Accepted Manuscript

Title: DABCO-catalyzed multi-component domino reactions for green and efficient synthesis of novel 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives in water

Author: <ce:author id="aut0005" author-id="S1001841717300281-7936a2b0d083aec6137d4b1142977263"> Razieh Mohebat<ce:author id="aut0010" author-id="S1001841717300281-9b58f26c2cc282346323f0aaedb7b222"> Afshin Yazdani-Elah-Abadi<ce:author id="aut0015" author-id="S1001841717300281-a23f20f84befa987600ba608225d2598"> Malek-TaherMaghsoodlou<ce:author id="aut0020" author-id="S1001841717300281-d2193528db276f77449628568759cb61"> Nourallah Hazeri

PII: S1001-8417(17)30028-1
DOI: http://dx.doi.org/doi:10.1016/j.cclet.2016.12.042
Reference: CCLET 3955

To appear in: *Chinese Chemical Letters*

Received date: 24-10-2016
Revised date: 29-11-2016
Accepted date: 7-12-2016

Please cite this article as: Razieh Mohebat, Afshin Yazdani-Elah-Abadi, Malek-TaherMaghsoodlou, Nourallah Hazeri, DABCO-catalyzed multi-component domino reactions for green and efficient synthesis of novel 3-oxo-3H-benzo[a]pyrano[2,3-c]phenazine-1-carboxylate and 3-(5-hydroxybenzo[a]phenazin-6-yl)acrylate derivatives in water, Chinese Chemical Letters http://dx.doi.org/10.1016/j.cclet.2016.12.042

Original article

DABCO-catalyzed multi-component domino reactions for green and efficient synthesis of novel 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives in water

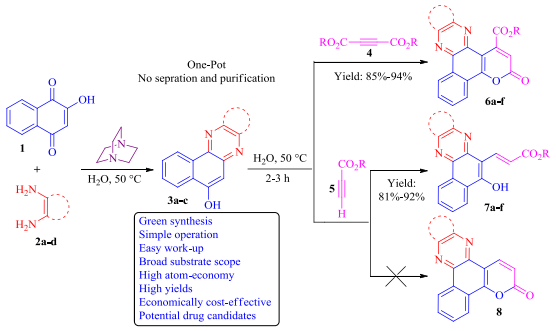
Razieh Mohebat [a], Afshin Yazdani-Elah-Abadi [b, *], Malek-Taher Maghsoodlou [b, *], Nourallah Hazeri [b]

[a] *Department of Chemistry, Yazd Branch, Islamic Azad University, Yazd, Iran*
[b] *Department of Chemistry, Faculty of Science, University of Sistan and Baluchestan, P. O. Box 98135-674, Zahedan, Iran*

∗ Corresponding authors.
E-mail addresses: *afi_yazdani@yahoo.com; (A. Yazdani-Elah-Abadi) mt_maghsoodlou@yahoo.com; mt_maghsoodlou@chem.usb.ac.ir (M.-T. Maghsoodlou)*

ARTICLE INFO
Article history:
Received 24 October 2016
Received in revised form 29 November 2016
Accepted 7 December 2016
Available online

Graphical Abstract



ABSTRACT: An efficient, convenient and environmentally benign procedure for the synthesis of novel 3-oxo-3H-benzo[a]pyrano[2,3-c]phenazine-1-carboxylate and 3-(5-hydroxybenzo[a]phenazin-6-yl)acrylate derivatives has been developed by domino three-component condensation reaction between 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamines and acetylenic esters in the presence of a catalytic amount of DABCO as an expedient, eco-friendly and reusable base catalyst in water. This green process produces biologically and pharmacologically significant heterocycles in a one-pot single operation and offers considerable advantages such as: operational simplicity, short reaction time, high yields, reusability of catalyst, absence of any tedious workup or purification and avoids hazardous reagents/solvents.

Keywords:
Multi-component domino reactions (MDRs)
DABCO
Acetylenic esters
Benzo[a]phenazin derivatives
Green chemistry

1. Introduction

Synthesis of polyfunctionalized heterocyclic compounds from readily available starting materials in a cost and time effective manner has been received significant attention in organic synthesis due to their extensive applications in pharmaceuticals, agrochemicals and in materials sciences [1-3]. In this area, multi-component domino reactions (MDRs), in which more than two components are combined in a single synthetic operation, have been extensively used as a powerful strategy in the synthesis of complex heterocyclic molecules due to their advantages such as higher productivity, simple procedures, facile execution, lower costs, minimum waste production, structural diversity, shorter reaction times, environmentally friendliness, atom economy, high selectivity and allowing savings of both solvents and reagents [4-7].

Furthermore, replacement of hazardous solvents with environmentally benign solvents [8-10] is one of the major focus areas of green chemistry. Organic solvents used in most of the synthetic organic chemistry evaporate into the atmosphere with destructive effects on the environment and ozone layer [11]. Thus, aqueous phase organic synthesis has attracted the attention of chemists as it overcomes the harmful effects associated with the organic solvents and is environmentally benign. Moreover, using water as the medium, surfactants can be used to build micelles and provide better chemical yields and shorter reaction times due to its strong hydrogen bonding ability, hydrophobic effects and high polarity [12-14].

