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TITANIUM TETRAIODIDE PROMOTED REDUCTIVE OPENING OF 2-(1-BENZYLOXYIMINOETHYL)AZIRIDINES, LEADING TO AZA-ALDOL REACTION

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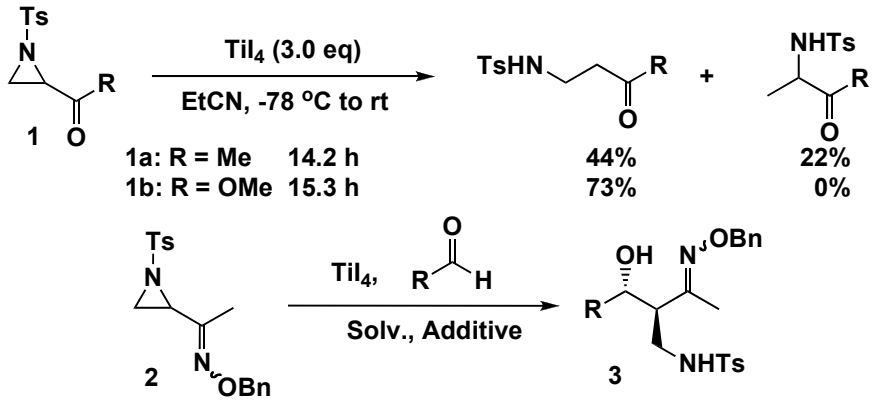
Abstract – Reductive ring-opening of 2-(1-benzyloxyiminoethyl)aziridines was regioselectively carried out with titanium tetraiodide to form the titanium aza-enolates, which in turn were subjected to addition reaction with aldehydes to give aza-aldol products in good yields with high diastereoselectivities.

We have recently reported that titanium tetraiodide promotes the reductive ring-opening aldol and Mannich-type reactions of 2-alkoxycarbonyl aziridines (**1b**) with aldehydes and aldimines in a highly regioselective manner.[1] This procedure offers a convenient method for the reductive formation of the β-amino ester enolate that is a useful synthon for the preparation of β-amino acid derivatives. However, when 2-acetylaziridine (**1a**) was used as a substrate, poor regioselectiviy was observed at the reduction stage (Scheme 1). In an effort to improve regioselectivity of the reductive ring-opening, several 2-acetyl derivatives were examined. We have now found that 2-(1-benzyloxyiminoethyl)aziridine (**2**)[2] is an excellent precursor to the β-amino aza-enolate that undergoes further aza-aldol reaction with aldehydes.

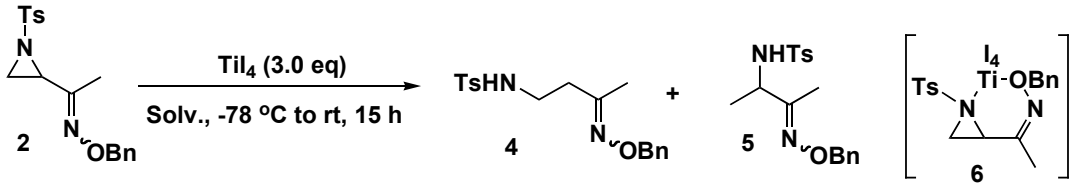


Scheme 1.

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

The initial examination was carried out to examine the regioselectiviy and efficiency of the reductive ring-opening of the 2-(1-benzyloxyiminoethyl)aziridine (**2**) with titanium tetraiodide, and Table 1 summarizes the results.

