1,3-Dipolar Cycloaddition or Nucleophilic Addition: Influence of Solvents and Nature of Substituents in the Reagent and Substrate Molecules on the Reaction of 4,5-Dihydro-1*H*-imidazole 3-oxides with Alkynes

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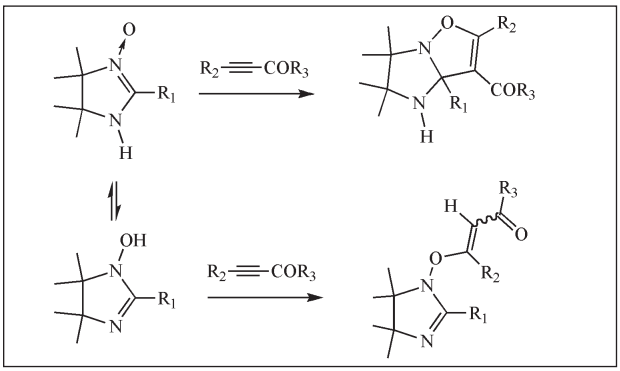
Received May 16, 2005



Two competitive processes - 1,3-dipolar cycloaddition and nucleophilic addition - in the reaction of 4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole 3-oxides with asymmetrically substituted alkynes were shown to occur. The influence of solvents and the nature of substituents in the reagent and substrate molecules on the rate ratio of these competitive processes were studied.

J. Heterocyclic Chem., **43**, 293 (2006).

Introduction.

It was recently demonstrated that N-substituted derivatives of 4,5-dihydro-1*H*-imidazole 3-oxide can be involved in 1,3-dipolar cycloaddition reactions with alkynes and alkenes [1-4]. On the other hand, this transformation for N-non-substituted derivatives seemed unobvious up to a recent time because these compounds, as we have shown previously [5], exist in solution as the mixture of two tautomeric forms - aminonitrone **1A** and N-hydroxyaminoimine **1B** (Scheme 1). The equilibrium between these two forms depends essentially on the solvent and the nature of a substituent at position 2 of the heterocycle. Apparently, only form **1A** can act as dipole (Scheme 1, path I), while N-hydroxyaminoimine **1B** is capable of taking part in the reaction only as a nucleophile, that should result in the addition on the activated triple bond (products **3(*E*, *Z*)**, Scheme 1, path II). The presence of substituent at position 2 of 4,5-dihydro-1*H*-imidazole 3-oxide can, therefore, be an important factor influencing the reaction path and even excluding the possibility of cycloaddition, at all.

In our previous paper it was shown, however, that derivatives of 4,5-dihydro-1*H*-imidazole 3-oxide without substituent at position 1 can act as dipoles in the reaction with alkynes bearing electron withdrawing substituent [6]. Taking into account both the above statements as well as the essential difference between the transition states in the cycloaddition and nucleophilic addition, one can imply that the solvent nature should influence on the ratio of the reaction paths. Thus, the aim of the present work is to study the influence of solvent on the reaction of 4,5-dihydro-1*H*-imidazole 3-oxide with alkynes.

Results and Discussion.

Tautomeric equilibrium **1A** $\rightleftharpoons$ **1B** itself is not a sufficient condition for the reaction of nucleophilic addition to compete with 1,3-dipolar cycloaddition. The possibility of this alternative path and formation of the corresponding nucleophilic addition products is, however, confirmed by analysis of ^{1}H NMR spectra of the reaction mixtures formed upon reacting of asymmetric alkynes with **1**. Since 1,3-dipolar cycloaddition to nitrones usually is considered as a concerted process [7,8], the alteration of the solvent properties (polarity) should not change significantly the k_1 value [9-11] (Scheme 1). The solvent, however, influences equilibrium concentrations of **1A** and **1B**: the increase of solvent polarity enlarges the amount of nitrone form **1A** [5]. Thereby, the total 1,3-dipolar cycloaddition reaction rate mainly changes not because of the influence of the solvent on k_1 but as a result of changing reactive substrate concentration. The rate constant of the addition process k_2, on the contrary, depends considerably on parameters of the medium. One can suppose that the limiting stage of the process is the formation of zwitterion **4** or anion **5** and thus, the value of a total constant k_2 is seemed to be close

