Tetrahedron 68 (2012) 2045–2051

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 1,3,5-trisubstituted-1,2,4-triazoles by microwave-assisted N-acylation of amide derivatives and the consecutive reaction with hydrazine hydrochlorides

Jongbok Lee [a], Myengchan Hong [b], Yoonchul Jung [b], Eun Jin Cho [b,*], Hakjune Rhee [a,b,*]

[a] Department of Bionanotechnology, Hanyang University, Sa 3-Dong 1271, Ansan, Kyunggi-Do 426-791, Republic of Korea
[b] Department of Chemistry and Applied Chemistry, Hanyang University, Sa 3-Dong 1271, Ansan, Kyunggi-Do 426-791, Republic of Korea

ARTICLE INFO

Article history:
Received 30 December 2011
Accepted 4 January 2012
Available online 8 January 2012

Keywords:
Microwave-assisted reaction
1,2,4-Triazole
N-Acylation reaction
Cyclization reaction
One-pot sequential reaction

ABSTRACT

Facile and efficient procedures for the N-acylation reaction of amide derivatives with various acid anhydrides and the cyclization reaction of *N*-acylated amide derivatives with various hydrazine hydrochlorides were described. The reactions were carried out under microwave irradiation to give products in good yields in a few minutes. The synthesis of 1,3,5-trisubstituted-1,2,4-triazoles from benzamides can also be accomplished in a simple one-pot sequential reaction.

1. Introduction

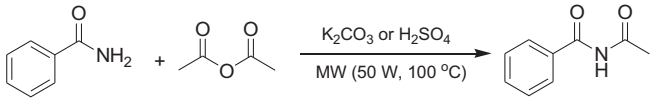
1,2,4-Triazole analogues have been attracting attention over the last decade due to their biological activities, such as antiviral, antitumor, and anti-inflammatory activities.[1–3] 1,2,4-Triazoles can be prepared by the reaction of hydrazonyl chlorides with aromatic or aliphatic nitriles in the presence of $AlCl_3$ or $Yb(OTf)_3$.[4,5] Its synthesis can also be accomplished by cyclization of 1,2,4-triazene from hydrazonyl chlorides with a primary amine in the presence of triethylamine followed by oxidation using various oxidizing agents, such as Ag_2CO_3, NaOCl, $Ca(OCl)_2$, Dess–Martin periodinane, Ley's TPAP/NMO, and H_2O_2/KOH.[6–8] These methods, however, have limited functional group tolerance and require more than stoichiometric amounts of reagents. Thus it is desirable to develop more efficient and general method for the preparation of 1,3,5-trisubstituted-1,2,4-triazoles under mild reaction conditions.

Over recent years, a great number of publications have reported the chemical reactions using microwave irradiation.[9,10] This can lead to a significantly reduced reaction time, improved yields of product, chemoselectivity, and regioselectivity.[9] Herein we report facile and efficient methods for the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles under microwave irradiation conditions. It can be synthesized by N-acylation of amides followed by cyclization with hydrazines. These stepwise syntheses can also be accomplished by the one-pot sequential reaction.

2. Results and discussion

First, we examined the N-acylation of benzamide with acetic anhydride using K_2CO_3 or H_2SO_4 under microwave irradiation (Table 1). The use of microwave irradiation was effective so that the

Table 1
Microwave-assisted N-acylation of benzamide with acetic anhydride in the presence of K_2CO_3 or H_2SO_4[a]



1a

Entry	Acetic anhydride (equiv)	Base or acid	Time (min)	Yield[b] (%)
1	1.5	K_2CO_3 (1.0 equiv)	3	38
2	3.0	K_2CO_3 (1.0 equiv)	3	58
3	5.0	K_2CO_3 (1.0 equiv)	3	59
4	3.0	K_2CO_3 (2.0 equiv)	3	57
5	2.0	H_2SO_4 (2 drops)[c]	3	78
6	3.0	H_2SO_4 (2 drops)[c]	3	97

[a] Used 1.0 mmol of benzamide.
[b] Isolated yield.
[c] Used concd sulfuric acid.

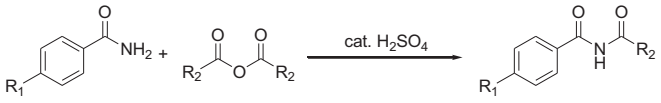
* Corresponding authors. Tel.: +82 31 400 5498; fax: +82 31 400 4554; e-mail addresses: echo@hanyang.ac.kr (E.J. Cho), hrhee@hanyang.ac.kr (H. Rhee).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.01.003

reaction was completed within 3 min. Treating benzamide with 3.0 molar equiv of acetic anhydride and 2 drops of concd sulfuric acid for 3 min gave the best result (entry 6).

The enhanced reactivity under microwave irradiation was proven by comparison with the reaction under conventional heating conditions (Table 2). N-Acylation of benzamides under conventional heating conditions required relatively longer reaction times and *N*-acylated benzamides were obtained in lower yields[11–13] while the reaction under microwave irradiation gave higher yields of the products in 3 min.

Table 2
Effect of microwave irradiation for the N-acylation reaction[a]

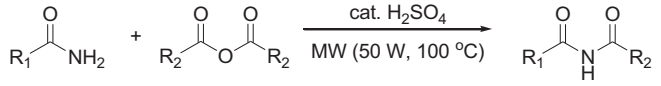


Entry	$-R_1$	$-R_2$	Conventional heating[b]		Microwave irradiation[c]	
			Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
1	H	CH_2CH_3	180	79	3	97
2	H	$(CH_2)_4CH_3$	180	91	3	98
3	CH_3	CH_3	240	45	3	97
4	OCH_3	CH_3	240	49	3	95

[a] Used benzamide derivatives (1.0 mmol), acid anhydrides (3.0 mmol), and H_2SO_4 (2 drops).
[b] Neat, 100 °C.[14]
[c] 50 W, 100 °C.
[d] Isolated yield.

With the optimized microwave irradiation conditions, we performed the synthesis of *N*-acylated amides **1a**–**22a** using various amides and acid anhydride derivatives (Table 3). Both aromatic and aliphatic amides were good substrates for the N-acylation reactions. Regarding aromatic amides, the substituents of benzamides did not affect the reactivity of the reaction electronically and sterically. In general, benzamides with both electron-donating and electron-withdrawing groups reacted well with acetic anhydride. However, benzamide with a nitro group at *meta*-position gave slightly lower yield of the corresponding product (entry 11). A heteroaromatic amide, 2-pyridinecarboxamide, was acetylated to afford *N*-acetyl-2-pyridinecarboxamide in 65% yield (entry 19). Reactivities of *ortho*-substituted benzamides were as good as those with *meta*- or *para*-substituents (entries 6 and 12). On the other hand, sterically demanding acid anhydrides were less reactive toward the reaction. The reaction of an acid anhydride with *tert*-butyl groups gave the corresponding product in 62% yield (entry 16).

