A Novel and Regiospecific Synthesis of 1-Aryl-1*H*-benzotriazoles *via* Copper(I)-Catalyzed Intramolecular Cyclization Reaction

by **Qi-Lun Liu**, **Di-Di Wen**, **Chen-Chen Hang**, **Qiu-Lian Li**, and **Yong-Ming Zhu***

School of Pharmacy, Soochow University, Suzhou, 215123, P. R. China
(phone: +86-512-62880109; fax: +86-512-67166591; e-mail: zhuyongming@suda.edu.cn)

1-Aryl-1*H*-benzotriazole derivatives were synthesized *via* intramolecular cyclization of easily obtained triazenes, using CuI as the catalyst, DMSO as the solvent, *t*-BuONa as the base, and 1,10-phenanthroline as the ligand, in up to 97% yield. The synthesis is regiospecific and functional group-tolerant.

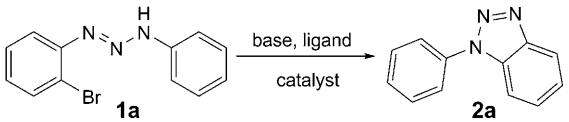
Introduction. –The structure of 1-aryl-1*H*-benzotriazole is an important moiety in compounds that possess antibacterial [1], antimalarial [2], and potassium channel-activating properties [3], and in selective small-molecule agonists of the human orphan G-protein-coupled receptor GPR109b (HM74) [4]. In addition, the special characteristics, due to the tautomerism of the molecule, had attracted many researchers' and entrepreneurs' attention [5]. Some methodologies for the synthesis of these 1-aryl-1*H*-benzotriazoles have been developed; the most important are: *1*) reaction of benzotriazoles with aryl halides [6], *2*) diazotization and then coupling of benzene-1,2-diamines [7], and *3*) azide–benzyne cycloaddition [8]. Either harsh reaction conditions or hazardous materials are employed in the above strategies, and difficulties in directing the newly introduced substituents as a result of the tautomerism of benzotriazoles still exist.

Recently, transitional metal-catalyzed coupling reactions have gained much interest due to their high regiospecificity and broad compatibility regarding functional groups [9]. *Zimmermann* and *Bräse* [10] obtained a wide range of benzotriazoles by a combinatorial-chemistry approach using the *Hartwig–Buchwald* amination reaction. However, the strategy has to be performed on solid supports and is thus confined to academic uses. This, together with our previous efforts [11] at the construction of heterocycles *via* Cu^{I} catalyzed intramolecular cyclization reactions, prompted us to investigate the feasibility of establishing a regiospecific benzotriazole synthesis strategy using the corresponding triazenes (*Scheme*).

Scheme

Results and Discussion. – To explore the feasibility of the proposed reaction, we first focused on a brief optimization of the reaction conditions for the synthesis of **2a** from **1a** (*Table 1*), which was easily obtained according to the protocols described in [12]. In the light of the work of *Bulgakova* and *Gornostaev* [13], we considered it possible to obtain benzotriazoles from the corresponding triazenes. However, no target compound was obtained, when the reaction was carried out in the absence of either catalyst or ligand (*Entries 13* and *14*). When $Pd(OAc)_2$ was utilized as the catalyst, only small amounts of product were identified (*Entry 12*). Addition of Cu improved the yield significantly (*Entry 3*), suggesting that Cu^I was a catalyst superior to Pd, and CuI was much more efficient than CuBr (*Entries 1* and *7*). To improve the yield further, we surveyed a series of reaction conditions, and found that all ligands gave **2a** in as good a yield as with 1,10-phenanthroline (**La**; *Entries 8–11*). Among the solvents employed, DMSO gave the best result (*Entries 1*, *5*, and *6*) due to its better solubility. The base used played a critical role in the present coupling reaction. When weaker bases were utilized, 1-(2-bromophenyl)-1*H*-benzotriazole was isolated apart from the desired product. The mechanism remains unclear. However, its ratio decreased with increasing base strength, and the optimal result was achieved with *t*-BuONa (*Entries 1–4*).