Table 1. Reductive Ring-Opening of **2** with TiI_4 under Various Conditions[a]



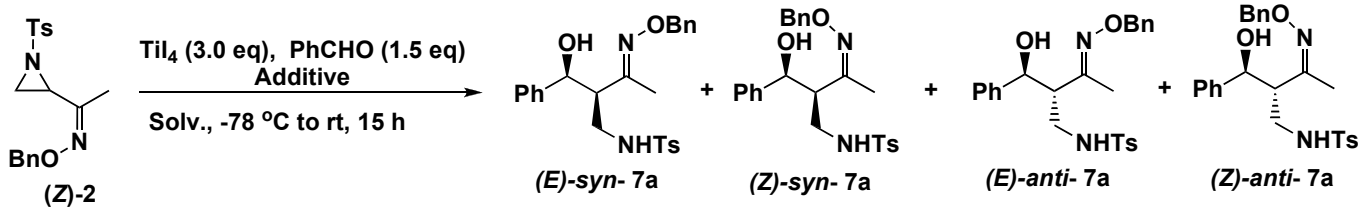
Entry	Geometry of **2**	Solvent	**4**/%[b]	*E* : *Z* of **4**[c]	**5**/%
1	*E*	EtCN	69	56 : 44	0
2	*E*	THF	73	76 : 24	0
3	*E*	$PhCH_3$	61	77 : 23	0
4	*E*	DME	64	70 : 30	0
5	*Z*	EtCN	94	40 : 60	0
6	*Z*	THF	63	73 : 27	0

[a]Reaction was carried out with TiI_4 (3.0 equiv) at -78 °C to rt for 15 h. [b]Isolated yield. [c]Determined by ^1H and ^{13}C NMR.

In all the cases examined, the reaction proceeded in a regioselective manner to give the oxime (**4**) as the sole product in good to excellent yields. When EtCN was used as a solvent in which the reduction proceeded most effectively, the (*Z*)-isomer recorded a better result than the (*E*)-counterpart (Entries 1 and 5). The chelated intermediate (**6**) may account for the efficient ring-opening with (*Z*)-**2**.

Since the generation of the β-amino aza-enolate was found to be practical using (*Z*)-**2** and TiI_4, we next examined the subsequent aldol reaction. Table 2 summarizes the results. As can be seen from Table 2, although the reaction proceeded relatively well in the presence of a 1 : 1 mixture of TiI_4 and $Ti(O^iPr)_4$ in THF,[3] the use of EtCN as a solvent recorded good diastereoselectivity (Entries 3 and 5). While it was previously reported that the presence of SiO_2 or molecular sieves 4A considerably improved the yields of the aza-Mannich-type reaction products,[4] such effects were not observed in the present aldol reaction (Entries 6 and 7). The use of $BF_3{\cdot}OEt_2$ increased the product yield without affecting the diastereoselectivity (Entries 8 and 9). Regarding the diastereoselectivity with respect to the *syn* vs *anti* relative stereoselectivity, the reactions conducted in EtCN usually gave good to excellent *anti*-selectivities (Entries 5 to 9). Under the best reaction conditions found for the reaction with benzaldehyde, a variety of aldehydes were subjected to the addition reaction, and Table 3 collects the results.[5,6]

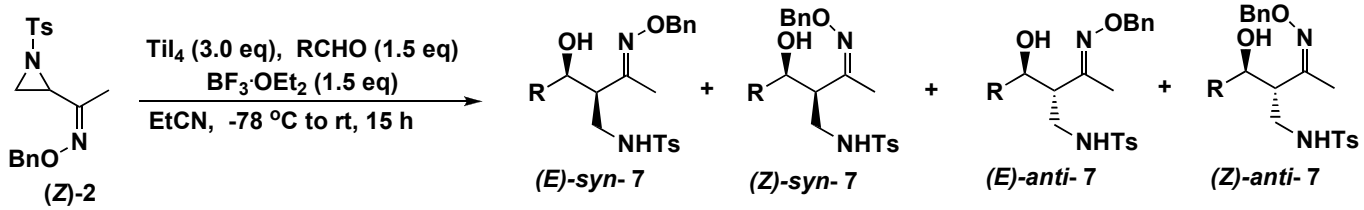
Table 2. Reductive Ring-Opening Aldol Reaction of (*Z*)-**2** with Benzaldehyde under Various Conditions[a]



