# A Novel Approach for the Conversion of Primary Amides into Tetrazoles by Using Tributyltin Chloride and Sodium Azide in the Presence of DMF

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**Abstract:** A novel and efficient one-pot synthesis of tetrazole derivatives such as Irbesartan and its analogues has been described from the primary acid amide derivatives. Thus 2-alkyl-3-[*p*-(*o*-amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one derivatives or 4-[α-(acylamino)cyclopentamidomethyl]-2′-carboxamidobiphenyl derivatives were treated with tributyltin chloride and sodium azide in *o*-xylene in the presence of DMF to afford irbesartan and its analogues without generation of nitriles. The synthesis of these new starting materials is also described, and two of the derivatives have been used as new intermediates in the preparation of irbesartan.

**Key words:** primary acid amides, tributyltin chloride, sodium azide, *o*-xylene, DMF, irbesartan

Tetrazole compounds have been used as anticancer[1] and antimicrobial[2] agents. Recently tetrazole compounds were found to be very useful drugs in the treatment of cardiovascular complaints. Irbesartan is one of the important drugs in this class of tetrazole compounds.[3–6] Very few synthetic approaches have been reported for the conversion of amides into tetrazoles. In 1990, Duncia et al. discovered that the protected primary amides were selectively converted into 5-substituted tetrazole derivatives by reacting with azidotrimethylsilane in presence of triphenylphosphine and diethyl azidocarboxylate (DEAD). Thus cyanoethyl group has been used as protecting group to facilitate the formation of tetrazole without the conversion of the primary amide back into its corresponding nitrile.[7] In 1997, Elmorsy et al., for the first time, found that the primary acid amides can be converted into the corresponding 5-substituted tetrazole derivatives by treating them with triazidochlorosilane, which was prepared in situ from tetrachlorosilane and sodium azide in acetonitrile.[8] Based on the available literature, it is the only method which can be used for the conversion of primary amides into tetrazole derivatives. To the best of our knowledge, there is no report for the conversion of primary acid amides into tetrazoles by using tributyltin chloride and sodium azide.

In the present contribution, we report the reaction of primary amides with tributyltin chloride and sodium azide in the presence of DMF in *o*-xylene, which generates the corresponding tetrazole derivative, without formation of nitriles, in good yields (Scheme 1).

Our initial investigation was directed towards the conversion of primary amides into nitriles with *p*-toluenesulfonyl chloride in presence of pyridine. But we failed to achieve the desired yields and quality due to the formation of unwanted impurities.

Immediately we started the investigation on the direct conversion of primary amides **4a**–**e** into tetrazoles. The new compounds **3a**–**e** and **4a**–**e** were prepared and used for the study. Compound **1a**–**e** were synthesized according to the method described in the literature.[9] Compounds **3a**–**e** were synthesized by the coupling of compounds **1a**–**e** with amine **2**.[10,11] Compounds **3b** and **4b** were found to be key intermediates for the synthesis of irbesartan. Initially we started investigating by using primary amides **4a**–**e**. We examined different reagents such as triazidochlorosilane, trimethylsilylazide and a mixture of tributyltin chloride and sodium azide. Tributyltin chloride and sodium azide were found to be the most effective combination for this tetrazole formation. A significant solvent effect was found in the cyclization. When the reaction was carried out in *o*-xylene, the yield was 30–40%, the reactions did not go to completion on large scale, and two molar equivalents each of tributyltin chloride and sodium azide were required. However, *o*-xylene was suitable for the preparation of small samples of tetrazole compounds by using this technique. The yields were increased by about 30–40% by introducing one molar equivalent of DMF in the reaction (Table 1, entries 1–5).

Thereafter, we started investigating the direct conversion of amides **3a**–**e** into the corresponding tetrazoles without formation of nitriles. However, the reactions proceeded through the formation of amides **4a**–**e** and the overall yields went up by about 10% (Table 1).

The selective formation of tetrazoles (entries 1–5) is considered to proceed as follows: (i) formation of iminotributyltin ether **6** from amide, (ii) greater tendency of formation of oxonium salt **7** to prevent the formation of nitrile, (iii) elimination of tributyltin hydroxide enhances the intermolecular cyclization to form the tetrazole **5** in the presence of DMF. The reaction mechanism is depicted in Scheme 2.