Table 1. *Optimization of the Reaction Conditions*[a])



1a **2a**

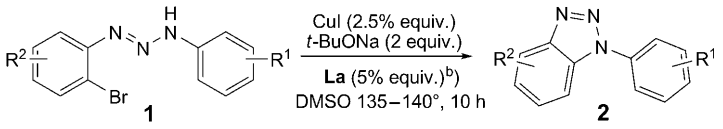
Entry	Base	Catalyst	Solvent	Ligand [b])	Yield [%]
1	*t*-BuONa	CuI	DMSO	**La**	90
2	K_2CO_3	CuI	DMSO	**La**	52
3	Cs_2CO_3	CuI	DMSO	**La**	58
4	KOH	CuI	DMSO	**La**	60
5	*t*-BuONa	CuI	Toluene[c])	**La**	73
6	*t*-BuONa	CuI	1,4-Dioxane[c])	**La**	75
7	*t*-BuONa	CuBr	DMSO	**La**	80
8	*t*-BuONa	CuI	DMSO	**Lc**	50
9	*t*-BuONa	CuI	DMSO	**Ld**	80
10	*t*-BuONa	CuI	DMSO	**Le**	85
11	*t*-BuONa	CuI	DMSO	**Lf**	83
12	Cs_2CO_3	$Pd(OAc)_2$	Toluene [c])	**Lb**	18
13	K_2CO_3	CuI	DMSO	–	–
14	K_2CO_3	–	DMSO	**La**	–

[a]) Reaction conditions: a mixture of **1a**, catalyst, ligand, base (1 : 2.5% : 5% : 2) reacted at 135–140° under Ar for 10 h. [b]) **La**: 1,10-phenanthroline, **Lb**: bis[2-(diphenylphosphino)phenyl]ether. **Lc**: L-proline, **Ld**: ethane-1,2-diamine, **Le**: *N*,*N*′-dimethylethane-1,2-diamine, **Lf**: (±)-*trans*-cyclohexane-1,2-diamine. [c]) Reflux.

On the basis of the above results, the scope of the reaction was explored with different substrates. As shown in *Table 2*, the catalyst system was of quite general character and tolerant of a wide range of functionalities. The yield was almost

quantitative where R^2 was 4-Me, followed by where R^1 was 4-Cl, H, and 4-Br (*Entries 1–3* and *8*). Interestingly, where R^1 was 4-Cl, only intramolecular cyclization product was isolated, and no intermolecular coupling product was identified, whereas traces of intermolecular coupling product were detected, when R^1 was 4-Br. This observation was indicative of and in accord with the reported reactivity order of I–Ar > Br–Ar > Cl–Ar [14]. *Entries 1–8* suggested that electron-donating or electron-withdrawing functional groups were also well-tolerated. However, the yields dropped drastically with a F-substituent in either of the rings (*Entries 9* and *12*) due to its special electronic features. As can be seen from *Entries 10*, *11*, and *13*, steric hindrance led to slightly lower yields.

Table 2. *Cyclization of Triazenes*[a])



Entry	Substrate	R^1	R^2	Product	Yield [%]
1	**1a**	H	H	**2a**	90
2	**1b**	4-Cl	H	**2b**	92
3	**1c**	4-Br	H	**2c**	88
4	**1d**	3-NO_2	H	**2d**	73.5
5	**1e**	3-Me	H	**2e**	75.3
6	**1f**	H	*x*-MeO[c])	**2f**	65.7
7	**1g**	H	*x*-Br[c])	**2g**	72.1
8	**1h**	H	*x*-Me[c])	**2h**	97
9	**1i**	H	*x*-F[c])	**2i**	40
10	**1j**	2-Me	H	**2j**	88
11	**1k**	4-Cl, 2-Me	H	**2k**[d])	63.6
12	**1l**	4-F	H	**2l**	41.8
13	**1m**	2-Me, 4-NO_2	H	**2m**	78

[a]) Reaction condition: **1** (0.5 mmol), **La** (25 μmol), *t*-BuONa (1 mmol), CuI (12.5 μmol), DMSO (5 ml). [b]) **La**: 1,10-Phenanthroline. [c]) For **1**, $x = 4$; for **2**, $x = 6$. [d]) 15 h.

Conclusions. – A new protocol that involves CuI-catalyzed intramolecular amination cyclization in DMSO in the presence of 1,10-phenanthroline and *t*-BuONa for the synthesis of benzotriazoles is reported. As a regiospecific synthetic strategy, the present methodology, using easily accessible starting materials, shows wide functional group tolerance.