Table 3
Microwave-assisted N-acylation reaction of amides with acid anhydrides[a]



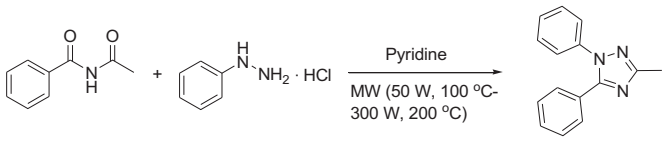
1a-22a

Entry	$-R_1$	$-R_2$	Time (min)	Yield[b] (%)
1	Ph	CH_3	3	97
2	*p*-MeC_6H_4	CH_3	3	97
3	*p*-EtC_6H_4	CH_3	3	96
4	*p*-$MeOC_6H_4$	CH_3	3	95
5	*m*-$MeOC_6H_4$	CH_3	3	84
6	*o*-$MeOC_6H_4$	CH_3	3	90
7	*p*-$EtOC_6H_4$	CH_3	3	95
8	*p*-ClC_6H_4	CH_3	3	97
9	*p*-BrC_6H_4	CH_3	3	96
10	*p*-$NO_2C_6H_4$	CH_3	3	88
11	*m*-$NO_2C_6H_4$	CH_3	3	70
12	*o*-$NO_2C_6H_4$	CH_3	3	96
13	Ph	CH_2CH_3	3	97
14	Ph	$(CH_2)_4CH_3$	3	98
15	Ph	$CH(CH_3)_2$	3	92
16	Ph	$C(CH_3)_3$	3	62
17	Ph	Ph	3	85
18	*p*-ClC_6H_4	$(CH_2)_5CH_3$	3	85
19[c]	2-Pyridyl	CH_3	3	65
20	CH_3	CH_3	3	45
21	CH_2CH_3	CH_3	3	71
22	Benzyl	CH_3	3	85

[a] Used amide derivatives (1.0 mmol), acid anhydrides (3.0 mmol), and H_2SO_4 (2 drops).
[b] Isolated yield.
[c] DMF (1 mL) was used as a solvent.

Next, we investigated the reaction between *N*-acetylbenzamide **1a** and phenyl hydrazine under various microwave irradiation conditions for the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles (Table 4). Interestingly, a free form of phenyl hydrazine did not participate in the reaction (entry 1) while the reaction of phenyl hydrazine hydrochloride gave the desired product, 3-methyl-1,5-diphenyl-1*H*-1,2,4-triazole **1b**. The best result was obtained by using 2.0 molar equiv of phenyl hydrazine hydrochloride, increased microwave irradiation power (300 W), and higher temperature (200 °C) (entries 7 and 8).

Table 4
The preparation of 3-methyl-1,5-diphenyl-1*H*-1,2,4-triazole (**1b**) under various reaction conditions by microwave irradiation[a]



1a **1b**

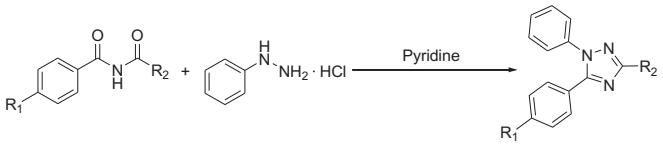
Entry	Microwave power (W)	Temp (°C)	Phenyl hydrazine hydrochloride (equiv)	Time (min)	Yield[b] (%)
1	50	100	1.0[c]	1	—[d]
2	50	100	1.0	1	30
3	50	100	1.0	5	33
4	50	100	2.0	5	58
5	100	150	2.0	5	55
6	200	200	2.0	5	75
7	300	200	2.0	1	83
8	300	200	2.0	5	85

[a] Used *N*-acetylbenzamide (1.0 mmol), phenyl hydrazine hydrochloride (2.0 mmol), and pyridine (1 mL).
[b] Isolated yield.
[c] Used free form of phenyl hydrazine.
[d] Starting material **1a** was recovered.

We also confirmed that the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles was more effective under microwave irradiation than conventional heating (Table 5). The previously reported reactions under conventional heating conditions required a long reaction time at high reaction temperatures and the isolated yields of products were not satisfactory.[16,17] As shown in Table 5, we could increase reactivity and efficiency of the reaction using microwave irradiation. The transformations under microwave irradiation conditions were completed within 1 min and gave the corresponding triazoles in higher yields.

Under the optimized reaction conditions, we explored substrate scope of the transformation with various *N*-acylated amides **2a**–**22a** and hydrazine hydrochloride derivatives (Table 6). Regardless of the substituent position on the aromatic ring, *N*-acylated benzamides with electron-donating substituents reacted well under the conditions to give good yields of 1,3,5-trisubstituted-1,2,4-triazoles (entries 2–7). On the other hand, reactions of those with electron-withdrawing substituents produced the corresponding triazoles in low to moderate yields (entries 8–12). An *N*-

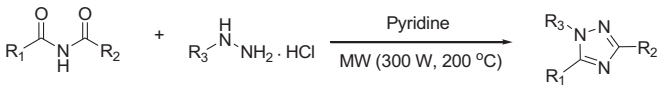
Table 5
Effect of microwave irradiation for the synthesis of 1,3,5-trisubstituted-1,2,4-triazole[a]



Entry	$-R_1$	$-R_2$	Conventional heating[b]		Microwave irradiation[c]	
			Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
1	CH_3	CH_3	240	63	1	84
2	OCH_3	CH_3	240	76	1	85
3	H	CH_2CH_3	240	47	1	69
4	H	$(CH_2)_4CH_3$	240	45	1	68

[a] Used *N*-acylated benzamide derivatives (1.0 mmol), phenyl hydrazine hydrochloride (2.0 mmol), and pyridine (1 mL).
[b] Reflux.[15]
[c] 300 W, 200 °C.
[d] Isolated yield.

Table 6
The preparation of 1,3,5-trisubstituted-1,2,4-triazoles with various hydrazine hydrochlorides under microwave irradiation[a]



1a - 22a **1b - 28b**

Entry	*N*-Acylated amide			$-R_3$	Time (min)	Yield[b] (%)
		$-R_1$	$-R_2$			
1	**1a**	Ph	CH_3	Ph	1	83
2	**2a**	*p*-MeC_6H_4	CH_3	Ph	1	84
3	**3a**	*p*-EtC_6H_4	CH_3	Ph	1	85
4	**4a**	*p*-$MeOC_6H_4$	CH_3	Ph	1	85
5	**5a**	*m*-$MeOC_6H_4$	CH_3	Ph	1	70
6	**6a**	*o*-$MeOC_6H_4$	CH_3	Ph	1	82
7	**7a**	*p*-$EtOC_6H_4$	CH_3	Ph	1	88
8	**8a**	*p*-ClC_6H_4	CH_3	Ph	1	71
9	**9a**	*p*-BrC_6H_4	CH_3	Ph	1	72
10	**10a**	*p*-$NO_2C_6H_4$	CH_3	Ph	2	48
11	**11a**	*m*-$NO_2C_6H_4$	CH_3	Ph	2	48
12	**12a**	*o*-$NO_2C_6H_4$	CH_3	Ph	2	32
13	**13a**	Ph	CH_2CH_3	Ph	1	69
14	**14a**	Ph	$(CH_2)_4CH_3$	Ph	1	68
15	**15a**	Ph	$CH(CH_3)_2$	Ph	2	14[c]
16	**16a**	Ph	$C(CH_3)_3$	Ph	2	—[d]
17	**17a**	Ph	Ph	Ph	2	19
18	**18a**	*p*-ClC_6H_4	$(CH_2)_5CH_3$	*o*, *p*-ClC_6H_4	1	50
19	**19a**	2-Pyridyl	CH_3	Ph	1	82
20	**20a**	CH_3	CH_3	Ph	1	73
21	**21a**	CH_2CH_3	CH_3	Ph	1	59[e]
22	**22a**	Benzyl	CH_3	Ph	1	60[f]
23	**1a**	Ph	CH_3	*p*-$MeOC_6H_4$	1	62
24	**1a**	Ph	CH_3	*p*-$NO_2C_6H_4$	1	50
25	**1a**	Ph	CH_3	*o*, *p*-$CH_3C_6H_4$	1	74
26	**1a**	Ph	CH_3	Benzyl	1	48
27	**1a**	Ph	CH_3	$C(CH_3)_3$	1	—[g]
28	**1a**	Ph	CH_3	2-Pyridyl[h]	1	41

