Intramolecular thermal cyclizations of methyl (*E*)-3-arylamino-2-benzoylaminobut-2-enoates

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Dedicated to Professor Sándor Antus on the occasion of his 60th anniversary

(received 30 Dec 03; accepted 03 Apr 04; published on the web 05 Apr 04)

Abstract

Methyl 3-anilino-2-(benzoylamino)but-2-enoates **3a–h** were prepared from methyl 2-benzoylamino-3-oxobutanoate **1** and anilines **2a–h**. Heating of butenoates **3a–h** in refluxing anisole resulted in intramolecular cyclocondensation between the arylamino and benzoyl group to give methyl 1-aryl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylates **4a–h**. In the case of butenoates **3g,h**, 4-[1-(arylamino)ethylidene]-2-phenyl-1,3-oxazol-5(4*H*)-ones **5g,h** were also formed as side products.

Keywords: Imidazoles, oxazoles, enaminones, cyclizations, thermal reactions

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Introduction

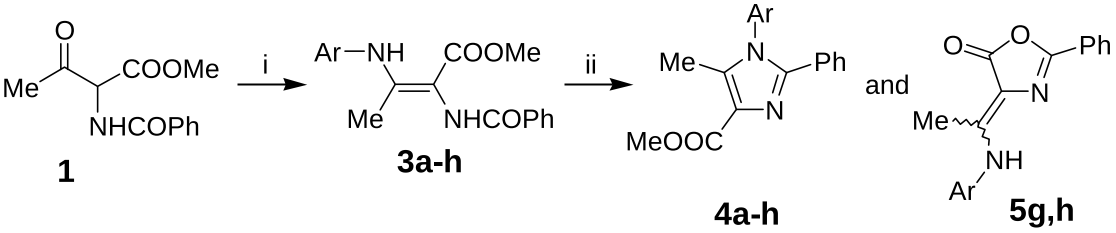
Imidazoles certainly belong among the most important, significant, and abundant five-membered heterocycles, which are constituents of a variety of natural and synthetic products. Therefore, it is not surprising, that many different synthetic methods for the construction of the imidazole ring have been developed. However, there has been only a limited number of syntheses described in the literature, in which acyclic precursors containing the C–N–C–C–N structural element have been used.[1] Such examples are cyclizations of α-acylaminocarboxylic acid derivatives,[2–5] *N*-substituted derivatives of α-aminocarbonitriles,[6] *N*-substituted 1,2-diaminoalkanes,[7] and bis amides of oxalic acid.[8]

Alkyl 3-(dimethylamino)propenoates and related enaminones are easily available and have proven to be versatile reagents for the preparation of a variety of heterocyclic systems, 3-substituted dehydroalanine esters, functionalized heterocycles, and natural product analogs.[9] Recently, we reported the preparation of methyl 3-anilino-2-(benzoylamino)but-2-enoates **3a–e**, available in three steps from hippuric acid *via* transformation into 4-[1-

(dimethylamino)ethylidene]-2-phenyl-5(4*H*)-oxazolone, followed by methanolysis and treatment with anilines.[10] Heating of **3a–c** in polyphosphoric acid (PPA) at 130–140 °C resulted in formation of oxazolo[4,5–*c*]quinolines as the main products and methyl 1-aryl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylates **4a–c** as the side products.[11] Formation of imidazoles **4** prompted us to continue this research and now we report thermal cyclisations of methyl 3-anilino-2-(benzoylamino)but-2-enoates **3a–h** under neutral conditions into imidazoles **4a–h**.

Results and Discussion

Methyl 3-anilino-2-(benzoylamino)but-2-enoates **3a–h** were prepared by treatment of methyl 2-benzoylamino-3-oxobutanoate **1**[10] with anilines **2a–h** in refluxing ethanol in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA) according to a slightly modified procedure described previously in the literature.[11] Heating of butenoates **3a–f** in anisole under reflux afforded the corresponding methyl 1-aryl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylates **4a–f** in 14–57% yield. On the other hand, heating of butenoates **3g,h** gave imidazoles **4g,h** as the major products and 4-[1-(anilino)ethylidene]-2-phenyl-1,3-oxazol-5(4*H*)-ones **5g,h** as the minor products (Scheme 1).

