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ARTICLE

Catalyst-Free Synthesis of Fused 1,2,3-Triazole and Isoindoline Derivatives *via* Intramolecular Azide-Alkene Cascade Reaction

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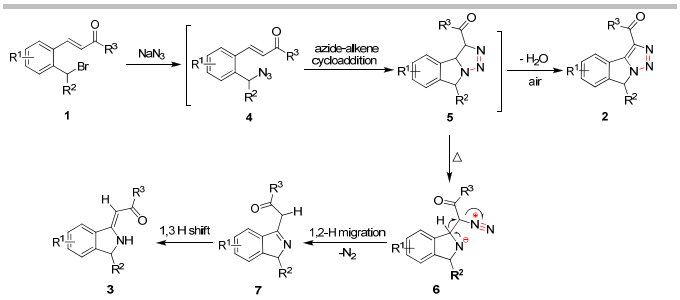
Yu-Yang Xie,[a,+] Ying-Chun Wang,[b,+] Yan-He,[a] Da-Chao Hu,[a] Heng-Shan Wang[a,*] and Ying-Ming Pan[a,*]

Benzyl bromides bearing *ortho*-substituted *α*, *β*-unsaturated ketone moiety are found to be promising precursors for synthesis of fused 1,2,3-triazole and isoindoline derivatives *via* intramolecular azide-alkene cascade reaction under catalyst free conditions. Fused 1,2,3-triazole derivatives **2** were synthesized in excellent yields by treating compounds **1** with sodium azide in DMF at room temperature, whereas isoindoline derivatives **3** were produced in moderate to good yields only by slight modification of the reaction conditions, and both reactions call for simple and mild conditions, display broad substrate scopes and result in good regiospecificity.

Introduction

Development of an efficient strategy for rapid synthesis of skeletally distinct molecular scaffolds is crucial to the generation of diverse chemical libraries for biological screening.[1] Among various approaches to the synthesis of N-heterocycles, intramolecular azide-alkene cascade reaction has proven to be versatile method for providing ready access to diverse N-heterocycles.[2] However, under metal-free conditions, these cascade reactions normally require high temperature (>100 °C),[2b, 2c] the use of microwaves[2e] or photocatalysis.[2a] Herein, we report a simple and efficient methodology for the synthesis of fused 1,2,3-triazole and isoindoline derivatives from benzyl bromides containing ortho-substituted *α*, *β*-unsaturated ketone moiety and sodium azide, in which, intramolecular azide-alkene cascade reaction can be easily induced under very mild and catalyst free conditions. Fused 1,2,3-triazole derivatives were synthesized in excellent yields by treating compounds **1** with sodium azide in DMF at room temperature, whereas isoindoline derivatives were selectively produced in moderate to good yields only by slight modification of the reaction conditions.

Fused 1,2,3-triazoles represent a class of important heterocycles which display significant biological activities.[3] For example, 1,2,3-triazolo[1,5-*a*]quinoxaline is a potent inhibitor of human methionine aminopeptidase type 2 (hMetAP2).[3a] Bicyclic[1,2,3]triazoles can suppress UVA-induced damage in human fibroblasts, which may provide potential prevention against photoaging.[3b] So far, extensive works have generated many approaches for the synthesis of 1,2,3-triazoles derivatives.[4] Likewise, isoindoline derivatives have also received considerable attention due to their diverse array of pharmaceutical functionalities such as antihypertensive,[5] antipsychotic,[6] antiulcer,[7] antiviral[8] and antileukemic activities.[9] Consequently, convenient access to these heterocyclic frameworks is highly appealing. In connection with our interest in the development of new synthetic routes for the preparation of nitrogen-containing heterocycles,[10] we hypothesized that the intramolecular azide-alkene cycloaddition of benzyl azides **4** *in situ* generated from the corresponding benzyl bromides **1** and subsequent oxidation of the resulting triazolines **5** would produce fused 1,2,3-triazoles **2**,[10a] if the unstable triazoline intermediates **5** underwent decomposition and 1,2-H migration,[10b] cyclic imines **7** could be obtained, which tautomerize to the corresponding exocyclic enamines[2e, 11] **3** as shown in Scheme 1.



