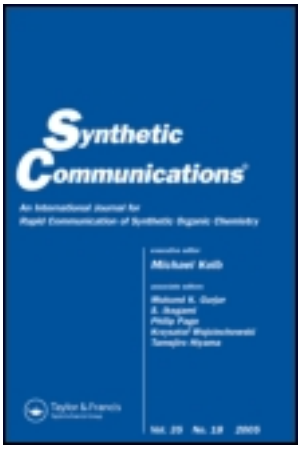

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Synthesis of Fused [5,5]-1,2,4-Triazoles via Tandem Thioimidate Cyclopropane Rearrangement-Cyclization

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Synthesis of Fused [5,5]-1,2,4-Triazoles via Tandem Thioimidate Cyclopropane Rearrangement–Cyclization

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Department of Medicinal Chemistry, Merck Research Laboratories, West Point, Pennsylvania, USA

Abstract: The synthesis of fused [5,5]-1,2,4-triazoles via a tandem cyclopropane rearrangement–cyclization sequence is described. Optimization of the cyclization reaction was achieved thermally using *i*PrOH as the solvent in the presence of TEA. This method was applied to the preparation of 3-substituted-7-aryl-pyrrolo-1,2,4-triazoles in good to excellent yields.

Keywords: Cyclizations, cyclopropane, fused-ring systems, rearrangements, triazoles

The synthesis of fused 1,2,4-triazoles has attracted considerable attention because of the varied biological activities of these compounds.[1] In connection with an ongoing synthesis program, we were interested in preparing fused [5,5]-1,2,4-triazoles. A typical approach to 1,2,4-fused triazoles involves the condensation of an imino ether or thioether with an acyl hydrazide to provide an amidrazone intermediate that undergoes cyclodehydration to yield the triazole.[2] Recently, we reported that the thioimidate cyclopropane rearrangement is an efficient method for the synthesis of 2,3-diaminodihydropyrroles.[3] As shown in Scheme 1, we envisioned that the initial product of the rearrangement, *S*-methyl thioimidate **I**, could also serve as a useful intermediate in the preparation of fused [5,5]-1,2,4-

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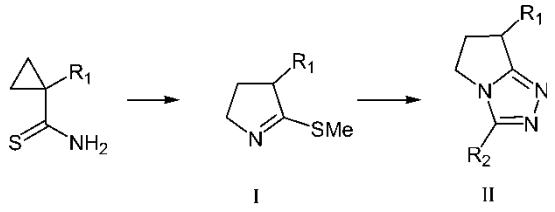


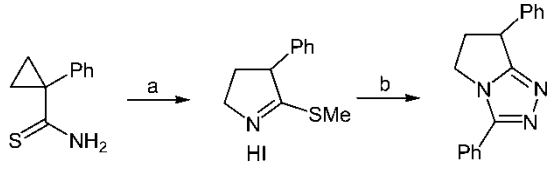
I II

Scheme 1. Thioimidate cyclopropane rearrangement–cyclization.

triazoles such as **II**. As such, a tandem rearrangement–cyclization sequence would represent a viable method for the synthesis of this type of fused [5,5]-1,2,4-triazole. Herein, we describe the execution of this plan and report our results to prepare 3-substituted-7-aryl-pyrrolo-1,2,4 triazoles using this approach.

The methyl iodide–mediated rearrangement of thioamide **1** proceeded smoothly in acetone at 60°C to afford HI salt **2a** in essentially quantitative yield (Scheme 2). The reaction of **2a** with benzhydrazide to form triazole **3a** was then investigated in various solvents and temperatures. Results are shown in Table 1.