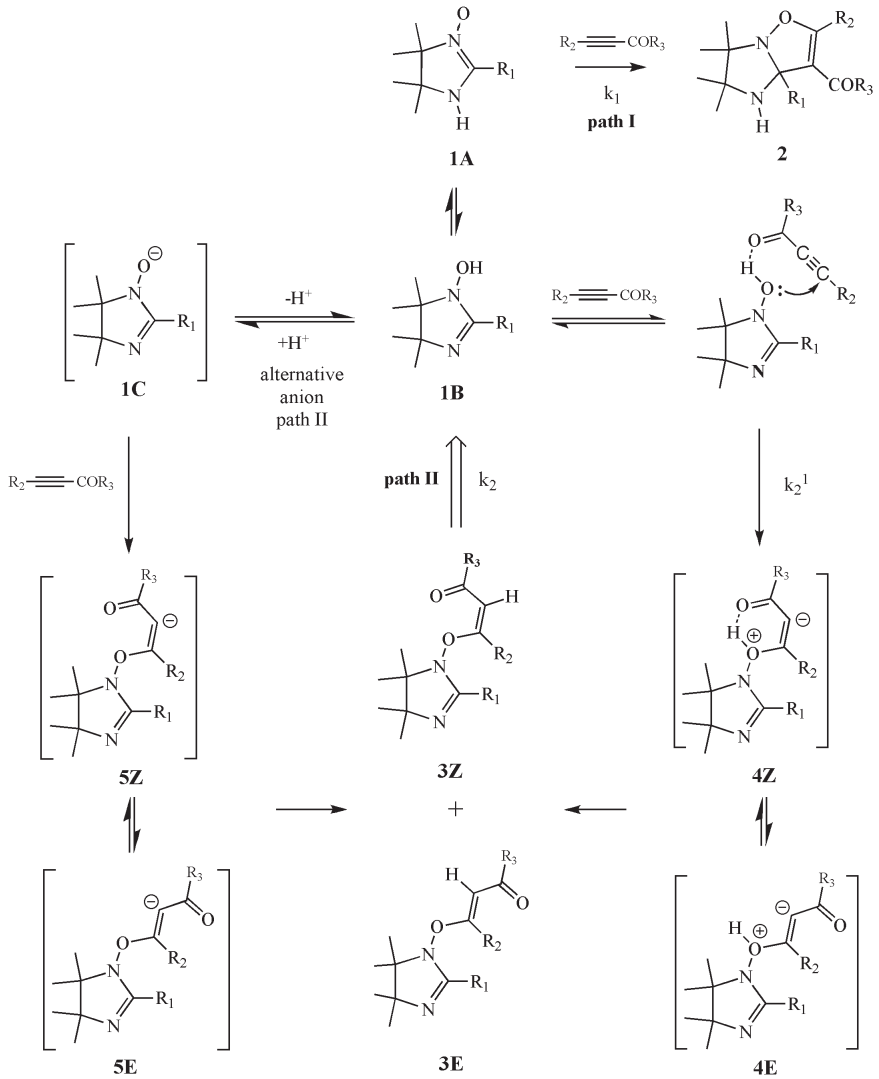
to k_2 [1] (Scheme 1). The enhance of solvent polarity has to increase the k_2 value because the intermediate compounds **4(*E*, *Z*)** are much more polar than the initial substrates. At the same time, as it was mentioned, concentration of reagent **1B** decreases. Consequently, the resultant reaction rate increases due to the influence of the solvent on k_2 but, on the other, hand it diminishes because of decreasing concentration of reagent **1B**.

methyl propiolate (Table 1).

The data presented on Figure 1 shows a linear dependence between dipole moment (μ) of the solvent and the ratio of the addition and cycloaddition products **(3*E*+3*Z*** and **2**, respectively) for solvents not capable of specific significant interacting both with reagents and products.

