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Pyrolysis of 3-hydroxy-2-arylhydrazonoalkanoic acid derivatives

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ABSTRACT

1,2-Diaza-1,3-butadienes have been obtained from readily available 3-hydroxy-2-arylhydrazonopropano ates under various reaction conditions including pyrolysis, dehydration under Mitsunobu conditions or with acetic anhydride or acetic acid. According to their method of synthesis these 1,2-diaza-1,3-butadienes underwent subsequent reactions to give interesting products, and in the presence of proper dienophiles gave the corresponding cycloaddition products. Also, a new approach to pyrazole-3-carboxylic acid derivatives was discovered during an attempt to dehydrate 3-hydroxy-2-arylhydrazonobutanoic esters.

1. Introduction

The chemistry of 1,2-diaza-1,3-butadienes **1** has been widely reported, however, the number of synthetic procedures is limited.[1] These compounds, whether isolated or trapped, undergo a variety of reactions including addition of nucleophiles[2] and cycloaddition with structurally diverse groups of electron-rich and electron deficient olefins, as well as 1,3-dipolar cycloadditions affording a variety of heterocyclic systems.[3] Synthetic procedures for these 1,2-diazadienes include dehydrohalogenation of α-halohydrazones,[4] and oxidation of hydrazones with I_2 or HgO.[5] Pyrolysis of 2,5-dihydro-1,2,3-thiadiazole-1,1-dioxides **2**, 3,6-dihydro-1-oxa-3,4-diazin-2-ones **3** and their sulfur analogues readily takes place affording good access to derivatives of **1**, which have been trapped with *N*-phenylmaleimide to give the corresponding cycloadducts **4**[6] (Scheme 1).

2. Results and discussion

In the present work, we report an easy access to these 1,2-diaza-1,3-butadienes starting with β-ketoesters. Treatment of ethyl acetoacetate, ethyl benzoylacetate or acetoacetanilide with different arenediazonium salts yielded the corresponding hydrazones **5a**–**i**, which, upon reduction with sodium borohydride, gave the corresponding 3-hydroxy-2-arylhydrazonoalkanoic acids **6a**–**i**. Pyrolysis of **6a**–**d** (R=Ph) at 200 °C for 30 min yielded benzaldehyde, ethyl glyoxalate arylhydrazones **7a**–**d**, and ethyl 3-(2-ethoxycarbonyl-1-phenyl-2-phenylhydrazono-ethoxy)-3-phenyl-2-phenylhydrazono propionate **8a**–**d**. Interestingly, the latter were readily isolated chromatographically as two diastereoisomers (racemic and *meso* compound) in the case of **8a**, and identified by their ^{1}H and ^{13}C NMR spectra in the cases of **8b**–**d**. Each of these two isomers showed a singlet for the OCH at δ=5.01–5.07 and 5.18–5.25. On the other hand, pyrolysis of **6e**–**i** (R=CH_3) yielded ethyl glyoxalate arylhydrazones **7a**–**d**, 1,2-bis-(2-ethoxycarbonylindol-3-yl)ethane **9a**,**b**, and 6-(ethoxycarbonyl-arylhydrazono-methyl)-4-methyl-1-aryl-1,4,5,6-tetrahydropyridazine-3-carboxylates **10e**–**i** (Scheme 2) (Table 1).

The structures of the diastereomeric ethers **8**, bis-indolylethenes **9** and pyridazines **10** were established by their NMR spectroscopic data. ^{1}H NMR spectra of each of the diastereomers **8** showed different methine proton and NH signals at δ=5.22 (s, 2H, CH), 11.96 (s, 2H, NH) for one diastereomer, and at δ=5.06 (s, 2H, CH), 12.05 (s, 2H, NH) for the other diastereomer. The methylene protons signals (of the $COOC_2H_5$) appeared as two signals as expected for nonidentical diastereotopic proton signals.

The structures of compounds **9a** and **10e** were readily confirmed by 2D NMR experiments. Fig. 1 shows ^{1}H and ^{13}C signal assignments and the H–C correlations in the HMBC 2-D experiment.

3. Mechanism

Formation of **7a**–**d** and benzaldehyde from each of **6a**–**d** can be explained as a retro Baylis Hillman reaction as shown in Scheme 3. Compounds **7** were also isolated from the pyrolysis of **6e**–**h**; however, the expected acetaldehyde yield was so much diminished most probably due to polymerization under the reaction conditions.

The formation of **9** and **10** can be explained by first dehydration of **6** to intermediate 1,2-diaza-1,3-butadienes **11**, which can then undergo further reaction depending on the R group. When R=Ph,

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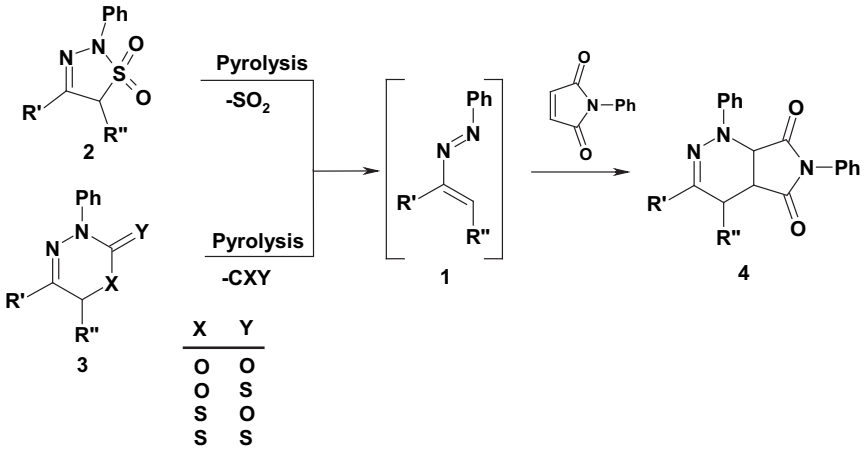
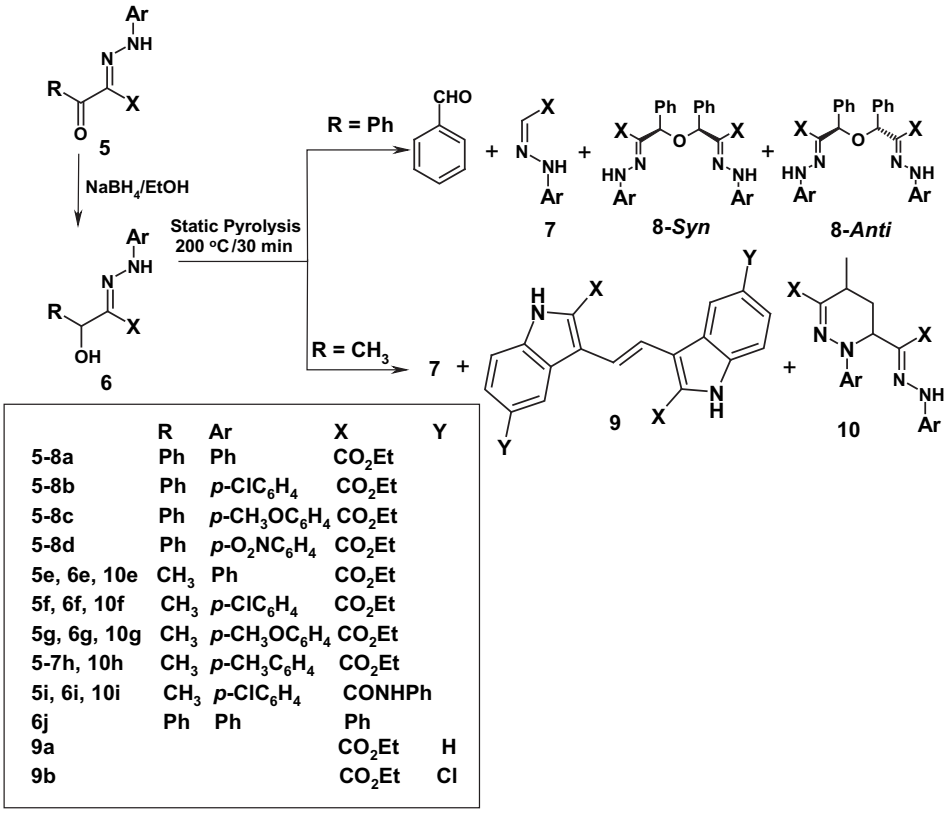


Scheme 1.



Scheme 2.

compound **11** reacts with the starting hydroxyl compound to give the bis-ether **8**. When R=CH_3, compounds **11** undergo a 1,5-H shift to give the corresponding vinylhydrazones **12**, which undergo [4+2] cycloaddition with **11** to give the corresponding cycloadduct pyridazines **10** (Scheme 4).

The formation of the bis-indole derivatives **9** presumably starts by dimerisation of two molecules of **12** to give **13**, which undergo thermal Fischer indolization to give **14**. The latter undergoes two successive 1,5-*H*-shift to give **15**, which finally undergo another thermal Fischer indolization to give the isolated products **9** (Scheme 5).

Attempted acetylation of compound **6** with acetic anhydride led to identifiable isolated products only with **6e**–**i** after refluxing for 5 h, and yielded mainly 1-arylpyrazole-3-carboxylates **16**, in addition to their 4-acetyl derivatives **17** and the pyridazine derivatives **10** as a minor by-product. This method offers an easy access to this class of pyrazole derivative, which are important intermediates in the synthesis of agrochemicals, herbicides, microbicides,[7] plant growth and protectants.[8] Different methods have been reported in the literature for the synthesis of pyrazole-3(5)-alkyl esters:[9] compound **16a** was prepared from the reaction of phenylhydrazine with β-alkoxyvinyl trichloromethyl ketones.[9a] The formation of pyrazole derivatives **16** involves dehydration of **6** to give intermediates **12**, which undergo 6π-electrocyclization followed by 1,2-hydrogen shift to give **18**, this will then oxidize in a similar fashion to the recently reported fused pyrazolo[3,4-*b*]pyrazines and pyrazolo[4,3-*c*]pyridazines.[10] Interestingly, compounds **16f**,**i** have been obtained as the only product in good yield upon heating **6f**,**i** in acetic acid (Scheme 6) (Table 2).