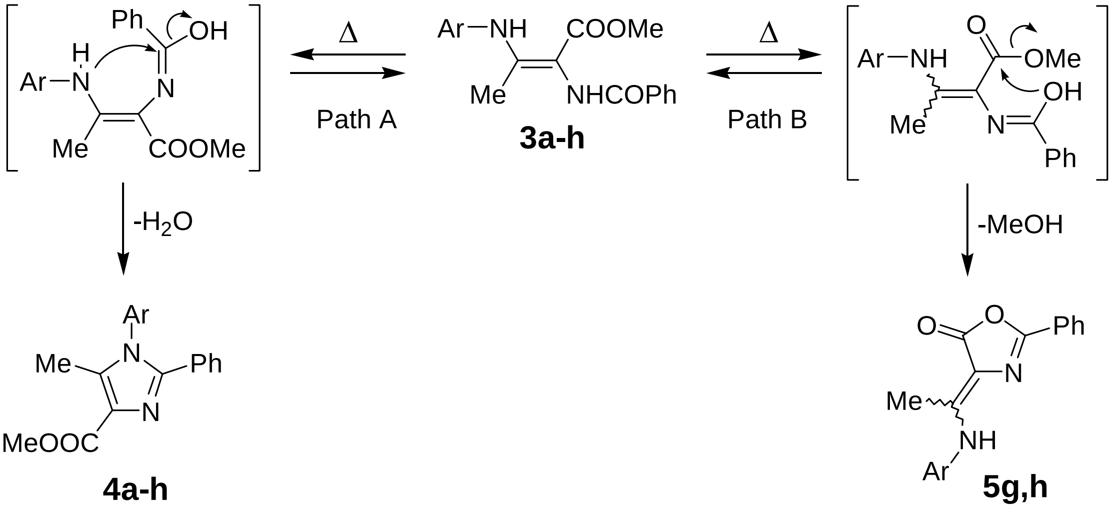


Compound	Ar	Yield [%]		
		3	**4**	**5**
2a–4a	phenyl	*a*	14	0
2b–4b	4-methoxyphenyl	*a*	22	0
2c–4c	4-fluorophenyl	*a*	57	0
2d–4d	3-hydroxyphenyl	*a*	46	0
2e–4e	3-methylphenyl	78	46	0
2f–4f	3-methoxyphenyl	74	22	0
2g–5g	4-bromophenyl	67	35	18
2h–5h	3-chloro-4-fluorophenyl	40	33	18

a) This compound was prepared according to the literature procedure.[11]

Scheme 1. Reagents and conditions: (i) Ar–NH$_2$ (**2a–h**), EtOH, PTSA (cat.), reflux, Dean-Stark; (ii) anisole, reflux, then crystallization or chromatographic separation.

Formation of imidazoles **4a–h** can be explained by intramolecular cyclocondensation between the arylamino group and the benzoyl group resulting in elimination of water (Path A). On the other hand, formation of oxazolones **5g,h** revealed another competitive cyclocondensation reaction, which takes place between the benzoylamino group and the ester group by elimination of methanol (Path B) (Scheme 2).



Scheme 2

Structures of all novel compounds were determined by spectroscopic methods (IR, NMR) and by analyses for C, H, and N. Oxazolones **5g,h** were isolated as mixtures of the major (*Z*)- and the minor (*E*)-isomers. The (*Z*)-configuration around the exocyclic C=C double bond in the major isomer of oxazolone **5h** was determined by X-Ray diffraction (Figure 1).

