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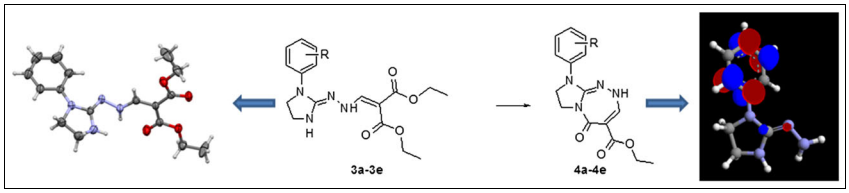

The pseudo-Michael reaction of 2-hydrazinylidene-1-arylimidazolidines with diethyl ethoxymethylenemalonate (DEEM) was investigated. The reaction yields the chain adduct, namely diethyl{[2-(1-arylimidazolidin-2-ylidene) hydrazinyl]methylidene}propanedioates. This is contrary to the pseudo-Michael reaction of DEEM with 1-aryl-4,5-dihydro-1*H*-imidazol-2-amines that does not allow isolation of chain derivatives and leads to cyclic imidazo [1,2-*a*]pyrimidine derivatives while even at thermodynamic control. At first cyclization of diethyl{[2-(1-arylimidazolidin-2-ylidene)hydrazinyl]methylidene}propanedioates leads to ethyl 1-aryl-5(1*H*,8*H*)oxo-2,3-dihydro-imidazo[2,1-*c*][1,2,4]triazepine-6-carboxylates. 1,5-Sigmatropic shift, following the cyclization, caused isomerization of 5(1*H*,8*H*)oxo-2,3-dihydro-imidazo[2,1-*c*][1,2,4]triazepine-6-carboxylates to ethyl 1-aryl-5(1*H*)hydroxy-2,3-dihydroimidazo[2,1-*c*][1,2,4]triazepine-6-carboxylates. Presence of both isomers in the reaction product was detected in the NMR spectra. The structure of all the compounds was confirmed with spectroscopic studies (^{1}H NMR and MS). The structure of diethyl{[2-(1-phenylimidazolidin-2-ylidene)hydrazinyl] methylidene}propanedioate was also confirmed by X-ray crystallography. In the addition reaction, thermodynamics and HOMO–LUMO orbitals of the reactants were studied by using quantum chemical calculations.

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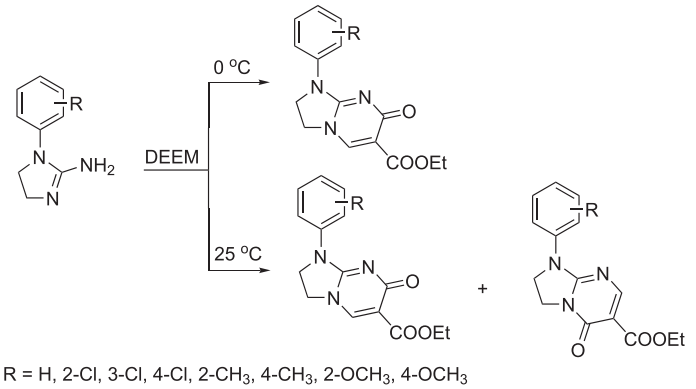
INTRODUCTION

Among various methods of synthesis of heterocyclic compounds, reactions of 1,4-addition, such as Michael reaction, have a wide range of usage and practical importance. The Michael reaction is a nucleophilic addition of enolate or analogous anions to the carbon–carbon double bond of α,β-unsaturated ketones, aldehydes, nitriles, or carboxylic acid derivatives [1]. It is a method for alkylation of active methylene compounds [1].

Diethyl ethoxymethylenemalonate (DEEM) is a Michael reagent that has been extensively applied in organic synthesis, particularly in preparation of pharmacologically active substances [1]. It is used in synthesis of chain, cyclic, heterocyclic, and fused heterocyclic compounds. In our research on the pseudo-Michael reaction, we have previously reported the reaction of 1-aryl-4,5-dihydro-1*H*-imidazol-2-amines with DEEM (Scheme 1) [2]. The isolation of chain enamines was not possible in this case [2]. This finding agrees with corresponding literature data [1]. The cyclic imidazo[1,2-*a*] pyrimidine derivatives were obtained even at low temperature instead. We also investigated the pseudo-Michael reaction of 1-aryl-4,5-dihydro-1*H*-imidazol-2-amines with ethyl ethoxymethylenecyanoacetate (EMCA; Scheme 2). In the case of this Michael reagent, we were successful in isolating the chain enamines [3].

