (d, 3H, J=6.6 Hz), 1.39–1.58 (m, 1H), 1.66–1.91 (m, 3H), 1.99–2.18 (m, 1H), 2.43 (s, 3H), 2.90–3.12 (m, 2H), 3.75 (dd, 1H, J=8.1, 9.9 Hz), 4.05 (d, 1H, J=15.6 Hz), 4.34 (dd, 1H, J=8.0, 9.6 Hz), 4.44 (d, 1H, J=9.2 Hz), 7.30 (d, 2H, J=7.9 Hz), 7.72 (d, 2H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.6, 21.8, 28.9, 30.0, 31.0, 45.5, 51.5, 61.0, 75.1, 127.7, 130.1, 138.6, 144.0, 163.6. Anal. Calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.32. Found: C, 60.30; H, 7.06; N, 8.21.

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17. Crystallographic data (excluding structure factors) for the structures *cis*-**6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 687340. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].