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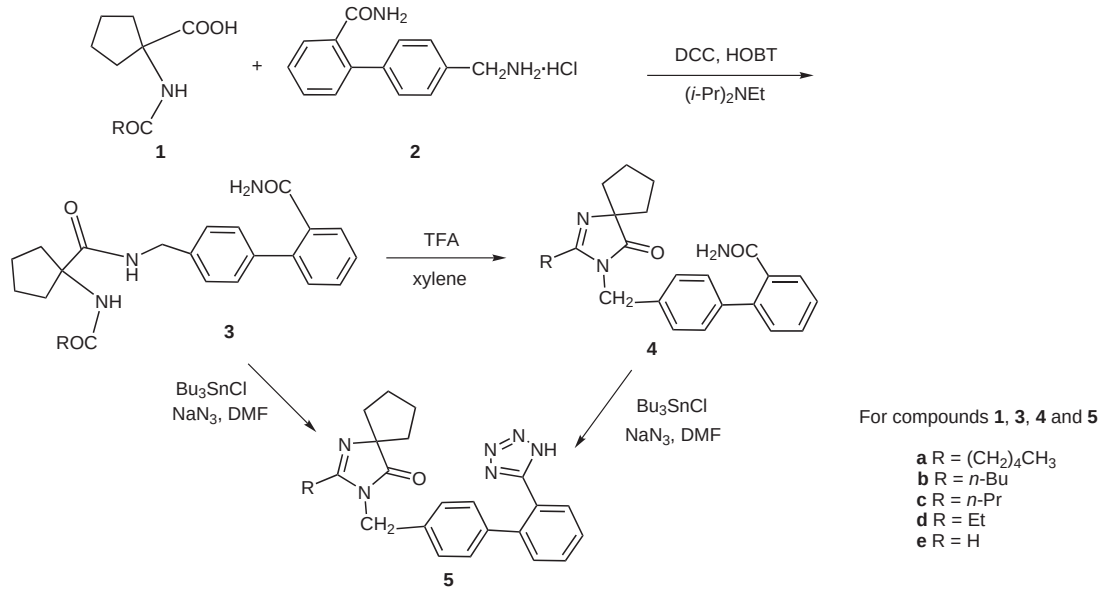
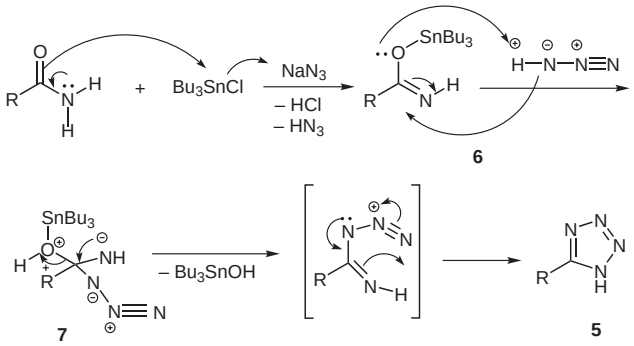



**Scheme 1**

**Table 1** Preparation of Primary Acid Amides **3a**–**e**[12] and **4a**–**e**[13] and Their Conversion into Tetrazoles **5a**–**e**[14] with Tributyltin Chloride and Sodium Azide in the Presence of DMF

| Entry | R | Starting compound | Product | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $(CH_2)_4CH_3$ | **1a** | **3a** | 6 | 85 |
| 2 | *n*-Bu | **1b** | **3b** | 4.5 | 90 |
| 3 | *n*-Pr | **1c** | **3c** | 3 | 80 |
| 4 | Et | **1d** | **3d** | 3 | 72 |
| 5 | H | **1e** | **3e** | 1 | 60 |
| 6 | $(CH_2)_4CH_3$ | **3a** | **4a** | 24 | 60 |
| 7 | *n*-Bu | **3b** | **4b** | 17 | 65 |
| 8 | *n*-Pr | **3c** | **4c** | 15 | 40 |
| 9 | Et | **3d** | **4d** | 15 | 33 |
| 10 | H | **3e** | **4e** | 15 | 55 |
| 11 | $(CH_2)_4CH_3$ | **4a** | **5a** | 40 | 53 |
| 12 | *n*-Bu | **4b** | **5b** | 40 | 60 |
| 13 | *n*-Pr | **4c** | **5c** | 40 | 50 |
| 14 | Et | **4d** | **5d** | 40 | 42 |
| 15 | H | **4e** | **5e** | 18 | 35 |
| 16 | $(CH_2)_4CH_3$ | **3a** | **5a** | 60 | 56 |
| 17 | *n*-Bu | **3b** | **5b** | 50 | 65 |
| 18 | *n*-Pr | **3c** | **5c** | 40 | 60 |
| 19 | Et | **3d** | **5d** | 40 | 52 |
| 20 | H | **3e** | **5e** | 25 | 40 |

