Action of Some Nitrogen and Carbon Nucleophils on 4-Arylidene-1, 3-oxazolones

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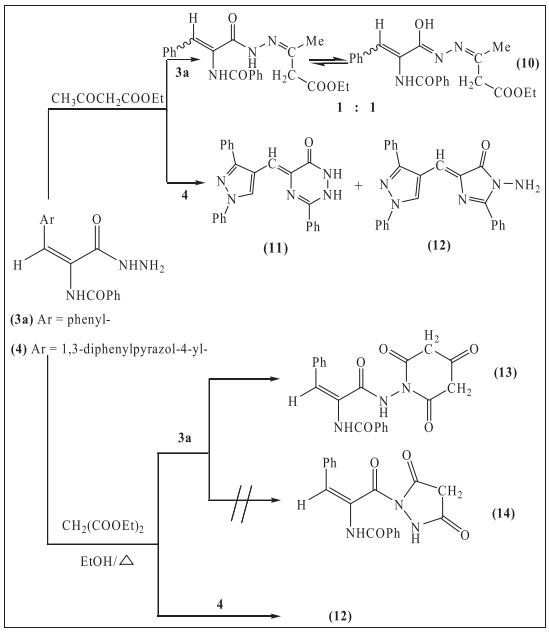


1,3-Oxazolones 1 and 2 were reacted with hydrazine hydrate to afford the corresponding hydrazides 3 and 4. Treatment of the hydrazides withacetylacetone, acetonylacetone, ethyl acetoacetate and diethyl malonateyielded different heterocycles. However, oxazolones 1 and 2 reacted with methyl p-aminobenzoate to afford the imidazolones 5a,b which were converted into the hydrazide 3a or the triazinone derivative 6 upon treating with hydrazine hydrate. The structures of the newly synthesized compounds were established using IR, 1H-NMR, EIMS, and elemental analyses.

INTRODUCTION

Oxazolones are considered as key starting materials for the construction of many heterocycles of synthetic and biological importance as analgesic [1], anti-inflammatory [2], antidepressant [3], anticancer [4], antimicrobial, antidiabetic, and antiobesity [5,6].

The key step in these transformations is the formation of the acid hydrazides that are formed by the action of hydrazine hydrate on the oxazolones, a reaction that occurs smoothly and mostly at room temperature. An extension of conjugation through an exocyclic double bond present at C-4 position of oxazolone moiety and a phenyl ring present at C-2 plays a pivotal role in the reactivity of these oxazolones [7,8].

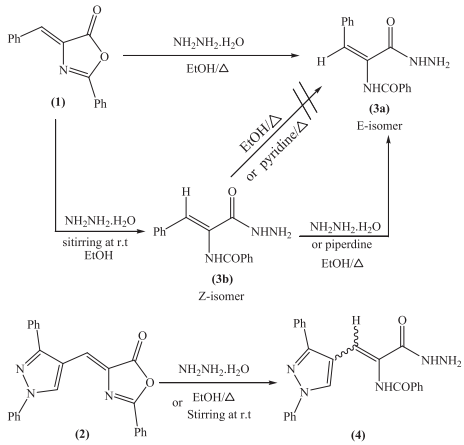
In the present investigation, we aimed to make a comparative study between the action of methyl-4-aminobenzoate, hydrazine hydrate, on 4-phenylmethylene-2-phenyl-1,3-oxazole-5(4*H*)-one **1** and 4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-1,3-oxazole-5(4*H*)-one **2** and also on the action of acetonylacetone, acetylacetone, ethyl acetoacetate, and diethyl-malonate on the obtained acid hydrazide derivatives **3a** and **4**.

RESULTS AND DISCUSSION

The action of hydrazine hydrate on different oxazolones in different conditions was previously studied [9–12], but the stereochemistry of the product obtained was not discussed. Thus, treatment of **1** with hydrazine hydrate in refluxing ethanol afforded the *E*- configurated isomer hydrazide derivative (*E*) **3a** (low yield). However, doing the same reaction by stirring at room temperature gave the *Z*- configurated isomer hydrazide derivative (*Z*) **3b** in a good yield.

Aforementioned findings prompted the authors to carry out this reaction to show the effective factor (temperature

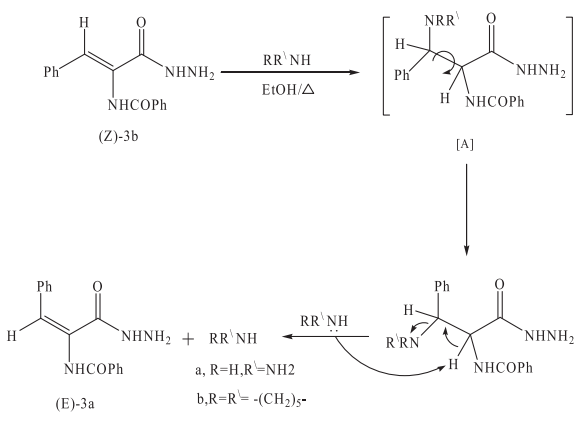
Scheme 1



and/or nucleophile) on this isomerization (Scheme 1). Thus, when *Z*- isomer **3b** was heated under reflux in ethanol or in pyridine, the isomerization did not occur; however, the isomerization occurred upon heating an ethanolic solution of **3b** with prototype nucleophiles as hydrazine hydrate or piperidine. This can be explained on the basis of the attack by a molecule of hydrazine hydrate or piperidine at C_β of the α,β-unsaturated carbonyl system to give the saturated intermediate [A] not isolated. Rotation around C–C single bond followed by removal of a hydrazine hydrate or a piperidine molecule gave the *E*-configurated isomer (*E*)- **3a** (Scheme 2).

