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Diastereoselective Reduction of *E* and *Z* α-alkoxyimino-β-ketoesters by Sodium Borohydride

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Abstract: The reduction of (*Z*)-α-alkoxyimino-β-ketoesters, $R_1COC(=NOR_3)CO_2R_2$ (R_1=Me, Et, $MeOCH_2$, Ph; R_2=Me, Et, $PhCH_2$; R_3=Me, $PhCH_2$) with $NaBH_4$/THF-MeOH at 0 °C gave the corresponding (*Z*)-α-alkoxyimino-β-hydroxyesters in 72-85% yield while the *E* isomers gave a mixture of corresponding (*Z*)- and (*E*)-2-alkoxyimino-1,3-diols in 71-85% yield. The (*E*)-α-alkoxyimino-β-hydroxyesters were obtained in 71-85% yield when the reaction temperature was -72 °C. The ^{13}C-NMR and IR spectra of (*E*)- and (*Z*)-α-oxyimino-β-ketoesters and (*E*)- and (*Z*)-α-alkoxyimino-β-ketoesters, were used for determination of *E/Z* configuration. The C_γ signals in ^{13}C-NMR of *Z* are shifted to higher field and the IR spectra of *E* isomers show a splitting of C=O ester band.

Keywords: oximes; configuration; reduction; sodium borohydride

1. INTRODUCTION

Amino alcohols and amino acids are important components of biologically active compounds.[1] Moreover, they have been widely used in organic synthesis as building blocks and chiral auxiliaries,[2] and offer a considerable challenge to stereochemical controlled and efficient synthetic methods.[3] The reduction of nitrogen containing prochiral ketones[4,5,6] and the addition of carbon nucleophiles to C=N bonds[7,8] were recently reported in the preparation of amino alcohols using α-oxyimino ketones as precursors.

In connection with our interests to find alternative routes to amino acids and amino alchools, we have reported a practical and efficient method to synthesize norephedrine by microbial reduction of a α-methyloxyimino ketone.[9] We are studying now the sodium borohydride reduction of α-alkoxyimino-β-ketoesters. Sodium borohydride is accepted as a mild reducing agent.[10] However, the reducing properties of borohydride can be increased by varying the solvent,[11] by changing the cation,[12] use of catalysts[13] or by the presence of activating substituents.[14]

In this paper, we describe a remarkable selective reduction of esters by $NaBH_4$ influenced by the configuration of the C=N bond in α-alkoxyiminos. Also a spectroscopic method was developed for determination of *E* and *Z* diastereoisomeric configurations of α-oxyimino- and α-alkoxyimino-β-ketoesters using ^{13}C-NMR and IR spectroscopy.

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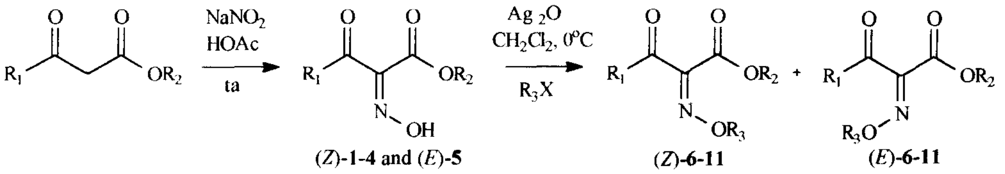
2. RESULTS AND DISCUSSION

The oximation of the corresponding β-ketoesters with sodium nitrite in acetic acid gave α-oxyiminos **1-4** in 51-92% yields with predominantly *Z* configuration as the major product, while α-oxyimino **5** was obtained with *E* configuration in 87% yield. The alkylation of α-oxyiminos **1-5** with alkyl halide/Ag_2O in CH_2Cl_2 gave a mixture of *E/Z* isomers of the corresponding α-alkoxyiminos **6-11** in 86-97% yields (Scheme 1). The (*E*)- and (*Z*)-α-alkoxyimino isomers could be separated and isolated by flash chromatography on silica gel. The methodology that has been used for determination of *E/Z* stereochemistry employs the observation that *Z*-acetoxyimino acids are hydrolyzed to give hydroxylamines whereas the *E*-isomers undergo *trans* decarboxylative elimination to give nitriles.[15] To avoid any problem with isomerization when (*Z*)- or (*E*)-α-oxyimino- and α-alkoxyimino-β-ketoesters are transformed to the corresponding acetoxyimino acids, the ^{13}C-NMR and IR spectra of (*E*)- and (*Z*)-α-oxyimino-β-ketoesters and (*E*)- and (*Z*)-α-alkoxyimino-β-ketoesters were used for determination of *E/Z* configuration.



1	R_1=Me, R_2=Et	**6**	R_1=Me, R_2=Et, R_3=Me
2	R_1=Me, R_2=PhCH$_2$	**7**	R_1=Me, R_2=PhCH$_2$, R_3=Me
3	R_1=Et, R_2=Me	**8**	R_1=Me, R_2=Et, R_3=PhCH$_2$
4	R_1=MeOCH$_2$, R_2=Me	**9**	R_1=Et, R_2=Me, R_3=Me
5	R_1=Ph, R_2=Et	**10**	R_1=MeOCH$_2$, R_2=Me, R_3=Me
		11	R_1=Ph, R_2=Et, R_3=Me

Scheme 1

2.1 NMR Analysis

The NMR spectroscopic characterization of unsymmetrical oxyiminos X-C(=NOH)-Y, where X and Y are alkyl, halide, ether or amine groups, has been performed from studies of the solvent effect,[16] coupling constants $^nJ(^{13}C, ^{13}C)$,[17] chemical displacement with lanthanides,[18] relaxation[19] and steric compression effects.[20] However, there are few systematic studies of *E/Z* oxyimino isomerism when X and Y are ketones, esters, amides, aromatic and heteroaromatic functional groups. Among them, we could mention the use of spin-spin coupling constants $^2J(^{15}N, ^{13}C)$ and ^{15}N-NMR by Jirman *et al.*[21]

The C_γ of α-oxyiminos **1-5** and those of the C_β and C_γ for α-alkoxyiminos-β-ketoesters **6-11** chemical shifts in the ^{13}C-NMR spectra are presented in Tables 1 and 2. The values of chemical shifts of α-oxyiminos (*E*)-**1-4** were obtained from mixtures with prevailing *Z* isomers.