[a] Used *N*-acylated amides (1.0 mmol), hydrazine hydrochloride derivatives (2.0 mmol), and pyridine (1 mL).
[b] Isolated yield.
[c] 4% of regioisomer **15c** was obtained.
[d] 18% of regioisomer **16c** was obtained.
[e] The two isomeric mixture was obtained in 84% yield (**21b**/**21c**=7:3).
[f] 11% of regioisomer **22c** was obtained.
[g] 25% of starting amide **1a** and 48% of benzamide were obtained.
[h] 2-Hydrazinopyridine hydrochloride was prepared by 2-hydrazinopyridine (1.0 equiv) with concd HCl (1.0 equiv) in MeOH.

acetyl heteroaromatic amide **19a** was also tried and transformed into the corresponding triazole in 82% yield (entry 19).

In general, we have obtained high regioselectivities from the reaction with *N*-acylated benzamides by the selective attack of the more basic hydrazine amino group onto the more electrophilic carbonyl carbon atom of the acyl group.[16] However, the reaction showed a low regioselectivity when using *N*-acylated benzamide with bulky R_2 groups or *N*-acylated aliphatic amides. Reactions of **15a** and **16a** showed not only low regioselectivity but also low reactivity. The reaction of *N*-acylated benzamide **15a** containing an isopropyl group provided **15b** in 14% yield with 4% of the undesired regioisomer **15c** (entry 15), and the reaction of **16a** containing a *tert*-butyl group on the acyl group only generated undesired regioisomer **16c** in 18% yield (entry 16). It is likely that the amino group of phenyl hydrazine favorably attacked a less hindered carbonyl carbon atom of **16a**, not the more electrophilic carbonyl carbon atom. The structure of the undesired regioisomer **16c** was confirmed by X-ray crystallography (Fig. 1). As expected, reactions of substrates with alkyl groups on R_1 and R_2 also gave mixtures of regioisomers. Reaction of **21a** containing ethyl and methyl groups produced two regioisomers **21b** and **21c** in a 7:3 ratio, and the reaction of **22a** provided 60% of **22b** along with 11% of its regioisomer **22c**. The structures of **21b**, **21c**, **22b**, and **22c** were confirmed by $^1H-^1H$ NOESY experiments.

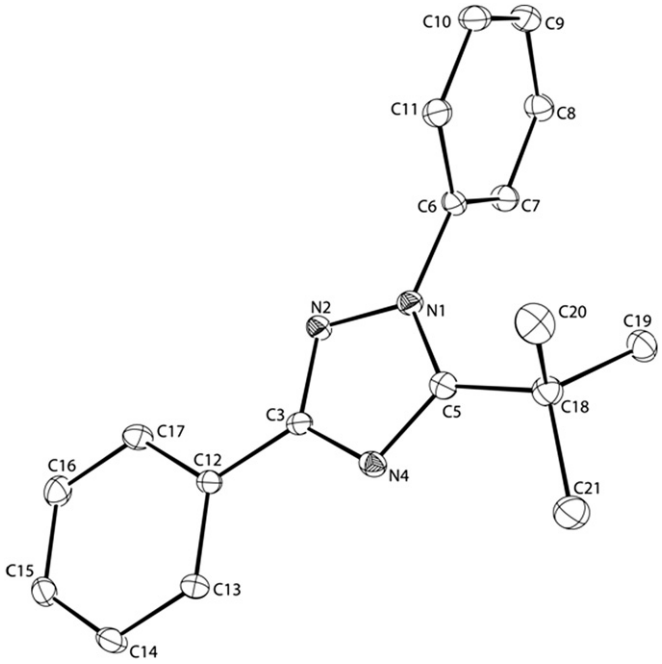


Fig. 1. ORTEP plot of the molecular structure of the 5-*tert*-butyl-1,3-diphenyl-1*H*-1,2,4-triazole **16c**.[18]

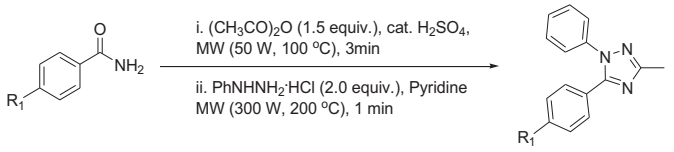
We demonstrated the utility and efficiency of the reaction by applying this method to the synthesis of a neutral cannabinoid CB_1 receptor antagonist, LH-21 **18b**, which was synthesized by the Jagerovic group in 3.6% overall yield.[11] Contrastively, we obtained LH-21 in 43% overall yield in a very short reaction time under microwave irradiation conditions (entry 18).

We also tried the reaction with various substituted phenyl hydrazine hydrochlorides. Both electron-rich and electron-poor phenyl hydrazine hydrochlorides worked for the reaction and the corresponding triazoles were obtained in moderate to good yields (entries 18 and 23–25). The desired product was also obtained when using an aliphatic hydrazine, benzyl hydrazine hydrochloride (entry 26). However, sterically demanding *tert*-butyl hydrazine hydrochloride did not participate in the reaction at all (entry 27).

The reaction of a heteroaromatic hydrazine, 2-pyridyl hydrazine also gave the desired triazole although yield was low (entry 28).

We also found that these efficient microwave-assisted N-acylation and cyclization could be combined to a simple one-pot reaction for the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles (Table 7). The best results were obtained when using 1.5 molar equiv acid anhydrides with 2 drops of sulfuric acid and 2.0 molar equiv phenyl hydrazine hydrochloride in pyridine. Under the optimized conditions, various 1,3,5-trisubstituted-1,2,4-triazoles were obtained within short reaction time in good yields.

Table 7
One-pot sequential reaction for the preparation of 1,3,5-trisubstituted-1,2,4-triazoles[a]



Entry	$-R_1$	Yield[b] (%)
1	H	69
2	CH_3	72
3	CH_2CH_3	70
4	OCH_3	75
5	Cl	62
6	Br	62

[a] Used benzamide derivatives (1.0 mmol), H_2SO_4 (2 drops), and pyridine (2 mL).[19]
[b] Isolated yield.