On the other hand, when the pyrazol-3-yl-methylene oxazolone derivative **2** was treated with the hydrazine hydrate in refluxing ethanol, it afforded one isomer of the hydrazide derivative **4** in low yield. However, on doing the same reaction by stirring at room temperature, the same isomer was isolated but in a good yield, and the other isomer did not, which may be due to the high steric effect of the 1,3-diphenylpyrazolyl ring (Scheme 1). We suggest

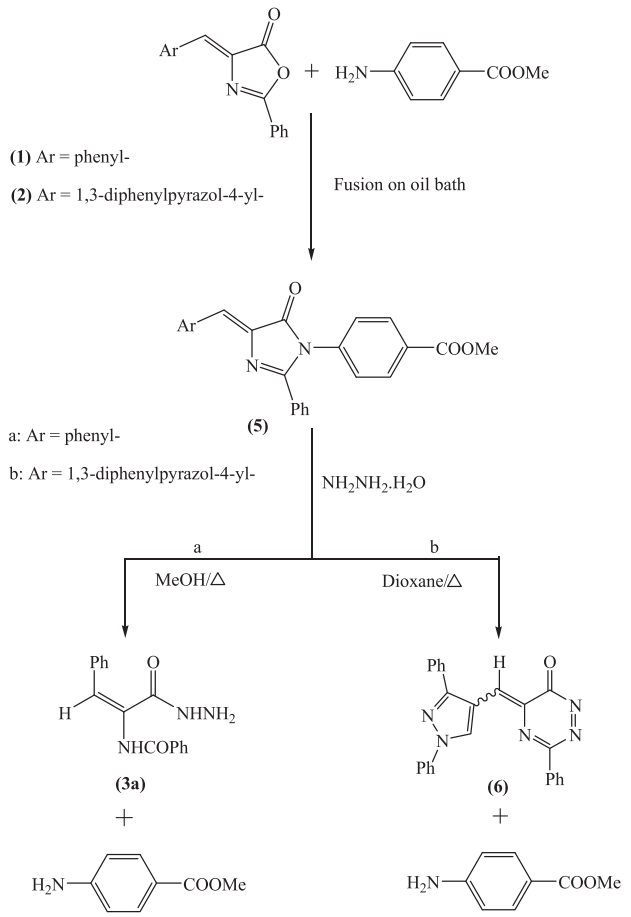
Scheme 2



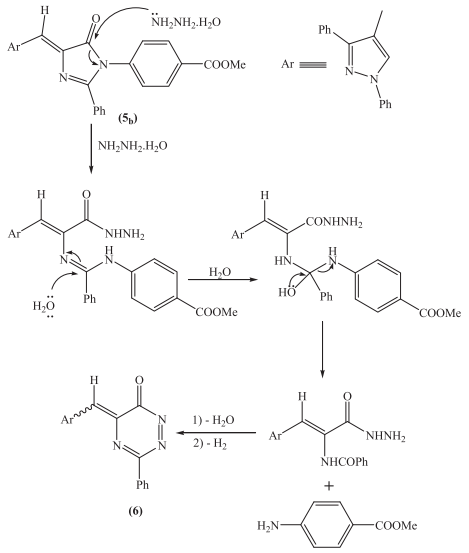
that the isolated isomer is the *E*- configurated one as it is of lower steric interaction as compared with the *Z*-counterpart.

Fusion of oxazolones **1** and **2** with methyl-4-aminobenzoate on an oil bath gave the imidazolone derivatives **5a** and **5b**, respectively. The structure of **5** is substantiated from its spectral data. The IR spectrum shows disappearance of absorption of C=O group of azlactone and the appearance of an absorption of C=O group for cyclic amide. The assigned structure is supported from ^{1}H-NMR and mass spectra. The MS spectrum shows the correct molecular ion peak beside some of abundant peaks (cf. Experimental section). Refluxing **5a** with hydrazine hydrate in methanol for 3 h gave the acid hydrazide derivative **3a**, as *E*- configurated isomer with a better yield together and a compound that was identical in all respects (m.p., mm.p., and TLC) with methyl-4-aminobenzoate (Scheme 3), while the treatment of the imidazolone **5b** with hydrazine hydrate in dioxane for 20 h gave the triazinone derivative **6**. The structure of **6** was illustrated from its analytical, as well as, spectral data (cf. Experimental section). The mechanistic pathway for the transformation of imidazolone **5b** to **6** is represented in (Scheme 4).

Scheme 3

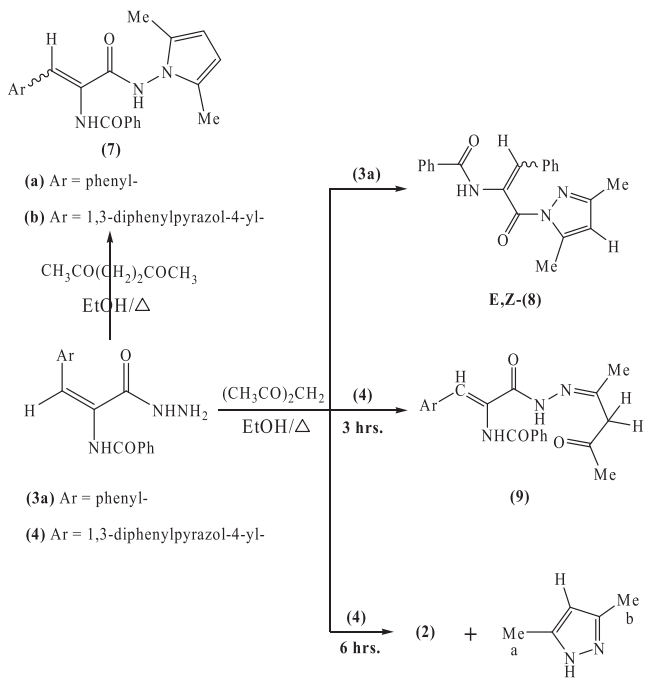


Scheme 4



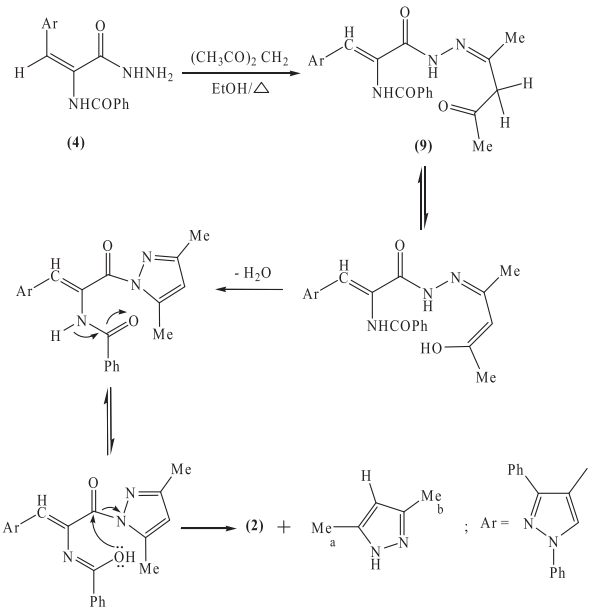
N-Pyrrolo derivatives **7a,b** were obtained upon treatment of the acid hydrazide derivative **3a** or **4** with acetonylacetone in refluxing ethanol (Scheme 5). Inspection of the ^{1}H-NMR spectrum of compound **7b** revealed its existence as a mixture of *E*,*Z*- stereoisomers in the ratio of 2:3, respectively, based on the appearance of four singlets for methyl groups (cf. Experimental section).