Polar aprotic solvents such as DMSO influence the aminonitrone - N-hydroxyaminoimine equilibrium

Scheme 1



R_1 = Me (a), CF_3 (b), tert-Bu (c), Ph (d), CH=CHPh (e), 4-NO_2-C_6H_4 (f)
R_2 = H, Ph; R_3 = H, OMe

Variation of solvents has been shown to change noticeably the composition of reaction products, which is revealed on an example of reaction of 2,4,4,5,5-pentamethyl-4,5-dihydro-1*H*-imidazole 3-oxide **1A** with

increasing **1B** concentration due to formation of more stable hydrogen bond in this tautomer form [5] (Figure 2). This impedes, at the same time, nucleophilic attack of the hydroxy group, and, as a result, no addition products are

Table 1

Ratio of addition products **3(E,Z)** and cycloaddition product **2** in the reaction of methyl propiolate with 2,4,4,5,5-pentamethyl-4,5-dihydro-1*H*-imidazole 3-oxide **1a**.†

Solvent	ε	μ (D)	2 / 3*Z*	***3Z* / 3*E***	**2 / (3*E* + 3*Z*)**
Hexane	1.89	0.08	2.2	20	2.10
CCl_4	2.23	0	2	6.6	1.74
Benzene	2.28	0	3.3	4	2.64
Hexafluorobenzene	-	0	3	8	2.67
Ether	4.34	1.15	16	2.8	11.79
Octafluorotoluene	-	1.26	3	5	2.5
Pentafluorobenzene	-	1.6	3	3.5	2.33
$CHCl_3$	4.7	1.87	7	2.1	4.74
Fluorobenzene	5.42	1.6	3.2	3	2.4
Ethylacetate	6.02	1.78	23	2.1	15.58
THF	7.32	1.63	58	1.9	38
CH_2Cl_2	8.9	1.6	6.3	2.8	4.64
$PhCF_3$	9.18	2.86	1.6	3.2	1.22
1,2-Dichloroethane	10.4	1.44	5.4	3.4	4.17
Acetone	20.7	2.88	70	4	56
CH_3CN	36.2	3.92	20	4.5	16.36
CH_3NO_2	38.6	3.46	2.8	2.4	1.98
Triethylamine	2.42	0.66	15.5	0.025	0.38
DMSO	49	3.96	> 100	-	> 100
MeOH	32.6	1.70	0.023	4.4	0.019

† Ratio of addition products **3E, 3Z** and cycloaddition product **2** was shown to be constant on the varying of reaction time from 1 hour to 1 week.

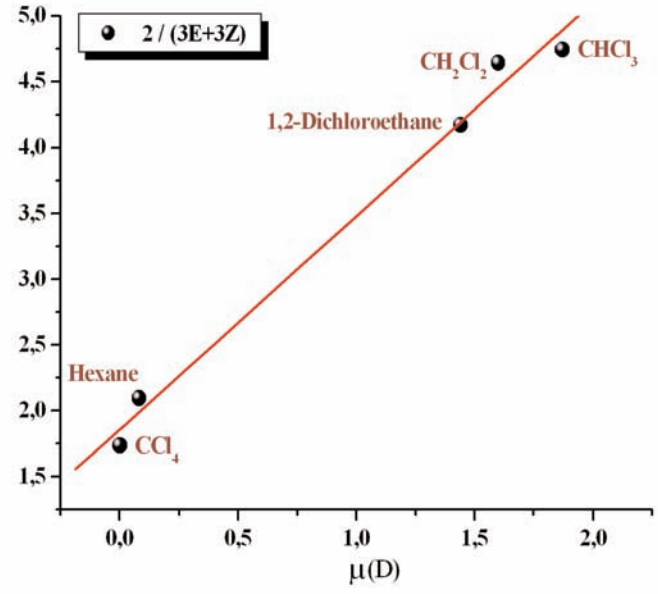


Figure 1. Dependence of the ratio of reaction products **2 / (3E+3Z)** on dipole moment μ (D) of the solvent. **2 / (3E+3Z)** = 1.86 + 1.62·μ(D), R = 0,995.

formed in reaction in DMSO solution (Table 1).

