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Isothiazoles. Part X. New 3-Substituted-2-arylpropenamidines by Base Catalyzed Ring Opening of 3-Amino-4-arylisothiazole 1,1-dioxides.

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Abstract. Starting from 5-unsubstituted or 5-alkyl-, aryl-, heteroarylsubstituted 3-diethylamino-4-arylisothiazole 1,1-dioxides by base induced ring opening 3-alkoxypropenamidines were synthesized in excellent yields in a mild and efficient way. When 5-bromo-3-diethylamino-4-arylisothiazole 1,1-dioxide was used as the reagent, 3,3-dialkoxy-propenamidines, a new class of unsaturated amidines, were obtained. By using Grignard reagents 3-substituted acrylamidines can be produced.

Keywords: Ring opening; Isothiazoles; Amidines; Sulfur heterocycles.

Introduction

Amidines are structural parts of numerous compounds of biological interest and form important medical and biochemical agents. [1-2]

As known, amidines find widespread applications in organic synthesis especially for preparation of various heterocyclic systems. Although syntheses of amidines have been vigorously explored, few examples of unsaturated amidines (*e.g.* propenamidines) are reported in the literature and, particularly, of 3-hetero-substituted propenamidines.[3-6] The interest in this field prompted us to explore the possibility of using the 3-amino-isothiazole 1,1-dioxide ring as an appropriate precursor of a new class of substituted propenamidines. In our laboratory we developed three main synthetic approaches to make available 3-amino-isothiazole 1,1-dioxides substituted at C-5.[7-9] By these methodologies the preparation of derivatives unsubstituted or bearing at C-5 alkyl-, aryl-, heteroaryl-, vinyl- groups or substituents linked through an O- S- or N- atom is possible. In this paper we describe an efficient synthesis of 3- and 3,3-disubstituted 2-arylpropenamidines by base induced ring opening of 3-amino-4-arylisothiazole 1,1-dioxides. The availability of a great number of substituted 3-amino-4-arylisothiazole 1,1-dioxides, allowed the preparation both of a wide range of propenamidines with 3-alkyl-, aryl-, heteroaryl-, alkynyl-substitution which are not easy to synthesize by other methods and of several 3-alkoxy or 3,3-dialkoxy-propenamidines representing a new class of unsaturated amidines.

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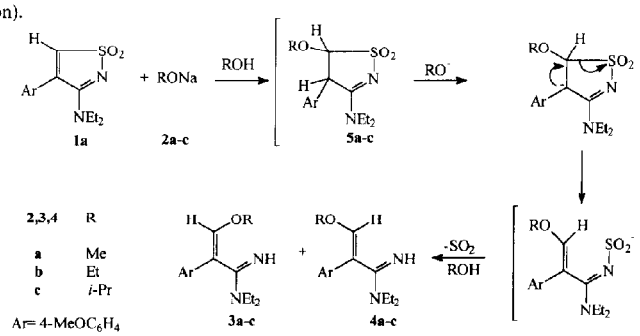
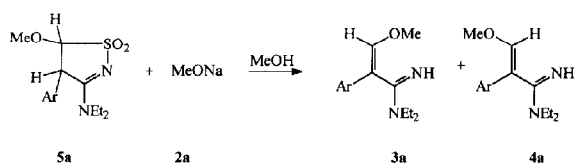
Results and Discussion

By reacting 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**1a**) with a solution of two equivalents of sodium alkoxide (**2a-c**) in the corresponding alcohol at room temperature rapid disappearance of **1a** was observed. Upon work-up, the reaction mixture afforded in good yield (70-90%) two stereoisomeric products which were identified as 3-alkoxy-*N,N*-diethyl-2-(4-methoxyphenyl)-propenamidines **3a-c** (*Z* form) and **4a-c** (*E* form) in a ratio of about 3:1 respectively. Compounds **3b,c** and **4b,c** were obtained in mixture as uncristallizable oils while pure **3a** could be isolated from the isomeric mixture by cristallizing with Et_2O. Pure samples of all isomers could be easily obtained by HPLC separation (see: Structure Characterization).