The structure of the acetyl derivative **17** has been established by preparing the isomeric 5-acetyl derivative **20**. Thus, treatment

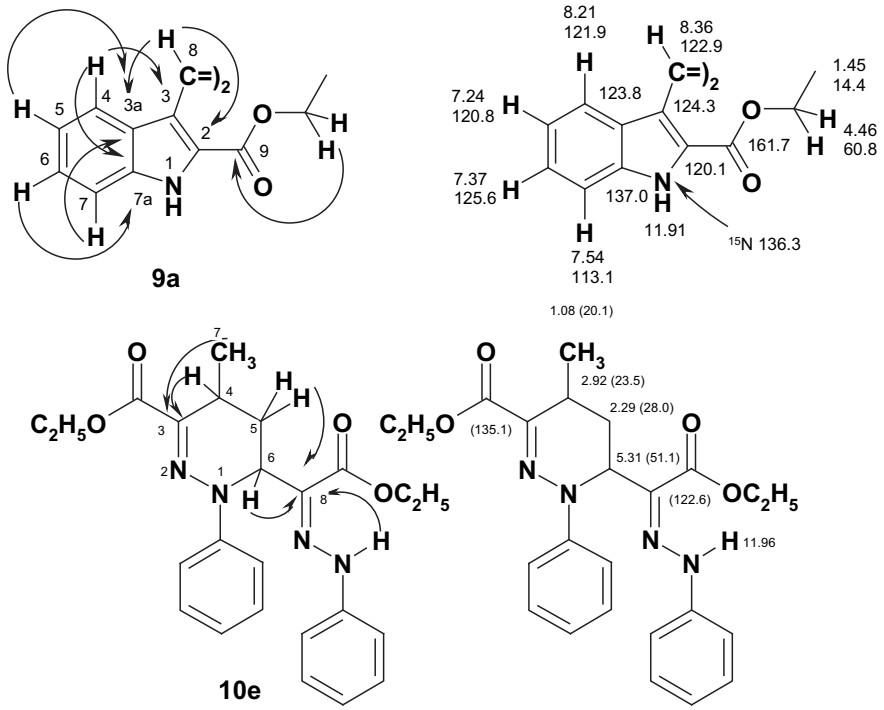
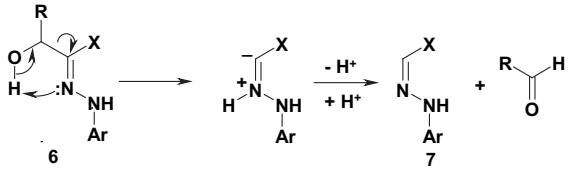


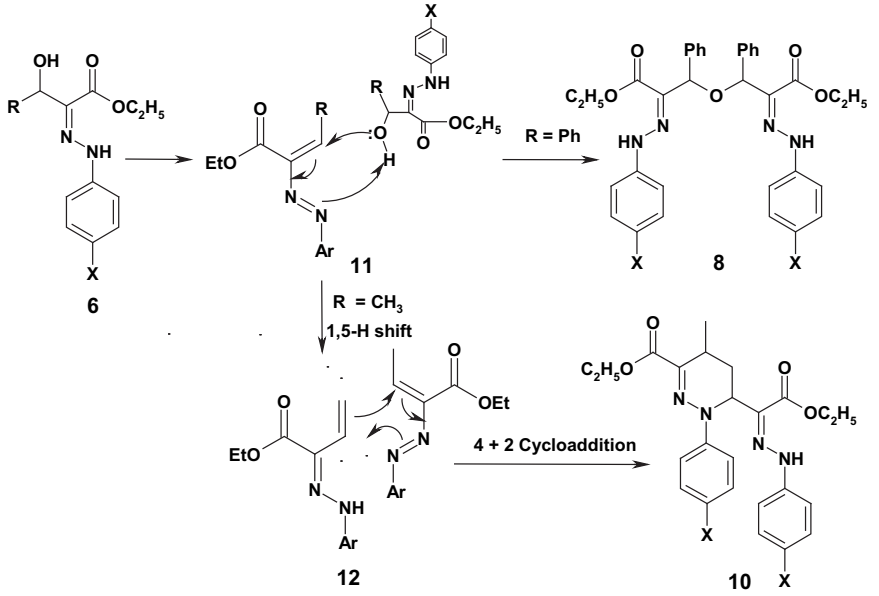
Fig. 1. NMR assignment of compounds **9a** and **10e**, arrows indicates the HMBC H–C correlation.



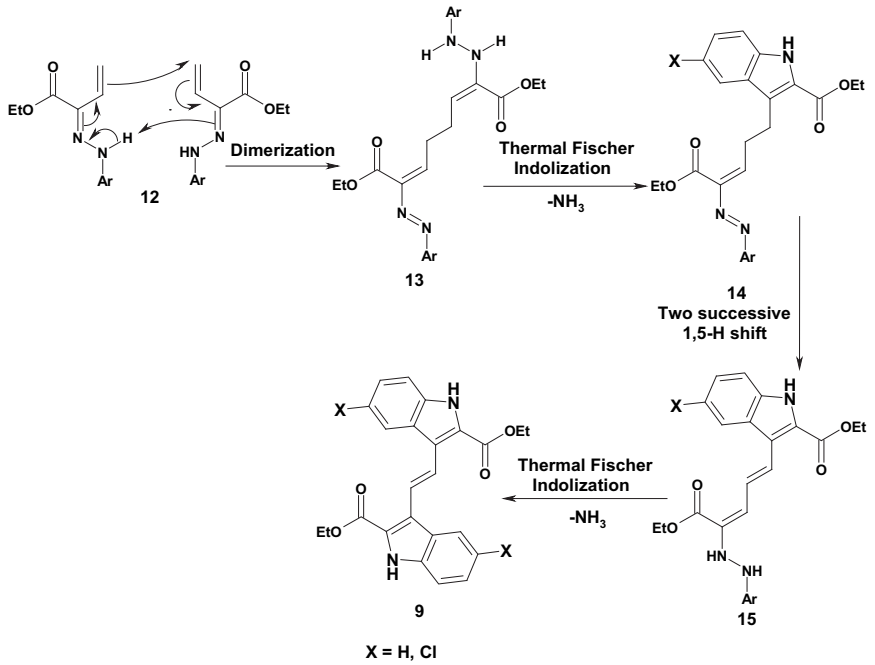
Scheme 3.

of ethyl 2-*p*-chlorophenylhyradono-3-oxopropionate **19** with chloroacetone in ethanol in the presence of K_2CO_3 following reported procedure[11] for the synthesis of 2-acetylpyrazole derivatives gave good yield of 5-acetylpyrazole derivative **20** (Scheme 7).

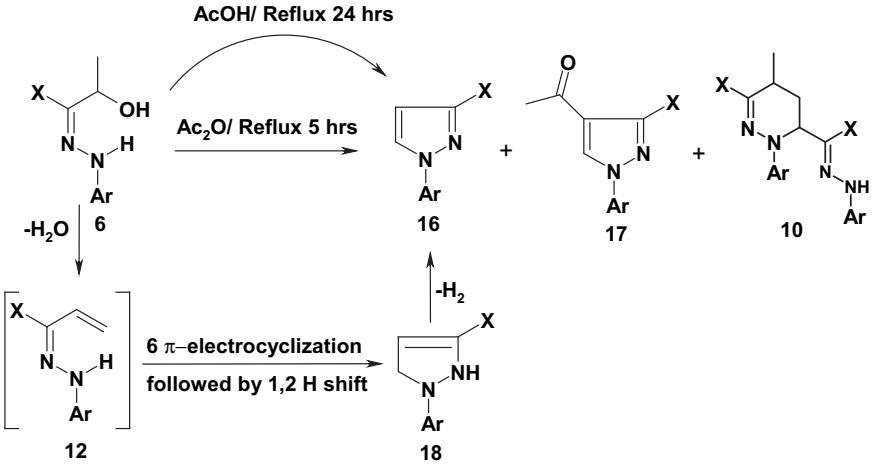
Dehydration of compounds **6** using Mitsunobu conditions (Ph_3P and DEAD) yielded different products depending on the substrate **6**. Thus, treating **6bj** with Ph_3P (1.2 equiv) and DEAD (1.2 equiv) led to the formation of the corresponding diazadienes **11bj** in good yields (these two compounds exist as two stereoisomeric forms most probably around the C=C as indicated by their ^{13}C NMR spectra, which show double the expected number of ^{13}C signals). On the other hand, similar treatment of **6e** gave the corresponding



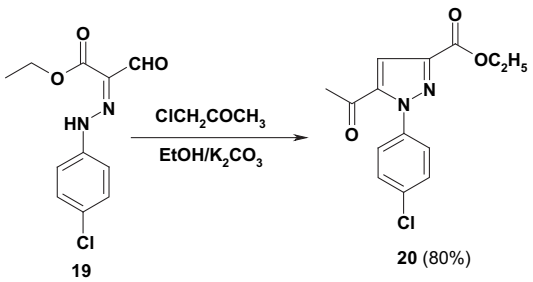
Scheme 4.



Scheme 5.



Scheme 6.



