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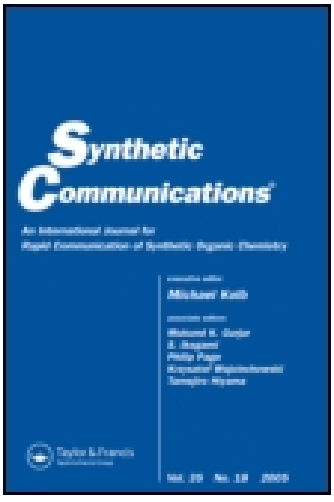

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Tandem Ring Opening and Oximation of Ethyl 3-Aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexa by Hydroxylamine

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Tandem Ring Opening and Oximation of Ethyl 3-Aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate by Hydroxylamine

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Abstract: The reaction of hydroxylamine hydrochloride with ethyl 3-aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate has led to the formation of ethyl 2-[amino(hydroxyimino)methyl]-3-aryl-5-(hydroxyimino)-5-arylpentanoate via a tandem ring opening and oximation process. The structures of the products are confirmed by NMR and X-ray techniques, and the conformational features of the product arrived at are compared with a molecular dynamics simulation study.

Keywords: 3-aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate, NMR analysis, PM3 calculation, tandem reaction, X-ray structure

1,2-Benzisoxazoles are a class of important heterocyclic compounds showing a variety of biological and potential therapeutic activities. For example, some of the derivatives of 1,2-benzisoxazoles have been found to exhibit neuroleptic[1] antipsychotic-like activities[2] in mice and anti-inflammatory activity[3] in the rat. (*Z*)-2-(1,2-Benzisoxazol-3-yl)-3-[2-(2-piperidinoethoxy)-phenyl]acrylonitrile and their analogs having a methoxy substituent at C-5 of the benzoisoxazole ring showed potent antispasmodic activities during in vitro and in vivo

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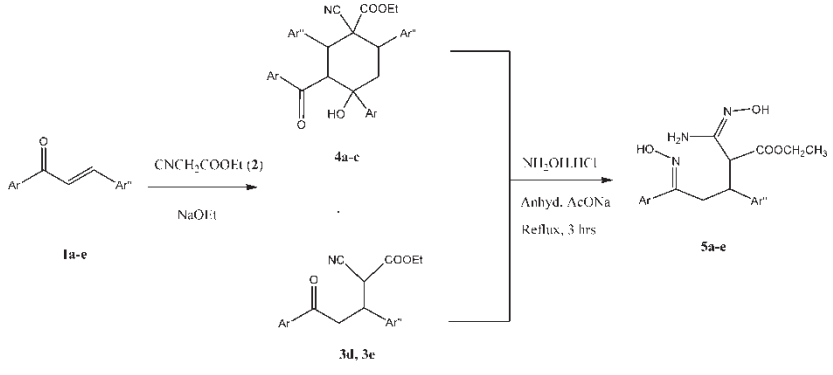
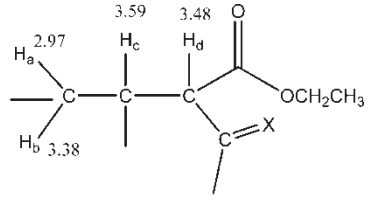
studies.[4] 3a,4,5,6,7,7a-Hexahydro-3-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,2-benzisoxazole was found to be an antibacterial agent in vivo.[5] We are interested in the synthesis of new hydrogenated benzfused isoxazole from easily available starting materials following a related reported route[6] and expect the resultant compounds to be biologically interesting. The reaction of hydroxylamine hydrochloride with ethyl 3-aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate (**4**) was carried out, ultimately aiming at the targeted new hydrogenated benzfused isoxazole and pyrazole. This attempt has ended up in the formation of an unexpected product **5** whose structural features are confirmed by NMR and X-ray studies.

The precursors for the present investigation, ethyl 3-aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylates (**4a**–**c**), were obtained by the 1,4-addition of ethyl cyanoacetate (**2**) on substituted benzylideneacetophenone (**1a**–**d**) in the presence of a sodium ethoxide catalyst (Scheme 1).[7] Compounds **1a** to **1c** reacted with **2** to give **4a**–**c** in very good yield, but under identical conditions **1d** and **1e** have led to the formation of **3d** and **3e** in good yield. The reaction of excess hydroxylamine hydrochloride with **4a**–**4c** in the presence of anhydrous sodium acetate in ethanol has been carried out under reflux for 3 hours. The product (obtained in approximately 50% yield, with the rest being unreacted starting material) is not the oxime derivative of the cyclic compound **4,** but a different one (**5a**–**c**), the structural features of which are described next.



	Ar	Ar"
a	C_6H_5	C_6H_5
b	4-Cl-C_6H_4	4-CH_3-C_6H_4
c	4-OCH_3-C_6H_4	C_6H_5
d	C_6H_5	2,4-diCl- C_6H_3
e	4-OCH_3-C_6H_4	2,4-diCl- C_6H_3

Scheme 1.



