Tetrahedron 65 (2009) 8367–8372

Contents lists available at ScienceDirect

Tetrahedron

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

Microwave-assisted cycloadditions of 2-alkynylbenzonitriles with sodium azide: selective synthesis of tetrazolo[5,1-*a*]pyridines and 4,5-disubstituted-2*H*-1,2,3-triazoles

Chih-Wei Tsai [a], Shyh-Chyun Yang [a], Ya-Ming Liu [b], Ming-Jung Wu [c,*]

[a] *Graduate Institute of Pharmaceutical Science, Kaohsiung Medical University, Kaohsiung City 807, Taiwan, ROC*
[b] *Faculty of medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung City 807, Taiwan, ROC*
[c] *Department of Chemistry, National Sun Yat-sen University, Kaohsiung City 804, Taiwan, ROC*

ARTICLE INFO

Article history:
Received 29 June 2009
Received in revised form 3 August 2009
Accepted 6 August 2009
Available online 9 August 2009

Keywords:
Tetrazolo[5,1-*a*]pyridines
4,5-Disubstituted-2*H*-1,2,3-triazoles

ABSTRACT

Under microwave irradiation (75 W), treatment of 2-alkynylbenzonitriles with 1.5 equiv of sodium azide in DMSO at 140 °C gave 4,5-disubstituted-2*H*-1,2,3-triazoles in 60–99% yields. Additionally, adding 8 equiv of $ZnBr_2$ and using 8 equiv of sodium azide in DMF at 100 °C lead to the formation of tetrazolo[5,1-*a*]isoquinolines up to 87% yield.

1. Introduction

1,2,3-Triazoles are important molecules for pharmaceutical and agricultural use.[1] Recently, Shi reported that the *N*-2-aryl-2*H*-1,2,3-triazoles have unique photonic properties.[2] Therefore the development of an efficient method for constructing substituted-2*H*-1,2,3-triazoles has become an important synthetic organic chemistry topic. The general synthetic method for synthesizing 1,2,3-triazoles involves the thermal 1,3-dipolar cycloaddition reaction of organic azides with alkynes pioneered by Huisgen.[3] The drawbacks of this method are poor regioselectivity and long reaction time. Improved methods were reported by the Sharpless group with so-called 'click chemistry'[4] and by the Meldal group.[5] They reported that cycloaddition reactions of terminal alkynes with alkyl azides using Cu(I) as a catalyst can be performed under mild conditions and give products with high yields and high regioselectivities. However, these methods cannot be applied to the internal alkynes.

Recently, the Weinreb group reported successful cycloadditions of internal alkynes with alkyl azides over a ruthenium catalyst to give 4,5-disubstituted triazoles.[6] Still, a direct method to produce 4,5-disubstituted-1,2,3-triazoles by cycloadditions of internal alkynes with unsubstituted azides, such as sodium azide, is limited.[7] Normally, the reaction required longer time at high temperature to give the adducts in low to modest yields[7b–d] unless there is a strong electron-withdrawing group attached to the alkyne terminus.[7e–f]

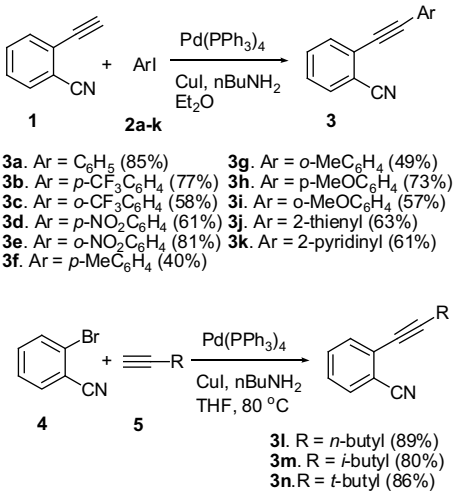
Tetrazolo[5,1-*a*]isoquinolines are also compounds with pharmaceutical interest. It has been shown that these molecules show good monoamine oxidase inhibition activity.[8] Under thermal or photochemical conditions, these compounds can be converted to various heterocyclic compounds through pyridylnitrene intermediates.[9] However, the available methods for synthesizing tetrazolo[5,1-*a*]isoquinolines and related molecules are limited.[9,10] Herein, we report efficient methods to selectively synthesize 4,5-disubstituted-2*H*-1,2,3-triazoles and tetrazolo[5,1-*a*]isoquinolines via reaction of 2-alkynylbenzonitriles with sodium azide.

2. Results and discussion

The starting internal alkynes were prepared by the following two routes: 2-(2-arylethynyl)benzonitriles **3a–k** were prepared by Sonogashira coupling of 2-ethynylbenzonitrile (**1**)[11] with various aryl iodides **2a–k** in 40–81% yields (Scheme 1). The 2-alkynylbenzonitriles **3l–n** were synthesized by coupling of 2-bromobenzonitrile (**4**) with alkynes **5a–c** in 80–89% yields (Scheme 1).

* Corresponding author. Tel.: +886 7 5252000; fax: +886 7 5253909.
E-mail address: mijuwu@faculty.nsysu.edu.tw (M.-J. Wu).

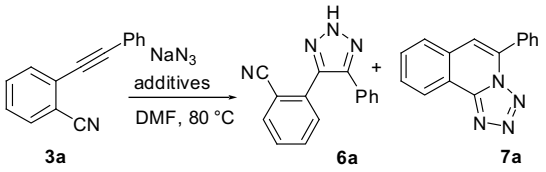
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.08.009



Scheme 1. Synthesis of intermediates **3a–n**.

