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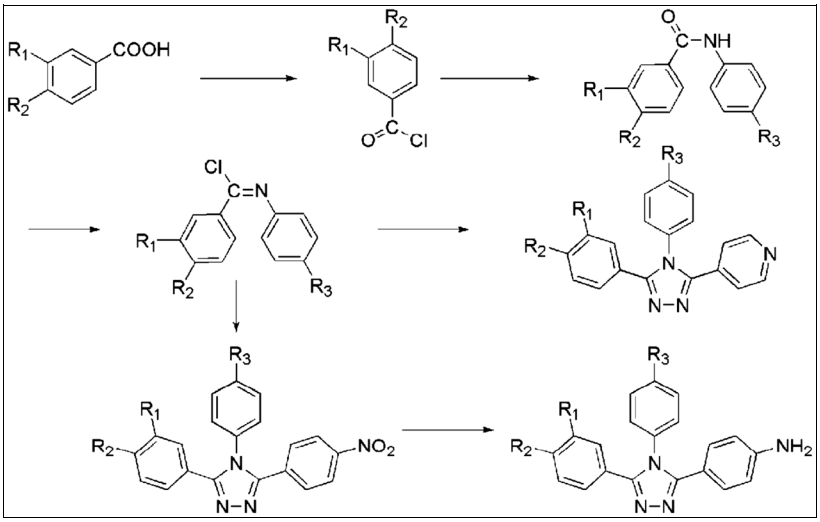

A new series of substituted 1,2,4-triazole derivatives have been synthesized using substituted imido derivatives and isonicotinyl hydrazine (or 4-nitrobenzoylhydrazine) as the key intermediates. These compounds include different donor or acceptor substituents on the 1,2,4-triazole derivatives. The structures of these compounds were confirmed by FTIR, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis.

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INTRODUCTION

1,2,4-Triazole and its derivatives constitute an important class of organic compounds with diverse biological activities. They can be widely used in agriculture and industry, as well as other fields [1–9]. These compounds are also very interesting ligands because they combine the coordination geometry of both pyrazoles and imida-zoles with regard to the arrangement of their three heteroatoms [10]. The zomethine (CH═N) linkages present in the backbone provide an attractive class of high performance materials [11]. The synthesis of these heterocycles has received considerable attention in recent years [7, 12–14]. In this article, a series of new 3,4,5-trisubstituted-1,2,4-triazole and their derivatives have been synthesized through molecular cyclization [15]. This method is not only simple but also has a high yield compared with traditional synthetic methods [2, 16]. The synthetic route for the 1,2,4-triazole derivatives is depicted in Scheme 1.

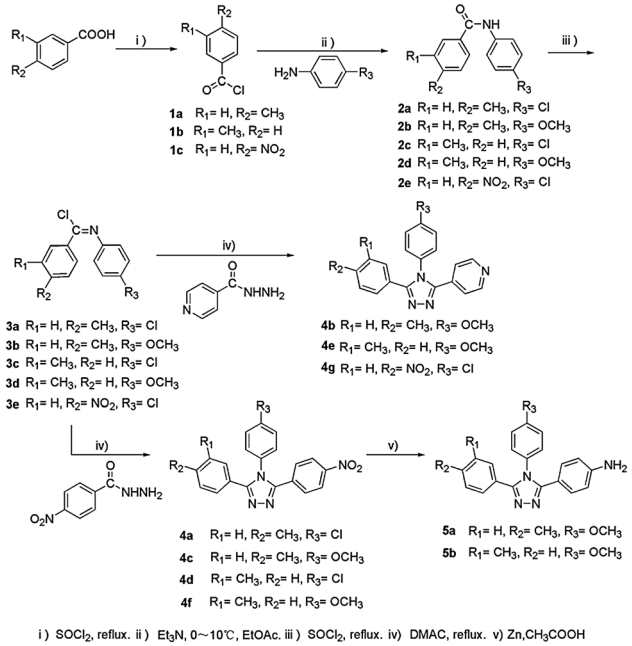
RESULTS AND DISCUSSION

Synthesis. The preparation of compounds **1–5** is shown in Scheme 1. Compounds **1a** and **1b** were prepared according to a literature method [17]. Compounds **1c** [18], **2a**–**2e** [19], and **3a**-**3e** [19] were synthesized and purified according to procedures in the literature. The starting material 4-nitrobenzoylhydrazine and 4-pyridinecarbonylhydrazine were also prepared according to a literature method [20]. Compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, and **4g** were prepared by refluxing a 1:1 mixture of the corresponding **3** and isonicotinyl hydrazine (or 4-nitrobenzoylhydrazine) in *N*,*N*-dimethylacetamide for several hours. After removal of the solvent, recrystallization or column chromatography yielded 53–79% of the corresponding 1,2,4-triazoles derivate **4** (Scheme 1).