3. Conclusion

We have described microwave-assisted facile and efficient N-acylation of amides and cyclization with hydrazines for the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles. Reactions were carried out under mild reaction conditions in a very short reaction time and produced good yields of products. The synthesis can also be accomplished in a cost-effective one-pot sequential reaction. These methods will provide an easier way to synthesize active pharmaceutical ingredients containing 1,3,5-trisubstituted-1,2,4-triazoles.

4. Experimental

4.1. General information

^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 with Bruker and Varian spectrometer operating at 300 MHz, 400 MHz, and 500 MHz for ^{1}H and 75 MHz, 100 MHz, and 125 MHz for ^{13}C with TMS as an internal standard. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer. Melting points were determined with a Sanyo Gallenkamp melting point apparatus. HRMS were obtained on a JMS 700 spectrometer. All of the microwave-assisted reactions were carried out with Discover System 908005 (CEM Corporation). Analytical thin layer chromatography (TLC) was conducted on E. Merck 60 F_{254} aluminum-backed silica gel plates (0.2 mm) with a fluorescent indicator. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh) under positive pressure. All starting materials, reagents, and solvents were of reagent grade, and solvents were purified by the known procedure before use.[20]

4.2. Typical procedure for the synthesis of N-acylation of amide derivatives

Amide derivatives (1.0 mmol), acid anhydrides (3.0 mmol), and 2 drops of concd H_2SO_4 were placed in a 50 mL round bottom flask equipped with a reflux condenser. The reaction flask was microwave irradiated (50 W, 100 °C) for 3 min with stirring. After the reaction, the solution was extracted with ethyl acetate (2×10 mL), and the combined organic layer was washed with 5% aq $NaHCO_3$ (2×10 mL), and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to provide the crude material. The crude material was purified by flash column chromatography using various hexane/ethyl acetate eluent systems to afford the desired products **1a**–**22a**.

*4.2.1. N-Acetylbenzamide (**1a**).*[21] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (br s, 1H), 7.87–7.84 (m, 2H), 7.65–7.60 (m, 1H), 7.54–7.49 (m, 2H), 2.63 (s, 3H).

*4.2.2. N-Acetyl-4-methylbenzamide (**2a**).*[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 7.94 (d, J=8.7 Hz, 2H), 7.24 (d, J=9.0 Hz, 2H), 2.61 (s, 3H), 2.34 (s, 3H).

*4.2.3. N-Acetyl-4-ethylbenzamide (**3a**).* Mp: 90–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (br s, 1H), 7.78 (d, J=8.0 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 2.73 (q, J=7.7 Hz, 2H), 2.62 (s, 3H), 1.27 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 165.8, 150.3, 129.9, 128.5, 128.0, 28.9, 25.7, 15.2; IR (KBr): 3249, 3151, 2968, 2877, 1936, 1710, 1610, 1521, 1477 cm^{-1}; HRMS (EI$^+$): m/z [M+H]$^+$ calcd for $C_{11}H_{13}NO_2$: 191.0946; found: 191.0944.

*4.2.4. N-Acetyl-4-methoxybenzamide (**4a**).*[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (br s, 1H), 7.82 (d, J=9.3 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 3.89 (s, 3H), 2.61 (s, 3H).

*4.2.5. N-Acetyl-3-methoxybenzamide (**5a**).* Mp: 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (br s, 1H), 7.42–7.38 (m, 3H), 7.15–7.13 (m, 1H), 3.87 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 165.5, 160.1, 134.1, 130.0, 119.7, 119.4, 112.7, 55.5, 25.5; IR (KBr): 3283, 2995, 2966, 1784, 1695, 1586, 1507, 1461, 1373, 1268, 1021, 924, 801, 738, 676, 580 cm^{-1}; HRMS (EI$^+$): m/z [M+H]$^+$ calcd for $C_{10}H_{11}NO_3$: 193.0739; found: 193.0738.

*4.2.6. N-Acetyl-2-methoxybenzamide (**6a**).* Mp: 80–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.18 (br s, 1H), 8.16 (d, J=8.0 Hz, 1H), 7.54 (t, J=5.8 Hz, 1H), 7.11 (t, J=7.6 Hz, 1H), 7.02 (d, J=8.4 Hz, 1H), 5.01 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 164.2, 158.0, 135.0, 133.1, 121.9, 120.5, 112.0, 56.4, 26.4; IR (KBr): 3319, 3010, 2935, 2843, 1707, 1686, 1598, 1509, 1467, 1369, 1273, 1018, 892, 761, 682, 601 cm^{-1}; HRMS (EI$^+$): m/z [M+H]$^+$ calcd for $C_{10}H_{11}NO_3$: 193.0739; found: 193.0738.

*4.2.7. N-Acetyl-4-ethoxybenzamide (**7a**).*[23] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (br s, 1H), 7.82 (d, J=9.0 Hz, 2H), 6.96 (d, J=8.7 Hz, 2H), 4.11 (q, J=7.1 Hz, 2H), 2.61 (s, 3H), 1.45 (t, J=7.1 Hz, 3H).

*4.2.8. N-Acetyl-4-chlorobenzamide (**8a**).*[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.06 (br s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.7 Hz, 2H), 2.62 (s, 3H).

*4.2.9. N-Acetyl-4-bromobenzamide (**9a**).*[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (br s, 1H), 7.75 (d, J=8.7 Hz, 2H), 7.66 (d, J=9.0 Hz, 2H), 2.61 (s, 3H).

*4.2.10. N-Acetyl-4-nitrobenzamide (**10a**).*[24] ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.2 (br s, 1H), 8.30 (d, J=8.5 Hz, 2H), 8.09 (d, J=8.5 Hz, 2H), 2.32 (s, 3H).

*4.2.11. N-Acetyl-3-nitrobenzamide (**11a**).* Mp: 199–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.32 (br s, 1H), 8.70 (s, 1H), 8.46 (d, J=8.4 Hz, 1H), 8.32 (d, J=8.0 Hz, 1H), 7.82 (t, J=8.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9, 164.7, 147.5, 134.8,

134.6, 130.1, 126.9, 123.0, 25.4; IR (KBr): 3275, 3088, 1696, 1617, 1527, 1465, 1373, 1350, 1311, 1291, 1247, 1024, 920, 854, 719, 578 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_9H_8N_2O_4$: 208.0484; found: 208.0486.

*4.2.12. N-Acetyl-2-nitrobenzamide (**12a**).* Mp: 112–113 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (br s, 1H), 8.19 (d, *J*=8.4 Hz, 1H), 7.74 (d, *J*=7.6 Hz, 1H), 7.64 (t, *J*=8.0 Hz, 1H), 7.47 (d, *J*=7.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 167.1, 145.8, 134.4, 132.3, 131.1, 128.0, 124.7, 25.0; IR (KBr): 3259, 3173, 3001, 1737, 1521, 1279, 1124, 1072, 969, 844, 710, 571 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_9H_8N_2O_4$: 208.0484; found: 208.0488.