Our initial attempt at the cycloaddition of an internal alkyne with sodium azide was carried out by mixing compound **3a** with 5 equiv of sodium azide in DMF at 80 °C. We found that this reaction requires 6 days to consume the starting material but gives the corresponding triazole **6a** in 98% yield (Table 1, entry 1). Doubling the amount of sodium azide to 10 equiv did not accelerate the reaction rate (Table 1, entry 2). Addition of copper sulfate along with sodium ascorbate into the reaction mixture did not improve the reaction (Table 1, entry 3). Magnesium bromide was also employed; however, no significant improvement was observed (Table 1, entry 4). Ammonium and zinc salts have been used to promote and catalyze, respectively, the reaction of organonitriles with sodium azide to give tetrazoles in high yields.[12] Therefore, we introduced ammonium chloride into the reaction mixture, and the reaction gave tetrazolo[5,1-*a*]isoquinoline and triazole adducts in 47% and 50% yields, respectively (Table 1, entry 5). However, when zinc bromide was introduced to the reaction mixture, although the reaction still took place very slowly, tetrazolo[5,1-*a*]isoquinoline was obtained as the only product (Table 1, entry 6). The high selectivity of the formation of tetrazolo[5,1-*a*]isoquinoline is because of zinc bromide could coordinate and activate the cyano group. Thus, sodium azide would react with the cyano group first to form the tetrazole and followed by cyclization to give the tetrazolo[5,1-*a*]isoquinoline. This exciting initial result encourages us to continue the investigation of these cycloaddition reactions.

Table 1
The result of the reactions of **3a** with sodium azide using various additives

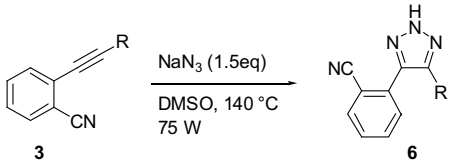


Entry	NaN_3 (equiv)	Additive	Time (d)	Isolated yields (%) 3a	6a	7a
1	5	None	6	0	98	0
2	10	None	10	0	95	0
3	5	$CuSO_4$/Sodium ascorbate	6	0	86	8
4	10	NH_4Cl/LiCl (10 equiv)	6	19	50[a]	47[a]
5	10	$ZnBr_2$ (10 equiv)	10	46	0	86[a]
6	10	$MgBr_2$ (10 equiv)	6	30	95[a]	4[a]

[a] Yields are calculated base on recovered starting materials.

Use of microwave irradiation to enhance reaction rates has been known for years.[13] Hallberg has applied this method to prepare a variety of tetrazoles by the reaction of sodium azide with corresponding nitriles.[12a] Fokin also found that microwave irradiation could accelerate the reaction rate of ruthenium-catalyzed cycloaddition reactions of substituted azides with terminal alkynes.[14] We carried out the reaction of **3a** with 1.5 equiv of sodium azide in dimethyl sulfoxide under microwave irradiation (75 W) at 140 °C. The reaction went to completion within 10 min and produced the triazole adduct **6a** in 98% yield. At the optimal reaction conditions, we then turned our attention to the scope and generality of this method. Thus, various substituted 2-alkynylbenzonitriles **3b–n** were prepared (Scheme 1) and submitted to the cycloaddition conditions to afford the 4,5-disubstituted-2*H*-1,2,3-triazoles in 60–99% yields (Table 2). The results show that all of the attempted reactions were successfully completed under the optimal reaction conditions. The reaction only required longer time when trazole has a phenyl ring bearing electron-donating groups (Table 2, entries 6–9). Triazoles with strong electron-withdrawing group, such as a nitro group, resulted in slightly lower yields but faster than the others (Table 2, entries 4 and 5). The *ortho*-substituted phenyl rings and bulky *tert*-butyl group also gave cycloadditon adducts in somewhat lower yields (Table 2, entries 3, 5, 7, 9, and 14).

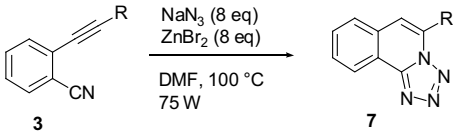
Table 2
The result of the reactions of **3a–n** with sodium azide by microwave irradiation



Entry	R	Time (min)	Isolated products/yields (%)
1	C_6H_5	10	**6a**/98
2	*p*-$CF_3C_6H_4$	4	**6b**/99
3	*o*-$CF_3C_6H_4$	10	**6c**/95
4	*p*-$NO_2C_6H_4$	5	**6d**/72
5	*o*-$NO_2C_6H_4$	5	**6e**/66
6	*p*-MeC_6H_4	25	**6f**/96
7	*o*-MeC_6H_4	30	**6g**/60
8	*p*-$MeOC_6H_4$	40	**6h**/99
9	*o*-$MeOC_6H_4$	90	**6i**/92
10	2-Thienyl	7	**6j**/87
11	2-Pyridinyl	6	**6k**/84
12	*n*-Butyl	12	**6l**/99
13	*i*-Butyl	15	**6m**/81
14	*tert*-Butyl	20	**6n**/70

Previously, we found that the reaction of sodium azide with **3a** in the presence of zinc bromide gave tetrazolo[5,1-*a*]isoquinoline **7a** in good yield, albeit, in long reaction time. When the reaction was carried out under microwave irradiation (75 W) at 100 °C, the reaction went to completion in 4 h and gave the product **7a** in 69% yield. The other substrates **3b–n** were also reacted under the described conditions. The results are summarized in Table 3. Most of the substrates gave the desired products in good to excellent yields (Table 3, entries 1–3, 5–9, and 11–13). The only exceptions occurred for the phenyl ring bearing a nitro group, which gave the tetrazoloisoquinoline adduct **7d** in 30% yield, (Table 3, entry 4) and for compound **3k** bearing the 2-pyridinyl group at the terminus alkyne, which was consumed very quickly under this reaction condition, but was mostly decomposed (Table 3, entry 10).

