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SIMPLE AND EFFICIENT ROUT FOR SYNTHESIS OF NEW 9-(PHENYL IMINO HYDRAZINE)-ACENAPHTHO [1,2-e]-1,2,4- TRIAZIN DERIVATIVES

Somayeh ADIBI SEDEH,[a,b] Mohammad Kazem MOHAMMADI,[b,*]
Masood FEREIDOONNEZHAD [c,d] and Ali JAVID[e]

[a] Department of Chemistry, Khouzestan Science and Research Branch, Islamic Azad University, Ahvaz, Iran.
E-mail: adibis28@yahoo.com
[b] Department of Chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran
[c]Toxicology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[d]Department of Medicinal Chemistry, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[e] Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran

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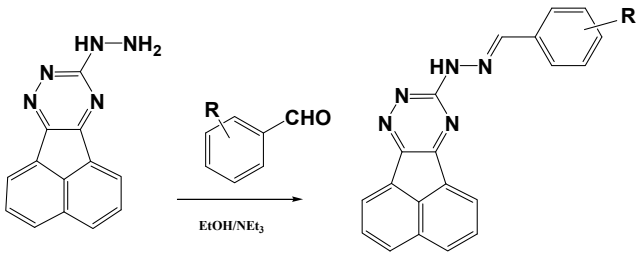
We present the convenient syntheses of seven new phenyl hydrazin derivatives **8 (a-h)**. For this purpose, acenaphtho [1,2-e]-1,2,4-triazine-9(8H)-thione **(3)** prepared, starting from acenaphthylene-1, 2-dione **(1)** and thiosemicabazide in good yield. The reaction of **(3)** with benzyl chloride resulted to synthesis of 9-(benzylthio)-acenaphtho[1,2-e]-1,2,4-triazines **(5)** that reacted with hydrazine to synthesis of 9-(hydrazino)-acenaphtho [1, 2-e]-1, 2, 4-triazines **(6)**. This compound reacted with different aromatic aldehyde derivatives **(7 a-h)** that resulted to synthesis of final product, 9-(phenyl imino hydrazine)-acenaphtho [1, 2-e]-1, 2, 4-triazine derivatives **(8 a-h)** in good yield.



INTRODUCTION

Considerable attention in the field of synthesis of organic compound has been focused on synthesis of new structures, which exhibit biological activities.[1] Among wide variety of synthetic organic molecules, those having biologically effects, structures such as fused poly cyclic structures have been concerned due to their very different chemical and biological properties.[2]

Synthesis of biologically activated compounds has been a major concern in modern organic chemistry.[3] In this regard, development of novel compounds and especially diverse small molecule scaffolds caused higher attention of medicinal and biological chemists.[4-7] This can be attributed to the growing requirement in assembling libraries of structurally complex substances to be evaluated as hit/lead compounds in drug discovery projects.

Polycyclic aromatic hydrocarbon (PAH) are highly important structural units in a variety of pharmacologically active substances.[8-10] In other hand, these structures have a very different effects like the photochromic properties that can make them a good candidate for synthesis of new molecules with different chemical properties.[11]

At first glance, rigid polycyclic structures seem to have role in the development of antitumor agents owing to their ability in insertion between stacked base pairs of oligonucleotides and action as intercalator.[12,13] Particularly important is that when these planar polycyclic heterocycles bear appropriate side chains, further interactions with other important macromolecules might be envisaged.[14,15]

* Corresponding authors: mkmohamadi@gmail.com

In this view, privileged heterocyclic structures have been constructed around the acenaphthene core.[16] Some of the acenaphthene derivatives containing thiazole backbone have been reported as antitumor agents.[17]

Various reactions of acenaphthaquinone with nucleophiles, organic and inorganic reagents have been reviewed elsewhere. [18] In the continuous of our program to develop the chemistry of potentially bioactive heterocyclic compounds and in connection with our ongoing interests in this field, [19-21] we represent here a facile procedure for the synthesis of 9-(phenyl imino hydrazin)-acenaphtho[1,2-e]-1,2,4-triazine derivatives via four step condensation of thiosemicarbazide and acenaphtylene -9,10 Quinone to form acenaphtho[1,2-e]-1,2,4-triazine-9(8H)-thiones and subsequent reaction with benzyl chloride derivatives. Prepared compound was subjected to other reaction with hydrazine and then with different benzaldehyde derivatives for achieving the final products. The products of step 1 and 2 (3 and 5) were synthesized by our research team in 2014. [22]

RESULTS AND DISSCUSSION

The results of optimization experiments for the four step condensation involving acenaphtylene-9,10 Quinone, thio semicarbazid, hydrazin and benzyl halide derivatives are presented in Table 1.