[a] Isolated yield. With the exception of compounds **3b**, **4b** and **5b** the yields were not optimized; the reaction was generally run once.




**Scheme 2**

The chemistry reported above permits the direct formation of tetrazoles from primary acid amides. The reaction proceeds at higher temperature and in good to excellent yields without catalyst. It is regioselective for preparing 5-substituted tetrazole derivatives. The method outlined will be of high interest not only for the conversion of simple primary amides, it is also useful for the synthesis of tetrazoles from compounds containing multiple amide linkages.

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(11) Solvents and reagents were obtained from commercial sources and used without purification. Melting points were determined on a Polmon melting point apparatus. All melting points are uncorrected. The $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker 300 spectrometer at 300 MHz and 75 MHz, respectively. The chemical shifts are reported in δ (ppm) relative to TMS. The mass spectra were recorded on a API 2000 Perkin Elmer PE-SCIEX mass spectrometer.

**Synthesis of 2-(4-Aminomethylphenyl)benzamide Hydrochloride (2)**: 2-(4-Aminomethylphenyl)benzonitrile hydrochloride (150 g, 0.614 mol) was neutralized in a mixture of $CH_2Cl_2$ (750 mL) and $H_2O$ (300 mL) at 15–20 °C by the addition of NaOH (25.90 g, 0.647 mol). The organic layer was separated and washed with $H_2O$ and concentrated. The concentrated mass was dissolved in *t*-BuOH (450 mL) and heated to 65 °C. Freshly prepared KOH powder (48.52 g, 85%, 0.736 mol) was added and heated to reflux for 7 h. The reaction mixture was cooled to r.t. and diluted with $CH_2Cl_2$ (750 mL) followed by $H_2O$ (600 mL). The aqueous layer was separated and extracted with $CH_2Cl_2$ (750 mL). The combined $CH_2Cl_2$ extract was washed with $H_2O$ (300 mL) and dried over anhyd $Na_2SO_4$. The pH was adjusted to 1.2–1.4 with HCl acid at 2–5 °C over a period of 60 min and stirring was continued for another 60 min. The precipitate obtained was collected by filtration and dried to afford the title compound (135 g, 83.8%) as a white crystalline powder; mp 140–142 °C (Lit.[3] 182 °C). $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 4.03 (br s, 2 H), 7.33–7.57 (m, 10 H), 8.66 (br s, 3 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 42.7, 128.1, 128.4, 129.3, 129.7, 130.1, 130.7, 133.8, 138.2, 139.1, 141.4, 171.9. MS: *m*/*z* = 227.2 [M$^+$].

(12) **Typical Experimental Procedure for the Synthesis of 4-[α-(*n*-Acylamino)cyclopentamidomethyl]-2′-carboxamidobiphenyls 3a–e**: Compound **2** (115 g, 0.438 mol) was added to a mixture of dicyclohexylcarbodiimide (DCC; 99.36 g, 0.482 mol) in $CH_2Cl_2$ (2300 mL) followed by compound **1a**[10] (93.38 g, 0.438 mol) at 25–30 °C. Thereafter, *N*-hydroxybenzotriazole (11.85g, 0.087 mol) was added followed by diisopropylethylamine (62.70 g, 0.482 mol) and heated to reflux for 6 h. The reaction mixture was cooled to 25 °C and the salts were filtered. The filtrate was washed with $H_2O$ (230 mL) followed by sat. $Na_2CO_3$ solution (575 mL) and concentrated to a 1200-mL volume. The slurry obtained was cooled to 10–15 °C and stirred for 1 h. The solid was filtered and washed with precooled $CH_2Cl_2$ (230 mL) and dried to afford compound **3b** as a white powder; mp 100–101 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.83–0.88 (t, *J* = 7.41 Hz, 3 H), 1.22–1.29 (m, 2 H), 1.45–1.50 (m, 2 H), 1.60–2.00 (m, 4 H), 1.87–2.07 (m, 4 H), 2.11–2.16 (t, *J* = 7.41 Hz, 2 H), 4.28–4.30 (d, *J* = 6.04 Hz, 2 H), 7.22–7.48 (m, 8 H), 7.27, 7.62 (2 × br s, 2 H), 7.89 (s, 1 H), 8.02–8.06 (t, *J* = 6.04 Hz, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.7, 22.7, 24.8, 28.2, 36.1, 37.1, 42.9, 67.1, 127.3, 127.7, 128.9, 130, 130.7, 138.2, 139.4, 139.6, 139.8, 171.1, 173.4, 174.7. MS: *m*/*z* = 422.2 [M$^+$]. Anal. Calcd for $C_{25}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 71.01; H, 7.41; N, 9.99.