As mentioned, functionalized heterocyclic compounds play significant roles in the drug discovery process, and analysis of drugs [15,16]. Among them, phenazine systems are nitrogen-containing heterocycles that are found in natural and synthetic products [17-20] and they have been demonstrated to possess a myriad of biological functions, including antimalarial [21,22], trypanocidal [23], fungicidal [24,25], antiplatelet [26], and antitumour [27] activities. For example, pyridophenazinediones and pyridazinophenazinedione derivatives have shown the antitumor activity [28,29].

As part of our research on the development of new synthetic methods in heterocyclic chemistry and our interest in acetylenic ester-based MCRs [30-36], in this paper, we would like to report new sequence of a one-pot, three-component condensation reaction between 2-hydroxynaphthalene-1,4-dione **1**, benzene-1,2-diamines **2** and acetylenic esters **4**, **5** in the presence of DABCO as an efficient, non-toxic and reusable solid base catalyst for the synthesis of novel 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives **6**, **7** in aqueous medium at 50 °C (Scheme 1).

2. Results and discussion

Considering the importance of phenazine derivatives, we were willing to find a practical and general method for their synthesis in high yields and purities and also, owing to the development of efficient and environmentally friendly synthetic procedures is always desirable, we decided to peruse whether those phenazines could be prepared by condensation of 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamines and acetylenic esters in the absence of any organic solvent.

In order to investigate the optimizing reaction conditions for the synthesis of 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylates, we carried out the three-component domino reaction between 2-hydroxynaphthalene-1,4-dione **1** (1 mmol), benzene-1,2-diamine **2a** (1 mmol) and dimethyl acetylenedicaboxylate **4** (1 mmol) in ethanol as a model. Initially, to minimize the formation of byproducts, the 2-hydroxynaphthalene-1,4-dione and benzene-1,2-diamine were refluxed in EtOH until in less than 10 minutes an orange solid of benzo[*a*]phenazine **3a** was formed without using any catalyst. Next, dimethyl acetylenedicaboxylate was added and the mixture was heated in EtOH under reflux. The desired product **6a** was not obtained when the reaction was carried out in EtOH for 4 h under reflux and catalyst-free conditions (Table 1, entry 1). However, **6a** was obtained in 81% yield when the reaction was conducted in the presence of triethylamine (20 mol%) in EtOH (Table 1, entry 2). Several bases were evaluated in the reaction as catalyst, including Et_3N, pyridine, isoquinoline, Ph_3P, DBU and DABCO; these were all added in substoechiometric amount (20 mol%) and the reactions were carried out in EtOH under reflux conditions. DABCO showed excellent catalytic activity in terms of reaction time as well as yield of the product (Table 1, entry 7). Then, water was appraised to determine the impact of the solvent on the reaction yields.

Water due to its strong hydrogen bonding ability, hydrophobic effects and high polarity showed better performance in comparison with ethanol and gave the higher product yield (Table 1, entry 8). We then evaluated the amount of catalyst required for this transformation. An increase in the amount of DABCO more than 20 mol% showed no remarkable improvement in the yield, whereas the yield was reduced by decreasing the amount of DABCO to 10 mol% (Table 1, entries 8-10). Finally, the reaction was performed at different temperatures to determine the optimum reaction temperature. The reaction was conducted with 20 mol% DABCO in water at r.t., 50, 70 and 100 °C, and the desired product **6a** was formed in yields of trace, 94%, 91% and 95% (Table 1, entries 8 and 11-13), respectively.

After extensive screening, we found that the optimized best yields and time profiles were obtained with 20 mol% of DABCO in H_2O at 50 °C, which furnished the corresponding methyl 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate **6a** in 94% yield within 2 h (Table 1, entry 12).

Using these optimized conditions, we turned our attention to investigate the scope and general applicability of this methodology by carrying out the synthesis of 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylates using different benzene-1,2-diamines and various electron defficient acetylenic esters (Table 2).

All the reactions were complete in 2-3 h and resulted in the formation of the target structures (Scheme 1, Table 2, entries 1-6) in high yields using the DABCO as environment-friendly catalyst [37] and this domino reaction was efficiently promoted using benzene-1,2-diamine with reduced reaction times and increased yields rather than other benzene-1,2-diamines and dimethyl acetylenedicaboxylate with less steric hindrance reacted rapidly and gave higher yields in comparison with diethyl acetylenedicaboxylate.

On the next step, in order to achieve 3*H*-benzo[*a*]pyrano[2,3-*c*]phenazin-3-one derivatives, we carried out the reaction between 2-hydroxynaphthalene-1,4-dione **1** (1 mmol), benzene-1,2-diamine **2a** (1 mmol) and methyl propiolate **5** (1 mmol) in the presence of triethylamine (20 mol%) as catalyst in aqueous medium under reflux. In the event we did not observe the expected MDR product **8**; instead the reaction afforded the corresponding 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives **7** with three-component domino reaction (Scheme 2).

