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Four-Component Domino Strategy for the Combinatorial Synthesis of Novel 1,4-Dihydropyrano[2,3-*c*]pyrazol-6-amines

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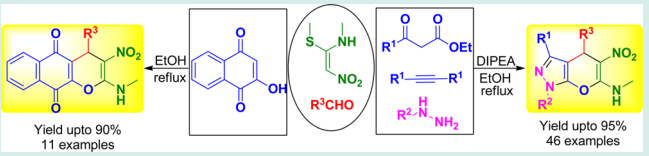
Supporting Information

ABSTRACT: An efficient one-pot four-component domino protocol for the combinatorial synthesis of novel 1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines has been achieved. This transformation presumably occurs via cyclization−Knoevenagel condensation−Michael addition−tautomerism−intramolecular *O*-cyclization−elimination sequence of reactions. The significant features of this reaction include expedient one-pot process, short reaction time, no column chromatographic purification, excellent yield, and readily available starting materials.



KEYWORDS: *1,4-dihydropyrano[2,3-c]pyrazol-6-amine, (E)-N-methyl-1-(methylthio)-2-nitroethenamine, domino, 2-hydroxy-1,4-naphthoquinone, DIPEA*

INTRODUCTION

Multicomponent domino reactions (MDR) constitute a versatile class of organic chemistry widely employed for the synthesis of complex heterocycles and natural products.[1] According to Tietze, a domino reaction is a process in which two or more bond-forming transformations occur based on functionalities formed in the previous step. Further no additional reagents or catalyst can be added to the reaction vessel, nor can reaction conditions be changed.[1,2] It is noteworthy that MDR are environmentally benign processes as they obey the principles of "Green Chemistry" on the basis of prevention of waste and avoiding time-consuming purification or protection/deprotection steps. In the past few decades investigations pertaining to the development of domino strategies toward the synthesis of novel heterocycles from simple and readily available substrates have received much of the attention of synthetic organic chemists.[3]

Pyrano[2,3-*c*]pyrazole derivatives are known for their wide range of biological activities such as antimicrobial,[4] insecticidal,[5] and anti-inflammatory.[6] Furthermore, compounds containing pyrano[2,3-*c*]pyrazole moiety have been reported to exhibit enzyme inhibition,[7] anticancer[8] and antifungal[9] activity apart from being significant intermediates for the construction of complex heterocycles.[10] In view of the biological significance, there has been extensive attention toward the development of synthetic routes for the synthesis of compounds containing pyrano[2,3-*c*]pyrazole core (Figure 1).[11]

As a consequence of our continued interest in the synthesis of novel heterocycles employing domino protocols,[12] herein we report for the first time a facile synthesis of a library of novel 1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines via the one-pot four-component domino reactions of ethyl acetoacetate **1**{1}/ethyl benzoylacetate **1**{2}/DMAD **1**{3} with hydrazines **2**, aromatic aldehydes **3**, and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4** in the presence of DIPEA. Incidentally, the ethenamine **4** is an ambiphilic substrate widely employed in the synthesis of several heterocycles which include the antiulcer drugs ranitidine and nizatidine.[13] Moreover, the present work is the first report on the use of **4** in the synthesis of pyrano[2,3-*c*]pyrazol-6-amines.

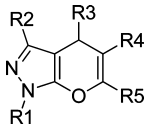


Figure 1. Pyrano[2,3-*c*]pyrazole derivatives.

RESULTS AND DISCUSSION

Initially, to identify the optimum reaction condition, a representative reaction of ethyl acetoacetate **1**{1}, phenylhydrazine **2**{1}, *p*-chlorobenzaldehyde **3**{2}, and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4**{1} affording 4-(4-chlorophenyl)-*N*,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-amine **5**{1,1,2,1} was investigated. To begin with, the reaction was performed without base in ethanol at room temperature (Table 1, entry 1), which after 8 h afforded 4-(4-chlorophenyl)-3,5-dimethyl-1,7-diphenyl-4,7-dihydro-1*H*-

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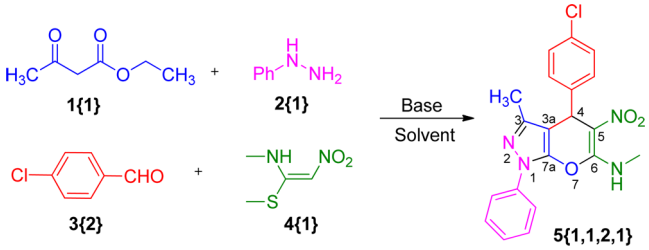
Table 1. Optimization of the Reaction Conditions for the Synthesis of 5



