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Mild synthesis of 5-(9-ethyl-9*H*-carbazol-3-yl)-*N*-aryl-1,3,4-thiadiazol-2-amines

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Abstract An efficient synthetic method for heterocycles containing both carbazole and 1,3,4-thiadiazole moieties is described. 9-Ethyl-9*H*-carbazol-3-carbaldehyde reacted with 4-arylthiosemicarbazides, with acetic acid as catalyst, to give 1-(9-ethyl-9*H*-carbazol-3-yl)methylene-4-arylthiosemicarbazides, which were further treated with manganese dioxide at room temperature in acetone to give 5-(9-ethyl-9*H*-carbazol-3-yl)-*N*-aryl-1,3,4-thiadiazol-2-amines in good to high yield. This procedure has the advantages of mild conditions, easy separation, and simple manipulation.

Keywords Thiadiazole · Carbazole · Thiosemicarbazide · Synthesis

Introduction

1,3,4-Thiadiazole derivatives are of interest in medicine and agriculture because of their wide range of biological activity, for example antibacterial [1], fungicidal [2], anticancer [3–6], antitubercular [7], anti-inflammatory [8], leishmanicidal [9], herbicidal [10], insecticidal [11], and anti-depressant [12]. Compounds bearing a carbazole moiety have antiproliferative [13, 14], cytotoxic [15], antimitotic [16], and antimicrobial [17] activity. Compounds bearing both 1,3,4-thiadiazole and carbazole moieties, especially, have anticancer [3], antimicrobial, anticonvulsant, and anti-inflammatory [18] activity, and are also used as optoelectronic [19] and polymeric [20] materials. Reported methods for the preparation of 1,3,4-thiadiazole heterocycles include

1. Dehydration of acylthiosemicarbazides in the presence of acids (HOAc, H_2SO_4, CH_3SO_3H) [21, 22] or other dehydrating agents (PEG-$OPOCl_2$, DCC, TMSCl, *p*-TsCl, PPh_3, $SOCl_2$, and PCl_5) [23, 24];

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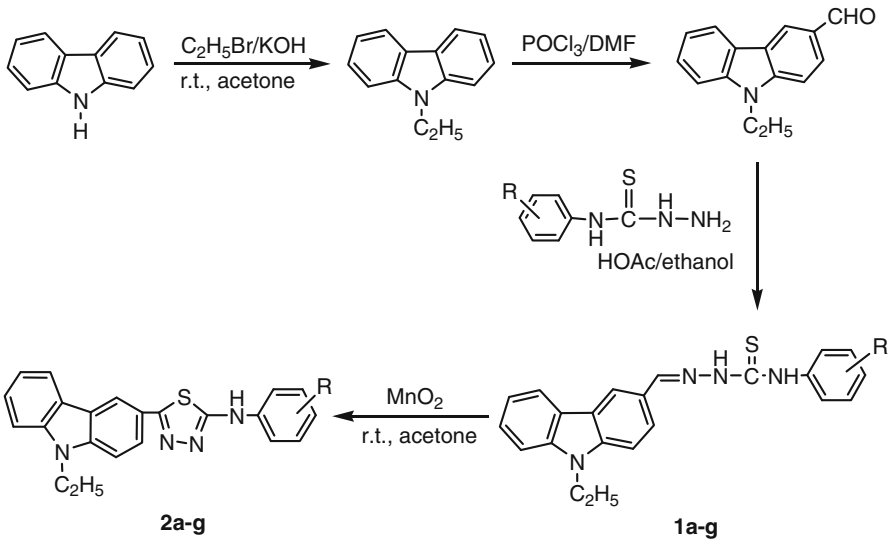
2. Condensation of diacylhydrazines in the presence of P_2S_5 or Lawesson reagent [25];
3. Dehydrogenating cyclization of thiosemicarbazones in the presence of $FeCl_3$ or Br_2 [26, 27]; and
4. Reaction of aldehydes with sulfur and hydrazine hydrate under microwave irradiation [28].

However, the most methods suffer from the drawbacks of difficult separation and release of corrosive and odorous hydrogen sulfide.