Table 1

Synthesis of 9-(phenyl imino hydrazin)-acenaphtho[1,2-e]-1,2,4-triazine derivatives (8 a-h)

Entry	Ar	Product	Yield (%)	m.p. (°C)
1	2-Chloro-C_6H_5	**8a**	84	202-204
2	4-Chloro-C_6H_4	**8b**	80	221-223
3	3-NO_2-C_6H_4	**8c**	82	200-202
4	3-Fluoro-C_6H_4	**8d**	77	207-209
5	4-Fluoro-C_6H_4	**8e**	80	258-261
6	3-Bromo-C_6H_4	**8f**	75	203-205
7	4-Bromo-C_6H_4	**8g**	78	204-206
8	4-Me-C_6H_4	**8h**	79	207-208

It is remarkable to note that the condensation, proceeded no need to any catalyst or hard reaction conditions like a reflux heating. We examined the proceed of the reaction with different benzyl halid derivatives and find that the reaction time and yield of the reaction with electron withdrawing groups are improved. The schematic of the overall reaction is given here (Fig. 1):

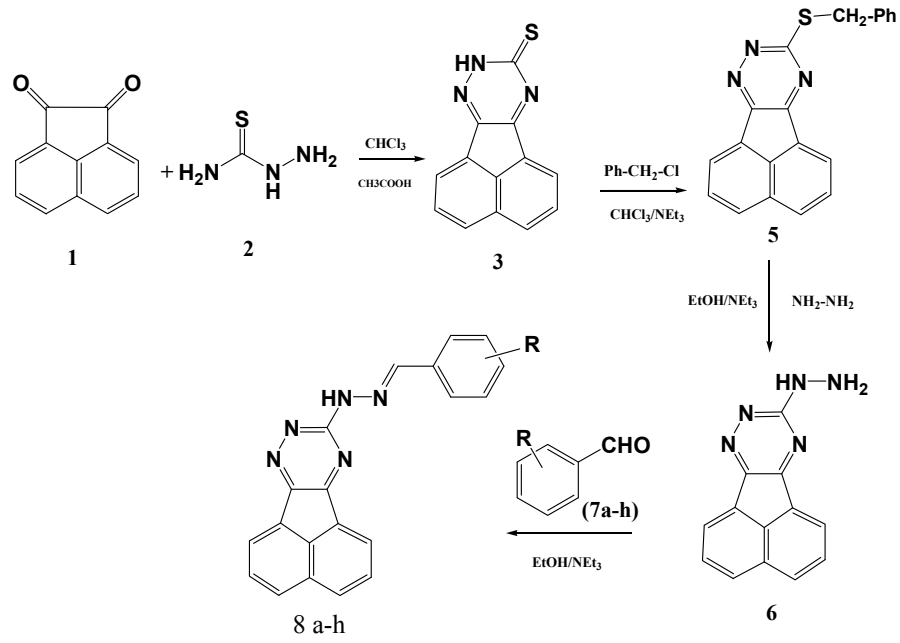
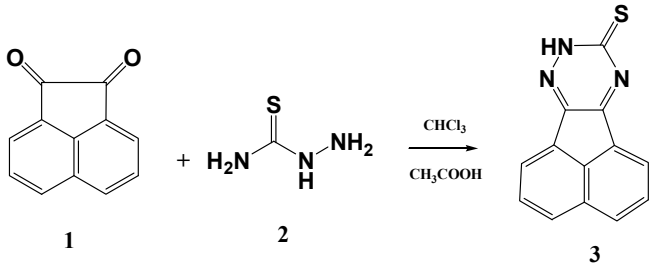


Fig. 1 – Schematic of the overall reaction.