**4-[α-(*n*-Hexanoylamino)cyclopentamidomethyl]-2′-carboxamidobiphenyl (3a)**: mp 137–138 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.82–0.86 (t, *J* = 7.41 Hz, 3 H), 1.24–1.28 (m, 2 H), 1.47–1.52 (m, 2 H), 1.61–1.63 (m, 4 H), 1.88–2.07 (m, 8 H), 2.10–2.15 (t, *J* = 7.41 Hz, 2 H), 4.29–4.30 (d, *J* = 6.04 Hz, 2 H), 7.22–7.48 (m, 8 H), 7.27, 7.62 (2 × br s, 2 H), 7.89 (s, 1 H), 8.02–8.06 (t, *J* = 6.04 Hz, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.8, 22.8, 24.8, 25.7, 31.8, 36.3, 37.1, 42.8, 67.1, 127.3, 127.7, 128.3, 128.9, 130.0, 130.6, 138.2, 139.4, 139.5, 139.8, 172.1, 173.4, 174.7. MS: *m*/*z* = 434.2 [M$^-$]. Anal. Calcd for $C_{26}H_{33}N_3O_3$: C, 71.70; H, 7.64; N, 9.65. Found: C, 71.44; H, 7.65; N, 9.67.

**4-[α-(*n*-Butanoylamino)cyclopentamidomethyl]-2′-carboxamidobiphenyl (3c)**: mp 108–109 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.82–0.85 (t, *J* = 7.41 Hz, 3 H), 1.47–1.52 (m, 2 H), 1.60–1.62 (m, 4 H), 1.88–2.03 (m, 4 H), 2.08–2.13 (t, *J* = 7.41 Hz, 2 H), 4.28–4.30 (d, *J* = 6.04 Hz, 2 H), 7.22–7.46 (m, 8 H), 7.25, 7.45 (2 × br s, 2 H), 7.88 (s, 1 H), 8.01–8.05 (t, *J* = 6.04 Hz, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.5, 19.4, 24.8, 37.1, 38.3, 39.5, 42.8, 67.1, 127.3, 127.7, 128.3, 128.9, 130.0, 138.2, 139.4, 139.5, 139.8, 172.1, 173.2, 174.7. MS: *m*/*z* = 406.3 [M$^-$]. Anal. Calcd for $C_{24}H_{29}N_3O_3$: C, 70.74; H, 7.17; N, 10.31. Found: C, 71.00; H, 7.16; N, 10.31.

**4-[α-(*n*-Propylamino)cyclopentamidomethyl]-2′-carboxamidobiphenyl (3d)**: mp 189–190 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.96–1.00 (t, *J* = 7.41 Hz, 3 H), 1.62–1.64 (m, 4 H), 1.86–2.10 (m, 4 H), 2.13–2.18 (t, *J* = 7.41, 2 H), 4.28–4.30 (d, *J* = 6.04 Hz, 2 H), 7.22–7.49 (m, 8 H), 7.32, 7.61 (2 × br s, 2 H), 7.86 (s, 1 H), 8.03–8.07 (t, *J* = 6.04 Hz, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 10.5, 24.9, 29.4, 37.2, 42.8, 67, 127.3, 127.7, 128.3, 130, 130.7, 138.2, 139.4, 139.5, 139.9, 172.1, 174, 174.7. MS: *m*/*z* = 392.2 [M$^-$]. Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.50; H, 6.91; N, 10.70.