Then, to prepare 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives in a more efficient way, and to minimize the reaction time and the amount of catalyst required, the three-component domino reaction between 2-hydroxynaphthalene-1,4-dione **1** (1 mmol), benzene-1,2-diamine **2a** (1 mmol) and methyl propiolate **5** (1 mmol) in water was selected as a model system. After broad screening, we found that the optimized best yields and time profiles were obtained with 10 mol % of DABCO in H_2O at 50 °C, which furnished the corresponding methyl 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate **7a** in 92% yield within 2 h proceed efficiently (Table 3, entry 10).

Using these optimized reaction conditions, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives. The results are summarized in Table 4.

The isolated products **6** and **7** were fully characterized on the basis of IR, NMR and MS spectroscopy and elemental analysis.

Reusability of catalyst is a significant feature in green organic synthesis. Our findings revealed that DABCO was a recoverable catalyst. For this purpose, we investigated the recycling of the catalyst in aqueous medium at 50 °C using a selected model reaction of 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamine and dimethyl acetylenedicaboxylate in the presence of DABCO as homogeneous catalyst (Table 2, entry 1). After completion of the reaction, then reaction mixture was cooled to room temperature. Then, 5 mL of water was added to the mixture and filtered for separation of the crude product. The separated product was washed twice with water (2×5 mL). The resulting product subsequently recrystallized from hot ethanol to give the pure solid. In order to recover the catalyst, since DABCO is soluble in water, the filtrate was extracted with diethyl ether. The aqueous layer (including DABCO) was separated, and its solvent was evaporated under reduced pressure and DABCO was recovered and reused.

As shown in Fig. 1, the recovered catalyst works with the same performance up to 2nd run, while in the 3rd, 4th and 5th runs product yield gets reduced slightly that may be due to little weight loss of catalyst during each recovery process.

In order to determine the catalytic behavior of DABCO, the suggested mechanism for the formation of the products **6** and **7** is shown in Scheme 3. On the basis of this mechanism, at first, 2-hydroxynaphthalene-1,4-dione **1** tautomrizes to intermediate **9**. The primary condensation of 4-hydroxy-1,2-naphthoquinone **9** with benzene-1,2-diamine **2** obtain benzo[*a*]phenazin-5-ol **3**. Then, based on nucleophilicity of DABCO, the nucleophilic addition of DABCO to the acetylenic ester **4** or **5** and subsequent protonation in the presence of compound **3** gives intermediates **10** or **11**, followed by attack of the anion on the cation part of intermediates **10** or **11** to

form the intermediates **12** or **13**. Intramolecular lactonization of the intermediate **12** leads to produce compound **6** and also, intermediate **13** followed by a tautomeric proton shift leads to the formation of desired product **7**.

3. Conclusion

In summary, we have described a novel domino three-component coupling reaction leading to selective and high-yielding 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives from readily avaible starting materials in aqueous medium. This protocol also offers several advantages such as convenient one-pot operation, high atom economy, easy work-up, short reaction time, use of DABCO as a highly reactive, non-toxic and reusable catalyst and avoidance of conventional volatile organic solvents that make it a green, economically cost-effective and attractive process for the synthesis of these heterocycles. Furthermore, our work is expected to exhibit interesting pharmacology activities and may act as potential drug candidates, since phenazine and pyran motifs have a vast range of biological activity.

4. Experimental

4.1. Chemistry

All melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a shimadzu IR-470 spectrometer. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer at Iranian Central Research of Petroleum Company. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 and 400 Avanve instrument with $CDCl_3$ and DMSO-d_6 as solvent and using TMS as internal reference at 300, 400, 75, and 100 MHz, respectively. Thin-layer chromatography (TLC) was performed on silica-gel Polygram SILG/UV 254 plates. All reagents and solvent were purchased from Merck and Aldrich and used without further purification.

*4.2. General procedure for the synthesis of novel 3-oxo-3H-benzo[a]pyrano[2,3-c]phenazine-1-carboxylate and 3-(5-hydroxybenzo-[a]phenazin-6-yl)acrylate derivatives (**6**, **7**)*

Initially, a mixture of 2-hydroxynaphthalene-1,4-dione **1** (1 mmol), benzene-1,2-diamine **2** (1 mmol), DABCO (20 or 10 mol%) and water (10 mL) was placed in a 50 mL round-bottomed flask mounted over a magnetic stirrer. The contents were stirred magnetically in an oil-bath maintained at 50 °C until in less than 10 minutes benzo[*a*]phenazin-5-ol **3** was formed. Then, dialkyl acetylenedicarboxylate **4** (1 mmol) or alkyl propiolate **5** (1 mmol) was added to the above reaction mixture which was heated further at the same temperature for an appropriate time as shown in Tables 2 and 4. Upon completion of the reaction, monitored by TLC, the reaction mixture was allowed to cool to room temperature. Then, 5 mL of water was added to the mixture and filtered for separation of the crude product. The separated product was washed twice with water (2×5 mL). The solid crude product subsequently recrystallized from hot ethanol to give the pure product **6** and **7**. Some spectral and analytical data are presented below, others are deposited in Supporting information.

