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Green Approach to Synthesis of Novel and Broad-Range of 4,10-Dihydro-4-Aryl-3-(Phenylsulfonyl)Pyrano[2,3-B]Carbazol-2-Amine Derivatives

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ABSTRACT

One-pot, three-component condensation reaction between (phenylsulfonyl) acetonitrile, aromatic aldehydes, and 4-hydroxy carbazole for preparation of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl) pyrano[2,3-b]carbazol-2-amine derivatives has been reported. The method involves domino Knoevenagel condensation/Michael addition, and cyclization cascade. The reaction was performed in glycerol, which is a commercially available, inexpensive and non-toxic compound. High purity of the products, very high yields and wide scope of substrates are advantages of this protocol.

Keywords: 4,10-dihydro-4-Aryl-3-(phenylsulfonyl)pyrano[2,3-b]carbazol-2-amine(Phenylsulfonyl)acetonitrile; Glycerol; Green chemistry; Multi-component reactions

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INTRODUCTION

Green chemistry is a novel technique of looking at organic molecules to design drugs for pharmaceutical companies [1]. Green, environmentally benign processes offer several important economic advantages over traditional synthetic protocols, conveying high energy, hazardous, and wasteful processes towards the ‘‘ideal synthesis’’ that more useful for the economy, environment and society [2,3].

The carbazole scaffold is found in a wide range of bioactive natural products and pharmaceuticals. These carbazole-containing molecules show antiviral, antimalarial and antitumor activity. Some of them are currently being used as lead compounds for drug development. Among them, pyranocarbazole analogs can be frequently found as structural core motif in a great number of natural and synthetic compounds exhibiting interesting medicinal and biological activities such as mosquitocidal, antimicrobial, anti-inflammatory, antioxidant, and anticancer activity. Therefore identifying new approaches for the efficient synthesis of different carbazole scaffolds have received considerable attention. Recently, we have developed the synthesis of pyrano [3,2-c] carbazole derivatives as potent inhibitors of tubulin polymerization.

However, most of these methods suffer from such drawbacks as low yields, long reaction times, harsh reaction conditions, tedious work-up procedures, tedious steps for the preparation of catalyst, application of toxic and expensive catalysts, application of hazardous solvents for the work-up and lack of generality. Moreover, in most of the reported methods, catalysts are not recyclable. In this backdrop glycerol has emerged as an attractive solvent. It possesses the benefits of both water and ionic liquids like low toxicity, relatively low vapor pressure, easy availability, reusability, in expensiveness, renewability, high boiling point and ability to dissolve a wide range of organic and inorganic compounds [4-7]. Development of catalyst-free reactions is another area that has attracted

much attention in green chemistry due to the inherent advantages involved in terms of cost and environment [8,9]. Literature survey revealed that there is only one report involving a three-component condensation between aldehydes, (phenylsulfonyl) acetonitrile, and 4-hydroxy carbazole [10]. Indeed, to the best of our knowledge, there are no reports on the diversity-oriented, catalyst-free synthesis of a library of this type of biologically active compound. In continuation of our research on multi-component reactions [11-13], a simple, new, and efficient protocol for the preparation of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl) pyrano[2,3-b]carbazol-2-amine by use (phenylsulfonyl) acetonitrile, aromatic aldehydes, and 4-hydroxy carbazole in glycerol media (Figure 1).

EXPERIMENTAL SECTION

All reagents were purchased from Merck or Aldrich companies and were used without further purification. All yields refer to separated products after purification. The FT-IR spectra were recorded on a FT-IR spectroscopy Perkin Elmer BX-II. 1H NMR and 13C NMR spectra were recorded on Bruker 300 MHz spectrometer in DMSO-d6 with TMS as an internal standard. Mass spectra were recorded using Agilent Technologies Model: 5975C VL MSD with Tripe-Axis Detector; EI mode at 70 eV. The spectral and analytical data for the selected compounds are presented below. Melting points were determined in open capillaries using a BUCHI510 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica-gel Poly Gram SIL G/UV 254 plates.