In the ^{1}H-NMR spectra of compounds **4a–4f**, a new singlet peak in the region 2.28–2.37 ppm was observed which is due to CH_3 protons. In the ^{1}H-NMR spectra of **5a** and **5b**, the CH_3 protons gave a singlet peak at 2.33 and 2.34 ppm, respectively. The methoxy protons of **4b**, **4c**, **4e**, **4f**, **5a**, and **5b** exhibited a signal peak in the 3.81–3.88 ppm region. All spectra are shown in Figure 1.

To prepare **5a** and **5b**, **4c** and **4f** had to be reduced with Zn in CH_3COOH. Purification of **5a** and **5b** by recrystallization with methanol gave good yields (78% and 68%, respectively) (Scheme 1).

Scheme 1. Synthetic route of polysubstituted-1,2,4-triazoles derivatives.



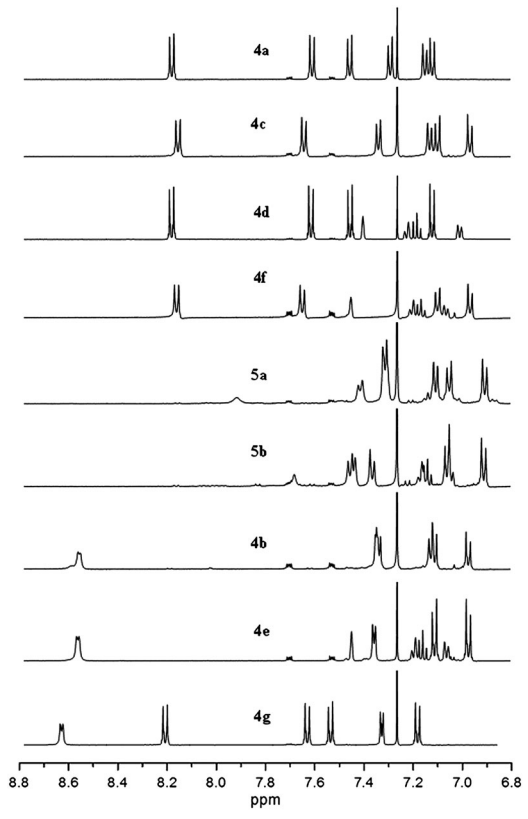


Figure 1. ^{1}H-NMR spectra of **4a, 4b, 4c, 4d, 4e, 4f, 4g, 5a,** and **5b.**

The infrared spectra of compounds **4a–g** (Table 1) exhibited a characteristic strong absorption band at 1511–1523 cm^{-1} which is attributable to the C═N of the 1,2,4-triazole residues.

CONCLUSIONS

A series of new 1,2,4-triazole derivatives was successfully synthesized with a mild and effective method using substituted benzoic acids as the starting material. The method has some salient features such as faster reaction rates, high yields and environmental friendliness. The synthesized compounds were characterized by spectral data (^{1}H-NMR, ^{13}C-NMR, IR) and elemental analysis.

EXPERIMENTAL

Materials. Reactions were monitored by thin layer chromatography on 0.20 mm Anhui Liangchen silica gel plates and the spots were detected with UV light. Silica gel (200–300 mesh) (from Anhui Liangchen Company) was used for flash chromatography. Compounds **1a** and **1b** were prepared according to a literature method [16]. Compounds **1c** [17], **2a–2e** [18], and **3a–3e** [18] were synthesized and purified according to other procedures in the literature. The starting material 4-nitrobenzoylhydrazine and 4-pyridinecarbonylhydrazine were also prepared according to a literature method [19]. Other chemicals or reagents were obtained from commercial sources.