Similarly, an increase of dielectric constant of the solvent noticeably decreases the ratio of addition products in case of oxygen-containing aprotic solvents which are also

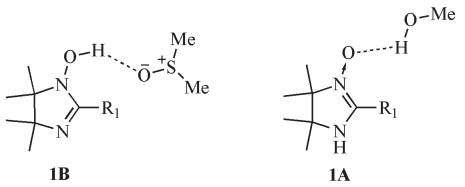


Figure 2. Stabilisation of tautomeric forms **1A** and **1B** by intermolecular hydrogen bonds.

capable of forming hydrogen bonds of the same type (Table 1, Figure 3).

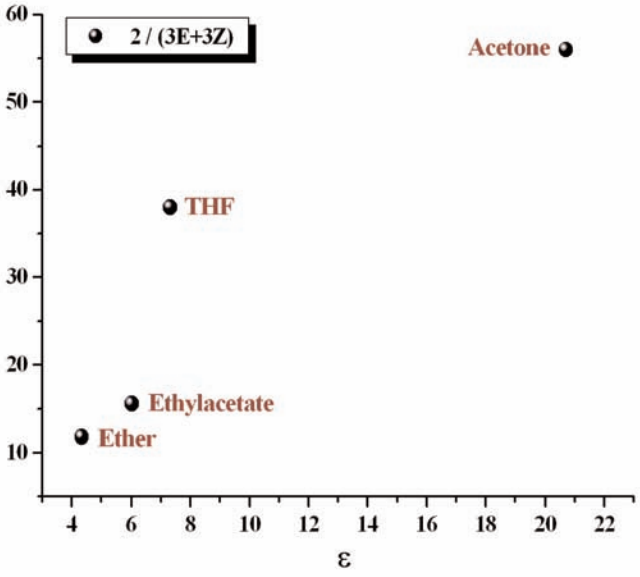


Figure 3. Dependence of the ratio of the reaction products **2 / (3E+3Z)** on dielectric constant ε of the solvent.

Methanol as protic solvent, *vice versa*, stabilizes form **1A** (Figure 2), and the hydrogen bond in this case blocks the nitrone group that impede 1,3-dipolar cycloaddition. For example, the reaction of **1a** with methyl propiolate in methanol results in the predominance of the addition products over the cycloaddition product (Table 1). The overall reaction in methanol proceeds much slower than in chloroform that is the result of decreasing cycloaddition reaction rate rather than accelerating competitive nucleophilic addition process.

In basic solvent such as triethylamine, which promotes deprotonation of the hydroxy group, the alternative anion path of the addition (path II, Scheme 1) is possible, and thus, the addition reaction is accelerated while the rate of the cycloaddition process is decreased.

The distinctive influence of the solvent on the products composition is observed when the reaction is carried out in aromatic solvents. Thus, in case of fluorinated benzenes,

the reverse proportion between the content of cycloaddition product and solvent polarity is observed (Figure 4, *cf.* Figure 1).

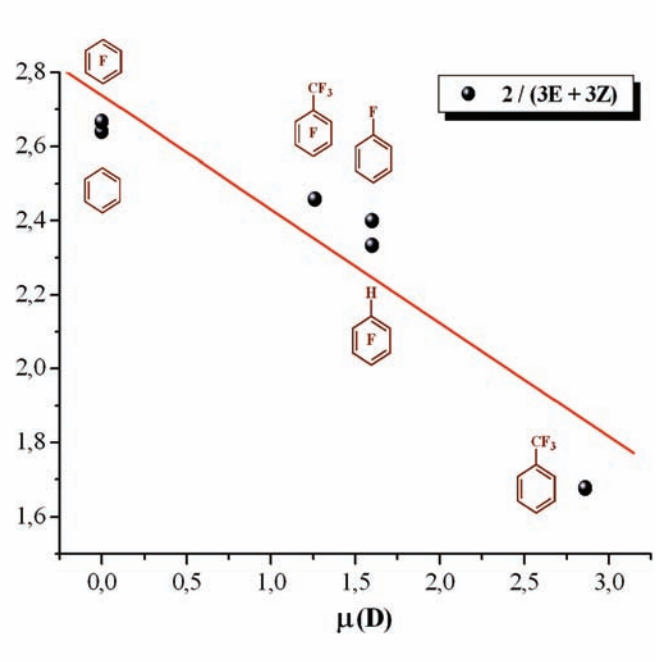


Figure 4. Dependence of the ratio of the reaction products **2** / (**3*E*+3*Z***) on polarity μ (D) of aromatic solvent.