Table 3
The result of the reactions of **3a–n** with sodium azide by microwave irradiation in the presence of $ZnBr_2$



3 7

Entry	R	Time (h)	Isolated products/yields (%)
1	C_6H_5	4	**7a**/69
2	*p*-$CF_3C_6H_4$	3	**7b**/85
3	*o*-$CF_3C_6H_4$	3	**7c**/70
4	*p*-$NO_2C_6H_4$	0.5	**7d**/30
5	*p*-MeC_6H_4	5	**7f**/70
6	*o*-MeC_6H_4	5	**7g**/63
7	*p*-$MeOC_6H_4$	6	**7h**/70
8	*o*-$MeOC_6H_4$	5	**7i**/68
9	2-Thienyl	2	**7j**/87
10	2-Pyridinyl	5 (min)	**7k**/0
11	*n*-Butyl	5	**7l**/85
12	*i*-Butyl	2	**7m**/73
13	*tert*-Butyl	2	**7n**/83

3. Conclusion

In conclusion, we have developed methods for selectively synthesizing 4,5-disubstituted-2*H*-1,2,3-triazoles and tetrazolo[5,1-*a*]isoquinolines by the reactions of 2-alkynylbezonitriles with sodium azide. Moreover, the reaction rate can be accelerated by microwave irradiation. It is known that reactions of internal alkynes with unsubstituted azides always require long reaction times. Herein, we have demonstrated that use of microwave irradiation to assist these cycloaddition reactions is an efficient method for directly preparing a variety of 4,5-disubstituted-2*H*-1,2,3-triazoles.

4. Experimental section

4.1. Microwave irradiation experiments

All microwave irradiation experiments were carried out in a dedicated monomode microwave reactor Synthwave 402 (Prolabo), operating at a frequency of 2455 MHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. The machine was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 10 mL glass vials, which can be exposed to a maximum of 250 °C. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature.

4.2. General procedure for cross-coupling reaction (3a–k)

To a degassed solution of 2-ethynylbenzonitrile (**1**) (2.0 mmol) in Et_2O (20 mL) containing CuI (0.54 mmol) and *n*-$BuNH_2$ (5.0 mrnol) was added a degassed solution of aryl iodide (**2a–k**) (2.0 mmol) containing $Pd(PPh_3)_4$ (0.14 mmol) in Et_2O (20 mL). The resulting solution was stirred for 4 h and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc (30 mL×3) and the combined organic extracts were washed with saturated aqueous Na_2CO_3 solution (40 mL) and dried over anhydrous $MgSO_4$. After filtration and removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes as eluent) to give the desired products **3a–k**, in yields indicated as in Eq. 1.

The following compounds, prepared by the above procedure, have been previously reported: 2-(2-(phenyl)ethynyl)benzonitrile[15] (**3a**), 2-(2-(4-(trifluoromethyl)phenyl)ethynyl)benzonitrile[16] (**3b**), 2-(2-(2-(trifluoromethyl)phenyl)ethynyl)benzonitrile[17] (**3c**), 2-(2-(4-(methyl)phenyl)ethynyl)benzonitrile[15] (**3f**), 2-(2-(4-methoxyphenyl)ethynyl)benzonitrile[17] (**3h**), 2-(2-(2-methoxyphenyl)ethynyl)benzonitrile[17] (**3i**), 2-(2-(2-thienyl)ethynyl)benzonitrile[18] (**3j**), and 2-(2-(pyridin-2-yl)ethynyl)benzonitrile[18] (**3k**).

*4.2.1. 2-(2-(4-Nitrophenyl)ethynyl)benzonitrile (**3d**).* Yellow solid; mp 133–134 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J*=8.8 Hz, 2H), 7.75 (d, *J*=8.8 Hz, 2H), 7.72 (d, *J*=7.6 Hz, 1H), 7.67 (d, *J*=7.6 Hz, 1H), 7.62 (t, *J*=7.6 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 132.8, 132.7, 132.6, 132.3, 129.3, 128.7, 125.9, 123.7, 117.2, 115.6, 93.4, 90.1; GC/MS (70 eV): *m*/*z* (%): 248 (100) [M^+], 218 (49), 203 (28), 190 (39), 175 (16); HRMS (EI) calcd for $C_{15}H_8N_2O_2$ 248.0586, found 248.0586. Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.25; N, 11.28. Found: C, 72.68; H, 3.35; N, 11.25.

*4.2.2. 2-(2-(2-Nitrophenyl)ethynyl)benzonitrile (**3e**).* Brown solid; mp 143–144 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J*=8.4 Hz, 1H), 7.86 (d, *J*=7.6 Hz, 1H), 7.73–7.59 (m, 4H), 7.54 (t, *J*=7.6 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 135.4, 133.2, 132.8, 132.7, 132.5, 129.6, 129.2, 126.2, 124.8, 117.6, 117.3, 115.4, 92.5, 90.8; GC/MS (70 eV): *m*/*z* (%): 248 (21) [M^+], 231 (30), 220 (60), 201 (21), 192 (34), 176 (24), 164 (36), 130 (100), 102 (36); HRMS (EI) calcd for $C_{15}H_8N_2O_2$ 248.0586, found 248.0586. Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.25; N, 11.28. Found: C, 72.55; H, 3.35; N, 11.25.