*4.2.13. N-Propionylbenzamide (**13a**).*[21] ^1H NMR (300 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 7.93–7.90 (m, 2H), 7.63–7.59 (m, 1H), 7.53–7.48 (m, 2H), 3.04 (q, *J*=7.3 Hz, 2H), 1.22 (t, *J*=7.4 Hz, 3H).

*4.2.14. N-(1-Oxohexyl)benzamide (**14a**).*[25] ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (br s, 1H), 7.88–7.85 (m, 2H), 7.64–7.59 (m, 1H), 7.53–7.48 (m, 2H), 3.00 (t, *J*=7.8 Hz, 2H), 1.73 (quintet, *J*=7.5 Hz, 2H), 1.41–1.36 (m, 4H), 0.92 (t, *J*=6.9 Hz, 3H).

*4.2.15. N-Isobutyrylbenzamide (**15a**).*[21] ^1H NMR (300 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 7.87–7.85 (m, 2H), 7.64–7.59 (m, 1H), 7.53–7.47 (m, 2H), 3.66 (septet, *J*=7.2 Hz, 1H), 1.24 (d, *J*=7.2 Hz, 6H).

*4.2.16. N-Pivaloylbenzamide (**16a**).*[21] ^1H NMR (300 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 7.77–7.75 (m, 2H), 7.62–7.57 (m, 1H), 7.52–7.47 (m, 2H), 1.34 (s, 9H).

*4.2.17. N-Benzoylbenzamide (**17a**).*[21] ^1H NMR (300 MHz, $CDCl_3$): δ 8.98 (br s, 1H), 7.89–7.86 (m, 4H), 7.64–7.59 (m, 2H), 7.54–7.48 (m, 4H).

*4.2.18. N-Heptanoyl-4-chlorobenzamide (**18a**).*[11] ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (br s, 1H), 7.78 (d, *J*=8.4 Hz, 2H), 7.48 (d, *J*=8.4 Hz, 2H), 2.97 (t, *J*=7.4 Hz, 2H), 1.71 (quintet, *J*=7.4 Hz, 2H), 1.42–1.37 (m, 2H), 1.34–1.30 (m, 4H), 0.90 (t, *J*=6.8 Hz, 3H).

*4.2.19. N-Acetyl-2-pyridinecarboxamide (**19a**).*[26] ^1H NMR (400 MHz, $CDCl_3$): δ 10.47 (br s, 1H), 8.63–8.61 (m, 1H), 8.26 (dt, *J*=7.6 Hz, 1.2 Hz, 1H), 7.93 (td, *J*=7.6 Hz, 1.6 Hz, 1H), 7.54 (ddd, *J*=7.6 Hz, 4.8 Hz, 1.2 Hz, 1H), 2.62 (s, 3H).

*4.2.20. Diacetamide (**20a**).*[27] ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (br s, 1H), 2.31 (s, 6H).

*4.2.21. N-Acetylpropanamide (**21a**).*[28] ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (br s, 1H), 2.56 (q, *J*=7.6 Hz, 2H), 2.37 (s, 3H), 1.17 (t, *J*=7.6 Hz, 3H).

*4.2.22. N-Acetylphenylacetamide (**22a**).*[29] Mp: 128–129 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.39–7.27 (m, 3H), 7.25–7.24 (m, 2H), 3.78 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 171.0, 133.1, 129.7, 129.3, 128.0, 44.6, 25.5; IR (KBr): 3264, 3174, 3012, 1727, 1529, 1369, 1237, 1143, 724, 697 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_{10}H_{11}NO_2$: 177.0790; found: 177.0792.

4.3. Typical procedure for the synthesis of 1,3,5-trisubstituted-1,2,4-triazoles

N-Acylated amides **1a**–**22a** (1.0 mmol), hydrazine hydrochlorides (2.0 mmol), and pyridine (1 mL) were placed in a 50 mL round bottom flask equipped with a reflux condenser. The reaction flask was microwave irradiated (300 W, 200 °C) for 1 min with stirring. After the reaction, ethyl acetate (20 mL) was added to the reaction mixture to precipitate residual hydrazine hydrochloride, and then filtered. The solvent was evaporated to the crude material. The crude material was roughly purified by flash column chromatography using hexane/triethylamine (10:1) eluent system then purified by flash column chromatography using various hexane/ethyl acetate eluent systems to afford the desired products **1b**–**28b**.

*4.3.1. 1,5-Diphenyl-3-methyl-1H-1,2,4-triazole (**1b**).*[30] ^1H NMR (300 MHz, $CDCl_3$): δ 7.49–7.46 (m, 2H), 7.42–7.29 (m, 8H), 2.51 (s, 3H).

*4.3.2. 3-Methyl-5-(4-methylphenyl)-1-phenyl-1H-1,2,4-triazole (**2b**).* Mp: 84–87 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.33 (m, 7H), 7.13 (d, *J*=8.0 Hz, 2H), 2.51 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 154.2, 140.1, 138.4, 129.3, 129.2, 128.7, 128.6, 125.3, 125.0, 21.4, 13.9; IR (KBr): 3072, 3048, 2917, 1595, 1507, 1395, 1337, 1273, 1165, 1030, 993, 827, 763, 737, 689, 584, 517 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_3$: 249.1266; found: 249.1270.

*4.3.3. 5-(4-Ethylphenyl)-3-methyl-1-phenyl-1H-1,2,4-triazole (**3b**).* Mp: 78–82 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.38 (m, 5H), 7.36–7.34 (m, 2H), 7.15 (d, *J*=8.0 Hz, 2H), 2.64 (q, *J*=7.7 Hz, 2H), 2.51 (s, 3H), 1.22 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 154.2, 146.3, 138.4, 129.3, 128.7, 128.0, 128.6, 125.3, 125.2, 28.7, 15.1, 13.9; IR (KBr): 3061, 3036, 2966, 2936, 1598, 1511, 1429, 1396, 1339, 1277, 1167, 1072, 988, 849, 835, 763, 734, 694, 583, 526 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_3$: 263.1422; found: 263.1427.

*4.3.4. 5-(4-Methoxyphenyl)-3-methyl-1-phenyl-1H-1,2,4-triazole (**4b**).*[31] Mp: 75–77 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.33 (m, 7H), 6.84 (d, *J*=9.0 Hz, 2H), 3.79 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 160.8, 154.2, 138.6, 130.5, 129.6, 128.8, 125.5, 120.4, 114.1, 55.5, 14.1; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_3O$: 265.1215; found: 265.1212.

*4.3.5. 5-(3-Methoxyphenyl)-3-methyl-1-phenyl-1H-1,2,4-triazole (**5b**).* Gummy solid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.33 (m, 5H), 7.21 (t, *J*=8.0 Hz, 1H), 7.05–7.00 (m, 2H), 6.94–6.91 (m, 1H), 3.70 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 159.7, 154.2, 138.5, 129.8, 129.5, 129.3, 128.9, 125.6, 121.5, 116.7, 113.8, 55.5, 14.1; IR (KBr): 3064, 3002, 2934, 2835, 1596, 1515, 1340, 1244, 1046, 855, 766, 696 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_3O$: 265.1215; found: 265.1217.