**4-[α-(*n*-Formyloxyamino)cyclopentamidomethyl]-2′-carboxamidobiphenyl (3e)**: mp 87–88 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.65–1.67 (m, 4 H), 1.90–2.11 (m, 4 H), 4.29–4.31 (d, *J* = 6.04 Hz, 2 H), 7.22–7.48 (m, 8 H), 7.26, 7.61 (2 × br s, 2 H), 7.96 (s, 1 H), 8.20–8.24 (t, *J* = 6.04 Hz, 1 H), 8.27 (s, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 24.8, 38.0, 42.9, 66.7, 127.3, 127.7, 128.3, 129.0, 129.1, 130.0, 130.7, 138.2, 139.4, 139.5, 139.7, 162.1, 165.4, 172.1, 174.1. MS: *m*/*z* = 434.2 [M$^-$]. Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.11; H, 6.34; N, 11.51.

(13) **Typical Experimental Procedure for the Synthesis of 2-Alkyl-3-[*p*-(*o*-amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-ones 4a–e**: Trifluoroacetic acid (15.5 g, 0.136 mol) was added to a preheated suspension of 4-[α-(*n*-pentanoylamino)cyclopentamidomethyl]-2′-carboxamidobiphenyl (**3b**; 50 g, 0.124 mol) in *o*-xylene (500 mL) over a period of 30 min. Thereafter, the mixture was heated to reflux for 18 h. Xylene was distilled off and a mixture of EtOAc (750 mL) and $H_2O$ (250 mL) was added at 55 °C and the reaction mixture was cooled to r.t. The pH was adjusted to 9.0–9.5 with aq $NH_3$ and stirred for 5 min. The organic layer was separated and washed with $H_2O$ (250 mL). The organic layer was concentrated to a volume of about 250 mL and cooled to 0–5 °C. The slurry obtained was stirred for 30 min to complete the crystallization. The solid obtained was filtered and washed with precooled EtOAc (50 mL) and dried to afford 2-(*n*-butyl)-3-[*p*-(*o*-amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one (**4b**) as a white crystalline powder; mp 146–147 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.79–0.83 (t, *J* = 7.41 Hz, 3 H), 1.20–1.29 (m, 2 H), 1.48–1.51 (m, 2 H), 1.67–1.85 (m, 8 H), 2.32–2.37 (t, *J* = 6.04 Hz, 2 H), 4.71 (s, 2 H), 7.15–7.50 (m, 8 H), 7.30, 7.66 (2 × br s, 2 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.5, 22.4, 26.3, 27.5, 28.4, 37.7, 43.2, 76.7, 127.0, 127.9, 128.4, 129.6, 130.1, 130.7, 131.9, 136.8, 138.2, 139.2, 140.5, 162.0, 172.0, 186.6. MS: *m*/*z* = 404.5 [M$^+$]. Anal. Calcd for $C_{25}H_{29}N_3O_2$: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.70; H, 7.25; N, 10.43.

**2-(*n*-Pentyl)-3-[*p*-(*o*-amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one (4a)**: mp 142–144 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.78–0.82 (t, *J* = 7.41 Hz, 3 H), 1.20–1.23 (m, 2 H), 1.25–1.85 (m, 10 H), 2.31–2.36 (t, *J* = 6.04 Hz, 2 H), 4.71 (s, 2 H), 7.15–7.49 (m, 8 H), 7.30, 7.65 (2 × br s, 2 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.7, 22.6, 25.1, 26.3, 28.6, 31.5, 37.7, 43.2, 76.7, 127.0, 127.9, 128.4, 129.6, 130.1, 130.7, 136.8, 138.2, 139.2, 140.4, 162.0, 171.9, 186.6. MS: *m*/*z* = 418.0 [M$^+$]. Anal. Calcd for $C_{26}H_{31}N_3O_2$: C, 74.79; H, 7.48; N, 10.06. Found: C, 75.00; H, 7.48; N, 10.11.