Scheme 1

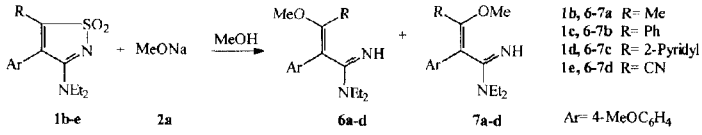
In a previous work we demonstrated that C-5 in the 3-amino-4-aryl-isothiazole 1,1-dioxide moiety is the more electrophilic carbon and nucleophiles attack at this position by a Michael-type reaction.[10] It is known that 3-amino-4-arylisothiazole 1,1-dioxides easily react with alcohols in presence of a catalytic amount of the corresponding alkoxide and form *trans* and *cis* 5-alkoxy-4,5-dihydroisothiazole dioxide derivatives in a mixture where the *trans* isomer is the major one.[9]



Scheme 2

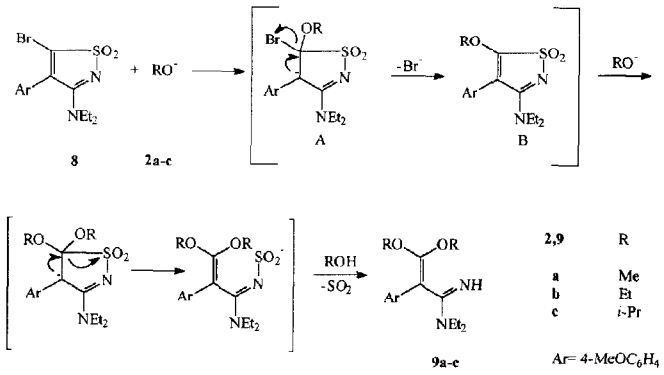
In the present case by using two equivalents of alkoxide we assumed that the 4,5-dihydro intermediate would react with another equivalent of the alkoxide with deprotonation at C-4. Ring opening of the anion and

spontaneous SO_2 elimination results in the formation of **3** and **4** (Scheme 1). This was confirmed by an independent experiment where 3-diethylamino-4,5-dihydro-5-methoxy-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide **5a** was reacted with sodium methoxide in methanol at room temperature. Rapid disappearance of **5a** was observed and elaboration of the reaction mixture afforded **3a** and **4a** in a ratio of about 3:1. The results were the same, also in terms of isomer ratio, performing the reaction with sodium methoxide on the *cis* or on the *trans* or on the mixture of the two isomers (Scheme 2). These results prompted us to investigate the possibility to make this reaction more general to obtain 3-substituted-3-alkoxypropenamidines from 5-substituted isothiazole 1,1-dioxides. Starting from 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxides (**1b-e**) with the same procedure described above, 3-alkoxypropenamidines **6a-d** (*E* form) and **7a-d** (*Z* form), with different substituents on C-3, were synthesized. The *E* isomer was predominant possibly owing to the lower steric hindrance and in the case of compounds **a-c** only traces of the *Z* isomer 7 were detected (Scheme 3).



Scheme 3

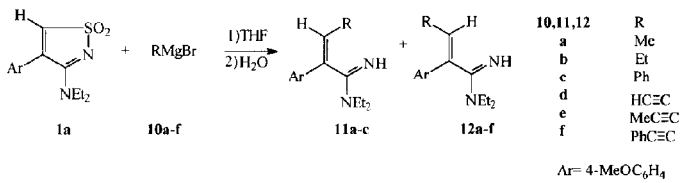
When the reaction using different alkoxides in alcohols was performed on 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**8**), 3,3-dialkoxysubstituted propenamidines **9a-c** were formed. A reasonable mechanism for the formation of compounds **9** is depicted in Scheme 4.



Scheme 4

As an extension, we took into consideration the applicability of this ring opening reaction for the synthesis of the 3-alkyl, aryl, alkynyl-substituted propenamidines by reacting isothiazole 1,1-dioxide with Grignard reagents. Reaction of compound **1a** with **10a-f** in anhydrous THF at room temperature afforded in good yields the expected isomeric propenamidines **11a-c** and **12a-f**. It appeared reasonable that a reaction mechanism similar to that described above for the reaction between **1** or **8** and alkoxides was operative.

In the case of **11a-c** and **12a-c** a mixture of *E* and *Z* isomers in a ratio of about 2/3:1 was obtained. Only one isomer was observed performing the reaction between **1a** and **10 d-f** affording *E* isomer **12 d-f**. By this way highly conjugated systems of promising reactivity could be easily prepared (Scheme 5).



Scheme 5

Structure Characterization

^{1}H-, ^{13}C-NMR and IR spectra were performed in order to characterize all compounds and to clarify, when needed, the configuration at the double bond. HPLC analyses of the isomeric mixtures were also performed using a CH_3CN : H_2O mixture in a 2:8 ratio as mobile phase with NaH_2PO_4 1mg/mL and flow rate 0.7 mL/min. By this method analytical pure samples of each isomer or of the major one were obtained and analyzed by NMR techniques. To establish the configuration of the double bond we performed NOE difference and NOESY experiment observing the spatial relationship between the *o,o'* hydrogens of the 4-methoxy substituted aromatic ring on C-2 and the characteristic substituent on C-3, that is, for compounds **3/4a-c** and **6/7a-d**, the methoxy group and for **11/12a-f** the hydrogen or the alkyl group.