*4.3.6. 5-(2-Methoxyphenyl)-3-methyl-1-phenyl-1H-1,2,4-triazole (**6b**).* Mp: 134–135 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J*=7.6 Hz, 1H), 7.39 (t, *J*=5.6 Hz, 1H), 7.31–7.22 (m, 5H), 7.02 (t, *J*=7.6 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 3.30 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 156.5, 151.9, 138.8, 131.7, 131.2, 128.6, 127.6, 123.0, 117.9, 111.1, 54.7, 13.8; IR (KBr): 3070, 3001, 2933, 2835, 1608, 1503, 1410, 1336, 1295, 1270, 1049, 800, 697, 543 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_3O$: 265.1215; found: 265.1215.

*4.3.7. 5-(4-Ethoxyphenyl)-3-methyl-1-phenyl-1H-1,2,4-triazole (**7b**).* Mp: 76–78 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.33 (m, 7H), 6.81 (d, *J*=9.0 Hz, 2H), 3.99 (q, *J*=7.0 Hz, 2H), 2.49 (s, 3H), 1.38 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 159.9, 153.8, 138.1, 129.9, 129.1, 128.3, 125.0, 119.7, 114.1, 63.2, 14.4, 13.6; IR (KBr): 3064, 2976, 2932, 1613, 1515, 1467, 1435, 1250, 1181, 1167, 1041, 921, 843, 773, 698 cm^{-1}; HRMS (EI^+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_3$: 279.1372; found: 279.1375.

*4.3.8. 5-(4-Chlorophenyl)-3-methyl-1-phenyl-1H-1,2,4-triazole (**8b**).*[32] ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.41 (m, 5H), 7.35–7.30

(m, 4H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 153.3, 138.2, 136.4, 130.3, 129.7, 129.1, 126.6, 125.5, 14.1.

*4.3.9. 5-(4-Bromophenyl)-3-methyl-1-phenyl-1H-1,2,4-triazole (**9b**).* Mp: 100–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48–7.41 (m, 5H), 7.36–7.32 (m, 4H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 153.2, 138.1, 132.0, 130.4, 129.7, 129.1, 126.9, 125.4, 124.6, 14.0; IR (KBr): 3055, 2928, 1595, 1509, 1433, 1341, 1282, 1169, 1090, 1072, 1031, 989, 922, 831 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{15}H_{12}BrN_3$: 313.0215; found: 313.0212.

*4.3.10. 3-Methyl-5-(4-nitrophenyl)-1-phenyl-1H-1,2,4-triazole (**10b**).* Mp: 120–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20–8.18 (m, 2H), 7.69–7.67 (m, 2H), 7.48–7.47 (m, 3H), 7.35–7.33 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 151.9, 148.3, 137.6, 133.8, 129.8, 129.7, 129.5, 125.4, 123.8, 13.8; IR (KBr): 3094, 3076, 2931, 2854, 2768, 1599, 1510, 1366, 1166, 1111, 1031, 988, 923, 859 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{15}H_{12}N_4O_2$: 280.0960; found: 280.0963.

*4.3.11. 3-Methyl-5-(3-nitrophenyl)-1-phenyl-1H-1,2,4-triazole (**11b**).* Mp: 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (m, 1H), 8.24 (d, *J*=4.8 Hz, 1H), 7.81 (d, *J*=7.6 Hz, 1H), 7.54–7.47 (m, 4H), 7.46–7.33 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 152.0, 148.5, 137.8, 134.5, 130.0, 129.9, 129.8, 129.7, 125.6, 124.7, 123.9, 14.0; IR (KBr): 3089, 2931, 2855, 1595, 1351, 1076, 778, 697 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{15}H_{12}N_4O_2$: 280.0960; found: 280.0959.

*4.3.12. 3-Methyl-5-(2-nitrophenyl)-1-phenyl-1H-1,2,4-triazole (**12b**).* Mp: 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J*=7.6 Hz, 1H), 7.70–7.60 (m, 2H), 7.55 (d, *J*=7.5 Hz, 1H), 7.33–7.30 (m, 3H), 7.26–7.23 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 450.6, 148.5, 137.2, 133.6, 132.5, 131.3, 129.5, 128.8, 125.1, 124.7, 124.3, 14.1; IR (KBr): 3095, 3059, 2924, 2858, 1526, 1348, 1076, 992, 775, 695 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{15}H_{12}N_4O_2$: 280.0960; found: 280.0963.

*4.3.13. 1,5-Diphenyl-3-ethyl-1H-1,2,4-triazole (**13b**).*[33] Mp: 41–43 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.47 (m, 2H), 7.39–7.30 (m, 8H), 2.87 (q, *J*=7.7 Hz, 2H), 1.42 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 154.1, 138.4, 129.4, 129.0, 128.7, 128.6, 125.4, 21.9, 12.8.

*4.3.14. 1,5-Diphenyl-3-pentyl-1H-1,2,4-triazole (**14b**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.47 (m, 2H), 7.40–7.28 (m, 8H), 2.82 (t, *J*=7.8 Hz, 2H), 1.86 (quintet, *J*=7.8 Hz, 2H), 1.47–1.36 (m, 4H), 0.92 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 154.2, 138.5, 130.1, 129.5, 129.1, 128.8, 128.7, 128.3, 125.5, 32.0, 28.7, 28.5, 22.7, 14.3; IR (KBr): 3066, 2929, 2859, 1597, 1509, 1448, 1405, 1359, 1072, 988, 765, 694, 592 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{18}H_{19}N_3$: 291.1735; found: 291.1738.

*4.3.15. 1,5-Diphenyl-3-isopropyl-1H-1,2,4-triazole (**15b**).* Mp: 51–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.46 (m, 2H), 7.41–7.29 (m, 8H), 3.19 (septet, *J*=7.0 Hz), 1.44 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 153.9, 138.4, 129.8, 129.3, 129.0, 128.5, 128.3, 125.4, 28.3, 21.7; IR (KBr): 3060, 2961, 2924, 2869, 1596, 1505, 1404, 1357, 1268, 1160, 990, 919, 855, 763, 695, 603, 520 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{17}H_{17}N_3$: 263.1422; found: 263.1419.

*4.3.16. 1,3-Diphenyl-5-isopropyl-1H-1,2,4-triazole (**15c**).* Gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17–8.15 (m, 2H), 7.56–7.38 (m, 8H), 3.15 (septet, *J*=6.8 Hz), 1.37 (d, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 161.5, 137.7, 131.1, 129.5, 129.1, 129.1, 128.5, 126.6, 125.7, 26.0, 21.7; IR (KBr): 3061, 2971, 2929, 2852, 1596, 1499, 1445, 1355, 1220, 1015, 923, 772, 713, 694 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{17}H_{17}N_3$: 263.1422; found: 263.1423.

*4.3.17. 5-tert-Butyl-1,3-diphenyl-1H-1,2,4-triazole (**16c**).* Mp: 128–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15–8.12 (m, 2H), 7.54–7.35 (m, 8H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 160.0, 140.0, 131.1, 129.8, 129.1, 129.0, 128.5, 128.2, 126.5, 33.6, 33.0; IR (KBr): 3060, 2967, 2928, 1594, 1447, 1354, 1215, 1071, 1014, 772, 717, 696, 612 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{18}H_{19}N_3$: 277.1579; found: 277.1576.