$^2J_{ab}$ = 13.5 Hz; $^3J_{bc}$ = 11.7 Hz
$^3J_{ac}$ = 3.6 Hz; $^3J_{cd}$ = 11.7 Hz

Figure 1. Fragment arrived at from the NMR data of **5**.

The compound **5a** is not freely soluble in chloroform, suggesting the presence of more polar groups in the molecule. Only signals due to two aryl systems, not four, can be observed in the proton and carbon-13 NMR spectra (DMSO-d_6). The presence of a -CH_2-CH-CH(COOEt)-C(=X)- grouping, as shown in Fig. 1, has been unambiguously established by two-dimensional NMR connectivities. The signal at 3.38 ppm makes two intense heteronuclear multiple bond correlation (HMBC) contours with the carbons at 155.8 ppm and 136.3 ppm, the latter one being a quaternary carbon of an aryl system. Thus the methylene end of the -CH_2-CH-CH chain is connected to an aryl ring (three-bond connection) and an sp^2 hybridized carbon with attached hetero atom (two-bond connection). It is surprising that the other geminal hydrogen at 2.97 ppm has not exhibited this connectivity in the HMBC spectrum. The presence of two slightly broadened singlets at 9.38 ppm and 10.57 ppm, each accounting for one hydrogen and another sharp singlet at 5.15 ppm accounting for two hydrogens, which are all exchanging with D_2O, prompted us to assign the structure of the product formed (**5a**) to be an open chain analog with two hydroxy imino groups and an amino group (Fig. 2). Bands at 3469, 3419, and 3370 cm^{-1} in the IR spectrum of **5a** also confirm the presence of NH_2 and OH groups.

It is clear that it is the mono-adduct that has undergone the addition of hydroxylamine and not the bis adduct. Hence the formation of the product **5a**–**c** can be explained by a mechanism (Scheme 2) involving retro-aldol

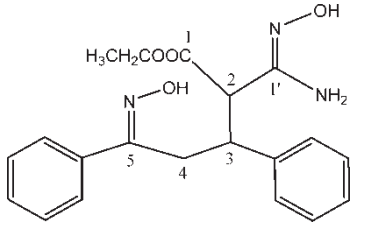


Figure 2. Structure of compound **5a**.

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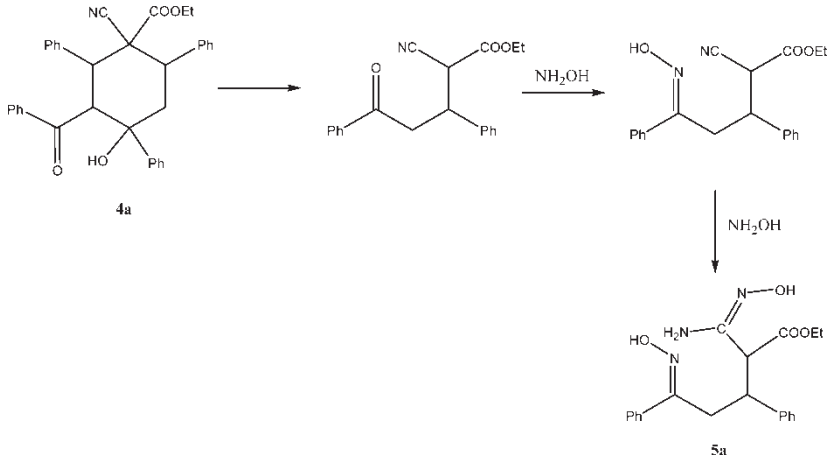

Scheme 2.

and Michael reactions to give the mono adduct in the first step of the reaction, followed by the subsequent oximation reaction. The ring-opening process requires hydroxylamine, proved by the fact that the simple treatment with sodium acetate on **4** does not lead to any change under identical reaction conditions. To prove the involvement of this tandem process, we have taken the mono adduct ethyl 2-cyano-3-(2,4-dichlorophenyl)-5-oxo-5-arylpentanoate (**3d** and **3e**) and carried out the reaction under identical condition to get **5d** and **5e** respectively in moderate yield. The single-crystal X-ray structural analysis of **5d** confirms the assigned structure (vide infra). The orientation of the hydroxyl group of the two oximino functions, which are not clearly inferred from the NMR data because the nuclear overhauser effect correlation spectroscopy (NOESY) contours due to the hydroxyl groups are not clear, have been unambiguously solved by molecular modeling and X-ray studies.