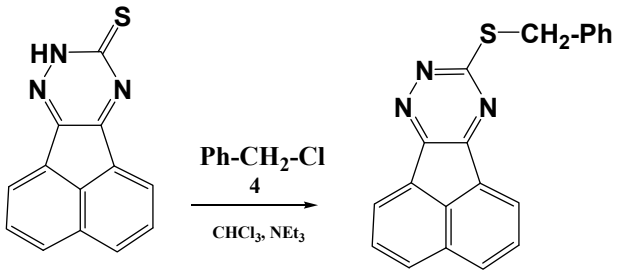
The procedure that we developed for the synthesis of 8 a-b is outlined in Scheme 1. First, using a below procedure, the synthesis of 5 acenaphtho[1,2-e]-1,2,4-triazine-9(8H)-thione (3) (Fig. 2) and then 9-(benzylthio)-acenaphtho[1,2-e]-1,2,4-triazines (5) were achieved (Fig. 3).

Thio semicarbazid (5 mmol), the acenaphtylene-9,10 Quinone (5 mmol) and acetic acid (small amount) were mixed in chloroform (20 mL) at reflux condition. After the purification of its product with recrystallization in ethanol and then adding a benzyl chloride and then hydrazine and finally, different derivatives of benzyl chlorides (all intermediate products, simply purified in ethanol in high yield) to achieved the target molecules (8a-h) that summarized in Table 1, Figs. 4, 5).



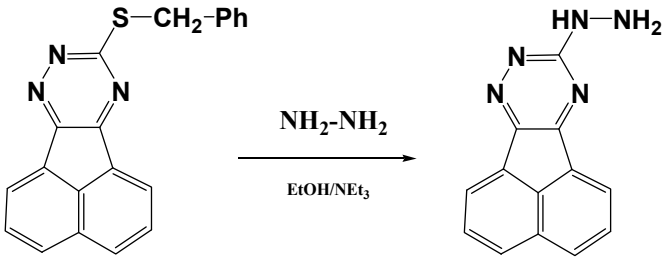
1 2 3

Fig. 2 – Synthesis of acenaphtho[1,2-e]-1,2,4-triazine-9(8H)-thione.



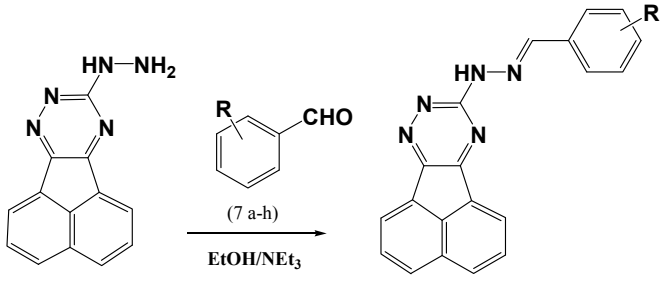
3 5

Fig. 3 – Synthesis of 9-(benzylthio)-acenaphtho[1,2-e]-1,2,4-triazines.



5 6

Fig. 4 – Synthesis of 9-(hydrazino)-acenaphtho[1,2-e]-1,2,4-triazines.



6 8 (a-h)

Fig. 5 – Synthesis of 9-(phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives.

All prepared compound was characterized using Ft-IR, ^{1}H NMR, ^{13}C NMR and elemental analyses (8a-h) (Table 1). In the ^{1}H NMR spectroscopy, we noticed that the chemical shift of the key hydrogen (NH=N-) be seen in δ 4.5-5.5 because of its connection to conjugated system. The simplicity of the reaction was more emphasized when the work-up of all the products carried out with simple crystallization and no need to other methods or technique, for purification of products.

EXPERIMENTAL

Material and methods

All of the reagents were purchased from commercial sources and were freshly used after being purified by standard procedures. Melting points were determined on the Electro-thermal Melting Point apparatus and were uncorrected. Infrared spectra were recorded on the Shimadzu-420 infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d6 on Brucker 300 MHz spectrometer (Chemical shifts are given in parts per million or ppm). Elemental analyses (C, H, N) were performed by the Micro analytical Unit.