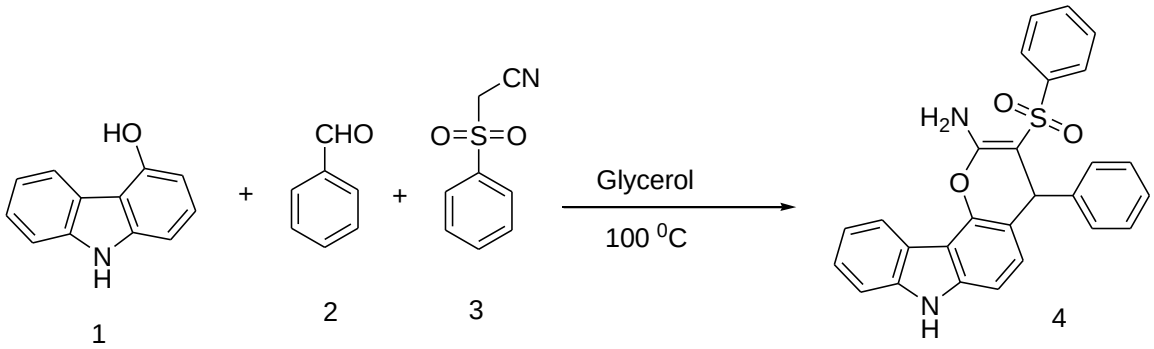


Figure 1: Synthesis 4,10-dihydro-4-Aryl-3-(phenylsulfonyl)-pyrano[2,3-b]carbazol-2-amine derivatives via three component reaction of aromatic aldehydes,(phenylsulfonyl) acetonitrile, and 4-hydroxy crbazole in glycerol media under thermal conditions

General Procedure for the Asymmetric Synthesis of 4,10-Dihydro-4-Aryl-3-(Phenylsulfonyl)Pyrano[2,3-B]Carbazol-2-Amine Derivatives

(Phenylsulfonyl)acetonitrile (1 mmol) was added to a round-bottom flask containing glycerol (5 mL) and benzaldehyde (1 mmol). The mixture was stirred at 80 0C.After formation of the cyano-olefin (verified with TLC), 4-hydroxy carbazole (1 mmol) was added to the reaction mixture, and it was allowed to stir until completion (TLC). Then, for the work-up procedure, warm water was added to the reaction mixture, glycerol dissolved and the insoluble solid crude product was separated by simple filtration. The desired solid product was washed by warm water. Experimental observation showed us that pure isolated product was obtained. The filtrate containing glycerol was extracted with methyl t-butyl ether (30 mL) to remove any organic compounds dissolved in the aqueous phase. The aqueous layer was separated and the water was evaporated under reduced pressure to give pure glycerol which was used for the next run under similar reaction conditions.

RESULTS AND DISCUSSION

At first, to optimize reaction conditions for the synthesis of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl) pyrano[2,3b]-carbazol-2-amine, the pilot reaction was subjected using (phenylsulfonyl) acetonitrile, 4-hydroxy carbazole and benzaldehyde (reaction model). In a model reaction, a mixture of (phenylsulfonyl)acetonitrile (1 mmol) (Figure 2), 4-hydroxy carbazole (1 mmol) and benzaldehyde (1 mmol) was stirred in different amounts of glycerol and also at various temperatures (Tables 1 and 2). To find the best efficiency, we carried out this reaction in different common

solvents such as acetonitrile, DMF, toluene, DMSO, and neat conditions at 90 0C; no product was observed (Table 3). Only a trace amount of products was detected in methanol, ethanol and water (Table 3). In summary, the best results were obtained in glycerin (5 mL) at 80 0C in 100 min, and glycerol shows higher reactivity than other solvents because of multiple hydrogen bonds.