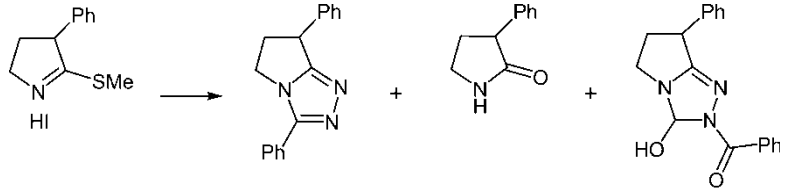
The condensation of thio-imino ethers with hydrazides to form triazoles can be capricious and in some cases requires extensive heating in solvents such as DMF, leading to only moderate isolated yields.[4] Accordingly, we chose to investigate microwave heating as an approach to improve the rate and efficiency of this transformation. Initial attempts involved reaction of HI salt **2a** with 1.5 equivalents of the hydrazide in the absence of base. Reaction progress was monitored by liquid chromatography/mass spectrometry (LC/MS). Low yields ($\leq$15%) and multiple side products were observed when the mixtures were subjected to heating via microwave in various solvents for 30 min (entries **1**–**4**). For reactions carried out in N,N-dimethylformamide (DMF), the primary side products **4** and **5** resulted from hydrolysis and incorporation of a formyl group due to decomposition of the solvent under the experimental conditions that were employed. Addition of triethylamine did not improve either the conversion of the reactions or the purity of the products with microwave heating (entry **5**).



1 2a 3a

Scheme 2. Synthesis of 3,7-diphenyl-pyrrolo-1,2,4-triazole.

Table 1. Optimization of triazole **3a** synthesis

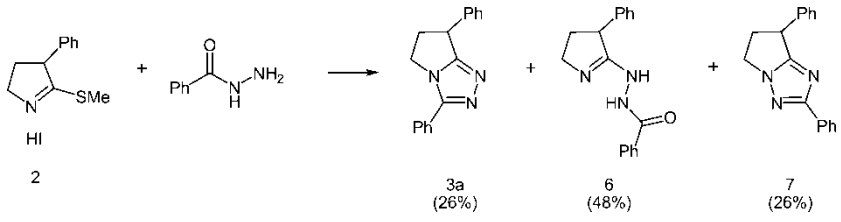


2 3a 4 5

Entry	Solvent	Additive	Temp (°C)	t (h)	Conversion (%)[a]	Yield (%)[b]
1	DMSO	—	180 (μwave)	0.5	<5	—
2	EtOH	—	180 (μwave)	0.5	<5	—
3	DMF	—	180 (μwave)	0.5	15	15
4	*i*PrOH	—	180 (μwave)	0.5	<5	—
5	DMSO	TEA	180 (μwave)	0.5	<5	—
6	DMF	—	120	3	<5	—
7	DMF	TEA	150	24	72	66
8	DMSO	—	120	24	<5	—
9	DMSO	TEA	120	72	>97	71
10	DMSO	K_2CO_3	120	48	<15	—
11	*i*PrOH	—	180	24	>97[c]	—
12	*i*PrOH	TEA	150	3	>97	>97

Notes: Reaction conditions: 0.10 M solutions, sealed vials.
[a]Conversion based on LC/MS.
[b]Isolated yield.
[c]Total conversion. Contains mixture of **3a**:**6**:**7** (see Scheme 3).

As a consequence of the poor results obtained using microwave technology, we next evaluated the cyclization under standard thermal conditions. Employing polar aprotic solvents such as DMF or dimethylsulfoxide (DMSO) in the absence of base, we again observed poor yields (entries **6**, **8**). Use of the inorganic base potassium carbonate also led to slow reaction times and incomplete conversions even after extended reaction times (entry **10**). By contrast, addition of triethylamine (2.0 eq.) in DMF or DMSO led to efficient conversions under these thermal conditions (entries **7**, **9**) to provide **3a** in 66% isolated yield. As previously described, reactions in DMF also produced side products **4** and **5**, which were not observed when DMSO was employed as the solvent. Additionally, an increase in overall reaction yield was obtained with DMSO. Because thermal cyclizations of amidrazones have been previously reported in alcohols,[1b,4] the use of isopropanol was examined, and this led to the best conversions and highest product yields (>97%). The high yield is noteworthy because cyclizations to form fused [5,5]-1,2,4-triazoles have been reported to proceed in low yields, as a result of ring strain.[2a,5] It is interesting to note that in the absence of base,

