HETEROCYCLES, Vol. 68, No. 12, 2006, pp. 2635 - 2645. © The Japan Institute of Heterocyclic Chemistry
Received, 14th September, 2006, Accepted, 30th October, 2006, Published online, 2nd November, 2006. COM-06-10886

EFFICIENT NEW APPROACH FOR THE SYNTHESIS OF *N,N*-DIALKYLAMINO-1,2,4-TRIAZOLES

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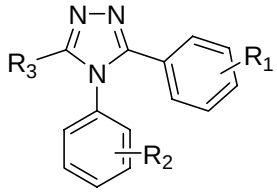
Abstract – A series of 3-*N*,*N*-dialkylamino-4,5-diaryl-1,2,4-triazoles were synthesized in high yield under mild reaction conditions by coupling functionalized arylmagnesiums with isothiocyanates and cyclization with Viehe's salts. No selective thionation reaction was required for the preparation of carbamoyl derivatives.

INTRODUCTION

The 1,2,4-triazoles are a large family of heterocyclic compounds, examples of which exhibit a wide range of biological activities. They have been reported as novel glycogen synthase kinase-3 (GSK-3) inhibitors,[1] large-conductance Ca^{2+} activated potassium channel openers,[2] and anti-inflammatory/antipyretic agents with low acute toxicity.[3] In our efforts to discover small-molecule probes that target specific biological targets, an efficient method was achieved for the preparation of a series of 3-*N*,*N*-dialkylamino-4,5-diaryl-1,2,4-triazole derivatives (Figure 1). Surprisingly, a search of the literature on the subject revealed that these compounds have not been fully explored until recently.[4-6] In this paper, we describe an efficient method to synthesize 3-*N*,*N*-dialkylamino-4,5-diaryl-1,2,4-triazoles.

Figure 1

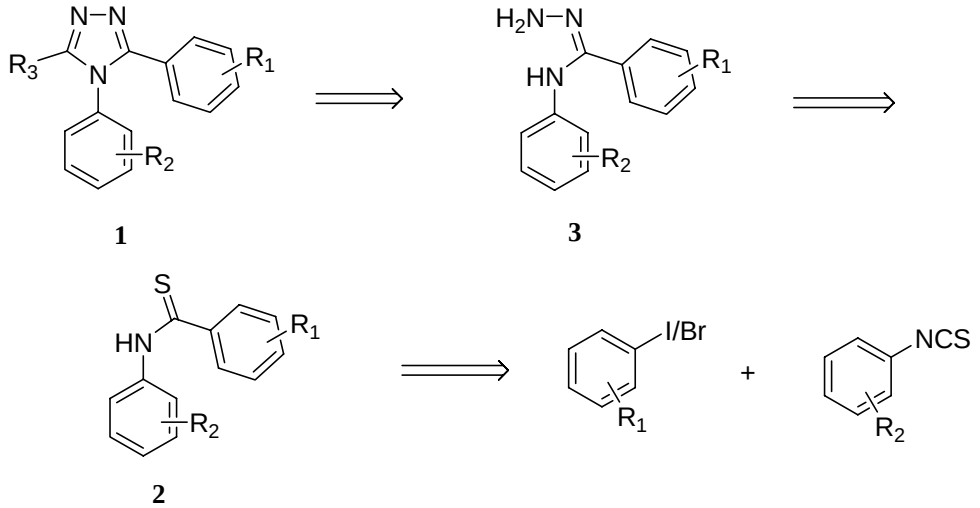


R_1, R_2 = alkyl, aryl, R_3 = *N*,*N*-dialkylamino

RESULTS AND DISCUSSION

Although many synthetic methods have been proposed for the preparation of trisubstituted 1,2,4- triazoles, such as the Einhorn-Brunner reaction[7] and the methods developed by Katritzky and Larson *et al*..[8-12] In most cases the reaction conditions are vigorous and the chemistry is not clean. Here, we report a new approach for the synthesis of 3-(*N*,*N*-dialkylamino)-1,2,4-triazoles with few steps, mild conditions and high yield. In our strategy, functionalized thioamides served as key intermediates in the synthesis of **1** (Scheme 1). Normally, thioamides are synthesized from amides with P_4S_{10}, Lawesson's reagent or