The results of X-ray analysis for **5d** (Table 1) unambiguously proved the structure assigned by NMR data. The ORTEP and packing diagrams are given in Figs. 3 and 4. In the crystal structure of **5d**, the 2,4-dichlorophenyl group is *gauche* to the imino carbon in the conformational preference around the CH_2-CH bond and the two hydrogens of CH-CH bond prefer the *anti* position. The conformational arrangement found around CH-CH and CH_2-CH in the crystal structure is in consonance with that observed in solution as revealed by the coupling constants (Fig. 1). Crystal data have been deposited at the CCDC, number 614664.

The PM3 molecular modeling method shows all four possible stereochemical arrangements around C═N bond have comparable binding energy with equally stable structures (Table 2). However, in the crystal structure of **5d**, one of the oximino group exists in *cis*-configuration with respect to the NH_2 group, and the other oximino group is *trans* to the phenyl group. It should be noted

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Table 1. Crystal data and structural refinement for **5d**

Parameters	**5d**
Empirical formula	$C_{20}H_{21}Cl_2N_3O_4$
Formula weight	438.30
Temperature	293 (2) K
Wavelength	0.71069 Å
Crystal system, space group	Monoclinic, P 21/c
Unit cell dimensions	a = 11.802 Å; $\alpha = 90.00^\circ$; b = 11.759 Å; $\beta = 107.99^\circ$ deg; c = 16.754 Å; $\gamma = 90.00^\circ$
Z, volume	4, 2211.3 Å ^{3}
Density (calculated)	1.317 Mg/m^3
Absorption coefficient	0.323 mm^{-1}
F(000)	912
Crystal size	0.18 × 0.16 × 0.14 mm
Theta range for data collection	2.15 to 25.00°
Index ranges	$0 \le h \le 14$, $-1 \le k \le 13$, $-19 \le l \le 18$
Reflections collected	4519
Independent reflections	3889 [$R_{int} = 0.0183$]
Absorption correction	Psi-scans
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3889/0/271
Goodness of fit on F^2	1.027
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0524$, $wR_2 = 0.1428$
R indices (all data)	$R_1 = 0.0938$, $wR_2 = 0.1696$
Largest diff. peak and hole	0.920 and -0.358 e · Å^{-3}

that although compound **5d** possesses a number of acidic hydrogens and a variety of electron donor atoms, the molecule is not involved in intramolecular hydrogen bonding; rather it exhibits intermolecular hydrogen bonding, even though the oxime group exists in *cis*-configuration with respect to the NH_2 group. The structure reveals intermolecular hydrogen bonding between N8...N5 and O6...O9, forming an infinite chain of molecules along the crystallographic axis *c* as shown in the packing diagram (Fig. 4). The linear chains of molecule are additionally connected by classical $R_2^2(6)$ intermolecular hydrogen bonding motif [O9...N9] and $R_2^2(12)$ intermolecular hydrogen bonding motif [N8...O11], forming three-dimensional networks. Selected hydrogen bond geometries are given in Table 3.

To explore the scope of this reaction, we carried out the same reaction with the adduct formed from another nucleophile. Thus, the mono adduct **6** formed from benzyl cyanide and benzylideneacetophenone has been subjected to hydroxylamine treatment as described (Scheme 3). In this case, compound **7**, similar to the one obtained in the previous reaction, has been

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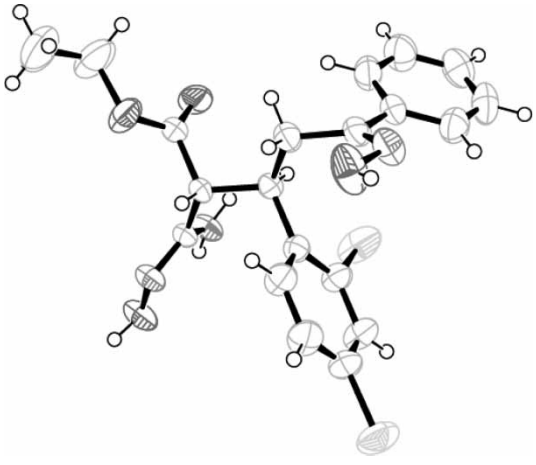

Figure 3. ORTEP diagram of ethyl 2-[amino(hydroxyimino)methyl]-3-(2,4-dichlorophenyl)-5-(hydroxyimino)-5-phenylpentanoate (**5d**).