Table 1. Chemical Shifts (δ) in ^{13}C-NMR of oxyiminos $R_1COC(=NOH)CO_2R_2$

R_1	R_2	Comp.	C_γ (δ)	Comp.	C_γ (δ)
Me	Et	(*Z*)-**1**	25.0	(*E*)-**1**	30.0
Me	PhCH$_2$	(*Z*)-**2**	25.0	(*E*)-**2**	30.0
Et	Me	(*Z*)-**3**	30.9	(*E*)-**3**	35.9
MeOCH$_2$	Me	(*Z*)-**4**	73.6	(*E*)-**4**	77.1
Ph	Et			(*E*)-**5**	134.1

Table 2. Chemical Shifts (δ) in ^{13}C-NMR of alkoxyiminos $R_1COC(=NOR_3)CO_2R_2$

R_1	R_2	R_3	Comp.	C_β (δ)	C_γ (δ)	Comp.	C_β (δ)	C_γ (δ)
Me	Et	Me	(*Z*)-**6**	193.1	24.7	(*E*)-**6**	196.7	29.6
Me	$PhCH_2$	Me	(*Z*)-**7**	192.6	25.0	(*E*)-**7**	196.2	30.0
Me	Et	$PhCH_2$	(*Z*)-**8**	193.2	24.9	(*E*)-**8**	196.8	29.7
Et	Me	Me	(*Z*)-**9**	196.1	30.7	(*E*)-**9**	200.1	35.8
$MeOCH_2$	Me	Me	(*Z*)-**10**	190.4	73.2	(*E*)-**10**	197.0	76.8
Ph	Et	Me	(*Z*)-**11**	185.6	135.9	(*E*)-**11**	188.6	134.8

The ^{13}C-NMR chemical shifts of carbon C_γ for (*Z*)- and (*E*)-**1** were assigned to δ=25.3 and 30.3 respectively, by Jirman[21] on the basis of the magnitude of $^2J(^{15}N, ^{13}C)$ coupling constants. They found that $^2J(^{15}N, ^{13}C)$ of the carbon atom *syn* to the non-bonded electron pair at oxyimino nitrogen is 11.2 Hz and the carbon *anti* to the electron pair at nitrogen shows this coupling constant as 0.3 Hz.

The displacement of C_γ signal in ^{13}C-NMR spectrum for the *Z* isomers to lower chemical shift values was also observed in this work for α-oxyimino-**1-4** and α-alkoxyimino-β-ketoesters **6-11**. We found similar chemical shift differences of 5.0 ppm for (*Z*)-oxyiminos **1-3** and 4.8-5.1 ppm for (*Z*)-alkoxyiminos **6-9** where R_1 group is methyl or ethyl. No significant change of these values was observed due to the bulkiness of the R_3 group. When R_1 group is methoxymethyl, chemical shift differences of 3.5 ppm for (*Z*)-oxyimino **4** and 3.6 ppm for (*Z*)-alkoxyimino **10** were observed. We also found 3.0-6.6 ppm shielding for the C_β signal of *Z* isomers **6-11**. The C_β signal of *E* isomers in the *E*/*Z* mixtures of α-oxyiminos **1-4** was not observed due to the low intensity of C_β signals.

2.2 *Infrared Analysis*

The IR stretching vibrations $\nu_{C=O}$ and $\nu_{C=N}$ for α-oxyiminos **1-5** and α-alkoxyiminos-β-ketoesters **6-11** are presented in Tables 3, 4 and 5:

Table 3. Comparison of C=O and C=N Stretching Frequencies (cm^{-1}) in IR of oxyiminos $R_1COC(=NOH)CO_2R_2$

Comp.	R_1	R_2	$\nu_{C=O}$ (ketone)	$\nu_{C=O}$ (ester)	$\nu_{C=N}$
(*Z*)-**1**	Me	Et	1698(s)	1731(s)	1629(w)
(*Z*)-**2**	Me	$PhCH_2$	1684(s)	1744(s)	1627(w)
(*Z*)-**3**	Et	Me	1691(s)	1738(s)	1629(w)
(*Z*)-**4**	$MeOCH_2$	Me	1705(s)	1752(s)	1627(w)
(*E*)-**5**	Ph	Et	1684(s)	1745(s) and 1721(s)	1598(w)

Table 4. Comparison of C=O and C=N Stretching Frequencies (cm^{-1}) of (*Z*)-alkoxyiminos $R_1COC(=NOR_3)CO_2R_2$

Comp.	R_1	R_2	R_3	$\nu_{C=O}$ (ketone)	$\nu_{C=O}$ (ester)	$\nu_{C=N}$
(*Z*)-**6**	Me	Et	Me	1692(s)	1744(s)	1600(w)
(*Z*)-**7**	Me	$PhCH_2$	Me	1693(s)	1746(s)	1599(w)
(*Z*)-**8**	Me	Et	$PhCH_2$	1699(s)	1744(s)	1602(w)
(*Z*)-**9**	Et	Me	Me	1694(s)	1749(s)	1601(w)
(*Z*)-**10**	$MeOCH_2$	Me	Me	1711(s)	1744(s)	1601(w)
(*Z*)-**11**	Ph	Et	Me	1658(s)	1745(s)	1598(w)

Table 5. Comparison of C=O and C=N Stretching Frequencies (cm^{-1}) of (*E*)-alkoxyiminos $R_1COC(=NOR_3)CO_2R_2$

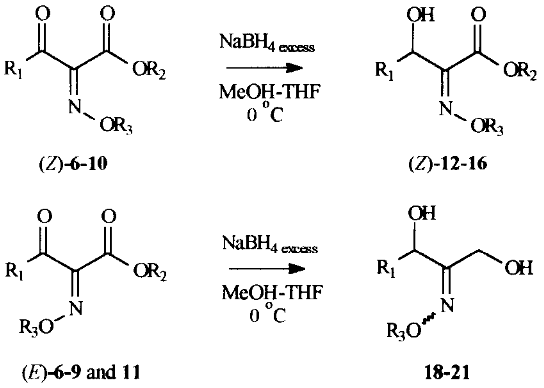
Comp.	**R$_1$**	**R$_2$**	**R$_3$**	**$\nu_{C=O}$ (ketone)**	**$\nu_{C=O}$ (ester)**	**$\nu_{C=N}$**
(*E*)-**6**	Me	Et	Me	1710(s)	1726(s) and 1750(s)	1599(w)
(*E*)-**7**	Me	PhCH$_2$	Me	1712(s)	1725(s) and 1746(s)	1597(w)
(*E*)-**8**	Me	Et	PhCH$_2$	1711(s)	1725(s) and 1746(s)	1600(w)
(*E*)-**9**	Et	Me	Me	1710(s)	1731(s) and 1751(s)	1599(w)
(*E*)-**11**	Ph	Et	Me	1685(s)	1719(s) and 1743(s)	1596(w)

While *E*-isomers show a splitting of C=O ester bands, the *Z*-isomers show only one C=O ester band. Therefore, we can use the IR spectrum of α-oxyimino- and α-alkoxyimino-β-ketoesters for the determination of *E/Z* configuration. Reviewing the literature data, we found that the IR spectrum of oxyimino (*E*)-**5**, that had the stereochemistry assigned by derivatization to acetoxyimino acids, shows a splitting of C=O ester bands while the IR spectrum of oxyimino (*Z*)-**5** shows only one C=O ester band.[22] In addition, the IR spectra of all ethyl (*Z*)-2-alkoxyimino-3-oxobutyrate[22,23] have only one C=O ester band. Another interesting observation is that the C=O ketone band in the IR spectra of *Z* isomers of **6-11** are 12-27 cm^{-1} lower than those for *E* isomers. This may be an indication that the ketone-alkoxyimino conjugation is more pronounced for *Z* isomers.