Methyl 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate (**6a**): Brown powder; yield 0.334 g (94%), mp 243-245 °C; IR (KBr, cm^{-1}): ν_{max} 1729 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (s, 3H, OCH_3), 6.61 (s, 1H, CH), 7.86-7.94 (m, 4H, Ar-H), 8.11-8.13 (m, 1H, Ar-H), 8.30-8.32 (m, 1H, Ar-H), 8.56-8.58 (m, 1H, Ar-H), 9.31-9.33 (m, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9 (OCH_3), 108.5 (CH), 113.9, 123.5, 125.0, 125.5, 128.7, 129.7, 130.3, 130.6, 130.8, 131.0, 132.0, 137.9, 139.7, 141.2, 141.5, 146.9 and 155.5 (17$C_{olefinic}$ and C_{arom}), 159.2 and 166.9 (2C=O); MS (*m/z*, %): 356 (M^+, 74), 297 (100), 241 (67), 125 (19), 97 (62), 57 (83); Anal. Calcd. for $C_{21}H_{12}N_2O_4$: C, 70.78; H, 3.39; N, 7.86. Found: C, 70.96; H, 3.51; N, 8.01.

Methyl 12-methyl-3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate (**6c**): Yellow powder; yield 0.342 g (92%), mp 234-236 °C; IR (KBr, cm^{-1}): ν_{max} 1721 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3), 4.19 (s, 3H, OCH_3), 6.64 (s, 1H, CH), 7.90-7.96 (m, 3H, Ar-H), 7.99 (td, 1H, J_1 = 6.0 Hz, J_2 = 1.2 Hz, Ar-H), 8.36-8.39 (m, 1H, Ar-H), 8.65-8.67 (m, 1H, Ar-H), 9.42-9.44 (m, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5 (CH_3), 52.7 (OCH_3), 108.3 (CH), 113.1, 123.9, 124.5, 125.6, 128.7, 129.7, 130.5, 131.6, 131.7, 132.9, 133.1, 137.3, 139.9, 140.3, 140.4, 143.4 and 155.2 (17$C_{olefinic}$ and C_{arom}), 159.9 and 166.2 (2C=O); MS (*m/z*, %): 370 (M^+, 100), 311 (92), 284 (90), 188 (14), 127 (36), 69 (64): Anal. Calcd. for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.57; H, 3.69; N, 7.70.

Methyl 11-nitro-3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate (**6e**): Yellow powder; yield 0.353 g (88%), mp 260-262 °C; IR (KBr, cm^{-1}): ν_{max} 1747, 1726 (2C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.11 (s, 3H, OCH_3), 6.97 (s, 1H, CH), 7.88-8.04 (m, 2H, Ar-H), 8.28-8.44 (m, 2H, Ar-H), 8.57-8.68 (m, 1H, Ar-H), 8.83 (s, 1H, Ar-H), 9.12-9.18 (m, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 52.8 (OCH_3), 108.3 (CH), 112.9, 121.5, 123.6, 125.9, 128.3, 129.7, 129.8, 130.8, 131.6, 131.8, 132.2, 137.4, 139.8, 141.1, 141.6, 147.8 and 155.2 (17$C_{olefinic}$ and C_{arom}), 159.2 and 166.4 (2C=O); MS (*m/z*, %): 401 (M^+, 2), 311 (60), 284 (100), 255 (59), 127 (26), 69 (90); Anal. Calcd. for $C_{21}H_{11}N_3O_6$: C, 62.85; H, 2.76; N, 10.47. Found: C, 62.76; H, 2.99; N, 10.41.

Methyl 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate (**7a**): Yellow powder; yield 0.304 g (92%), mp 134-136 °C; IR (KBr, cm^{-1}): ν_{max} 1714 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H, OCH_3), 5.52 (d, 1H, J = 6.6 Hz, CH), 6.00 (d, 1H, J = 12.0 Hz, CH), 7.37-7.50 (m, 1H, Ar-H), 7.87-7.90 (m, 3H, Ar-H), 8.14-8.36 (m, 3H, Ar-H), 9.41 (d, 1H, J = 6.0 Hz, Ar-H), 11.80 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.6 (OCH_3), 105.2, 108.4, 122.3, 125.4, 127.2, 128.7, 129.0, 129.5, 129.7, 129.9, 130.2, 131.6, 140.7,

141.3, 142.8, 143.5, 150.7, and 156.3 (18$C_{olefinic}$ and C_{arom}), 166.8 (C=O); MS (*m/z*, %): 330 (M^+, 34), 271 (100), 217 (35), 190 (14), 89 (13), 43 (28); Anal. Calcd. for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.80; H, 4.05; N, 8.57.

Methyl 3-(5-hydroxy-9-methylbenzo[*a*]phenazin-6-yl)acrylate (**7c**): Yellow powder; yield 0.306 g (89%), mp 146-148 °C; IR (KBr, cm^{-1}): ν_{max} 1706 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.72 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 5.54 (d, 1H, J = 6.6 Hz, CH), 6.03 (dd, 1H, J_1 = 12.0 Hz, J_2 = 8.1 Hz, CH), 7.83-7.96 (m, 3H, Ar-H), 8.13-8.30 (m, 3H, Ar-H), 9.20-9.23 (m, 1H, Ar-H), 11.53 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.5 (CH_3), 52.0 (OCH_3), 105.5, 108.5, 122.2, 125.3, 127.2, 128.1, 128.9, 129.1, 129.6, 129.7, 129.9, 131.6, 132.9, 140.1, 141.4, 142.8, 150.6 and 156.1 (18$C_{olefinic}$ and C_{arom}), 166.4 (C=O); MS (*m/z*, %): 344 (M^+, 45), 271 (64), 217 (23), 149 (46), 105 (15), 57 (100); Anal. Calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.48; H, 4.83; N, 8.06.