Scheme 1 Proposed intramolecular azide-alkene cascade reaction.

[a] State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University Guilin 541004, People's Republic of China
[b] College of Chemistry and Chemical Engineering, Jishou University, Jishou 416000, People's Republic of China
Phone: (+86)-773-5846279; fax: (+86)-773-5803930; e-mail: panym2013@hotmail.com; whengshan@163.com
†These authors contributed equally to this work
Electronic Supplementary Information (ESI) available: [General experimental procedures, and spectral data, NMR spectra, high resolution mass spectra for all compounds]. See DOI: 10.1039/x0xx00000x

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Results and discussion

To test our hypothesis, fused 1,2,3-triazole formation *via* the intramolecular azide-alkene cycloaddition was first evaluated and representative results are summarized in Table 1. As expected, under catalyst free conditions, the reaction proceeded smoothly by treating ready available (*E*)-3-(2-(bromomethyl)phenyl)-1-phenylprop-2-en-1-one **1a** with sodium azide in DMF at room temperature for 6 h to give fused 1,2,3-triazole **2a** in an excellent yield of 89% (Table 1, entry 1), and the structure of the product **2a** was unambiguously confirmed by X-ray crystallography (Fig. 1). The addition 5 mol% of metal triflates to the reaction mixture did not speed up the cycloaddition progress and improve the yield (Table 1, entries 2-5 *vs.* entry 1). Other metal catalyzed reactions were also attempted, however, the results were not encouraging as either poor yield or no reaction was observed in these cases (Table 1, entries 7-10). DMF was found as a suitable solvent for this transformation, other solvents, such as toluene, PhCl, dioxane and CH_2Cl_2 did not give any reaction (Table 1, entries 11-14). Use of DMSO and CH_3CN resulted in no formation of **2a** (Table 1, entries 15-16). Furthermore, when the reaction was conducted under nitrogen, only a trace amount of desired product was detected, confirming that air (O_2) acts as the oxidant for the success formation of fused 1,2,3-triazole (Table 1, entry 17).

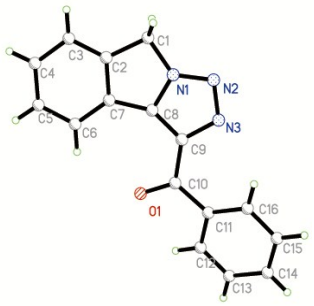
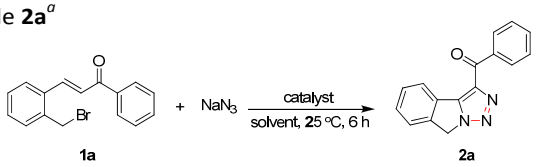


Fig.1 X-ray crystal structure of fused 1,2,3-triazole **2a** (CCDC 1414992).

A series of benzyl bromides **1** were prepared (see the Supporting Information for details) to investigate the scope for the synthesis of fused 1,2,3-triazole derivatives under catalyst free conditions as described for **2a** (Table 1, entry 1), and the results are outlined in Table 2. It was observed that a wide range of R^3 groups (aryl, heteroaryl and alkyl) were well tolerated, providing the corresponding desired products in excellent yields (85%-92%) (**2b**-**j**). Furthermore, no obvious electronic and steric effects of substituents on the phenyl ring of the R^3 moiety were observed. The electronic nature of the R^1 group was also studied. The results show that electron-donating (-OCH_3) and -withdrawing (-F) substituents had no substantial impact on the efficacy of the reaction because the fused 1,2,3-triazoles **2k**-**l** were obtained in similar high yields. Appreciatively, substrate with steric hindrance (R^2 = alkyl) fairly tolerated the reaction conditions and led to good yield (78%) (**2m**).