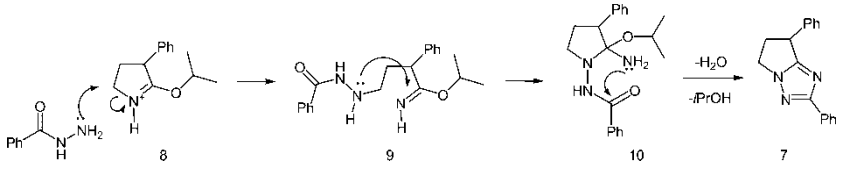


Scheme 3. Formation of triazole isomer.

the reaction in isopropanol proceeded slowly and resulted in a mixture of desired product **3a**, uncyclized intermediate **6**, and isomer **7** (Scheme 3). The structure of the unanticipated isomer **7** was determined through the assignment of proton and carbon chemical shifts from the analysis of HMQC and HMBC spectra. The two-, three-, and four-bond HMBC correlations and ROEs are consistent with the structure depicted.

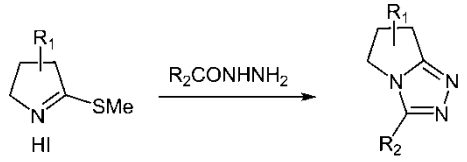
We propose that regioisomer **7** is formed as a consequence of the formation of isopropyl imidate **8** (Scheme 4). (Heating **2** in *i*PrOH at 180°C afforded isopropyl imidate **8**.) The resultant steric hindrance provided by the isopropyl group at the 2-position leads to ring-opening of the pyrrolidine core. The hydrazide preferentially attacks at the 5-position, which is activated by virtue of the adjacent protonated imine nitrogen. Subsequent condensation of the hydrazide with the isopropyl imidate in **9**, followed by cyclodehydration, affords isomer **7**. This isomer is not observed under basic conditions or with the nonnucleophilic solvents DMF and DMSO.

Having improved the conditions (*i*PrOH, TEA, 150°C) for synthesizing 1,2,4-triazoles, we next sought to explore the scope of our protocol for the preparation of other 3-substituted 1,2,4-triazoles (Table 2). Yields were notably higher for reactions conducted in *i*PrOH relative to those observed in DMSO (Table 2, entries **1**–**4**), which is consistent with the results obtained with benzhydrazide. The fastest reaction rates were observed with the least sterically hindered hydrazide **3g**. As predicted by its decreased nucleophilicity, the analog bearing the trifluoromethyl group, **3e**, was the least reactive of the substrates which were examined. Extended reaction times were required to form products with aromatic hydrazides bearing pyridyl (**3c**, **d**) and phenyl (**3a**, **f**, **h**) substituents. To further expand upon the diversity of this reaction, various 3-phenyl-pyrrolo-1,2,4-triazole



Scheme 4. Proposed mechanism for formation of triazole isomer.

Table 2. Synthesis of substituted pyrrolo-1,2,4-triazoles[a]



2a-e 3a-i, 12a-d

Entry	Product	R_1 =	R_2 =	t (h)	Yield (%)[b]
1	**3a**	3-Ph	Ph	7	>97 (71)
2	**3b**	3-Ph	Me	4	>97 (14)
3	**3c**	3-Ph	2-pyridyl	24	>97 (54)
4	**3d**	3-Ph	3-pyridyl	7	87 (37)
5	**3e**	3-Ph	CF_3	24	52
6	**3f**	3-Ph	*p*-OMePh	24	>97
7	**3g**	3-Ph	H	2	69
8	**3h**	3-Ph	*p*-NO_2Ph	6	92
9	**3i**	3-Ph	*t*-Bu	3	>97
10	**12a**	5-Ph	Ph	24	75
11	**12b**	3-(*p*-OMe-Ph)	Ph	24	58
12	**12c**	5-CO_2Bn[c]	Ph	24	70
13	**12d**	3-NHCBz	Ph	24	39