entry	reaction condition	yield[a] (%)
1	no base, ethanol, RT, 8 h	0[b]
2	no base, ethanol, reflux, 5 h	65
3	triethylamine (1.0 equiv), ethanol, reflux, 4 h	74
4	DIPEA (1.0 equiv), ethanol, reflux, 45 m	93
5	L-proline (1.0 equiv), ethanol, reflux, 4 h	69
6	pyrrolidine (1.0 equiv), ethanol, reflux, 3 h	0[c]
7	morpholine (1.0 equiv), ethanol, reflux, 3 h	0[c]
8	piperidine (1.0 equiv), ethanol, reflux, 3 h	0[c]
9	pyridine (1.0 equiv), ethanol, reflux, 3 h	60
10	DBU (1.0 equiv), ethanol, reflux, 3 h	51
11	DIPEA (1.0 equiv), acetonitrile, reflux, 3 h	67
12	DIPEA (1.0 equiv), methanol, reflux, 3 h	71
13	DIPEA (1.0 equiv), dioxane, reflux, 3 h	57
14	DIPEA (1.0 equiv), 2-propanol, reflux, 3 h	80
15	DIPEA (1.0 equiv), THF, reflux, 3 h	30

[a]Isolated yields. [b]The reaction afforded **5′** as sole product (Figure 2). [c]No reaction took place.

pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]pyrazole **5′** as the sole product (Figure 2). The expected product **5**{1,1,2,1} was not obtained

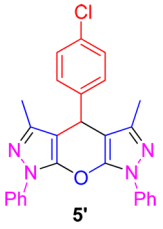


Figure 2. Structure of **5′**.

in the reaction. Interestingly, the above reaction upon reflux gave **5**{1,1,2,1} in 65% isolated yield (Table 1, entry 2). This test reaction was then investigated using different bases in refluxing ethanol. In the presence of triethylamine, the reaction afforded better yield of 74% after 4 h when compared to the reaction without base (Table 1, entry 3). The reaction was then performed in the presence of DIPEA wherein the reaction completed within 45 min with almost quantitative yield of 93% (Table 1, entry 4). *L*-proline led to 69% yield after 4 h (Table 1, entry 5) whereas the reaction completely failed to occur in the cases of pyrrolidine, morpholine, and piperidine (Table 1, entries 6−8). The test reaction was then carried out in the presence of pyridine, which afforded a moderate yield of 60% after 3 h while DBU led to further decrement in yield (51%, Table 1, entries 9 and 10).

From the above results, DIPEA emerged as the best choice of base for this domino reaction. Having determined the optimum base for the reaction, investigation pertaining to the choice of an appropriate solvent was performed. The above test reaction was examined in solvents such as dioxane, acetonitrile, tetrahydrofuran (THF), methanol, and 2-propanol (Table 1, entries 11−15). From the data in Table 1, ethanol was found to be the ideal solvent for this domino reaction which afforded maximum yield of **5**{1,1,2,1}. Further, it is pertinent to note that in ethanol−DIPEA condition (Table 1, entry 4) the product is precipitated in the reaction vessel and hence no column chromatographic purification is required. After completion of the reaction the product is filtered and washed with ethanol to obtain pure **5**{1,1,2,1} whereas in the other cases the product has to be isolated by conventional workup and column chromatography.

The optimal reaction conditions thus established were then employed for library construction with 3 esters **1**{1−3}, 3 hydrazines **2**{1−3}, 21 aromatic aldehydes **3**{1−21}, and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4**{1} (Figure 3). The corresponding 1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines **5** were obtained in good to excellent yields (Table 2). It is pertinent to note that the reaction proceeded smoothly with aromatic aldehydes bearing electron-withdrawing or electron-donating group affording the **5** in good yields. Further, the presence of sterically hindered groups in the aldehyde and bulky 1-naphthaldehyde too had no adverse effects in the yield of the product. However, the reaction failed to occur with aliphatic aldehydes.

The structure of all 1,4-dihydropyrano[2,3-*c*]pyrazol-6-amines **5** were elucidated with the help of elemental analysis, ^{1}H, ^{13}C, and 2D NMR spectroscopic techniques. As a representative case the ^{1}H and ^{13}C NMR chemical shifts of **5**{1,1,3,1} are given in Figure 4. The structure of compounds **5**{1,1,9,1} and **5**{3,1,15,1} was further confirmed by single crystal X-ray diffraction studies (Figure 5).[14]

A plausible mechanism for the formation of **5** is given in Scheme 1. Initially, the reaction of ester **1** and hydrazine **2** affords pyrazol-3-one **A** which undergoes Knoevenagel condensation with the aromatic aldehyde **3** to give arylmethylidene-2,4-dihydro-3*H*-pyrazol-3-one **B**. The intermediate **B** upon Michael addition with (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4** affords the iminol **C** which can undergo either an intramolecular *O*- or *N*-cyclization to afford **5** or **6**, respectively. The iminol **C** presumably can undergo rotation around single bond to give **E** followed by tautomerism to afford **F**. The iminol **F** upon *N*-cyclization can afford **6** via dehydration. However, in the present work the dihydropyrano[2,3-*c*]pyrazol-6-amines **5** were obtained as the sole product whereas the *N*-cyclized product **6** was not formed even in traces in the course of the reaction. Thus the iminol **C** apparently tautomerizes to aminol **D** followed by intramolecular *O*-cyclization to form **5** through the elimination of MeSH. The plausible mechanism for the formation of the product (Table 2, entries 35−41) via the domino reactions involving DMAD, phenylhydrazine, aromatic aldehydes, and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine is depicted in Scheme 2.