The ^{13}C-NMR and IR spectra analysis should provide a systematic method for determination of *E/Z* configurations of α-oxyimino- and α-alkoxyimino-β-ketoesters. However it is important to mention that the IR spectrum analysis needs only a pure isomer and the ^{13}C-NMR spectrum analysis needs both isomers for comparison.

2.3 Reduction of E and Z α-alkoxyimino-β-ketoesters by sodium borohydride

The reactions of (*Z*)-α-alkoxyimino-β-ketoesters **6-10** with $NaBH_4$ in large excess using THF-MeOH (10:1) as solvent at 0 °C gave the corresponding (*Z*)-α-alkoxyimino-β-hydroxyesters **12-16** in 72-85% yield (Table 6), where only the ketone group was reduced. On the other hand, the reduction of (*E*)-alkoxyiminos **6-9** and **11** with $NaBH_4$ under the same reaction condition gave a mixture of (*Z*)- and (*E*)-2-alkoxyimino-1,3-diols **18-21** in 71-85% yield, where both ketone and ester groups were reduced (Scheme 2).



12 R_1=Me, R_2=Et, R_3=Me
13 R_1=Me, R_2=PhCH$_2$, R_3=Me
14 R_1=Me, R_2=Et, R_3=PhCH$_2$
15 R_1=Et, R_2=Me, R_3=Me
16 R_1=MeOCH$_2$, R_2=Me, R_3=Me

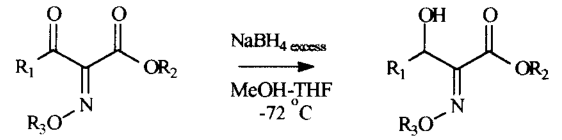
17 R_1=Ph, R_2=Et, R_3=Me
18 R_1=Me, R_3=Me
19 R_1=Me, R_3=PhCH$_2$
20 R_1=Et, R_3=Me
21 R_1=Ph, R_3=Me

Scheme 2

Table 6. Reduction Reaction of (*Z*)- and (*E*)-α-alkoxyimino-β-ketoesters **6-11** by $NaBH_4$ in THF-MeOH (10:1) as Solvent at 0 °C.

Compound	Reaction time (min)	Reaction product	Yield (%)
(*Z*)-**6**	10	(*Z*)-**12**	79
(*Z*)-**7**	10	(*Z*)-**13**	78
(*Z*)-**8**	10	(*Z*)-**14**	85
(*Z*)-**9**	10	(*Z*)-**15**	72
(*Z*)-**10**	10	(*Z*)-**16**	78
(*E*)-**6**	30	**18**	71
(*E*)-**7**	30	**18**	74
(*E*)-**8**	30	**19**	83
(*E*)-**9**	30	**20**	77
(*E*)-**11**	30	**21**	80

It is generally accepted that esters are not resistant to reduction by $NaBH_4$, although the rate of reduction is much slower than for aldehydes and ketones.[24] Therefore one can postulate that for (*Z*)-alkoxyiminos **6-10**, the only reduced group was the ketone group, while for (*E*)-alkoxyiminos **6-9** and **11**, the ketone group should be reduced before the ester group. Two experiments were designed to verify this hypothesis: one with a milder reducing reagent and another with lower reaction temperature. In the first case, the reduction of (*E*)-alkoxyimino **6** was performed by $NaBH_3CN$ in methanol at pH 3 and room temperature.[25] The product was obtained as a mixture of (*E*)-α-alkoxyimino-β-hydroxyester **12** and (*E*/*Z*)-2-alkoxyimino-1,3-diol **18** and some starting material was recovered yet. In the second using the $NaBH_4$ reaction conditions at -72 °C, the isolated product was only the (*E*)-α-alkoxyimino-β-hydroxyester **12** where only the ketone group was reduced. We could therefore prepare the (*E*)-α-alkoxyimino-β-hydroxyester **18-21** in 71-85% yield using the $NaBH_4$ reaction condition at -72 °C (Table 7).



(*E*)-**6-9 and 11** (*E*)-**12-15 and 17**

Scheme 3

Table 7. Reduction Reaction of (*E*)-α-alkoxyimino-β-ketoesters **6-9** and **11** by $NaBH_4$ in THF-MeOH (10:1) as Solvent at -72 °C

Compound	Reaction time (h)	Reaction product	Yield (%)
(*E*)-**6**	3	(*E*)-**12**	71
(*E*)-**7**	3	(*E*)-**13**	84
(*E*)-**8**	6	(*E*)-**14**	81
(*E*)-**9**	4	(*E*)-**15**	71
(*E*)-**11**	12	(*E*)-**17**	85

One can assume that the isomers *Z* and *E* of alkoxyiminos **6-11** have different chemical properties relative to the reduction of the ester group by $NaBH_4$. The ester group, which is less reactive than ketone group, should be more susceptible to small effects which could be influencing this reduction in order to differentiate *Z* and *E* isomers. One possibility is that a steric effect could be operating for *Z* isomer, which has the alkoxy group of the alkoxyimino *syn* to the ester group. Also the nitrogen lone pair *syn* to the ester group for *E* isomers may interact with boron facilitating the hydride transference.

3. CONCLUSIONS

In conclusion, we observed that the isomers *Z* and *E* of alkoxyiminos **6-11** have different chemical properties relative to reduction by $NaBH_4$, and this may be used in selective synthesis of polyfunctional compounds. While the *Z* isomers are reduced only in the keto group, the *E* isomers are reduced in both keto and ester groups. The ^{13}C-NMR and IR spectroscopy were used for determination of *E/Z* configuration of α-oxyimino- and α-alkoxyimino-β-ketoesters.

4. EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FT or Bomem MB series spectrophotometer. NMR spectra were recorded on a Bruker AC 300P or Varian Gemini 300 spectrometer (300 and 75 MHz resonance frequencies for ^1H and ^{13}C , respectively) with $CDCl_3$ as solvent and as internal standard. HRMS spectra were obtained on a Fisons VG Autoespec. Commercially available chemicals and solvents were used without further purification.