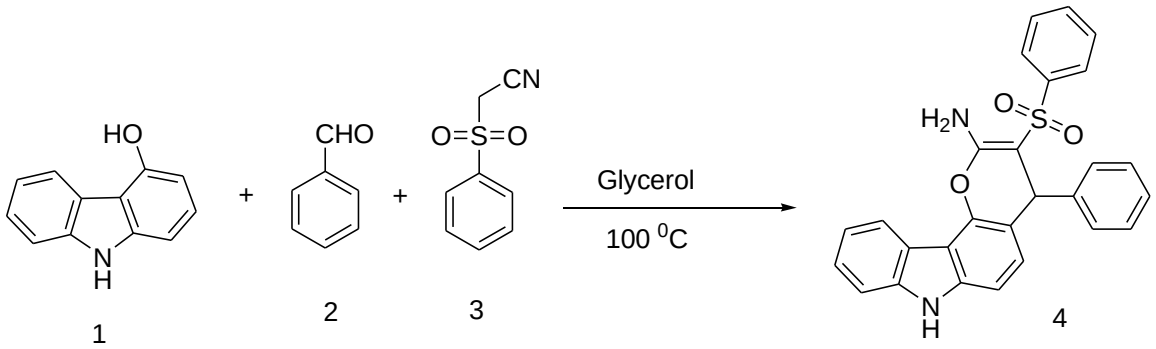


Figure 2: Optimizing of glycerol amounts in the synthesis of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl)pyrano[2,3-b]carbazol-2-amine

Table 1: Synthesis of 4a in different temperatures and yields

Entry	Glycerol (mL)	Time (min)	Yield (%)b
1	5	120	80
2	10	100	82
3	15	100	75
4	20	90	70

The reaction was carried out with 1 (1 mmol), 2 (1 mmol), 3 (1 mmol) in different amounts of glycerolat 100 ^{0}C, Isolated yields.

Table 2: Synthesis of 4a in different temperatures

Entry	Temperature (0C)	Time (min)	Yield (%)b
1	r.t.	120	0
2	70	100	52
3	90	100	80
4	100	90	82

Table 3: The study of effects of different solvents in the synthesis of 4aa

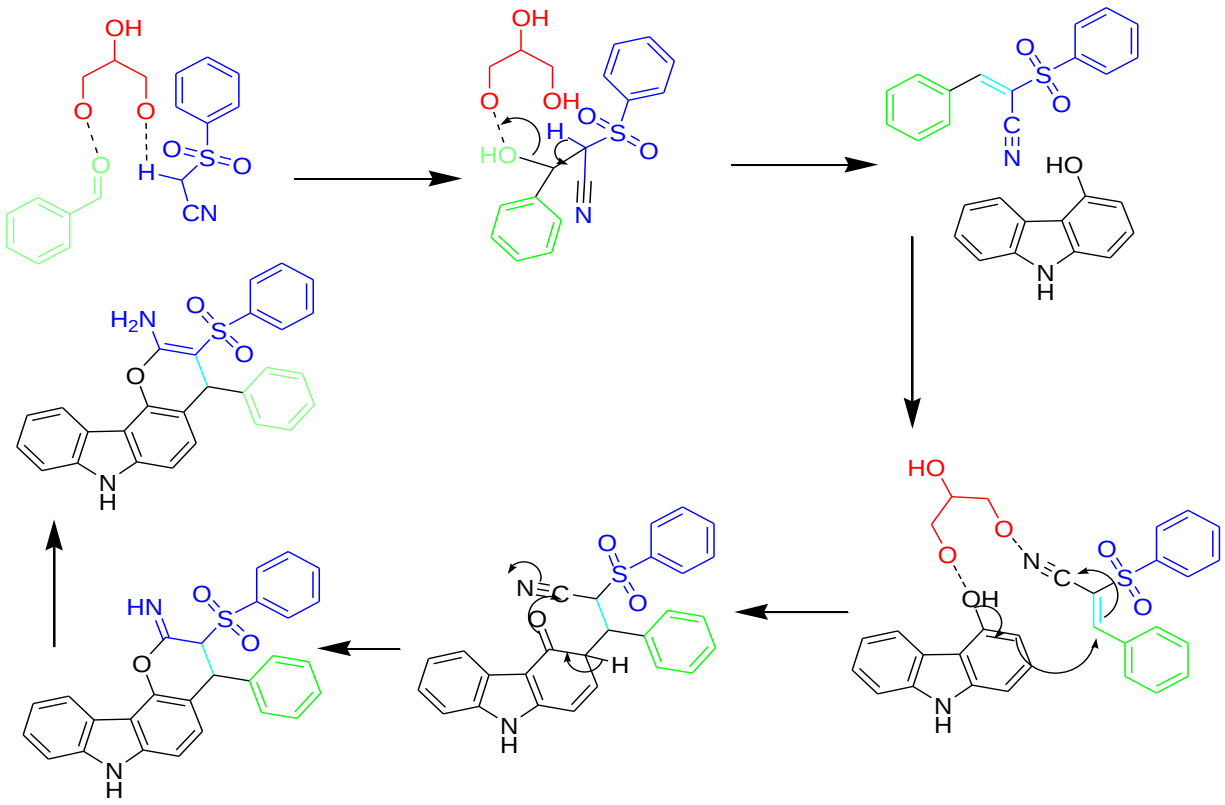
Entry	Solvent (5mL))	Temperature (0C)	Time (hr)	Yield (%)b
1	Acetonitrile	90	12	No reaction
2	DMF	90	12	No reaction
3	Toluene	90	12	No reaction
4	Neat	90	12	No reaction
5	DMSO	90	12	No reaction