^{1}H-NMR of compounds **3a-c** and **4a-c** were mainly characterized by a sharp singlet in the range of 6.40-6.50 δ associated with H-3 and a broad singlet exchangeable with D_2O clearly associated with the NH group (IR NH 3300-3600 cm^{-1}). The signals associated with the *o,o'* hydrogens of the 4-methoxy substituted aromatic ring appeared to be shifted by 0.3-0.4 δ in one isomer of each pair with respect to the other. In the ^{13}C-NMR spectra of **3a** and **4a** the chemical shift (55.70 δ) of the methoxy groups on the aromatic ring and of the methoxy groups on C-3 (60.8 δ) of each isomer appeared to be overlapped. A little difference (about 2 δ) in the chemical shifts are evident for C-3 and C-1. The double bond configuration of the *Z*-isomer **3a**, isolated from the reaction mixture through crystallization from Et_2O, was assigned by NOESY experiment showing a clear relationship between the aromatic protons (7.20 δ) and the hydrogen on C-3 (6.43 δ). The couple **3b/4b, 3c/4c** were separated by HPLC and configuration was established through n.O.e experiments

as explained above. ^{1}H-NMR spectra of compounds **6/7** were mainly characterized by two singlets associated with the two methoxy groups and by the double doublets of the AX system associated with the hydrogens of the 4-methoxy substituted aromatic ring that always show a clear difference of chemical shift between the two isomers. It has to be noted that only one isomer was obtained pure in the case of **6/7 a-c**, only traces of the other isomer being detected by NMR and HPLC analyses. For **6a/7a** a small difference of the chemical shift of the methyl group on C-3 (*Z* isomer 1.97 δ; *E* isomer 2.06 δ) was also observed. In the ^{1}H-NMR spectra of **6c/7c** characteristic signals of the aromatic pyridine hydrogens were observed. In the case of the couple **6,7d** the isomer **7d** could be isolated by crystallizing from Et_2O and the configuration at the double bond was assigned by NMR performing NOESY and NOE difference experiments: the methoxy signal at lower field could be associated with the methoxy group on the aromatic ring due to a clear n.O.e with the hydrogens of the 4-methoxy substituted aromatic ring on C-2 at 6.92 δ. The other methoxy group showed no effect with the aromatic ring thus confirming the *Z* configuration of **7d.** Compounds **9a-e** showed very simple ^{1}H-and ^{13}C-NMR spectra mainly characterized by the signals of two methoxy-, ethoxy or *iso*propoxy group respectively. The same procedure applied for **3/4** and **6/7** were also applied to establish the structure of compounds **11/12**. ^{1}H-NMR spectra of compounds **11a/12a** and **11b/12b** were mainly characterized by the signals associated with H-3 shifted by 0.2-0.3 δ in one isomer with respect to the other. In the ^{13}C-NMR spectra the signals associated with the methoxy groups of each isomer appeared overlapped. Instead, the singlets associated with C-3, C-1 and the aromatic quaternary carbons are separated by about 2 δ in each isomer . Only one isomer was obtained when the reaction with **1a** was performed with Grignard reagents **10d-f**. In all cases the configuration of the double bond of the more abundant *E* isomer was assigned by performing n.O.e experiments as explained above.

Conclusion

In conclusion we have demonstrated that 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxides are suitable materials for the synthesis of substituted 2-arylpropenamidines through base induced ring opening. By this method two new classes of compounds, 3-alkoxy- and 3,3-dialkoxypropenamidines could be synthesized. This reaction could be applied also for the synthesis of 2-arylpropenamidines bearing alkyl-, alkynyl-, aryl substituents on C-3 and represents a good alternative to the known methods due to the mild reaction conditions and the high yields (70-90%).

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were obtained with Bruker AC 200, Bruker AC 300 and Varian Gemini 200 instruments. Melting points were determined using a Buchi 510 (capillary) or a Electrothermal 9100 apparatus. Mass spectra were obtained by electron impact ionization at 70 eV from a Finningan INCOS 50

instrument using the direct exposure probe (DEP). IR spectra were recorded on a JASCO IR Report 100 spectrophotometer. HPLC analyses were performed on a Perkin Elmer LC 250 instrument, UV-visible detector LC 290, column Lichrocart 125-3 Purosphere RP18e (5μm). Mobile phase, CH_3CN : H_2O (2:8) NaH_2PO_4 1mg/mL, flow rate 0.7 mL/min..

Materials

Compounds **1a-e, 5** and **8** have already been described.[7-11] Grignard reagents **10a-c** are commercially available in 3.0 *M* sol. in Et_2O, **10d** in 1.0 *M* sol. in THF, **10e,f** in 0.5 *M* sol. in THF (Aldrich).