Further, to envisage the scope of the above methodology in cyclic systems, the optimized reaction conditions were tested with 2-hydroxy-1,4-naphthoquinone **1**{4}, aromatic aldehydes **3** and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4**. This reaction led to the formation of novel 2-(methylamino)-3-nitro-4-aryl-4*H*-benzo[*g*]chromene-5,10-diones **7** in excellent yields (Table 3). Further, it is to be noted that this domino reaction works well affording the product even in the absence of base. The structure of all these benzo[*g*]chromene-5,10-diones **7** was

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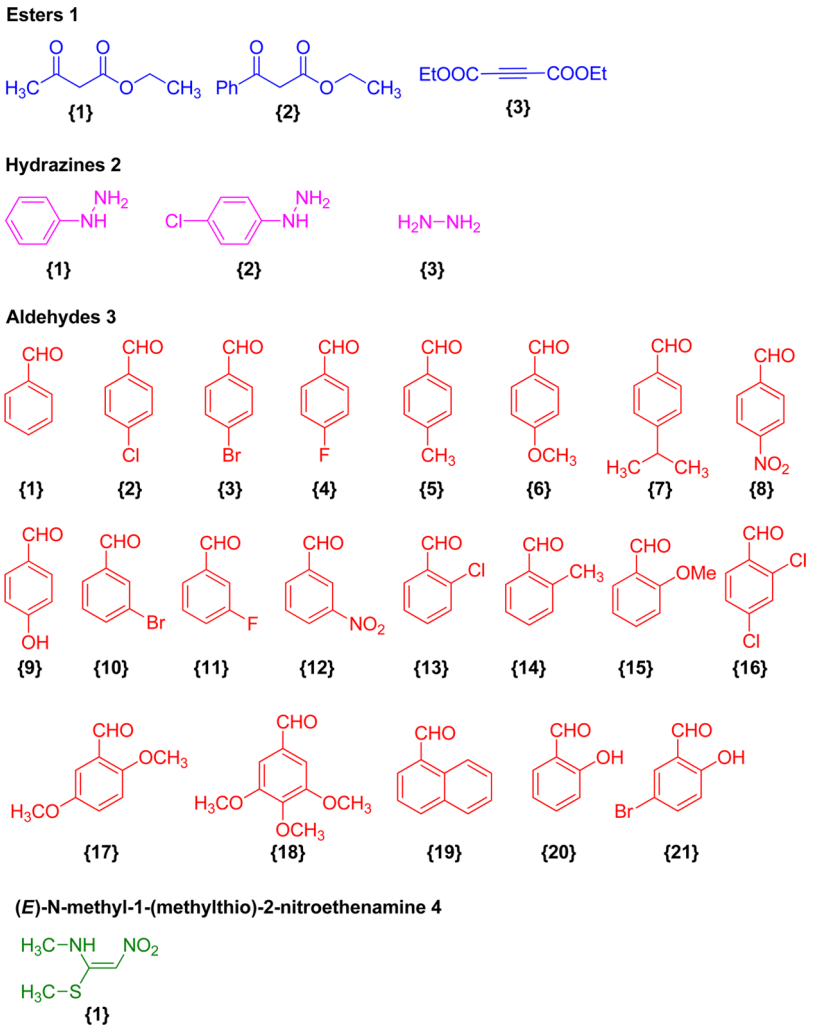

Figure 3. Diversity of reagents.

elucidated with the help of elemental analysis, ^{1}H, ^{13}C, and 2D NMR spectroscopic techniques. As a representative case the ^{1}H and ^{13}C chemical shifts of **7**{3,2,1} are shown in Figure 6.

A plausible mechanism for the formation of **7** is depicted in Scheme 3 which involves a domino Aldol reaction−Michael addition−tautomerism−*O*-cyclization sequence of reactions. That the formation of **7** is regioselective is evident from the fact that the other regioisomer **7′** (Figure 7) is not obtained even in traces in the course of the reaction. This observation can probably be attributed to the steric effects in **7′**. Moreover, no reaction was observed when the product obtained from the above reaction was treated with *o*-phenylenediamine. This presumably can be an indirect evidence for the regioselectivity observed in this reaction.

CONCLUSIONS

The present investigation reports a simple and efficient one-pot multicomponent domino protocol for the expedient synthesis of hitherto unreported 1,4-dihydro-pyrano[2,3-*c*]pyrazol-6-amines and benzo[*g*]chromene-5,10-diones in excellent yields. The significant advantages of this protocol include readily available substrates, short reaction time, simple workup, and no column chromatographic purification. These advantages make this methodology facile and appropriate to create diverse libraries. The presence of reactive $-NO_2$ and −NHMe groups at 5 and 6 positions, respectively, renders these compounds for further transformations toward more complex heterocycles.