Spectroscopic procedures. ^{1}H-NMR and ^{13}C-NMR spectra were acquired in $CDCl_3$ on a Varian 400 or a Varian 500 spectrometer. Unless otherwise noted, chemical shifts are reported as values in ppm relative to $CDCl_3$ (δ 7.26) for ^{1}H-NMR spectra, and relative to $CDCl_3$ (77.16 ppm) for ^{13}C-NMR spectra. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet. Coupling constants (*J*) are given in Hz at 500 MHz for the ^{1}H-NMR spectra. Infrared spectra were recorded on a Perkin-Elmer Model 1600 FTIR spectrophotometer. Elemental analyses were determined using a Perkin-Elmer 2400 CHN elemental analyzer. Melting points were determined using an electrothermal digital melting point apparatus and are uncorrected.

Synthetic procedures. All experiments were carried out in 100-mL Synthware glass round-bottom flasks, equipped with magnetic stir bars. Products were identified by comparing their IR, ^{1}H-NMR, and ^{13}C-NMR spectra and elemental analyses with those of known samples.

Synthesis of compounds 4. A flask was charged with **3**, 4-nitrobenzoylhydrazine (or 4-pyridinecarbonylhydrazine) and 15 mL *N*,*N*-dimethylacetamide. The mixture was refluxed about 30 h and then cooled to room temperature after the reaction finished. Removal of the solvent from the filtrate under vacuum gave the crude product of **4**. Compounds **4** were purified by recrystallization or column chromatography.

4-(4-Chloro-phenyl)-3-(4-nitro-phenyl)-5-p-tolyl-4H-[1,2,4]triazole 4a. With **3a** (2.89 g, 11.00 mmol) and 4-nitrobenzoylhydrazine (1.97 g, 10.00 mmol). Recrystallization with ethyl acetate: **4a** (2.42 g, 62%). Yellow solid. Melting point: 250–251°C. Analytical data. Found (calcd) for: $C_{20}H_{15}ClN_4O_2$ C, 64.46 (64.54); H, 3.76 (3.87); N, 14.22 (14.34). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.20 (d, *J* = 9.0 Hz, 2H, C*H*ar),

Table 1

Infrared spectral data of compounds in KBr (cm^{-1}).

No.	4a	4b	4c	4d	4e	4f	4g	5a	5b
C=N	1511	1515	1521	1523	1515	1519	1519	1516	1514
N-H	–	–	–	–	–	–	–	3227	3253

7.62 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.46 (d, *J* = 8.5 Hz, 2H, C*H*ar), 7.30 (d, *J* =8.0 Hz, 2H, C*H*ar), 7.16 (m, 4H, C*H*ar), 2.36 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.3, 123.1, 123.7, 128.7, 128.9, 129.4, 130.6, 132.7, 133.2, 136.3, 140.5, 148.2, 152.5, 155.6. IR (KBr, cm^{-1}) *v*: 3064, 3015, 2917, 1601, 1486, 1511, 1286, 1094 cm^{-1}.

4-[4-(4-Methoxy-phenyl)-5-p-tolyl-4H-[1,2,4]triazol-3-yl]-pyridine 4b. With **3b** (1.29 g, 5.00 mmol) and 4-pyridinecarbonylhydrazine (0.69 g, 5.00 mmol). Purification by flash column chromatography on silica using pentanes/ethyl acetate (1:8) as the eluent: **4b** (1.32 g, 77%). White solid. Melting point: 178–179°C. Analytical data. Found (calcd) for: $C_{21}H_{18}N_4O$ C, 73.76 (73.67); H, 5.22 (5.30); N, 16.56 (16.36). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.57 (d, *J* = 5.0 Hz, 2H, C*H*), 7.35 (m, 4H, C*H* & C*H*ar), 7.13 (m, 4H, C*H*ar), 6.98 (d, *J* =9.0 Hz, 2H, C*H*ar), 3.88 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.3, 55.6, 115.3, 122.2, 123.5, 127.1, 128.5, 128.7, 129.2, 134.6, 140.1, 150.1, 160.5. IR (KBr, cm^{-1}) *v*: 3061, 3031, 2932, 1664, 1599, 1515, 1350, 1101 cm^{-1}.