[a]Reaction conditions: *i*PrOH, TEA, 150°C (sealed vial).
[b]Yields in parentheses are for reactions run in DMSO.
[c]Product formed is the isopropyl ester from transesterification with solvent.

analogues from other thioimidate cyclopropane rearrangement products (**2b**–**e**, Table 2) were prepared in fair to good yields (**12a**–**d**, Table 2).

In summary, an efficient method for the synthesis of fused [5,5]-1,2,4-triazoles via tandem thioimidate cyclopropane rearrangement–cyclization is described. The cyclization of the amidrazone intermediate was improved through the use of *i*PrOH in the presence of TEA. This versatile approach was used to prepare a number of 3-substituted-7-aryl-pyrrolo-1,2,4-triazoles in good to excellent yields.

EXPERIMENTAL

Materials

All reagents were purchased from Aldrich Chemical Company (USA) or Acros Organics (USA). All the solvents used were of analytical grade. ^{1}H and ^{13}C (400-MHz) NMR spectra were recorded on a Varian VXR 400 spectrometer unless otherwise noted. The chemical shifts are reported in δ (ppm)

using the δ 0.00 signal of Me_4Si as an internal standard. High-resolution MS data were obtained on a Bruker Daltonics FTICR/MS. High pressure liquid chromatography (HPLC) spectra were recorded on a Hewlett-Packard 1100 with a CombiScreen Pro C-18 column. The purity of compounds were assessed by analytical HPLC: 1) Linear gradient over 10 min of CH_3CN/0.1% trifluoroacetic acid (TFA) and H_2O/0.1% TFA 10:90 to 95:5 and 2 min at 95:5; flow rate 1.0 mL/min, detection at 215 and 254 nm (YMC-Pack Pro C18, 50 × 4.6 mm column). 2) Linear gradient over 3.5 min of CH_3CN/0.1% TFA and H_2O/0.1% TFA 5:95 to 95:5; flow rate 1.5 mL/min, detection at 215 nm (YMC-Pack Pro C18, 50 × 4.6 mm column). Microwave reactions were carried out using a Biotage Initiator SW version 1.1 build 2795.

General Procedure for the Synthesis of 3-Substituted-7-aryl-pyrrolo-1,2,4-triazoles

To a solution of 1-phenyl-1-cyclopropanecarboxylic acid (24.0 g, 148 mmol) in DCM (200 mL) containing DMF (0.5 mL), oxalyl chloride (24.4 g, 193 mmol) was added dropwise. After 1 h, the reaction was concentrated in vacuo, and the resultant residue was redissolved in DCM (500 mL) and saturated with $NH_{3(g)}$. After 1.5 h, the reaction was quenched with water and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to provide 1-phenylcyclopropanecarboxamide as an off-white solid. Crude 1-phenylcyclopropanecarboxamide (12.0 g, 74.4 mmol) was suspended in THF (200 mL). Lawesson's reagent (18.0 g, 44.7 mmol) was added, and the reaction was heated to 70°C for 1 h. The mixture was cooled to room temperature and concentrated in vacuo. The resultant residue was subjected to silica-gel chromatography eluted with 20–75% EtOAc in hexanes to provide 1-phenylcyclopropanecarbothioamide **1** as an off-white solid. Yield: 10.5 g, 80%, mp 108–109°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (br s, 1H), 7.38–7.46 (m, 4H), 7.32–7.35 (m, 1H), 6.56 (br s, 1H), 2.07 (q, $J = 7.1$ Hz, 2H), 1.36 (q, $J = 7.1$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 139.54, 131.23, 129.56, 128.64, 38.00, 22.42. HRMS calcd. for $C_{10}H_{12}NS$ (M + 1): 178.0685. Found: 178.0681. Anal. calcd for $C_{10}H_{11}NS \cdot 0.10\ H_2O$: C, 67.07; H, 6.30; N, 7.82. Found: C, 66.99; H, 6.17; N, 7.62.