Scheme 1

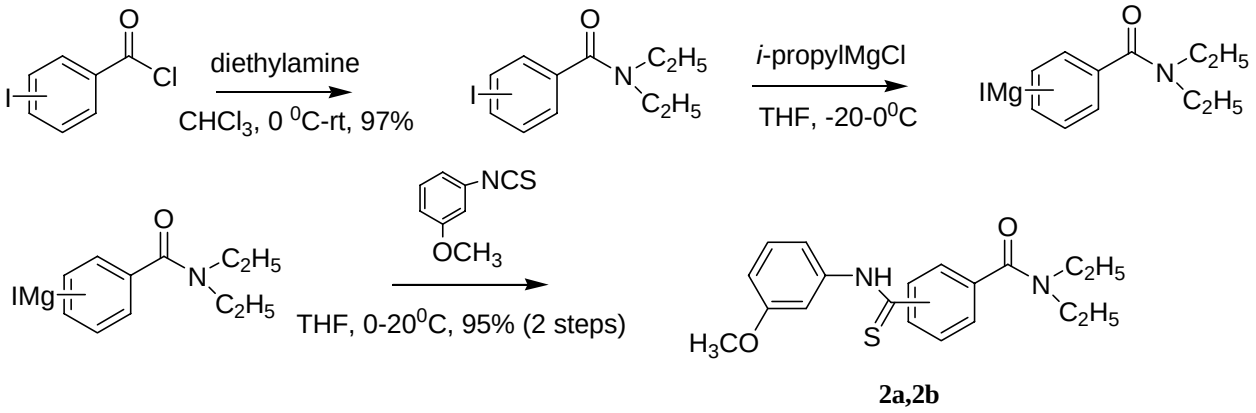


2a: R_1=3-CON$(CH_2CH_3)_2$, R_2=3-OCH_3; **2b**: R_1=4-CON$(CH_2CH_3)_2$, R_2=3-OCH_3;
2c: R_1=3-C$(CH_3)_3$, R_2=3-OCH_3; **2d**: R_1=3-C$(CH_3)_3$, R_2=4-OCH_3;
2e: R_1=3-C_6H_5, R_2=3-OCH_3; **2f**: R_1=4-C_6H_5, R_2=4-OCH_3

thionation reagent composed of P_4S_{10} and siloxane.[13,14] However, these methods require selective thionation of amide functional groups in the synthesis of carbamoyl derivatives. In our synthesis, the

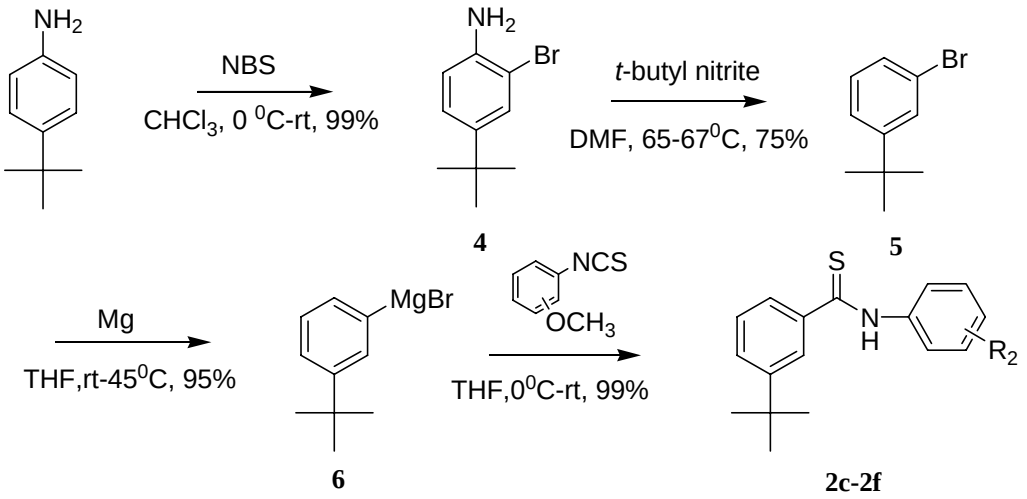
thioamides were directly obtained by coupling arylmagnesiums with isothiocyanates. This reaction can be conducted smoothly at room temperature in excellent yield. After exploring various procedures for arylmagnesium preparation, Knochel's procedure[15-18] of low-temperature iodine-magnesium exchange was found the best way to prepare arylmagnesium reagents. This reaction is mild and occurs within 3 hours at 0°C in high yield. For thioamides (**2a** and **2b**), the desired chemical selectivity was achieved while the number of synthetic steps was minimized (Scheme 2).[18,19]