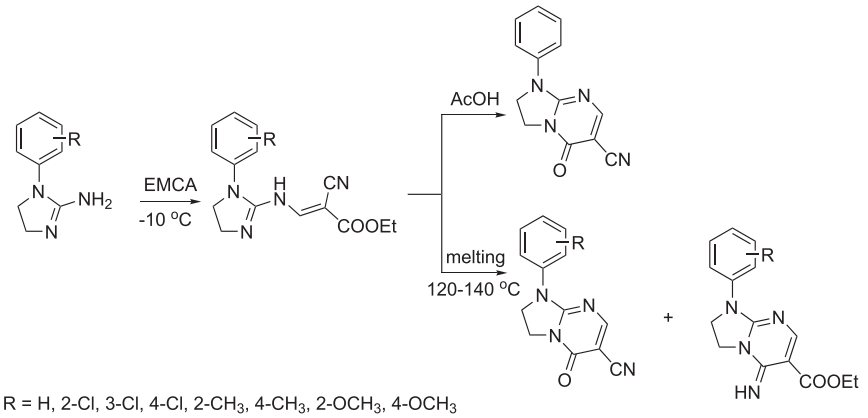
Here, we report our experimental and computational studies on the pseudo-Michael reaction 2-hydrazinylidene-1-arylimidazolidines with DEEM, which leads to diethyl {[2-(1-arylimidazolidin-2-ylidene)hydrazinyl]methylidene} propanedioates [4]. Cyclization of diethyl{[2-(1-arylimidazolidin-2-ylidene)hydrazinyl]methylidene}propanedioates makes it possible to obtain 5(1*H*,8*H*)oxo-2,3-dihydro-imidazo[2,1-*c*] [1,2,4]triazepine-6-carboxylates, which isomerize to ethyl 1-aryl-5(1*H*)hydroxy-2,3-dihydroimidazo[2,1-*c*][1,2,4]triazepine-6-carboxylates. So far, synthesis of imidazo[2,1-*c*][1,2,4] triazepine system has only been reported a few times. Britton and Trepanier obtained derivatives of imidazo[1,2-*a*][1,3,4] benzo[e]triazepine in reaction of 2-amino-phenones, substituted hydrazines and thiophosgene [5]. Priimienko synthesized imidazo[2,1-*c*][1,2,4] triazepine system from 2-bromoimidazol, chloromethyloxirane, and substituted hydrazines [6]. Savelli *et al.* obtained 7-substituted 5-oxo-2,3,6,9-tetrahydroimidazo [2,1-*c*][1,2,4]triazepines in reaction of 2-hydrazinoimidazolines-2 with β-ketoesters [7].

Scheme 1



R = H, 2-Cl, 3-Cl, 4-Cl, 2-CH_3, 4-CH_3, 2-OCH_3, 4-OCH_3

Scheme 2

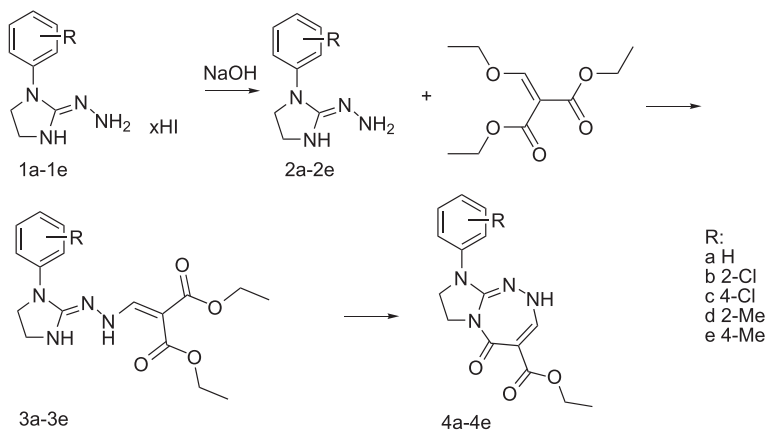


R = H, 2-Cl, 3-Cl, 4-Cl, 2-CH_3, 4-CH_3, 2-OCH_3, 4-OCH_3

RESULTS AND DISCUSSION

In this study, 2-hydrazinylidene-1-arylimidazolidine hydroiodides **1a–e** were transformed into free 2-hydrazin ylidene-1-arylimidazolidines **2a–e** by means of neutralization with sodium hydroxide (Scheme 3). Compounds **2a–e** were subjected to pseudo-Michael reaction with DEEM in 96% ethyl alcohol, yielding chain adducts **3a–e**. The isolation of chain derivatives was possible in this case, similarly as in our previously reported reaction of 1-aryl-4,5-dihydro-1*H*-imidazol-2-amines with EMCA (Scheme 2) [3] and contrary to the earlier reported reaction of DEEM with 1-aryl-4,5-dihydro-1*H*-imidazol-2-amines [2].

Scheme 3



2-Hydrazinylidene-1-arylimidazolidines were found to be very interesting reagents for synthesis of fused 5:5 and 5:6 heterocyclic systems [8]. Our achievement heading toward synthesis of 5:7 system were not so far successful. Reaction of 2-hydrazinylidene-1-arylimidazolidines with diethyl acetylenedicarboxylate leads to the formation of derivatives of (2,3-dihydroimidazo[2,1-*c*][1,2,4]triazin-6-yl) acetic acid [8]. The formation of 1,2,4-triazine six-membered ring instead of 1,2,4-triazepine seven-membered one in this reaction can be explained by the presence of two unequally reactive ester groups in chain intermediate product. Basing on this observation, exchange of diethyl acetylenedicarboxylate by Michael reagents having two equal ester groups (e.g., DEEM) should lead to formation of fused 1,2,4-triazepine ring. 2-Hydrazinylidene-1-arylimidazolidines have been widely used in synthesis of compounds with biological activity, in particular by Sztanke *et al.* [9–12]. Cyclocondensation of 2-hydrazinylidene-1-arylimidazolidines with pyruvic acid makes it possible to obtain derivatives of imidazo [2,1-*c*][1,2,4]triazin-4-one [9]. Furthermore, 8-aryl-3,4-dioxo-2*H*,8*H*-6,7-dihydroimidazo[2,1-*c*][1,2,4]triazines were synthesized from 2-hydrazinylidene-1-arylimidazolidines by a cyclization reaction with ethyl oxalate [10]. Next, 3-unsubstituted and 3-substituted-7-aryl-5*H*-6,7-dihydroimidazo[2,1-*c*][1,2,4]triazoles were prepared from 2-hydrazinylidene-1-arylimidazolidines by a cyclocondensation reaction with triethyl orthoformates, phenoxyacetic acid derivatives, and carbon disulfide, respectively [11]. Finally, ethyl 1-(4-oxo-8-aryl-4,6,7,8-tetrahydroimidazo[2,1-*c*][1,2,4]triazin-3-yl)formates were obtained by two independent synthesis methods from 2-hydrazinylidene-1-arylimidazolidines by a cyclocondensation reaction with a diethyl 2-(hydroxyimino) malonate and a diethyl 2-oxomalonate [12].