Scheme 5

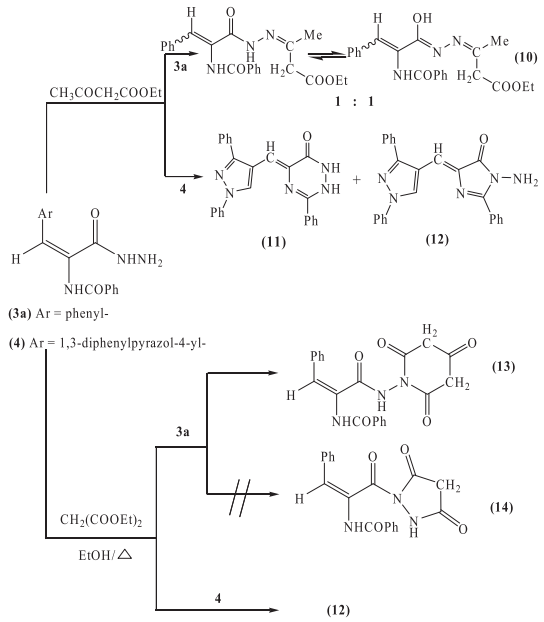


Treatment of the acid hydrazide derivative 3a with acetylacetone in refluxing ethanol gave the pyrazolyl derivative **8**. The ^{1}H-NMR spectrum of compound **8** showed that it exists as a mixture of *E*- and *Z*- isomers in the ratio of 48:52%, respectively (Scheme 5). The *E*- isomer is the minor adduct due to the steric interaction between the pyrazolyl and the phenyl group. Thus, the pyrazolyl group becomes out of plane and the conjugation with the carbonyl group is no longer present, so the pyrazolyl hydrogen appears in the downfield region (as the ring becomes more aromatic). However, in the *Z*- isomer (major), the pyrazolyl moiety is in conjugation with the rest of the molecule, which leads to the upfield for the signal of the pyrazolyl hydrogen. In addition, the extension of conjugation in the molecule leads to downfield for the signal of NH proton. Both *E*- and *Z*- isomers will be planarized to a greater or lesser extent by intramolecular H-bonding between the NH and the pyrazole N-2. In the E-isomer, steric interaction between the (pyrazolyl-linked) carbonyl oxygen and the Ph group will make the array less planar resulting in weaker H-bonding (resulting in an upfield shift of the NH proton – 8.37 ppm) compared with the *Z*- isomer in which no such interaction is possible as reflected by the deshielding of the NH to 9.03 ppm. A quick look using Chem3D does indicate the existence of intramolecular H-bonding (cf. Experimental section).Similarly, treatment of the acid hydrazide **4** with acetylacetone in refluxing ethanol for 6 h gave a product that was proved by IR and ^{1}H-NMR spectra to be a mixture of oxazolone **2** and 3,5-dimethylpyrazole. The appearance of absorption bands in the IR spectrum at 1790 cm^{-1} (C=O lactone) and at 3275, 3141 cm^{-1} (NH) is a good evidence for the existence of oxazolone **2** and 3,5-dimethyl pyrazole. Further support for the existence of the components mixture was gained from ^{1}H-NMR spectrum that revealed signals for olefinic protons, CH (pyrazolo), $2CH_3$, broad singlet signal for NH proton and multiplet signals for aromatic protons (cf. Experimental section). A chemical proof for the identity of the mixture was ascertained by carrying TLC for the mixture with oxazolone **2** and an authentic sample of 3,5-dimethylpyrazole prepared from reacting hydrazine hydrate with acetylacetone in dioxane. However, the reaction of **4** with acetylacetone in refluxing ethanol for 3 h gave the open chain compound **9** (Scheme 5). The structure of compound **9** was substantiated from its analytical and spectral data. Thus, its IR spectrum revealed the appearance of bands corresponding to NH and C=O groups. Further evidence was gained from its ^{1}H-NMR that shows signals for protons of NH, CH=, CH_2, CH_3, and aromatic protons (cf. Experimental section).The conversion of **4** to compounds **2** and 3,5-dimethylpyrazole could be visualized as shown in Scheme 6. A good evidence for the suggested mechanism was gained from the formation of the open chain adduct **9** on refluxing in ethanol for 3 h.

Scheme 6



Scheme 7



A good explanation for the removal of the 3,5-dimethylpyrazolyl group in case of the acid hydrazide **4** as compared with the acid hydrazide **3a** is the higher steric interaction between 1,3-diphenylpyrazolyl and 3,5-dimethylpyrazolyl groups. This forces the 3,5-dimethylpyrazolyl group to come out of plane of the molecule. So, this prevents the conjugation between the C=O group and 3,5-dimethylpyrazole moiety. This means that the *N*-pyrazolyl group is singly bonded to C=O group, which makes the *N*-carbonyl bond easy to be broken. In addition, the electrophilicity at the carbonyl carbon is high, which facilitates the nucleophilic attack by OH group followed by the removal of 3,5-dimethylpyrazole molecule. This is a good evidence for the existence of the acid hydrazide **4** as the *E*- configurated isomer as mentioned before.

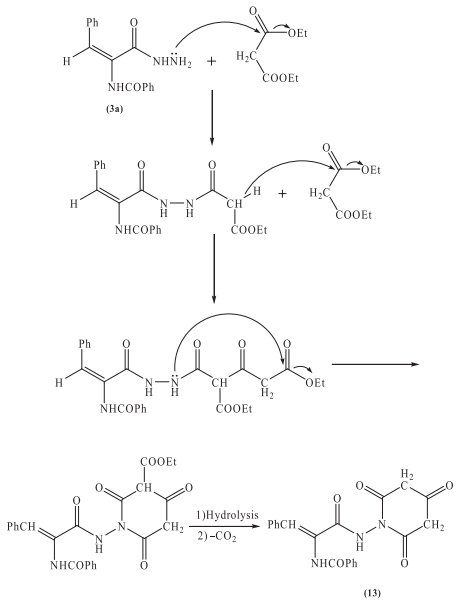
Treatment of an ethanolic solution of the acid hydrazide **3a** with ethyl acetoacetate afforded the open chain adduct butanoate derivative **10** (Scheme 7). The structure of compound **10** was substantiated from its spectral and microanalytical data. The IR spectrum exhibits bands that correspond to NH at 3304, C=O (ester) at 1736, and C=O (amide) at 1695 cm^{-1}. Further evidence was ascertained from its ^{1}H-NMR spectrum. Compound **10** exists in DMSO solution as a mixture of two tautomers involving the NH hydrazono and the neighboring C=O group in the ratio of 1:1 (cf. Experimental section).