Entry	Solvent	Additive (eq)	**7a**/%[b]	(*E*)-*syn* : (*Z*)-*syn* : (*E*)-*anti* : (*Z*)-*anti*[c]
1	THF	none	32	0 : 0 : 79 : 21
2	THF	$Ti(O^iPr)_4$ (1.0)	34	47 : 0 : 0 : 53
3	THF	$Ti(O^iPr)_4$ (3.0)	70	39 : 10 : 12 : 39
4	THF	$Ti(O^iPr)_4$ (3.0)[d]	25	36 : 0 : 8 : 56
5	EtCN	none	64	3 : 2 : 6 : 89
6	EtCN	SiO_2[e]	26	6 : 7 : 9 : 78
7	EtCN	MS 4A[f]	59	3 : 2 : 10 : 85
8	EtCN	$BF_3{\cdot}OEt_2$ (1.5)	81	4 : 5 : 3 : 88
9	EtCN	$BF_3{\cdot}OEt_2$ (1.0)	80	4 : 9 : 4 : 83

[a]Reaction was carried out according to the typical procedure (Ref. 5). [b]Isolated yield. [c]Based on isolated isomers. Determination of the relative stereochemistry, see Ref. 6. [d]TiI_4 (1.0 eq) was used. [e]SiO_2 (300 mg / mmol of (*Z*)-**2**) was used. [f]Molecular sieves 4A (300 mg / mmol of (*Z*)-**2**) was used.

Table 3. Reductive Ring-Opening Aldol Reaction of (*Z*)-**2** with Various Aldehydes[a]

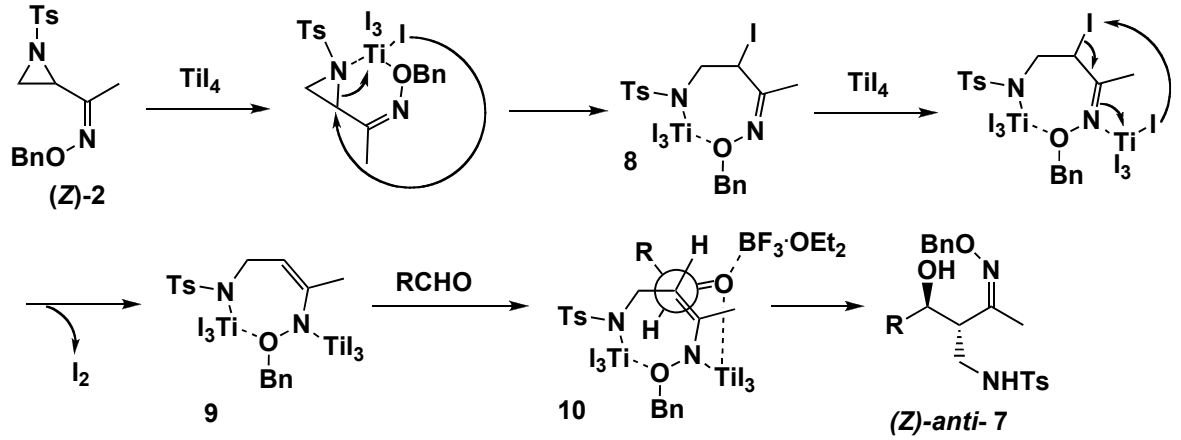


Entry	R	**7**/%[b]	(*E*)-*syn* : (*Z*)-*syn* : (*E*)-*anti* : (*Z*)-*anti*[c]
1	4-$MeOC_6H_4$	100	7 : 14 : 2 : 77
2[d]	4-ClC_6H_4	93	6 : 21 : 4 : 69
3	*cyclo*-C_6H_{11}	54	0 : 23 : 0 : 77
4	$PhCH_2CH_2$	25	0 : 30 : 7 : 63
5[e]	(*E*)-PhCH=CH	85	10 : 15 : 3 : 72

[a]Reaction was carried out according to the typical procedure (Ref. 5). [b]Isolated yield. [c]Based on isolated isomers. [d]The reaction was carried out at -78 to -26 °C for 6 h. [e]The reaction was carried out at -78 to -31 °C for 6 h.

The aromatic aldehydes possessing both electron-donating and electron-withdrawing substituents well participated in the present aza-aldol reaction to give the adducts (**7**) in excellent yields (Entries 1 and 2).