Under nitrogen, **1** (4.1 g, 22.9 mmol) was dissolved in dry acetone (150 mL). Iodomethane (4.9 g, 34.4 mmol) was added, and the solution was then heated at 45°C. After 1.5 h, a precipitate crashed out of the reaction solution. The reaction continued to be heated for another 1.5 h until completion as determined by LC/MS. The reaction solution was concentrated in vacuo to provide 5-(methylthio)-4-phenyl-3,4-dihydro-2*H*-pyrrolium iodide **2** as a yellow solid. Yield: 7.3 g, >97%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.46 (m, 3H), 7.25 (m, 2H), 4.51 (t, $J = 9.2$ Hz, 1H), 4.44 (m, 1H),

4.27 (m, 1H), 3.06 (s, 3H), 2.90 (m, 1H), 2.47 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 195.74, 136.62, 129.28, 128.74, 128.67, 56.72, 53.25, 31.67, 14.73. HRMS calcd. for $C_{11}H_{13}NS$ (M + 1): 192.0841. Found: 192.0860.

To a solution of **2** (0.100 g, 0.313 mmol) in *i*PrOH (3 mL), benzhydrazide (0.064 g, 0.47 mmol) and triethylamine (0.090 mL, 0.65 mmol) were added. The reaction was heated in a sealed 20-mL scintillation vial at 150°C for 7 h, then cooled to room temperature, and concentrated in vacuo. The resultant residue was subjected to silica-gel chromatography eluted with 0–3% MeOH in DCM to provide 3,7-diphenyl-6,7-dihydro-5H-pyrrolo [2,1-c][1,2,4]triazole **3a**.

Spectral Data and Elemental Analyses

3a: Off-white solid. Yield: >97%, mp 123–125°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 7.1 Hz, 2H), 7.46–7.52 (m, 3H), 7.35–7.36 (m, 4H), 7.26–7.31 (m, 1H), 4.57 (d, J = 7.8 Hz, 1H), 4.23–4.37 (m, 2H), 3.16–3.35 (m, 1H), 2.72–2.88 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.54, 131,68, 129.65, 129.32, 128.16, 127.44, 127.36, 127.22, 45.31, 40.04, 38.66. HRMS calcd. for $C_{17}H_{16}N_3$ (M + 1): 262.1339. Found: 262.1332. Anal. calcd. for $C_{17}H_{15}N_3 \cdot 2.0H_2O \cdot 0.4CH_2Cl_2$: C, 63.08; H, 6.02; N, 12.68. Found: C, 63.17; H, 5.72; N, 13.08.

3b: Beige solid. Yield: >97%, mp 115–116°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.38 (m, 2H), 7.30–7.33 (m, 1H), 7.27–7.29 (m, 2H), 4.62 (t, J = 8.2 Hz, 1H), 4.10–4.19 (m, 2H), 3.28–3.35 (m, 1H), 2.83–2.90 (m, 1H), 2.68 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.12, 129.33, 128.22, 127.33, 43.09, 40.44, 38.16, 9.86. HRMS calcd. for $C_{12}H_{14}N_3$ (M + 1): 200.1182. Found: 200.1177.

3c: Yellow oil. Yield: >97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 4.6 Hz, 1H), 8.34 (d, J = 3.9 Hz, 1H), 7.80–7.84 (m, 1H), 7.33–7.36 (m, 4H), 7.28–7.32 (m, 2H), 4.54–4.64 (m, 2H), 4.44–4.48 (m, 1H), 3.25–3.32 (m, 1H), 2.76–2.84 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.02, 150.21, 149.44, 147.67, 139.78, 137.15, 129.16, 127.67, 127.60, 124.10, 121.93, 46.42, 45.62, 39.93, 39.41. HRMS calcd. for $C_{16}H_{15}N_4$ (M + 1): 263.1291. Found: 263.1284.