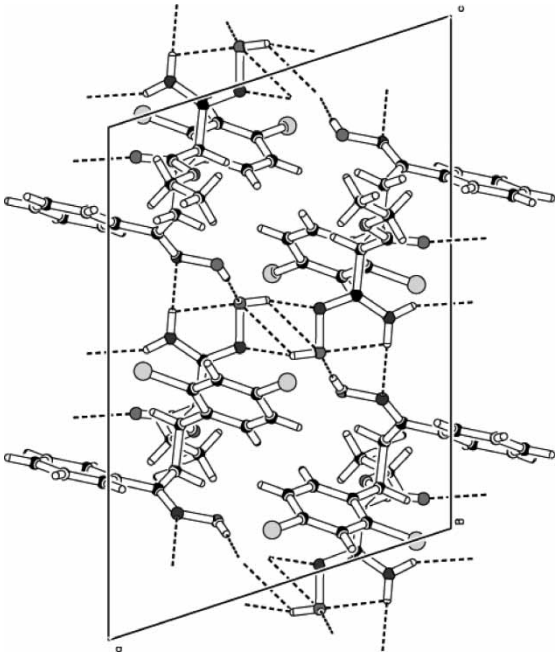

Figure 4. Packing diagram of ethyl 2-[amino(hydroxyimino)methyl]-3-(2,4-dichlorophenyl)-5-(hydroxyimino)-5-phenylpentanoate (**5d**).

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Table 2. Energy calculated by PM3 method for various orientation of hydroxylamine groups for **5**

Orientation of C═N-OH	Total energy (kcal/mol)	Binding energy (kcal/mol)	Heat of formation (kcal/mol)	Dipole moment (Debye)
5E-1′Z	−114950.4	−5186.172	−39.01444	1.531439
5E-1′E	−114949.1	−5184.91	−37.75183	1.201498
5Z-1′Z	−114950.5	−5186.249	−39.09102	1.604297
5Z-1′E	−114949.2	−5184.999	−37.84047	1.333146

obtained as evidenced by its IR and NMR spectra. In addition, another product, **8**, which is identified as the mono oxime of **6** by IR and NMR spectroscopy, has been obtained in which the cyanide group is not disturbed (IR stretching at 2238 cm^{-1}) by the hydroxylamine, with only the carbonyl group undergoing the reaction.

This study has demonstrated the unusual cleavage of the cyclic compound, 3-aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate, under mild basic conditions to its monomer, ethyl 2-cyano-5-oxo-3,5-diarylpentanoate, followed by the reaction of hydroxylamine with the ketone and the cyanide functionalities. The structure and conformation of the obtained product have been studied by NMR and X-ray crystallography.

EXPERIMENTAL

Melting points are uncorrected. One- and two-dimensional NMR spectra were recorded on a Bruker 300-MHz instrument in DMSO-d_6 using TMS as internal standard. Chemical shifts are given in parts per million (δ scale), and coupling constants are given in hertz. IR spectra were recorded on a Jasco FT-IR

Table 3. Selected hydrogen-bonding geometry for **5d**

D-H. . . A	D-H (Å)	H. . .A (Å)	D. . .A (Å)	D-H. . .A (deg)	Symmetry code
O9-H9. . .N9	0.89(5)	1.85 (5)	2.718 (3)	164 (4)	$-x+1, -y, -z+1$
N8-H8A. . .N5	0.86	2.36	3.091 (4)	143.3	$x, -y+1/2, z+1/2$
N8-H8B. . .O11	0.86	2.16	2.971 (3)	156.5	$-x+2, -y, -z+1$
O6-H6. . .O9	0.71 (4)	2.07 (4)	2.754 (4)	160 (5)	$x, -y+1/2, z-1/2$

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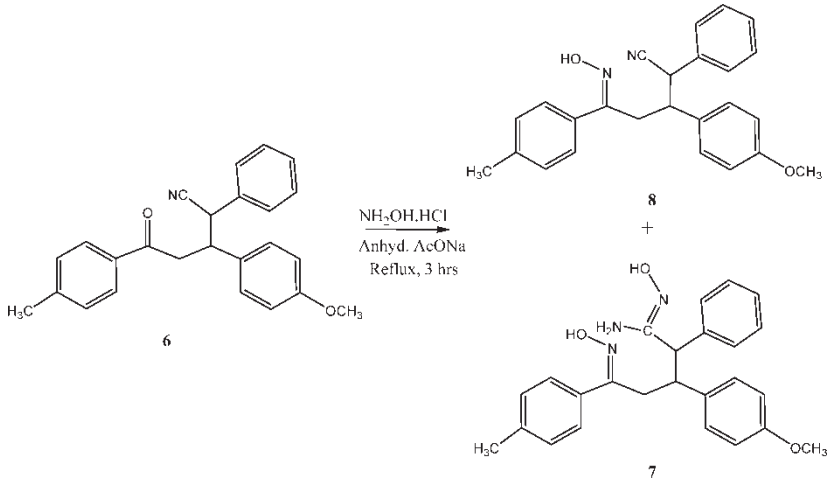

Scheme 3.

instrument (KBr pellet). Column chromatography was carried out in silica gel (60–120 mesh) using petroleum ether–ethyl acetate as an eluent.

All the computational calculations for **5** were carried out on an MS Windows 2000 platform with the software package of Hyperchem,[8] version 7.0. The geometry optimization was performed with the Polak–Ribiere algorithms included in the semi-empirical PM3 method.[9] Structure was deemed to be minimized when the gradient root mean square was less than 0.01 kcal/mol. This optimized structure was then subjected to conformational search using a molecular dynamics simulation.