6	Ethanol	80	12	Trace
7	Water	90	12	Trace
8	Methanol	70	12	Trace

With these results in hand, three-component condensation of substituted aromatic aldehydes, (phenylsulfonyl)acetonitrile, and 4-hydroxy carbazole was investigated under the optimized reaction conditions for preparation of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl)pyrano[2,3-b]carbazol-2-amine (Figures 3 and 4). The substrate scope of the reaction was then evaluated using a variety of structurally diverse aldehydes. The presences of electron-withdrawing groups relate to electron-donating groups afforded the corresponding products in shorter reaction times with higher yield (Figure 4).

The mechanism proposed for preparation of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl)pyrano [2,3-b]carbazol-2-amine from benzaldehyde, (phenylsulfonyl)acetonitrile and 4-hydroxy carbazole in the presence of glycerol is depicted in Figure 3. According to the literature, glycerol activated staring materials and intermediates by hydrogen bonding characters. Benzylidene (phenylsulfonyl) acetonitrile, containing an electron-poor C=C double bond, is formed quantitatively by Knoevenagel addition of (phenylsulfonyl) -acetonitrile to the aromatic aldehyde in glycerol media.

C-alkylation of 4-hydroxy carbazole occurs by the nucleophilic attack on electron-poor C=C double and gave intermediate (I), which is then cyclized by intramolecular nucleophilic attack of an OH group on the cyano (CN) moiety to give intermediate (II). Subsequent tautomerization produced the 4,10-dihydro-4-Aryl-3-(phenylsulfonyl) pyrano[2,3-b]carbazol-2-amine.