In order to confirm the reaction course, an X-ray crystal structure analysis of compound **3a** were performed. Derivatives **3a–e** exist as imidazolidin-2-yliden form in the solid state, which, in comparison to the NMR spectra, suggests that this form of lower energy can be predominant in solution as well. The molecular structure of derivative **3a** is presented in Figure 1, and the selected bond lengths are given in Table 1. The distance between the hydrogen atom at N7 and O11 oxygen atom enables formation of intramolecular hydrogen bond, making both ester groups nonequivalent.

The compounds **3a–e** were confirmed through NMR spectroscopy. The assignment of ^{1}H resonance was achieved by a combined employment of 1D and 2D techniques. These techniques include gradient versions of COSY, HSQC, and HMBC. Moreover, a common feature of all molecules is a malonic acid ethyl ester moiety. The malonic acid ethyl ester moiety displayed a typical diastereotopic behavior. It came up as two sets of triplets and quartets for the ethyl groups. A vinylic proton displayed coupling to a neighboring proton on a nitrogen

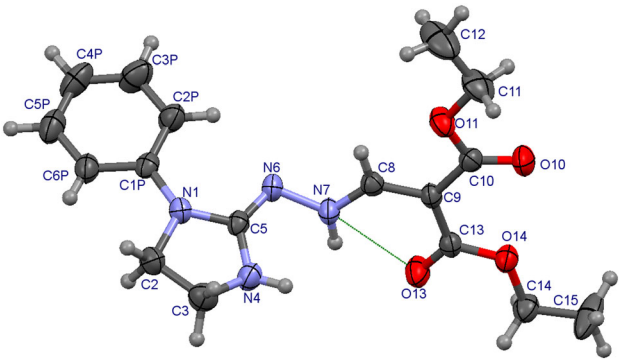


Figure 1. The perspective view of molecule **3a** along with atom numbering. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

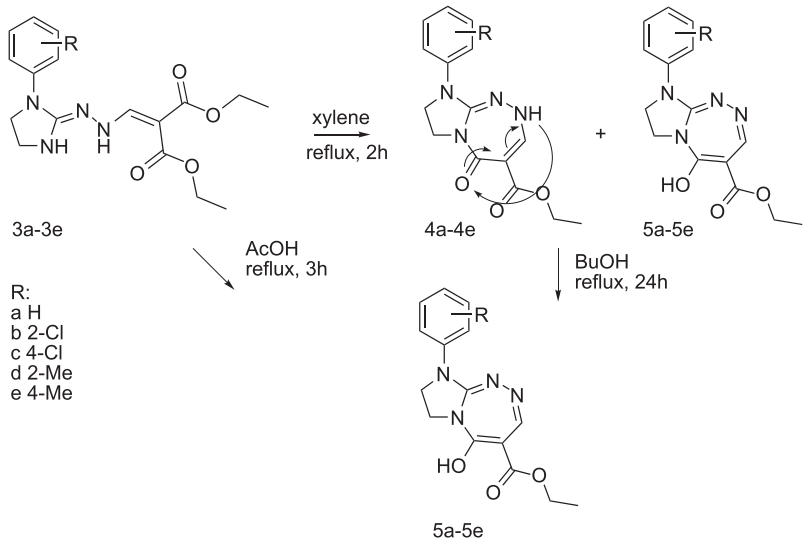
The selected bond lengths for **3a**.

Bond	Bond length (Å)
C1–N2	1.386(2)
N2–C3	1.469(2)
C3–C4	1.518(3)
C4–N5	1.449(3)
N5–C1	1.335(2)
N6–C1	1.295(2)
N6–N7	1.420(2)

and appeared downfield. Also, two methylenes in imidazolidine ring were reported either as triplets or multiplets depending on separation of the lines. Furthermore, it is important to mention that these are diastereotopic in nature and are strongly coupled to each other. All of the aromatic protons displayed typical behavior of the respective spin systems.