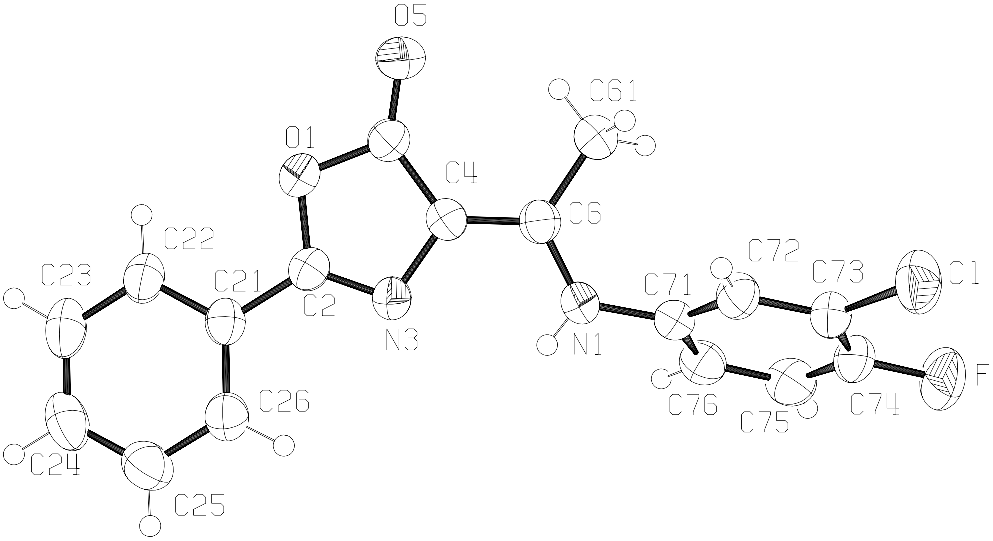


Figure 1. ORTEP view of the major (*Z*)-isomer of compound **5h** showing atom labels of the non-hydrogen atoms. Ellipsoids are plotted at a 50% probability level.

Experimental Section

General Procedures. Melting points were taken with a Kofler micro hot stage. The ^{1}H NMR spectra (300 MHz) spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. IR spectra were recorded with a Perkin-Elmer Spectrum BX FTIR spectrophotometer (KBr discs). The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyser 2400. TLC was run using Merck Alufolien Kieselgel 60 F 254, 0.2 mm. Column chromatography (CC) was performed on silica gel (Fluka, Kieselgel 60, 0.04–0.063 mm).

All starting materials were commercially available (in most cases from Fluka) and purified following the standard techniques. Methyl 2-benzoylamino-3-oxobutanoate **1**[10] and methyl 3-anilino-2-(benzoylamino)but-2-enoates **3a–d**[11] were prepared according to the procedures described in the literature.

General procedure for the preparation of methyl 3-anilino-2-(benzoylamino)but-2-enoates 3e–h

These compounds were prepared according to a slightly modified procedure described in the literature.[11] A mixture of aniline **2e–h** (0.001 mol), **1** (0.235 g, 0.001 mol), anhydrous ethanol (4 mL), and a catalytic amount of *p*-toluenesulfonic acid was heated under reflux for 5–12 h. A Dean-Stark trap, filled with molecular sieves (3Å), was used to remove water formed during the reaction. Volatile components were evaporated *in vacuo*, the residue was triturated with diethyl ether (3 mL), and the precipitate was collected by filtration to give **3e–h**.

Methyl 2-(benzoylamino)-3-(3-methylanilino)but-2-enoate (3e). Prepared from **1** and 3-methylaniline **2e** (0.107 g), reflux for 5.5 h. Yield: 0.253 g (78%) of colorless crystals; m.p. 105–108 °C (Et_2O–EtOH). MS: *m*/*z* = 324 (M^+). IR (cm^{-1}): 3252 (NH), 1649 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.07 and 2.35 (6H, 2s, 1:1, 2×Me), 3.71 (3H, s, OMe), 6.91–7.08 (4H, m, NH and 3H of Ph), 7.21 (1H, m, 1H of Ph), 7.43–7.58 (3H, m, 3H of Ph), 7.84–7.92 (2H, m, 2H of Ph), 10.78 (1H, br s, NH). Anal. Calcd. For $C_{19}H_{20}N_2O_3$ (324.28): C, 70.35; H, 6.21; N, 8.64. Found: C, 70.43; H, 6.38; N, 8.43.