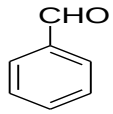
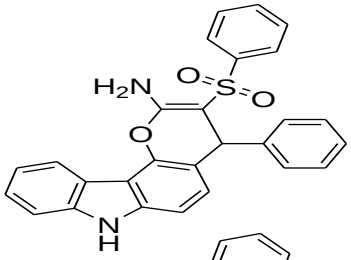
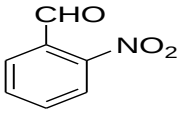
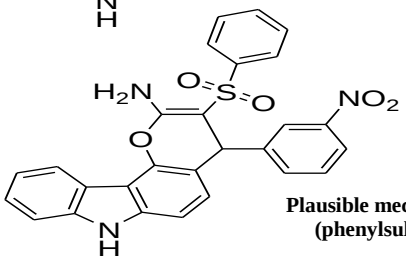
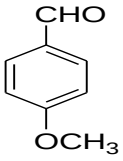
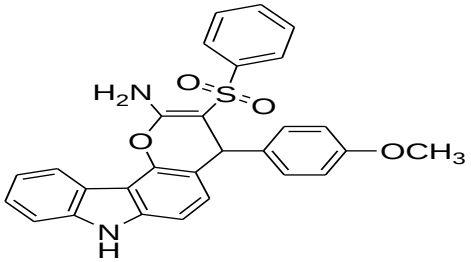
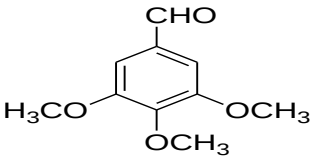
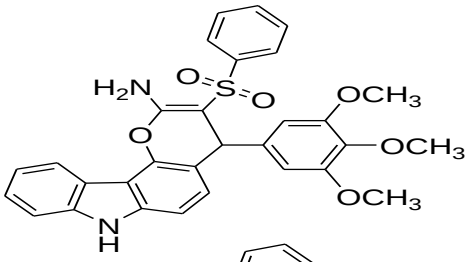
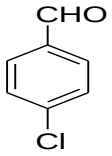
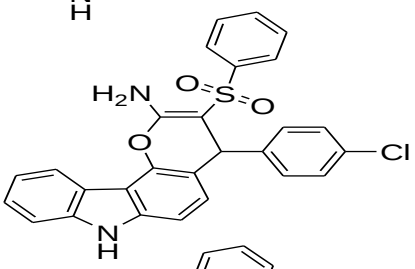
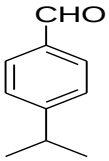
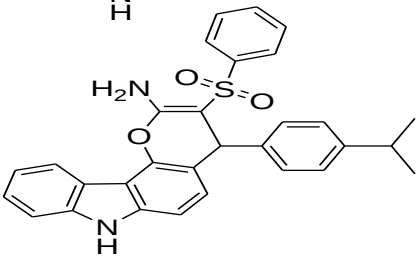
No	Aldehyde	Products	Time (min)	Yield (%) a
4a			100min	80
4b			100min	80
4c			100min	78
4d			100min	78
4e			100min	80
4f			100min	77

Figure 3: 3- **Plausible mechanism for preparation of 4,10-dihydro-4-Aryl-(phenylsulfonyl)pyrano[2,3-b]carbazol-2-amine**

Figure 4: Scope and generality of the synthesis of the 4-(aryl)-3-(phenylsulfonyl)-4H-benzo[h]chromen-2-amine derivatives (4a–4f)

General Procedure for the Asymmetric Synthesis of 4,10-Dihydro-4-Aryl-3-(Phenylsulfonyl)Pyrano[2,3-B]Carbazol-2-Amine

(Phenylsulfonyl)acetonitrile (1 mmol) was added to a round-bottom flask containing glycerol (5 mL) and benzaldehyde (1 mmol). The mixture was stirred at 80 0C. After formation of the cyano-olefin (verified with TLC), 4-hydroxy carbazole (1mmol) was added to the reaction mixture, and it was allowed to stir until completion (TLC). Then, for the work-up procedure, warm water was added to the reaction mixture, glycerol dissolved and the insoluble solid crude product was separated by simple filtration.

4,7-dihydro-4-aryl-3-(phenylsulfonyl)-Pyrano[3,2-c]carbazol-2-amine (4a)