**2-(*n*-Propyl)-3-[*p*-(*o*-amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one (4c)**: mp 182–184 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.85–0.90 (t, *J* = 7.41 Hz, 3 H), 1.53–1.58 (m, 2 H), 1.60–1.99 (m, 10 H), 2.30–2.35 (t, *J* = 6.04 Hz, 2 H), 4.78 (s, 2 H), 7.08–7.50 (m, 8 H), 7.30, 7.65 (2 × br s, 2 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.3, 18.8, 26.3, 30.5, 37.7, 43.1, 76.7, 127.0, 127.9, 128.4, 129.6, 130.1, 136.8, 138.2, 139.2, 140.4, 161.8, 172.0, 86.6. MS: *m*/*z* = 390.3 [M$^+$]. Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 74.20; H, 7.00; N, 10.80.

**2-Ethyl-3-[*p*-(*o*-amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one (4d)**: mp 102–104 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.95–0.99 (t, *J* = 7.41 Hz, 3 H), 1.60–1.63 (m, 8 H), 2.20–2.25 (t, *J* = 6.04 Hz, 2 H), 4.78 (s, 2 H), 7.18–7.40 (m, 8 H), 7.30, 7.65 (2 × br s, 2 H). $^{13}$C NMR (MHz, DMSO-$d_6$): δ = 14.3, 19.8, 24.3, 37.2, 38.5, 39.4, 42.1, 76.7, 127.4, 127.9, 128.4, 129.6, 130.1, 138.2, 139.2, 139.9, 161.7, 172.0, 186.5. MS: *m*/*z* = 376.1 [M$^+$]. Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.90. Found: C, 73.61; H, 6.70; N, 11.91.

**3-[*p*-(*o*-Amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one (4e)**: mp 152–154 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.67–1.84 (m, 8 H), 4.67 (s, 2 H), 7.23–7.50 (m, 8 H), 7.29, 7.66 (2 × br s, 2 H), 8.03 (s, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 26.2, 37.5, 44.2, 77.7, 127.7, 127.9, 128.0, 129.6, 130.1, 130.7, 136.6, 138.2, 139.2, 140.6, 153.3, 171.9, 185.6. MS: *m*/*z* = 390.3 [M$^+$]. Anal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.70; H, 6.10; N, 12.11.

(14) **Typical Experimental Procedure for the Synthesis of 2-Alkyl-3-[2′-(1*H*-tetrazol-5-yl)(1,1′-biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-ones 5a–e**: Sodium azide (16.20 g, 0.249 mol) was added to tributyltin chloride (81 g, 0.249 mol) at 25–30 °C under a nitrogen atmosphere and the contents were stirred for 30 min at the same temperature. Thereafter, DMF (13 g, 0.18 mol) was added at 25–30 °C and the stirring continued for 30 min at temperatures below 45 °C. *o*-Xylene (50 mL) was added followed by 2-(*n*-butyl)-3-[*p*-(*o*-amidophenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one (**4b**; 50 g, 0.124 mol). The temperature was raised to 150–155 °C and the stirring was continued for 60 h at the same temperature under nitrogen atmosphere. Thereafter, the reaction mixture was cooled to 25 °C and diluted with $CH_2Cl_2$ (200 mL), *o*-xylene (100 mL) and $H_2O$ (100 mL) at the same temperature. HCl acid (13 g, 35%) was added in 15 min at 25 °C and stirring was continued for 1 h at the same temperature. The precipitated solid was filtered and washed with a $CH_2Cl_2$ and *o*-xylene (1:1) mixture. The wet material was dried under reduced pressure at 65–70 °C to afford the compound **2b** (54.5 g). It was dissolved in EtOH (1090 mL) at reflux temperature to get a cloudy solution and was cooled to 60 °C. Carbon (5 g) and hyflo (10 g) were added and the mixture was again refluxed for 15 min. Thereafter, the temperature was brought down to 60 °C and the mixture was filtered to remove carbon. The filtrate was concentrated to 500-mL volume under reduced pressure at 55–65 °C. The resulting suspension was cooled to 5–10 °C and stirred for 1 h at the same temperature. The solid was filtered and washed with precooled EtOH (100 mL) and dried under reduced pressure at 65–70 °C to afford the title compound, 2-(*n*-butyl)-3-[2′-(1*H*-tetrazol-5-yl)(1,1′-biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one [irbesartan (**5b**); 42.5 g, 80%)] as a white crystalline powder; mp 181–182 °C (Lit.[3] 182 °C). $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.70–0.91 (t, *J* = 7.41 Hz, 3 H), 1.20–1.40 (sext, 2 H), 1.45–1.60 (quint, 2 H), 1.60–2.00 (m, 8 H), 2.20–2.40 (t, *J* = 6.04 Hz, 2 H), 3.00–3.60 (br s, 1 H), 4.60–4.80 (s, 2 H), 7.32–7.95 (m, 8 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.5, 22.4, 26.3, 27.4, 28.3, 37.7, 43.1, 76.7, 124.3, 127.1, 128.7, 130.1, 131.4, 131.9, 137.2, 139.2, 141.9, 155.9, 162.0, 186.5. MS: *m*/*z* = 429 [M$^+$].