In this paper we report an efficient method with manganese dioxide as a mild oxidizing agent for synthesis of a series of new heterocyclic compounds containing both carbazole and 1,3,4-thiadiazole moieties.

Results and discussion

Reaction of carbazole with bromoethane in the presence of potassium hydroxide gave 9-ethyl-9*H*-carbazole in high yield. 9-Ethylcarbazole on treatment with phosphorus oxychloride and *N*,*N*-dimethylformamide under reflux for 2 h afforded 9-ethyl-9*H*-carbazol-3-carbaldehyde with high selectivity (no 3,6-dicarbaldehyde by-product was observed). 9-Ethyl-9*H*-carbazol-3-carbaldehyde reacted with 4-arylthiosemicarbazides, with acetic acid as catalyst, to give 1-(9-ethyl-9*H*-carbazol-3-yl)methylene-4-arylthiosemicarbazides (**1a–g**), which were further treated with manganese dioxide at room temperature in acetone to give 5-(9-ethyl-9*H*-carbazol-3-yl)-*N*-aryl-1,3,4-thiadiazol-2-amines (**2a–g**) in good to high yield (Scheme 1; Table 1).



Scheme 1

Table 1 Synthesis of Compounds **1a–g** and **2a–g**

Compound	R	Reaction time (h)	m.p. (°C)	Yield (%)
1a	H	1	206–208	93
1b	2-CH_3	1	224–226	86
1c	4-CH_3	1	199–201	90
1d	4-CH_3O	1	218–221	92
1e	4-Cl	1	202–204	89
1f	3-Br	1	206–208	86
1g	4-Br	1	214–216	87
2a	H	15	246–248	71
2b	2-CH_3	9	164–166	80
2c	4-CH_3	16	210–212	75
2d	4-CH_3O	18	200–202	73
2e	4-Cl	18	238–240	62
2f	3-Br	18	212–214	69
2g	4-Br	14	258–260	70

Yields refer to isolated product

It was observed that compounds **1a–g** bearing electron-donating groups (methyl, methoxyl) on aromatic rings were obtained in higher yield than those bearing electron-withdrawing groups (chloro, bromo). In addition, the solvent used was important for synthesis of products **2a–g**. Many solvents were tested for the reactions. Ethanol and dichloroethane gave low yield because of the poor solubility of the reactants. The reactions could proceed smoothly in DMF, but separation of the products could be a problem. However, it was found acetone was an acceptable solvent for the reactions and gave the products in good to high yield.

Other cyclizing agents were also investigated for formation of 1,3,4-thiadiazole rings. It was found that ferric chloride also gave the products. However, the reactions had to be conducted under reflux and gave the products in lower yield.

The structures of compounds **1a–g** and **2a–g** were determined by ^{1}H NMR, IR, and elemental analysis. The ^{1}H NMR spectra of compounds **1a–g** in DMSO-d_6 contained –CH= group proton peaks at $\delta = 8.63$–8.65 ppm and –NH– group proton peaks at $\delta = 9.95$–10.14 and 11.72–11.91 ppm. The ^{1}H NMR spectra of compounds **2a–g** contained –NH– proton peaks at $\delta = 10.42$–10.63 ppm. The IR spectra of compounds **1a–g** showed characteristic absorption at 3,115–3,350 cm^{-1} and 1,191–1,225 cm^{-1}, attributable to imino and thiocarbonyl groups, respectively. IR spectra of compounds **2a–g** showed the characteristic absorption of –NH– groups at 3,225–3,262 cm^{-1}.

Conclusion

In summary, an efficient synthetic method for a series of compounds containing both carbazole and thiadiazole moieties has been developed. This procedure has features of mild conditions and easy work-up.

Experimental

IR spectra were recorded as KBr pellets on a Digilab FTS 3000 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Mercury-400BB instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. Elemental analysis was performed with a Vario E1 elemental analysis instrument. Melting points were measured with an electrothermal melting point apparatus. 4-Arylthiosemicarbazides [29] and 9-ethyl-9*H*-carbazole-3-carbaldehyde [30] were prepared by methods reported in the literature.