Solid, yield: 80%, m.p. >250 0C; 1H NMR (300 MHz, DMSO-d6): δ 10.90 (s, 1H, –NH –), 10.51 (d, 1H, J = 4.5 Hz, –NH–), 1H NMR: δ 5.45 (1H, s), 7.13-7.38 (7H, 7.33 (dddd, J = 7.7, 6.9, 1.9, 0.5 Hz), 7.26 (ddd, J = 8.2, 5.1, 1.6 Hz), 7.25 (ddd, J = 8.0, 5.1, 1.6 Hz), 7.21 (dddd, J = 6.9, 1.3, 1.1, 0.5 Hz), 7.16 (tt, J = 7.7, 1.1 Hz)), 7.44-7.57 (3H, 7.49 (dddd, J = 8.1, 7.5, 1.4, 0.4 Hz), 7.54 (tt, J = 7.5, 1.4 Hz)), 7.62 (1H, d, J = 8.3 Hz), 7.64-7.79 (5H, 7.76 (d, J = 8.3 Hz), 7.75 (ddd, J = 8.0, 1.6, 0.5 Hz), 7.70 (ddd, J = 8.2, 1.6, 0.5 Hz), 7.68 (dtd, J = 8.1, 1.4, 0.4 Hz)). 13 C NMR (75 MHz, DMSO): δ 159.32, 153.74, 142.81, 141.22723, 140.33933, 139.95263, 133.02092, 131.44266, 129.29709, , 128.92353, 128.63568, , 128.25714, 127.82146, 121.115, 120.74048, 117.80333, 115.28, 111.8, 40.95 MS (EI): m/z 451.14.

4,7-dihydro-4-(3-nitro aryl)-3-(phenylsulfonyl)-pyrano[3,2-c]carbazol-2-amine (4b)

Solid, yield: 80%, m.p. 220–221 0C; 1H NMR: δ 5.59 (1H, s), 7.21-7.31 (2H, 7.25 (ddd, J = 8.0, 5.1, 1.6 Hz), 7.26 (ddd, J = 8.2, 5.1, 1.6 Hz)), 7.39-7.58 (4H, 7.43 (ddd, J = 8.4, 8.0, 0.4 Hz), 7.49 (dddd, J = 8.1, 7.5, 1.4, 0.4 Hz), 7.54 (tt, J = 7.5, 1.4 Hz)), 7.59-7.79 (6H, 7.76 (d, J = 8.3 Hz), 7.75 (ddd, J = 8.0, 1.6, 0.5 Hz), 7.70 (ddd, J = 8.2, 1.6, 0.5 Hz), 7.68 (dtd, J = 8.1, 1.4, 0.4 Hz), 7.62 (d, J = 8.3 Hz)), 7.93 (1H, ddd, J = 8.0, 1.5, 1.4 Hz), 8.15-8.24 (2H, 8.17 (ddd, J = 1.7, 1.5, 0.4 Hz), 8.21 (ddd, J = 8.4, 1.7, 1.4 Hz)). 13C NMR (76 MHz, DMSO) (d, ppm): 159.32793, 153.74575, 141.22723, 140.33933, 139.95263, 133.02092, 129.13195, 128.25714, 127.82146, 121.115, 117.29385, 111.79899, 40.9508 MS (EI): m/z 497.20

4,7-dihydro-4-(4-methoxyaryl)-3-(phenylsulfonyl)-pyrano[3,2-c]carbazol-2-amine (4c)

Solid, yield: 80%, m.p. 230–235 0C; 1H NMR (300 MHz, DMSO-d6) (d, ppm):: δ 3.73 (3H, s), 5.43 (1H, s), 7.09 (2H, ddd, J = 8.8, 1.1, 0.6 Hz), 7.21-7.31 (2H, 7.25 (ddd, J = 8.0, 5.1, 1.6 Hz), 7.26 (ddd, J = 8.2, 5.1, 1.6 Hz)), 7.38 (2H, ddd, J = 8.8, 1.1, 0.6 Hz), 7.44-7.57 (3H, 7.49 (dddd, J = 8.1, 7.5, 1.4, 0.4 Hz), 7.54 (tt, J = 7.5, 1.4 Hz)), 7.61 (1H, d, J = 8.3 Hz), 7.64-7.79 (5H, 7.76 (d, J = 8.3 Hz), 7.75 (ddd, J = 8.0, 1.6, 0.5 Hz), 7.70 (ddd, J = 8.2, 1.6, 0.5 Hz), 7.68 (dtd, J = 8.1, 1.4, 0.4 Hz)). 13 C NMR (75 MHz, DMSO): 159.32793, 153.74575, 141.22723, 140.33933, 139.95263, 133.02092, 129.13195, 128.25714, 127.82146, 121.115, 117.29385, 111.79899, 55.50, 40.9508 MS (EI): m/z 482.0