Methyl 3-(5-hydroxy-10-nitrobenzo[*a*]phenazin-6-yl)acrylate (**7e**): Brown powder; yield 0.319 g (85%), mp 265-267 °C; IR (KBr, cm^{-1}): ν_{max} 1710 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 5.59 (d, 1H, J = 6.6 Hz, CH), 6.13 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.4 Hz, CH), 7.82-7.93 (m, 2H, Ar-H), 8.23-8.38 (m, 3H, Ar-H), 8.69-8.75 (m, 1H, Ar-H), 9.05 (d, 1H, J = 5.1 Hz, Ar-H), 11.84 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.9 (OCH_3), 103.2, 106.1, 121.2, 122.8, 125.4, 127.5, 129.5, 129.8, 130.1, 130.5, 130.6, 131.3, 131.5, 140.7, 141.6, 145.7, 147.1 and 155.9 (18$C_{olefinic}$ and C_{arom}), 166.1 (C=O); MS (*m/z*, %): 375 (M^+, 24), 291 (100), 245 (42), 182 (23), 83 (22), 43 (44); Anal. Calcd. for $C_{20}H_{13}N_3O_5$: C, 64.00; H, 3.49; N, 11.20. Found: C, 64.08; H, 3.57; N, 11.23.

Acknowledgment

We gratefully acknowledge financial support from the Research Council of the Islamic Azad University of Yazd and University of Sistan and Baluchestan.

References

[1] J. Yu, F. Shi, L.Z. Gong, Brønsted-acid-catalyzed asymmetric multicomponent reactions for the facile synthesis of highly enantioenriched structurally diverse nitrogenous heterocycles, Acc. Chem. Res. 44 (2011) 1156-1171.
[2] M.S. Singh, G.C. Nandi, T. Chanda, β-Oxodithioesters: a new frontier for diverse heterocyclic architectures, RSC Adv. 3 (2013) 14183-14198.
[3] Z. Xu, M. Ayaz, A. A. Cappelli, C. Hulme, General one-pot, two-step protocol accessing a range of novel polycyclic heterocycles with high skeletal diversity, ACS Comb. Sci. 14 (2012) 460-464.
[4] B. Jiang, S.J. Tu, P. Kaur, W. Wever, G. Li, Four-component domino reaction leading to multifunctionalized quinazolines, J. Am. Chem. Soc. 131 (2009) 11660-11661.
[5] J.M. Knapp, J.S. Zhu, D.J. Tantillo, M.J. Kurth, Multicomponent assembly of highly substituted indoles by dual palladium‐catalyzed coupling reactions, Angew. Chem. Int. Ed. 51 (2012) 10588-10591.
[6] M. Li, H. Cao, Y. Wang, X.L. Lv, L.R. Wen, One-pot multicomponent cascade reaction of N, S-ketene acetal: Solvent-free synthesis of imidazo[1,2-a]thiochromeno[3,2-e]pyridines, Org. Lett. 14 (2012) 3470-3473.
[7] J.M. Khurana, A. Chaudhary, A. Lumb, B. Nand, An expedient four-component domino protocol for the synthesis of novel benzo [a] phenazine annulated heterocycles and their photophysical studies, Green Chem. 14 (2012) 2321-2327.
[8] J. McNulty, P. Das, Highly stereoselective and general synthesis of (E)-stilbenes and alkenes by means of an aqueous Wittig reaction, Eur. J. Org. Chem. (2009) 4031-4035.
[9] J. McNulty, P. Das, D. McLeod, Microwave-assisted, aqueous wittig reactions: organic‐solvent‐and protecting-group-free chemoselective synthesis of functionalized alkenes, Chem.–Eur. J. 16 (2010) 6756-6760.
[10] S. Narayan, J. Muldoon, M.G. Finn, et al., On water": Unique reactivity of organic compounds in aqueous suspension, Angew. Chem. Int. Ed. 44 (2005) 3275-3279.
[11] M. B. Smith, J. March, March's advanced organic chemistry: reactions, mechanisms, and structure, John Wiley & Sons (2007).
[12] R. Breslow, In Organic Reactions in Water; Lindstrom, M., Ed.; Blackwell: Oxford (2007) pp: 1-28.
[13] D. C. Rideout, R. Breslow, Hydrophobic acceleration of Diels-Alder reactions, J. Am. Chem. Soc. 102 (1980) 7816-7817.
[14] R. Breslow, Hydrophobic effects on simple organic reactions in water, Acc. Chem. Res. 24 (1991) 159-164.
[15] A. Dö◌mling, I. Ugi, Multicomponent reactions with isocyanides, Angew. Chem. Int. Ed. 39 (2000) 3168-3210.
[16] A. Dö◌mling, Recent developments in isocyanide based multicomponent reactions in applied chemistry, Chem. Rev. 106 (2006) 17-89.
[17] N.V. de Witte, A.O. Stoppani, M. Dubin, 2-Phenyl-β-lapachone can affect mitochondrial function by redox cycling mediated oxidation, Arch. Biochem. Biophys. 432 (2004) 129-135.
[18] L.M. Lopez, A. Pellegrino de Iraldi, P.H. Carrizo, M. Dubin, A.O.M. Stoppani, Effect of the lipophilic o-naphthoquinone CG 10-248 on rat liver mitochondria structure and function, Biocell 26 (2002) 237-245.
[19] S.B. Ferreira, K. Salomão, F.C. da Silva, et al., Synthesis and anti-Trypanosoma cruzi activity of β-lapachone analogues, Eur. J. Med. Chem. 46 (2011) 3071-3077.
[20] J. Bloxham, C.P. Dell, C. Smith, Preparation of some new benzylidenemalononitriles by an SNAr reaction: application to naphtho [1, 2-b] pyran synthesis, Heterocycles 38 (1994) 399-408.