*4.2.3. 2-(2-(2-(Methyl)phenyl)ethynyl)benzonitrile (**3g**).* White solid; mp 77–78 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.72–7.52 (m, 4H), 7.45–7.38 (m, 1H), 7.26–7.15 (m, 3H), 2.59 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.9, 132.7, 132.4, 132.3, 132.2, 129.6, 129.3, 128.1, 127.5, 125.6, 121.8, 117.7, 114.9, 94.9, 89.2, 20.9; GC/MS (70 eV): *m*/*z* (%): 217 (100) [M^+], 191 (12), 189 (14); HRMS (EI) calcd for $C_{16}H_{11}N$ 217.0891, found 217.0892. Anal. Calcd for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.34; H, 5.10; N, 6.40.

4.3. General procedure for cross-coupling reaction (3l–n)

To a degassed solution of each 1-alkyne (**5a–c**) (2.0 mmol) in THF (20 mL) containing CuI (0.54 mmol) and *n*-$BuNH_2$ (5.0 mrnol) was added a degassed solution of 2-bromobenzonitrile (**4**) (2.0 mmol) containing $Pd(PPh_3)_4$ (0.14 mmol) in THF (20 mL). The resulting solution was stirred at 80 °C for 4 h and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc (30 mL×3) and the combined organic extracts were washed with saturated aqueous Na_2CO_3 solution (40 mL) and dried over anhydrous $MgSO_4$. After filtration and removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes as eluent) to give the desired products **3l–n**, in yields indicated as in (Scheme 1).

The following compounds, prepared by the above procedure, have been previously reported: 2-(hex-1-ynyl)benzonitrile[15] (**3l**) and 2-(3,3-dimethylbut-1-ynyl)benzonitrile[18] (**3n**).

*4.3.1. 2-(4-Methylpent-1-ynyl)benzonitrile (**3m**).* Yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J*=7.6 Hz, 1H), 7.53–7.48 (m, 2H), 7.37–7.32 (m, 1H), 2.39 (d, *J*=6.4 Hz, 2H), 1.97 (sept, *J*=6.4 Hz, 1H), 1.08 (d, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 132.21, 132.16, 128.0, 127.5, 117.7, 115.1, 96.8, 78.0, 28.6, 27.9, 21.9; GC/MS (70 eV): *m*/*z* (%): 183 (20) [M^+], 141 (100), 114 (47); MS (ESI): 206 [M+Na]$^+$; HRMS (ESI) calcd for $C_{13}H_{13}NNa$ [M+Na]$^+$ 206.0946, found 206.0945.

4.4. General procedure for the microwave-assisted reactions to synthesize 4,5-disubstituted triazoles

An appropriate 2-alkynylbenzonitrile (0.4 mmol) and sodium azide (0.6 mmol) were suspended in DMSO (3 mL) in a 10 mL

glass vial. The mixture was then irradiated for the time and temperature indicated in Table 2, using an irradiation power of 75 W. After completion of the reaction, the vial was cooled to 25 °C. The mixture was then diluted with water (20 mL), extracted with EtOAc (10 mL×3), and dried over anhydrous $MgSO_4$. After filtration and removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel to furnish the product triazoles **6a–n**, in yields indicated as in Table 2.

*4.4.1. 2-(5-Phenyl-2H-1,2,3-triazol-4-yl)benzonitrile (**6a**).* Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.50 (t, J=8.0 Hz, 1H), 7.44 (d, J=8.0 Hz, 2H), 7.35–7.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 140.3, 134.4, 133.7, 132.8, 130.9, 129.1, 128.9, 128.84, 128.82, 127.6, 117.7, 112.4; GC/MS (70 eV): m/z (%): 246 (100) [M^+], 219 (30), 190 (27); HRMS (EI) calcd for $C_{15}H_{10}N_4$ 246.0905, found 246.0908.

*4.4.2. 2-(5-(4-(Trifluoromethyl)phenyl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6b**).* Yellow solid; mp 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J=8.0 Hz, 1H), 7.65 (t, J=8.0 Hz, 1H), 7.59 (s, 4H), 7.57–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.8, 133.9, 133.2, 133.0, 130.8, 130.6, 129.4, 128.7, 127.9, 125.7, 123.8, 117.6, 112.5; GC/MS (70 eV): m/z (%): 314 (100) [M^+], 288 (26), 258 (23), 190 (34); HRMS (EI) calcd for $C_{16}H_9F_3N_4$ 314.0779, found 314.0780. Anal. Calcd for $C_{16}H_9F_3N_4$: C, 61.15; H, 2.89; N, 17.83. Found: C, 61.08; H, 2.85; N, 17.85.

*4.4.3. 2-(5-(2-(Trifluoromethyl)phenyl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6c**).* Light yellow solid; mp 169–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.30 (br s, 1H), 7.78–7.73 (m, 2H), 7.57–7.53 (m, 2H), 7.46–7.36 (m, 3H), 7.19 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1 (2), 134.1, 133.2, 132.8, 132.6, 131.8, 130.1, 129.9, 129.5, 128.8, 128.3, 126.8, 123.5, 118.2, 111.9; GC/MS (70 eV): m/z (%): 314 (100) [M^+], 288 (40), 265 (32), 245 (34), 239 (16), 190 (31), 167 (38), 88 (36); HRMS (EI) calcd for $C_{16}H_9F_3N_4$ 314.0779, found 314.0781. Anal. Calcd for $C_{16}H_9F_3N_4$: C, 61.15; H, 2.89; N, 17.83. Found: C, 61.18; H, 2.85; N, 17.83.