4,7-dihydro-4-(3,4,5-trimethoxyarnyl)-3-(phenylsulfonyl)pyrano[3,2-c]carbazol-2-amine (4d)

Solid, yield: 78%, m.p. >250 0C; 1H NMR (300 MHz, DMSO-d6) (d, ppm): δ 3.70 (3H, s), 3.77 (6H, s), 5.40 (1H, s), 6.69 (2H, d, J = 2.7 Hz), 7.21-7.31 (2H, 7.25 (ddd, J = 8.0, 5.1, 1.6 Hz), 7.26 (ddd, J = 8.2, 5.1, 1.6 Hz)), 7.44-7.57 (3H, 7.49 (dddd, J = 8.1, 7.5, 1.4, 0.4 Hz), 7.54 (tt, J = 7.5, 1.4 Hz)), 7.59-7.79 (6H, 7.76 (d, J = 8.3 Hz), 7.75 (ddd, J = 8.0, 1.6, 0.5 Hz), 7.70 (ddd, J = 8.2, 1.6, 0.5 Hz), 7.68 (dtd, J = 8.1, 1.4, 0.4 Hz), 7.62 (d, J = 8.3 Hz)). 13C NMR (75 MHz, DMSO): δ 159.32793, 153.74575, 141.22723, 140.33933, 139.95263, 133.02092, 129.13195, 128.25714, 127.82146, 121.115, 117.29385, 111.79899, 56.62, 56.50.9, 50.80, 40.60. MS (EI): m/z 528.40

4,7-dihydro-4-(4-isopropylarnyl)-3-(phenylsulfonyl)-pyrano[3,2-c]carbazol-2-amine (4f)

Solid, yield: 77%, m.p. >250 0C; 1H NMR (300 MHz, CDCl3) (d, ppm): δ 1.20-1.24 (6H, 1.22 (d, J = 6.9 Hz), 1.22 (d, J = 6.9 Hz)), 2.99 (1H, sept, J = 6.9 Hz), 5.47 (1H, s), 7.02 (2H, ddd, J = 8.2, 1.3, 0.5 Hz), 7.14 (2H, ddd, J = 8.2, 1.5, 0.5 Hz), 7.21-7.31 (2H, 7.25 (ddd, J = 8.0, 5.1, 1.6 Hz), 7.26 (ddd, J = 8.2, 5.1, 1.6 Hz)), 7.44-7.57 (3H, 7.49 (dddd, J = 8.1, 7.5, 1.4, 0.4 Hz), 7.54 (tt, J = 7.5, 1.4 Hz)), 7.62 (1H, d, J = 8.3 Hz), 7.64-7.79 (5H, 7.76 (d, J = 8.3 Hz), 7.75 (ddd, J = 8.0, 1.6, 0.5 Hz), 7.70 (ddd, J = 8.2, 1.6, 0.5 Hz), 7.68 (dtd, J = 8.1, 1.4, 0.4 Hz)). 13C NMR (75 MHz, CDCl3): δ 159.32793, 153.74575, 141.22723, 140.33933, 139.95263, 133.02092, 129.13195, 128.25714, 127.82146, 121.115, 117.29385, 111.79, 40.60, 23.99. MS (EI): m/z 494.45

CONCLUSIONS

In summary, an efficient protocol for the one-pot preparation of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl)pyrano[2,3-b]carbazol-2-amine derivatives via three-component reaction of aromatic aldehydes, (phenylsulfonyl)acetonitrile, and 4-hydroxy carbazole in glycerol media as a commercially available, environmental friendly and reusable compound was described. The reactions were carried out under thermal conditions with short reaction times and produced the corresponding products in good to excellent yields. Also, eco-friendly material make it an interesting alternative towards diversity-oriented synthesis of 4,10-dihydro-4-Aryl-3-(phenylsulfonyl) pyrano[2,3-b]carbazol-2-amine.

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