[21] M.E. Makgatho, R. Anderson, J.F. O'Sullivan, et al., Tetramethylpiperidine-substituted phenazines as novel anti-plasmodial agents, Drug. Develop. Res. 50 (2000) 195-202.
[22] V.F. de Andrade-Neto, M.O. Goulart, J.F. da Silva Filho, et al., Antimalarial activity of phenazines from lapachol, β-lapachone and its derivatives against Plasmodium falciparum in vitro and Plasmodium berghei in vivo, Bioorg. Med. Chem. Lett. 14 (2004) 1145-1149.
[23] C. Neves-Pinto, V. Malta, M. Pinto, et al., A trypanocidal phenazine derived from β-lapachone, J. Med. Chem. 45 (2002) 2112-2115.
[24] D.K. Cartwright, W.S. Chilton, D.M. Benson, Pyrrolnitrin and phenazine production by Pseudomonas cepacia, strain 5.5 B, a biocontrol agent of Rhizoctonia solani, Appl. Microbiol. Biotechnol. 43 (1995) 211-216.
[25] J.M. Ligon, D.S. Hill, P.E. Hammer, et al., Natural products with antifungal activity from Pseudomonas biocontrol bacteria, Pest. Manag. Sci. 56 (2000) 688-695.
[26] M. Muller, T.C. Sorrell, Inhibition of the human platelet cyclooxygenase response by the naturally occurring phenazine derivative, 1-hydroxyphenazine, Prostaglandins 50 (1995) 301-311.
[27] G.W. Rewcastle, W.A. Denny, B.C. Baguley, Potential antitumor agents. 51. Synthesis and antitumor activity of substituted phenazine-1-carboxamides, J. Med. Chem. 30 (1987) 843-851.
[28] H.J. Lee, J.S. Kim, S.Y. Park, et al., Synthesis and cytotoxicity evaluation of 6, 11-dihydro-pyridazo-and 6, 11-dihydro-pyrido[2,3-b]phenazine-6,11-diones, Bioorg. Med. Chem. 12 (2004) 1623-1628.
[29] J.S. Kim, H.K. Rhee, H.J. Park, et al., Synthesis of 6-chloroisoquinoline-5, 8-diones and pyrido[3,4-b]phenazine-5,12-diones and evaluation of their cytotoxicity and DNA topoisomerase II inhibitory activity, Bioorg. Med. Chem. 15 (2007) 451-457.
[30] M.T. Maghsoodlou, S.M. Habibi-Khorassani, A. Moradi, et al., One-pot three-component synthesis of functionalized spirolactones by means of reaction between aromatic ketones, dimethyl acetylenedicarboxylate, and N-heterocycles, Tetrahedron 67 (2011) 8492-8495.
[31] P. Dastoorani, M.T. Maghsoodlou, M.A. Khalilzadeh, E. Sarina, Synthesis of new dibenzofuran derivatives via Diels–Alder reaction of euparin with activated acetylenic esters, Tetrahedron Lett. 57 (2016) 314-316.
[32] M.T. Maghsoodlou, S.M.H. Khorassani, R. Heydari, et al., Highly stereoselective construction of functionalized cyclopropanes from the reaction between acetylenic esters and C–H acids in the presence of triphenylarsine, Tetrahedron Lett. 50 (2009) 4439-4442.
[33] F. Rostami Charati, M.T. Maghsoodlou, S.M. Habibi-Khorassani, M. Makha, Green diastereoselective synthesis of highly functionalised trifluoromethylated γ-lactone phosphonate esters bearing a thioester or ketothiophene, Tetrahedron Lett. 49 (2008) 343-347.
[34] R. Doostmohammadi, M.T. Maghsoodlou, N. Hazeri, S.M. Habibi-Khorassani, Acetic acid as an efficient catalyst for the one-pot preparation of 3,4,5-substituted furan-2(5H)-ones, Res. Chem. Intermed. 39 (2013) 4061-4066.
[35] R. Doostmohammadi, M.T. Maghsoodlou, N. Hazeri, S.M. Habibi-Khorassani, An efficient one-pot multi-component synthesis of 3, 4, 5-substituted furan-2 (5H)-ones catalyzed by tetra-n-butylammonium bisulphate, Chin. Chem. Lett. 24 (2013) 901-903.
[36] S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri, A simple and efficient approach to one-pot synthesis of mono-and bis-N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates catalyzed by $InCl_3$, Chin. Chem. Lett. 25 (2014) 58-60.
[37] B. Bita, 1,4-Diazabicyclo[2.2.2]octane (DABCO) as a useful catalyst in organic synthesis, Eur. J. Chem. 1 (2010) 54-60.