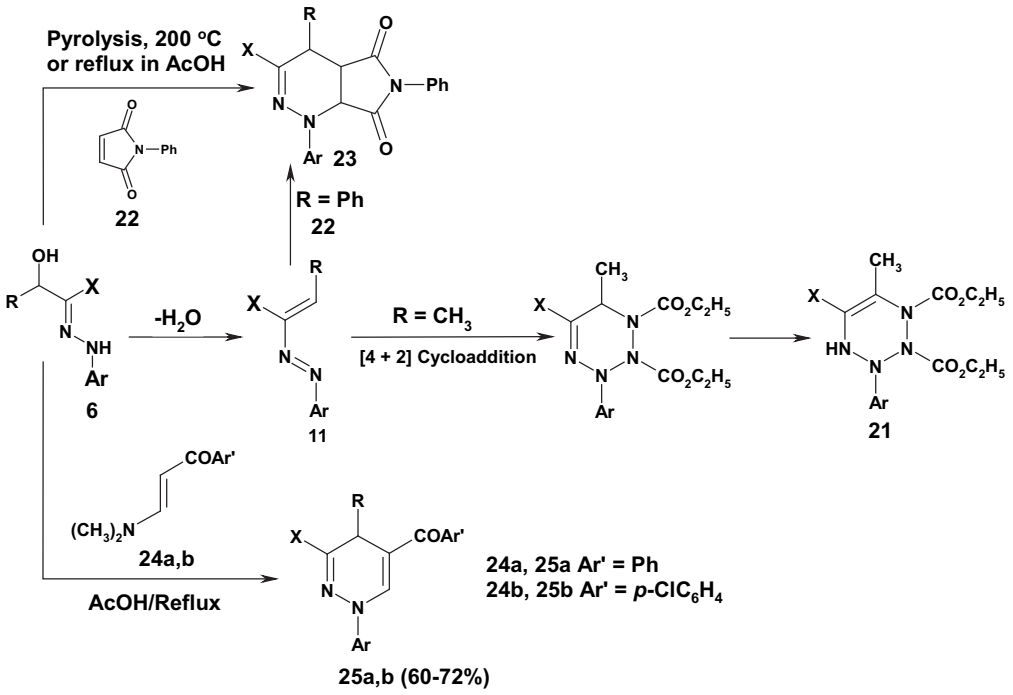
Scheme 7.

cycloadduct tetrazine derivative **21**. Diazadiene **11b** readily undergoes cycloaddition with *N*-phenylmaleimide (**22**) in refluxing xylene to give the corresponding pyridazine derivative **23b**. Pyrolysis of **6b**–**f**,**i**,**j** in the presence of **22** also yielded the corresponding cycloaddition pyridazine derivatives **23b**–**f**,**i**,**j**. Improved yields of **23b**,**e**,**f**,**j** were obtained upon heating **6b**,**e**,**f**,**j** with **22** in acetic acid. Interestingly, compound **6b** reacts with 3-dimethylamino-1-arylpropenones **24a**,**b** in acetic acid to give the corresponding pyridazine derivatives **25a**,**b** (Scheme 8) (Table 3).

The structure of compound **21e** was readily confirmed by 2D-NMR experiments. Fig. 2 shows ^{1}H and ^{13}C important signal assignments and the H–C correlations in the HMBC 2-D experiment.

4. Conclusion

This work presents a new approach to the 1,2-diaza-1,3-butadiene system, which provides versatile intermediates for the synthesis of important heterocyclic compounds. Some of these diazadienes were successfully isolated and used in cycloaddition reactions. Also, a new interesting bis-indole derivative was serendipously obtained although in low yield but certainly will open a new route to the synthesis of this interesting class of compound. An interesting approach to pyrazole-3-carboxylic acid derivatives was discovered during the dehydration of 3-hydroxy-2-arylhydrazonobutanoic esters.



Scheme 8.

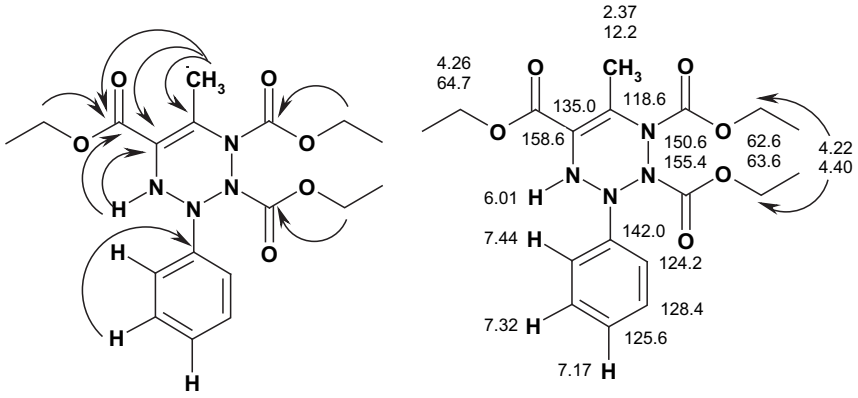


Fig. 2. NMR assignment of compounds **21e**, arrows indicates the HMBC H–C correlation.

5. Experimental

5.1. General

All melting points are uncorrected. IR spectra were recorded in KBr disks on Perkin Elmer System 2000 FT-IR spectrophotometer. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on Bruker DPX 400, 400 MHz, Avance^{II} 600, 600 MHz super-conducting NMR spectrometers. Mass spectra were measured on a GCMSDFS-Thermo and with LCMS using Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode. Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer. The starting compounds **5a**,[12] **5b**,**c**,[13] **5d**,[14] **5e**–**g**,[15] **5h**,[16] **5i**,[17] **6e**,[18] **6j**,[19] **24**,[23] were prepared by the reported methods. The products **7a**,[22] **7b**,[20,21] **7c**,[24] **7d**,[22] were characterized by comparison with reported data.

5.2. Synthesis of compounds 6. General procedure

To a solution of **5a**–**i** (10 mmol) in ethanol (10 mL), sodium borohydride (0.57 g, 15 mmol, dissolved in 0.5 mL of 2 M NaOH, diluted with 2 mL of water) was added and stirred overnight at room temperature. Ethanol was evaporated in vacuo and the residue was extracted with ether, washed several times with water, and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo and remaining product was recrystallised from ethanol.

5.2.1. Ethyl 3-hydroxy-3-phenyl-2-phenylhydrazonopropionate ***6a***. Yellow crystals, yield 2.44 g (82%), mp 140 °C. IR: 3417, 3293, 3063, 3015, 2958, 2920, 2851, 1696, 1563, 1235, 1097, 755. ^{1}H NMR ($CDCl_3$): δ 10.14 (s, 1H, NH), 7.48 (d, 2H, *J* 7.2), 7.37 (t, 2H, *J* 7.2), 7.31 (t, 1H, *J* 7.2), 7.27 (t, 2H, *J* 8.4), 7.10 (dd, 2H, *J* 8.4, 0.6), 6.96 (tt, 1H, *J* 8.4, 0.6), 6.27 (d, 1H, *J* 3.6), 4.31 (q, 2H, *J* 7.2), 3.23 (d, 1H, *J* 3.6), 1.38 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 165.1, 142.9, 138.7, 131.8, 129.2, 128.8, 128.2, 126.1, 122.2, 113.9, 71.8, 61.4, 14.3. HRMS: *m*/*z*=298.1311 (calcd for $C_{17}H_{18}N_2O_3$: 298.1310).

5.2.2. Ethyl 2-p-chlorophenylhydrazono-3-hydroxy-3-phenylpropionate ***6b***. Yellow crystals, yield 3.09 g (93%), mp 149 °C. MS: *m*/*z*=332 (M^+, 100%), 334 (M+2, 32%). IR: 3378, 3291, 1695, 1596, 1566, 1513, 1487, 1370, 1329, 1238, 1170, 1088, 1034, 835, 809. ^{1}H NMR ($CDCl_3$): δ 10.18 (s, 1H, NH), 7.48 (d, 2H, *J* 7.6), 7.40 (t, 2H, *J* 7.6), 7.33 (t, 1H, *J* 7.2), 7.25 (d, 2H, *J* 8.8), 7.06 (d, 2H, *J* 8.8), 6.30 (d, 1H, *J* 4.0),

4.32 (m, 2H), 2.94 (d, 1H, *J* 4.0), 1.39 (t, 3H, *J* 7.0). ^{13}C NMR ($CDCl_3$): δ 164.8, 141.6, 138.6, 132.4, 129.2, 128.9, 128.4, 127.0, 126.1, 115.1, 72.3, 61.5, 14.3. Anal. Calcd for $C_{17}H_{17}N_2O_3Cl$ (332.8): C 61.36, H 5.15, N 8.42. Found C 61.11, H 5.42, N 8.40.

5.2.3. Ethyl 3-hydroxy-2-p-methoxyphenylhydrazono-3-phenylpropionate ***6c***. Yellow crystals, yield 2.96 g (90%), mp 150 °C. IR: 3338, 3282, 1687, 1566, 1517, 1309, 1228, 1209, 1187, 1118, 1093, 1028, 827, 578. ^{1}H NMR ($CDCl_3$): δ 9.99 (s, 1H, NH), 7.49 (d, 2H, *J* 7.6), 7.38 (t, 2H, *J* 7.2), 7.32 (t, 1H, *J* 7.2), 7.06 (d, 2H, *J* 6.8), 6.85 (d, 2H, *J* 7.2), 6.29 (d, 1H, *J* 4.0), 4.33 (m, 2H), 3.79 (s, 3H), 3.01 (d, 1H, *J* 4.0), 1.39 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 165.2, 155.3, 138.8, 136.9, 130.6, 128.8, 128.2, 126.1, 115.2, 114.6, 71.8, 61.2, 55.6, 14.3. Anal. Calcd for $C_{18}H_{20}N_2O_4$ (328.4): C 65.84, H 6.14, N 8.53. Found C 65.41, H 6.23, N 8.51.