General procedure for preparation of acenaphtho[1,2-e]-1,2,4-triazine-9(8H)-thione (3)

To the acenaphtylene-9,10 Quinone compound (1) (5 mmol) and thio semicarbazide (2) (5 mmol), chloroform (30 ml) and small amount of acetic acid as a catalyst was added while heating and stirring in reflux condenser. The progress of the reaction was monitored with TLC and at the completion of the reaction, the yellow precipitate was formed which was filtered and washed with the mixture of H_2O / EtOH and recrystallized in ethanol and completely dried in oven (100°C) for synthesis of pure product (3) (Scheme 2).

Acenaphtho[1,2-e]-1,2,4-triazine-9(8H)-thione **(3)**
Yield 88%, . ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.81 (d, 2H, *J* = 7.5Hz, CH aromatic), 7.65 (dd, 2H, *J* = 7 Hz, CH aromatic), 7.46 (d, 2H, *J* = 8Hz , CH aromatic), 3.21 (s, 1H, SH); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 163, 150, 131, 128, 126, 124, 123; IR (KBr, cm^{-1}): 3245, 3151, 2922, 1689, 1607, 777. m.p. 182°C -184°C. Anal. Calcd for $C_{13}H_7N_3S$: C, 65.80; H, 2.97; N, 17.71. Found: C, 65.62; H, 2.98; N, 17.58.

General procedure for preparation of 9-(benzylthio)-acenaphtho[1,2-e]-1,2,4-triazines (5)

To the formed product in previous section (3) (1 mmol), chloroform (10 ml) and tri ethylamine (3 mmol) was added. The solution was stirred and then the benzyl chloride (4) was added, heated and stirred in reflux condenser. After completion of the reactions, the precipitated residue was filtered, recrystallized in ethanol, filtered, washed with water (2×5 ml) and then completely dried in electrical oven (Scheme 2). Prepared compound (5) was characterized using Ft-IR, ^{1}H NMR, ^{13}C NMR and elemental analyses (Scheme 3).

9-(benzylthio)-acenaphtho[1,2-e]-1,2,4-triazine **(5)**
Yield 87%. ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.78 (d, 2H, *J* = 7.6Hz,), 7.61 (dd, 2H, *J* = 7.4 Hz), 7.46 (d, 2H, *J* = 8.5Hz), 7.05-7.19 (m, 5H), 3.26 (s, 2H); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 170.9, 139.7, 142.4, 138.9, 133.5, 128.5, 128.3, 128, 127.8, 127.7, 127.3, 127.2, 126.6, 124.5, 42.2; IR (KBr, cm^{-1}): 3153, 3050, 1694, 1606. m.p. 184°C -186 °C. Anal. Calcd for $C_{20}H_{13}N_3S$: C, 73.37; H, 4.00; N, 12.83. Found: C, 73.62; H, 3.88; N, 12.58.

General procedure for preparation of 9-(hydrazino)-acenaphtho[1,2-e]-1,2,4-triazines (6)

To the formed product in previous section (5) (1 mmol), ethanol (10 ml) and triethylamine (3 mmol) was added. The solution was stirred and then the hydrazine was added, heated and stirred in reflux condenser. After completion of the reactions, the precipitated residue was filtered, recrystallized in ethanol, filtered, washed with water (2×5 ml) and then completely dried in electrical oven (Scheme 3). Prepared compound (6) was characterized using Ft-IR, ^{1}H NMR, ^{13}C NMR and elemental analyses.

9-(hydrazino)-acenaphtho [1, 2-e]-1, 2, 4-triazines (**6**)
Yield 94% . ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.78 (d, 2H, *J* = 7.8 Hz), 7.61 (dd, 2H, *J* = 7.2 Hz), 7.46 (d, 2H, *J* = 8.5Hz) ;4.12 (m, 1H), 2.34 (t, 2H , NH_2) ; ^{13}C-NMR (300 MHz, DMSO-d6) δ: 161.4, 138.2, 142.0, 138.1, 132.8, 129.2, 128.8, 128, 127.8, 127.1, 126.1; IR (KBr, cm^{-1}): 3325, 3287, 3153, 3050, 1694, 1606. m.p. 180°C -181°C .Anal. Calcd for $C_{13}H_9N_5$: C, 66.37; H, 3.86; N, 29.77. Found: C, 66.78; H, 3.15; N, 30.02.