EXPERIMENTAL PROCEDURES

General Information. The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C, and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ or DMSO as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale), and the coupling constants are given in hertz (Hz). Elemental analyses were performed on Elementar Analysensysteme GmbH Vario EL-III and Perkin-Elmer 2400 Series II CHNS analyzer. Silica gel-G plates (Merck) were used for thin layer chromatography (TLC) analysis with a mixture of petroleum ether (60−80 °C) and ethyl acetate as eluent. All the chemicals were purchased from Aldrich and used without any further purification. The single crystal X-ray data set for compound **5**{1,1,9,1} was collected on Bruker Kappa APPEXII diffractometer with Mo−K_α (λ = 0.71073 Å) radiation. SHELXTL software was used for structure solution and refinement. Intensity data of suitably sized crystals of **5**{3,1,15,1} was collected on an Oxford Xcalibur S diffractometer (4-circle κ goniometer, Sapphire-3 CCD detector, ω scans, graphite monochromator and a single wavelength

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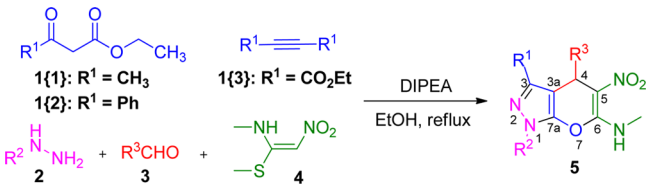
Table 2. Synthesis of Pyrano[2,3-*c*]pyrazol-6-amines 5



entry	product	yield (%)[a]	mp (°C)
1	5{1,1,1,1}	87	208−209
2	5{1,1,2,1}	93	210−211
3	5{1,1,3,1}	95	228−229
4	5{1,1,4,1}	89	223−224
5	5{1,1,5,1}	87	219−220
6	5{1,1,6,1}	86	220−221
7	5{1,1,7,1}	93	218−219
8	5{1,1,8,1}	90	217−218
9	5{1,1,9,1}	80	236−237
10	5{1,1,10,1}	89	238−239
11	5{1,1,11,1}	83	220−221
12	5{1,1,12,1}	92	228−229
13	5{1,1,13,1}	89	244−245
14	5{1,1,14,1}	96	238−239
15	5{1,1,15,1}	93	214−215
16	5{1,1,16,1}	88	225−226
17	5{1,1,17,1}	87	229−230
18	5{1,1,18,1}	95	218−219
19	5{1,1,19,1}	88	241−242
20	5{1,1,20,1}	88	240−241
21	5{1,1,21,1}	76	243−244
22	5{1,2,1,1}	74	251−252
23	5{1,2,2,1}	71	248−249
24	5{1,2,12,1}	88	242−243
25	5{1,2,14,1}	77	257−258
26	5{2,1,1,1}	69	257−258
27	5{2,1,2,1}	72	254−255
28	5{2,1,3,1}	70	256−257
29	5{2,1,7,1}	85	272−273
30	5{2,1,10,1}	70	243−245
31	5{2,1,12,1}	74	275−276
32	5{2,1,15,1}	68	268−269
33	5{2,1,18,1}	84	253−254
34	5{2,1,19,1}	75	260−261
35	5{3,1,1,1}	76	251−252
36	5{3,1,2,1}	86	261−262
37	5{3,1,3,1}	78	253−254
38	5{3,1,12,1}	74	243−244
39	5{3,1,15,1}	63	246−247
40	5{3,1,18,1}	61	234−235
41	5{3,1,19,1}	69	236−237
42	5{1,3,6,1}	62	265−266
43	5{1,3,7,1}	57	259−260
44	5{1,3,14,1}	67	273−274
45	5{2,3,6,1}	58	283−284
46	5{3,3,1,1}	55	271−272

[a]Isolated yields.

Enhance X-ray source with MoKα radiation).[15] Pre-experiment, data collection, data reduction, and absorption corrections were performed with the CrysAlisPro software suite.[16] The structures were solved by direct methods using SIR 92,[17] which revealed the atomic positions, and refined using the SHELX-97 program package[18] and SHELXL-97 (within the WinGX program package).[19] Non-hydrogen atoms were refined anisotropically. C−H hydrogen atoms were placed in geometrically calculated positions by using a riding model.

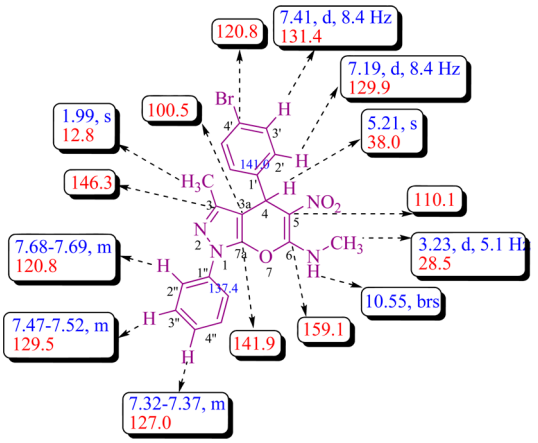


Figure 4. ^{1}H and ^{13}C chemical shifts of 5{1,1,3,1}.