5.2.4. Ethyl 3-hydroxy-2-p-nitrophenylhydrazono-3-phenylpropionate ***6d***. Yellow crystals, yield 2.92 g (85%), mp 151 °C. IR: 3375, 3271, 1701, 1602, 1574, 1508, 1484, 1335, 1242, 1191, 1167, 1111, 1090, 1009, 852. ^{1}H NMR ($CDCl_3$): δ 10.79 (s, 1H, NH), 8.21 (d, 2H, *J* 10.4), 7.47 (d, 2H, *J* 7.6), 7.42 (m, 3H), 7.21 (d, 2H, *J* 10.4), 6.35 (d, 1H, *J* 4.0), 4.33 (m, 2H), 3.03 (d, 1H, *J* 4.0), 1.40 (t, 3H, *J* 6.0). ^{13}C NMR ($CDCl_3$): δ 164.2, 148.1, 142.0, 138.2, 135.9, 129.1, 128.8, 126.9, 125.8, 113.3, 73.4, 61.8, 14.3. Anal. Calcd for $C_{17}H_{17}N_3O_5$ (343.3): C 59.47; H 4.99, N 12.24. Found C 59.19, H 5.08, N 12.17.

5.2.5. Ethyl 3-hydroxy-2-phenylhydrazonobutyrate ***6e***. Yellow crystals, yield 4.6 g (50%), mp 83–84 °C (lit.[18] mp 93 °C). LCMS: *m*/*z*=237 (M+1). IR: 3416, 3274, 2980, 1696, 1600, 1566, 1500, 1286, 1234, 1169, 1110, 1069, 752. ^{1}H NMR ($CDCl_3$): δ 10.35 (s, 1H), 7.19 (t, 2H, *J* 8.0), 7.01 (d, 2H, *J* 8.4), 6.87 (t, 1H, *J* 7.4), 5.14 (q, 1H, *J* 7.2), 4.16 (m, 2H), 3.08 (s, 1H), 1.40 (d, 3H, *J* 7.2), 1.27 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 164.6, 143.1, 133.6, 129.2, 121.9, 113.7, 67.3, 61.2, 18.5, 14.2. HRMS=236.1155 ($C_{12}H_{16}N_2O_3$ requires 236.1155).

5.2.6. Ethyl 2-p-chlorophenylhydrazono-3-hydroxybutyrate ***6f***. Colorless crystals, yield 0.7 g (26%), mp 99–100 °C. LCMS: *m*/*z*=271 (M+1). IR: 3398, 3252, 2982, 1703, 1577, 1490, 1282, 1240, 1164, 1120, 1093, 833, 819. ^{1}H NMR ($CDCl_3$): δ 10.49 (s, 1H), 7.18 (d, 2H, *J* 9.2), 6.97 (d, 2H, *J* 9.2), 5.19 (dq, 1H, *J* 7.2, 3.2), 4.23 (m, 2H), 3.52 (d, 1H, *J* 3.2), 1.46 (d, 3H, *J* 7.2), 1.34 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 164.5, 141.7, 134.4, 129.2, 126.7, 114.8, 67.3, 61.4, 18.4, 14.2. HRMS=270.0765 ($C_{12}H_{15}N_2O_3Cl$ requires 270.0765).

5.2.7. Ethyl 3-hydroxy-2-p-methoxyphenylhydrazonobutyrate ***6g***. Red oil, yield 0.9 g (35%). LCMS: *m*/*z*=267 (M+1). IR: 3264, 2981, 2933, 2836, 1678, 1545, 1515, 1228, 1171, 1037, 909, 733. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 7.07 (d, 2H, *J* 9.2), 6.87 (d, 2H, *J* 9.2), 5.26 (q, 2H, *J* 7.2), 4.25 (m, 2H), 3.81 (s, 3H), 1.50 (d, 3H, *J* 7.2), 1.37 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 164.9, 155.3, 137.4, 132.6, 115.1, 114.8, 67.5, 61.2, 55.8, 18.7, 14.5. HRMS=266.1263 ($C_{13}H_{18}N_2O_4$ requires 266.1261).

5.2.8. Ethyl 3-hydroxy-2-p-tolylhydrazonobutyrate ***6h***. Yellow crystals, yield 0.75 g (30%), mp 73–74 °C. LCMS: *m*/*z*=251 (M+1). ^{1}H NMR ($CDCl_3$): δ 10.30 (s, 1H), 7.05 (m, 4H), 5.25 (dq, 1H, *J* 6.8, 3.6), 4.29 (m, 2H), 2.82 (d, 1H, *J* 3.6), 2.28 (s, 3H), 1.49 (d, 3H, *J* 6.8), 1.37 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 164.6, 140.9, 132.9, 131.4, 129.8, 113.7, 67.3, 61.1, 20.7, 18.6, 14.3. HRMS=250.1311 ($C_{13}H_{18}N_2O_3$ requires 250.1311).

5.2.9. 2-p-Chlorophenylhydrazono-3-hydroxybutyranilide ***6i***. Yellow oil, yield 3.10 g (98%). LCMS: *m*/*z*=318 (M+1). IR: 3375, 3289, 3060, 2979, 2927, 1652, 1597, 1532, 1495, 1441, 1315, 1239, 1155, 1085, 915, 823, 753. ^{1}H NMR ($CDCl_3$): δ 12.76 (s, 1H), 9.60 (s, 1H), 7.55 (d, 2H, *J* 8.4), 7.37 (t, 2H, *J* 8.4), 7.23 (d, 2H, *J* 8.8), 7.16 (t, 1H, *J* 7.4), 7.08 (d, 2H, *J* 8.9), 4.83 (m, 1H), 2.39 (d, 1H, *J* 5.2), 1.60 (d, 3H, *J* 6.8). ^{13}C NMR ($CDCl_3$): δ 162.6, 142.1, 137.0, 130.8, 129.3, 129.2, 126.5, 124.9, 120.5, 114.7, 71.6, 21.3. HRMS=317.0924 ($C_{16}H_{16}N_3O_2Cl$ requires 317.0924).

5.3. Action of acetic anhydride on 6e–i. General procedure

A mixture of compounds **6e**–**i** (1 mmol) and acetic anhydride (1 mL) was refluxed for 5 h. The reaction mixture was poured over crushed ice, extracted with DCM, washed with water and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo and the product was separated by column chromatography using pet. ether (60–80)/ethyl acetate as an eluent to give the corresponding compounds **10e**–**h**, **16f**,**g**,**i**, and **17f**,**h** (Table 2).

5.4. Static pyrolysis of 6a–i. General procedure

Compounds **6a**–**i** (0.5 mmol) were introduced in a reaction tube (1.5×12 cm Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.045 Torr) and placed in the pyrolyzer for 30 min at 200 °C. The products obtained **7**–**10** (Table 1) were isolated by column chromatography using pet. ether (60–80)/ethyl acetate as an eluent.

Table 1
Static pyrolysis of compounds **6a**–**i**[a]

Entry	Substrate	Products (yield%[b])
1	**6a**	PhCHO (31), **7a** (38), **8a** (32, 19)
2	**6b**	PhCHO (15), **7b** (15), **8b** (25, 13)
3	**6c**	PhCHO (6), **7c** (6), **8c** (10, 7)
4	**6d**	PhCHO (8), **7d** (7), **8d** (5, 4)
5	**6e**	AcH (3), **7a** (20), **9a** (2), **10e** (4)
6	**6f**	AcH (4), **7b** (20), **9b** (2), **10f** (8)
7	**6g**	AcH (3), **7c** (18), **10g** (8)
8	**6h**	AcH (3), **7h** (20), **10h** (5)
9	**6i**	**10i** (30)

[a] The substrate (0.5 mmol) was pyrolyzed at 200 °C for 30 min.
[b] Conversion yield.

Table 2
Products of heating **6e**–**i** in acetic anhydride and acetic acid

Entry	Substrate	Products (yield%)
1[a]	**6e**	**10e** (4)
2[a]	**6f**	**10f** (**8**), **16f** (24), **17f** (10)
3[b]	**6f**	**16f** (97)
4[a]	**6g**	**10g** (8), **16g** (40)
5[a]	**6h**	**10h** (5), **17h** (25)
6[a]	**6i**	**16i** (12)
7[b]	**6i**	**16i** (30)

[a] Refluxing in acetic anhydride for 5 h.
[b] Refluxing in acetic acid for 24 h.

Table 3
Cycloaddition products of dehydration of compounds **6** under various conditions

Entry	Substrate	Products (yield)
1[a]	**6b**	**11b** (53%)
2[b]	**6b**	**23b** (10%)
3[c]	**6b**	**23b** (44%)
4[d]	**11b**	**23b** (21%)
5[a]	**6e**	**21e** (26%)
6[b]	**6e**	**23e** (15%)
7[c]	**6e**	**23e** (51%)
8[b]	**6f**	**23f** (10%)
9[c]	**6f**	**23f** (48%)
10[b]	**6i**	**23i** (20%)
11[a]	**6j**	**11j** (90%)
12[b]	**6j**	**23j** (20%)
13[c]	**6j**	**23j** (49%)

[a] DEAD, Ph_3P, THF, rt 24 h.
[b] Pyrolysis with NPMA, 200 °C, 30 min.
[c] NPMA in acetic acid, reflux 2 h.
[d] NPMA+**11b**, in xylene, reflux 2 h.

5.4.1. Ethyl glyoxalate phenylhydrazone ***7a***. Yellow crystals, mp 130 °C (lit.[22] mp 130 °C). ^{1}H NMR ($CDCl_3$): δ 12.32 (s, 1H), 7.32 (t, 2H, *J* 7.6), 7.21 (d, 2H, *J* 7.2), 7.03 (t, 1H, *J* 7.2), 6.67 (s, 1H, *J* 8.8), 4.27 (q, 2H, *J* 7.2), 1.37 (t, 3H, *J* 7.2). HRMS=192.0893 ($C_{10}H_{12}N_2O_2$ requires 192.0893).