The single-crystal X-ray data for **5d** were collected on a Nonius MACH3 kappa diffractometer with MoK_α radiation ($\lambda = 0.71069$ Å). The structure was solved by direct methods from SHELXA97[10] and refined by full-matrix least squares on F^2 by SHELXTL97.[11] Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 614664. Copies of the data can be obtained, free of charge, by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (E-mail: data_request@ccdc.cam.ac.uk; fax: +44 1223 336033).

General Procedure for the Preparation of Ethyl 3-Aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate (4a–c)

The adducts, ethyl 3-aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylates, have been prepared by a reported procedure.[7] Ethyl cyanoacetate

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(0.0200 m) was added to different substituted chalcone (0.0200 m) in ether solution in the presence of sodium ethoxide (0.0040 m) in ethanol, and the reaction mixture was stirred at room temperature for about 24 h. The product was purified by crystallization in ethanol. Compounds **4a** and **4c** have already been reported.[7,12]

Ethyl 3-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-1-cyano-4-hydroxy-2,6-bis(4-methylphenyl)cyclohexanecarboxylate (4b)

Yield 78%, mp 207°C. Anal. calcd. for $C_{37}H_{33}Cl_2NO_4$: C, 70.93; H, 5.31; N, 2.24. Found: C, 70.97; H, 5.40; N, 2.31. IR (KBr pellet): $\nu_{max} = 3030, 2925, 2854, 2341, 1736, 1660, 1589, 1402, 1247\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.76$ (t, $J = 7.2$ Hz, 3H); 2.11 (s, 3H); 2.13 (dd, $J = 12.6$, 3.0 Hz, 1H); 2.30 (s, 3H); 2.84 (td, $J = 13.5$, 2.4 Hz, 1H); 3.77 (q, $J = 7.2$, 2H); 4.20 (dd, $J = 12.6$, 3.0 Hz, 1H); 4.24 (d, $J = 12.3$ Hz, 1H); 4.78 (d, $J = 12.3$ Hz, 1H); 5.25 (d, $J = 2.1$ Hz, 1H); 6.83 (d, $J = 8.1$ Hz, 2H); 7.10–7.21 (m, 8H); 7.29–7.35 (m, 4H); 7.50 (d, $J = 8.4$ Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.5, 20.9, 21.1, 41.7, 44.7, 48.7, 52.2, 59.9, 62.3, 117.8, 126.2, 128.2, 128.4, 128.5, 129.0, 129.3, 129.4, 131.3, 133.4, 134.6, 135.5, 137.9, 138.2, 140.2, 143.3, 166.3, 203.8$ ppm.

General Procedure for the Preparation of Ethyl 2-Cyano-5-oxo-3,5-diarylpentanoate (3d, 3e)

The adducts, ethyl 2-cyano-5-oxo-3,5-diarylpentanoates, have all been prepared by the reported procedure. Ethyl cyanoacetate (0.0200 m) was added to different chalcones (0.0200 m) in ether solution in the presence of sodium ethoxide (0.0020 m) in ethanol, and the reaction mixture was stirred at room temperature for about 24 h. The product was obtained by recrystallization from ethanol.

Ethyl 2-Cyano-3-(2,4-dichlorophenyl)-5-oxo-5-phenylpentanoate (3d)

Yield 82%, mp 93°C. Anal. calcd. for $C_{20}H_{17}Cl_2NO_3$: C, 61.55; H, 4.39; N, 3.59. Found: C, 61.61; H, 4.43; N, 3.61. IR (KBr pellet): $\nu_{max} = 3066, 2924, 2854, 2249, 1739, 1689, 1473, 1373, 1305, 1188, 1039\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.2$ Hz, 3H); 3.58 (dd, $J = 18.0$, 5.1 Hz, 1H); 3.85 (dd, $J = 18.0$, 9.0 Hz, 1H); 3.98 (d, $J = 5.1$ Hz, 1H); 4.26 (q, $J = 7.2$ Hz, 2H); 4.69 (qui, $J = 5.1$ Hz, 1H); 7.23 (dd, $J = 8.4$, 2.1 Hz, 1H); 7.32 (d, $J = 8.4$ Hz, 1H); 7.45 (d, $J = 2.1$ Hz, 1H); 7.49 (d, $J = 7.8$ Hz, 2H); 7.60 (tt, $J = 7.8$, 1.2 Hz, 1H); 7.95 (d, $J = 8.4$ Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.9, 36.2, 38.8, 42.4, 63.3,$

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114.9, 127.7, 128.0, 128.8, 130.0, 133.7, 133.8, 134.3, 134.5, 135.0, 136.0, 164.6, 195.7 ppm.