*4.4.4. 2-(5-(4-Nitrophenyl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6d**).* Yellow solid; mp 205–206 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 8.2 (d, J=8.8 Hz, 2H), 7.89 (d, J=8.0 Hz, 1H), 7.80 (t, J=8.0 Hz, 1H), 7.70–7.64 (m, 2H), 7.67 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 149.0, 138.0, 135.5, 134.9, 134.6, 132.3, 131.1, 129.2, 125.0, 118.2, 113.9; GC/MS (70 eV): m/z (%): 291 (100) [M^+], 261 (55), 205 (19), 190 (59), 178 (30), 151 (15); HRMS (EI) calcd for $C_{15}H_9N_5O_2$ 291.0756, found 291.0756. Anal. Calcd for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.04. Found: C, 61.83; H, 3.21; N, 24.10.

*4.4.5. 2-(5-(2-Nitrophenyl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6e**).* Orange solid; mp 181–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.00 (br s, 1H), 7.95 (d, J=8.0 Hz, 1H), 7.73 (d, J=8.0 Hz, 1H), 7.67 (t, J=8.0 Hz, 1H), 7.60–7.52 (m, 3H), 7.47 (t, J=8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 142.1, 141.9, 133.9, 133.2, 133.0, 132.9, 132.7, 130.4, 130.2, 129.2, 124.9, 124.8, 117.6, 111.9; GC/MS (70 eV): m/z (%): 291 (9) [M^+], 245 (100), 190 (35), 163 (7); HRMS (EI) calcd for $C_{15}H_9N_5O_2$ 291.0756, found 291.0753. Anal. Calcd for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.04. Found: C, 62.00; H, 3.12; N, 24.24.

*4.4.6. 2-(5-p-Tolyl-2H-1,2,3-triazol-4-yl)benzonitrile (**6f**).* Light brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.57–7.45 (m, 2H), 7.32 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.5, 140.1, 138.8, 134.6, 133.7, 132.7, 130.9, 129.5, 128.8, 127.5, 126.2, 117.7, 112.6, 21.2; GC/MS (70 eV): m/z (%): 260 (100) [M^+], 233 (33), 231 (28), 204 (17); HRMS (EI) calcd for $C_{16}H_{12}N_4$ 260.1062, found 260.1064.

*4.4.7. 2-(5-o-Tolyl-2H-1,2,3-triazol-4-yl)benzonitrile(**6g**).* Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, J=7.6, 1.6 Hz, 1H), 7.49 (td, J=7.6, 1.6 Hz, 1H), 7.42 (td, J=7.6, 1.6 Hz, 1H), 7.34–7.29 (m, 2H), 7.24 (dd, J=7.6, 0.4 Hz, 1H), 7.19–7.17 (m, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 141.7, 137.2, 134.0, 132.7, 130.8, 130.4, 130.0, 129.2, 128.62, 128.56, 126.0, 118.1, 111.7, 20.0; GC/MS (70 eV): m/z (%): 260 (40) [M^+], 231 (100), 204 (28), 177 (8); HRMS (EI) calcd for $C_{16}H_{12}N_4$ 260.1062, found 260.1061.

*4.4.8. 2-(5-(4-Methoxyphenyl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6h**).* Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.0 Hz, 1H), 7.54–7.47 (m, 2H), 7.35 (d, J=8.8 Hz, 1H), 6.85 (d, J=8.8 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 143.2, 139.9, 134.6, 133.7, 132.7, 130.8, 129.0, 128.8, 121.4, 117.7, 114.3, 112.5, 55.2; GC/MS (70 eV): m/z (%): 276 (100) [M^+], 233 (16), 205 (33), 178 (18), 151 (14); HRMS (EI) calcd for $C_{16}H_{12}N_4O$ 276.1011, found 276.1011.

*4.4.9. 2-(5-(2-Methoxyphenyl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6i**).* Brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (d, J=7.6 Hz, 1H), 7.60–7.37 (m, 3H), 7.29 (t, J=7.6 Hz, 2H), 6.91 (t, J=7.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.1, 141.1, 137.0, 135.6, 133.3, 132.4, 130.6, 130.2, 129.9, 128.3, 120.9, 117.6, 117.0, 112.0, 111.4, 55.1; GC/MS (70 eV): m/z (%): 276 (100) [M^+], 248 (54), 233 (52), 219 (87), 205 (56), 190 (30), 178 (19); HRMS (EI) calcd for $C_{16}H_{12}N_4O$ 276.1011, found 276.1010.

*4.4.10. 2-(5-(Thiophen-2-yl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6j**).* Absinthe-green liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J=8.0 Hz, 1H), 7.70–7.63 (m, 2H), 7.56 (t, J=8.0 Hz, 1H), 7.32 (dd, J=5.2, 1.2 Hz, 1H), 7.05 (dd, J=4.0, 1.2 Hz, 1H), 6.98 (dd, J=5.2, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 139.6, 133.9, 133.7, 132.8, 131.0, 130.8, 129.4, 127.6, 126.7, 126.4, 117.5, 113.0; GC/MS (70 eV): m/z (%): 252 (100) [M^+], 223 (16), 196 (20); HRMS (EI) calcd for $C_{13}H_8N_4S$ 252.0470, found 252.0471.

*4.4.11. 2-(5-(Pyridin-2-yl)-2H-1,2,3-triazol-4-yl)benzonitrile (**6k**).* Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 7.77–7.63 (m, 6H), 7.51 (t, J=7.6 Hz, 1H), 7.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 148.6, 141.3, 137.2, 134.7, 133.4, 132.7, 131.2, 129.0, 123.6, 122.2, 117.8, 113.0; GC/MS (70 eV): m/z (%): 247 (23) [M^+], 246 (100), 219 (16), 218 (28), 192 (30), 191 (44), 164 (11); HRMS (EI) calcd for $C_{14}H_9N_5$ 247.0858, found 247.0860.