5.4.2. Ethyl glyoxalate p-chlorophenylhydrazone ***7b***. Colorless crystals, mp 68 °C. MS: *m*/*z*=226 (M^+, 100%), 228 (M+2, 31%). IR: 2981, 1713, 1551, 1493, 1458, 1320, 1215, 1149, 1096, 824. ^{1}H NMR ($CDCl_3$): δ 12.47 (s, 1H), 7.29 (d, 2H, *J* 8.8), 7.14 (d, 2H, *J* 8.8), 6.68 (s, 1H), 4.27 (q, 2H, *J* 7.2), 1.37 (t, 3H, *J* 7.2). HRMS=226.0503 ($C_{10}H_{11}ClN_2O_2$ requires 226.0503).

5.4.3. Ethyl glyoxalate p-methoxyphenylhydrazone ***7c***. Yellow crystals, mp 152 °C. IR: 2986, 2937, 2908, 2837, 1721, 1696, 1550, 1506, 1248, 1145, 1030, 830, 742. ^{1}H NMR ($CDCl_3$): δ 12.30 (s, 1H), 7.13 (d, 2H, *J* 8.8), 6.87 (d, 2H, *J* 9.2), 6.59 (s, 1H), 4.23 (q, 2H, *J* 7.2), 3.79 (s, 3H), 1.34 (t, 3H, *J* 7.2). HRMS=222.0998 ($C_{11}H_{14}N_2O_3$ requires 222.0998).

5.4.4. Ethyl glyoxalate p-nitrophenylhydrazone ***7d***. Yellow crystals, mp 165 °C (lit.[22] mp 130 °C). ^{1}H NMR ($CDCl_3$): δ 12.54 (s, 1H), 8.22 (d, 2H, *J* 7.6), 7.23 (d, 2H, *J* 7.6), 6.81 (s, 1H), 4.23 (q, 2H, *J* 7.2), 1.36 (t, 3H, *J* 4.4). HRMS=237.0744 ($C_{10}H_{11}N_3O_4$ requires 237.0744).

5.4.5. Ethyl glyoxalate p-tolylhydrazone ***7h***. Colorless oil. IR: 2981, 2927, 1683, 1544, 1517, 1229, 1203, 1171, 1137, 1105, 816. ^{1}H NMR ($CDCl_3$): δ 12.30 (s, 1H), 7.25–7.26 (m, 4H), 6.64 (s, 1H), 4.29 (q, 2H, *J* 7.2), 2.33 (s, 3H), 1.36 (t, 3H, *J* 7.2). HRMS=206.1049 ($C_{11}H_{14}N_2O_2$ requires 206.1049).

5.4.6. Ethyl 3-(2-ethoxycarbonyl-1-phenyl-2-phenylhydrazonoethoxy)-3-phenyl-2-phenylhydraz-onopropionate ***8a*** *(isomer* ***1****).* Yellow crystals, yield 0.09 g (32%), mp 188–190 °C. FAB-MS: *m*/*z*=579 (M+1). IR: 3251, 1678, 1598, 1544, 1499, 1447, 1365, 1209, 1165, 1130, 1071, 1026, 697, 628. ^{1}H NMR ($CDCl_3$): δ 12.05 (s, 2H, NH), 7.30 (t, 4H, *J* 8.4), 7.21 (d, 4H, *J* 7.6), 7.12 (d, 4H, *J* 8.4), 7.07 (t, 4H, *J* 7.2), 7.01 (m, 2H), 6.96 (tt, 2H, *J* 7.2, 1.2), 5.06 (s, 2H), 4.19 (m, 4H), 1.36 (t, 6H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 163.4, 143.9, 140.7, 129.9, 129.24, 129.22, 127.7, 126.1, 121.6, 113.4, 60.7, 50.9, 14.1. ^{15}N NMR ($CDCl_3$): δ 352.7, 155.5. Anal. Calcd for $C_{34}H_{34}N_4O_5$ (578.6): C 70.57, H 5.92, N 9.68. Found C 70.30, H 6.02, N 9.49.

5.4.7. Ethyl 3-(2-ethoxycarbonyl-1-phenyl-2-phenylhydrazonoethoxy)-3-phenyl-2-phenylhydraz-onopropionate ***8a*** *(isomer* ***2****).* Yellow crystals, yield 0.06 g (19%), mp 214 °C. FAB-MS: *m*/*z*=579 (M+1). IR: 3258, 1678, 1601, 1550, 1502, 1449, 1368, 1244, 1210, 1164, 1134, 1074, 1024, 911, 746, 695, 630. ^{1}H NMR ($CDCl_3$): δ 11.96 (s, 2H, NH), 7.44 (d, 4H, *J* 7.2), 7.34 (t, 4H, *J* 8.0), 7.20 (m, 8H), 7.09 (t, 2H, *J* 7.2), 6.98 (t, 2H, *J* 7.2), 5.22 (s, 2H), 4.13 (m, 4H), 1.33 (t, 6H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 163.2, 143.7, 141.8, 129.3, 129.2, 129.1, 128.0, 126.2, 121.7, 113.8, 60.6, 50.2, 14.1. Anal. Calcd for $C_{34}H_{34}N_4O_5$ (578.7): C 70.57, H 5.92, N 9.68. Found C 70.28, H 6.00, N 9.51.

5.4.8. Ethyl 2-p-chlorophenylhydrazono-3-(2-p-chlorophenylhydrazono-2-ethoxycarbonyl-1-phenylethoxy)-3-phenylpropionate ***8b*** *(isomer* ***1****).* Yellow crystals, yield 0.08 g (25%), mp 207 °C. FAB-MS: *m*/*z*=647 (M+1). IR: 3237, 3203, 2920, 1676, 1539, 1496, 1206, 1162, 1126, 1093, 824, 707. ^{1}H NMR ($CDCl_3$): δ 11.95 (s, 2H, NH), 7.40 (d, 4H, *J* 7.2), 7.28 (d, 4H, *J* 7.2), 7.21 (t, 4H, *J* 7.6), 7.10 (t, 6H, *J* 7.2), 5.18 (s, 2H), 4.14 (m, 4H), 1.32 (t, 6H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 163.1, 142.3, 141.5, 129.7, 129.3, 129.1, 128.1, 126.5, 126.4, 114.9, 60.8, 50.2, 14.1. Anal. Calcd for $C_{34}H_{32}Cl_2N_4O_5$ (647.6): C 63.06, H 4.98, N 8.65. Found C 63.40, H 5.31, N 8.52.

5.4.9. Ethyl 2-p-chlorophenylhydrazono-3-(2-p-chlorophenylhydrazono-2-ethoxycarbonyl-1-phenylethoxy)-3-phenylpropionate ***8b*** *(isomer* ***2****).* Yellow crystals, yield 0.042 g (13%), mp 204 °C. FAB-MS: *m*/*z*=647 (M+1). IR: 3239, 3202, 2972, 2929, 1677, 1539, 1496, 1207, 1162, 1128, 1095, 952, 824, 708. ^{1}H NMR ($CDCl_3$): δ 12.05 (s, 2H, NH), 7.24 (d, 4H, *J* 8.0), 7.13–7.01 (m, 14H), 5.01 (s, 2H), 4.25 (m, 4H), 1.35 (t, 6H, *J* 7.2). Anal. Calcd for $C_{34}H_{32}Cl_2N_4O_5$ (647.6): C 63.06, H 4.98, N 8.65. Found C 63.35, H 5.23, N 8.62.

5.4.10. Ethyl 2-p-methoxyphenylhydrazono-3-(2-p-methoxyphenylhydrazono-2-ethoxycarbonyl-1-phenylethoxy)-3-phenylpropionate ***8c*** *(isomer* ***1****).* Yellow crystals, yield 0.03 g (10%), mp 197 °C. FAB-MS: *m*/*z*=639 (M+1). IR: 3026, 2980, 2958, 2928, 2832, 1674, 1537, 1513, 1455, 1221, 1204, 1155, 1029. ^{1}H NMR ($CDCl_3$): δ 11.94 (s, 2H, NH), 7.43 (d, 4H, *J* 8.0), 7.19 (t, 4H, *J* 7.6), 7.11 (m, 6H), 6.90 (d, 4H, *J* 8.8), 5.18 (s, 2H), 4.13 (m, 4H), 3.82 (s, 6H), 1.32 (t, 6H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 163.4, 154.9, 142.1, 137.7, 129.2, 127.94, 127.86, 126.1, 114.9, 114.7, 60.4, 55.7, 50.1, 14.1. Anal. Calcd for $C_{36}H_{38}N_4O_7$ (638.7): C 67.70, H 6.00, N 8.77. Found C 67.41, H 6.29, N 8.61.

5.4.11. Ethyl 2-p-methoxyphenylhydrazono-3-(2-p-methoxyphenylhydrazono-2-ethoxycarbonyl-1-phenylethoxy)-3-phenylpropionate ***8c*** *(isomer* ***2****).* Yellow crystals, yield 0.02 g (7%), mp 204 °C. FAB-MS: *m*/*z*=639 (M+1). IR: 3060, 3027, 2982, 2958, 2928, 1674, 1544, 1514, 1228, 1208, 1164, 1136, 1106, 1033, 826, 756, 701. ^{1}H NMR ($CDCl_3$): δ 12.03 (s, 2H, NH), 7.17 (d, 4H, *J* 9.2), 7.11 (m, 10H), 6.87 (d, 4H, *J* 9.2), 5.03 (s, 2H), 4.13 (m, 4H), 3.81 (s, 6H), 1.33 (t, 6H, *J* 7.2). Anal. Calcd for $C_{36}H_{38}N_4O_7$ (638.7): C 67.70, H 6.00, N 8.77. Found C 67.45, H 6.21, N 8.55.