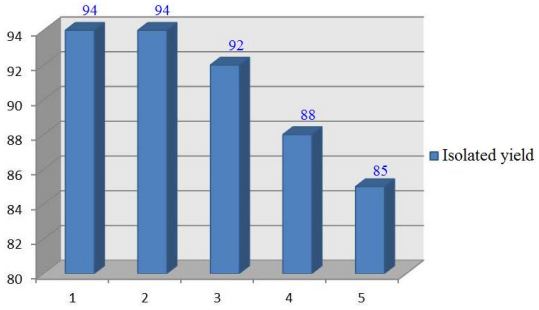
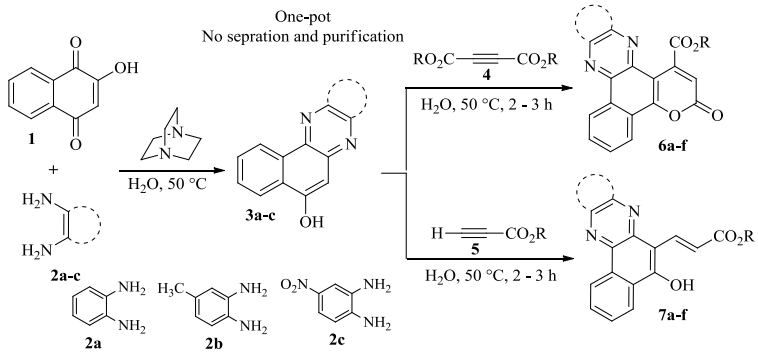
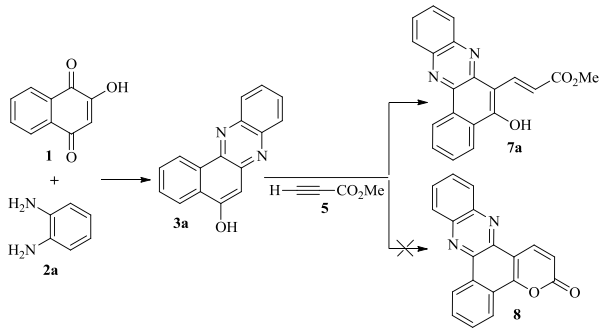


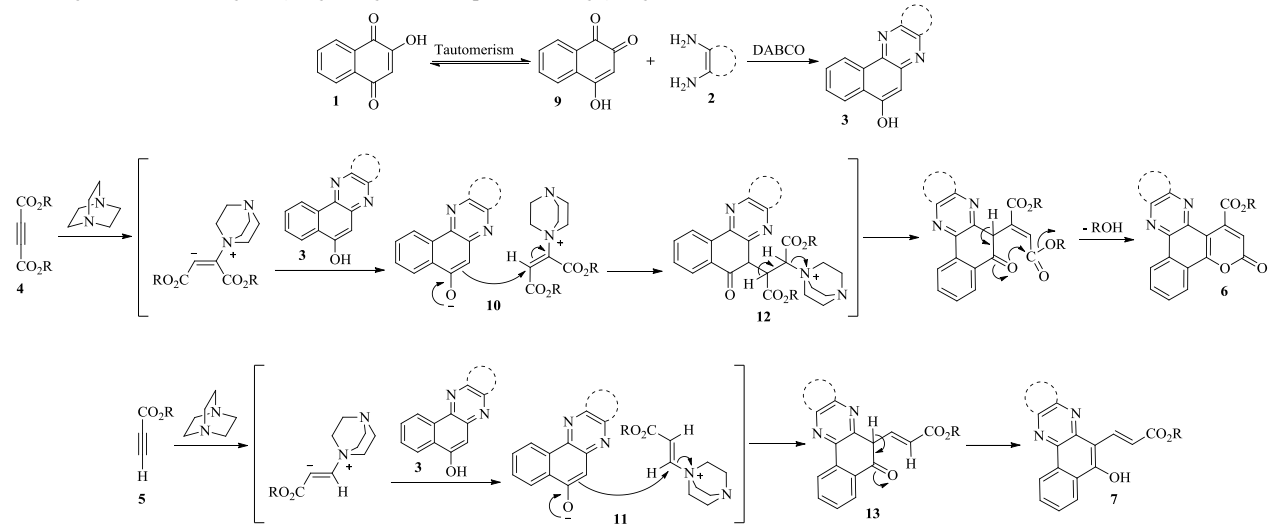
Fig. 1. The reusability of the catalyst (20 mol%) in the synthesis of **6a** in water at 50 °C (2 h).



Scheme 1. One-pot, three-component domino synthesis of novel 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives in the presence of DABCO as catalyst.