Cinnamaldehyde was also a good electrophile for the present reaction, and the adduct (**7**) was obtained in good yield (Entry 5). Cyclohexanecarbaldehyde, an α-branched aliphatic aldehyde, gave the adduct in moderate yield, whereas 3-phenylpropanal recorded a poor result (Entries 3 and 4). Regarding the diastereoselctivity, in all the cases studied here, (*Z*)-*anti*-isomers were formed with good selectivities. Although more concise experimental outcomes appear to be needed, the high yield and diastereoselectivity in particular case with benzaldehyde may be due to an appropriate coordination ability of the carbonyl oxygen of benzaldehyde to the Lewis acid. The following Scheme 2 shows a possible reaction pathway explaining the predominant formation of the (*Z*)-*anti*-isomer.



Scheme 2.

First, the chelation of TiI_4 to the aziridine ring and to the oxygen atom of the oxime facilitates the ring-opening iodination at the C-2 carbon to form the α-iodo oxime (**8**), which in turn is attacked by another iodide anion to form the aza-enolate (**9**). The addition of an aldehyde is effected by added $BF_3{\cdot}OEt_2$ and also by the chelation with TiI_4 via an intermediate (**10**) to give the adduct (*Z*)-*anti*-(**7**) as a major product.

In conclusion, we have found that TiI_4 promotes the regioselective reductive ring-opening aza-aldol reaction of 2-(1-benzyloxyiminoethyl)aziridines in good to excellent yields with high diastereoselectivities, which contrasts to the case with the corresponding 2-acetyl *N*-tosylaziridine,[1] where the regioselectivity was considerably lost. Since TiI_4 is commercially available and inexpensive, this procedure offers a convenient method for the reductive formation of the β-amino aza-enolate that is a useful synthon for the preparation of hydroxy diamine or hydroxy amino ketones.[7]

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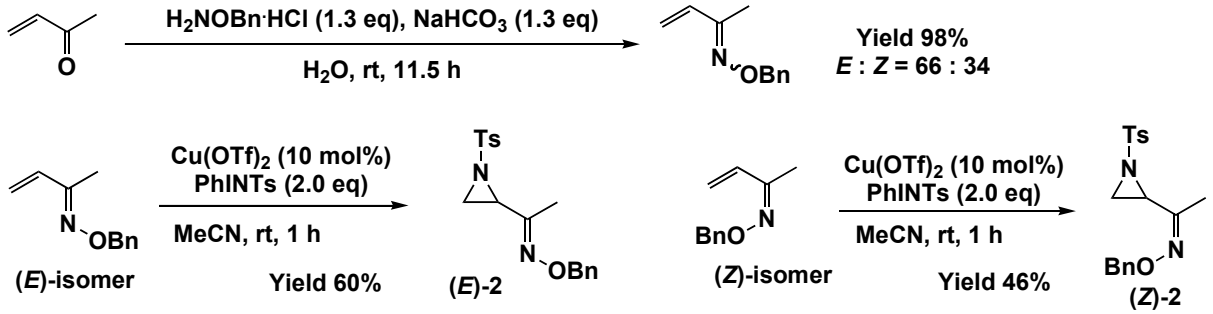
2. The starting 2-(1-benzyloxyiminoethyl)aziridine (**2**) was prepared as follows. Methyl vinyl ketone was transformed into the *O*-benzyl oxime as a mixture of (*E*)- and (*Z*)-isomers under standered conditions. The isomers were readily separated by flash silica gel column chromatography. Each isomer was subjected to the Evans aziridine formation to give (*E*)- and (*Z*)-**2**. For the formation of aziridines, see, D. A. Evans, M. M. Faul, and M. T. Bilodeau, *J. Am. Chem. Soc*., 1994, **116**, 2742.