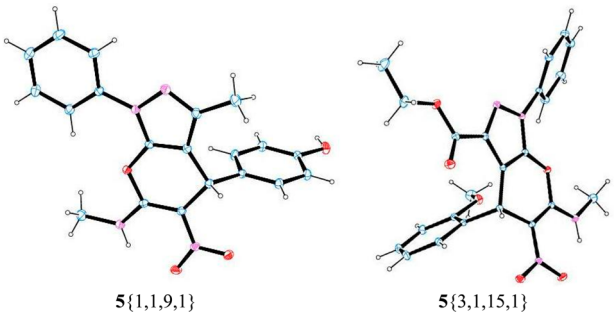


Figure 5. ORTEP diagrams of pyrano[2,3-*c*]pyrazol-6-amines.[14]

General Procedure for the Synthesis of 5. An equimolar mixture of the appropriate ester (1{1−3}, 1.3 mmol), hydrazine (2{1−3}, 1.3 mmol), aromatic aldehyde (3{1−21}, 1.3 mmol), and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (**4**, 1.3 mmol) were dissolved in ethyl alcohol (3−5 mL). To this DIPEA was added and refluxed for 45 min to 2 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the mixture was cooled to room temperature, and the precipitated solid was filtered, washed with ethanol (5 mL), and dried to obtain **5** as white solid.

Compound 5{1,1,1,1}. White solid; Yield: 87%, mp 208−209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.00 (s, 3H), 3.23 (d, J = 5.1 Hz, 3H), 5.25 (s, 1H), 7.18−7.25 (m, 1H), 7.28−7.29 (m, 4H), 7.34 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 10.58 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.7, 28.4, 38.4, 101.2, 110.6, 120.7, 126.8, 127.0, 128.1, 128.2, 129.3, 137.6, 141.9, 142.0, 146.4, 159.2. Anal. Calcd. for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46%. Found: C, 66.32; H, 5.09; N, 15.68%.

Compound 5{1,1,2,1}. White solid; Yield: 93%, mp 210−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.99 (s, 3H), 3.24 (d, J = 5.1 Hz, 3H), 5.23 (s, 1H), 7.25−7.27 (m, 4H), 7.35 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.9 Hz, 2H), 7.68 (d, J = 9.0 Hz, 2H), 10.56 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.8, 28.5, 37.9, 100.6, 110.2, 120.8, 127.0, 128.4, 129.4, 129.6, 132.7, 137.4, 140.5, 142.0, 146.3, 159.1. Anal. Calcd. for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12%. Found: C, 60.53; H, 4.64; N, 14.32%.

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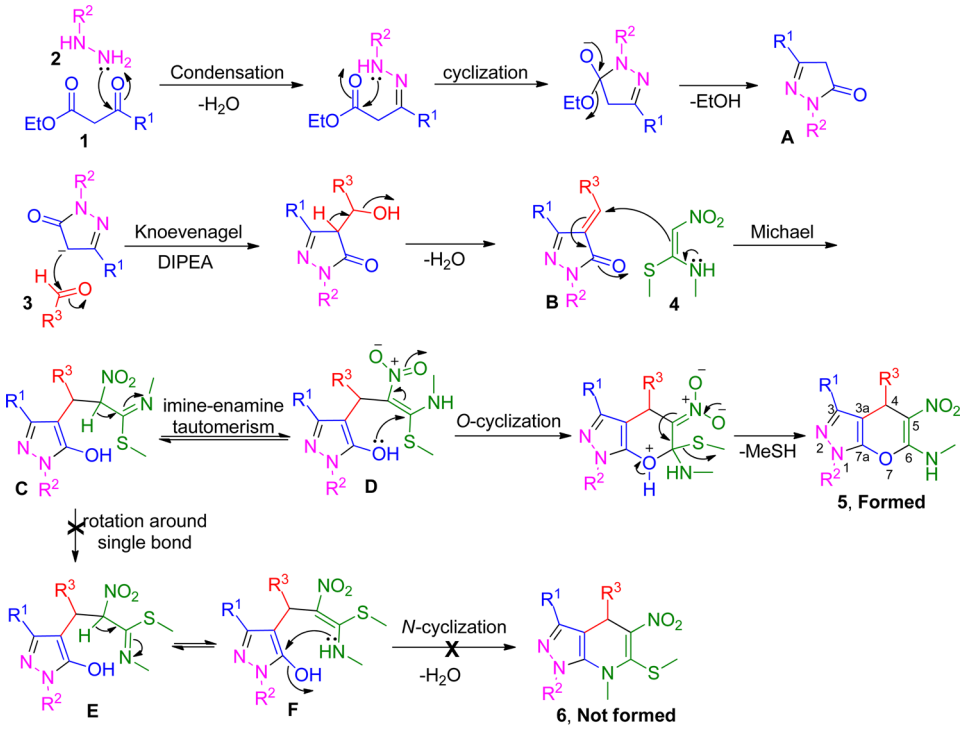
Scheme 1. Plausible Mechanism for the Formation of 5 (R^1 = CH_3 and Ph)