General procedure for synthesis of α-oxyimino-β-ketoesters:

The following Adkins and Reeve's method[26] was used: β-ketoester (10 mmol) in glacial acetic acid (5 mL) was cooled to *ca.* 5 °C and treated with a solution of sodium nitrite (12 mmol) in water (3 mL) in a dropwise fashion such that the temperature was maintained lower than 10 °C. After 30 min at room temperature, the solution was poured into water (5 mL) and stirred for 15 min. The product was filtered off, washed with brine and then with water, and dried over $MgSO_4$ to give the respective α-oxyimino-β-ketoester.

Ethyl (Z)-2-hydroxyimino-3-oxobutanoate, (Z)-1

Obtained from ethyl acetoacetate, following the general procedure using similar molar amounts, as a yellow oil in 82% yield, witch solidified when refrigerated to an inseparable mixture 8:92 of *E:Z* isomers. IR (film) ν_{max} cm^{-1}: 3315 (O-H), 1731 and 1698 (C=O), 1629 (C=N); ^1H NMR: δ 1.34 (t, *J*=7.1, 3H, CH_3), 2.40 (s, 3H, $COCH_3$), 4.37 (q, *J*=7.1, 2H, CH_2); ^{13}C NMR: δ 13.6, 25.0, 30.0 (*E*), 62.3, 151.3, 162.1, 194.4; HRMS found *m/z*: 159.0531; calcd. for $C_6H_9NO_4$ $[M]^+$: 159.0532.

Benzyl (Z)-2-hydroxyimino-3-oxobutanoate, (Z)-2

Obtained from benzyl acetoacetate, following the general procedure using similar molar amounts, as a pale yellow oil in 92% yield, as an inseparable mixture 9:91 of *E:Z* isomers. IR (film) ν_{max} cm^{-1}: 3336 (O-H), 1744 and 1684 (C=O), 1627 (C=N); ^1H NMR: δ 2.38 (s, 3H, $COCH_3$, *Z*), 2.44 (s, 3H, $COCH_3$, *E*), 5.29 (s, 2H, CH_2Ph, *E*), 5.34 (s, 2H, CH_2Ph, *Z*), 7.36 (s, 5H, Ph), 10.14 (s, 1H, NOH); ^{13}C NMR: δ 25.0 (*Z*), 30.0 (*E*), 67.7 (*Z*), 68.0 (*E*), 128.4 (*Z*), 128.7 (*Z*), 128.8 (*Z*), 128.6 (*E*), 128.9 (*E*), 130.0 (*E*), 134.5 (*E*), 134.6 (*Z*), 149.7 (*E*), 151.1 (*Z*), 161.9, 194.4; HRMS found *m/z*: 221.0687; calcd. for $C_{11}H_{11}NO_4$ $[M]^+$: 221.0688.

Methyl (Z)-2-hydroxyimino-3-oxopentanoate, (Z)-3

Obtained from methyl propionylacetate, following the general procedure using similar molar amounts, as a yellow oil in 84% yield, witch solidified when refrigerated to an inseparable mixture 8:92 of *E:Z* isomers. IR (film) ν_{max} cm^{-1}: 3353 (O-H), 1738 and 1691 (C=O), 1629 (C=N); ^1H NMR: δ 1.11 (t, *J*=7.3, 3H, CH_3), 2.82 (q, *J*=7.3, 2H, CH_2), 3.90 (s, 3H, OCH_3), 9.97 (s, 1H, NOH); ^{13}C NMR: δ 6.2 (*E*), 7.1, 30.9, 35.9 (*E*), 52.7, 53.0 (*E*), 150.6, 161.6 (*E*), 162.6, 197.2; HRMS found *m/z*: 159.0533; calcd. for $C_6H_9NO_4$ $[M]^+$: 159.0532.

Methyl (Z)-2-hydroxyimino-4-methoxy-3-oxobutanoate, (Z)-4

Obtained from methyl 4-methoxy-acetoacetate, following the general procedure using similar molar amounts, as a yellow solid in 51% yield (m.p. 102-104 °C) as an inseparable mixture 12:88 of *E*:*Z* isomers. IR (KBr) ν_{max} cm^{-1}: 3423 (O-H), 1752 and 1705 (C=O), 1627 (C=N); ^{1}H NMR: δ 3.48 (s, 3H, CH_2OCH_3), 3.89 (s, 3H, CO_2CH_3, *E*), 3.92 (s, 3H, CO_2CH_3, *Z*), 4.35 (s, 2H, CH_2, *E*), 4.57 (s, 2H, CH_2, *Z*), 10.71 (s, 1H, NOH); ^{13}C NMR: δ 52.8 (*Z*), 53.0 (*E*), 59.5 (*Z*), 59.8 (*E*), 73.6 (*Z*), 77.1 (*E*), 148.5 (*E*), 148.9 (*Z*), 161.4, 191.7 (*Z*), 197.9 (*E*); HRMS found *m/z*: 175.0487; calcd. for $C_6H_9NO_5$ $[M]^+$: 175.0481.

Ethyl (E)-2-hydroxyimino-3-oxo-3-phenylpropanoate, (E)-5

Obtained from ethyl benzoylacetate, following the general procedure using similar molar amounts, as a white solid in 87% yield (m.p. 121-122 °C) as an inseparable mixture 2:98 of *Z*:*E* isomers. IR (KBr) ν_{max} cm^{-1}: 3320 (O-H), 1731 and 1672 (C=O), 1596 (C=N); IR (CH_2Cl_2) ν_{max} cm^{-1}: 1745, 1721 and 1684 (C=O), 1598 (C=N); ^{1}H NMR: δ 1.21 (t, *J*=7.1, 3H, CH_3), 4.27 (q, *J*=7.1, 2H, CH_2), 7.51-7.64 (m, 3H, Ph), 7.85-7.89 (m, 2H, Ph); ^{13}C NMR: δ 13.8, 62.6, 129.0, 129.2, 134.1, 134.7, 149.5, 160.7, 190.0; HRMS found *m/z*: 221.0688; calcd. for $C_{11}H_{11}NO_4$ $[M]^+$: 221.0688.

General procedure for synthesis of α-alkoxyimino-β-ketoesters:

The following modified Buehler[27] method was used: silver oxide (5.5 mmol) was slowly added with stirring to a solution of α-alkoxyimino-β-ketoester (5 mmol) and the respective alkyl halide (25 mmol) in CH_2Cl_2 (10 mL) cooled in a ice-water bath. After 30 min, the green precipitate was filtered off and washed with CH_2Cl_2. The solvent was evaporated to give a yellow oil containing *E* and *Z* α-alkoxyimino-β-ketoesters, which were separated by flash chromatography on silica gel with hexane/ethyl acetate (95:5).