Preparation of 1-(9-ethyl-9*H*-carbazol-3-yl)methylene-4-arylthiosemicarbazides (1a–g)

A mixture of 4-arylthiosemicarbazide (2 mmol), 9-ethyl-9*H*-carbazole-3-carbaldehyde (2 mmol), and acetic acid (0.2 mmol) in 20 mL ethanol was heated under reflux for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the precipitate was isolated by filtration and washed with ethanol (3 × 5 mL), and the solid was recrystallized from DMF–H_2O to give the corresponding product. The analytical data for compounds **1a–g** are given below.

1a: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.83 (*s*, 1H, NH), 10.07 (*s*, 1H, NH), 8.64 (*s*, 1H, –CH=), 7.21–8.35 (*m*, 12H, Ar–H), 4.48 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 1.33 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,238, 3,141 (N–H), 1,201 (C=S). Anal. Calcd. for $C_{22}H_{20}N_4S$: *C*, 70.94; *H*, 5.41; *N*, 15.04. Found: *C*, 70.85; *H*, 5.39; *N*, 15.10.

1b: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.79 (*s*, 1H, NH), 9.95 (*s*, 1H, NH), 8.63 (*s*, 1H, –CH=), 7.20–8.33 (*m*, 11H, Ar–H), 4.45 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 2.24 (*s*, 3H, CH_3), 1.32 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,296, 3,167 (N–H), 1,198 (C=S). Anal. Calcd. for $C_{23}H_{22}N_4S$: *C*, 71.47; *H*, 5.74; *N*, 14.50. Found: *C*, 71.60; *H*, 5.76; *N*, 14.48.

1c: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.80 (*s*, 1H, NH), 9.96 (*s*, 1H, NH), 8.65 (*s*, 1H, –CH=), 7.17–8.35 (*m*, 11H, Ar–H), 4.47 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 2.25(*s*, 3H, CH_3), 1.32 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,284, 3,170 (N–H), 1,191 (C=S). Anal. Calcd. for $C_{23}H_{22}N_4S$: *C*, 71.47; *H*, 5.74; *N*, 14.50. Found: *C*, 71.38; *H*, 5.73; *N*, 14.49.

1d: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.72 (*s*, 1H, NH), 9.99 (*s*, 1H, NH), 8.64 (*s*, 1H, –CH=), 6.94–8.34 (*m*, 11H, Ar–H), 4.48 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 3.78 (*s*, 3H, –OCH_3), 1.33 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,294, 3,137 (N–H), 1,216 (C=S). Anal. Calcd. for $C_{23}H_{22}N_4OS$: *C*, 68.63; *H*, 5.51; *N*, 13.92. Found: *C*, 68.56; *H*, 5.53; *N*, 13.84.

1e: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.85 (*s*, 1H, NH), 10.10 (*s*, 1H, NH), 8.65 (*s*, 1H, –CH=), 7.23–8.34 (*m*, 11H, Ar–H), 4.49 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 1.34 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,350, 3,127 (N–H), 1,214 (C=S). Anal. Calcd. for $C_{22}H_{19}ClN_4S$: *C*, 64.93; *H*, 4.71; *N*, 13.77. Found: *C*, 65.00; *H*, 4.73; *N*, 13.80.

1f: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.90 (*s*, 1H, NH), 10.12 (*s*, 1H, NH), 8.64 (*s*, 1H, –CH=), 7.23–8.33 (*m*, 11H, Ar–H), 4.50 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 1.35 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,335, 3,130 (N–H), 1,220 (C=S). Anal. Calcd. for $C_{22}H_{19}BrN_4S$: *C*, 58.54; *H*, 4.24; *N*, 12.41. Found: *C*, 58.38; *H*, 4.25; *N*, 12.44.

1g: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.91 (*s*, 1H, NH), 10.14 (*s*, 1H, NH), 8.64 (*s*, 1H, –CH=), 7.24–8.36 (*m*, 11H, Ar–H), 4.51 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 1.33 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,327, 3,115 (N–H), 1,225 (C=S). Anal. Calcd. for $C_{22}H_{19}BrN_4S$: *C*, 58.54; *H*, 4.24; *N*, 12.41. Found: *C*, 58.62; *H*, 4.22; *N*, 12.39.