3d: Beige solid. Yield: 87%, mp 163–165°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (d, J = 1.5 Hz, 1H), 8.71 (dd, J = 1.7, 4.9 Hz, 1H), 8.32–8.34 (m, 1H), 7.44–7.47 (m, 1H), 7.36–7.39 (m, 4H), 7.28–7.32 (m, 1H), 4.60 (t, J = 7.9 Hz, 1H), 4.36–4.40 (m, 1H), 4.28–4.33 (m, 1H), 3.31–3.38 (m, 1H), 2.85–2.92 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 151.01, 146.92, 139.02, 134.30, 129.22, 127.80, 127.59, 124.23, 124.01, 44.31, 39.67, 39.22. HRMS calcd. for $C_{16}H_{15}N_4$ (M + 1): 263.1291. Found:

263.1285. Anal. calcd. for $C_{16}H_{14}N_4 \cdot 0.15CH_2Cl_2$: C, 70.52; H, 5.24; N, 20.37. Found: C, 70.36; H, 5.34; N, 20.11.

3e: Yellow oil. Yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.39 (m, 2H), 7.29–7.36 (m, 3H), 4.58 (t, $J = 8.0$ Hz, 1H), 4.22–4.31 (m, 1H), 4.15–4.22 (m, 1H), 3.29–3.37 (m, 1H), 2.83–2.92 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 129.16, 127.93, 127.24, 43.77, 39.64, 38.65. HRMS calcd. for $C_{12}H_{11}F_3N_3$ (M + 1): 254.0900. Found: 254.0891.

3f: White solid. Yield: >97%, mp 156–158°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, $J = 8.9$ Hz, 1H), 7.74 (d, $J = 6.9$ Hz, 1H), 7.32–7.35 (m, 4H), 7.27–7.30 (m, 1H), 7.00 (d, $J = 8.9$ Hz, 1H), 6.92 (d, $J = 7.0$ Hz, 1H), 4.57 (t, $J = 7.9$ Hz, 1H), 4.23–4.34 (m, 2H), 3.27–3.35 (m, 1H), 2.77–2.86 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.48, 137.50, 129.22, 129.15, 128.03, 127.48, 115.11, 55.64, 45.34, 39.96, 38.50. HRMS calcd. for $C_{18}H_{18}N_3O$ (M + 1): 292.1445. Found: 292.1442.

3g: Beige solid. Yield: 69%, mp 74–76°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00, (s, 1H), 7.31–7.39 (m, 4H), 7.24–7.26 (m, 1H), 4.65 (t, $J = 8.0$ Hz, 1H), 4.39–4.43 (m, 1H), 4.27–4.34 (m, 1H), 3.29–3.37 (m, 1H), 2.83–2.92 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 138.83, 137.45, 129.44, 128.29, 127.36, 44.13, 39.84, 38.34. HRMS calcd. for $C_{11}H_{12}N_3$ (M + 1): 186.1026. Found: 186.1019.

3h: Beige solid. Yield: 92%, mp 208–210°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, $J = 9.0$ Hz, 2H), 8.10 (d, $J = 9.0$ Hz, 2H), 7.34–7.38 (m, 4H), 7.29–7.32 (m, 1H), 4.61 (d, $J = 8.0$ Hz, 1H), 4.41–4.45 (m, 1H), 4.30–4.39 (m, 1H), 3.34–3.40 (m, 1H), 2.87–2.95 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.42, 148.46, 148.29, 138.59, 133.12, 129.06, 127.68, 127.35, 126.89, 124.42, 44.39, 39.47, 38.98. HRMS calcd. for $C_{17}H_{15}N_4O_2$ (M + 1): 307.1190. Found: 307.1173. Anal. calcd. for $C_{17}H_{14}N_4O_2 \cdot 0.4H_2O$: C, 65.12; H, 4.76; N, 17.87. Found: C, 65.11; H, 4.53; N, 18.01.