Ethyl 2-methoxyimino-3-oxobutanoate, 6

Obtained from (*Z*)-**1**, following the general procedure using similar molar amounts, in 97% yield as a 36:64 of *E*:*Z* isomers.

(*Z*)-**6**: IR (film) ν_{max} cm^{-1}: 1744 and 1692 (C=O), 1600 (C=N); ^{1}H NMR: δ 1.27 (t, *J*=7.1, 3H, CH_3), 2.34 (s, 3H, $COCH_3$), 4.04 (s, 3H, $NOCH_3$), 4.28 (q, *J*=7.1, 2H, CH_2); ^{13}C NMR: δ 13.5, 24.7, 61.8, 64.1, 150.2, 161.3, 193.1; HRMS found *m/z*: 173.0681; calcd. for $C_7H_{11}NO_4$ $[M]^+$: 173.0688.

(*E*)-**6**: IR (film) ν_{max} cm^{-1}: 1750, 1726 and 1710 (C=O), 1599 (C=N); ^{1}H NMR: δ 1.25 (t, *J*=7.1, 3H, CH_3), 2.30 (s, 3H, $COCH_3$), 3.99 (s, 3H, $NOCH_3$), 4.25 (q, *J*=7.1, 2H, CH_2); ^{13}C NMR: δ 13.5, 29.6, 62.1, 63.9, 150.0, 160.1, 196.7; HRMS found *m/z*: 173.0685; calcd. for $C_7H_{11}NO_4$ $[M]^+$: 173.0688.

Benzyl 2-methoxyimino-3-oxobutanoate, 7

Obtained from (*Z*)-**2**, following the general procedure using similar molar amounts, in 94% yield as a 19:81 of *E*:*Z* isomers.

(*Z*)-**7**: IR (film) ν_{max} cm^{-1}: 1746 and 1693 (C=O), 1599 (C=N); ^{1}H NMR: δ 2.38 (s, 3H, $COCH_3$), 4.08 (s, 3H, $NOCH_3$), 5.31 (s, 2H, CH_2Ph), 7.36 (s, 5H, Ph); ^{13}C NMR: δ 25.0, 64.3, 67.4, 128.1, 128.4, 128.5, 134.6, 149.7, 161.0, 192.6; HRMS found *m/z*: 204.0661; calcd. for $C_{12}H_{13}NO_4$ $[M-CH_3O]^+$: 204.0661.

(*E*)-**7**: IR (film) ν_{max} cm^{-1}: 1746, 1725 and 1712 (C=O), 1597 (C=N); ^{1}H NMR: δ 2.27 (s, 3H, $COCH_3$), 3.97 (s, 3H, $NOCH_3$), 5.21 (s, 2H, CH_2Ph), 7.27 (s, 5H, Ph); ^{13}C NMR: δ 30.0, 64.2, 67.7, 128.3, 128.6, 134.5, 149.6, 159.8, 196.2 HRMS found *m/z*: 204.0660; calcd. for $C_{12}H_{13}NO_4$ $[M-CH_3O]^+$: 204.0661.

Ethyl 2-benzyloxyimino-3-oxobutanoate, 8

Obtained from (*Z*)-**1**, following the general procedure using similar molar amounts, in 86% yield as a 45:55 of *E*:*Z* isomers.

(*Z*)-**8**: IR (film) ν_{max} cm^{-1}: 1744 and 1699 (C=O), 1602 (C=N); ^{1}H NMR: δ 1.31 (t, *J*=7.1, 3H, CH_3), 2.38 (s, 3H, $COCH_3$), 4.35 (q, *J*=7.1, 2H, CH_2), 5.32 (s, 2H, CH_2Ph), 7.37 (s, 5H, Ph); ^{13}C NMR: δ 13.7, 24.9, 61.9, 78.5, 128.2, 128.6, 128.7, 136.0, 150.7, 161.4, 193.2; HRMS found *m/z*: 249.1006; calcd. for $C_{13}H_{15}NO_4$ $[M]^+$: 249.1001.

(*E*)-**8:** IR (film) ν_{max} cm^{-1}: 1746, 1725 and 1711 (C=O), 1600 (C=N); ^{1}H NMR: δ 1.32 (t, *J*=7.1, 3H, CH_3), 2.35 (s, 3H, $COCH_3$), 4.32 (q, *J*=7.1, 2H, CH_2), 5.30 (s, 2H, CH_2Ph), 7.35 (s, 5H, Ph); ^{13}C NMR: δ 13.6, 29.7, 62.2, 78.6, 128.4, 128.6, 128.7, 135.7, 150.5, 160.3, 196.8 HRMS found *m/z*: 249.1001; calcd. for $C_{13}H_{15}NO_4$ $[M]^+$: 249.1001.

Methyl 2-methoxyimino-3-oxopentanoate, ***9***

Obtained from (*Z*)-**3**, following the general procedure using similar molar amounts, in 93% yield as a 25:75 of *E*:*Z* isomers.

(*Z*)-**9:** IR (film) ν_{max} cm^{-1}: 1749 and 1694 (C=O), 1601 (C=N); ^{1}H NMR: δ 1.11 (t, *J*=7.3, 3H, CH_3), 2.81 (q, *J*=7.3, 2H, CH_2), 3.86 (s, 3H, CO_2CH_3), 4.08 (s, 3H, $NOCH_3$); ^{13}C NMR: δ 7.2, 30.7, 52.4, 64.2, 149.5, 161.9, 196.1; HRMS found *m/z*: 173.0681; calcd. for $C_7H_{11}NO_4$ $[M]^+$: 173.0688.

(*E*)-**9:** IR (film) ν_{max} cm^{-1}: 1751, 1731 and 1710 (C=O), 1599 (C=N); ^{1}H NMR: δ 1.14 (t, *J*=7.3, 3H, CH_3), 2.66 (q, *J*=7.3, 2H, CH_2), 3.87 (s, 3H, CO_2CH_3), 4.07 (s, 3H, $NOCH_3$); ^{13}C NMR: δ 6.2, 35.8, 52.9, 64.1, 150.1, 161.0, 200.1; HRMS found *m/z*: 173.0686; calcd. for $C_7H_{11}NO_4$ $[M]^+$: 173.0688.

Methyl 2-methoxyimino-4-methoxy-3-oxobutanoate, ***10***

Obtained from (*Z*)-**4**, following the general procedure using similar molar amounts, in 85% yield correspondent to a 13:87 of *E*:*Z* isomers.