Table 2

Ratio of the products in the reaction of 2-substituted derivatives of 4,5-dihydro-1*H*-imidazole 3-oxide **1a-f** with alkynes according to NMR ^{1}H data.

	R_2	R_3	2 (%)	***3Z* (%)**	***3E*** (%)	Solvent
	H	H	68	0	32	$CHCl_3$
	H	OMe	83	12	5	$CHCl_3$
	H	OMe	24	3	73	$CHCl_3$ + NEt_3 (≈1%)
1a	H	OMe	2	80	18	MeOH
	Ph	H	100	0	0	$CHCl_3$
	Ph	H	90	10	0	MeOH
	Ph	OMe	100	0	0	$CHCl_3$
	Ph	OMe	90	10	0	MeOH
	Ph	OMe	79,5	20,5	0	MeOH + NEt_3 (10:1)
1b	H	OMe	82,5	0	17,5	$CHCl_3$
	H	OMe	98	0	2	THF
1c	H	OMe	90	10	0	$CHCl_3$
	H	OMe	28	58	14	MeOH
	H	OMe	100	0	0	$CHCl_3$
1d	H	OMe	80	17	3	MeOH
	H	OMe	48	17	35	MeOH + NEt_3 (10:1)
1e	H	OMe	100	0	0	$CHCl_3$
1f	H	OMe	100	0	0	$CHCl_3$

Thus, on the example of reaction of 2,4,4,5,5-pentamethyl-4,5-dihydro-1*H*-imidazole 3-oxide **1a** with methyl propiolate it was shown that cycloaddition and nucleophilic addition are competitive processes, and solvents essentially influence their ratio.

Since, as it was mentioned above, the substituent nature can also affect the reaction path, reactions of a scope of 2-substituted derivatives of 4,5-dihydro-1*H*-imidazole 3-oxide **1a-e** with asymmetric alkynes were studied (Table 2).

The results presented in Table 2 demonstrate significant influence of the nature of the substituent at position 2 of the derivatives of 4,5-dihydro-1*H*-imidazole 3-oxide on the ratio of products of competitive reactions. In case of substituents capable of efficient conjugation with π-system of imidazoline ring (compounds **1d-f**), as against to 2-alkyl substituted substrates **1a-c**, the addition products **4** are not formed when the reaction is carried out in chloroform. Both in chloroform and in methanol the addition reaction of **1** with methyl propiolate results in formation of less thermodynamically stable isomer ***Z***. This fact can be associated with the initial coordination of alkyne molecule with **1B** due to the formation of hydrogen bond between hydroxyl and ester groups. As a consequence, zwitterion **4*Z*** and then *trans*-addition product **3*Z*** are predominantly formed (Scheme 1). *Trans*-addition product **3*E*** can be formed either as a result of the initial nucleophilic attack of the lone electron pair of oxygen of the hydroxyl group or because of rotation round the C=C bond in zwitterion **4*Z***.

When **1b**, bearing strong electron withdrawing trifluoromethyl group at position 2, reacts with methyl propiolate, the only addition product is isomer **3*E***. In this case, ionized form **1C** acts as nucleophile, probably, that excludes a possibility of stabilization of anions **5*Z*** or **5*E*** through the intermolecular hydrogen bond, and more thermodynamically stable anion **5*E*** and corresponding product **3*E*** are predominantly formed (Scheme 1). Just the alternative anionic path of the reaction likely provides a significant change of the ratio of methyl propiolate addition products in favour of isomer ***E*** in the case of **1a** and **1d** when ionization ability of the medium increases (*e.g.*, on addition of triethylamine) (Table 2). Addition of 3-phenylprop-2-ynal and methyl 3-phenylprop-2-ynoate results in the formation of more stable isomers **3*Z*** corresponding to intermediates **4*Z*** formation, stabilized by hydrogen bond.