**2-(*n*-Pentyl)-3-[2′-(1*H*-tetrazol-5-yl)(1,1′-biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (5a)**: mp 184–185 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.78–0.83 (t, *J* = 7.41 Hz, 3 H), 1.19–1.21 (m, 4 H), 1.48–1.84 (m, 10 H), 2.25–2.30 (t, *J* = 6.04 Hz, 2 H), 3.00–3.60 (br s, 1 H), 4.67 (s, 2 H), 7.08–7.70 (m, 8 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.7, 22.6, 25.0, 26.3, 27.4, 28.6, 31.4, 37.7, 43.1, 76.7, 124.3, 127.1, 128.7, 130.1, 131.4, 131.5, 131.9, 137.2, 139.2, 141.9, 155.9, 162.0, 186.5. MS: *m*/*z* = 443.2 [M$^+$]. Anal. Calcd for $C_{26}H_{30}N_6O$: C, 70.56; H, 6.83; N, 18.99. Found: C, 70.71; H, 6.84; N, 19.00.

**2-(*n*-Propyl)-3-[2′-(1*H*-tetrazol-5-yl)(1,1′-biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (5c)**: mp 110–112 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.83–0.89 (t, *J* = 7.41 Hz, 3 H), 1.55–1.60 (quint, 4 H), 1.85–2.02 (m, 8 H), 2.72–2.77 (t, *J* = 6.04 Hz, 2 H), 3.20–3.80 (br s, 1 H), 7.10–7.20 (m, 4 H), 7.50–7.70 (m, 4 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 14.0, 19.0, 26.1, 29.8, 37.6, 44.2, 72.7, 124.4, 127.7, 128.8, 130.2, 131.4, 131.5, 131.9, 134.9, 139.9, 141.8, 155.9, 172.5, 180.4. MS: *m*/*z* = 413.2 [M$^-$]. Anal. Calcd for $C_{24}H_{26}N_6O$: C, 69.54; H, 6.32; N, 20.27. Found: C, 69.23; H, 6.32; N, 20.29.

**2-Ethyl-3-[2′-(1*H*-tetrazol-5-yl)(1,1′-biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (5d)**: mp 104–106 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.19–1.24 (t, *J* = 7.41 Hz, 3 H), 1.94–2.03 (m, 8 H), 2.76–2.78 (q, 2 H), 3.50 (br s, 1 H), 4.86 (s, 2 H), 7.20–7.30 (m, 4 H), 7.60–7.78 (m, 4 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 9.8, 22.3, 26.2, 37.5, 44.0, 73.5, 124.3, 127.7, 128.7, 130.2, 131.4, 131.5, 131.9, 135.3, 139.7, 141.8, 155.9, 171.6, 181.5. MS: *m*/*z* = 399.1 [M$^-$]. Anal. Calcd for $C_{23}H_{24}N_6O$: C, 68.98; H, 6.04; N, 20.99. Found: C, 69.11; H, 6.03; N, 21.00.

**3-[2′-(1*H*-Tetrazol-5-yl)(1,1′-biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (5e)**: mp 190–191 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.65–1.86 (m, 8 H), 4.65 (s, 2 H), 7.08–7.19 (m, 4 H), 7.54–7.71 (m, 4 H), 8.0 (s, 1 H), 16.37 (br s, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 26.2, 37.4, 44.1, 77.7, 124.3, 127.8, 128.7, 130.1, 131.5, 132.0, 137, 139.4, 141.9, 153.3, 155.9, 185.5. MS: *m*/*z* = 371.1 [M$^-$]. Anal. Calcd for $C_{21}H_{20}N_6O$: C, 67.73; H, 5.41; N, 22.57. Found: C, 67.91; H, 5.41; N, 22.60.