General procedure for preparation of 9-(phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (8 a-h)

To the formed product in previous section (6) (1 mmol), ethanol (10 ml) and triethylamine (3 mmol) was added. The solution was stirred and then the 2-chloro benzaldehyde (7 a) (1 mmol) was added, heated and stirred in reflux condenser. After completion of the reactions, the precipitated residue was filtered, recrystallized in ethanol, filtered, washed with water (2×5 ml) and then completely dried in electrical oven (Scheme 4). For other benzaldehyde derivatives, this procedures were performed. All prepared compound was characterized using Ft-IR, ^{1}H NMR, ^{13}C NMR and elemental analyses (8a-h) (Scheme 5, Table 1).

(2-chloro phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8a**)
Yield 84%.^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.78 (d, 2H, *J* = 7.5 Hz), 7.61 (dd, 2H, *J* = 7.3 Hz), 7.46 (d, 2H, *J* = 8.5 Hz), 7.05-7.19 (m, 4H), 5.11 (s, 1H, N-H), 4.27 (s, 1H, =C-H); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 170.9, 139.7, 142.4, 138.9, 133.5, 128.5, 128.3, 128, 127.8, 127.7, 127.3, 127.2, 126.6, 124.5; IR (KBr, cm^{-1}): 3153, 3050, 1694, 1606;. m.p. 202 °C -204 °C. Anal. Calcd for $C_{20}H_{12}ClN_5$: C, 67.14; H, 3.28; N, 19.57. Found: C, 67.35; H, 3.42; N, 19.24.

(4-chloro phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8b**)
Yield 90 %. ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.72 (d, 2H, *J* = 7.4 Hz), 7.67 (dd, 2H, *J* = 7.2 Hz), 7.46 (d, 2H, *J* = 8.5Hz), 7.05-7.19 (m, 5H), 4.85 (s, 1H, N-H), 4.32 (s, 1H, =C-H); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 172.3, 138.4, 141.8, 138.5, 134.2, 130.2, 129.5, 129.3, 128.4, 127.7, 127.3, 127.1, 126.5, 125.5;IR (KBr, cm^{-1}): 3150, 3064, 1688, 1630. m.p. 221°C -223 °C (dec). Anal. Calcd for $C_{20}H_{12}ClN_5$: C, 67.14; H, 3.38; N, 19.57. Found: C, 67.29; H, 3.44; N, 19.39.

(3-nitro phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8c**)
Yield 82 % . ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.65 (d, 2H, *J* = 7.6 Hz), 7.37 (dd, 2H, *J* = 7.6 Hz), 7.22 (d, 2H, *J* = 8.5Hz), 7.0-7.35 (m, 4H), 4.94 (s, 1H,N-H) , 4.11 (s, 1H, =C-H); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 171.4, 143.34, 142.7, 138.7, 135.3, 133.5, 132.3, 130, 19.2, 128.1, 127.7, 127.1, 126.3, 125.2; IR (KBr, cm^{-1}): 3150, 3043, 1688, 1623. m.p. 200 °C-202 °C (dec). Anal. Calcd for $C_{20}H_{12}N_6O_2$: C, 65.18; H, 3.22; N, 22.78. Found: C, 65.43; H, 3.45; N, 22.54.

(3-fluoro phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8d**)
Yield 86 %, ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.74 (d, 2H, J = 7.3 Hz), 7.57 (dd, 2H, J = 7.7 Hz), 7.42 (d, 2H, *J* = 7.3 Hz), 7.21-7.35 (m, 4H), 4.85 (s, 1H, N-H), 4.63 (s, 1H, =C-H); IR (KBr, cm^{-1}): 3168, 3064, 1713, 1676; ^{13}C-NMR (300 MHz, DMSO-d6) δ: 171.6, 144.9, 142.5, 138.2, 134.6, 130.3, 129.7, 128.8, 128.4, 127.9, 127.1, 126.5, 126.1, 125.2. m.p. 207°C - 209 °C (dec). Anal. Calcd for $C_{20}H_{12}FN_5$: C, 70.37; H, 3.54, N, 20.52. Found: C, 70.44; H, 3.65, N, 20.68.