Experimental Part

General. Reagents and chemicals were purchased from commercial suppliers and used without further purification. Flash chromatography (FC): silica gel (SiO_2; 200–300 mesh) from *Qingdao Ocean Chemicals*, P. R. China. TLC: Silica-gel *GF254* plates. M.p.: *XT5* Digital melting-point apparatus from *Beijing Keyi Elec-opti Instrument Factory*; uncorrected. IR: *ProStarLC240*; KBr pellets; $\tilde{\nu}$ in cm^{-1}. NMR

Spectra: *UNITY INOVA* 400 MHz, $CDCl_3$ soln., unless otherwise noted; δ in ppm and J in Hz. MS: *Micromass.*

General Procedure. A mixture of **1** (0.5 mmol), CuI (2.4 mg, 12.5 μmol), *t*-BuONa (96.0 mg, 1 mmol), 1,10-phenanthroline (4.5 mg, 25.0 μmol), and anh. DMSO (5 ml) in a flask filled with Ar was stirred at 135–140° for 10 h. After removal of the solvent, the cyclized product **2** was obtained by FC (hexane/AcOEt). For anal. data for compounds **2a**, **2b**, **2c**, and **2l**, see [10].

*1-(3-Nitrophenyl)-1*H*-benzotriazole* (**2d**). Pale brown solid (88 mg, 73.5%). M.p. 187–189°. IR: 3069, 1598, 1501, 1468, 1270, 1061, 927, 814, 755, 690. ^{1}H-NMR: 8.72 (*s*, 1 H); 8.37 (*d*, *J* = 8.26, 1 H); 8.24 (*d*, *J* = 8.06, 1 H); 8.20 (*d*, *J* = 8.38, 1 H); 7.80–7.87 (*m*, 2 H); 7.66 (*t*, *J* = 7.67, 1 H); 7.51 (*t*, *J* = 7.67, 1 H). ^{13}C-NMR ((D_6)DMSO): 148.7; 145.9; 137.1; 131.73; 129.26; 128.74; 125.1; 123.2; 119.9; 117.5; 110.9. HR-MS: 240.0646 (M^+, $C_{12}H_8N_4O_2^+$; calc. 240.0647).

*1-(3-Methylphenyl)-1*H*-benzotriazole* (**2e**). Pale yellow liquid (78 mg, 74.3%). IR: 3058, 2921, 1612, 1593, 1496, 1064, 786, 746, 693. ^{1}H-NMR: 8.14 (*d*, *J* = 8.35, 1 H); 7.74 (*d*, *J* = 8.37, 1 H); 7.39–7.63 (*m*, 5 H); 7.31 (*d*, *J* = 7.53, 1 H); 2.49 (*s*, 3 H). ^{13}C-NMR: 146.9; 140.6; 137.3; 132.8; 130.0; 129.9; 128.6; 124.8; 124.0; 120.7; 120.3; 110.9; 21.9. HR-MS: 209.0953 (M^+, $C_{13}H_{11}N_3^+$; calc. 209.0953).

*6-Methoxy-1-phenyl-1*H*-benzotriazole* (**2f**). White solid (74 mg, 65.7%). M.p. 65–67°. IR: 3058, 2968, 2839, 1494, 1460, 1265, 1051, 833, 804, 761. ^{1}H-NMR: 7.98 (*d*, *J* = 9.05, 1 H); 7.75 (*d*, *J* = 7.49, 2 H); 7.62 (*t*, *J* = 7.84, 2 H); 7.51 (*t*, *J* = 7.44, 1 H); 7.04–7.09 (*dd*, *J* = 9.06, 2.21, 1 H); 7.01 (*d*, *J* = 1.75, 1 H); 3.87 (*s*, 3 H). ^{13}C-NMR: 160.5; 141.6; 136.9; 133.3; 129.7; 128.4; 122.8; 120.7; 116.4; 90.5; 55.7. HR-MS: 225.0902 (M^+, $C_{13}H_{11}N_3O^+$; calc. 225.0902).