On the other hand, ring closure of the acid hydrazide **4** occurred upon treatment of **4** with ethyl acetoacetate. The six- and five-membered closed forms **11** and **12**, respectively, were obtained (Scheme 7). The separation of **11** and **12** was discussed in the Experimental section. Compound 11 exists in deuterated dimethyl sulfoxide (DMSO-d_6) solution as the cyclic lactim form. This is evidenced from the higher δ value at 12.69 ppm, which corresponds to OH proton. Also, solution of **11** in alcohol with aq. $FeCl_3$ gives orange color (cf. Experimental section). The structure of compound 12 was established from its infrared spectrum, which exhibits bands for NH_2 at 3355, 3322, 3300 cm^{-1} and C=O at 1704 cm^{-1}. The ^{1}H-NMR spectrum is in good agreement with the suggested structure as it showed signals for protons of NH_2, =CH, =CH (pyrazolo), and aromatic protons.

Treatment of the acid hydrazide **3a** with diethyl malonate gave an adduct that may have one of the two possible structures: the trioxopiperidine **13** or the pyrazolidindione **14** (cf. Scheme 7). The correct structure of the product was inferred from its spectroscopic data. Its infrared spectrum displays absorption bands corresponding to NH (3247 cm^{-1}) and C=O (1643 cm^{-1}). The lower frequency of absorption for C=O group suggests its existence as structure **13** and not **14** [13–17]. The ^{1}H-NMR spectrum supports structure **13** as it shows two broad singlet signals in the downfield region for protons of 2NH as well as two doublets of doublets in the upfield region corresponding to two CH_2 groups, which is in a good agreement with structure **13**. Further evidence for the structure of compound **13** was gained from its EIMS spectrum. It does not show the molecular ion peak; instead, it shows a peak at $m/z = 363$ corresponding to $(M^+ - CO)$. The conversion of **3a** to compound **13** could be visualized as shown in Scheme 8.

However, similar treatment of the hydrazide **4** with diethyl malonate yielded a compound identical in all

Scheme 8



respects (m.p., mm.p., and TLC) with the imidazolone derivative **12** (Scheme 7).

EXPERIMENTAL

Melting points are uncorrected and were measured on a Gallen Kamp electric melting point apparatus. The infrared spectra were recorded using potassium bromide disks on Fourier transform infrared Thermo Electron Nicolet 7600 (Thermo Fisher Scientific Inc., Waltham, MA, USA) spectrometer at the Central Laboratory of the Faculty of Science, Ain Shams University. The ^{1}H-NMR spectra were run at 300 MHz on a GEMINI 300 BB NMR spectrometer using tetramethylsilane as internal standard in DMSO-d_6 at the Main Defense Chemical Laboratory. The mass spectra were recorded on a Shimadzu GC-MS QP-1000EX mass spectrometer operating at 70 eV at the Microanalytical Center of Cairo University. The reactions and the purity of all the synthesized compounds were monitored by thin layer chromatography using Merck Kieselgel 60 F_{254} aluminum backed plates. Spots visualization was carried out using a UV lamp.

General procedure for synthesis of 4-arylidene-2-phenyloxazol-5-one (1 and 2). A mixture of *N*-benzoylglycine [18] (22.5 g, 0.125 mol), aldehyde (0.125 mol), acetic anhydride (36 mL and 0.375 mol), and anhydrous sodium acetate (11.0 g, 0.125 mol) was refluxed for 2 h. The reaction mixture was cooled to room temperature, and then 100 mL of ethanol was added and kept overnight at 6°C. The yellow precipitate was filtered off and washed with 10 mL of cold ethanol and 15 mL of hot water twice successively to give **1** and **2**.

4-Benzylidene-2-phenyloxazol-5-one (1). Yellow crystals; m.p.: 167–168°C (benzene), yield = 80% (Lit. [7] m.p. = 166–167°C).

4-((1,3-Diphenyl-H-pyrazol-4-yl)methylene)-2-phenyloxazol-5-one (2). Yellow crystals; m.p.: 189–191°C (dioxane), yield = 60%. IR (KBr) (ν_{max}, cm^{-1}) 3056 (aryl-H), 1789 (C=O oxazolone), 1652 (C=N), 1595, 1556 (C=N), 1556 (C=C), 756, 694 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 7.15 (s, 1H, CH=), 7.57–8.25 (m, 15H, ArH), 9.36 (1s, 1H, pyrazolyl). EIMS, *m/z* (%): 392 ($M^+ + 1$, 3.6), 391 (M^+ 22.6), 105 (100), 104 (24), 77 (52.6), 60 (12.4), 52 (13). *Anal.* Calcd for $C_{25}H_{17}N_3O_2$ (391): C, 76.71; H, 4.38; N, 10.74. Found: C, 76.50; H, 4.43; N, 10.86.

General procedure for synthesis of N-(3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl)benzamide (3). Method 1 from methyl 4-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl) benzoate (**5a**).A solution of **5a** (0.001 mol, 0.38 g) and hydrazine hydrate 80% 0.38 mL in methanol (30 mL) was refluxed for 6 h and then cooled. The reaction mixture was left to evaporate at room temperature to give a yellowish white solid, which was fractionally crystallized from benzene to give methyl *p*-aminobenzoate, which was identified by m.p., mixed m.p., and TLC. The insoluble part in benzene was recrystallized from ethanol to give compound **3a**; yield = 45%.

Method 2 from azlactone (**1**).A solution of **1** (0.001 mol, 0.249 g) and hydrazine hydrate 80% 0.2 mL in ethanol (30 mL) was stirred at room temperature or refluxed for 3 h and then cooled. The reaction mixture was left to evaporate at room temperature to give a white solid that was recrystallized from ethanol to give compounds **3b** and **3a**, respectively.