5.4.12. Bis-1,2-(2-ethoxycarbonylindol-3-yl)ethene ***9a***. Yellow crystals, yield 0.004 g (2%), mp 331 °C. MS: *m*/*z*=402 (M^+). IR: 3435, 3322, 2926, 1666, 1456, 1380, 1333, 1255, 740. ^{1}H NMR (DMSO-d_6): δ 11.91 (s, 2H), 8.36 (s, 2H), 8.21 (d, 2H, *J* 8.4), 7.54 (d, 2H, *J* 8.4), 7.37 (t, 2H, *J* 7.6), 7.24 (t, 2H, *J* 7.6), 4.46 (q, 4H, *J* 7.2), 1.45 (t, 6H, *J* 7.2). ^{13}C NMR (DMSO-d_6): δ 161.7, 137.0, 125.3, 124.3, 123.8, 122.9, 121.8, 120.9, 120.1, 113.1, 60.8, 14.4. HSQC ^{13}N NMR (DMSO-d_6): δ 136.3. HRMS=402.1574 ($C_{24}H_{22}N_2O_4$ requires 402.1574).

5.4.13. Bis-1,2-(5-chloro-2-ethoxycarbonylindol-3-yl)ethene ***9b***. Yellow crystals, yield 0.005 g (2%), mp >360 °C. MS: *m*/*z*=470 (M^+, 100%), 472 (M+2, 65%), 474 (M+4, 11%). IR: 3439, 3311, 2923, 1674, 1465, 1252. ^{1}H NMR (DMSO-d_6): δ 12.20 (s, 2H), 8.18 (s, 2H), 8.17 (d, 2H, *J* 2.0), 7.56 (d, 2H, *J* 8.8), 7.40 (dd, 2H, *J* 8.8, 2.0), 4.49 (q, 4H, *J* 7.2), 1.46 (t, 6H, *J* 7.2). HRMS=470.0795 ($C_{24}H_{20}Cl_2N_2O_4$ requires 470.0795).

5.5. Action of acetic anhydride on 6e–i. General procedure

A mixture of compounds **6e–i** (1 mmol) and acetic anhydride (1 mL) was refluxed for 5 h. The reaction mixture was poured over crushed ice extracted with DCM, washed with water, and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo and the product was separated by column chromatography using pet. ether (60–80)/ethyl acetate as an eluent to give the corresponding compounds **10e–h**, **16f**,**g**,**i**, and **17f**,**h** (Table 2).

5.6. Action of acetic acid on 6f,i. General procedure

Compounds **6f**,**i** (1 mmol) were refluxed in acetic acid (1 mL) for 24 h. The solvent was removed in vacuo and the products **16f**,**i** were isolated by column chromatography using pet. ether (60–80)/DCM/ethyl acetate as an eluent.

5.6.1. Ethyl 6-[ethoxycarbonyl-(phenylhydrazono)-methyl]-4-methyl-1-phenyl-1,4,5,6-tetrahydro-pyridazine-3-carboxylate ***10e***. Colorless oil. LCMS=437 (M+1). IR: 2923, 2855, 1693, 1596, 1554, 1498, 1275, 1230, 1169, 1077, 751. ^{1}H NMR ($CDCl_3$): δ 11.96 (s, 1H,

NH), 7.38 (d, 2H, *J* 7.8), 7.29 (t, 2H, *J* 7.2), 7.20 (t, 2H, *J* 8.4), 6.97 (d, 2H, *J* 9.0), 6.96 (t, 1H, *J* 7.2), 6.92 (t, 1H, *J* 7.2), 5.33 (t, 1H, *J* 3.6), 4.45 (q, 1H, *J* 7.2), 4.36 (m, 3H), 2.93 (m, 1H), 2.30 (t, 1H, *J* 7.2), 2.29 (q, 1H, *J* 7.2), 1.45 (t, 3H, *J* 7.2), 1.41 (t, 3H, *J* 7.2), 1.08 (d, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 165.2, 162.4, 145.9, 142.8, 135.1, 129.2, 128.9, 122.6, 122.5, 121.8, 115.3, 114.0, 61.1, 60.6, 51.5, 29.0, 23.5, 20.1, 14.5, 14.3. HRMS=436.2105 ($C_{24}H_{28}N_4O_4$ requires 436.2105).

5.6.2. Ethyl 6-[ethoxycarbonyl-(p-chlorohydrazono)-methyl]-4-methyl-1-p-chlorophenyl-1,4,5,6-tetrahydro-pyridazine-3-carboxylate ***10f***. Colorless oil. LCMS=506 (M+1). IR: 2978, 2930, 1699, 1557, 1495, 1266, 1234, 1167, 1139, 1092, 827. ^{1}H NMR ($CDCl_3$): δ 11.95 (s, 1H), 7.16–7.19 (m, 4H), 7.17 (d, 2H, *J* 9.2), 6.88 (d, 2H, *J* 9.2), 5.27 (m, 1H), 4.49–4.33 (m, 4H), 2.94 (m, 1H), 2.39–2.29 (m, 2H), 1.46 (d, 3H, *J* 7.3), 1.41 (d, 3H, *J* 7.2), 1.06 (d, 3H, *J* 10.4). HRMS=504.1325 ($C_{24}H_{26}Cl_2N_4O_4$ requires 504.1325).

5.6.3. Ethyl 6-[ethoxycarbonyl-(p-methoxyphenylhydrazono)-methyl]-1-p-methoxyphenyl-4-methyl-1,4,5,6-tetrahydropyridazine-3-carboxylate ***10g***. Colorless oil. LCMS=497 (M+1). IR: 2921, 2851, 1691, 1512, 1244, 1169, 909, 733. ^{1}H NMR ($CDCl_3$): δ 11.99 (s, 1H, NH), 7.29 (d, 2H, *J* 6.8), 6.96 (d, 2H, *J* 6.8), 6.81 (m, 4H), 5.24 (t, 1H, *J* 3.6), 4.35 (m, 4H), 3.77 (m, 6H), 2.92 (t, 1H, *J* 7.2), 2.27 (m, 2H), 1.42 (m, 6H), 1.07 (d, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 165.3, 162.5, 155.5, 155.0, 140.2, 136.8, 134.1, 121.5, 117.3, 115.1, 114.6, 114.2, 60.8, 60.4, 55.6, 55.5, 52.2, 29.3, 23.5, 20.1, 14.5, 14.3. HRMS=496.2315 ($C_{26}H_{32}N_4O_6$ requires 496.2316).

5.6.4. Ethyl 6-[ethoxycarbonyl-(p-tolylhydrazono)-methyl]-4-methyl-1-p-tolyl-1,4,5,6-tetrahydro-pyridazine-3-carboxylate ***10h***. Colorless oil. LCMS=465 (M+1). IR: 2925, 2854, 1680, 1542, 1521, 1463, 1203, 1132, 1107, 909, 817, 735. ^{1}H NMR ($CDCl_3$): δ 11.98 (s, 1H, NH), 7.26 (d, 2H, *J* 9.2), 7.05 (m, 4H), 6.91 (d, 2H, *J* 9.2), 5.29 (m, 1H), 4.38 (m, 4H), 2.92 (m, 1H), 2.28 (s, 3H), 2.26 (s, 3H), 2.27 (m, 2H), 1.41 (m, 6H), 1.06 (d, 3H, *J* 7.6). ^{13}C NMR ($CDCl_3$): δ 163.9 (2CO), 140.7, 139.2, 132.2, 129.9, 128.4, 117.7, 116.2, 113.9, 112.5, 112.4, 60.3 ($2CH_2$), 58.9, 58.8, 29.7, 28.3, 20.7, 19.2, 14.2, 12.7. HRMS=464.2418 ($C_{26}H_{32}N_4O_4$ requires 464. 2418).

5.6.5. 1-p-Chlorophenyl-6-[(p-chlorophenylhydrazono)-phenylcarbamoylmethyl]-4-methyl-1,4,5,6-tetrahydro-pyridazine-3-carboxanilide ***10i***. Colorless oil. LCMS=599 (M+1). IR: 3380, 3296, 3060, 2967, 2931, 2871, 1667, 1596, 1522, 1495, 1442, 1310, 1251, 1216, 1170, 1091, 908, 825, 750, 734. ^{1}H NMR ($CDCl_3$): δ 8.87 (s, 1H, NH), 8.69 (s, 1H, NH), 8.64 (s, 1H, NH), 7.63 (t, 4H, *J* 8.8), 7.41–7.31 (m, 5H), 7.21–7.26 (m, 4H), 7.18–7.11 (m, 3H), 6.90 (d, 2H, *J* 8.8), 5.62 (dd, 1H, H-6, *J* 12.2, 4.6), 3.36 (m, 1H, H-4), 2.36 (dt, 1H, H-5, *J* 13.4, 5.0), 2.07 (ddd, 1H, H-5, *J* 13.4, 4.4, 1.2), 1.38 (d, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 161.2, 160.9, 144.9, 143.4, 141.0, 137.5, 137.4, 133.5, 130.3, 129.5, 129.4, 129.2, 129.1, 127.8, 124.5, 124.3, 119.9, 119.63, 119.56, 115.0, 46.2, 25.0, 23.2, 20.2. HRMS=598.1645 ($C_{32}H_{28}Cl_2N_6O_2$ requires 598.1645).