Scheme 2. Plausible Mechanism for the Formation of 5

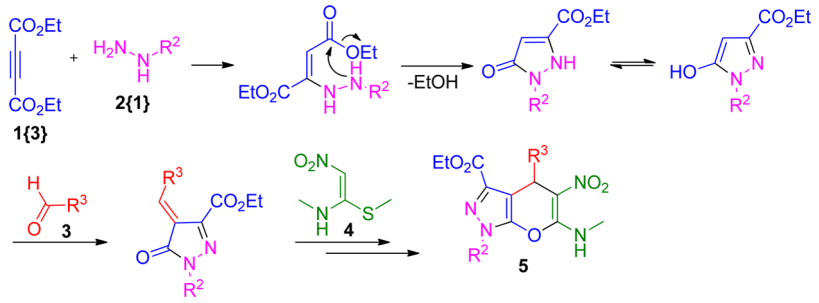
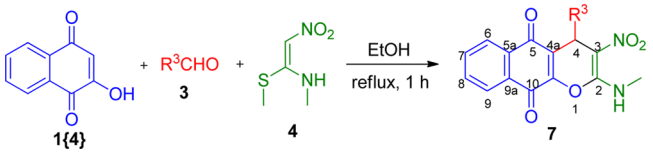


Table 3. Synthesis of 4*H*-benzo[*g*]chromene-5,10-diones 7



entry	product	yield (%)[a]	mp (°C)
47	7{4,1,1}	88	267–268
48	7{4,2,1}	90	264–265
49	7{4,3,1}	86	268–269
50	7{4,7,1}	85	249–250
51	7{4,10,1}	85	245–246
52	7{4,13,1}	87	259–260
53	7{4,14,1}	89	251–252
54	7{4,15,1}	90	265–266
55	7{4,16,1}	87	244–245
56	7{4,17,1}	87	261–262
57	7{4,19,1}	86	260–261

[a]Isolated yields.

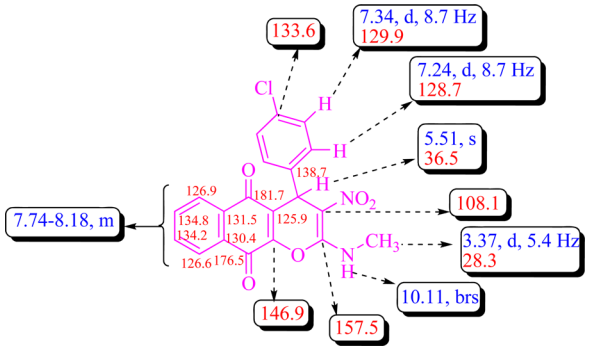


Figure 6. ^{1}H and ^{13}C chemical shifts of 7{4,2,1}.

Compound 5{1,1,10,1}. White solid; Yield: 89%, mp 238–239 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.01 (s, 3H), 3.25 (d, J = 5.1 Hz, 3H), 5.22 (s, 1H), 7.14–7.19 (t, J = 7.7 Hz, 1H), 7.29–7.37 (m, 4H), 7.50 (t, J = 7.9 Hz, 2H), 7.69 (d, J = 7.8 Hz, 2H), 10.57 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ_C 12.8, 28.8, 38.3, 100.2, 109.4, 120.7, 122.2, 126.9, 127.1, 129.4, 129.9, 130.0, 130.8, 137.4, 142.0, 144.9, 146.0, 159.0.

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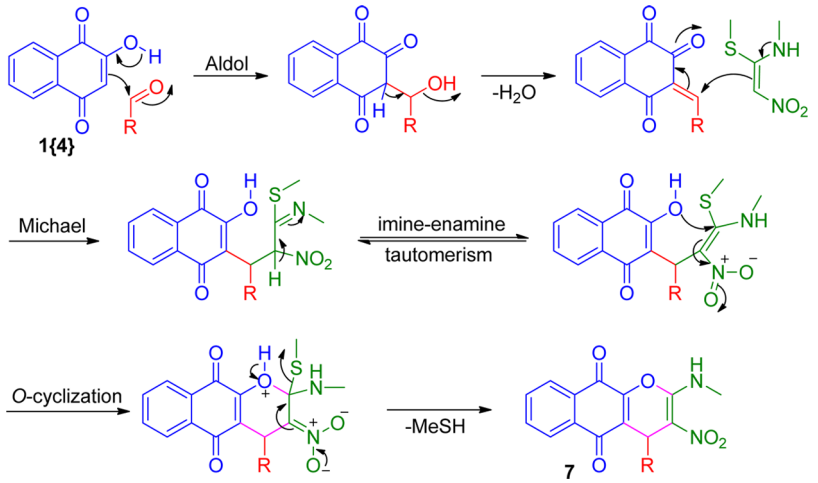
Scheme 3. Plausible Mechanism for the Formation of 7



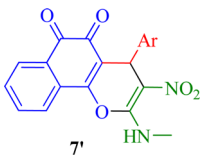


Figure 7. Regioisomer of 7 not formed in the reaction.