Synthesis of Propenamidines 3a-c and 4a-c:

Compound **1a** (0.15 g, 0.5 mmol) was dissolved in the appropriate alcohol (10 mL) and sodium alkoxide **2a-c** (5 mL of a 0.2 molar solution) was added under stirring at room temperature. When the reagent disappeared (T.L.C. cyclohexane/ethyl acetate 1:1; CH_2Cl_2/MeOH 10:1) water (5 mL) was added and stirring continued for 1 h. Alcohol evaporation and extraction with CH_2Cl_2 (10 mL) afforded the mixture of isomeric compounds **3a-c** and **4a-c**. Compounds **3b,c** and **4b,c** were obtained in mixture as oils while pure **3a** could be isolated from the isomeric mixture by cristallizing with Et_2O. Pure samples of all isomers could be easily obtained by HPLC separation.

N,N-Diethylamino-3-methoxy-2-(4-methoxyphenyl)-propenamidines Z-3a, E-4a. Total yield 85%. **3a** (white crystals): M.p. 86°C (Et_2O). IR (Nujol) 3100-3600 cm^{-1} (NH).^{1}H-NMR ($CDCl_3$): 0.90-1.20 (m, 6H, CH_3); 3.20-3.50 (m, 4H, CH_2); 3.74 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 6.43 (s, 1H, H-3); 6.83 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.00-7.30 (bs, 1H, NH, exch.); 7.20 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 13.50, 42.36, 55.70, 60.87, 114.68, 119.31, 126.4, 127.24, 144.53, 158.73, 163.75. Calcd. for $C_{15}H_{22}N_2O_2$ (262.35): C 68.67, H 8.45, N 10.68 found C 68.64, H 8.37, N 11.10. *m/z* 262 (M^+) **4a** (mixture with **3a**): ^{1}H-NMR ($CDCl_3$): 0.90-1.20 (m, 6H, CH_3); 3.10-3.40 (m, 4H, CH_2); 3.74 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 6.36 (s, 1H, H-3); 6.85 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.20-7.40 (bs, 1H, NH, exch.); 7.46 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 13.70, 42.20, 56.15, 61.20, 114.10, 118.52, 128.42, 129.50, 146.60, 159.00, 166.30. *m/z* 262 (M^+).

N,N-Diethylamino-3-ethoxy-2-(4-methoxyphenyl)-propenamidines Z-3b, E-*4b.* Total yield 90%. IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 1.03-1.15 (m, 6H+6H); 1.29 (t, *J* 7 Hz, 3H); 1.34 (t, *J* 7 Hz, 3H); 3.10-3.50 (m, 4H+4H, NCH_2); 3.78 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 3.95 (q, *J* 7 Hz, 2H); 3.97 (q, *J* 7 Hz, 2H); 6.00-6.30 (bs, 1H, NH, exch.); 6.41 (s, 1H, H-3, *E* isomer); 6.43 (s, 1H, H-3, *Z* isomer); 6.82 (d, AB system, *J* 9 Hz, 2H, aryl-H); 6.85 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.20 (d, AB system, *J* 9 Hz, 2H, aryl-H, *Z* isomer); 7.48 (d, AB system, *J* 9 Hz, 2H, aryl-H, *E* isomer). ^{13}C-NMR ($CDCl_3$): 13.39, 15.82, 42.91, 55.70, 69.54 (*E*), 70.06, 114.22 (*E*), 114.81, 126.43, 129.57 (*E*), 127.06, 128.16 (*E*), 144.16, 146.40 (*E*), 158.78, 159.18 (*E*), 163.61, 166.31 (*E*). Calcd. for $C_{16}H_{24}N_2O_2$ (276.38): C 69.53, H 8.75, N 10.14 found C 69.84, H 8.62, N 9.80. *m/z* 276 (M^+). HPLC: *E* isomer r. t. 5.9 min., *Z* isomer r.t. 9.93 min.

N,N-Diethylamino-3-isopropoxy-2-(4-methoxyphenyl)-propenamidines Z-3c, E-4c. Total yield 70%. IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 1.04 (t, J 7 Hz, 6H+6H); 1.27 (d, J 6.2 Hz, 6H); 1.33 (d, J