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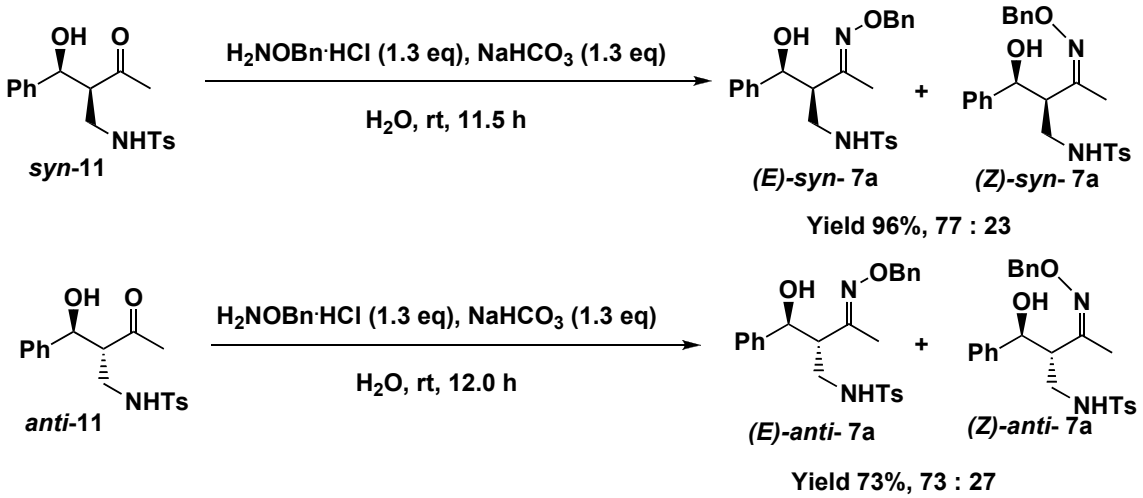
5. Typical experimental procedure is as follows: To a solution of TiI_4 (166 mg, 0.30 mmol) in EtCN (0.6 mL) was added a solution of benzaldehyde (15.9 mg, 0.15 mmol) in EtCN (0.7 ml) at –78 °C under an argon atmosphere. To the resulting solution was added $BF_3{\cdot}OEt_2$ (21.3 mg, 0.15 mmol) and a EtCN (0.7 mL) solution of the (*Z*)-1-(*N*-*p*-tosyl-2-aziridinyl)ethanone *O*-benzyl oxime (**2**) (34.4 mg, 0.10 mmol) at –78 °C. The mixture was allowed to warm to ambient temperature with stirring for 15.0 h. The reaction was quenched with sat. $NaHCO_3$ aq, and AcOEt and 10% $NaHSO_3$ aq. were added successively. The mixture was filtered through a Celite® pad and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification on preparative silica gel TLC (*n*-hexane/CH_2Cl_2/Et_2O = 5 : 3 : 2 as an eluent, developed twice) gave the adducts 4-hydroxy-4-phenyl-3-[(*p*-tosylamino)methyl]butan-2-one *O*-benzyl oxime (**7a**) (81%). (*E*)-*syn*-**7a** (1.6 mg, 3%): Rf = 0.39 (*n*-hexane/CH_2Cl_2/Et_2O = 5 : 3 : 2, developed twice); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.65 (s, 3H), 2.42 (s, 3H), 2.52 (dt, *J* = 4.6, 5.2 Hz, 1H), 3.07-3.10 (m, 2H), 3.30 (d, *J* = 3.1 Hz, 1H), 5.01 (dd, *J* = 3.1, 5.2 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 5.27 (t, *J* = 6.1 Hz, 1H), 7.10-7.12 (m, 2H), 7.21-7.26 (m, 5H), 7.32-7.34 (m, 3H), 7.37-7.41 (m, 2H), 7.58-7.60 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 15.4, 21.5, 41.3, 51.6, 73.8, 75.9, 125.9, 127.0, 127.6, 127.9, 128.0, 128.4, 128.6, 129.6, 136.7, 137.9, 141.0, 143.2, 158.0; IR (neat) 3498, 3295, 3031, 2924, 1598, 1494, 1452, 1409, 1328, 1159, 1092, 1022, 912, 814, 735, 701, 665, 553 cm^{-1}. (*Z*)-*syn*-**7a** (1.1 mg, 2%): Rf = 0.31 (*n*-hexane/CH_2Cl_2/Et_2O = 5 : 3 : 2, developed twice); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58 (s, 3H), 2.42 (s, 3H), 2.75 (dt, *J* = 5.2, 6.7 Hz, 1H), 3.08 (dd, *J* = 6.4, 6.7 Hz, 2H), 3.26 (d, *J* =