Conclusion.

The tautomeric equilibrium of N-unsubstituted derivatives of 4,5-dihydro-1*H*-imidazole 3-oxide **1** in solutions provides their two competitive reaction paths with asymmetrically substituted alkynes – addition and cycloaddition. The solvent is shown to influence significantly the rate ratio of these two processes that allows, in some cases, the reaction to be directed almost totally on one or another path. In particular, methanol as a solvent directs reaction towards the addition products, while DMSO, *vice versa*, promotes the 1,3-cycloaddition reaction. The nature of substituent at position 2 of the imidazoline ring also influences noticeably the composition of the reaction mixtures.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Bruker AC–200 spectrometer and ^{19}F NMR spectra were recorded on WP–200 spectrometer; solvents were used as internal standards (C_6F_6 was used as internal standards in case of ^{19}F NMR). IR spectra were recorded with a Bruker IFS 66 spectrometer for 1% solutions in CCl_4. UV spectra were measured with Specord M-40 spectrophotometer in EtOH. High resolution mass spectra were recorded on a Finnigan MAT 8200 mass spectrometer with direct sample injection at a resolution of 10,000 with ionized power 70 eV. Thin layer chromatography was carried out on alumina plates (Fluka, Switzerland) with chloroform and chloroform/MeOH (from 50:1 to 20:1) as eluents. The solutions were evaporated *in vacuo* in all cases.

4,4,5,5-Tetramethyl-4,5-dihydro-1*H*-imidazole 3-oxides **1** were synthesized according to ref. [5] Spectral data of cycloadducts **2** are identical to obtained earlier [6].

General Procedure.

A solution of alkyne (0.12 mmol) in 1 ml of corresponding solvent was added to a cooled (0 -10 °C) solution of **1** (0.1 mmol) in 3 ml of the same solvent with vigorous stirring. The reaction was carried out at room temperature up to disappearance of starting **1** (TLC monitoring). After the completion of the reaction the solvent was evaporated, ^1H NMR spectra of the reaction mixture were registered, and the ratio of products was determined. ^1H NMR spectral data are presented in Table 3.

Methyl (2*E*)-3-[(2,4,4,5,5-Pentamethyl-4,5-dihydro-1H-imidazol-1-yl)oxy]acrylate (**3E**) and Methyl (2*Z*)-3-[(2,4,4,5,5-Pentamethyl-4,5-dihydro-1H-imidazol-1-yl)oxy]acrylate (**3Z**) (R_1=Me, R_2=H, R_3=OMe).

Methyl propiolate (0.63 mmol) solution in 2 ml of methanol was added to the cooled (0 - -10 °C) solution of **1a** (0.082 g, 0.53 mmol) in 3 ml of methanol with vigorous stirring. The reaction was carried out at room temperature. After the completion of the reaction (20 h) the solvent was evaporated. Isomers ***E*** and ***Z*** were separated chromatographically on alumina with hexane-ethylacetate (8:1) mixture as eluent. The yield was 0.009 g (7%) and 0.065 g (52%), respectively (oil in both cases).

Isomer ***E***: NMR ^1H ($CDCl_3$, 200.13 MHz, δ, ppm) 1.11 (s, 12H, 4,4,5,5-CH_3), 1.90 (s, 3H, 2-CH_3), 3.70 (s, 3H, CO_2CH_3), 5.64 (d, J_3=12.2 Hz, 1H, OCH=C*H*-CO_2CH_3), 7.67 (d, J_3=12.2 Hz, 1H, OC*H*=CH-CO_2CH_3). λ_{max}, (ethanol), nm (lg ε): 226 (4.18), 259 (3.94). ν_{max} (CCl_4), cm^{-1}: 2985, 2931, 2858, 1721, 1638, 1436, 1381, 1312, 1278, 1166, 1123, 1048, 958, 890, 839. Found, m/z: 240,14751. Calculated for $C_{12}H_{20}N_2O_3$, m/z: 240,14738.