Cyclization of chain derivatives **3a–e**, depending on location of the N–H bond in aminoguanidine moiety, leads to formation of fused imidazo-triazepine system (Scheme 3). Refluxing of **3a–e** in different media (such as xylene or acetic acid) yielded similar products although showing some spectral differences. ^{1}H NMR spectra of products obtained from xylene exhibited some special features, for example, singlet at d ~3.7 ppm attainable for N8-H hydrogen atom, and singlet at d ~10.5 ppm of enolic C5-OH group. Comparison of integration of each signal shows about 33% of form **4a–e** and 66% of form **5a–e** (Scheme 4). All aromatic protons are strongly coupled exhibiting expected multiplet within aromatic region of the spectrum. The same behavior was displayed by methylene protons leading to poorly resolved singlet at around 4 ppm. In case of our previously reported reaction of 1-aryl-4,5-dihydro-1*H*-imidazol-2-amines with EMCA, cyclization of chain adducts yielded derivatives of imidazo[1,2-a]pyrimidine (Scheme 2).

Scheme 4



Further heating of xylene yielded products in polar solvents as *n*-butanol leads to diminishing of NH signal integration up to complete its disappearing after 24 h. Probable course of reaction comprising formation of ethyl 1-aryl-5(1*H*,8*H*)oxo-2,3-dihydroimidazo[2,1-*c*][1,2,4]triazepine-6-carboxylates **4a–e** at the first and transformation to ethyl 1-aryl-5(1*H*)hydroxy-2,3-dihydroimidazo[2,1-*c*][1,2,4]triazepine-6-carboxylates **5a–e** due to 1,5-sigmatropic shift is presented in Figure 3. Products yielded from acetic acid were only 5-hydroxy derivatives **5a–e.**

Furthermore, we calculated the enthalpy, Gibbs free energy, and entropy of the studied reactions (Tables 2 and 3). The reaction leading to the derivatives **3a–e** is characterized by the negative Gibbs free energy, negative enthalpy, and negative entropy. This reaction is spontaneous and enthalpy-driven. The most negative Gibbs free energy was found for compound with a chlorine atom at ortho position of the aryl ring **2b**. However, compound **2a** is the most reactive because it is characterized with the lowest HOMO–LUMO gap (Table 2). The comparison of distribution of HOMO and LUMO orbitals for the most reactive compound **2a** and the least reactive compound **2b** is presented in Figure 2. There are some differences in the HOMO orbital that are not present in the aryl ring for **2b** as it is for **2a**. The further differences in the reactivity may be explained by the different pattern of electrostatic potential distribution, which is visible for aryl ring of **2a** and **2b** (Fig. 3). The discovery that the ortho chloro substituent is responsible for the greatest reactivity is in accordance to our earlier reported pseudo-Michael reaction of 1-aryl-4,5-dihydro-1*H*-imidazol-2-amines with EMCA.

As shown in Table 3, the reaction of cyclization of **3a–e** into **4a–e** is characterized by positive enthalpy, positive free energy, and positive entropy; thus, it is not spontaneous, and it is entropy-driven. Considering HOMO–LUMO gap, the most reactive is derivative **2b**, and the least reactive is compound **2d**.

In our research concerning use of DEEM as an annelation reagent, not only for 6-membered rings formation but larger (e.g., 7-membered) as well, we investigated reaction of DEEM with 1-aryl-2-hydrazinoimidazolines-2. In conclusion, we found that the pseudo-Michael reaction of 2-hydrazinylidene-1-arylimidazolidines with DEEM results in chain adducts on N7 nitrogen atom, and the ortho chloro substituent is responsible for the greatest reactivity. Besides cyclization of 1,2,4-triazepine ring, we observed

Table 2

Thermodynamics of the reaction leading to chain adducts **3a–e** and HOMO and LUMO energies of **2a–2e**.

Derivative	Enthalpy (kcal/mol)	Gibbs free energy (kcal/mol)	Entropy (cal/mol)	HOMO energy	LUMO energy	HOMO–LUMO gap of compound **2**
a	−15.44	−13.91	−5.13	−7.71	0.10	7.81
b	−18.34	−16.76	−5.29	−7.73	0.47	8.20
c	−15.04	−13.85	−4.00	−7.85	0.12	7.97
d	−13.24	−11.77	−4.94	−7.70	0.41	8.11
e	−2.36	−0.70	−5.56	−7.69	0.47	8.16

Table 3

Thermodynamics of cyclization of **3a–e** into **4a–e** and HOMO and LUMO energies of **3a–e**.

Derivative	Enthalpy (kcal/mol)	Gibbs free energy (kcal/mol)	Entropy (cal/mol)	HOMO energy	LUMO energy	HOMO–LUMO gap of compound **3**
a	19.75	8.35	38.24	−8.20	0.06	8.25
b	18.69	7.90	36.19	−8.19	−0.20	7.99
c	20.13	8.83	37.92	−8.29	−0.21	8.08
d	15.11	3.98	37.35	−8.18	0.10	8.28
e	6.12	−5.43	38.73	−8.21	−0.02	8.19