Anal. Calcd. for $C_{20}H_{17}BrN_4O_3$: C, 54.44; H, 3.88; N, 12.70%. Found: C, 54.41; H, 3.84; N, 12.57%.

Compound ***5****{1,1,13,1}*. White solid; Yield: 89%, mp 244–245 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.01 (s, 3H), 3.26 (d, J = 5.1 Hz, 3H), 5.66 (s, 1H), 7.12–7.23 (m, 2H), 7.30–7.37 (m, 3H), 7.50 (t, J = 8.1 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 10.67 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ_C 11.8, 27.7, 35.4, 98.6, 108.1, 119.8, 125.9, 126.1, 127.3, 128.4, 128.8, 129.8, 132.3, 136.4, 138.1, 141.2, 145.1, 158.4. Anal. Calcd. for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12%. Found: C, 60.68; H, 4.30; N, 13.97%.

Compound ***5****{1,1,16,1}*. White solid; Yield: 88%, mp 225–226 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.01 (s, 3H), 3.26 (d, J = 5.1 Hz, 3H), 5.62 (s, 1H), 7.16–7.25 (m, 2H), 7.32–7.37 (m, 2H), 7.50 (t, J = 7.8 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 10.64 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.8, 28.5, 36.3, 99.1, 109.1, 120.9, 127.0, 127.2, 129.4, 129.8, 131.7, 133.3, 134.1, 137.3, 137.4, 142.2, 146.3, 159.5. Anal. Calcd. for $C_{20}H_{16}Cl_2N_4O_3$: C, 55.70; H, 3.74; N, 12.99%. Found C, 56.11; H, 3.73; N, 13.08%.

Compound ***5****{1,1,18,1}*. White solid; Yield: 95%, mp 218–219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.06 (s, 3H), 3.24 (d, J = 5.1 Hz, 3H), 3.80 (s, 3H), 3.83 (s, 6H), 5.22 (s, 1H), 6.50 (s, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.9 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 10.56 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.9, 28.5, 38.6, 56.4, 60.7, 100.9, 105.6, 106.0, 110.4, 120.7, 126.8, 129.4, 137.5, 142.0, 146.4, 153.1, 159.2. Anal. Calcd. for $C_{23}H_{24}N_4O_6$: C, 61.05; H, 5.35; N, 12.38%. Found: C, 61.83; H, 5.55; N, 11.85%.

Compound ***5****{1,1,19,1}*. White solid; Yield: 88%, mp 241–242 °C; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ_H 1.71 (s, 3H), 3.30 (d, J = 4.8 Hz, 3H), 6.11 (s, 1H), 7.29–7.42 (m, 4H), 7.45–7.53 (m, 3H), 7.57–7.62 (m, 1H), 7.69–7.73 (m, 2H), 7.82–7.88 (m, 2H), 10.63 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ_C 13.1, 28.7, 33.6, 101.8, 110.7, 120.7, 123.1, 125.5, 125.6, 126.0, 126.1, 126.8, 127.5, 128.7, 128.8, 129.4, 131.5, 133.5, 137.5, 142.0, 146.1, 159.3. Anal. Calcd. for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58%. Found: C, 69.74; H, 5.02; N, 13.73%.

Compound ***5****{1,2,1,1}*. White solid; Yield: 74%, mp 251–252 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.99 (s, 3H), 3.24 (d, J = 5.1 Hz, 3H), 5.24 (s, 1H), 7.18–7.25 (m, 1H), 7.28–7.29 (m, 4H), 7.46 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 10.55 (brs, 1H); ^{13}C NMR (75 MHz, DMSO) δ_C 10.5, 26.8, 36.0, 99.0, 107.0, 120.0, 124.6, 125.9, 126.1, 126.7, 127.5, 128.9, 134.1, 140.0, 141.1, 156.7; Anal. Calcd. for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12%. Found: C, 60.55; H, 4.30; N, 14.11%.

Compound ***5****{2,1,2,1}*. White solid; Yield: 72%, mp 254–255 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.25 (d, J = 5.1 Hz, 3H), 5.64 (s, 1H), 7.17 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H), 7.31–7.35 (m, 3H), 7.37–7.43 (m, 1H), 7.52–7.62 (m, 4H), 7.78–7.83 (m, 2H), 10.47 (brs, 1H); ^{13}C NMR (75 MHz, CDCl3) δ_C 28.5, 38.0, 100.3, 110.8, 121.2, 127.1, 127.4, 128.3, 128.4, 128.6, 129.5, 129.8, 132.1, 132.9, 137.5, 140.3, 143.3, 147.8, 158.9; Anal. Calcd. for $C_{25}H_{19}ClN_4O_3$: C, 65.43; H, 4.17; N, 12.21%. Found: C, 65.48; H, 4.22; N, 12.15%.