Preparation of 5-(9-ethyl-9*H*-carbazol-3-yl)-*N*-aryl-1,3,4-thiadiazol-2-amines (2a–g)

Manganese dioxide (2 mmol) was added to compound **1a–1g** (1 mmol) in 20 mL acetone and 1 mL DMF. The suspension was stirred at room temperature for an appropriate time (indicated in Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was filtered to remove the solid. The filtrate was concentrated and the pure product was obtained by chromatography using petroleum ether–ethyl acetate (4:1) as eluent. The analytical data for compounds **2a–g** are given below.

2a: Yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.49 (*s*, 1H, NH), 7.00–8.62 (*m*, 12H, Ar–H), 4.47 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 1.31 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,231 (N–H). Anal. Calcd. for $C_{22}H_{18}N_4S$: *C*, 71.32; *H*, 4.90; *N*, 15.12. Found: *C*, 71.14; *H*, 4.89; *N*, 15.09.

2b: Red–brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.43 (*s*, 1H, NH), 6.98–8.61 (*m*, 11H, Ar–H), 4.46 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 2.36 (*s*, 3H, –CH_3), 1.30 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,227 (N–H). Anal. Calcd. for $C_{23}H_{20}N_4S$: *C*, 71.85; *H*, 5.24; *N*, 14.57. Found: *C*, 71.77; *H*, 5.23; *N*, 14.54.

2c: Purple solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.42 (*s*, 1H, NH), 7.01–8.60 (*m*, 11H, Ar–H), 4.45 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 2.37 (*s*, 3H, –CH_3), 1.30 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,225 (N–H). Anal. Calcd. for $C_{23}H_{20}N_4S$: *C*, 71.85; *H*, 5.24; *N*, 14.57. Found: *C*, 71.95; *H*, 5.26; *N*, 14.56.

2d: Yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.52 (*s*, 1H, NH), 7.09–8.63 (*m*, 11H, Ar–H), 4.47 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 3.81 (*s*, 3H, –OCH_3),1.32 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,237 (N–H). Anal. Calcd. for $C_{23}H_{20}N_4OS$: *C*, 68.98; *H*, 5.03; *N*, 13.99. Found: *C*, 69.06; *H*, 5.01; *N*, 13.97.

2e: White solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.63 (*s*, 1H, NH), 7.21–8.64 (*m*, 11H, Ar–H), 4.48 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 1.34 (*t*, ^3J = 7.2 Hz, 3H, –CH_3). IR (KBr, *v*, cm^{-1}): 3,262 (N–H). Anal. Calcd. for $C_{22}H_{17}ClN_4S$: *C*, 65.26; *H*, 4.23; *N*, 13.84. Found: *C*, 65.33; *H*, 4.22; *N*, 13.81.

2f: Yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.62 (*s*, 1H, NH), 7.22–8.63 (*m*, 11H, Ar–H), 4.49 (*q*, ^3J = 7.2 Hz, 2H, –CH_2–), 1.34 (*t*, ^3J = 7.2 Hz, 3H,

$-CH_3$). IR (KBr, v, cm^{-1}): 3,259 (N–H). Anal. Calcd. for $C_{22}H_{17}BrN_4S$: *C*, 58.80; *H*, 3.81; *N*, 12.47. Found: *C*, 58.86; *H*, 3.85; *N*, 12.51.

2g: Yellow solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.62 (*s*, 1H, NH), 7.25–8.64 (*m*, 11H, Ar–H), 4.48 (*q*, $^3J = 7.2$ Hz, 2H, $-CH_2-$), 1.34 (*t*, $^3J = 7.2$ Hz, 3H, $-CH_3$). IR (KBr, v, cm^{-1}): 3,260 (N–H). Anal. Calcd. for $C_{22}H_{17}BrN_4S$: *C*, 58.80; *H*, 3.81; *N*, 12.47. Found: *C*, 58.74; *H*, 3.83; *N*, 12.45.

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