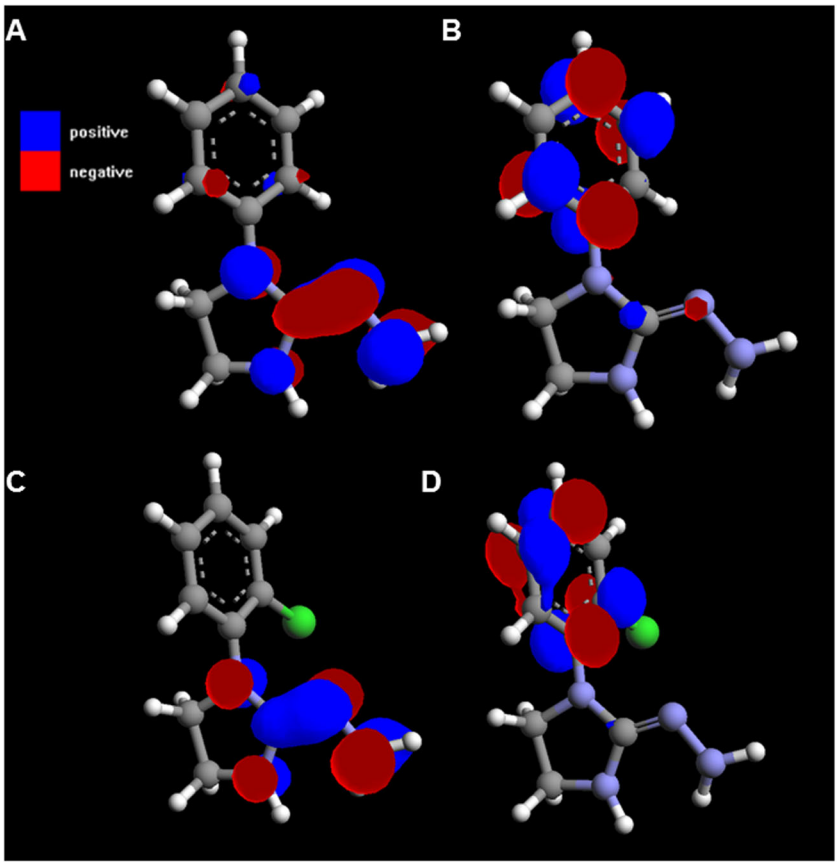


Figure 2. HOMO (A, C) and LUMO (B, D) orbitals for **2a** (A, B) and **2b** (C, D). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

1,5-sigmatropic shift leading to transformation of 5 (1*H*,8*H*)oxo group into 5(1*H*)hydroxy one.

EXPERIMENTAL

Chemistry. All the reagents and solvents were purchased and used without additional purification. In particular, the DEEM (diethyl(ethoxymethylidene)propanedioate) was purchased from (Merck, Darmstadt, Germany). Furthermore, the purity of the synthesized compounds was tested using thin-layer chromatography employing an HPTLC Silica gel 60F_{254} (Merck) and a mixture of chloroform and methanol (9:1) as a mobile phase. The spots were visualized under an ultraviolet light of 254 nm wavelength. The elementary analysis was performed with the application of a Perkin Elmer Series II CNHS/O analyzer 2400. Melting points were determined on a Boetius apparatus and are given uncorrected. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz and Bruker AVANCE III 600 MHz in $CDCl_3$ with TMS as an internal standard at 293 K. EIMS was recorded on AMD-604 spectrometer at 15 eV.

General procedure to obtain compounds 3a–e. 2-Hydrazinylidene-1-arylimidazolidine hydroiodide (0.001 mol) **1a–e** dissolved in 20 mL of distilled water was added to NaOH (0.004 mol) dissolved in 20 mL of distilled water and stirred. The whole mixture was extracted three times with 50 mL of

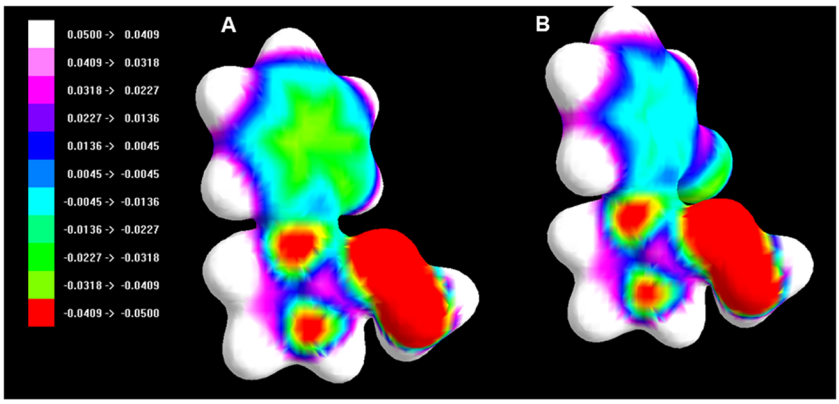


Figure 3. The map of the electrostatic potential onto a surface of the electron density for **2a** (A) and **2b** (B). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

dichloromethane. The organic layer was dried over anhydrous K_2CO_3 and filtered from the drying agent. The obtained filtrate provided a freebase of 2-hydrazinylidene-1-arylimidazolidine derivatives **2a–e** in the dichloromethane. After removing the dichloromethane on a rotavap, the residue was added to a 10 mL of 96% ethanol and stirred until complete dissolution. Next, DEEM (0.001 mol) was added, and the mixture was stirred for another 2 h at room temperature.