Scheme 2



For **2c-2f**, preliminary studies indicated an efficient synthesis of 3-*tert*-butylbenzoic acid is required, but the separation of 3- and 4- isomers is tedious using literature methods.[20] To overcome the difficulty in purification, a concise synthesis of 3-*tert*-butyphenyl substituted thioamides is proposed here (Scheme 3).

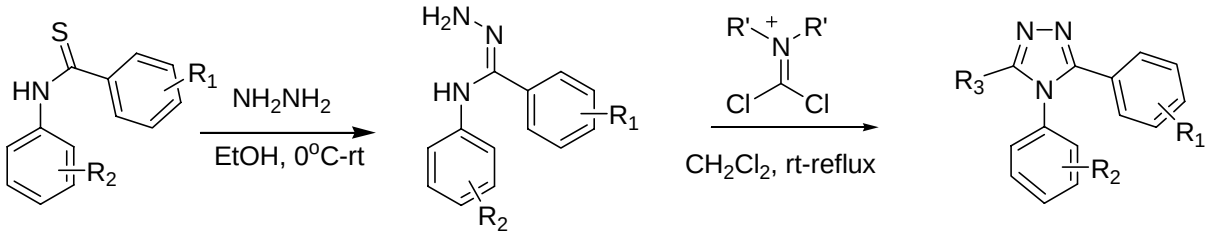
Scheme 3



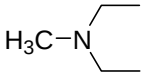
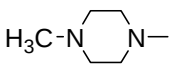
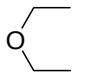
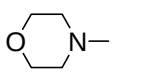
2-Bromo-4-*tert*-butylaniline (**4**) could be synthesized in nearly 100% yield by bromination of 4-*tert*-butylamine with *N*-bromosuccinimide (NBS) at 0°C. After diazonation and deamination reactions,

the key intermediate 1-bromo-3-*tert*-butylbenzene (**5**) was obtained in 75% overall yield.[21] The corresponding magnesium reagent (**6**) was prepared without any difficulty under standard conditions.[22] Moreover, all reactions developed here are mild and most of intermediates can be used for the subsequent reaction without separation. With **2** in hand, the amidrazones were synthesized smoothly with excess hydrazine in anhydrous alcohol in 100% yield, after which the final cyclization reaction was pursued. Although **1** can be obtained by condensing amidrazone with carbamoyl chlorides or corresponding acids,[7] the reaction condition is vigorous and the yield is not satisfactory. Therefore, phosgeniminium chlorides (Viehe's salts) were used to complete the cyclization reaction.[23-30] Viehe's salts are valuable synthons for heterocyclic synthesis, notably because of their ability to dechloroalkylate.[28] The reaction is extremely mild and the cyclization can be finished within 5 hours (Table 1). Viehe's salts, which are stable for weeks at room temperature, can be synthesized in a straightforward manner and used directly for cyclization to yield triazoles with sufficiently high purity.[31-34]

Table 1: Synthesis of 3-*N*,*N*-dialkylamino-4,5-diaryl-1,2,4-triazoles (1)



2 **3** **1**

No.	R_1	R_2	R'	R_3	Total yield (%)[a]
1a	3-$CON(CH_2CH_3)_2$	3-OCH_3	-CH_3	$N(CH_3)_2$	79
1b	4-$CON(CH_2CH_3)_2$	3-OCH_3	-CH_3	$N(CH_3)_2$	76
1c	3-$C(CH_3)_3$	3-OCH_3	-CH_3	$N(CH_3)_2$	81
1d	3-$C(CH_3)_3$	4-OCH_3	-CH_3	$N(CH_3)_2$	81
1e	3-$C(CH_3)_3$	3-OCH_3			72
1f	3-$C(CH_3)_3$	3-OCH_3			73
1g	3-C_6H_5	3-OCH_3	-CH_3	$N(CH_3)_2$	76
1h	4-C_6H_5	3-OCH_3	-CH_3	$N(CH_3)_2$	74

a: isolated yield of analytically pure products from **2**

In summary, we have developed an efficient and practical method to synthesize *N*,*N*-dialkylamino-1,2,4-triazoles under mild reaction conditions and in high overall yield, which can be used for library synthesis and scale-up production.