Ethyl 2-Cyano-3-(2,4-dichlorophenyl)-5-(4-methoxyphenyl)-5-oxopentanoate (3e)

Yield 77%, mp 96°C. Anal. calcd. for $C_{21}H_{19}Cl_2NO_4$: C, 60.01; H, 4.56; N, 3.33. Found: C, 60.05; H, 4.58; N, 3.36. IR (KBr pellet): $\nu_{max} = 3068$, 2933, 2852, 2244, 1743, 1674, 1601, 1469, 1421, 1234, 1173, 1024 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.2$ Hz, 3H); 3.51 (dd, $J = 17.7$, 4.8 Hz, 1H); 3.74 (dd, $J = 17.7$, 9.0 Hz, 1H); 3.87, (s, 3H); 3.98 (d, $J = 4.8$ Hz, 1H); 4.26 (q, $J = 7.2$ Hz, 2H); 4.68 (qui, $J = 4.8$ Hz, 1H); 6.94 (d, $J = 9.0$ Hz, 2H); 7.22 (dd, $J = 8.4$, 2.1 Hz, 1H); 7.32 (d, $J = 8.4$ Hz, 1H); 7.44 (d, $J = 2.1$ Hz, 1H); 7.93 (d, $J = 9.0$ Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$, 36.7, 38.8, 42.9, 55.9, 63.7, 114.3, 115.4, 128.1, 129.3, 129.6, 130.4, 130.8, 134.7, 135.0, 135.5, 164.4, 165.1, 194.6 ppm.

General Procedure for the Reaction of Ethyl 3-Aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate (4)/Ethyl 2-Cyano-5-oxo-3,5-diarylpentanoate (3) with Hydroxylamine Hydrochloride

To a warm solution of 0.0040 m of ethyl 3-aroyl-1-cyano-4-hydroxy-2,4,6-triarylcyclohexanecarboxylate (**4**)/ethyl 2-cyano-5-oxo-3,5-diarylpentanoate (**3**) in 50 mL of ethanol, a solution of 1.85 g (0.0260 m) of hydroxylamine hydrochloride and 2.18 g (0.0260 m) of anhydrous sodium acetate in 15 ml of water was added by portions, and the reaction mixture was refluxed in a water bath for 3 h. The reaction mixture was filtered off, and the filtrate was poured onto crushed ice and extracted with chloroform. The product was washed with petroleum ether and dried.

Ethyl 2-[Amino(hydroxyimino)methyl]-5-(hydroxyimino)-3,5-diphenylpentanoate (5a)

Yield 50%, mp 177°C. Anal. calcd. for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.08; H, 6.26; N, 11.38. IR (KBr pellet): $\nu_{max} = 3469$, 3419, 3370, 3249, 2981, 2927, 1724, 1666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.79$ (t, $J = 7.2$ Hz, 3H); 2.97 (dd, $J = 13.5$, 3.6 Hz, 1H); 3.38 (dd, $J = 13.5$, 11.7 Hz, 1H); 3.48 (d, $J = 11.7$ Hz, 1H); 3.59 (td, $J = 11.7$, 3.6 Hz, 1H); 3.76 (q, $J = 7.2$ Hz, 2H); 5.15 (s, 2H); 6.98–7.02 (m, 2H); 7.07–7.09 (m, 3H); 7.22–7.30 (m, 5H); 9.38 (bs, 1H); 10.57 (bs, 1H) ppm.

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^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.5$, 29.3, 43.4, 54.3, 60.6, 126.3, 126.8, 127.6, 127.9, 128.2, 128.3, 136.3, 139.5, 149.9, 155.8, 170.9 ppm.

Ethyl 2-[Amino(hydroxyimino)methyl]-5-(4-chlorophenyl)-5-(hydroxyimino)-3-(4-methylphenyl)pentanoate (5b)

Yield 46%, mp 160–162°C. Anal. calcd. for $C_{21}H_{24}ClN_3O_4$: C, 60.36; H, 5.79; N, 10.06. Found: C, 60.40; H, 5.82; N, 10.09. IR (KBr pellet): $\nu_{max} = 3444$, 2925, 2856, 1736, 1760, 1589, 1248, 1093 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$ (t, $J = 7.2$ Hz, 3H); 2.22 (s, 3H); 2.89 (d, $J = 12.6$ Hz, 1H); 3.36–3.61 (m, 3H); 3.77 (q, $J = 7.2$ Hz, 2H); 5.25 (s, 2H); 6.89 (s, 4H); 7.22 (d, $J = 8.1$ Hz, 2H); 7.27 (d, $J = 8.1$ Hz, 2H); 9.53 (bs, 1H); 10.87 (bs, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.5$, 19.9, 28.1, 41.7, 53.2, 59.6, 126.7, 127.0 one carbon merges with the other, 127.9, 132.6, 133.9, 135.0, 135.3, 148.7, 153.7, 169.6 ppm.