(*Z*)-**10:** IR (film) ν_{max} cm^{-1}: 1744 and 1711 (C=O), 1601 (C=N); ^{1}H NMR: δ 3.46 (s, 3H, OCH_3), 3.88 (s, 3H, CO_2CH_3), 4.10 (s, 3H, $NOCH_3$), 4.55 (s, 2H, CH_2); ^{13}C NMR: δ 52.5, 59.2, 64.4, 73.2, 76.8 (*E*), 147.7, 160.3, 190.4, 197.0 (*E*); HRMS found *m/z*: 189.0636; calcd. for $C_7H_{11}NO_5$ $[M]^+$: 189.0637.

Ethyl 2-methoxyimino-3-oxo-3-phenylpropanoate, ***11***

Obtained from (*E*)-**5**, following the general procedure using similar molar amounts, in 96% yield correspondent to a 95:5 of *E*:*Z* isomers.

(*Z*)-**11:** IR (film) ν_{max} cm^{-1}: 1745 and 1658 (C=O), 1598 (C=N); ^{1}H NMR: δ 1.36 (t, *J*=7.1, 3H, CH_3), 4.10 (s, 3H, $NOCH_3$), 4.32 (q, *J*=7.1, 2H, CH_2), 7.38-7.55 (m, 3H, Ph), 8.00-8.02 (m, 2H, Ph); ^{13}C NMR: δ 14.0, 61.3, 63.7,. 128.2, 130.7, 133.2, 135.9, 150.1, 160.1, 185.6; HRMS found *m/z*: 235,0845; calcd. for $C_{12}H_{13}NO_4$ $[M]^+$: 235,0845.

(*E*)-**11:** IR (film) ν_{max} cm^{-1}: 1743, 1719 and 1685 (C=O), 1596 (C=N); ^{1}H NMR: δ 1.29 (t, *J*=7.1, 3H, CH_3), 3.96 (s, 3H, $NOCH_3$), 4.24 (q, *J*=7.1, 2H, CH_2), 7.42-7.53 (m, 3H, Ph), 7.75-7.77 (m, 2H, Ph); ^{13}C NMR: δ 13.9, 61.5, 63.6, 129.0, 129.1, 134.1, 134.8, 149.1, 160.0, 188.6; HRMS found *m/z*: 235,0843; calcd. for $C_{12}H_{13}NO_4$ $[M]^+$: 235,0845.

General procedure for synthesis of (Z)-α-alkoxyimino-β-hydroxyesters:

To a solution of 1 mmol of (*Z*)-α-alkoxyimino-β-ketoesters (*Z*)-**6-10** in 10 mL THF/methanol (10:1) cooled in an ice bath, 4 mmol of sodium borohydride was slowly added. The reaction progress was monitored by TLC. After 10 minutes, a solution of dilute HCl was added until neutralization. The solvent was distillated and the residue was dissolved in 10 mL of water, saturated with NaCl and extracted with ethyl ether (4x15 mL). The extracts were combined, washed with brine and then dried with $MgSO_4$. The solvent was removed by vacuum yielding a pale yellow oil corresponding to the respective (*Z*)-α-alkoxyimino-β-hydroxyesters (*Z*)-**12-16**.

*Ethyl 3-hydroxy-(Z)-2-methoxyiminobutanoate, (Z)-**12***

Obtained in 79% yield from (*Z*)-**6** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3424 (O-H), 1731 (C=O), 1633 (C=N); ^{1}H NMR: δ 1.35 (t, *J*=7.1, 3H, CH_2CH_3), 1.42 (d, *J*=6.6, 3H, $CHOHCH_3$), 3.90 (s, 3H, $NOCH_3$), 4.34 (q, *J*=7.1, 2H, CH_2), 4.59 (q, *J*=6.6, 1H, CHOH); ^{13}C NMR: δ 14.2, 20.8, 62.0, 62.9, 66.9, 153.9, 163.2; HRMS found *m/z*: 160.0610; calcd. for $C_6H_{10}NO_4$ $[M-CH_3]^+$: 160.0610.

*Benzyl 3-hydroxy-(Z)-2-methoxyiminobutanoate, (Z)-**13***

Obtained in 78% yield from (*Z*)-**7** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3423 (O-H), 1735 (C=O), 1629 (C=N); ^{1}H NMR: δ 1.38 (d, *J*=6.6, 3H, CH_3), 2.57 (d, *J*=5.1, 1H, OH), 3.90 (s, 3H, $NOCH_3$), 4.60 (dq, J_1=6.6, J_2=5.9, 1H, CHOH), 5.31 (s, 2H, CH_2Ph), 7.38 (s, 5H, Ph); ^{13}C NMR: δ 20.8, 63.0, 67.0, 67.5, 128.,7, 129.0, 129.1, 135.4, 153.2, 162.8; HRMS found *m/z*: 206.0811; calcd. for $C_{11}H_{12}NO_3$ $[M-CH_3O]^+$: 206.0817.

*Ethyl 3-hydroxy-(Z)-2-benzyloxyiminobutanoate, (Z)-**14***

Obtained in 85% yield from (*Z*)-**8** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3447 (O-H), 1733 (C=O), 1631 (C=N); ^{1}H NMR: δ 1.32 (t, *J*=7.1, 3H, CH_2CH_3), 1.41 (d, *J*=6.6, 3H, $CHOHCH_3$), 2.53 (d, *J*=5.1, 1H, OH), 4.33 (q, *J*=7.1, 2H, CH_2CH_3), 4.59 (dq, J_1=6.6, J_2=5.1, 1H, CHOH), 5.14 (s, 2H, CH_2Ph), 7.33 (s, 5H, Ph); ^{13}C NMR: δ 13.,9, 20.6, 61.7, 66.7, 76.7, 127.9, 127.9, 128.4, 137.0, 153.8, 162.5; HRMS found *m/z*: 206.0817; calcd. for $C_{11}H_{12}NO_3$ $[M-C_2H_5O]^+$: 206.0817.

*Methyl 3-hydroxy-(Z)-2-methoxyiminopentanoate, (Z)-**15***

Obtained in 72% yield from (*Z*)-**9** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3443 (O-H), 1738 (C=O), 1628 (C=N); ^{1}H NMR: δ 0.98 (t, *J*=7.3, 3H, CH_2CH_3), 1.62-1.81 (m, 2H, CH_2), 2.59 (l, 1H, CHOH), 3.85 (s, 3H, CO_2CH_3), 3.91 (s, 3H, $NOCH_3$), 4.35 (l, 1H, CHOH); ^{13}C NMR: δ 8.9, 27.4, 52.2, 62.7, 71.7, 152.4, 163.1; HRMS found *m/z*: 146.0455; calcd. for $C_5H_8NO_4$ $[M-C_2H_5]^+$: 146.0453.