7.6 Hz, 1H), 4.79 (dd, *J* = 5.2, 7.6 Hz, 1H), 4.87 (t, *J* = 6.4 Hz, 1H), 5.03 (d, *J* = 12.5 Hz, 1H), 5.06 (d, *J* = 12.5 Hz, 1H), 7.01-7.02 (m, 2H), 7.21-7.40 (m, 10H), 7.61-7.63 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 16.4, 21.5, 43.3, 52.5, 72.9, 75.8, 125.6, 127.0, 127.5, 128.0, 128.1, 128.3, 128.6, 129.7, 136.8, 137.9, 141.8, 143.4, 158.0; IR (neat) 3506, 3279,3031, 2928, 1706, 1598, 1495, 1452, 1327, 1159, 1092, 1020, 815, 738, 701, 664, 552 cm^{-1}. (*E*)-*anti*-**7a** (2.0 mg, 4%): Rf = 0.25 (*n*-hexane/CH_2Cl_2/Et_2O = 5 : 3 : 2, developed twice); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.49 (s, 3H), 2.15 (d, *J* = 3.4 Hz, 1H), 2.42 (s, 3H), 3.25-3.34 (m, 2H), 3.40-3.44 (m, 1H), 4.92-4.95 (m, 2H, including a doublet at δ = 4.93, *J* = 11.9 Hz), 4.96-5.00 (m, 2H, including a doublet at δ = 4.98, *J* = 11.9 Hz), 7.14-7.16 (m, 2H), 7.25-7.38 (m, 10H), 7.66-7.68 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 19.7, 21.5, 42.6, 48.4, 74.0, 75.9, 126.2, 127.2, 128.0, 128.3, 128.4, 128.5, 128.5, 129.7, 136.8, 137.3, 141.6, 143.3, 155.8; IR (neat) 3495, 3290, 3032, 2924, 2254, 1599, 1494, 1452, 1328, 1159, 1092, 1052, 912, 814, 734, 701, 666, 553 cm^{-1}. (*Z*)-*anti*-**7a** (32.6 mg, 72%): Rf = 0.21 (*n*-hexane/CH_2Cl_2/Et_2O = 5 : 3 : 2, developed twice); colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.65 (s, 3H), 2.39 (s, 3H), 2.71 (d, *J* = 4.3 Hz, 1H), 2.91 (ddd, *J* = 5.8, 6.7, 12.8 Hz, 1H), 3.00 (ddd, *J* = 5.8, 8.5, 12.8 Hz, 1H), 3.57 (ddd, *J* = 6.7, 7.3, 8.5 Hz, 1H), 4.77 (dd, *J* = 4.3, 7.3 Hz, 1H), 4.80 (t, *J* = 5.8 Hz, 1H), 4.93 (d, *J* = 11.9 Hz, 1H), 4.99 (d, *J* = 11.9 Hz, 1H), 7.11-7.13 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.24-7.25 (m, 3H), 7.29-7.37 (m, 5H), 7.52 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 18.4, 21.4, 41.4, 46.4, 72.6, 75.8, 126.1, 127.0, 128.0, 128.0, 128.4, 128.5, 129.6, 136.4, 137.2, 141.4, 143.3, 156.6; IR (neat) 3504, 3289, 3032, 2925, 1599, 1494, 1451, 1328, 1159, 1092, 1023, 912, 815, 734, 703, 665, 553 cm^{-1}.

6. The relative stereochemistry of the aza-aldol adducts was determined using the following chemical transformations. We have already established the relative stererochemistry of the adduct *syn*- and *anti*-(**11**).[1] The oxime formation was readily carried out under standard conditions to give a mixture of (*E*)- and (*Z*)-isomers. Examination and comparison of the ^{1}H- and ^{13}C-NMR spectra established the relative stereochemistry.



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