Ethyl 2-[Amino(hydroxyimino)methyl]-5-(hydroxyimino)-5-(4-methoxyphenyl)-3-phenylpentanoate (5c)

Yield 45%, mp 180–182°C. Anal. calcd. for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 63.18; H, 6.36; N, 10.55. IR (KBr pellet): $\nu_{max} = 3413$, 3292, 3236, 2933, 2837, 1722, 1637, 1606, 1514, 1304, 1248, 1188 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 6.9$ Hz, 3H); 2.85 (d, $J = 10.5$ Hz, 1H); 3.26–3.59 (m, 3H); 3.75 (q, $J = 6.9$ Hz, 2H); 3.79 (s, 3H); 5.22 (s, 2H); 6.79 (d, $J = 8.4$ Hz, 2H); 6.93–7.07 (m, 5H); 7.31 (d, $J = 8.4$ Hz, 2H); 9.48 (bs, 1H); 10.51 (bs, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.5$, 27.9, 41.6, 53.9, 57.8, 59.4, 112.2, 125.4, 126.3, 126.4, 127.2, 127.5, 138.8, 153.5, 158.3, 167.7, 168.2 ppm.

Ethyl 2-[Amino(hydroxyimino)methyl]-3-(2,4-dichlorophenyl)-5-(hydroxyimino)-5-phenylpentanoate (5d)

Yield 55%, mp 167°C. Anal. calcd. for $C_{20}H_{21}Cl_2N_3O_4$: C, 54.81; H, 4.83; N, 9.59. Found: C, 54.79; H, 4.85; N, 9.61. IR (KBr pellet): $\nu_{max} = 3446$, 3361, 2987, 2906, 1726, 1670, 1475, 1315, 1174 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (t, $J = 7.2$ Hz, 3H); 2.99 (dd, $J = 13.2$, 4.5 Hz, 1H); 3.34–3.62 (m, 2H); 4.15–4.33 (m, 3H); 4.76 (s, 2H); 7.03 (d, $J = 8.1$ Hz, 1H); 7.10 (d, $J = 2.4$ Hz, 1H); 7.25–7.26 (m, 4H); 7.35–7.38 (m, 2H); 9.18 (bs, 1H); 10.81 (bs, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.5$, 27.7, 36.3, 51.1, 59.8, 124.5, 124.8, 126.4, 126.7, 129.7, 130.3, 133.2, 134.4, 134.7, 147.1, 152.7, 158.2, 169.2 ppm.

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Ethyl 2-[Amino(hydroxyimino)methyl]-3-(2,4-dichlorophenyl)-5-(hydroxyimino)-5-(4-methoxyphenyl)pentanoate (5e)

Yield 49%, mp 152–154°C. Anal. calcd. for $C_{21}H_{23}Cl_2N_3O_5$: C, 53.86; H, 4.95; N, 8.97. Found: C, 53.90; H, 4.96; N, 8.94. IR (KBr pellet): $\nu_{max} = 3444, 3344, 3215, 2974, 2935, 2843, 1724, 1670, 1606, 1514, 1307, 1252, 1186\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (t, $J = 7.2$ Hz, 3H); 2.94 (dd, $J = 13.2$, 4.2 Hz, 1H); 3.35–3.58 (m, 2H); 3.78 (s, 3H); 4.16–4.32 (m, 3H); 4.85 (s, 2H); 6.77 (d, $J = 8.7$ Hz, 2H); 7.05–7.14 (m, 2H); 7.31 (d, $J = 8.7$ Hz, 2H); 7.40 (d, $J = 8.7$ Hz, 1H); 9.09 (bs, 1H); 10.68 (bs, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.8$, 28.1, 36.8, 51.5, 53.9, 60.2, 112.1, 125.1, 126.1, 126.9, 127.2, 129.9, 130.8, 133.6, 134.9, 147.5, 152.6, 158.4, 169.6 ppm.

Procedure for Preparation of 3-(4-Methoxyphenyl)-5-(4-methylphenyl)-5-oxo-2-phenyl-pentanenitrile (6)

The adduct, 3-(4-methoxyphenyl)-5-(4-methylphenyl)-5-oxo-2-phenyl-pentanenitrile, has been prepared by the reported procedure. Benzyl cyanide (0.0160 m) was added to substituted chalcone (0.0160 m) in ether solution in the presence of sodium ethoxide (0.0035 m) in ethanol, and the reaction mixture was stirred at room temperature for about 24 h. The product was obtained by recrystallization from ethanol.