Methyl 2-(benzoylamino)-3-(3-methoxyanilino)but-2-enoate (3f). Prepared from **1** and 3-methoxyaniline **2f** (0.123 g), reflux for 6 h. Yield: 0.252 g (74%) of colorless crystals; m.p. 108–110 °C (toluene–hexane). IR (cm^{-1}): 3258 (NH), 1648 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.08 (3H, s, Me), 3.71 and 3.79 (6H, 2s, 1:1, 2×OMe), 6.65–6.76 (3H, m, 3H of Ph), 7.20 (1H, br s, NH), 7.19–7.26 (1H, m, 1H of Ph), 7.43–7.54 (3H, m, 3H of Ph), 7.83–7.89 (2H, m, 2H of Ph), 10.80 (1H, br s, NH). Anal. Calcd. For $C_{19}H_{20}N_2O_4$ (340.37): C, 67.05; H, 5.92; N, 8.23. Found: C, 66.92; H, 6.11; N, 8.08.

Methyl 2-(benzoylamino)-3-(4-bromoanilino)but-2-enoate (3g). Prepared from **1** and 4-bromoaniline **2g** (0.172 g), reflux for 5 h. Yield: 0.260 g (67%) of colorless crystals; m.p. 163–166 °C (EtOH). MS: *m*/*z* = 388 (M^+). IR (cm^{-1}): 3283 (NH), 1646 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.07 (3H, s, Me), 3.70 (3H, s, OMe), 6.98–7.06 (3H, m, 3H of Ph, NH), 7.43–7.58 (5H, m, Ph), 7.83–7.7.89 (2H, m, 2H of Ph). Anal. Calcd. For $C_{18}H_{17}BrN_2O_3$ (389.24): C, 55.54; H, 4.40; N, 7.20. Found: C, 55.53; H, 4.62; N, 6.99.

Methyl 2-(benzoylamino)-3-(3-chloro-4-fluoroanilino)but-2-enoate (3h). Prepared from **1** and 3-chloro-4-fluoroaniline **2h** (0.146 g), reflux for 12 h. Yield: 0.145 g (40%) of colorless crystals; m.p. 147–150 °C (EtOH). MS: *m*/*z* = 362 (M^+). IR (cm^{-1}): 3238 (NH), 1643 (C=O). ^1H NMR ($CDCl_3$): δ2.03 (3□, s, Me), 3.71 (3H, s, OMe), 6.98–7.05 (2H, m, NH, 1H of Ar), 7.08–7.15 (1H, m, 1H of Ar), 7.17–7.24 (1H, m, 1H of Ar), 7.44-7.57 (3H, m, 3H of Ph), 7.84-7.90 (2H, m, 2H of Ph), 10.70 (1H, br s, NH). Anal. Calcd. For $C_{18}H_{16}ClFN_2O_3$ (362.79): C, 59.59; H, 4.45; N, 7.72. Found: C, 59.61; H, 4.47; N, 7.53.

Thermal cyclizations of methyl 3-anilino-2-(benzoylamino)but-2-enoates (3a–h)

Procedure A. A mixture of **3** (0.001 mol) and anisole (6 mL) was heated under reflux for 1.5–3.5 h, volatile components were evaporated *in vacuo*, the residue was triturated with toluene–hexane or with Et_2O, and the precipitate was collected by filtration to give **4**.

Procedure B. A mixture of **3** (0.001 mol) and anisole (6 mL) was heated under reflux for 2.5–15 h and volatile components were evaporated *in vacuo*. The residue was purified by column chromatography (CC). Fractions containing the product were combined and evaporated *in vacuo*. The residue was triturated with Et_2O (3 mL) and the precipitate was collected by filtration to give **4** and **5**.

Methyl 1,2-diphenyl-5-methyl-1*H*-imidazole-4-carboxylate (4a). This compound was prepared from **3a** (0.310 g), Procedure A, reflux for 1.5 h, trituration with toluene–hexane. Yield: 0.041 g (14 %) of colorless crystals; m.p. 132–135 °C (toluene–hexane), lit.[11] m.p. 132–135 °C. Spectral data were identical to those reported in the literature.[11]