6.2 Hz, 6H); 3.28 (q, NCH_2, J 7 Hz, 4H+4H); 3.79 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 4.07 (sept, J 6.2 Hz, 1H+1H); 5.80-6.01 (bs, 1H, NH, exch.); 6.45 (s, 1H, H-3); 6.47 (s, 1H, H-3); 6.83 (d, AB system, *J* 9 Hz, 2H, aryl-H, *E* isomer); 6.85 (d, AB system, *J* 9 Hz, 2H, aryl-H, *Z* isomer); 7.21 (d, AB system, *J* 9 Hz, 2H, aryl-H, *Z* isomer); 7.51 (d, AB system, *J* 9 Hz, 2H, aryl-H, *E* isomer). ^{13}C-NMR ($CDCl_3$): 13.49, 22.94, 42.55, 55.63, 76.13 (*E*), 76.73, 114.10 (*E*), 114.70, 126.36, 129.48 (*E*), 117.41 (*E*), 118.26, 127.44 (*E*), 128.72, 142.56 (*E*), 144.60, 158.58 (*E*), 158.98, 164.04, 166.73. Calcd. for $C_{17}H_{26}N_2O_2$ (290.41): C 70.31, H 9.02, N 9.65 found C 70.64, H 8.87, N 9.40. (*E*). *m/z* 290 (M^+). HPLC: *E* isomer r. t. 25.13 min., *Z* isomer r.t. 38.7 min.

*Synthesis of Propenamidines **6a-d** and **7a-d**:*

Compounds **1b-e** (0.65 mmol) were dissolved in methanol (10 mL) and sodium methoxide **2a** (70.10 mg, 1.30 mmol) was added under stirring at room temperature. When the reagent disappeared (T.L.C. cyclohexane/ethyl acetate 1:1; CH_2Cl_2/MeOH 10:1) water (5 mL) was added and stirring continued for 1 h. Methanol evaporation and extraction with CH_2Cl_2 (20 mL) afforded compounds **6a-d** and **7a-d**. In the case of compounds **a-c** the *E* isomers **6** were obtained and only traces of **7** were detected by NMR and/or HPLC analyses. A mixture of **6d/7d** was obtained (**6**/**7** about 1:5 calculated by NMR) and pure **7d** isolated by crystallization with Et_2O.

*N,N-Diethylamino-3-methoxy-2-(4-methoxyphenyl)-3-methylpropenamidines E-**6a**, Z-**7a**.* Total yield 90%. **6a** (pale yellow oil): IR (Nujol) 3100-3600 cm^{-1} (NH).^{1}H-NMR ($CDCl_3$) 0.90-1.10 (m, 6H, CH_3); 1.97 (s, 3H, 3-CH_3); 3.20-3.40 (m, 4H, CH_2); 3.64 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 5.00-5.30 (bs, 1H, NH, exch.); 6.84 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.18 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 16.54, 55.59, 113.80, 118.79, 128.05, 129.88, 150.19, 158.26, 166.87. Calcd. for $C_{16}H_{24}N_2O_2$ (276.38): C 69.53, H 8.75, N 10.14 found C 69.85, H 8.55, N 10.00. *m/z* 276 (M^+). **7a**: (mixture with **6a**): ^{1}H-NMR ($CDCl_3$): 0.80 (t, *J* 7 Hz, 6H); 2.06 (s, 3H, 3-CH_3); 3.20-3.40 (m, 4H, CH_2); 3.63 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 5.55-5.90 (bs, 1H, NH, exch.); 6.82 (d, AB system, *J* 10 Hz, 2H, aryl-H); 7.44 (d, AB system, *J* 10 Hz, 2H, aryl-H).^{13}C-NMR ($CDCl_3$): 15.07, 55.70, 114.10, 130.48, 151.09, 158.73, 165.77.

*N,N-Diethylamino-3-methoxy-2-(4-methoxyphenyl)-3-phenylpropenamidines E-**6b**, Z-**7b**.* Total yield 90%. **6b** (pale yellow oil): IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) 0.80-1.14 (m, 6H, CH_3); 3.10-3.50 (m, 4H, CH_2); 3.43 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 6.10-6.50 (bs, 1H, NH, exch.); 6.65 (d, AB system, *J* 9 Hz, 2H, aryl-H); 6.99 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.15-7.35 (m, 5H, aryl-H).). ^{13}C-NMR ($CDCl_3$): 13.66, 42.20, 55.15, 58.24, 113.78, 122.08, 127.44, 128.45, 128.86, 130.16, 131.00, 133.00, 152.90, 158.50, 165.10. Calcd. for $C_{21}H_{26}N_2O_2$ (338.45): C 74.53, H 7.74, N 8.28 found C 74.94, H 7.37, N 8.11. *m/z* 338 (M^+). **7b** (mixture with **6b**): ^{1}H-NMR ($CDCl_3$): 0.70-1.20 (m, 6H, CH_3); 3.00-3.50 (m, 4H, CH_2); 3.49 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 6.85 (d, AB system, *J* 10 Hz, 2H, aryl-H); 7.30-7.50 (m, 5H, aryl-H); 7.50 (d, AB system, *J* 10 Hz, 2H, aryl-H). HPLC: *E* isomer r. t. 4.99 min., *Z* isomer r.t. 7.4 min.