Isomer ***Z***: NMR ^1H ($CDCl_3$, 200.13 MHz, δ, ppm) 1.03, 1.08 (each s, 6H, 4,4,5,5-CH_3), 1.89 (s, 3H, 2-CH_3), 3.61 (s, 3H, CO_2CH_3), 4.76 (d, J_3=7.4 Hz, 1H, OCH=C*H*-CO_2CH_3), 6.78 (d, J_3=7.4 Hz, 1H, OCH=C*H*-CO_2CH_3). NMR ^{13}C ($CDCl_3$, 50.32 MHz, δ, ppm): 14.2 (2-CH_3), 18.9 (broad s, 4-CH_3 & 5-CH_3), 23.3 (4,5-$(CH_3)_2$), 50.7 (CO_2CH_3), 67.2 (C-4), 72.2 (C-5), 95.0 (OCH=*C*H-CO_2CH_3), 161.2 (O*C*H=CH-CO_2CH_3), 163.1 (C-2), 164.7 (CO_2CH_3). λ_{max}, (ethanol), nm (lg ε): 232 (4.18). ν_{max} (CCl_4), cm^{-1}: 2988, 2950, 1724, 1639, 1437, 1381, 1301, 1260, 1193, 1170, 1095, 1074, 1006, 891. Found, m/z: 240,14727. Calculated for $C_{12}H_{20}N_2O_3$, m/z: 240,14738.

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Table 3

NMR ^1H data of the addition products **3** in $CHCl_3$.

R_1	R_2	R_3	Isomer	NMR ^1H and ^{19}F, ppm				
				R_1	R_2	R_2C=C*H*-	R_3	4,4,5,5-CH_3
CF_3	H	OMe	***E***	85.09 s, 3F	7.48 d, 1H (12.5 Hz)	5.02 d, 1H (12.5 Hz)	3.79 s, 3H	1.13, 1.14 s, 12H
	H	H	***E***	1.87 s, 3H	7.45 d, 1H (12.5 Hz)	5.93 dd, 1H (12.5 Hz, 8.1 Hz)	9.37 d, 1H (8.1 Hz)	1.08 s, 12H
Me	H	OMe	***Z***	1.89 s, 3H	6.78 d, 1H (7.4 Hz)	4.76 d, 1H (7.4 Hz)	3.61 s, 3H	1.03, 1.08 s, 12H
	H	OMe	***E***	1.90 s, 3H	7.67 d, 1H (12.2 Hz)	5.64 d, 1H (12.2 Hz)	3.70 s, 3H	1.11 s, 12H
	Ph	H	***Z***	1.96 s, 3H	7.30-7.57 m, 5H	6.33 d, 1H (8.1 Hz)[b]	9.48 d, 1H (8.1 Hz)	1.17 s, 12H
	Ph	OMe	***Z***	1.94 s, 3H	7.34-7.85 m, 5H	6.05 s, 1H[c]	3.55 s, 3H	1.02, 1.17 s, 12H
t-Bu	H	OMe	***Z***[a]	1.24 s, 9H	7.06 d, 1H (7.5 Hz)	4.96 d, 1H (7.5 Hz)	3.67 s, 3H	1.22 s, 12H
	H	OMe	***E***[a]	1.24 s, 9H	7.65 d, 1H (12.6 Hz)	5.27 d, 1H (12.6 Hz)	3.71 s, 3H	1.22 s, 12H
Ph	H	OMe	***Z***	7.09-8.12 m, 5H	6.34 d, 1H (7.1 Hz)	4.74 d (7.1 Hz)	3.73 s, 3H	1,14 s, 12H
	H	OMe	***E***	7.09-8.12 m, 5H	7.52 d, 1H (12.5 Hz)	5.09 d, 1H (12.5 Hz)	3.59 s, 3H	1,14 s, 12H

[a][D_4]methanol; [b]6.35; [c]5.59 - chemical shifts for similar structures, *cf*. [12].

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