EXPERIMENTAL

^{1}H-NMR spectra were recorded at 400 MHz on Varian Gemini-400 spectrometer, in deuterated chloroform ($CDCl_3$) or DMSO (DMSO-d_6) solution at room temperature, using TMS (0.00 ppm) as internal standards and were reported in parts per million (ppm). ^{13}C-NMR spectra were recorded on a Varian Gemini 100 MHz NMR spectrometer at room temperature in $CDCl_3$ and were internally referenced to $CDCl_3$ (77.23 ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; w, wide. Coupling constants, *J*, are reported (Hz). Analytical Thin Layer Chromatography (TLC) was performed on pre-coated plastic backed plates purchased from Aldrich (silica gel 60 F_{254}; 0.25mm thickness). Flash column chromatography was conducted with silica gel 60 (230-400 mesh) from Natland Co. MS and MS-MS were conducted on a Finnigan LCQ DUO Mass Spectrum (Thermo Quest Co.). Gas chromatographic analyses were performed on a Hewlett-Packard 6890 GC-MS instrument with a FID detector using 25 m × 0.20 mm capillary column with cross-linked methylsiloxane as a stationary phase. Melting points were taken on a Mel-temp melting point apparatus in open capillary tubes without calibration.

All reactions were carried out with anhydrous solvents in oven-dried and argon-charged glassware. All anhydrous solvents except as mentioned were freshly distilled and stored in 4Å molecular sieves. All solvents used in workup, extraction procedures, recrystallization process and chromatography were used as received from commercial supplier without further purification. All reagents were purchased from Aldrich Chemical Company.

General procedure for the synthesis of thioamides (2a-2f):

a: arylmagnesium preparation:

A 50ml three-necked flask containing THF (15mL) was flushed with argon, and iodide compound (13.6 mmol) was added in one portion. The solution was cooled to -20°C. Isopropylmagnesium chloride (1.0 M in THF, 1.05 equiv.) was dropped into the iodide solution via syringe. The yellow solution was stirred at -20°C for 30 min and warmed to rt.

For **2c** and **2d** arylmagnesium preparation, a 50mL three-necked flask containing THF (15mL) was flushed with argon. Bromide (13.6 mmol) was dissolved in THF and magnesium (0.39 g, 1.2 equiv.) was added in one portion. After a piece of iodine was added, the flask was immersed in 40-50°C water bath without stirring. The reaction took place within 10 min and the mixture was cloudy. The solution was stirred until clear (some magnesium remained). The flask was removed from the bath to cool to rt.

b: coupling with isothiocyanate

Isothiocyanate (1.0 equiv.) was dropped into above arylmagnesium solution slowly under vigorous stirring. The coupling reaction took place immediately and the solution color changed to brown. Following this procedure, the solution was stirred at rt for 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution. Solid was filtered and the organic solution was extracted by water (2 × 20mL) and the combined organic layers were dried with $MgSO_4$. After solvent evaporation, the residue was purified by recrystallization or flash chromatography using a mixture of hexane and EtOAc as eluent.

***N,N*-Diethyl-3-(3-methoxyphenylcarbamothioyl)benzamide (2a):** yellow syrup, yield 98%. TLC (EtOAc:hexane = 3:20), R_f = 0.35. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.09 (s, 3H), 1.18 (t, *J* = 8.2 Hz, 3H),3.21 (d, *J* = 6.1 Hz, 2H), 3.47 (d, *J* = 7.5 Hz, 2H), 3.81 (s, 3 H), 6.81(d, *J* = 7.4 Hz, 1H), 7.25-7.37 (m, 4 H), 7.65 (d, *J* = 6.2 Hz, 2H), 7.80 (d, *J* = 7.5 Hz, 1H), 10.48 (s, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ170.5, 159.9, 143.4, 140.5, 130.9, 129.6, 128.6, 128.4, 128.3, 124.4, 115.8, 112.7, 109.1, 55.9, 43.5, 39.5. MS (ESI) = 313.4 (M^++1).Anal. Calcd for $C_{19}H_{22}N_2O_2S$: C 66.64, H 6.48, N 8.18, O 9.34, S 9.36. Found: C 66.59, H 6.49, N 8.20, O 9.33, S 9.35.