4-(4-Methoxy-phenyl)-3-(4-nitro-phenyl)-5-p-tolyl-4H-[1,2,4]triazole 4c. With **3b** (2.50 g, 9.65 mmol) and 4-nitrobenzoylhydrazine (1.67 g, 8.50 mmol). Recrystallization with ethyl acetate: **4c** (2.17 g, 66%). Yellow solid. Melting point: 232–233 °C. Analytical Data. Found (calcd) for: $C_{22}H_{18}N_4O_3$ C, 63.48 (68.38); H, 4.56 (4.70); N, 14.59 (14.50). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.17 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.65 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.35 (d, *J* = 8.0 Hz, 2H, C*H*ar), 7.14 (d, *J* = 8.0 Hz, 2H, C*H*ar), 7.10 (d, *J* = 9.0 Hz, 2H, C*H*ar), 6.97 (d, *J* =9.0 Hz, 2H, C*H*ar), 3.87 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.2, 55.9, 115.5, 124.1, 124.3, 127.3, 128.8, 129.5, 129.9, 133.7, 140.0, 143.2, 153.2, 155.7, 158.0, 160.3. IR (KBr, cm^{-1}) *v*: 3074, 3025, 2927, 1604, 1524, 1461, 1259, 1105 cm^{-1}.

4-(4-Chloro-phenyl)-3-(4-nitro-phenyl)-5-m-tolyl-4H-[1,2,4]triazole 4d. With **3c** (2.89 g, 11.00 mmol) and 4-nitrobenzoylhydrazine (1.97 g, 10.00 mmol). Recrystallization with ethyl acetate: **4d** (2.13 g, 55%). Yellow solid. Melting point: 166–167°C. Analytical Data. Found (calcd) for: $C_{21}H_{15}ClN_4O_2$ C, 64.49 (64.54); H, 3.81 (3.87); N, 14.27 (14.34). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.21 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.62 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.46 (d, *J* = 8.5 Hz, 2H, C*H*ar), 7.40 (s, 1H, C*H*ar), 7.23 (m, 2H, C*H*ar), 7.13 (d, *J* =9.0 Hz, 2H, C*H*ar), 7.01 (s, 1H, C*H*ar), 2.32 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.3, 123.7, 125.6, 125.9, 128.4, 128.9, 129.4, 129.7, 130.6, 131.0, 132.7, 133.2, 136.3, 138.6, 148.3, 152.6, 155.7. IR (KBr, cm^{-1}) *v*: 3080, 3060, 2921, 1601, 1486, 1523, 1348, 1098 cm^{-1}.

4-[4-(4-Methoxy-phenyl)-5-m-tolyl-4H-[1,2,4]triazol-3-yl]-pyridine 4e. With **3d** (1.29 g, 5.00 mmol) and 4-pyridinecarbonylhydrazine (0.69 g, 5.00 mmol). Recrystallization with ethanol: **4e** (1.21g, 71 %). White solid. Melting point: 193–195°C. Analytical data. Found (calcd) for: $C_{21}H_{18}N_4O$ C, 73.58 (73.67); H, 5.26 (5.30); N, 16.39 (16.36). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.58 (d, *J* = 5.0 Hz, 2H, C*H*), 7.45 (s, 1H, C*H*ar), 7.36 (d, *J* = 6.0 Hz, 2H, C*H*), 7.21 (m, 2H, C*H*ar), 7.12 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.07 (d, *J* =7.5 Hz, 1H, C*H*ar), 6.98 (d, *J* = 9.0 Hz, 2H, C*H*ar), 3.88 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.3, 122.2, 125.6, 125.8, 128.4, 128.9, 129.7, 130.5, 130.9, 133.1, 134.2, 136.3, 138.6, 150.2, 152.2, 155.8. IR (KBr, cm^{-1}) *v*: 3064, 3035, 2953, 1605, 1454, 1515, 1258, 1098 cm^{-1}.

4-(4-Methoxy-phenyl)-3-(4-nitro-phenyl)-5-m-tolyl-4H-[1,2,4]triazole 4f. With **3d** (2.46 g, 9.50 mmol) and 4-nitrobenzoylhydrazine (1.67 g, 8.50 mmol). Recrystallization with ethyl acetate: **4f** (2.04g, 62 %). Yellow solid. Melting point: 172–174°C. Analytical data. Found (calcd) for: $C_{22}H_{18}N_4O_3$ C, 68.42 (68.38); H, 4.76 (4.70); N, 14.41 (14.50). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.18 (d, *J* = 8.5 Hz, 2H, C*H*ar), 7.66 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.45 (s, 1H, C*H*ar), 7.21 (m, 2H, C*H*ar), 7.10 (m, 3H, C*H*ar), 6.97 (d, *J* = 8.5 Hz, 2H, C*H*ar), 3.81 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 21.3, 55.6, 115.4, 123.6, 125.5, 126.3, 127.1, 128.2, 128.7, 129.2, 129.7, 130.7, 133.1, 138.4, 148.1, 160.5. IR (KBr, cm^{-1}) *v*: 3096, 3064, 2998, 1621, 1482, 1519, 1249, 1115 cm^{-1}.