*6-Bromo-1-phenyl-1*H*-benzotriazole* (**2g**). White solid (99 mg, 72.1%). M.p. 129–130°. IR: 3068, 1599, 1501, 1469, 1269, 1061, 814, 755, 691. ^{1}H-NMR: 8.02 (*d*, *J* = 8.81, 1 H); 7.93 (*s*, 1 H); 7.75 (*d*, *J* = 8.04, 2 H); 7.64 (*t*, *J* = 7.81, 2 H); 7.50–7.58 (*m*, 2 H). ^{13}C-NMR: 145.1; 136.3; 133.2; 129.9; 128.9; 128.0; 122.8; 122.5; 121.3; 113.1. HR-MS: 272.9903 (M^+, $C_{12}H_8BrN_3^+$; calc. 272.9902).

*6-Methyl-1-phenyl-1*H*-benzotriazole* (**2h**). White solid (104 mg, 97%). M.p. 126–127°. IR: 3057, 2974, 2858, 1597, 1505, 1089, 1058, 804, 766, 697. ^{1}H-NMR: 8.01 (*d*, *J* = 8.53, 1 H); 7.78 (*d*, *J* = 7.59, 2 H); 7.58–7.65 (*t*, *J* = 7.83, 2 H); 7.48–7.54 (*m*, 2 H); 7.24–7.29 (*m*, 1 H); 2.54 (*s*, 3 H). ^{13}C-NMR: 144.9; 138.8; 136.9; 132.5; 129.6; 128.3; 126.4; 122.7; 119.5; 109.4; 21.9. HR-MS: 209.0953 (M^+, $C_{13}H_{11}N_3^+$; calc. 209.0953).

*6-Fluoro-1-phenyl-1*H*-benzotriazole* (**2i**). Pale yellow solid (43 mg, 40%). M.p. 102–104°. IR: 3103, 1625, 1506, 1487, 1450, 1249, 1148, 1112, 762, 694. ^{1}H-NMR: 8.11 (*dd*, *J* = 9.04, 4.66, 1 H); 7.75 (*d*, *J* = 7.93, 2 H); 7.63 (*t*, *J* = 7.81, 2 H); 7.53 (*t*, *J* = 7.38, 1 H); 7.40 (*dd*, *J* = 8.11, 2.14, 1 H); 7.22 (*dt*, *J* = 9.03, 2.16, 1 H). ^{13}C-NMR: 163.9; 161.5; 143.2; 136.5; 132.7; 132.5; 129.9; 128.8; 122.6; 121.7; 121.6; 114.4; 114.1; 96.3; 96.0. HR-MS: 213.0702 (M^+, $C_{12}H_8FN_3^+$; calc. 213.0702).

*1-(2-Methylphenyl)-1*H*-benzotriazole* (**2j**). White solid (92 mg, 88%). M.p. 66–67°. IR: 3059, 3030, 2918, 2855, 1502, 1269, 1079, 787, 754. ^{1}H-NMR: 8.15 (*d*, *J* = 8.33, 1 H); 7.24–7.59 (*m*, 7 H); 2.13 (*s*, 3 H). ^{13}C-NMR: 145.3; 135.0; 134.9; 133.6; 131.4; 129.8; 127.8; 126.8; 126.6; 123.9; 119.8; 109.9; 17.5. HR-MS: 209.0952 (M^+, $C_{13}H_{11}N_3^+$; calc. 209.0953).

*1-(4-Chloro-2-methylphenyl)-1*H*-benzotriazole* (**2k**). White solid (77 mg, 63.6%). M.p. 86–88°. IR: 3065, 2980, 2856, 1602, 1497, 1454, 1272, 1078, 825, 756. ^{1}H-NMR: 8.15 (*d*, *J* = 8.33, 1 H); 7.53 (*t*, *J* = 7.57, 1 H); 7.43–7.48 (*m*, 2 H); 7.41 (*m*, 2 H); 7.37 (*t*, *J* = 7.45, 1 H); 2.11 (*s*, 3 H). ^{13}C-NMR: 145.4; 135.8; 133.6; 133.5; 132.6; 132.1; 129.9; 128.2; 126.8; 124.2; 120.1; 109.7; 17.3. HR-MS: 243.0563 (M^+, $C_{13}H_{10}ClN_3^+$; calc. 243.0563).