***N,N*-Diethyl-4-(3-methoxyphenylcarbamothioyl)benzamide (2b):** yellow solid, yield 96%. TLC (EtOAc:hexane = 3:20), R_f = 0.35, mp 85-87°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.05 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 6.4 Hz, 3H), 3.17 (d, *J* = 7.5 Hz, 2H), 3.45 (d, *J* = 7.5 Hz, 2H), 3.82 (s, 3 H), 6.82 (d, *J* = 7 Hz, 1H), 7.11(d, *J* = 8 Hz, 2H), 7.31(t, *J* = 8 Hz, 1H), 7.39 (d, *J* = 7 Hz, 1H), 7.66 (s, 1 H), 7.76 (d, J = 8 Hz, 2H), 10.62 (s,1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ170.7, 159.8, 143.5, 140.6, 138.5, 131.2, 129.4, 127.5, 125.9, 116.2, 112.6, 109.6, 55.4, 43.8, 39.5. MS (ESI) = 313.4 (M^++1). Anal. Calcd for $C_{19}H_{22}N_2O_2S$: C 66.64, H 6.48, N 8.18, O 9.34, S 9.36. Found: C 66.63, H 6.47, N 8.19, O 9.38, S 9.38.

3-*tert*-Butyl-*N*-(3-methoxyphenyl)benzothioamide (2c): yellow solid, yield 93%. TLC (EtOAc:hexane = 1:4), R_f = 0.32, mp 106-108°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.36 (s,9 H), 3.83 (s,3 H), 6.84 (d, *J* = 7.2 Hz, 1H), 7.24 (s,1 H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.55 (m, 3 H), 7.86 (s, 1 H), 8.95 (s,1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.0, 152.3, 142.9, 140.2, 134.5, 129.7, 128.5, 128.3, 124.1, 123.4, 115.6, 112.7, 109.2, 55.4, 34.9, 31.3. MS (ESI) = 300.3(M^++1). Anal. Calcd for $C_{18}H_{21}NOS$: C 72.70, H 7.07, N 4.68, O 5.34, S 10.71. Found: C 72.73, H 7.05, N 4.67, O 5.36, S 10.70.

3-*tert*-Butyl-*N*-(4-methoxyphenyl)benzothioamide (2d): yellow solid, yield 95%. TLC (EtOAc:hexane = 1:4), R_f = 0.32, mp 93-95°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.37 (s, 9 H), 3.84 (s,3 H),6.97 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 6.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 3H), 7.88 (s, 1 H), 8.89 (s,1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.2, 151.8, 142.9, 132.1, 130.3, 128.5, 128.3, 127.7, 124.1, 123.5, 122.8, 114.2, 55.5, 35.1, 31.3. MS (ESI) = 300.3 (M^++1). Anal. Calcd for $C_{18}H_{21}NOS$: C 72.70, H 7.07, N 4.68, O 5.34, S 10.71. Found: C 72.71, H 7.08, N 4.68, O 5.35, S 10.69

***N*-Phenylbiphenyl-3-carbothioamide (2e):** yellow syrup, yield 92%. TLC (EtOAc:hexane = 1:3), R_f =

0.28. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (s,3 H), 6.84(d, *J* = 8.2 Hz, 1H), 7.28-7.78 (m, 11 H), 8.03 (s, 1 H), 9.04 (s,1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.0, 140.1, 140.1, 130.9, 129.9, 129.8, 129.1, 128.9, 128.8, 127.8, 127.4, 127.1, 125.6, 125.4, 115.6, 112.7, 109.0, 55.5. MS (ESI) = 320.3(M^++1). Anal. Calcd for $C_{19}H_{15}NS$: C 78.86, H 5.22, N 4.84, S 11.08. Found: C 78.88, H 5.20, N 4.83, S 11.06.