Diethyl {[2-(1-phenylimidazolidin-2-ylidene)hydrazinyl]methylidene} propanedioate (3a). The formed precipitate was filtered, and the filtrate was evaporated on a rotavap. All combined residues were washed with MeOH and dried overnight to create white solids. mp 156–158°C; yield 94%; $R_f = 0.69$; ^{1}H NMR (600 MHz, $CDCl_3$) 11.0 (d, $J = 12.3$ Hz, 1H), 8.08 (d, $J = 12.3$ Hz, 1H), 7.02–7.61 (m, 5H), 7.16 (bs, 1H), 4.06/4.12 (dq, $J = 7.1$ Hz, 2H), 3.80–3.94 (m, 2H), 3.30–3.47 (m, 2H), 1.18/1.24 (dt, $J = 7.1$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) 169.93, 165.61, 156.34, 155.63, 139.65, 129.04, 123.59, 119.78, 86.98, 60.00, 59.44, 48.34, 40.51, 14.57, 14.46; EIMS, *m/z*: 346 (M^+, 21%), 194 (100%). *Anal.* Calcd for $C_{17}H_{22}N_4O_4$: C 58.95; H 6.40; N 16.18. Found: C 59.09; H 6.32; N 16.20. Crystal data: $C_{17}H_{22}N_4O_4$, $FW = 346.39$, triclinic, P $\bar{1}$, $a = 7.966(2)$ Å, $b = 9.578(2)$ Å, $c = 11{,}757(3)$ Å, $\alpha = 94.65(2)°$, $\beta = 99.60(2)°$, $\gamma = 91.51(2)°$, $V = 880.8(4)$ Å^3, $Z = 2$, $d_{calc} = 1.306$ g cm^{-3}, μ (MoKα) = 0.095 mm^{-1}, a colourless crystal of dimensions $0.46 \times 0.11 \times 0.1$ mm was used for measurements at 293 K on a CAD-4 diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) and $\omega - 2\theta$ scan, $\theta_{max} = 29.87$, number of reflections 5482, 314 parameters refined, final R1 [$I > 2\sigma(I)$] = 0.0596, $wR_2 = 0.1325$.

Diethyl ({2-[1-(2-chlorophenyl)imidazolidin-2-ylidene]hydrazinyl} methylidene) propanedioate (3b). The reaction mixture was evaporated on a rotavap to leave a residue, which was washed with MeOH and dried overnight to produce white solids. mp 142–144°C; yield 91%; $R_f = 0.74$; ^{1}H NMR (600 MHz, $CDCl_3$) 10.94 (d, $J = 12.3$ Hz, 1H), 8.12 (d, $J = 12.3$ Hz, 1H), 7.10–7.49 (m, 4H), 7.23 (bs, 1H), 4.04/4.1 (dq, $J = 7.1$ Hz, 2H), 3.72–3.85 (m, 2H), 3.38–3.42 (m, 2H), 1.18/1.24 (dt, $J = 7.1$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 170.10$, 165.62, 158.28, 155.49, 136.91, 132.63, 130.74, 129.75, 128.93, 127.98, 86.03, 59.85, 59.21, 49.71, 41.63, 14.52, 14.45. EIMS, *m/z*: 381 (M^+, 20%), 231 (100%). *Anal.* Calcd for $C_{17}H_{21}ClN_4O_4$: C 53.61; H 5.56; N 14.71; Cl 9.31. Found: C 53.72; H 5.50; N 14.81; Cl 9.26.

Diethyl ({2-[1-(4-chlorophenyl)imidazolidin-2-ylidene]hydrazinyl} methylidene) propanedioate (3c). The formed precipitate was filtered, and the filtrate was evaporated on a rotavap. All combined residues were washed with MeOH and dried overnight to create white solids. mp 165–167°C; yield 95%; $R_f = 0.75$; ^{1}H NMR (600 MHz, $CDCl_3$) 10.98 (d, 1H, $J = 12.2$ Hz); 8.09 (d, 1H, $J = 12.2$ Hz); 7.4–7.65 (m, 4H); 7.24 (bs, 1H); 4.03–4.09 (dq, 4H, $J = 7.1$ Hz); 3.81–3.93 (m, 2H); 3.47–3.58 (m, 2H); 1.2/1.26 (dt, 6H, $J = 7.1$ Hz); ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 169.95$, 165.80, 156.05, 155.29, 138.55, 128.79, 128.02, 120.31, 86.50, 59.92, 59.37, 47.90, 40.28, 14.57, 14.42. EIMS, *m/z*: 381 (M^+, 18%), 231 (100%). *Anal.* Calcd for $C_{17}H_{21}ClN_4O_4$: C 53.61; H 5.56; N 14.71; Cl 9.31. Found: C 53.52; H 5.48; N 14.79; Cl 9.34.

Diethyl ({2-[1-(2-methylphenyl)imidazolidin-2-ylidene]hydrazinyl} methylidene) propanedioate (3d). The reaction mixture was evaporated on a rotavap to leave a residue, which was washed with MeOH and dried overnight to produce white solids. mp 133–135°C; yield 89%; $R_f = 0.62$; ^{1}H NMR (600 MHz, $CDCl_3$) 10.95 (d, $J = 12.3$ Hz, 1H), 8.15 (d, $J = 12.3$ Hz, 1H), 7.16–7.54 (m, 4H), 7.22 (bs, 1H), 4.08/4.14 (dq, $J = 7.2$ Hz, 2H), 3.81–3.96 (m, 2H), 3.44–3.58 (m, 2H), 1.77 (s, 3H), 1.22/1.28 (dt, $J = 7.2$ Hz, 3H). EIMS, *m/z*: 360 (M^+, 22%), 210 (100%). *Anal.* Calcd for $C_{18}H_{24}N_4O_4$: C 59.98; H 6.71; N 15.55. Found: C 59.88; H 6.74; N 15.61.