Methyl 1-(4-methoxyphenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (4b). This compound was prepared from **3b** (0.340 g), Procedure B, reflux for 2.5 h, CC (EtOAc–hexanes, 1:2). Yield: 0.071 g (22 %) of colorless crystals; m.p. 136–141 °C (EtOH), lit.[11] m.p. 137–141 °C. Spectral data were identical to those reported in the literature.[11]

Methyl 1-(4-fluorophenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (4c). This compound was prepared from **3c** (0.328 g), Procedure A, reflux for 3.5 h, trituration with Et_2O. Yield: 0.071 g (22 %) of colorless crystals; m.p. 187–189 °C (EtOH), lit.[11] m.p. 188–190 °C. Spectral data were identical to those reported in the literature.[11]

Methyl 1-(3-hydroxyphenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (4d). This compound was prepared from **3d** (0.326 g), Procedure B, reflux for 15 h, CC (EtOAc–hexanes, 1:1). Yield: 0.142 g (46 %) of colorless crystals; m.p. 234–238 °C. MS: *m*/*z* = 308 (M^+). IR (cm^{-1}): 3405 (OH), 1715 (C=O). ^1H NMR ($CDCl_3$): δ2.35 (3H, s, Me), 3.97 (3H, s, OMe), 6.60–6.63 (1H, br s, OH), 6.64–6.69 (1H, m, 1H of Ar), 6.92–6.97 (1H, m, 1H of Ar), 7.10–7.23 (4H, m, 4H of Ar), 7.28–7.36 (3H, m, 3H of Ar). Anal. Calcd. For $C_{18}H_{16}N_2O_2$ (308.34): C, 70.12; H, 5.23; N, 9.09. Found: C, 69.92; H, 5.32; N, 8.99.

Methyl 5-methyl-1-(3-methylphenyl)-2-phenyl-1*H*-imidazole-4-carboxylate (4e). This compound was prepared from **3e** (0.324 g), Procedure B, reflux for 2.5 h, CC (EtOAc–hexanes, 1:2). Yield: 0.141 g (46 %) of colorless crystals; m.p. 139–145 °C. MS: *m*/*z* = 306 (M^+). IR (cm^{-1}): 1721 (C=O). ^1H NMR ($CDCl_3$): δ 2.40 and 2.43 (6H, 2s, 1:1, 2×Me), 3.97 (3H, s, OMe), 6.96–7.03 (2H, m, 2H of Ar), 7.18–7.27 (3H, m, 3H of Ar), 7.30–7.43 (4H, m, 4H of Ar). Anal. Calcd. For $C_{19}H_{18}N_2O_2$ (306.73): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.12; H, 5.98; N, 8.97.

Methyl 1-(3-methoxyphenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (4f). This compound was prepared from **3f** (0.340 g), Procedure A, reflux for 4 h, trituration with toluene–hexane. Yield: 0.071 g (22 %) of colorless crystals; m.p. 139–145 °C. IR (cm^{-1}): 1720 (C=O). ^1H NMR ($CDCl_3$): δ 2.42 (3H, s, Me), 3.76 and 3.95 (6H, 2s, 1:1, 2×OCH_3), 6.67–6.70 (1H, m, 1H of Ar), 6.74–6.79 (1H, m, 1H of Ar), 6.98–7.03 (1H, m, 1H of Ar), 7.17–7.25 (3H, m, 3H of Ar), 7.33–7.42 (3H, m, 3H of Ar).Anal. Calcd. For $C_{19}H_{18}N_2O_3$ (322.13): C, 70.79; H, 5.63; N, 8.69. Found: C, 70.89; H, 5.50; N, 8.54.

Methyl 1-(4-bromophenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (4g) and 4-[1-(4-bromoanilino)ethylidene]-2-phenyl-1,3-oksazol-5(4*H*)-one (5g). These compounds were prepared from **3g** (0.389 g), Procedure B, reflux for 7 h, CC (EtOAc–hexane, 1:2).