*4.4.12. 2-(5-Butyl-2H-1,2,3-triazol-4-yl)benzonitrile (**6l**).* Yellow solid; mp 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (br s, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.69 (t, J=7.6 Hz, 1H), 7.61 (d, J=7.6 Hz, 1H), 7.52 (t, J=7.6 Hz, 1H), 2.82 (t, J=7.6 Hz, 2H), 1.64 (quint, J=7.6 Hz, 2H), 1.30 (sext, J=7.6 Hz, 2H), 0.84 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 141.0, 134.5, 133.6, 132.8, 130.4, 128.7, 118.1, 112.2, 30.7, 24.1, 22.2, 13.5; GC/MS (70 eV): m/z (%): 226 (2) [M^+], 198 (27), 184 (100), 169 (13), 155 (55), 129 (29); HRMS (EI) calcd for $C_{13}H_{14}N_4$ 226.1218, found 226.1219. Anal. Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.03; H, 6.31; N, 24.42.

*4.4.13. 2-(5-Isobutyl-2H-1,2,3-triazol-4-yl)benzonitrile (**6m**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dt, J=8.0, 0.8 Hz, 1H), 7.67 (td, J=8.0, 1.2 Hz, 1H), 7.58 (dt, J=8.0, 0.8 Hz, 1H), 7.50 (td, J=8.0, 1.2 Hz, 1H), 2.70 (d, J=7.2 Hz, 2H), 1.92 (sept, J=7.2 Hz, 1H), 0.81 (d, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.7, 134.8, 133.6, 132.8, 130.6, 128.7, 118.1, 112.4, 33.3, 28.5, 22.2; GC/MS (70 eV): m/z (%): 226 (2) [M^+],

211 (33), 198 (83), 184 (58), 156 (36), 155 (100), 129 (37); MS (ESI): 227 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{15}N_4$ $[M+H]^+$ 227.1297, found 227.1299.

*4.4.14. 2-(5-tert-Butyl-2H-1,2,3-triazol-4-yl)benzonitrile (**6n**).* White solid; mp 188–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dt, J=8.0, 0.8 Hz, 1H), 7.66 (td, J=8.0, 1.2 Hz, 1H), 7.54 (td, J=8.0, 1.2 Hz, 1H), 7.51 (dt, J=8.0, 0.8 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 140.2, 137.0, 132.8, 132.2, 132.0, 129.2, 117.5, 114.7, 31.6, 30.3; GC/MS (70 eV): m/z (%): 226 (2) $[M^+]$, 211 (100), 184 (13), 168 (21), 156 (11), 129 (14); MS (ESI): 227 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{15}N_4$ $[M+H]^+$ 227.1297, found 227.1298. Anal. Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.04; H, 6.31; N, 24.33.

4.5. General procedure for the microwave-assisted reactions to synthesize tetrazoloisoquinolines

An appropriate 2-alkynylbenzonitrile (0.4 mmol), zinc bromide (3.2 mmol), and sodium azide (3.2 mmol) were suspended in DMF (3 mL) in a 10 mL glass vial. The mixture was then irradiated for the time and temperature indicated in Table 3, using an irradiation power of 75 W. After completion of the reaction, the vial was cooled to 25 °C. The mixture was then diluted with water (20 mL), extracted with EtOAc (10 mL×3), and dried over anhydrous $MgSO_4$. After filtration and removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel to furnish the product tetrazoloisoquinolines **7a**–**m**, in yields indicated as in Table 3.

*4.5.1. 5-Phenyltetrazolo[5,1-a]isoquinoline (**7a**).* White solid; mp 210–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.81 (dd, J=7.2, 1.6 Hz, 1H), 8.01–7.99 (m, 2H), 7.95 (dd, J=7.2, 1.6 Hz, 1H), 7.87–7.79 (m, 2H), 7.62–7.56 (m, 3H), 7.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 135.0, 132.2, 131.7, 131.0, 130.4, 129.3, 129.1, 128.8, 127.4, 125.1, 119.0, 116.3; GC/MS (70 eV): m/z (%): 220 (100, M-26), 194 (9), 165 (7); MS (ESI): 269 $[M+Na]^+$, 247 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{10}N_4Na$ $[M+Na]^+$ 269.0803, found 269.0805. Anal. Calcd for $C_{13}H_{14}N_4$: C, 73.16; H, 4.09; N, 22.75. Found: C, 73.12; H, 4.08; N, 22.46.

*4.5.2. 5-(4-(Trifluoromethyl)phenyl)tetrazolo[5,1-a]isoquinoline (**7b**).* Yellow solid; mp 182–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.83 (d, J=8.0 Hz, 1H), 8.15 (d, J=8.8 Hz, 2H), 7.99 (d, J=8.0 Hz, 1H), 7.91–7.84 (m, 4H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 134.4, 133.5, 132.2, 132.0, 131.9, 129.9, 129.5, 127.7, 125.8, 125.3, 123.6, 119.3, 117.2; GC/MS (70 eV): m/z (%): 288 (100, M-26); MS (ESI): 337 $[M+Na]^+$, 315 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_9F_3N_4Na$ $[M+Na]^+$ 337.0677, found 337.0674. Anal. Calcd for $C_{16}H_9F_3N_4$: C, 61.15; H, 2.89; N, 17.83. Found: C, 61.08; H, 2.85; N, 17.85.