4-[4-(4-Chloro-phenyl)-5-(4-nitro-phenyl)-4H-[1,2,4]triazol-3-yl]-pyridine 4g. With **3e** (2.95 g, 9.50 mmol) and 4-pyridinecarbonylhydrazine (1.71 g, 8.50 mmol). Recrystallization with ethyl acetate: **4g** (1.69g, 53 %). Yellow solid. Melting point: 239–240°C. Analytical data. Found (calcd) for: $C_{19}H_{12}ClN_5O_2$ C, 60.36 (60.41); H, 3.16 (3.20); N, 18.51 (18.54). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 8.64 (d, *J* = 5.5 Hz, 2H, C*H*), 8.22 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.64 (d, *J* = 9.0 Hz, 2H, C*H*ar), 7.54 (d, *J* = 9.0 Hz, 2H, C*H*), 7.33 (d, *J* = 6.0 Hz, 2H, C*H*ar), 7.19 (d, *J* = 8.5 Hz, 2H, C*H*ar). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 29.6, 122.1, 123.8, 128.7, 129.4, 131.1, 132.0, 132.5, 133.6, 137.2, 158.5, 150.3, 153.1, 153.5. IR (KBr, cm^{-1}) *v*: 3057, 3031, 1597, 1519, 1490, 1287, 1091 cm^{-1}.

Synthesis of compounds 5. A flask was charged with **4** (2.01 g, 5.00 mmol) and Zn (0.52 g, 8.00 mmol). After the mixture was cooled to 10–20°C, 30 mL (5.5 mmol) CH_3COOH was slowly added. The mixture was stirred for 1 h at room temperature and then continued to be stirred for 5 h at 50°C. After the reaction was finished, the solvent was removed from the filtrate. The filtrate was cooled to room temperature and 10% NaOH was added. The mixture was then extracted with ethyl acetate. The organic extracts were concentrated under vacuum and gave the crude product of **5**. Purification of **5** by recrystallization with methanol.

4-[4-(4-Methoxy-phenyl)-5-p-tolyl-4H-[1,2,4]triazol-3-yl]-phenylamine 5a. **5a** (1.39 g, 78%). Yellow solid. Melting point: 277–279°C. Analytical data. Found (calcd) for: $C_{22}H_{20}N_4O$ C, 74.19 (74.14); H, 5.71 (5.66); N, 15.69 (15.72). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 1H, N*H*), 7.42 (d, *J* = 8.5 Hz, 2H, C*H*ar), 7.32 (d, *J* = 8.0 Hz, 4H, C*H*ar), 7.11 (d, *J* = 8.0 Hz,

2H, C*H*ar), 7.06 (d, *J* = 8.5 Hz, 2H, C*H*ar), 6.91 (d, *J* = 9.0 Hz, 2H, C*H*ar), 3.85 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3). IR (KBr, cm^{-1}) *v*: 3227, 3189, 3068, 3017, 2967, 1606, 1516, 1257, 1098 cm^{-1}.

***4-[4-(4-Methoxy-phenyl)-5-m-tolyl-4H-[1,2,4]triazol-3-yl]-phenylamine 5b*. 5b** (1.21g, 68 %). Yellow solid. Melting point: 249–251°C. Analytical Data. Found (calcd) for: $C_{22}H_{20}N_4O$ C, 74.12 (74.14); H, 5.721 (5.66); N, 15.69 (15.72). ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 7.67 (s, 1H, N*H*), 7.46 (d, *J* = 8.5 Hz, 2H, C*H*ar), 7.43 (s, 1H, C*H*ar), 7.37 (d, *J* = 8.5 Hz, 2H, C*H*ar), 7.16 (m, 3H, C*H*ar), 7.06 (d, *J* = 9.0 Hz, 2H, C*H*ar), 6.91 (d, *J* = 9.0 Hz, 2H, C*H*ar), 3.85 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3). IR (KBr, cm^{-1}) *v*: 3253, 3117, 3097, 3046, 2920, 1603, 1469, 1514, 1255 cm^{-1}.

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