3i: Yellow oil. Yield: >97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 = 7.36 (m, 5H), 4.48 (t, $J = 7.9$ Hz, 1H), 4.16–4.20 (m, 1H), 4.07–4.14 (m, 1H), 3.21–3.25 (m, 1H), 2.71–2.78 (m, 1H), 1.21 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 129.18, 127.75, 127.69, 46.46, 39.62, 39.09, 28.76, 27.33, 8.82. HRMS calcd. for $C_{15}H_{20}N_3$ (M + 1): 242.1652. Found: 242.1648.

12a: Off-white solid. Yield: 75%, mp 53–55°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, $J = 7.9$ Hz, 2H), 7.28–7.40 (m, 6H), 7.04 (d, $J = 7.4$ Hz, 2H), 5.77–7.79 (m, 1H), 3.40–3.46 (m, 1H), 3.33–3.38 (m, 2H), 2.09–2.81 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.40, 131.69, 129.86, 129.46, 129.22, 127.63, 125.43, 123.42, 62.52, 39.45, 20.62. HRMS calcd. for $C_{17}H_{16}N_3$ (M + 1): 262.1339. Found: 262.1342.

12b: White solid. Yield: 58%, mp 193–196°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.89 (m, 2H), 7.54–7.57 (m, 3H), 7.23 (d, $J = 8.6$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 4.66 (t, $J = 8.1$ Hz, 1H), 4.41–4.49 (m, 2H), 3.81 (s, 3H), 3.30–3.37 (m, 1H), 2.85–2.92 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.22, 159.33, 131.25, 129.80, 128.58, 127.04, 124.96, 114.61, 55.47, 45.03, 39.26, 38.88. HRMS calcd. for $C_{18}H_{18}N_3O$ (M + 1): 292.1445. Found: 292.1459.

12c: Yellow oil. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.80 (m, 2H), 7.57–7.59 (m, 3H), 5.57 (dd, $J = 3.7$, 9.3 Hz, 1H), 4.87–4.94 (m, 1H), 3.17 (t, $J = 8.0$ Hz, 2H), 2.93–2.97 (m, 1H), 1.09 (d, $J = 6.4$ Hz, 2H), 1.03 (d, $J = 6.4$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.30, 131.39, 129.38, 126.93, 124.66, 71.28, 58.60, 34.09, 21.42, 21.12, 20.60. HRMS calcd. for $C_{15}H_{18}N_3O_2$ (M + 1): 272.1394. Found: 272.1396.

12d: White solid. Yield: 39%, mp 210–213°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.83 (m, 2H), 7.41–7.49 (m, 3H), 7.28–7.39 (m, 5H), 5.10 (s, 2H), 4.37–4.40 (m, 1H), 4.18–4.22 (m, 1H), 3.37–3.40 (m, 1H), 3.20–3.37 (m, 1H), 2.78–2.79 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 131.11, 129.46, 128.75, 128.41, 128.19, 126.87, 125.37, 67.34, 45.85, 44.80, 37.21. HRMS calcd. for $C_{19}H_{19}N_4O_2$ (M + 1): 335.1503. Found: 335.1497.

2,7-Diphenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole (7)

To a solution of **2** (0.050 g, 0.16 mmol) in *i*PrOH (3 mL), benzhydrazide (0.032 g, 0.23 mmol) was added. The reaction was heated via microwave at 200°C for 1 h, then cooled to room temperature, and concentrated in vacuo. The resultant residue was subjected to silica-gel chromatography eluted with 0–30% EtOAc in hexanes to provide **7** as a yellow oil. Spectral data and elemental analyses are given as follows: Yield: 0.010 g, 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09–8.12 (m, 2H), 7.33–7.44 (m, 6H), 7.28–7.30 (m, 2H), 4.48 (t, $J = 7.6$ Hz, 1H), 4.33–4.39 (m, 1H), 4.20–4.27 (m, 1H), 3.22–3.31 (m, 1H), 2.66–2.74 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 130.38, 130.10, 129.60, 129.33, 129.19, 128.98, 128.00, 127.45, 126.92, 126.68, 45.92, 40.57, 36.28. HRMS calcd. for $C_{17}H_{16}N_3$ (M + 1): 262.1339. Found: 262.1338.