***N*-Phenylbiphenyl-4-carbothioamide (2f):** yellow solid, yield 92%. TLC (EtOAc:hexane = 1:3), R_f = 0.28. mp 112-114°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3 H), 6.84 (d, *J* = 8.2 Hz, 1H), 7.28-7.78 (m, 11 H), 8.03 (s, 1 H), 9.04 (s, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.4, 140.2, 139.8, 129.8, 128.9, 128.1, 127.2, 127.1, 115.7, 112.8, 109.1, 55.4. MS (ESI) = 320.3 (M^++1). Anal. Calcd for $C_{19}H_{15}NS$: C 78.86, H 5.22, N 4.84, S 11.08. Found: C 78.83, H 5.25, N 4.80, S 11.09

General procedure to synthesize 1a-1f

In a 50 ml three-necked flask, thioamide (6.6 mmol) was suspended in anhydrous EtOH (60mL) and cooled to 0°C. Anhydrous hydrazine (2 mL, 10 equiv.) was dropped in slowly under vigorous stirring, while the temperature was kept under 0°C. Afterwards the flask was brought to rt and stirred for 5h at rt. TLC indicated the reaction was finished and EtOH and hydrazine were evaporated under high vacuum. The residue dissolved in $CHCl_3$ (30 mL) and extracted by water (3 × 20 mL). After drying by $MgSO_4$, the $CHCl_3$ was evaporated and amidrazone was dried overnight under vacuum before it was used for next step.

To a 50 ml three-necked flask which contained CH_2Cl_2 (10 mL), Viehe's salt (2.7mmol) was added quickly in one portion under stirring. 5 min later, amidrazone (0.9 equiv.) was added slowly. After stirring for 30 min at rt, the reaction was heated to reflux overnight. TLC indicated the reaction usually finished within 5 h. The mixture was cooled to rt and the organic solution was extracted by water; the organic layer was dried by $MgSO_4$ and concentrated. The triazoles were purified by flash chromatography by using $CHCl_3$ and MeOH or EtOAc and hexane as eluent.

3-(5-(Dimethylamino)-4-(3-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl)-*N*,*N*-diethylbenzamide (1a): white solid, yield 81%. TLC ($CHCl_3$: MeOH = 20:1), R_f = 0.35, mp112-114°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9 H), 3.84 (s, 3 H),6.97 (d, *J* = 7.2 Hz, 2H), 7.37 (t, J = 2.6 Hz, 1H), 7.53 (d, *J* = 8.0Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 3H), 7.88 (s, 1H), 8.89(s,1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.2, 160.6, 159.6, 151.4, 137.3, 136.1, 136.0, 130.6, 129.0, 128.6, 128.5, 127.8, 127.3, 126.5, 119.7, 114.9, 113.2, 55.5, 41.4, 39.2. MS(ESI) = 394.4 (M^++1). Anal. Calcd for $C_{19}H_{15}NS$: C 78.86, H 5.22, N 4.84, S 11.08. Found: C 78.83, H 5.25, N 4.80, S 11.09.

4-(5-(Dimethylamino)-4-(3-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl)-*N*,*N*-diethylbenzamide (1b): white solid, yield 79%. TLC ($CHCl_3$: MeOH = 20:1), R_f = 0.35, mp144-145°C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ1.00 (s, 3 H), 2.64 (s, 6 H),3.11 (s, 2 H), 3.40 (s, 2 H), 3.73 (s, 3 H), 6.96 (d, *J* = 6.5 Hz, 1 H), 7.04 (s, 1 H), 7.08 (d, *J* = 6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 5.0 Hz, 2 H), 7.43 (t, J =

8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170. 5, 160.6, 159.8, 151.5, 137.8, 135.9, 130.7, 128.6, 128.4, 126.2, 119.7, 114.7, 113.3, 55.5, 43.2, 41.4, 39.3. MS (ESI) = 394.3 (M^++1). Anal. Calcd for $C_{19}H_{15}NS$: C 78.86, H 5.22, N 4.84, S 11.08. Found: C 78.85, H 5.26, N 4.85, S 11.06.