*4.3.18. 1,3,5-Triphenyl-1H-1,2,4-triazole (**17b**).*[5] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26–8.24 (m, 2H), 7.58–7.56 (m, 2H), 7.34–7.56 (m, 11H).

*4.3.19. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1H-1,2,4-triazole (**18b**).*[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.41–7.39 (m, 4H), 7.31–7,29 (m, 2H), 2.82 (t, *J*=7.8 Hz, 2H), 1.83 (quintet, *J*=7.6 Hz, 2H), 1.45–1.41 (m, 2H), 1,35–1.32 (m, 4H), 0.89 (t, *J*=7.0 Hz, 3H).

*4.3.20. 3-Methyl-5-phenyl-1-(2-pyridyl)-1H-1,2,4-triazole (**19b**).* Mp: 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (m, 1H), 7.82 (td, *J*=8.0 Hz, 2.0 Hz, 1H), 7.51–7.32 (m, 7H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 155.1, 150.9, 149.2, 138.8, 130.2, 129.1, 128.6, 128.5, 123.8, 119.3, 14.1; IR (KBr): 3068, 3018, 2927, 1588, 1509, 1436, 1409, 1092, 1003, 782, 697 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{14}H_{12}N_4$: 236.1062; found: 236.1059.

*4.3.21. 3,5-Dimethyl-1-phenyl-1H-1,2,4-triazole (**20b**).*[30] Mp: 44–46 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.47 (m, 2H), 7.45–7.41 (m, 3H), 2.49 (s, 3H), 2.42 (s, 3H).

*4.3.22. 5-Ethyl-3-methyl-1-phenyl-1H-1,2,4-triazole (**21b**) and 3-ethyl-5-methyl-1-phenyl-1H-1,2,4-triazole (**21c**) 7:3 mixture (not separable).*[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.40 (m, 10H, 5H for **21b** and 5H for **21c**), 2.78 (q, *J*=7.6 Hz, 4H, 2H for **21b** and 2H for **21c**), 2.50 (s, 3H for **21c**), 2.44 (s, 3H for **21b**), 1.36 (t, *J*=7.6 Hz, 3H for **21c**), 1.33 (t, *J*=7.6 Hz, 3H for **21b**).

*4.3.23. 5-Benzyl-3-methyl-1-phenyl-1H-1,2,4-triazole (**22b**).* Gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.41 (m, 3H), 7.33–7.21 (m, 5H), 7.46–7.41 (m, 3H), 7.33–7.21 (m, 5H), 7.14–7.12 (m, 2H), 4.12 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 154.6, 137.5, 136.2, 129.5, 129.1, 128.9, 128.6, 127.1, 125.4, 32.6, 14.1; IR (KBr): 3063, 3030, 2928, 1599, 1520, 1425, 1339, 1125, 1053, 764, 696 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{16}H_{15}N_3$: 249.1266; found: 249.1263.

*4.3.24. 3-Benzyl-5-methyl-1-phenyl-1H-1,2,4-triazole (**22c**).* Gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.48 (m, 2H), 7.45–7.40 (m, 5H), 7.33–7.30 (m, 2H), 7.26–2.22 (m, 2H), 4.09 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 152.8, 138.3, 137.6, 129.6, 129.1, 128.8, 128.7, 126.7, 124.8, 34.9, 13.4; IR (KBr): 3062, 3030, 2925, 1599, 1511, 1454, 1363, 1028, 765, 696 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{16}H_{15}N_3$: 249.1266; found: 249.1264.

*4.3.25. 1-(4-Methoxyphenyl)-3-methyl-5-phenyl-1H-1,2,4-triazole (**23b**).* Mp: 99–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J*=6.8 Hz, 2H), 7.37–7.30 (m, 3H), 7.25 (d, *J*=8.8 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 3.84 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 1605, 159.7, 154.1, 131.3, 129.8, 128.7, 128.5, 128.0, 126.7, 114.5, 55.5, 13.9; IR (KBr): 3059, 2971, 2937, 1522, 1454, 1342, 1301, 1258, 1172, 1027, 834, 779, 720, 696 cm^{-1}; HRMS (EI$^+$): *m/z* [M+H]$^+$ calcd for $C_{16}H_{15}N_3O$: 265.1215; found: 265.1212.

*4.3.26. 3-Methyl-1-(4-nitrophenyl)-5-phenyl-1H-1,2,4-triazole (**24b**).* Mp: 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d,

J=9.0 Hz, 2H), 7.53 (d, J=9.0 Hz, 2H), 7.50–7.39 (m, 5H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 154.8, 146.9, 142.9, 130.6, 129.0, 128.9, 127.6, 125.0, 124.8, 13.9; IR (KBr): 3082, 3062, 2995, 2934, 2850, 1597, 1520, 1498, 1448, 1397, 1338, 1272, 1112, 982, 853, 771, 750, 697 cm^{-1}; HRMS (EI$^+$): m/z [M+H]$^+$ calcd for $C_{15}H_{12}N_4O_2$: 280.0960; found: 280.0962.

*4.3.27. 1-(2,4-Dimethylphenyl)-3-methyl-5-phenyl-1H-1,2,4-triazole (**25b**).* Gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J=8.0 Hz, 2H), 7.35–7.26 (m, 3H), 7.15–7.07 (m, 3H), 2.50 (s, 3H), 2.38 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 154.7, 139.8, 135.2, 134.8, 131.9, 129.7, 128.5, 127.9, 127.8, 127.7, 127.3, 21.2, 17.4, 13.9; IR (KBr): 3034, 2956, 2857, 1518, 1452, 1406, 1377, 1341, 1276, 1166, 1080, 988, 822, 777, 718, 694 cm^{-1}; HRMS (EI$^+$): m/z [M+H]$^+$ calcd for $C_{17}H_{17}N_3$: 263.1422; found: 263.1425.

*4.3.28. 1-Benzyl-3-methyl-5-phenyl-1H-1,2,4-triazole (**26b**).*[34] Mp: 44–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.55 (m, 2H), 7.47–7.41 (m, 3H), 7.37–7.30 (m, 3H), 7.17–7.15 (m, 2H), 5.36 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 155.8, 136.3, 130.3, 129.1, 129.0, 128.8, 128.2, 128.1, 126.9, 52.6, 14.2; IR (KBr): 3076, 3038, 2948, 2927, 1509, 1437, 1343, 1020, 777, 696 cm^{-1}; HRMS (EI$^+$): m/z [M+H]$^+$ calcd for $C_{16}H_{15}N_3$: 249.1266; found: 249.1263.

*4.3.29. 3-Methyl-1-phenyl-5-(2-pyridyl)-1H-1,2,4-triazole (**28b**).* Mp: 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51–8.49 (m, 1H), 7.81 (dt, J=7.6 Hz, 1.2 Hz, 1H), 7.75 (td, J=7.6 Hz, 2.0 Hz, 1H), 7.74–7.35 (m, 5H), 7.31–7.27 (m, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 152.9, 149.7, 147.6, 138.9, 136.9, 129.1, 128.7, 125.5, 124.5, 124.2, 14.1; IR (KBr): 3063, 3000, 2927, 1588, 1514, 1473, 1453, 1432, 1395, 1075, 778, 697 cm^{-1}; HRMS (EI$^+$): m/z [M+H]$^+$ calcd for $C_{14}H_{12}N_4$: 236.1062; found: 236.1058.