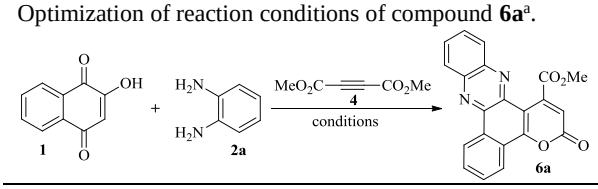


Scheme 2. Synthesis of methyl 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate.



Scheme 3. Plausible mechanism based on nucleophilicity of DABCO for the synthesis of 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate and 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives.

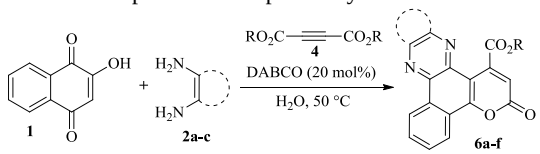
Table 1
Optimization of reaction conditions of compound **6a**[a].



Entry	Cat (mol%)	Reaction conditions	Time (h)	Yield[b] (%)
1	No catalyst	EtOH, Reflux	4	NR
2	Et_3N (20)	EtOH, Reflux	1.5	81
3	Pyridine (20)	EtOH, Reflux	2	72
4	Isoquinoline (20)	EtOH, Reflux	3	55
5	Ph_3P (20)	EtOH, Reflux	3	70
6	DBU (20)	EtOH, Reflux	3	63
7	DABCO (20)	EtOH, Reflux	1.5	87
8	DABCO (20)	H_2O, Reflux	1.5	95
9	DABCO (30)	H_2O, Reflux	1.5	94
10	DABCO (10)	H_2O, Reflux	1.5	82
11	DABCO (20)	H_2O, 70 °C	1.5	91
12	DABCO (20)	H_2O, 50 °C	2	94
13	DABCO (20)	H_2O, r.t.	4	Trace

[a] Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), DMAD (1 mmol) and various catalysts in solvent (10 mL) at different temperatures.
[b] Isolated yields.

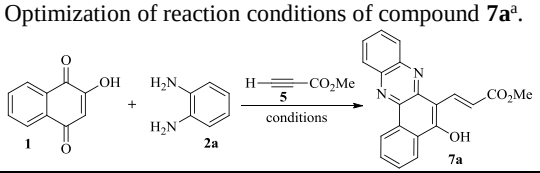
Table 2
Domino one-pot three-component synthesis of 3-oxo-3*H*-benzo[*a*]pyrano[2,3-*c*]phenazine-1-carboxylate derivatives.[a]



Entry	Diamine	R	Product	Time (h)	Yield (%)[b]
1	**2a**	Me	**6a**	2	94
2	**2a**	Et	**6b**	2	92
3	**2b**	Me	**6c**	3	92
4	**2b**	Et	**6d**	3	91
5	**2c**	Me	**6e**	3	88
6	**2c**	Et	**6f**	3	85

[a] Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), dialkyl acetylenedicarboxylate (1 mmol) and DABCO (20 mol %) in H_2O (10 mL) at 50 °C.
[b] Isolated yields.

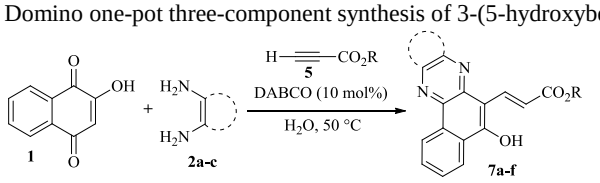
Table 3
Optimization of reaction conditions of compound **7a**[a].



Entry	Cat (mol%)	Reaction conditions	Time (h)	Yield (%)[b]
1	No catalyst	H_2O, Reflux	4	NR
2	Et_3N (20)	H_2O, Reflux	2	74
3	Pyridine (20)	H_2O, Reflux	2	78
4	Ph_3P (20)	H_2O, Reflux	2	63
5	DABCO (20)	H_2O, Reflux	2	92
6	DABCO (30)	H_2O, Reflux	2	90
7	DABCO (10)	H_2O, Reflux	2	92
8	DABCO (5)	H_2O, Reflux	2	77
9	DABCO (10)	H_2O, 70 °C	1.5	89
10	DABCO (10)	H_2O, 50 °C	2	92
11	DABCO (10)	H_2O, rt	4	Trace

[a] Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), methyl propiolate (1 mmol) and various catalysts in H_2O (10 mL) at different temperatures.
[b] Isolated yields.

Table 4
Domino one-pot three-component synthesis of 3-(5-hydroxybenzo[*a*]phenazin-6-yl)acrylate derivatives[a].



Entry	Diamine	R	Product	Time (h)	Yield[b] (%)
1	**2a**	Me	**7a**	2	92
2	**2a**	Et	**7b**	2	92
3	**2b**	Me	**7c**	3	89
4	**2b**	Et	**7d**	3	85
5	**2c**	Me	**7e**	3	85
6	**2c**	Et	**7f**	3	81

[a] Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), alkyl propiolate (1 mmol) and DABCO (10 mol %) in H_2O (10 mL) at 50 °C.
[b] Isolated yields.