(E)-N-(3-Hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl)benzamide (3a). White crystals; m.p.: 198–200°C (ethanol), yield = 30%. IR (KBr) (ν_{max}, cm^{-1}): 3307, 3185 (NH), 3029, 3059 (aryl-H), 1663, 1631 (C=O), 1579, 1530 (C=C), 752, 696 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 4.28 (br.s, 2H, NH_2 exchangeable), 7.23 (s, 1H, =CH), 7.15–7.80 (m, 10H, ArH), 8.62 (br.s, 1H, $CONHNH_2$ exchangeable), 9.33 (br.s, 1H, NHCOPh exchangeable). EIMS, *m/z* (%): 281 (M^+ 0.1), 252 (22.2), 253 ($M^+ - CO$, 3.7), 224 (14.9), 225 ($M^+ - 2CO$, 2.5), 104 (13.5), 105 (PhCO, 100), 91 (10.3), 77 (Ph, 44.5), 51 (13). *Anal.* Calcd for $C_{16}H_{15}N_3O_2$ (281): C, 68.31; H, 5.37; N, 14.94. Found: C, 67.99; H, 5.42; N, 15.08.

(Z)-N-(3-Hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl)benzamide (3b). White crystals; m.p.: 179–180°C (ethanol), yield = 85%. IR (KBr) (ν_{max}, cm^{-1}): 3423, 3230 (NH), 3030 (=CH), 1654, 1647 (C=O), 1606 (C=C), 758, 697 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 4.38 (br.s, 2H, NH_2 exchangeable), 7.17 (s, 1H, =CH), 7.07–8.08 (m, 10H, ArH), 9.5 (br.s, 1H, –CONHNH2 exchangeable), 9.84 (br.s, 1H, NHCOPh exchangeable). EIMS, *m/z* (%): 281 (M^+ 1), 263 ($M^+ - H_2O$, 6), 250 (11), 105 (100), 104 (64), 77 (60), 76 (27), 60 (91), 51 (22), 50 (12). *Anal.* Calcd for $C_{16}H_{15}N_3O_2$ (281): C, 68.31; H, 5.37; N, 14.94. Found: C, 68.59; H, 5.45; N, 14.67.

General procedure for synthesis of N-(1-(1,3-diphenyl-1H-pyrazol-4-yl)-3-hydrazinyl-3-oxoprop-1-en-2-yl) benzamide (4). To a solution of **2** (0.001 mol, 0.38 g) in ethanol (30 mL), hydrazine hydrate 80% (0.18 mL) was added. The reaction mixture was refluxed for 3 h and cooled to room temperature. A white solid was obtained, which was filtered off, washed with ethanol, and recrystallized from ethanol to give compound **4**; white powder, yield = 63%. When the reaction mixture was stirred at room temperature for 1 h, a white powder was obtained while stirring, which was filtered off, washed with dioxane, and recrystallized from dioxane to give compound **4**; white powder, yield = 84%.

N-(1-(1,3-Diphenyl-1H-pyrazol-4-yl)-3-hydrazinyl-3-oxoprop-1-en-2-yl)benzamide (4). White crystals; m.p.: 204–205°C, (dioxane) yield = 84%, IR (KBr) (ν_{max}, cm^{-1}): 3329, 3240, 3132 (NH), 1660, 1632 (C=O), 1506 (C=C), 756, 695 (monosubstituted benzene).^{1}H-NMR (DMSO-d_6): δ_H (ppm) 4.38 (br.s, 2H, NH_2 exchangeable), 7.16 (s, 1H, =CH), 7.30–8.05 (m,

15H, ArH), 8.50 (s, 1H, pyrazolyl proton), 9.50 (br.s, 1H, –$CONHNH_2$ exchangeable), 9.74 (br.s, 1H, Ph CONH exchangeable). EIMS, *m/z* (%): 424 ($M^+ + 1$, 1.2), 423 (M^+ 1.4), 405 ($M^+ - H_2O$, 4.1), 392 ($M^+ - NHNH_2$, 10.5), 365 (2.0), 260 (2.0), 105 (PhCO, 100), 104 (26), 77 (47), 76 (13), 51 (15). *Anal.* Calcd for$C_{25}H_{21}N_5O_2$ (423): C, 70.91; H, 5.00; N, 16.54. Found: C, 70.64; H, 4.87; N, 16.12.

General procedure for synthesis of methyl 4-(4-arylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)benzoate (5). An equimolar mixture of azlactone (**1** and/or **2**) and methyl *p*-aminobenzoate was heated on an oil bath at 140–150 or 160–170°C, respectively, for 1 h. The jelly product obtained was boiled with methanol. A yellow solid was separated out, filtered off while hot, washed with cold methanol, and recrystallized from the suitable solvent.

Methyl 4-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)benzoate (5a). White crystals; m.p.: 226–227°C (dioxane), yield = 78% (Lit. [19] m.p. 181°C).

Methyl 4-(4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)benzoate (5b). Yellow crystals; m.p.: 220–223°C (dioxane), yield = 65%. IR (KBr) (ν_{max}, cm^{-1}): 3052, 3029 (aryl-H), 2950, 2871 (alkyl-H), 1722, 1638 (C=O), 1599 (C=N), 1530 (C=C), 826 (δ_{2H}), 757, 696 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 3.87 (s, 3H, OCH_3), 7.18 (s, 1H, =CH), 7.39–8.04 (m, 19H, ArH), 9.34 (s, 1H, pyrazolo). EIMS, *m/z* (%): 524 (M^+, 52), 510 (39), 271 (18), 238 (100), 224 (55), 179 (15), 105 (22), 77 (21), 65 (16), 51 (10). *Anal.* Calcd for $C_{33}H_{24}N_4O_3$ (524): C, 75.56; H, 4.61; N, 10.68. Found: C, 75.98; H, 4.93; N, 10.73.

General procedure for synthesis of 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-3-phenyl-1,2,4-triazin-6(5H)-one (6). A solution of **5b** (0.001 mol, 0.52 g) and hydrazine hydrate 80% (0.52 mL) in dioxane (30 mL) was refluxed for 20 h and then cooled; then, the reaction mixture was left to evaporate at room temperature. The precipitated solid was boiled with ethanol, filtered off while hot, and recrystallized from dioxane to give compound **6**. The residual mother liquor after separation of **6** was investigated by TLC to show the presence of methyl *p*-aminobenzoate.