*N,N-Diethylamino-3-methoxy-2-(4-methoxyphenyl)-3-(2-pyridyl)-propenamidine E-**6c**, Z-**7c**.* Total yield 90%. **6c** (pale yellow oil): IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) 0.80-1.30 (m, 6H, CH_3); 3.00-

3.60 (m, 4H, CH_2); 3.48 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 4.10-4.90 (bs, 1H, NH, exch.); 6.62 (d, AB system, *J* 9 Hz, 2H, aryl-H), 6.94 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.09-7.18 (m, 2H, pyridyl-H); 7.48 (dt, J_{ortho} 7.7, J_{meta} 1.7 Hz, 1H); 8.63 (dd, J_{ortho} 4.4, J_{meta} 1.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$): 55.49, 58.67, 114.03, 123.40, 125.50, 126.85, 127.83, 130.78, 136.40, 150.25, 151.02, 153.65, 158.98, 165.22. Calcd. for $C_{20}H_{25}N_3O_2$ (339.44): C 70.77, H 7.42, N 12.38 found C 70.64, H 7.27, N 12.10. *m/z* 339 (M^+). HPLC: *E* isomer r. t. 5.65 min. **7c** was obtained only in trace.

3-Cyano-N,N-diethylamino-3-methoxy-2-(4-methoxyphenyl)-3-propenamidines E-**6d**, *Z*-**7d**. Total yield 70%. **7d** (white crystals): M.p. 127 °C (Et_2O). IR (Nujol) 3100-3600 cm^{-1} (NH); 2200 cm^{-1} (CN). ^{1}H-NMR ($CDCl_3$): 0.88-1.20 (m, 6H, CH_3); 3.11-3.46 (m, 4H, CH_2); 3.81 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 5.60-6.20 (bs, 1H, NH, exch.); 6.92 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.54 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 14.00, 42.50, 55.78, 59.51, 114.45, 114.86, 123.89, 125.33, 129.86, 136.94, 161.20, 161.44. Calcd. for $C_{16}H_{21}N_3O_2$ (287.36): C 66.88, H 7.37, N 14.62 found C 67.04, H 7.17, N 14.20. **6d** (mixture with **7d**): ^{1}H-NMR ($CDCl_3$): 0.80-1.20 (m, 6H, CH_3); 3.00-3.50 (m, 4H, CH_2); 3.65 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 6.78 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.29 (d, AB system, *J* 9 Hz, 2H, aryl-H).

Synthesis of Propenamidines **9a-c**:

Compound **8** (373 mg, 1 mmol) was dissolved in the appropriate alcohol (15 mL) and sodium alkoxide **2a-c**, (5 mL of a 0.4 molar solution) was added under stirring at room temperature. When the reagent disappeared (T.L.C. cyclohexane/ethyl acetate 1:1; CH_2Cl_2/MeOH 10:1) water (10 mL) was added and stirring continued for 1 h. Alcohol evaporation and extraction of the mixture with CH_2Cl_2 (20 mL) afforded compounds **9a-c** as pale yellow oils.

N,N-Diethylamino-3,3-dimethoxy-2-(4-methoxyphenyl)-propenamidine ***9a***: Yield: 81%; IR (Nujol) 3200-3400 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 1.05 (t, 6H, CH_3, *J* 7.2 Hz); 3.20-3.50 (m, 4H, CH_2); 3.68 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 6.15-6.40 (bs, 1H, NH, exch.); 6.84 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.36 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 11.70, 13.09, 44.06, 55.60, 56.79, 61.55, 90.13, 114.7, 125.13, 129.98, 158.93, 162.18, 163.36. Calcd. for $C_{16}H_{24}N_2O_3$ (292.38): C 65.73, H 8.27, N 9.58 found C 65.64, H 8.37, N 9.20. *m/z* 292(M^+).

N,N-Diethylamino-3,3-diethoxy-2-(4-methoxyphenyl)-propenamidine ***9b***: Yield: 76%; IR (Nujol) 3200-3400 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 0.80-1.20 (m, 6H, CH_3); 1.29 (t, 6H, CH_3, *J* 7.2 Hz); 3.00-3.80 (m, 4H, CH_2); 3.79 (s, 3H, OCH_3); 3.93 (q, 4H, OCH_2, *J* 7.2 Hz); 5.50-6.20 (bs, 1H, NH, exch.); 6.84 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.42 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 13.00, 14.98, 43.92, 55.25, 65.44, 68.14, 94.94, 114.06, 125.98, 129.34, 158.14, 158.20, 163.68. Calcd. for $C_{18}H_{28}N_2O_3$ (320.43): C 67.47, H 8.81, N 8.74 found C 67.67, H 8.58, N 8.95. *m/z* 320 (M^+).