*Methyl 3-hydroxy-(Z)-2-methoxyimino-4-methoxybutanoate, (Z)-**16***

Obtained in 78% yield from (*Z*)-**10** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3442 (O-H), 1736 (C=O), 1628 (C=N); ^{1}H NMR: δ 3.04 (d, *J*=5.1, 1H, OH), 3.41 (s, 3H, CH_2OCH_3), 3.62 (d, *J*=5.1, 2H, CH_2), 3.86 (s, 3H, CO_2CH_3), 3.93 (s, 3H, $NOCH_3$), 4.61 (dt, J_1=5.1, J_2=5.5, 1H, CHOH); ^{13}C NMR: δ 52.2, 59.1, 62.8, 69.3, 73.7, 150.0, 162.7; HRMS found *m/z*: 146.0464; calcd. for $C_5H_8NO_4$ $[M-C_2H_5O]^+$: 146.0453.

General procedure for (E)-α-alkoxyimino-β-hydroxyesters :

To a solution of 1 mmol of (*E*)-α-*O*-alkoxyimino-β-ketoesters (*E*)-**6-9** and **11** in 10 mL THF/methanol (10:1) cooled in a dry-ice/ethanol bath (-72 °C), 4 mmol of sodium borohydride was slowly added. The reaction progress was monitored from 3-12 hours by TLC. The work up was the same as described above, yielding a yellow oil corresponding to the respective (*E*)-α-alkoxyimino-β-hydroxyesters (*E*)-**12-15** and **17**.

*Ethyl 3-hydroxy-(E)-2-methoxyiminobutanoate, (E)-**12***

Obtained in 71% yield from (*E*)-**6** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3468 (O-H), 1727 (C=O), 1601 (C=N); ^{1}H NMR: δ 1.36 (t, *J*=7.1, 3H, CH_2CH_3), 1.43 (d, *J*=7.1, 3H, $CHOHCH_3$), 3.47 (d, *J*=11.0, 1H, OH), 4.05 (s, 3H, $NOCH_3$), 4.28-4.43 (m, 2H, CH_2), 4.99-5.07 (m, 1H, CHOH); ^{13}C NMR: δ 13.8, 20.9, 61.9, 63.4, 63.5, 153.7, 163.4; HRMS found *m/z*: 160.0609; calcd. for $C_6H_{10}NO_4$ $[M-CH_3]^+$: 160.0610.

*Benzyl 3-hydroxy-(E)-2-methoxyiminobutanoate, (E)-**13***

Obtained in 81% yield from (*E*)-**7** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3448 (O-H), 1718 (C=O), 1602 (C=N); ^{1}H NMR: δ 1.43 (d, *J*=6.8, 3H, CH_2CH_3), 3.38 (d, *J*=11.4, 1H, OH), 4.05 (s, 3H, $NOCH_3$), 5.04 (dq, J_1=6.8, J_2=11.4, 1H, CHOH), 5.31 (dt, J_1=12.4, J_2=8.3, 2H, CH_2Ph), 7.27-7.41 (m, 5H, Ph); ^{13}C NMR: δ 21.1, 63.5, 63.6, 67.3, 128.3, 128.4, 128.6, 135.0, 153.3, 162.9; HRMS found *m/z*: 206.0811; calcd. for $C_{11}H_{12}NO_3$ $[M-CH_3O]^+$: 206.0817.

*Ethyl 3-hydroxy-(E)-2-benzyloxyiminobutanoate, (E)-**14***

Obtained in 84% yield from (*E*)-**8** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3519 (O-H), 1722 (C=O), 1603 (C=N); ^{1}H NMR: δ 1.36 (t, *J*=7.0, 3H, CH_2CH_3), 1.43 (d, *J*=6.6, 3H, $CHOHCH_3$), 3.45 (d, *J*=11.3, 1H, OH), 4.26-4.41 (m, 2H, CH_2CH_3), 5.02-5.13 (m, 1H, CHOH), 5.28 (s, 2H, CH_2Ph), 7.36 (s, 5H, Ph); ^{13}C NMR: δ 14.0, 21.2, 62.0, 63.6, 78.1, 128.2, 128.3, 128.5, 136.0, 153.8, 163.1; HRMS found *m/z*: 206.0817; calcd. for $C_{11}H_{12}NO_3$ $[M-C_2H_5O]^+$: 206.0817.

*Methyl 3-hydroxy-(E)-2-methoxyiminopentanoate, (E)-**15***

Obtained in 71% yield from (*E*)-**9** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3460 (O-H), 1732 (C=O), 1602 (C=N); ^{1}H NMR: δ 0.98 (t, *J*=7.3, 3H, CH_2CH_3), 1.65-1.84 (m, 2H, CH_2), 3.31 (d, *J*=11.7, 1H, CHOH), 3.87 (s, 3H, CO_2CH_3), 4.05 (s, 3H, $NOCH_3$), 4.79-4.87 (m, 1H, CHOH); ^{13}C NMR: δ 9.5, 28.1, 52.6, 63.5, 68.5, 152.8, 164.0; HRMS found *m/z*: 146.0456; calcd. for $C_5H_8NO_4$ $[M-C_2H_5]^+$: 146.0453.

*Ethyl 3-phenyl-3-hydroxy-(E)-2-methoxyiminopropanoate, (E)-**17***

Obtained in 85% yield from (*E*)-**11** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3492 (O-H), 1719 (C=O), 1601 (C=N); ^{1}H NMR: δ 1.35 (t, *J*=7.1, 3H, CH_3), 3.95 (d, *J*=11.8, 1H, CHOH), 4.08 (s, 3H, $NOCH_3$), 4.24 (q, *J*=7.1, 2H, CH_2CH_3), 5.96 (d, *J*=11.8, 1H, CHOH), 7.29 (s, 5H, Ph); ^{13}C NMR: δ 13.8, 60.9, 62.9, 67.2, 125.2, 127.1, 127.9, 139.9, 150.8, 162.7; HRMS found *m/z*: 206.0809; calcd. for $C_{11}H_{12}NO_3$ $[M-CH_3O]^+$: 206.0817.