5-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-3-phenyl-1,2,4-triazin-6(5H)-one (6). Yellow crystals; m.p.: 210–212° C,(ethanol–dioxane), yield = 20% IR (KBr) (ν_{max}, cm^{-1}): 3056 (aryl-H), 1617 (C=O), 1596 (C=N), 1535 (C=C), 760, 693 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 7.34 (s, 1H, =CH), 7.37–8.68 (m, 15H, ArH), 8.81 (s, 1H, pyrazolyl proton). EIMS, *m/z* (%): 405 ($M^+ + 2$, 19), 403 (M^+ 15), 356 (22), 320 (23), 260 (28), 223 (23), 187 (25), 145 (25), 111 (31), 105 (25), 98 (30), 95 (34), 84 (44), 7 7(23), 71 (54), 57 (100), 55 (96). *Anal.* Calcd for $C_{25}H_{17}N_5O$ (403): C, 74.43; H, 4.25; N, 17.36. Found: C, 75.01; H, 4.57; N, 17.18.

General procedure for synthesis of N-(3-(2,5-dimethyl-1H-pyrrol-1-ylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (7a) and (E,Z)N-(3-2,5-dimethyl-1H-pyrazol-1-ylamino)-1-(1,3-diphenyl-1H-pyrazol-4-yl)-3-oxoprop-1-en-2-yl)benzamide (7b). To a solution of **3** (0.01 mol, 2.81 g) and/or **4** (0.01 mol, 4.23 g) in ethanol (40 mL), acetonylacetone (0.01 mol, 1.72 mL) was added. The reaction mixture was refluxed for 1 h. A solid product was precipitated while hot, filtered off, washed with ethanol, and recrystallized from the suitable solvent to give the **7a** and/or **7b**, respectively. After cooling, the residual mother liquor gave the same compounds **7a** and/or **7b**, respectively.

N-(3-(2,5-Dimethyl-1H-pyrrol-1-ylamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (7a). White crystals; m.p.: 229–231°C (dimethylformamide (DMF)), yield = 78%, IR (KBr) (ν_{max}, cm^{-1}): 3357, 3185 (NH), 3082, 3035 (aryl-H), 2933, 2901 (alkyl H), 1682, 1640 (C=O), 1578 (C=N), 1528 (C=C), 752, 702 (monosubstituted benzene). EIMS, *m/z* (%): 362 ($M^+ + 3$, 1.8), 361 ($M^+ + 2$, 5.8), 360 ($M^+ + 1$, 3.7), 105 (PhCO, 100), 104 (72.6), 94 (18.5), 93 (11.1), 90 (9.9), 77 (Ph, 47.6), 76 (19.4), 51 (16.2), 50 (11.8). *Anal.* Calcd for $C_{22}H_{21}N_3O_2$ (359): C, 73.52; H, 5.89; N, 11.69. Found: C, 73.96; H, 5.80; N, 11.21.

(E,Z)N-(3-(2,5-Dimethyl-1H-pyrazol-1-ylamino)-1-(1,3-diphenyl-1H-pyrazol-4-yl)-3-oxoprop-1-en-2-yl)benzamide (7b). Pale green crystals; m.p.: 244–246°C (DMF), yield = 80%. IR (KBr) (ν_{max}, cm^{-1}): 3219, 3171, 3114 (NH), 3056 (aryl-H), 2998, 2943, 2886 (alkyl-H), 1662, 1641 (C=O), 1601 (C=N), 1525 (C=C), 756, 696 (monosubstituted benzene).^{1}H-NMR (DMSO-d_6): δ_H (ppm) 1.78, 1.83, 1.87, 1.95 (four singlets, 12H, $4CH_3$), 7.08, 7.12 (two singlets, 2H, CH=), 7.20–7.93 (m, 17H, ArH + 2H of pyrrolo protons), 8.36, 8.43 (two singlets, 2H, pyrazolyl), 9.77, 9.88 (two br.s, 2H, N–NHCO exchangeable), 10.22, 10.33 (two br.s, 2H, 2NHPhCO, exchangeable). EIMS, *m/z* (%): 501 (M^+ 3.5), 406 (4), 405 (12), 391 (10.6), 378 (1.4), 275 (1.4), 243 (1.9), 195 (2.1), 172 (2.1), 119 (19), 106 (13.8), 105 (100), 104 (26), 95 (2.1), 91 (2.6), 81 (2.1), 77 (66), 76 (15.5), 51 (14.8). *Anal.* Calcd for $C_{31}H_{27}N_5O_2$ (501): C, 74.23; H, 5.43; N, 13.96. Found: C, 73.99; H, 5.75; N, 13.73.

General procedure for the reaction of 3 with acetyl acetone to give (E/Z)N-(3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (8). To a solution of **3** (0.01 mol, 2.81 g) in ethanol (30 mL), acetylacetone (0.01 mol, 1.03 mL) was added. The reaction mixture was refluxed for 10 h and then left to cool at room temperature. The solid obtained was filtered off, washed with ethanol, and recrystallized from benzene to give the title compound (**8**).

(E/Z)N-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (8). White crystals; m.p.: 184–185°C (benzene), yield = 53%. IR (KBr) (ν_{max}, cm^{-1}): 3350, 3179 (NH), 3062, 3029 (aryl-H), 1680, 1641 (C=O), 1580 (C=N), 1529 (C=C), 753, 697 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) for (*E*- isomer): δ 1.85, 2.19 (two singlets, 6H, 2CH3), 5.82 (s, 1H, H pyrazolyl), 6.95–7.77 (m, 11H, ArH + =CH), 8.37 (br.s, 1H, NH exchangeable). For (*Z*- isomer): δ 1.66, 2.05 (two singlets, 6H, $2CH_3$), 4.92 (s, 1H, H pyrazolyl), 6.95–7.77 (m, 11H, ArH + = CH), 9.03 (br.s, 1H, NH exchangeable). EIMS, *m/z* (%): 347 ($M^+ + 2$, 73), 346 ($M^+ + 1$, 58), 345 (M^+ 46), 240 (72), 225 (46), 145 (49), 129 (67), 116 (63), 80 (62), 77 (56), 60 (base), 58 (76), 52 (46). *Anal.* Calcd for $C_{21}H_{19}N_3O_2$ (345): C, 73.03; H, 5.54; N, 12.17. Found: C, 73.12; H, 5.65; N, 12.53.