*4.5.3. 5-(2-(Trifluoromethyl)phenyl)tetrazolo[5,1-a]isoquinoline (**7c**).* White solid; mp 200–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.83 (d, J=8.4 Hz, 1H), 7.95–7.84 (m, 4H), 7.78–7.73 (m, 2H), 7.62 (d, J=7.2 Hz, 1H), 7.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 132.3, 132.1, 131.8, 131.5, 131.0, 130.6, 130.1, 129.8, 129.1, 127.7, 126.8, 125.2, 123.4, 119.4, 118.3; GC/MS (70 eV): m/z (%): 288 (100, M-26), 247 (74), 222 (20), 207 (20); MS (ESI): 337 $[M+Na]^+$, 315 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_9F_3N_4Na$ $[M+Na]^+$ 337.0677, found 377.0675. Anal. Calcd for $C_{16}H_9F_3N_4$: C, 61.15; H, 2.89; N, 17.83. Found: C, 61.08; H, 2.85; N, 17.85.

*4.5.4. 5-(4-Nitrophenyl)tetrazolo[5,1-a]isoquinoline (**7d**).* Yellow solid; mp 240–241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J=9.2 Hz, 1H), 8.46 (d, J=8.8 Hz, 2H), 8.24 (d, J=8.8 Hz, 2H), 8.01 (d, J=9.2 Hz, 1H), 7.90 (m, 2H), 7.626 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.6, 137.0, 132.6, 132.1, 131.7, 130.3, 130.1, 127.9, 125.4, 124.1, 119.5, 117.9; MS (ESI): 292 $[M+H]^+$; HRMS (ESI) calcd for $C_{15}H_{10}N_5O_2$ $[M+H]^+$ 292.0834, found 292.0832. Anal. Calcd for $C_{15}H_9N_5O_2$: C, 61.85; H, 3.11; N, 24.04. Found: C, 61.81; H, 3.10; N, 24.00.

*4.5.5. 5-(4-(Methyl)phenyl)tetrazolo[5,1-a]isoquinoline (**7f**).* Yellow solid; mp 210–211 °C; ^{1}H NMR (200 MHz, $CDCl_3$); δ 8.80 (d, J=9.2 Hz, 1H), 7.96–7.78 (m, 5H), 7.46 (s, 1H), 7.39 (d, J=7.8 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.6, 140.7, 135.2, 132.2, 131.6, 129.5, 129.0, 128.9, 128.2, 127.3, 125.1, 118.9, 115.7, 21.4; GC/MS (70 eV): m/z (%): 234 (100, M-26); MS (ESI): 283 $[M+Na]^+$, 261 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{12}N_4Na$ $[M+Na]^+$ 283.0960, found 283.0958. Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.83; H, 4.55; N, 21.52.

*4.5.6. 5-(2-(Methyl)phenyl)tetrazolo[5,1-a]isoquinoline (**7g**).* Yellow solid; mp 153–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.82 (d, J=8.0 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.88–7.81 (m, 2H), 7.51–7.46 (m, 2H), 7.42–7.34 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 137.7, 134.8, 132.0, 131.6, 131.0, 130.6, 130.4, 130.3, 129.3, 127.4, 126.1, 125.1, 119.1, 117.4, 19.8; MS (ESI): 283 $[M+Na]^+$, 261 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{12}N_4Na$ $[M+Na]^+$ 283.0960, found 283.0958. Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.83; H, 4.63; N, 21.54.

*4.5.7. 5-(4-Methoxyphenyl)tetrazolo[5,1-a]isoquinoline (**7h**).* Yellow solid; mp 195–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.78 (d, J=8.0 Hz, 1H), 7.97 (d, J=8.8 Hz, 2H), 7.92 (d, J=8.0 Hz, 1H), 7.84–7.75 (m, 2H), 7.42 (s, 1H), 7.09 (d, J=8.8 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 148.6, 134.9, 132.3, 131.6, 130.6, 128.9, 127.2, 125.1, 123.3, 118.7, 115.3, 114.2, 55.4; MS (ESI): 299 $[M+Na]^+$, 277 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{12}N_4ONa$ $[M+Na]^+$ 299.0909, found 299.0911. Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.55; H, 4.38; N, 20.30.

*4.5.8. 5-(2-Methoxyphenyl)tetrazolo[5,1-a]isoquinoline (**7i**).* Yellow solid; mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J=7.2 Hz, 1H), 7.91 (d, J=7.2 Hz, 1H), 7.85–7.80 (m, 2H), 7.59–7.53 (m, 2H), 7.39 (s, 1H), 7.14 (t, J=8.0 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 148.1, 132.7, 132.1, 132.0, 131.4, 131.2, 129.1, 127.4, 125.1, 120.7, 120.4, 119.2, 117.5, 111.5, 55.6; MS (ESI): 299 $[M+Na]^+$, 277 $[M+H]^+$; HRMS (ESI) calcd for $C_{16}H_{12}N_4ONa$ $[M+Na]^+$ 299.0909, found 299.0910. Anal. Calcd for $C_{16}H_9N_5O_2$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.60; H, 4.40; N, 20.28.

*4.5.9. 5-(2-Thienyl)tetrazolo[5,1-a]isoquinoline (**7j**).* Yellow solid; mp 188–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J=8.0 Hz, 1H), 8.31 (dd, J=3.6, 1.2 Hz, 1H), 7.90 (d, J=8.0 Hz, 1H), 7.82–7.73 (m, 2H), 7.64 (s, 1H), 7.56 (dd, J=5.2, 1.2 Hz, 1H), 7.25 (dd, J=5.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 132.1, 132.0, 131.7, 130.2, 129.15, 129.11, 128.6, 128.2, 127.2, 125.0, 118.4, 113.9; MS (ESI): 275 $[M+Na]^+$; HRMS (ESI) calcd for $C_{13}H_8N_4SNa$ $[M+Na]^+$ 275.0367, found 275.0369. Anal. Calcd for $C_{13}H_8N_4S$: C, 61.89; H, 3.20; N, 22.21. Found: C, 61.88; H, 3.25; N, 22.25.