General procedure for (E/Z)-2-alkoxyimino-1,3-diols:

To a solution of 1 mmol of (*E*)-α-alkoxyimino-β-ketoesters (*E*)-**6-9** and **11** in 10 mL THF/methanol (10:1) cooled in an ice bath, 4 mmol of sodium borohydride was slowly added. The reaction progress was monitored from 10-30 minutes by TLC. The work up was the same as described above, yielding a yellow oil corresponding to a mixture 1:1 of (*E*)- and (*Z*)-2-alkoxyimino-1,3-diols **18-21**. The *E/Z* configuration of **18-21** was determined by observation of steric compression effect in the ^{13}C-NMR.[20]

*2-methoxyimino-1,3-butanediol, **18***

Obtained in 71% yield from (*E*)-**6** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3385 (O-H), 1638 (C=N); ^{1}H NMR: δ 1.37 (d, *J*=7.0, 3H, CH_3, *Z*), 1.39 (d, *J*=6.6, 3H, CH_3, *E*), 3.22 (l, 4H, two OH of *Z* and two OH of *E*), 3.84 (s, 3H, $NOCH_3$, *Z*), 3.85 (s, 3H, $NOCH_3$, *E*), 4.29 (d, *J*=5.5, 2H, CH_2OH, *Z*), 4.44 (s, 2H, CH_2OH, *E*), 4.51 (q, *J*=6.6, 1H, CHOH, *E*), 4.93 (q, *J*=7.0, 1H, CHOH, *Z*); ^{13}C NMR: δ 20.1 (*Z*), 20.5 (*E*), 57.2 (*E*), 60.6 (*Z*), 61.9 (*Z*), 62.0 (*E*), 64.4 (*Z*), 67.7 (*E*), 160.9 (*E*), 161.3 (*Z*); HRMS found *m/z*: 118.0505; calcd. for $C_4H_8NO_3$ $[M-CH_3]^+$: 118.0504. Also obtained from (*E*)-**7** in 74% yield.

*2-benzyloxyimino-1,3-butanediol, **19***

Obtained in 83% yield from (*E*)-**8** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3385 (O-H), 1633 (C=N); ^{1}H NMR: δ 1.39 (d, *J*=7.0, 3H, CH_3, *Z*), 1.41 (d, *J*=6.6, 3H, CH_3, *E*), 2.72-2.90 (ml, 4H, two OH of *Z* and two OH of *E*), 4.33 (s, 2H, CH_2OH, *Z*), 4.48 (s, 2H, CH_2OH, *E*), 4.53 (q, *J*=6.6, 1H, CHOH, *E*), 4.98 (q, *J*=7.0, 1H, CHOH, *Z*), 5.01 (s, 2H, CH_2Ph, *E* and 2H, CH_2Ph, *Z*), 7.34 (s, 5H, Ph, *E* and 5H, Ph, *Z*); ^{13}C NMR: δ 20.3 (*Z*), 20.7 (*E*), 57.7 (*E*), 60.9 (*Z*), 64.8 (*Z*), 67.8 (*E*), 76.4 (*Z*), 76.5 (*E*), 128.0, 128.1, 128.2, 128.5, 137.2 (*Z*), 137.3 (*E*), 161.2 (*E*), 161.4 (*Z*); HRMS found *m/z*: 191.0947; calcd. for $C_{11}H_{13}NO_2$ $[M-H_2O]^+$: 191.0946.

*2-methoxyimino-1,3-pentanediol, **20***

Obtained in 77% yield from (*E*)-**9** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3385 (O-H), 1636 (C=N); ^{1}H NMR: δ 0.97 (t, *J*=7.3, 3H, CH_3, *E*), 1.00 (t, *J*=7.3, 3H, CH_3, *Z*), 1.64-1.84 (m, 2H, CH_2CH_3, *E* and 2H, CH_2CH_3, *Z*), 2.76-2.93 (ml, 4H, OH), 3.86 (s, 3H, $NOCH_3$, *Z*), 3.89 (s, 3H, $NOCH_3$, *E*), 4.,3-4.29 (m, 1H, CHOH, *E*), 4.31 (dd, J_1=5.5, J_2=9.7, 2H, CH_2OH, *Z*), 4.41 (d, *J*=6.2, 2H, CH_2OH, *E*), 4.69-4.73 (m, 1H, CHOH, *Z*); ^{13}C NMR: δ 9.2 (*E*), 9.5 (*Z*), 27.2 (*Z*), 27.5 (*E*), 57.3 (*E*), 61.2 (*Z*), 61.9 (*Z*), 62.1 (*E*), 69.8 (*Z*), 73.0 (*E*), 160.2 (*E*), 160.4 (*Z*); HRMS found *m/z*: 118.0504; calcd. for $C_4H_8NO_3$ $[M\text{-}C_2H_5]^+$: 118.0504.

1-phenyl-2-methoxyimino-1,3-propanediol, ***21***

Obtained in 80% yield from (*E*)-**11** following the general procedure using similar molar amounts. IR (film) ν_{max} cm^{-1}: 3386 (O-H), 1631 (C=N); ^{1}H NMR: δ 2.77 (l, 1H, CH_2OH, *E*), 3.02 (l, 1H, CH_2OH, *Z*), 3.58-3.61 (l, 1H, CHOH, *E* and 1H, CHOH, *Z*), 3.85 (s, 3H, $NOCH_3$, *Z*), 3.93 (s, 3H, $NOCH_3$, *E*), 4.19 (dd, J_1=5.9, J_2=14.3, 1H, one of CH_2OH, *Z*), 4.23 (dd, J_1=5.5, J_2=13.9, 2H, CH_2OH, *E*), 4.37 (dd, J_1=5.1, J_2=14.3, 1H, one of CH_2OH, *Z*), 5.38 (d, *J*=5.5, 1H, CHOH, *E*), 5.98 (d, *J*=5.1, 1H, CHOH, *Z*), 7.26-7.41 (m, 5H, Ph, *E* and 5H, Ph, *Z*); ^{1}H NMR (D_2O): δ 3.82 (s, 3H, $NOCH_3$, *Z*), 3.90 (s, 3H, $NOCH_3$, *E*), 4.14 (d, *J*=14.3, 1H, one of CH_2OD, *Z*), 4.21 (d, *J*=3.3, 2H, CH_2OD, *E*), 4.32 (d, *J*=14.3, 1H, one of CH_2OD, *Z*), 5.36 (s, 1H, CHOD, *E*), 5.97 (s, 1H, CHOD, *Z*), 7.21-7.40 (m, 5H, Ph, *E* and 5H, Ph, *Z*). ^{13}C NMR: δ 57.2 (*E*), 60.7 (*Z*), 62.0 (*Z*), 62.3 (*E*), 69.3 (*Z*), 73.5 (*E*), 126.1, 126.3, 127.9, 128.0, 128.5, 128.6, 130.6, 139.6, 158.4 (*Z*), 159.0 (*E*); HRMS found *m/z*: 164.0705; calcd. for $C_9H_{10}NO_2$ $[M\text{-}CH_3O]^+$: 164.0712.

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