General procedure for the reaction of 4 with acetylacetone to give a mixture of pyrazolidene oxazolone (2) and 3,5-dimethylpyrazole. To a solution of **4** (0.01 mol, 4.23 g) in ethanol (30 mL), acetylacetone (0.01 mol, 1.03 mL) was added. The reaction mixture was refluxed for 6 h. Yellow crystals were formed while hot, which was filtered off, washed with cold ethanol, and recrystallized from ethanol–dioxane to give a product that was found to be a mixture of pyrazolidene oxazolone (**2**) and 3,5-dimethyl pyrazole.

Pyrazolidene oxazolone (2) and 3,5-dimethyl pyrazole. Yellow crystals; m.p.: 177–179°C (ethanol–dioxane), yield = 45%. IR (KBr) (ν_{max}, cm^{-1}): 3275, 3141 (NH), 3057 (aryl-H), 2957,

2886, 2851 (alkyl-H), 1790 (C=O lactone), 1652 (C=N), 1597, 1527 (C=C), 758, 699 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): For 3,5-dimethylpyrazole: δ 1.31 (s, 3H, CH_{3a}), 1.73 (s, 3H, CH_{3b}), 5.61 (br.s, 1H, NH exchangeable), 6.64 (s, 1H, pyrazolo). For pyrazolidene oxazolone: δ 7.15 (s, 1 H, CH=), 7.16–8.26 (m, 15H, ArH), 9.36 (s, 1H, pyrazolo proton). EIMS, *m/z* (%): For pyrazolidene oxazolone: 392 ($M^+ + 1$, 8.3), 391 (M^+ 9.7), 105 (100), 104 (26.9), 77 (64), 76 (14.9), 51 (15.6). For 3,5-dimethyl pyrazole: 96 (M^+, 0.8), 81 ($M^+ - CH_3$), 55 ($M^+ - CH_3CN$, 0.2).

General procedure for the reaction of 4 with acetylacetone for 3 h. To a solution of **4** (0.01 mol, 4.23 g) in ethanol (30 mL), acetylacetone (0.01 mol, 1.02 mL) was added. The reaction mixture was refluxed for 3 h. The excess solvent was removed under reduced pressure. The solid obtained was recrystallized from ethanol to give compound **9**.

(2Z,N'Z)-2-Benzamido-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N'-(4-oxopentan-2-ylidene)acrylohydrazide (9). White crystals; m.p.: 170–172°C (ethanol), yield = 58%. IR (KBr) (υ_{max}, cm^{-1}): 3526, 3233 (NH), 3113, 3061 (aryl-H), 2932, 3113 (alkyl-H), 1675 (C=O), 1593 (C=N), 1541, 1503 (C=C), 760, 699 (δ_{5H}). ^{1}H-NMR (DMSO-d_6): δ_H 1.78, 1.9 (two singlets, 6H, $2CH_3$), 2.8 (dd, 2H, CH_2, J = 18.3, 11.1 Hz), 6.19 (br.s, 1H, NH–N= exchangeable), 6.82 (s, 1H, CH=), 7.33–7.94 (m, 15H, ArH), 8.79 (s, 1H, pyrazolyl hydrogen), 9.88 (br.s, 1H, NHCOPh exchangeable). *Anal.* Calcd for $C_{30}H_{27}N_5O_3$ (505.57): C, 71.27; H, 5.38; N, 13.85. Found: C, 71.54; H, 5.50; N, 13.78.

General procedure for the reaction of 3a with ethyl acetoacetate to give ethyl 3-(2-(2-benzamido-3-phenylacryloyl) hydrazono)butanoate (10). To a solution of **3a** (0.01 mol, 2.81 g) in ethanol (30 mL), ethyl acetoacetate (0.01 mol, 1.26 mL) was added. The reaction mixture was refluxed for 6 h and then cooled at room temperature. A white solid was formed that was filtered off, washed with ethanol, and then recrystallized from ethanol to give the title compound (**10**).

Ethyl 3-(2-(2-benzamido-3-phenylacryloyl)hydrazono) butanoate (10). White crystals; m.p.: 142–144°C (ethanol), yield = 45%. IR (KBr) (ν_{max}, cm^{-1}): 3304 (NH), 3062, 3031 (aryl-H), 2983, 2929 (alkyl-H), 1736 (C=O ester), 1695 (C=O amide), 1631 (C=N), 1577, 1527 (C=C), 747, 699 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 1.19 (two triplets, 6H, $2CH_3CH_2OCO$, J = 6.6, 6.9 Hz), 1.91 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 3.00 (m, 4H, CH_2), 4.11 (two quartets, 4H, $2CH_3CH_2OCO$, J = 6.9 Hz), 7.16–7.82 (m, 22H, ArH + 2=CH), 8.49 (br.s, 1H, OH exchangeable), 9.39 (br.s, 1H, NH exchangeable), 10.40, 10.45 (two br.s, 2H, 2NHCOPh, exchangeable). *Anal.* Calcd for $C_{22}H_{23}N_3O_4$ (393): C, 67.16; H, 5.89;N, 10.68. Found: C, 66.97; H, 5.75; N, 10.43.

General procedure for the reaction of 4 with ethyl acetoacetate to give a mixture of (Z)-5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-3-phenyl-1,2-dihydro-1,2,4-triazin-6(5H)-one (11) major; and 1-amino-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol (12) minor. To a solution of **4** (0.01 mol, 4.23 g) in pyridine (20 mL), ethylacetoacetate (0.01 mol, 1.25 mL) was added. The reaction mixture was refluxed for 12 h, poured onto ice-water, and acidified with conc. HCl, which gave a yellow-orange precipitate that was fractionally crystallized from benzene to give compound **11**. The insoluble part in benzene was recrystallized from methanol to give compound **12**, which was filtered off and recrystallized from benzene–methanol to give the title compounds **11** and **12**.

(Z)-5-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-3-phenyl-1,2-dihydro-1,2,4-triazin-6(5H)-one (11). Orange crystals; m.p.: 225–228°C (benzene–methanol), yield = 40.3%. IR (KBr) (ν_{max}, cm^{-1}): 3272, 3171 (NH), 3056 (aryl-H), 1689 (C=O), 1643 (C=N), 1599, 1538 (C=C), 756, 694 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 7.34 (s, 1H, =CH), 7.36–8.02 (m, 15H, ArH), 8.66 (s, 1H, pyrazolyl), 9.87 (br.s, 1H, NH exchangeable), 12.69 (br.s, 1H, OH, exchangeable). EIMS, *m/z* (%):406 ($M^+ + 1$, 14), 405 (M^+, 32), 394 (43), 388 (46), 351 (51), 337 (46), 306 (49), 288 (43), 257 (60), 236 (53), 219 (61), 145 (52), 115 (51), 105 (100), 77 (58). *Anal.* Calcd for $C_{25}H_{19}N_5O$ (405): C, 74.06; H, 4.72; N, 17.27. Found: C, 73.99; H, 4.89; N, 17.43.