3-(4-Methoxyphenyl)-5-(4-methylphenyl)-5-oxo-2-phenylpentanenitrile (6)

Yield 89%, mp 146°C. Anal. calcd. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.31; H, 6.29; N, 3.82. IR (KBr pellet): $\nu_{max} = 3014, 2929, 2841, 2242, 1674, 1608, 1513, 1456, 1301, 1246, 1180, 1032\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H); 3.30 (dd, $J = 17.1$, 5.1 Hz, 1H); 3.63 (dd, $J = 17.1$, 9.0 Hz, 1H); 3.75 (s, 3H); 3.87–3.93 (m, 1H); 4.20 (d, $J = 5.7$ Hz, 1H); 6.79 (d, $J = 8.9$ Hz, 2H); 7.12 (d, $J = 8.9$ Hz, 2H); 7.18–7.23 (m, 4H); 7.29–7.31 (m, 3H); 7.77 (d, $J = 8.1$ Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.6$, 39.5, 44.0, 44.6, 55.1, 113.9, 119.8, 128.1, 128.2 one carbon merges with the other, 128.8, 129.0, 129.3, 131.4, 133.5, 134.1, 144.2, 158.8, 196.7 ppm.

Reaction of 3-(4-Methoxyphenyl)-5-(4-methylphenyl)-5-oxo-2-phenylpentanenitrile (6) with Hydroxylamine

3-(4-Methoxyphenyl)-5-(4-methylphenyl)-5-oxo-2-phenylpentanenitrile (1.00 g, 0.0028 m was dissolved in 50 mL of ethanol by gentle warming. To this, a

solution of 1.36 g (0.0196 m) of hydroxylamine hydrochloride and 1.61 g (0.0196 m) of anhydrous sodium acetate in 15 ml of water were added by portions, and the reaction mixture was refluxed on a water bath for 3 h. The reaction mixture was filtered off, and the filtrate was poured onto crushed ice and extracted with chloroform. The crude mixture was subjected to column chromatography to get two products, **7** and **8**.

N′-hydroxy-5-(hydroxyimino)-3-(4-methoxyphenyl)-5-(4-methylphenyl)-2-phenyl pentanimidamide (7)

Yield 55%, mp 157°C. Anal. calcd. for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.97; H, 6.55; N, 10.04. IR (KBr pellet): $\nu_{max} = 3384$, 3029, 2924, 2860, 1660, 1610, 1514, 1450, 1250, 1180, 1034 cm^{-1}. ^1H NMR NMR spectrum recorded in acetone-d_6 (300 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3H); 3.25 (dd, $J = 13.5$, 3.6 Hz, 1H); 3.52–3.55 (m, 1H); 3.55 (s, 3H); 3.83–3.96 (m, 2H); 5.47 (s, 2H); 6.45 (d, $J = 8.7$ Hz, 2H); 6.84 (d, $J = 8.7$ Hz, 2H); 6.97 (tt, $J = 7.5$, 1.2 Hz, 1H); 7.04 (d, $J = 7.5$ Hz, 2H); 7.07 (d, $J = 8.1$ Hz, 2H); 7.27 (d, $J = 7.5$ Hz, 2H); 7.40 (d, $J = 8.1$ Hz, 2H); 8.02 (bs, 1H); 10.65 (bs, 1H) ppm. ^{13}C NMR NMR spectrum recorded in acetone-d_6 (75 MHz, $CDCl_3$): $\delta = 21.6$, 31.7, 44.8, 55.5, 55.6, 113.9, 127.5, 127.8, 129.0, 129.8, 130.0, 130.8, 134.3, 135.2, 138.9, 141.6, 156.3, 157.5, 159.1 ppm.

5-(Hydroxyimino)-3-(4-methoxyphenyl)-5-(4-methylphenyl)-2-phenylpentanenitrile (8)

Yield 42%, mp 146°C. Anal. calcd. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 78.13; H, 6.33; N, 7.28. IR (KBr pellet): $\nu_{max} = 3236$, 3029, 2929, 2239, 1614, 1514, 1456, 1306, 1248, 1178, 1041 cm^{-1}. ^1H NMR NMR spectrum recorded in $CDCl_3$ (300 MHz, $CDCl_3$): $\delta = 2.33$ (s, 3H); 3.15 (dd, $J = 13.5$, 4.5 Hz, 1H); 3.37 (m, 1H); 3.60 (dd, $J = 13.5$, 10.8 Hz, 1H); 3.71 (s, 3H); 3.96 (d, $J = 6.6$ Hz, 1H); 6.65 (d, $J = 8.4$ Hz, 2H); 6.90 (d, $J = 8.4$ Hz, 2H); 7.01 (d, $J = 8.4$ Hz, 2H); 7.06 (d, $J = 8.4$ Hz, 2H); 7.14–7.18 (m, 1H); 7.26 (m, 4H); 8.65 (bs, 1H) ppm. ^{13}C NMR NMR spectrum recorded in $CDCl_3$ (75 MHz, $CDCl_3$): $\delta = 21.2$, 28.2, 44.6, 46.8, 55.1, 113.5, 119.8, 126.3, 128.0, 128.1, 128.6, 129.1, 129.2, 130.2, 132.2, 133.9, 139.1, 157.3, 158.8 ppm.

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