Compound ***5****{3,1,2,1}*. White solid; Yield: 86%, mp 261–262 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.32 (t, J = 7.2 Hz, 3H), 3.23 (d, J = 5.1 Hz, 3H), 4.28–4.36 (m, 2H), 5.64 (s, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.43–7.49 (m, 1H), 7.53–7.58 (m, 2H), 7.76–7.79 (m, 2H), 10.42 (brs, 1H); ^{13}C NMR (75 MHz, CDCl3) δ_C 14.3, 28.5, 37.9, 61.3, 104.6, 110.6, 122.1, 128.1, 128.6, 129.6, 130.1, 132.8, 136.8, 139.3, 140.4, 143.2, 158.7, 160.9; Anal. Calcd. for $C_{22}H_{19}ClN_4O_5$: C, 58.09; H, 4.21; N, 12.32%. Found: C, 58.16; H, 4.28; N, 12.29%.

Compound ***5****{1,3,6,1}*. White solid; Yield: 62%, mp 265–266 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ_H 1.97 (s, 3H), 3.27 (d, J = 5.1 Hz, 3H), 3.75 (s, 3H), 5.14 (s, 1H), 6.77 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 10.82 (brs, 1H), 11.98 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ_C 8.3, 26.6, 35.3, 53.6, 98.0, 108.3, 112.0, 127.0, 134.3, 134.8, 152.0, 156.4, 158.7. Anal. Calcd. for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71%. Found: C, 57.00; H, 5.02; N, 17.69%.

Compound ***5****{2,3,6,1}*. White solid; Yield: 58%, mp 283–284 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ_H 3.22 (d, J = 5.1 Hz, 3H), 3.65 (s, 3H), 5.49 (s, 1H), 6.70 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 7.30–7.41 (m, 3H), 7.52 (d, J = 7.5 Hz, 2H), 10.63 (brs, 1H), 13.06 (brs, 1H); ^{13}C NMR (75

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MHz, $CDCl_3$+DMSO) δ_C 26.4, 35.1, 53.2, 97.8, 108.4, 111.5, 124.5, 126.8, 126.9, 127.0, 127.3, 133.5, 136.6, 153.0, 156.2, 157.8. Anal. Calcd. for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81%. Found: C, 63.47; H, 4.84; N, 14.83%.

Compound ***5****{3,3,1,1}*. White solid; Yield: 55%, mp 271−272 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ_H 1.30 (t, J = 7.2 Hz, 3H), 3.29 (d, J = 5.4 Hz, 3H), 4.26 (q, J = 7.2 Hz, 2H), 5.54 (s, 1H), 7.14−7.27 (m, 5H), 10.68 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ_C 13.7, 27.8, 37.3, 60.9, 105.2, 109.8, 126.2, 127.3, 128.0, 129.4, 142.2, 154.0, 158.0, 159.5. Anal. Calcd. for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27%. Found: C, 55.82; H, 4.69; N, 16.21%.

General Procedure for the Synthesis of 7. An equimolar mixture of 2-hydroxy-1,4-naphthoquinone (**1**{4}, 1.3 mmol), aromatic aldehyde (**3** 1.3 mmol), and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (**4**, 1.3 mmol) were dissolved in ethyl alcohol (3−5 mL) and refluxed for 1−2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, and the precipitated solid formed was filtered, washed with ethanol (5 mL), and dried to obtain pure **7** as yellow solid.

Compound ***7****{4,2,1}*. Yellow solid; Yield: 90%, mp 264−265 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.37 (d, J = 5.4 Hz, 3H), 5.51 (s, 1H), 7.24 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.74−7.79 (m, 2H), 8.02−8.05 (m, 1H), 8.13−8.18 (m, 1H), 10.10 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.3, 36.5, 108.1, 125.9, 126.6, 126.9, 128.7, 129.9, 130.4, 131.5, 133.6, 134.2, 134.8, 138.7, 146.9, 157.5, 176.5, 181.7. Anal. Calcd. for $C_{20}H_{13}ClN_2O_5$: C, 60.54; H, 3.30; N, 7.06%. Found: C, 60.30; H, 3.12; N, 7.11%.

Compound ***7****{4,19,1}*. Yellow solid; Yield: 86%, mp 260−261 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.40 (d, J = 5.1 Hz, 3H), 6.34 (s, 1H), 7.22−7.34 (m, 2H), 7.51−7.56 (m, 1H), 7.64−7.77 (m, 4H), 7.80 (d, J = 8.1 Hz, 2H), 7.91 (dd, J = 7.4, 1.7 Hz, 1H), 8.14 (dd, J = 7.5, 1.5 Hz, 1H), 10.12 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 21.9, 25.2, 102.3, 118.6, 118.8, 119.0, 119.1, 119.2, 119.3, 119.4, 120.1, 121.2, 121.4, 123.8, 124.3, 124.8, 126.3, 127.8, 128.1, 132.9, 140.5, 150.2, 169.7, 175.4 Anal. Calcd. for $C_{24}H_{16}N_2O_5$: C, 69.90; H, 3.91; N, 6.79%. Found: C, 69.99; H, 3.86; N, 6.69%.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic characterization of **5** and **7**. ^{1}H and ^{13}C spectra for all products and the X-ray crystallographic information for compounds **5**{1,1,9,1} and **5**{3,1,15,1}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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