1-Amino-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol (12). Orange crystals; m.p.: 215–218°C (ethanol), yield = 45.7%. IR (KBr) (ν_{max}, cm^{-1}): 3355, 3322, 3300, 3154 (NH_2), 3051 (aryl H), 1704 (C=O), 1632 (C=N), 1597, 1528 (C=C), 736, 692 (monosubstituted benzene). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 5.36 (br.s, 2H, NH_2 exchangeable), 7.07 (s, 1H, =CH), 7.43–8.46 (m, 15H, ArH, J = 7.5, 8.4, 8.1 Hz), 9.31 (s, 1H, pyrazolyl). EIMS, *m/z* (%):405 (M^+ 100), 398 (13), 368 (13), 271 (15), 212 (20), 139 (28), 119 (93), 105 (15), 77 (53). *Anal.* Calcd for $C_{25}H_{19}N_5O$ (405): C, 74.06;H, 4.72; N, 17.27. Found: C, 73.97; H, 5.05; N, 17.42.

General procedure for the reaction of 3a with diethyl malonate to give N-(3-oxo-1-phenyl-3-(2,4,6-trioxopiperidin-1-ylamino)prop-1-en-2-yl)benzamide (13). To a solution of **3a** (0.01 mol, 2.81 g) in ethanol (30 mL), diethylmalonate (0.01 mol, 1.52 mL) was added. The reaction mixture was refluxed for 8 h. White crystals were formed while hot, filtered off, washed with cold ethanol, and recrystallized from DMF to give the title compound (**13**).

(E)-N-(3-oxo-1-Phenyl-3-(2,4,6-trioxopiperidin-1-ylamino) prop-1-en-2-yl)benzamide (13). White crystals; m.p.: 232–234°C (DMF), yield = 30%. IR (KBr) (ν_{max}, cm^{-1}):3247 (NH), 3057, 3031 (aryl-H), 2922 (alkyl-H), 1643 (C=O), 1578, 1527 (C=C), 742, 700 (monosubstituted benzene) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 3.01–3.05 (d-d, 2H, CH_2, J = 11.2 Hz), 3.20–3.23, (d-d, 2H, CH_2, J = 11.4 Hz), 7.24 (1H, C=CH), 7.17–7.79 (m, 10H, ArH), 8.58 (d, 1H, NH–N exchangeable), 10.29 (br.s, 1H, NHCOPh exchangeable). EIMS, *m/z* (%): 363 ($M^+ - CO$, 12), 248 (4), 223 (7), 177 (5), 146 (7), 105 (100), 77 (55). *Anal.* Calcd for $C_{21}H_{17}N_3O_5$ (391): C, 64.45; H, 4.38; N, 10.74. Found: C, 64.79; H, 4.75; N, 10.56.

General procedure for the reaction of 4 with diethyl malonate to give 1-amino-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol (12). To a solution of **4** (0.01 mol, 4.23 g) in ethanol (30 mL), diethylmalonate (0.01 mol, 1.52 mL) was added. The reaction mixture was refluxed for 10 h, poured onto ice-water, and acidified with conc. HCl. The precipitated solid was filtered off and recrystallized from ethanol to give compound 12 as yellow crystals.

REFERENCES AND NOTES

[1] Lesieur, D.; Aichaoui, H.; Lespagnol, C.; Bonnet, J. Eur Pat Appl 1990, 390, 673, 03 OCT; Chem Abstr 1991, 114, 783.

[2] Ando, K.; Asai, N.; Ito, F.; Mano, T.; Nakane, M.; Satake, K.; Shimada, K. Eur Pat Appl 1990, 385, 664, 05 SEPT; Chem Abstr 1991, 114, 783.

[3] Descas, P.; Panconi, E.; Jarry, C. Eur Pat Appl 1990, 392, 929, 17 OCT; Chem Abstr 1991, 114, 783.

[4] Benedlt, D.; Daniel, V. J Med Chem 1994, 37, 710.

[5] Pereira, E. R.; Sancelme, M.; Voldoire, A.; Prudhomme, M. Bio-org Med Chem Lett 1997, 7, 2503.

[6] Viti, G.; Namnicine, R.; Ricci, R.; Pestelline, V.; Abeli, L.; Funo, M. Eur J Med Chem 1994, 29, 401.

[7] Abdel-Aty, A. S. World J Agric Sci 2009, 5, 105.

[8] Khan, K. M.; Mughal, U. R.; Khan, M. T. H.; Ullah, Z.; Perveen, S.; Choudhary, M. I. Bioorg Med Chem 2006, 14, 6027.

[9] Youssef, A. S. A.; El-Mariah, F. A.; Abd-Elmottaleb, F. T.; Hashem, H. E. J Heterocycl Chem 2014, DOI: 10.1002/jhet.2178.

[10] Madkour, H. M. F. Chem Pap 2002, 56, 313.

[11] Badr, M. Z. A.; Mahgoub, S. A. E. Indian J Chem 1989, 28B, 829.

[12] Gucky, T.; Frysova, I.; Slouka, J.; Hajduch, M.; Dzubak, P. Eur J Med Chem 2009, 44, 891.

[13] Patel, P. S.; Shah, R. A.; Trivedi, D. K.; Vyas, P. J. Orient J Chem 2009, 25, 111.

[14] Patel, P. S.; Shah, R. A.; Trivedi, D. K.; Vyas, P. J. Orient J Chem 2010, 26, 159.

[15] Patel, P. S.; Shah, R. A.; Trivedi, D. K.; Vyas, P. J. Der Pharma Chem 2010, 2, 168.

[16] Kachroo, M.; Rao, G. K.; Rajasekaran, S.; Sanjay Pai, P. N.; Hemalatha, Y. R. Der Pharma Chem 2011, 3, 241.

[17] Mamtha, P.; Devi, C. S. J Chem Pharm Res 2012, 4, 2767.

[18] Benson, F. R.; Hartizel, L. W.; Savell, W. L. J Am Chem Soc 1952, 74, 4719.

[19] Patel, A.; Bari, S.; Talele, G.; Patel, J.; Sarangapani, M. Iran J Pharma Res 2006, 4, 249.