5.6.6. Ethyl 1-p-chlorophenylpyrazole-3-carboxylate ***16f***. Colorless oil. MS: *m*/*z*=250 (M^+, 100%), 252 (M+2, 33%). IR: 2926, 2854, 1721, 1493, 1462, 1380, 1264, 1178, 909, 735. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, 1H, *J* 2.4), 7.73 (d, 2H, *J* 8.8), 7.47 (d, 2H, *J* 8.8), 7.02 (d, 1H, *J* 2.4), 4.47 (q, 2H, *J* 7.2), 1.45 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 162.1, 145.5, 138.2, 133.3, 129.6, 128.3, 121.3, 110.7, 61.3, 14.4. HRMS250.0506 ($C_{12}H_{11}ClN_2O_2$ requires 250.0506).

5.6.7. Ethyl 1-p-methoxyphenylpyrazole-3-carboxylate ***16g***. Color less oil. MS: *m*/*z*=246 (M^+). IR: 2922, 2852, 1722, 1519, 1461, 1378, 1255, 1176, 909, 734. ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 1H, *J* 2.8), 7.64 (d, 2H, *J* 9.2), 6.97 (d, 1H, *J* 2.4), 6.97 (d, 2H, *J* 9.2), 4.44 (q, 2H, *J* 7.2), 3.85 (s, 3H), 1.42 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 162.4, 159.1, 144.8, 140.5, 128.4, 121.8, 114.5, 110.1, 61.1, 55.6, 14.4. HRMS=246.0998 ($C_{13}H_{14}N_2O_3$ requires 246.0998).

5.6.8. 1-p-Chlorophenylpyrazole-3-carboxylanilide ***16i***. Yellow oil. MS: *m*/*z*=297 (M^+, 100%), 299 (M+2, 32%). IR: 2922, 2852, 1684, 1600, 1542, 1499, 1439, 1380, 1312, 1256, 825, 771, 749, 688, 602, 503. ^{1}H NMR ($CDCl_3$): δ 8.77 (s, 1H), 7.95 (d, 1H, *J* 2.8), 7.71 (t, 4H, *J* 8.8), 7.49 (d, 2H, *J* 8.8), 7.39 (t, 2H, *J* 8.0), 7.15 (t, 1H, *J* 7.2), 7.11 (d, 1H, *J* 2.4). ^{13}C NMR ($CDCl_3$): δ 159.3, 148.5, 138.1, 137.7, 133.2, 129.8, 129.1, 129.0, 124.3, 120.9, 119.8, 109.1. HRMS=297.0663 ($C_{16}H_{12}ClN_3O$ requires 297.0663).

5.6.9. Ethyl 4-acetyl-1-p-chlorophenylpyrazole-3-carboxylate ***17f***. Colorless oil. MS: *m*/*z*=292 (M^+). IR: 2922, 1734, 1709, 1591, 1305, 1214, 1196, 1136, 771. ^{1}H NMR ($CDCl_3$): δ 7.53 (d, 2H, *J* 9.2), 7.05 (d, 2H, *J* 9.2), 6.61 (s, 1H), 4.29 (q, 2H, *J* 7.2), 2.61 (s, 3H), 1.32 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 173.3, 162.9, 136.1, 133.4, 131.7, 129.9, 128.8, 61.6, 21.8, 14.1(two sp^2 C overlap). ^{15}N NMR ($CDCl_3$): δ 362.4, 191.8. HRMS=292.0609 ($C_{14}H_{13}ClN_2O_3$ requires 292.0609).

5.6.10. Ethyl 4-acetyl-1-p-tolylpyrazole-3-carboxylate ***17h***. Color less crystals, mp 83–84 °C. MS: *m*/*z*=272 (M^+). IR: 2983, 2932, 1740, 1709, 1586, 1512, 1371, 1308, 1193, 1135, 1044, 614. ^{1}H NMR ($CDCl_3$): δ 7.30 (d, 2H, *J* 8.0), 6.94 (d, 2H, *J* 8.0), 6.60 (s, 1H), 4.25 (q, 2H, *J* 7.2), 2.56 (s, 3H), 2.38 (s, 3H), 1.29 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 173.5, 163.2, 140.1, 132.3 (2C), 131.5 (CH-5, C), 131.2 (ArCH), 128.1 (ArCH), 61.5, 21.8, 21.3, 14.1. ^{15}N NMR ($CDCl_3$): δ 364.1, 194.4. HRMS=272.1155 ($C_{15}H_{16}N_2O_3$ requires 272.1155).

5.7. Static pyrolysis of 6b–f,i,j with *N*-phenylmaleimide. General procedure

A mixture of compounds **6b–f,i,j** (0.5 mmol) and *N*-phenylmaleimide (1.5 mmol) was introduced into a reaction tube (1.5×12 cm Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.045 Torr) and placed in the pyrolyzer for 30 min at 200 °C. The products **23b–f,i,j** were isolated by column chromatography using pet. ether (60–80)/DCM/ethyl acetate as an eluent.

5.8. Cycloaddition of 6b–f,i with *N*-phenylmaleimide in acetic acid. General procedure

A mixture of compounds **6b–f**, **6i** (1 mmol) and *N*-phenylmaleimide (1.5 mmol) in acetic acid (1 mL) was heated under reflux for 2 h. The solvent was removed in vacuo and the products **23b–f,i** were isolated by column chromatography using pet. ether (60–80)/DCM/ethyl acetate as an eluent.

5.9. Procedure for synthesis of compound 23b from 11b

A mixture of compound **11b** (1 mmol) and *N*-phenylmaleimide (1.5 mmol) in xylene (1 mL) was refluxed for 2 h. The solvent was removed in vacuo and the product **23b** was isolated by column chromatography using pet. ether (60–80)/DCM/ethyl acetate as an eluent.

5.9.1. Ethyl 1-p-chlorophenyl-5,7-dioxo-4,6-diphenyl-4,4a,5,6,7,7a,-hexahydro-1H-pyrrolo[3,4-c]pyridazine-3-carboxylate ***23b***. Colorless crystals, yield 0.03 g (10%). Mp 265–266 °C. LCMS=488 (M+1). IR: 2926, 2853, 1727, 1493, 1378, 908, 734. ^{1}H NMR ($CDCl_3$): δ 7.68 (d, 2H, *J* 9.2), 7.37 (d, 2H, *J* 9.2), 7.29 (m, 6H), 7.09 (m, 2H), 6.39 (dd, 2H, *J* 8.0, 2.0), 5.02 (d, 1H, *J* 8.4), 4.79 (d, 1H, *J* 7.2), 4.26 (m, 2H), 3.53 (dd, 1H, *J* 8.4, 7.2), 1.31 (t, 3H, *J* 7.2). ^{13}C/DEPT ^{13}C NMR ($CDCl_3$): δ 172.4 (C), 172.2 (C), 163.2 (C), 145.5 (C), 133.9 (C),

133.87 (C), 130.1 (C), 129.4 (CH), 129.3 (C), 129.1 (CH), 128.9 (CH), 128.7 (CH), 126.0 (CH), 118.0 (CH), 61.7 (CH_2), 55.8 (CH), 39.4 (CH), 36.3 (CH), 14.2 (CH_3) (two ArCH's overlap). HRMS=487.1293 ($C_{27}H_{22}ClN_3O_4$ requires 487.1293).

5.9.2. Ethyl 4-methyl-5,7-dioxo-1,6-diphenyl-4,4a,5,6,7,7a,-hexahydro-1H-pyrrolo[3,4-c]pyridazine-3-carboxylate ***23e***. Colorless crystals, yield 0.03 g (15%), mp 154–155 °C. LCMS=392 (M+1). IR: 2966, 2929, 2857, 1723, 1592, 1496, 1376, 1258, 1200, 1146, 752, 691. ^{1}H NMR ($CDCl_3$): δ 7.65 (dd, 2H, *J* 8.8, 1.2), 7.51 (t, 2H, *J* 7.6), 7.44 (d, 1H, *J* 7.6), 7.37 (m, 4H), 7.14 (dt, 1H, *J* 7.6), 5.02 (d, 1H, *J* 8.4), 4.36 (m, 2H), 3.74 (quint, 1H, *J* 7.2), 3.30 (dd, 1H, *J* 8.4, 6.4), 1.42 (t, 3H, *J* 7.2), 1.15 (d, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 173.7, 172.7, 163.5, 146.8, 135.0, 130.8, 129.4, 129.13, 129.07, 126.0, 123.8, 116.6, 61.6, 55.3, 38.2, 25.7, 14.4, 13.1. HRMS=391.1526 ($C_{22}H_{21}N_3O_4$ requires 391.1526).

5.9.3. Ethyl 1-p-chlorophenyl-4-methyl-5,7-dioxo-6-phenyl-4,4a,5,6,7,7a,-hexahydro-1H-pyrrolo[3,4-c]pyridazine-3-carboxylate ***23f***. Colorless oil, yield 0.07 g (34%). MS: *m*/*z*=425 (M^+, 100%), 427 (M+2, 31%). IR: 2979, 2926, 1723, 1495, 1377, 1258, 1200, 1147, 911, 745. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H, *J* 9.2), 7.53 (t, 2H, *J* 8.0), 7.47 (t, 2H, *J* 7.2), 7.35 (m, 4H), 4.98 (d, 1H, *J* 8.4), 4.39 (q, 1H, *J* 7.2), 3.75 (quint, 1H, *J* 7.2), 3.32 (dd, 1H, *J* 8.4, 6.4), 1.42 (t, 3H, *J* 7.2), 1.15 (d, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 173.5, 172.6, 163.3, 145.5, 135.7, 130.7, 129.4, 129.2, 129.1, 126.0, 117.9, 61.7, 55.3, 38.2, 25.7, 14.4, 13.1 (one sp^2 C overlaps). HRMS=425.1136 ($C_{22}H_{20}N_3O_4Cl$ requires 425.1136).