Diethyl ({2-[1-(4-methylphenyl)imidazolidin-2-ylidene]hydrazinyl} methylidene) propanedioate (3e). The reaction mixture was evaporated on a rotavap to leave a residue, which was washed with MeOH and dried overnight to produce white solids. mp 148–150°C; yield 95%; $R_f = 0.73$; ^{1}H NMR (600 MHz, $CDCl_3$) 10.97 (d, $J = 12.1$ Hz, 1H), 8.16 (d, $J = 12.1$ Hz, 1H), 7.24–7.48 (m, 4H), 7.18 (bs, 1H), 4.05/4.11 (dq, $J = 7.1$ Hz, 2H), 3.78–3.9 (m, 2H), 3.45–3.58 (m, 2H), 1.85 (s, 3H), 1.21/1.27 (dt, $J = 7.1$ Hz, 3H). EIMS, *m/z*: 360 (M^+, 24%), 210 (100%). *Anal.* Calcd for $C_{18}H_{24}N_4O_4$: C 59.98; H 6.71; N 15.55. Found: C 59.72; H 6.67; N 15.67.

General procedures of synthesis of 5a–e. ***Method A (acetic acid).*** Respective ester (0.01 mol) of (1-arylimidazolidine-2-ylidene)hydrazinomethylenemalonate **3a–e** was solved in 25 mL of acetic acid and refluxed for 3 h. Solvent was removed under reduced pressure, and solid residue was solved in 15 mL of hot methanol. Precipitate was collected after cooling and recrystallized from ethanol or 2-propanol. The physical and spectral properties of obtained compounds are listed below.

Ethyl 1-phenyl-5(1H)hydroxy-2,3-dihydroimidazo[2,1-c][1,2,4] triazepine-6-carboxylate (5a). mp 218–220°C; yield 58%; $R_f = 0.48$; ^{1}H NMR (600 MHz, $CDCl_3$) 10.8 (bs, 1H), 7.85 (s, 1H),

7.04–7.6 (m, 5H), 4.3 (s, 4H), 4.22 (q, J = 7.2 Hz, 2H), 1.3 (t, J = 7.2 Hz, 3H). EIMS, *m/z*: 300 (M^+, 34%), 224 (100%). *Anal.* Calcd for $C_{15}H_{16}N_4O_3$: C 59.99; H 5.37; N 18.66. Found: C 60.11; H 5.29; N 18.71.

Ethyl 1-(2-chlorophenyl)-5(1*H*)hydroxy-2,3-dihydroimidazo [2,1-*c*][1,2,4]triazepine-6-carboxylate (5b). mp 199–201°C; yield 95%; R_f = 0.49; ^{1}H NMR (600 MHz, $CDCl_3$), 10.35 (bs, 1H), 7.67 (s, 1H), 7.06–7.64 (m, 4H), 4.42 (s, 4H), 4.16 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) 166.66, 164.02, 152.06, 150.05, 138.93, 129.12, 128.10, 125.82, 89.54, 58.68, 53.05, 42.08, 14.62. EIMS, *m/z*: 335 (M^+, 39%), 259 (100%). *Anal.* Calcd for $C_{15}H_{15}ClN_4O_3$: C 53.82; H 4.52; N 16.74; Cl 10.59. Found: C 53.66; H 4.54; N 16.81; Cl 10.63.

Ethyl 1-(4-chlorophenyl)-5(1*H*)hydroxy-2,3-dihydroimidazo [2,1-*c*][1,2,4]triazepine-6-carboxylate (5c). mp 224–226°C; yield 90%; R_f = 0.51; ^{1}H NMR (600 MHz, $CDCl_3$) 10.5 (bs, 1H), 7.65 (s, 1H), 7.14, 7.38 (2 × d, J = 9.2 Hz, 4H), 4.2 (s, 4H), 4.16 (q, J = 7.3 Hz, 2H), 1.27 (t, J = 7.3 Hz, 3H). EIMS, *m/z*: 335 (M^+, 31%), 259 (100%). *Anal.* Calcd for $C_{15}H_{15}ClN_4O_3$: C 53.82; H 4.52; N 16.74; Cl 10.59. Found: C 53.94; H 4.53; N 16.72; Cl 10.67.

mp 212–214°C; yield 64%; R_f = 0.48; ^{1}H NMR (600 MHz, $CDCl_3$) 10.5 (bs, 1H), 7.51 (s, 1H), 7.1–7.64 (m, 4H), 4.28 (s, 4H), 4.21 (q, J = 7.2 Hz, 2H), 1.78 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). EIMS, *m/z*: 314 (M^+, 43%), 238 (100%). *Anal.* Calcd for $C_{16}H_{18}N_4O_3$: C 61.13; H 5.77; N 17.82. Found: C 60.98; H 5.79; N 17.81.

Ethyl 1-(4-methylphenyl)-5(1*H*)hydroxy-2,3-dihydroimidazo [2,1-*c*][1,2,4]triazepine-6-carboxylate (5e). mp 229–231°C; yield 95%; R_f = 0.5; ^{1}H NMR (600 MHz, $CDCl_3$) 10.65 (bs, 1H), 7.62 (s, 1H), 7.2, 7.5 (2 × d, J = 9 Hz, 4H), 4.28 (s, 4H), 4.2 (q, J = 7.3 Hz, 2H), 1.84 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H). EIMS, *m/z*: 314 (M^+, 40%), 238 (100%). *Anal.* Calcd for $C_{16}H_{18}N_4O_3$: C 61.13; H 5.77; N 17.82. Found: C 61.24; H 5.73; N 17.90.