Compound **4g**. Yield: 0.130 g (35 %) of colorless crystals; m.p. 145–148 °C. MS: *m*/*z* = 370 (M^+). IR (cm^{-1}): 1714 (C=O). ^1H NMR ($CDCl_3$): δ 2.43 (3H, s, Me), 3.97 (3H, s, OMe), 7.05–7.10 (2H, m, 2H of Ar), 7.21–7.32 (3H, m, 3H of Ar), 7.35–7.40 (2H, m, 2H of Ar), 7.60–7.65 (2H, m, 2H of Ar). Anal. Calcd. For $C_{18}H_{15}BrN_2O_2$ (371.24): C, 58.24; H, 4.07; N, 7.55. Found: C, 58.06; H, 3.95; N, 7.42.

Compound **5g**. Yield: 0.064 g (18 %) of colorless crystals; m.p. 168–173 °C, *Z*:*E* = 67:33. MS: *m*/*z* = 357 (MH^+). IR (cm^{-1}): 1714 (C=O). ^1H NMR ($CDCl_3$): δ *major (Z)-isomer* 2.49 (3H, s, Me), 7.06–7.11 (2H, m, 2H of Ar), 7.42–7.48 (3H, m, 3H of Ar), 7.52–7.58 (2H, m, 2H of Ar), 7.96–8.02 (2H, m, 2H of Ar), 9.98 (1H, br s, NH); *minor (E)-isomer* 2.53 (3H, s, Me), 8.27 (1H, br s, NH). Anal. Calcd. For $C_{17}H_{13}BrN_2O_2$ (357.20): C, 57.16; H, 3.67; N, 7.84. Found: C, 56.80; H, 3.53; N, 7.63.

Methyl 1-(3-chloro-4-fluorophenyl)-5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (4h) and 4-[1-(3-chloro-4-fluoroanilino)ethylidene]-2-phenyl-1,3-oxazol-5(4*H*)-one (5h). These compounds were prepared from **3h** (0.363 g), Procedure B, reflux for 2.5 h, CC (EtOAc–hexane, 1:2).

Compound **4h**. Yield: 0.114 g (33 %) of colorless crystals; m.p. 203–205 °C. MS: *m*/*z* = 344 (M^+). IR (cm^{-1}): 1716 (C=O). ^1H NMR ($CDCl_3$): δ 2.43 (3H, s, Me), 3.95 (3H, s, OMe), 7.04–7.10 (1H, m, 1H of Ar), 7.21–7.32 (5H, m, Ph), 7.33–7.38 (2H, m, 2H of Ar). Anal. Calcd. For $C_{18}H_{14}ClFN_2O_2$ (344.78): C, 62.71; H, 4.09; N, 8.13. Found: C, 62.66; H, 4.27; N, 8.00.

Compound **5h**. Yield: 0.060 g (18 %) of colorless crystals; m.p. 155–158 °C, *Z*:*E* = 60:40. IR (cm^{-1}): 1725 (C=O). ^1H NMR ($CDCl_3$): δ *major (Z)-isomer* 2.46 (3H, s, Me), 7.06–7.14 (1H, m, 1H of Ar), 7.17–7.25 (1H, m, 1H of Ar), 7.27–7.33 (1H, m, 1H of Ar), 7.42–7.48 (3H, m, 3H of Ph), 7.96–8.02 (2H, m, 2H of Ph), 9.90 (1H, br s, NH); *minor (E)-isomer* 2.50 (3H, s, Me), 8.19

(1H, br s, NH). Anal. Calcd. For $C_{17}H_{12}ClFN_2O_2$ (330.74): C, 61.73; H, 3.66; N, 8.47. Found: C, 61.79; H, 3.61; N, 8.30.

Acknowledgements

Financial support from the Ministry of Education, Science and Sport, Slovenia, through grant PS-0502-0103, is gratefully acknowledged. The crystallographic dataset was collected on the Kappa CCD Nonius diffractometer in the Laboratory of Inorganic Chemistry, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. We acknowledge with thanks the financial contribution of the Ministry of Science and technology, Republic of Slovenia through grant Packet X-2000 and PS-511-102, which thus made the purchase of the apparatus possible.

Supporting information available

The crystal structure of 4-[(*Z*)-1-(3-chloro-4-fluoroanilino)ethylidene]-2-phenyl-1,3-oksazol-5(4*H*)-one (**5h**) has been deposited at the Cambridge Crystallographic Data Centre and allocated the description number CCDC 227477.

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