5.9.4. 1-p-Chlorophenyl-4-methyl-5,7-dioxo-6-phenyl-4,4a,5,6,7,7a,-hexahydro-1H-pyrrolo[3,4-c]pyridazine-3-carboxylanilide ***23i***. Colorless oil, yield 0.08 g (34%). LCMS=473 (M+1). IR: 2921, 2852, 1724, 1671, 1597, 1525, 1495, 1444, 1378, 1196, 908, 734. ^{1}H NMR ($CDCl_3$): δ 8.71 (s, 1H), 7.64 (d, 2H, *J* 7.6), 7.53 (m, 4H), 7.45 (m, 1H), 7.39 (m, 6H), 7.15 (t, 1H, *J* 7.6), 4.97 (d, 1H, *J* 8.0), 3.99 (quint, 1H, *J* 7.2), 3.33 (dd, 1H, *J* 8.0, 6.8), 1.18 (d, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 173.3, 172.9, 160.2, 145.5, 139.4, 137.4, 130.7, 129.44, 129.4, 129.3, 129.2 (2 overlapped CH), 126.0, 124.5, 119.7, 118.3, 55.9, 38.3, 24.0, 13.1. HRMS=472.1297 ($C_{26}H_{21}ClN_4O_3$ requires 472.1297).

5.9.5. 1,3,4,6-Tetraphenyl-1,4,4a,7a-tetrahydropyrrol[3,4-c]pyridazine-5,7-dione ***23j***. Colorless crystals, yield 0.05 g (20%), mp 216–217 °C. MS: *m*/*z*=457 (M^+). IR: 3019, 2921, 2852, 1714, 1496, 1386, 1212, 756. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, 4H, *J* 8.4), 7.40–7.28 (m, 13H), 7.10 (t, 1H, *J* 8.0), 6.47 (m, 2H), 5.03 (dd, 1H, *J* 8.8, 1.2), 4.73 (dd, 1H, *J* 6.8, 0.8), 3.60 (dd, 1H, *J* 7.6, 6.8). ^{13}C NMR ($CDCl_3$): δ 173.4, 173.2, 148.3, 140.6, 136.6, 134.2, 130.5, 129.5, 129.3, 129.1, 128.9, 128.8, 128.7, 128.6, 128.0, 126.2, 125.4, 122.4, 115.7, 55.6, 40.5, 38.2. HRMS=457.1785 ($C_{30}H_{23}N_3O_2$ requires 457.1785).

5.10. Reaction of 6b, 6e, and 6j under Mitsunobu conditions. General procedure

A mixture of compounds **6b**, **6e**, and **6j** (1 mmol), triphenylphosphine (1.2 mmol), and diethylazodicarboxylate (1.2 mmol) in THF (2 mL) was stirred for 24 h at room temperature. The reaction mixture was purified using column chromatography to give the corresponding compounds **11** and **21**.

5.10.1. Ethyl 2-p-chlorophenylazo-3-phenylacrylate ***11b***. Yellow oil, yield 0.17 g (53%). MS: *m*/*z*=314 (M^+, 100%), 316 (M+2, 29%). IR: 3062, 2963, 2926, 2856, 1730, 1622, 1577, 1481, 1452, 1391, 1373, 1252, 1203, 1124, 1093, 1016, 836, 753, 691. ^{1}H NMR ($CDCl_3$): δ 7.75 (d, 2H, *J* 8.4), 7.68 (s, 1H), 7.57 (m, 2H), 7.43 (m, 5H), 4.41 (q, 2H, *J* 7.2), 1.34 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 166.7, 164.9, 151.2, 150.7, 149.3, 144.7, 140.7, 137.7, 137.1, 135.9, 133.7, 133.1, 132.6, 130.3, 130.1, 129.54, 129.47, 129.3, 129.0, 128.6, 124.4, 124.1, 61.1, 61.4, 14.3, 14.1. HRMS=314.0816 ($C_{17}H_{15}ClN_2O_2$ requires 314.0816).

5.10.2. Triethyl 6-methyl-3-phenyl-1,2,3,4-tetrahydro-1,2,3,4-tetrazine-1,2,5-tricarboxylate ***21e***. Colorless crystals, yield 0.1 g (26%). MS: *m*/*z*=392 (M^+). IR: 3316, 2982, 2933, 2361, 2335, 1727, 1531, 1449, 1397, 1378, 1340, 1311, 1233, 1093, 1068, 793, 753. ^{1}H NMR ($CDCl_3$): δ 7.44 (d, 2H, *J* 7.6), 7.32 (t, 2H, *J* 8.4), 7.17 (tt, 1H, *J* 7.6, 0.8), 6.01 (s, 1H), 4.40 (q, 2H, *J* 7.2), 4.26 (q, 2H, *J* 7.2), 4.22 (q, 2H, *J* 7.2), 2.37 (s, 3H), 1.39 (t, 3H, *J* 7.2), 1.25 (q, 6H, *J* 7.2). ^{13}C ($CDCl_3$): δ 158.6, 155.4, 150.6, 142.0, 135.0, 128.4 (CH), 125.6 (CH), 124.2 (CH), 118.6, 64.7, 63.6, 62.6, 14.6, 14.5, 14.47, 12.2. HRMS=392.1659 ($C_{18}H_{24}N_4O_6$ requires 392.1659).

5.10.3. 1,3,4-Triphenyl-1,2-diaza-1,3-butadiene ***11j***. Red oil, yield 0.26 g (90%). MS: *m*/*z*=284 (M^+). IR: 3059, 3030, 2924, 2853, 1598, 1496, 1451, 1070, 1022, 920, 793. ^{1}H NMR ($CDCl_3$): δ 7.75–7.65 (m, 4H), 7.34 (m, 8H), 7.11 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 155.9, 153.5, 153.2, 152.9, 141.7, 137.1, 135.8, 135.4, 135.1, 134.6, 132.2, 130.9, 130.4, 130.3, 130.1, 129.5, 129.1, 128.9, 128.8, 128.56, 128.51, 128.3, 128.24, 128.13, 128.0, 127.9, 123.2, 122.6. HRMS=284.1307 ($C_{20}H_{16}N_2$ requires 284.1308).

5.11. Cycloaddition of 6 with 24a,b. General procedure

A mixture of **6b** (0.33 g, 1 mmol) and **24a**,**b** (1 mmol) in acetic acid (2 mL) was heated under reflux for 1 h. The solvent was then removed in vacuo and the remaining residue was crystallized from ethanol to give the corresponding products **25a**,**b**, respectively.

5.11.1. Ethyl 5-benzoyl-1-p-chlorophenyl-4-phenyl-1,4-dihydropyridazine-3-carboxylate ***25a***. Yellow crystals, yield 0.27 g (60%), mp 178 °C. MS: *m*/*z*=444 (M^+, 100%), 446 (M+2, 34%). IR: 3058, 3030, 2980, 2931, 1732, 1619, 1595, 1568, 1493, 1447, 1366, 1307, 1255, 1189, 1142, 1099, 1046, 954, 717, 702. ^{1}H NMR ($CDCl_3$): δ 7.55 (m, 4H), 7.42 (m, 6H), 7.33 (m, 4H), 7.25 (m, 1H), 5.56 (s, 1H), 4.33 (m, 2H), 1.35 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 193.5, 163.2, 141.8, 141.6, 141.5, 138.5, 135.7, 131.6, 131.2, 129.6, 128.9, 128.6, 128.5, 128.0, 127.6, 119.4, 116.1, 62.0, 36.4, 14.1. HRMS=444.1235 ($C_{26}H_{21}N_2O_3Cl$ requires 444.1235).

5.11.2. Ethyl 5-p-chlorobenzoyl-1-p-chlorophenyl-4-phenyl-1,4-dihydropyridazine-3-carboxylate ***25b***. Yellow crystals, yield 0.34 g (72%), mp 162–3 °C. MS: *m*/*z*=478 (M^+, 100%), 480 (M+2, 69%), 482 (M+4, 13%). IR: 3439, 2984, 1730, 1623, 1594, 1491, 1255, 1192, 1093, 833, 751. ^{1}H NMR ($CDCl_3$): δ 7.48 (m, 3H), 7.37 (m, 6H), 7.27 (m, 4H), 7.21 (m, 1H), 5.48 (s, 1H), 4.28 (m, 2H), 1.30 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 192.3, 163.1, 141.7, 141.4, 137.9, 136.7, 135.6, 131.4, 129.9, 129.7, 129.0, 128.9, 128.0, 127.7, 119.4, 115.8, 62.1, 36.3, 14.1 (one sp^2 C overlaps). HRMS=478.0845 ($C_{26}H_{20}N_2O_3Cl_2$ requires 478.0845).

5.11.3. Ethyl 5-acetyl-1-p-chlorophenylpyrazole-3-carboxylate ***20***. A mixture of **19** (0.24 g, 1 mmol), anhydrous K_2CO_3 (0.21 g, 1.5 mmol), and chloroacetone (0.13 mL, 1 mmol) was heated under reflux for 3 h. The solvent was then removed in vacuo and the remaining residue was crystallized from ethanol to give colorless crystals, yield 0.23 g (80%), mp 158–9 °C. MS: *m*/*z*=292 (M^+, 100%), 294 (M+2, 33%). IR: 3439, 3130, 2978, 2927, 1720, 1692, 1495, 1367, 1280, 1236, 1125, 1092, 1025, 839. ^{1}H NMR ($CDCl_3$): δ 7.43 (s, 1H), 7.35 (d, 2H, *J* 3.2), 7.26 (d, 2H, *J* 4.4), 4.37 (q, 2H, *J* 7.2), 2.48 (s, 3H), 1.34 (t, 3H, *J* 7.2). ^{13}C NMR ($CDCl_3$): δ 187.1, 161.4, 144.0, 140.6,

138.5, 135.2, 128.9, 127.4, 115.1, 61.7, 28.7, 14.4. HRMS=292.0609 ($C_{14}H_{13}ClN_2O_3$ requires 292.0609).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.074.

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