Method B (xylene/n-butanol). Respective ester (0.01 mol) of (1-arylimidazolidine-2-ylidene)hydrazinomethylenemalonate **3a–e** was refluxed in 50 mL of xylene for 2 h and left in ambient temperature overnight. Yielded precipitate was collected, solved in 50 mL of *n*-butanol, and refluxed for 24 h. Solvent was removed under reduced pressure. Crude solid was washed with 2-propanol and crystallized from ethanol. Physical and spectral properties were identical with compounds obtained by Method A. Solids separated from xylene were mixtures of **4a–e** and **5a–e** identified by their spectra.

4a and **5a**: R_f = 0.54/0.48; ^{1}H NMR (200 MHz, $CDCl_3$) d: 10.7 (bs, 0.65H, enol OH), 7.85 (s, 1H), 7.05–7.57 (m, 5H), 4.24 (q, J = 7.2 Hz, 2H), 4.2 (s, 4H), 3.74 (s, 0.35H, NH), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) 166.64, 164.14, 152.81, 151.09, 139.80, 130.29, 130.17, 128.88, 123.36, 119.59, 89.70, 58.86, 51.49, 42.38, 14.62. EIMS, *m/z*: 300 (M^+, 34%), 224 (100%). *Anal.* Calcd for $C_{15}H_{16}N_4O_3$: C 59.99; H 5.37; N 18.66. Found C 59.70, H 5.33, N 18.44.

4b and **5b**: R_f = 0.56/0.49; ^{1}H NMR (200 MHz, $CDCl_3$) d: 10.45 (bs, 0.66 H, enol OH), 7.67 (s, 1H), 7.02–7.6 (m, 4H), 4.2 (s, 4H), 4.1 (q, J = 7.1 Hz, 2H), 3.8 (s, 0.33H, NH), 1.25 (t, J = 7.1 Hz, 3H). EIMS, *m/z*: 335 (M^+, 36%), 259 (100%). *Anal.* Calcd for $C_{15}H_{15}ClN_4O_3$: C 53.82; H 4.52; N 16.74; Cl 10.59. Found: C 53.69; H 4.51; N 16.80; Cl 10.61.

4c and **5c**: R_f = 0.55/0.51; ^{1}H NMR (200 MHz, $CDCl_3$) d: 10.4 (bs, 0.64 H, enol OH), 7.6 (s, 1H), 7.15, 7.44 (2 × d, J = 9.1 Hz, 4H), 4.2 (s, 4H), 4.2 (q, J = 7.1 Hz, 2H), 3.72 (s, 0.36H, NH), 1.24 (t, J = 7.1 Hz, 3H). EIMS (15 eV), *m/z*: 335 (M^+, 24%), 259 (100%). *Anal.* Calcd for $C_{15}H_{15}ClN_4O_3$: C 53.82; H 4.52; N 16.74; Cl 10.59. Found: C 53.93; H 4.55; N 16.70; Cl 10.61.

4d and **5d**: R_f = 0.51/0.48; ^{1}H NMR (200 MHz, $CDCl_3$) d: 10.54 (bs, 0.7H, enol OH), 7.5 (s, 1H), 7.15–7.65 (m, 4H), 4.28 (s, 4H), 4.26 (q, J = 7.2 Hz, 2H), 3.8 (s, 0.3H, NH), 1.7 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H). EIMS, *m/z*: 314 (M^+, 43%), 238 (100%). *Anal.* Calcd for $C_{16}H_{18}N_4O_3$: C 61.13; H 5.77; N 17.82. Found: C 61.03; H 5.75; N 17.77.

4e and **5e**: R_f = 0.56/0.5; ^{1}H NMR (200 MHz, $CDCl_3$) d: 10.6 (bs, 0.6H, enol OH), 7.61 (s, 1H), 7.18, 7.46 (2 × d, J = 9 Hz, 4H), 4.24 (s, 4H), 4.22 (q, J = 7.3 Hz, 2H), 3.66 (s, 0.4H, NH), 1.8 (s, 3H), 1.25 (t, J = 7.3 Hz, 3H). EIMS (15 eV), *m/z*: 314 (M^+, 39%), 238 (100%). *Anal.* Calcd for $C_{16}H_{18}N_4O_3$: C 61.13; H 5.77; N 17.82. Found: C 61.23; H 5.69; N 17.66.

Molecular modeling. The molecular structures of **2a–e**, DEEM, **3a–e**, and **4a–4e** in the ground state were optimized with the B3LYP DFT (the variant of the DFT method using Becke's three-parameter hybrid functional (B3) [13] with correlation functional such as the one proposed by Lee, Yang, and Parr (LYP) [14]) using 6-311G(d,p) as included in Gaussian09 [15]. The calculations were performed using the Polarizable Continuum Model [16]. This method creates a solute cavity through a set of overlapping spheres. Furthermore, frontal molecular orbital analysis was performed with Gaussian09 on the 6-311G(d,p)/B3LYP level of theory.

Pymol v. 0.99 [17], Yasara Structure [18], and ArgusLab [19] were also used for the visualization of the results.

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