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REFERENCES

1. (a) Lawson, E. C.; Hoekstra, W. J.; Addo, M. F.; Andrade-Gordon, P.; Damiano, B. P.; Kauffman, J. A.; Mitchell, J. A.; Maryanoff, B. E. 1,2,4-Triazolo[3,4-*a*]pyridine as a novel, constrained template for fibrinogen receptor (GPIIb/IIIa) antagonists. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2619–2622; (b) Urban, F. J.; Anderson, B. G.; Orrill, S. L.; Daniels, P. Process research and large-scale synthesis of a novel 5,6-dihydro-(9H)-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine PDE-IV inhibitor. *Org. Process Res. Dev.* **2001**, *5*, 575–580; (c) Guryn, R.; Pakulska, W.; Brzezinska, E. Synthesis and action on the central nervous system of 8-substituted 6,7,8,9-tetrahydro-5h-1,2,4-triazolo[4,3-a]-diazepine derivatives. *Acta Poloniae Pharmaceutica* **2001**, *58*, 53–59; (d) Gineinah, M. M.; Nasr, M. N.; Abdelal, A. M.; El-Emaam, A. A.; Said, S. A. Synthesis and antiinflammatory evaluation of new 2- and 3-substituted 1,2,4-triazolo (4,3-*c*) and [1,5-*c*] quinazoline derivatives. *Med. Chem. Res.* **2000**, *10*, 243–252; (e) Roma, G.; DiBraccio, M.; Grossi, G.; Mattioli, F.; Ghia, M. 1,8-Naphthyridines, IV: 9-Substituted N,N-dialkyl-5-(alkylamino or cycloalkylamino) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridine-6-carboxamides, new compounds with anti-aggressive and potent anti-inflammatory activities. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035.
2. (a) Liu, F.; Palmer, D. C.; Sorgi, K. L. Diethoxyphosphinyl acetic acid hydrazide: A uniquely versatile reagent for the preparation of fused [5,5]-, [5,6]-, and [5,7]-3-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles. *Tetrahedron Lett.* **2004**, *45*, 1877–1880; (b) Rigo, B.; Gouni, I.; El Ghammarati, S.; Gautret, P.; Couturier, D. Studies on pyrrolidinones: A silylated approach to fused triazoles. *Synth. Commun.* **1994**, *24*, 3055–3063.
3. Kuduk, S. D.; Ng, C.; Chang, R. K.; Bock, M. G. Synthesis of 2,3-diaminodihydropyrroles via thioimidate cyclopropane rearrangement. *Tetrahedron Lett.* **2003**, *44*, 1437–1440.
4. Kakefuda, A.; Suzuki, T.; Tobe, T.; Tsukada, J.; Tahara, A.; Sakamoto, S.; Tsukamoto, S.-I. Synthesis and pharmacological evaluation of 5-(4-biphenyl)-3-methyl-4-phenyl-1,2,4-triazole derivatives as a novel class of selective antagonists for the human vasopressin V_{1A} receptor. *J. Med. Chem.* **2002**, *45*, 2589–2598.
5. Hansen, K. B.; Springfield, S. A.; Desmond, R.; Devine, P. N.; Grabowski, E. J. J.; Reider, P. J. Radical alkylation of *N*-alkyl 1,2,4-triazoles. *Tetrahedron Lett.* **2001**, *42*, 7353–7355.