5-(3-*tert*-Butylphenyl)-4-(3-methoxyphenyl)-*N*,*N*-dimethyl-4*H*-1,2,4-triazol-3-amine (1c): white crystal, yield 87%. TLC (EtOAc:hexane=1:2), R_f = 0.61, mp120-122°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.12 (s, 9 H), 2.73 (s, 6 H), 3.73 (s, 3 H), 6.74 (t, J = 2.5 Hz, 1 H), 6.84 (d, J = 6.2 Hz, 1 H), 6.95 (dd, J_1 = 2.0 Hz, J_2 = 4.0Hz 1 H), 7.18-7.20 (m, 1 H), 7.22 (s, 0.5 H), 7.28 (tt, J_1 = 2.0 Hz, J_2 = 5.0Hz, 2 H), 7.32(s, 0.5 H), 7.34 (s, 0.5 H), 7.36 (s, 0.5 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.5, 159.4, 152.5, 150.7, 136.4, 130.5, 128.0, 127.7, 126.1, 125.9, 125.8, 119.8, 114.6, 113.3, 55.5, 41.5, 34.5, 31.0. MS (ESI) = 351.3 (M^++1). Anal. Calcd for $C_{21}H_{26}N_4O$: C 71.97, H 7.48, N 15.99, O 4.57. Found: C 71.99, H 7.45, N 16.01, O 4.54.

5-(3-*tert*-Butylphenyl)-4-(4-methoxyphenyl)-*N*,*N*-dimethyl-4*H*-1,2,4-triazol-3-amine (1d): white crystal, yield 85%. TLC (EtOAc:hexane = 1:2), R_f = 0.61, mp118-120°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.14 (s,9 H), 2.75 (s, 6 H), 3.82 (s, 3 H), 6.93 (d, J = 5.3 Hz, 2 H), 7.16 (d, J = 5.5 Hz, 2 H), 7.17-7.22 (m, 3 H), 7.32 (d, J = 2.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.8, 159.7, 152.7, 150.8, 128.7, 128.0, 127.2, 126.0, 125.9, 125.8, 115.0, 114.9, 55.6, 41.5, 34.5, 31.0. MS (ESI) = 351.3 (M^++1). Anal. Calcd for $C_{21}H_{26}N_4O$: C 71.97, H 7.48, N 15.99, O 4.57. Found: C 72.01, H 7.50, N 15.97, O 4.56.

1-(5(3-*tert*-Butylphenyl)-4-(3-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl)-4-methylpiperazine (1e): white solid, yield 78%. TLC (EtOAc:hexane = 1:2), R_f = 0.43, mp164-166°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.12 (s, 9 H), 2.30 (s, 3 H), 2.38 (d, J = 5.0 Hz, 2H), 3.14(t, J=5Hz, 2H), 3.75(s, 3H), 6.74(t, J = 2Hz, 1H), 6.83(d, J = 1Hz, 1 H), 6.95(dd, J_1 = 2.0 Hz, J_2 = 6.0 Hz, 1 H), 7.19-7.27 (m, 3 H), 7.33 (t, J_1 = 5.0Hz, J_2 = 6.2 Hz, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.5, 158.0, 152.6, 150.8, 136.1, 130.6, 130.5, 128.1, 126.9, 126.2, 125.9, 119.2, 114.8, 112.7, 55.5, 54.4, 49.1, 46.1, 34.5, 31.0. MS (ESI) = 406.5 (M^++1). Anal. Calcd for $C_{24}H_{31}N_5O$: C 71.08, H 7.70, N 17.27, O 3.95. Found: C 71.12, H 7.65, N 17.30, O 3.98.

4-(5(3-*tert*-Butylphenyl)-4-(3-methoxyphenyl)-4*H*-1,2,4-triazol-3-yl)morpholine (1f): white crystal, yield 79%. TLC (EtOAc:hexane = 1:2), R_f = 0.51, mp155-156°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.12 (s, 9 H), 2.14 (t, J = 5.0 Hz, 2 H), 3.65 (t, J = 5.0 Hz, 2 H), 3.74 (S, 3 H), 6.78 (S, 1 H), 6.86 (d, J = 7.0 Hz, 1 H), 6.97 (dd, J_1 =2.0 Hz, J_2 = 6.4 Hz, 1 H), 7.21-7.28 (m, 3 H), 7.35 (t, J = 5.6 Hz, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.7, 157.2, 152.5, 151.0, 153.6, 130.7, 128.2, 126.6, 126.1, 126.0, 125.9, 119.2, 115.1, 112.9, 66.2, 55.6, 49.4, 34.5, 31.0. MS (ESI) = 393.5 (M^++1). Anal. Calcd for $C_{23}H_{28}N_4O_2$: C 70.38, H 7.19, N 14.27, O 8.15. Found: C 70.35, H 7.22, N 14.30, O 8.11.