*1-(2-Methyl-4-nitrophenyl)-1*H*-benzotriazole* (**2m**). Pale yellow solid (99 mg, 78%). M.p. 153–154°. IR: 3065, 2925, 1585, 1519, 1348, 1053, 747, 737. ^{1}H-NMR: 8.38 (*d*, *J* = 2.15, 1 H); 8.29 (*dd*, *J* = 8.63, 2.46, 1 H); 8.20 (*d*, *J* = 8.35, 1 H); 7.57–7.66 (*m*, 2 H); 7.50 (*t*, *J* = 7.64, 1 H); 7.40 (*d*, *J* = 8.31, 1 H); 2.36 (*s*, 3 H). ^{13}C-NMR: 142.9; 140.6; 135.1; 131.9; 128.1; 123.7; 122.3; 121.8; 119.6; 117.1; 115.3; 104.5; 13.3. HR-MS: 254.0805 (M^+, $C_{13}H_{10}N_4O_2^+$; calc. 254.0804).

REFERENCES

[1] P. P. Dixit, P. S. Nair, V. J. Patil, S. Jain, S. K. Arora, N. Sinha, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3002.

[2] N. Mishra, P. Arora, B. Kumar, L. C. Mishra, A. Bhattacharya, S. K. Awasthi, V. K. Bhasin, *Eur. J. Med. Chem.* **2008**, *43*, 1530.

[3] G. Biagi, V. Calderone, I. Giorgi, O. Livi, V. Scartoni, B. Baragatti, E. Martinotti, *Il Farmaco* **2001**, *56*, 841.

[4] G. Semple, P. J. Skinner, M. C. Cherrier, P. J. Webb, C. R. Sage, S. Y. Tamura, R. Chen, J. G. Richman, D. T. Connolly, *J. Med. Chem.* **2006**, *49*, 1227.

[5] M. D. Santa María, R. M. Claramunt, M. Á. García, J. Elguero, *Tetrahedron* **2007**, *63*, 3737.

[6] I. P. Beletskaya, D. V. Davydov, M. Moreno-Mañas, *Tetrahedron Lett.* **1998**, *39*, 5617.

[7] N. Nonoyama, H. Oshima, C. Shoda, H. Suzuki, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2385; A. E. Siegrist, *Helv. Chim. Acta* **1981**, *64*, 662; P. K. Sasmal, S. Sridhar, J. Iqbal, *Tetrahedron Lett.* **2006**, *47*, 8661.

[8] S. Chandrasekhar, M. Seenaiah, C. L. Rao, C. R. Reddy, *Tetrahedron* **2008**, *64*, 11325; M. Juríček, P. H. Kouwer, J. Rehák, J. Sly, A. E. Rowan, *J. Org. Chem.* **2009**, *74*, 21; H. Ankati, E. Biehl, *Tetrahedron Lett*. **2009**, *50*, 4677; F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.* **2008**, *10*, 2409; F. Zhang, J. E. Moses, *Org. Lett.* **2009**, *11*, 1587.

[9] S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1439; A. de Meijere, F. Diederich, 'Metal-Catalyzed Cross-Coupling Reactions', 2nd ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Vol. 1, 2004; J. Tsuji, 'Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis', John Wiley & Sons, Ltd., Chichester, 2000.

[10] V. Zimmermann, S. Bräse, *J. Comb. Chem.* **2007**, *9*, 1114.

[11] Y.-M. Zhu, L.-N. Qin, R. Liu, S.-J. Ji, H. Katayama, *Tetrahedron Lett.* **2007**, *48*, 6262; R. Liu, Y. Zhu, L. Qin, S. Ji, *Synth. Commun.* **2008**, *38*, 249; R. Liu, Y.-M. Zhu, L.-N. Qin, S.-J. Ji, H. Katayama, *Heterocycles* **2007**, *71*, 1755.

[12] S. Kruger, *J. Chem. Soc.* **1953**, 700; A. Chin, M.-H. Hung, L. M. Stock, *J. Org. Chem.* **1981**, *46*, 2203; W. B. Smith, O. C. Ho, *J. Org. Chem.* **1990**, *55*, 2543.

[13] N. A. Bulgakova, L. M. Gornostaev, *Russ. J. Org. Chem.* **2001**, *37*, 1351.

[14] R. A. Altman, S. L. Buchwald, *Org. Lett.* **2006**, *8*, 2779.

Received November 3, 2009