N,N-Diethylamino-3,3-diisopropoxy-2-(4-methoxyphenyl)-propenamidine ***9c***: Yield: 70%; IR (Nujol) 3200-3400 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 0.90-1.20 (m, 6H, CH_3); 1.22 (d, CH_3, *J* 6.2 Hz, 6H); 1.25 (d, CH_3, *J* 6.2 Hz, 6H); 3.20-3.60 (m, 4H, CH_2); 3.79 (s, 3H, OCH_3); 4.34 (sept, CH, *J* 6.2 Hz, 2H); 4.40-5.50 (bs, 1H, NH, exch.); 6.81 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.49 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR

($CDCl_3$): 22.40, 22.50, 55.53, 72.40, 72.58, 105.60, 113.76, 129.42, 127.97, 151.93, 157.91, 165.19. Calcd. for $C_{20}H_{32}N_2O_3$ (342.49): C 68.93, H 9.26, N 8.04 found C 68.67, H 8.97, N 8.36. *m/z* 342 (M^+).

Synthesis of Acrylamidines 11a-c and 12a-f:

Compound **1a** (0.1 g, 0.34 mmol) was dissolved in anhydrous THF (2.0 mL) under stirring at room temperature and Grignard reagents **10a-f** (0.71 mmol) were added dropwise to the solution under nitrogen atmosphere. Stirring was continued until the reagents disappeared (T.L.C. cyclohexane/ethyl acetate 1:1; CH_2Cl_2/MeOH 10:1). Water (5 mL) was added and stirring continued for 1 h. Evaporation of the solvent and extraction of the mixture with CH_2Cl_2 (20 mL) afforded compounds **11** and **12** as yellow oils except in the case of **12b** which crystallized with Et_2O on long standing from the mixture of the two isomers.

*N,N-Diethylamino-2-(4-methoxyphenyl)-2-butenamidines Z-***11a**, *E-***12a**. Total yield: 73%; IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 0.99 (t, CH_3, *J* 7 Hz, 3H); 1.15-1.40 (m, 6H, CH_3); 1.89 (d, 3-CH_3, *J* 7 Hz, 3H, *Z* form), 1.92 (d, 3-CH_3, *J* 7 Hz, 3H, *E* form), 3.05-3.30 (m, 4H, CH_2); 3.44 (q, CH_2, *J* 7 Hz, 4H), 3.80 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 4.80-5.00 (bs, 1H, NH, exch.); 6.15 (q, 3-H, *J* 7 Hz, 1H, *Z* form); 6.33 (q, 3-H, *J* 7 Hz, 1H, *E* form); 6.86 (d, AB system, *J* 9 Hz, 2H, aryl-H); 6.90 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.21 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.26 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 12.40, 15.30, 42.80, 55.65, 114.42, 122.15, 126.92, 129.99, 130.40, 139.58, 159.54, 165.35, 168.66. Calcd. for $C_{15}H_{22}N_2O$ (246.35): C 73.13, H 9.00, N 11.37 found C 73.00, H 8.77, N 11.05. *m/z* 246 (M^+). HPLC: *E* isomer r. t. 4.65 min., *Z* isomer r.t. 5.49 min.

*N,N-Diethylamino-2-(4-methoxyphenyl)-2-pentenamidines Z-***11b**, *E-***12b**. Total yield: 98%; **11b** (pale yellow crystals on long standing): M.p. 194-196 °C dec. (Et_2O). IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 0.98 (t, CH_3, *J* 7 Hz, 3H); 1.15 (t, CH_3, *J* 7 Hz, 3H); 1.43 (t, CH_3, *J* 7 Hz, 3H), 2.17-2.35, 2.38-2.54 (2m, 2H, CH_2); 3.25-3.30, (m, 2H, CH_2); 3.80 (s, 3H, OCH_3); 3.81-4.01 (m, 2H, CH_2); 5.00-5.50 (bs, 1H, NH, exch.); 6.21 (t, 3-H, *J* 7.7 Hz, 1H); 6.87 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.30 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 12.78, 14.30, 23.94, 44.15, 55.74, 114.60, 127.34, 129.36, 130.37, 136.29, 138.00, 159.96, 164.78. Calcd. for $C_{16}H_{24}N_2O$ (260.38): C 73.81, H 9.29, N 10.76 found C 74.00, H 9.37, N 10.95. *m/z* 260 (M^+). **12b** ^{1}H-NMR ($CDCl_3$): 0.80-1.40 (m, 9H, CH_3); 2.10-2.40 (m, 2H, CH_2); 2.95-3.65 (m, 4H, CH_2); 3.80 (s, 3H, OCH_3); 5.97 (t, 3-H, *J* 7.7 Hz, 1H); 6.90 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.20 (d, AB system, *J* 9 Hz, 2H, aryl-H).^{13}C-NMR ($CDCl_3$): 12.00-14.00, 22.71, 44.15, 55.27, 114.60, 130.30, 131.20, 134.82, 136.00, 167.08. *m/z* 260 (M^+).