(4-fluoro phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8e**)
Yield 80%. ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.72 (d, 2H, *J* = 7.2Hz), 7.55 (dd, 2H, *J* = 7.5 Hz), 7.35 (d, 2H, *J* = 7.8 Hz), 7.11-7.25 (m, 4H), 5.23 (s, 1H, N-H) , 4.26 (s, 1H, =C-H); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 172.3, 145.7, 142.7, 141.7, 139.5, 138.7, 130.4, 129, 128.8, 127.9, 127.2, 127.0, 126.3, 125.7; IR (KBr, cm^{-1}): 3150, 3065, 1694, 1657;.m.p. 258 °C-261 °C (dec). Anal. Calcd for $C_{20}H_{12}FN_5$: C, 70.37; H, 3.54; N, 20.52. Found: C, 70.42; H, 3.67, N, 20.6.

(3-bromo phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8f**)
Yield 85 %.^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.71 (d, 2H, *J* = 7.4 Hz), 7.57 (dd, 2H, *J* = 7.7 Hz), 7.43 (d, 2H, *J* = 7.8 Hz), 7.23-7.45 (m, 4H), 5.13 (s, 1H, N-H), 4.35 (s, 1H, =C-H) ; ^{13}C-NMR (300 MHz, DMSO-d6) δ: 172.3, 138.7, 143.2, 139.1, 133.3, 129.2, 128.9, 128.2, 127.8, 127.1, 127.3, 127.2, 126.6, 124.5; IR (KBr, cm^{-1}): 3144, 3093, 1702, 1632. m.p. 203 °C -205 °C. Anal. Calcd for $C_{20}H_{12}BrN_5$: C, 59.72; H, 3.01; N, 17.41. Found: C, 59.88; H, 3.11; N, 17.53.

(4-bromo phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8g**)
Yield 80 %. ^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.72 (d, 2H, *J* = 7.5 Hz), 7.55 (dd, 2H, *J* = 7.7 Hz), 7.47 (d, 2H, *J* = 8.5Hz), 7.12-7.27 (m, 4H), 4.92 (s, 1H, N-H), 4.56 (s, 1H, =C-H); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 171.9, 139.4, 143.5, 138.1, 133.2, 129.8, 129.1, 128.2, 127.8, 127.1, 126.8, 126.1, 125.4, 124.5; IR (KBr, cm^{-1}): 3167, 3047, 1690, 1621; m.p. 204 °C -206 °C. Anal. Calcd for $C_{20}H_{12}BrN_5$: C, 59.72; H, 3.01; N, 17.41. Found: C, 59.8; H, 3.14; N, 17.55.

(4-methyl phenyl imino hydrazin)-acenaphtho [1,2-e]-1,2,4-triazine derivatives (**8h**)
Yield 83 %.^{1}HNMR (300 MHz, DMSO-d_6) δ: 7.71 (d, 2H, *J* = 7.6Hz), 7.61 (dd, 2H, *J* = 7.2 Hz), 7.46 (d, 2H, *J* = 7.7 Hz), 7.21-7.34 (m, 4H), 5.11 (s, 1H, N-H), 4.43 (s, 1H, =C-H); ^{13}C-NMR (300 MHz, DMSO-d6) δ: 171.8, 142.2, 141.5, 138.9, 133.5, 128.5, 128.3, 128, 127.8, 127.7, 127.3, 127.2, 126.6, 124.5;IR (KBr, cm^{-1}): 3167, 3072, 1685, 1622; m.p. 207°C -208 °C. Anal. Calcd for $C_{21}H_{15}N_5$: C, 74.76; H, 4.48; N, 20.76. Found: C, 74.87; H, 4.57; N, 20.81.

CONCLUSION

In conclusion, we introduce the simple synthesis pathway for the preparation of substituted phenyl imino hydrazin)-acenaphtho[1,2-e]-1,2,4-triazine derivatives through four step condensation reactions that has been started from the reaction of acenaphtylene-9,10 Quinone and thiosemicarbazide and then reaction continued to react with benzyl chloride and then hydrazine and finally with the benzaldehyde derivatives to form the final products: phenyl imino hydrazine)-acenaphtho[1,2-e]-1,2,4-triazine in good yields. Simplicity of operation and easy separation of intermediate and final products are several advantages of this synthesis protocols.

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