Acknowledgements

J.L. acknowledges financial support from the Korean Ministry of Education through the second stage of the BK21 project for the Hanyang University graduate program. We thank Prof. M.S. Lah for X-ray crystallography.

Supplementary data

^{1}H NMR and ^{13}C NMR spectra for products, ^{1}H–^{1}H NOESY spectra for **21b**, **21c**, **22b**, **22c**, and **26b**, and X-ray crystallographic data for **16c**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.003.

References and notes

1. Al-Soud, Y. A.; Al-Dweri, M. N.; Al-Masoudi, N. A. *Farmaco* **2004**, *59*, 775.
2. Demirbas, N.; Ugurluoglu, R.; Demirbas, A. *Bioorg. Med. Chem.* **2002**, *10*, 3717.
3. Tozkoparan, B.; Gokhan, N.; Aktay, G.; Yesilada, E.; Ertan, M. *Eur. J. Med. Chem.* **2000**, *35*, 743.
4. Conde, S.; Corral, C.; Madronero, R. *Synthesis* **1974**, 28.
5. Su, W.; Yang, D.; Li, J. *Synth. Commun.* **2005**, *35*, 1435.
6. Paulvannan, K.; Chen, T.; Hale, R. *Tetrahedron* **2000**, *56*, 8071.
7. Paulvannan, K.; Hale, R.; Sedehi, D.; Chen, T. *Tetrahedron* **2001**, *57*, 9677.
8. Buzykin, B. I.; Bredikhina, Z. A. *Synthesis* **1993**, 59.
9. Caddik, S. *Tetrahedron* **1995**, *51*, 10403.
10. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
11. Jagerovic, N.; Hernandez-Folgado, L.; Alkorta, I.; Goya, P.; Navarro, M.; Serrano, A.; Fonseca, F. R.; Dannert, M. T.; Alsasua, A.; Suardiaz, M.; Pascual, D.; Martin, M. I. *J. Med. Chem.* **2004**, *47*, 2939.
12. Czollner, L.; Szilagyi, G.; Lango, J.; Janaky, J. *Arch. Pharm.* **1990**, *323*, 225.
13. Yoon, U. C.; Cho, S. J.; Lee, Y. J.; Mancheno, M. J.; Mariano, P. S. *J. Org. Chem.* **1995**, *60*, 2353.
14. Benzamide derivatives (1.0 mmol), acid anhydrides (3.0 mmol), and 2 drops of concd H_2SO_4 were placed in a 10 mL round bottom flask. The reaction was performed at 100 °C until reaction was finished by TLC monitoring. After the reaction, the solution was extracted with ethyl acetate (2×10 mL), and the combined organic layer was washed with 5% aq $NaHCO_3$ (2×10 mL), and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to provide the crude material. The crude material was purified by flash column chromatography using various hexane/ethyl acetate eluent systems to afford the desired products.
15. *N*-Acylated benzamides (1.0 mmol), phenyl hydrazine hydrochloride (2.0 mmol), and pyridine (1 mL) were placed in a 10 mL round bottom flask equipped with a reflux condenser. The reaction was refluxed until reaction was finished by TLC monitoring. After the reaction, ethyl acetate (20 mL) was added to the reaction mixture to precipitate residual phenyl hydrazine hydrochloride, and then filtered. The solvent was evaporated to the crude material. The crude material was roughly purified by flash column chromatography using hexane/triethylamine (10:1) eluent system then purified by flash column chromatography using various hexane/ethyl acetate eluent systems to afford the desired products.
16. Atkinson, M. R.; Polya, J. B. *J. Chem. Soc.* **1952**, 3418.
17. Pellizzari, G. *Gazz. Chim. Ital.* **1911**, *41*, 93.
18. CCDC-828998 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
19. Benzamide derivatives (1.0 mmol), acid anhydrides (1.5 mmol), and 2 drops of concd H_2SO_4 were placed in a 50 mL round bottom flask equipped with a reflux condenser. The reaction flask was microwave irradiated (50 W, 100 °C) for 3 min with stirring. After the reaction, phenyl hydrazine hydrochloride (2.0 mmol) and pyridine (2 mL) was added then the reaction flask was microwave irradiated (300 W, 200 °C) for 1 min with stirring. After the reaction the reaction mixture was extracted with ethyl acetate (2×10 mL), and the combined organic layer was washed with 5% aq $NaHCO_3$ (2×10 mL), and brine (20 mL), dried over anhydrous $MgSO_4$, and evaporated to provide the crude material. The crude material was roughly purified by flash column chromatography using hexane/triethylamine (10:1) eluent system then purified by flash column chromatography using various hexane/ethyl acetate eluent systems to afford the desired products.
20. *Purification of Laboratory Chemicals*, 6th ed.; Armarego, W. L. F., Chai, C. L. L., Eds.; Elsevier: Oxford, 2009.
21. Evans, D. A.; Nagorny, P.; Xu, R. *Org. Lett.* **2006**, *8*, 5669.
22. Nakayama, H.; Itoh, A. *Synlett* **2008**, 675.
23. Reynaud, P.; Nguyen-Tri-Xuong, E.; Davrinche, C.; Tran, G.; Rinjard, P.; Pieri, F.; Arnould-Guerin, M. L. *Eur. J. Med. Chem.* **1992**, *27*, 245.
24. Lin, Y.; Lang, S. A. *Synthesis* **1980**, 119.
25. Kametani, T.; Kigasawa, K.; Shimizu, H.; Saitou, S.; Hayashida, S.; Fujino, M. *Yakugaku Zasshi* **1983**, *103*, 1144.
26. Wang, L.; Fu, H.; Jinag, Y.; Zhao, Y. *Chem.—Eur. J.* **2008**, *14*, 10722.
27. Habibi, Z.; Salehi, P.; Zolfigol, M. A.; Yousefi, M. *Synlett* **2009**, 1506.
28. Habibi, Z.; Salehi, P.; Zolfigol, M. A.; Yousefi, M. *Synlett* **2007**, 812.
29. Krohn, K.; Franke, C.; Jones, P. G.; Aust, H. J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1992**, 789.
30. Metra, P.; Hamelin, J. *Can. J. Chem.* **1982**, *60*, 285.
31. Staben, S. T.; Blaquiere, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 325.
32. Lin, Y.; Hlavka, J. J.; Bitha, P.; Lang, S. A. *J. Heterocycl. Chem.* **1983**, *20*, 1693.
33. Jagerovic, N.; Goya Laza, M. P.; Hernandez Folgado, L.; Alcorta Osoro, I. J.; Martin Fontelles, M. I.; Suardiaz Garcia, M. L.; Dannert, M. T. World Patent WO03082833, 2003.
34. Jorgensen, K. B.; Olsen, R. B.; Carlsen, P. H. J. *Molecules* **2001**, *6*, 481.