*N,N-Diethylamino-2-(4-methoxyphenyl)-3-phenyl-propenamidines Z-***11c**, *E-***12c**. Total yield: 93%; IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 0.80 (t, CH_3, *J* 7 Hz, 3H, *Z* form); 1.04 (t, CH_3, *J* 7 Hz, 6H, *E* form); 1.34 (t, CH_3, *J* 7 Hz, 3H, *Z* form); 3.18-3.24 (m, 1H, CH_2, *Z* form); 3.39 (q, CH_2, *J* 7 Hz, 4H, *E* form); 3.65-3.83 (m, 3H, CH_2, *Z* form); 3.86 (s, 3H, OCH_3, *E* form); 3.89 (s, 3H, OCH_3, *Z* form); 5.40-5.80 (bs, 1H, NH, exch.); 6.70 (s, 1H, H-3, E form); 6.80 (d, AB system, *J* 9 Hz, 2H, aryl-H, E form); 6.93 (AB system, *J* 9 Hz, 2H, aryl-H, Z form); 7.50 (AB system, *J* 9 Hz, 2H, aryl-H, Z form); 7.11-7.73 (2m, 13H, aryl-H). ^{13}C-NMR ($CDCl_3$): 12.96, 42.14, 55.25, 114.06, 126.60, 127.80, 128.20, 128.26, 128.49, 129.32,

136.29, 140.47, 159.47, 168.90. Calcd. for $C_{20}H_{24}N_2O$ (308.42): C 77.89, H 7.84, N 9.08 found C 77.67, H 7.97, N 9.45. *m/z* 308 (M^+).

N,N-Diethylamino-2-(4-methoxyphenyl)-pent-2-en-4-ynamidine E-**12d**. Yield: 80%; IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 0.90 (t, CH_3, *J* 7 Hz, 6H); 3.18 (q, CH_2, *J* 7 Hz, 4H); 3.22 (d, *J* 2.65 Hz, 1H); 3.78 (s, 3H, OCH_3); 5.67 (d, *J* 2.65 Hz, 1H); 5.75 (bs, 1H, NH, exch.); 6.87 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.69 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 13.00, 41.90, 42.04, 55.27, 84.26, 94.25, 105.00, 113.80, 127.13, 129.80, 148.38, 160.25, 166.90. Calcd. for $C_{16}H_{20}N_2O$ (256.35): C 74.97, H 7.26, N 10.93 found C 74.67, H 7.17, N 10.85. *m/z* 256 (M^+).

N,N-Diethylamino-2-(4-methoxyphenyl)-hex-2-en-4-ynamidine E-**12e**. Total yield: 90%; IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 0.95 (t, CH_3, *J* 7 Hz, 6H); 1.96 (d, CH_3, *J* 2.65 Hz, 3H); 3.27 (q, CH_2, *J* 7 Hz, 4H); 3.76 (s, 3H, OCH_3); 5.71 (q, *J* 2.65 Hz, 1H); 6.40 (bs, 1H, NH, exch.); 6.85 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.65 (d, AB system, *J* 9 Hz, 2H, aryl-H). ^{13}C-NMR ($CDCl_3$): 4.73, 12.63, 42.89, 55.25, 70.00, 94.91, 108.83, 114.00, 126.84, 129.07, 143.89, 160.01, 162.24. Calcd. for $C_{17}H_{22}N_2O$ (270.37): C 75.52, H 8.20, N 10.36 found C 75.67, H 8.10, N 10.57. *m/z* 270 (M^+).

N,N-Diethylamino-2-(4-methoxyphenyl)-5-phenyl-pent-2-en-4-ynamidine E-**12f**. Total yield: 94%; IR (Nujol) 3100-3600 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$): 1.05 (t, CH_3, *J* 7 Hz, 6H); 3.29 (q, CH_2, *J* 7 Hz, 4H); 3.85 (s, 3H, OCH_3); 5.96 (s, 1H, H-3); 6.93 (d, AB system, *J* 9 Hz, 2H, aryl-H); 7.30-7.55 (m, 5H, aryl-H); 7.82 (d, AB system, *J* 9 Hz, 2H, aryl-H).^{13}C-NMR ($CDCl_3$): 13.46, 42.36, 55.78, 88.11, 96.51, 106.37, 114.18, 128.08-132.96 (CH arom.), 122.33, 123.73, 148.75, 160.62, 167.66. Calcd. for $C_{22}H_{24}N_2O$ (332.45): C 79.48, H 7.28, N 8.43 found C 79.77, H 7.18, N 8.59. *m/z* 332 (M^+).

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