*4.5.10. 5-Butyltetrazolo[5,1-a]isoquinoline (**7l**).* White solid; mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.70 (d, J=7.6 Hz, 1H), 7.84–7.70 (m, 3H), 7.15 (s, 1H), 3.28 (t, J=7.6 Hz, 2H), 1.90 (quint, J=7.6 Hz, 2H), 1.50 (sext, 7.2 Hz, 2H), 0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 136.0, 132.1, 131.4, 128.5, 126.8, 124.9, 118.5, 114.2, 30.4, 28.8, 22.3, 13.7; MS (ESI): 249 $[M+Na]^+$, 227

$[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{14}N_4Na$ $[M+Na]^+$ 249.1116, found 249.1115. Anal. Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.03; H, 6.31; N, 24.42.

*4.5.11. 5-(2-Methylpropyl)tetrazolo[5,1-a]isoquinoline (**7m**).* White solid; mp 71–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J=8.0 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.79 (td, J=8.0, 1.2 Hz, 1H), 7.74 (td, J=8.0, 1.2 Hz, 1H), 7.14 (s, 1H), 3.14 (d, J=7.2 Hz, 2H), 2.41 (sept, J=7.2 Hz, 1H), 1.03 (d, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 135.1, 132.0, 131.4, 128.6, 126.8, 125.0, 118.6, 115.5, 40.0, 26.4, 22.4; GC/MS (70 eV): m/z (%): 226 (6) $[M^+]$, 198 (68), 183 (100), 155 (33), 128 (28); MS (ESI): 227 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{15}N_4$ $[M+H]^+$ 227.1297, found 227.1298. Anal. Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.00; H, 6.31; N, 24.57.

*4.5.12. 5-(1,1-Dimethylethyl)tetrazolo[5,1-a]isoquinoline (**7n**).* White solid; mp 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (dt, J=7.6, 0.8 Hz, 1H), 7.86 (d, J=7.6 Hz, 1H), 7.79 (td, J=7.6, 1.2 Hz, 1H), 7.73 (td, J=7.6, 1.2 Hz, 1H), 7.22 (s, 1H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 143.8, 132.2, 131.4, 128.7, 127.2, 124.8, 118.7, 112.6, 35.9, 28.0; GC/MS (70 eV): m/z (%): 226 (4) $[M^+]$, 198 (54), 183 (100), 168 (15), 142 (32), 115 (19); MS (ESI): 227 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_{15}N_4$ $[M+H]^+$ 227.1297, found 227.1299. Anal. Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.04; H, 6.31; N, 24.43.

Acknowledgements

We thank the National Science Council of the Republic of China for financial support.

References and notes

1. Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339–379.
2. Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389–5392.
3. Sha, C. K.; Mohanakrishnan, A. K. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, NY, 2002.
4. (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68; (b) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216; (c) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855; (d) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (e) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
5. Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
6. Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680–8683.
7. (a) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 1493–1496; (b) Jarowski, P. D.; Wu, Y. L.; Schweizer, W. B.; Diederich, F. *Org. Lett.* **2008**, *10*, 3347–3350; (c) Kim, D. K.; Kim, J.; Park, H. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401–2405; (d) Trubulski, E. J.; Benjamin, L.; Vitone, S.; Walser, A.; Fryer, R. I. *J. Med. Chem.* **1983**, *26*, 367–372; (e) Zheng, W.; Degterev, A.; Hsu, E.; Yuan, J.; Yuan, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4932–4935; (f) Cheng, Z. Y.; Li, W. J.; He, F.; Zhou, J. M.; Zhu, X. F. *Bioorg. Med. Chem.* **2007**, *15*, 1533–1538.
8. Kai, M.; Noda, A.; Noda, H.; Goto, S. *Chem. Pharm. Bull.* **1988**, *36*, 3604–3608.
9. Keith, J. M. *J. Org. Chem.* **2006**, *71*, 9540–9543 and references cited therein.
10. (a) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 4851–4854; (b) Deady, L. W.; Devine, S. M. *J. Heterocycl. Chem.* **2004**, *41*, 549–555.
11. Wu, M. J.; Lin, C. F.; Lu, W. D. *J. Org. Chem.* **2002**, *67*, 5907–5912.
12. (a) Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984–7989; (b) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950; (c) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2003**, *125*, 9983–9987; (d) Shie, J. J.; Fang, J. M. *J. Org. Chem.* **2007**, *72*, 3141–3144.
13. (a) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2002; (b) Suna, E.; Mutule, I. *Top. Curr. Chem.* **2006**, *266*, 49–101.
14. Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337–5339.
15. Wu, M. J.; Chang, L. J.; Wei, L. M.; Lin, C. F. *Tetrahedron* **1999**, *55*, 13193–13200.
16. Kleinpeter, E.; Schulenburg, A. *J. Org. Chem.* **2006**, *71*, 3869–3875.
17. Lin, C. F.; Yang, J. H.; Hsieh, P. C.; Lu, W. D.; Wu, M. J. *J. Chin. Chem. Soc.* **2001**, *48*, 211–214.
18. Lu, W. D.; Lin, C. F.; Wang, C. J.; Wang, S. J.; Wu, M. J. *Tetrahedron* **2002**, *58*, 7315–7319.