5-(Biphenyl-3-yl)-4-(3-methoxyphenyl)-*N*,*N*-dimethyl-4*H*-1,2,4-triazol-3-amine (1g): white solid, yield 83%. TLC (ethyl acetate:hexane = 1:2), R_f = 0.57, mp116-118°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 6 H), 3.76 (s, 3 H), 6.81(t, J = 2.0 Hz, 1 H), 6.87 (d, J = 1.0 Hz, 2 H), 7.01 (dd, J_1= 1.0 Hz, J_2=

5.4 Hz, 1 H), 7.29-7.40 (m, 8 H), 7.51-7.54 (m, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.6, 159.3, 152.0, 141.0, 140.3, 136.4, 130.6, 128.7, 128.7, 128.0, 127.8, 127.5, 127.4, 127.3, 127.0, 119.9, 114.7, 113.4, 55.6, 41.5. MS (ESI) = 371.3 (M^++1). Anal. Calcd for $C_{23}H_{22}N_4O$: C 74.57, H 5.99, N 15.12, O 4.32. Found: C 74.56, H 6.02, N 15.11, O 4.30.

5-(Biphenyl-4-yl)-4-(3-methoxyphenyl)-*N*,*N*-dimethyl-4*H*-1,2,4-triazol-3-amine (1h): white solid, yield 81%. TLC (EtOAc:hexane = 1:2), R_f = 0.56, mp126-128°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.77 (s, 6 H), 3.76 (s, 3 H), 6.85 (t, J_1 = 2.5 Hz, J_2 = 5.0 Hz , 2 H), 6.99 (d, J = 1.2 Hz, 1 H), 7.34 (t, J = 7 Hz, 1 H), 7.40-7.49 (m, 5 H), 7.67 (t, J_1 = 7.2 Hz, J_2 = 9.0 Hz, 2 H), 7.77(d, J = 8.0 Hz, 1 H), 7.83 (m, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.6, 159.5, 152.0, 136.2, 130.6, 128.8, 128.5, 127.8, 127.7, 127.6, 127.0, 126.3, 125.5, 119.8, 114.8, 113.4, 55.6, 41.5. MS (ESI) = 371.3 (M^++1). Anal. Calcd for $C_{23}H_{22}N_4O$: C 74.57, H 5.99, N 15.12, O 4.32. Found: C 74.58, H 5.97, N 15.09, O 4.31.

ACKNOWLEDGEMENTS

The financial support from the Biotechnology Research and Development Corporation (BRDC, Peoria, IL) for this research is gratefully acknowledged.

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21. Procedure for the synthesis of 1-bromo-3-*tert*-butylbenzene: *p*-*tert*-butylaniline (8.5mL, 50.7 mmol) was dissolved in $CHCl_3$ (200 mL) and cool to 0 ^oC. NBS (9.03g, 1.0 equiv.) was added slowly under vigrous stirring to control the temperature <3 ^oC, and the brown solution was stirred at rt for 5 h. GC-MS indicated >99% product was the desired 2-bromo-4-*tert*-butylaniline. The $CHCl_3$ solution was extracted by water (3×50 mL) and concentrated to use directly for next step. *tert*-Butyl nitrite (10 mL, 1.5 equiv.) was dropped into DMF (30 mL) and the solution was stirred at 65-67 ^oC, to which 4-*tert*-butyl-2-bromoaniline (50 mmol) was added carefully. The black solution was stirred at 65 ^oC for over night. The product was purified by flash chromatography to obtain 1-bromo-3-*tert*-butylbenzene (8.0 g, 75%) as light yellow liquid. The structure was confirmed by GC-MS and NMR.
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