Table 1 Optimization of reaction conditions for fused 1,2,3-triazole **2a**[a]



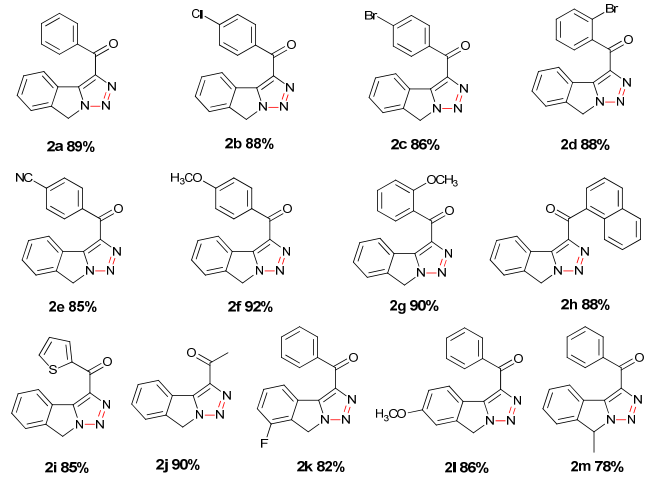
1a 2a

Entry	Catalyst	Solvent	Yield[b] (%)
1	**none**	**DMF**	**89**
2	$Sm(OTf)_3$ (5 mol%)	DMF	88
3	$Sc(OTf)_3$ (5 mol%)	DMF	87
4	$La(OTf)_3$ (5 mol%)	DMF	86
5	$Cu(OTf)_2$ (5 mol%)	DMF	83
6	$Cu(OAc)_2$ (5 mol%)	DMF	0
7	CuI (5 mol%)	DMF	0
8	$Pd(OAc)_2$ (5 mol%)	DMF	21
9	$Pd(Ph_3P)_4$ (5 mol%)	DMF	55
10	AgOAc (5 mol%)	DMF	52
11	none	toluene	N.R.
12	none	PhCl	N.R.
13	none	1,4-dioxane	N.R.
14	none	CH_2Cl_2	N.R.
15	none	CH_3CN	0
16	none	DMSO	0
17[c]	none	DMF	trace

[a] Reactions conditions: 0.5 mmol of **1a** and 0.6 mmol of sodium azide in the presence of catalyst in solvent at 25 °C for 6 h (except for entry 1 and entries 11-16). [b] Isolated yield of pure product based on **1a**. [c] The reaction was carried out under nitrogen atmosphere (1 atm).

The 1,3-dipolar cycloaddition reaction of organic azides with olefins has been intensively studied for the synthesis of triazolines.[11, 12] Triazolines usually decompose after the loss of nitrogen to form aziridines or imines through thermal[13] or photochemical decomposition,[14] which led us to envisage that under uncatalyzed thermal conditions, the regioselective synthesis of isoindoline derivatives may be realized. Thus, the optimization of the isoindoline derivatives synthesis, including the ratio of **1a** to NaN_3 and reaction temperature, was then investigated (Table S1 in the Supporting Information). After a series of experiments, the optimized reaction conditions were eventually identified as **1a** (0.5 mmol) and 1.0 equiv of sodium azide in 2 mL of DMF at 10 °C for 3 h and then at 60 °C for 1 h under the atmosphere of nitrogen (see Table S1, entry 4 in the Supporting Information).

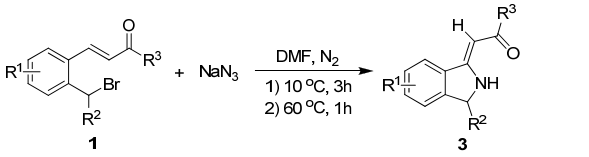
Table 2 Substrate scope for the synthesis of fused 1,2,3-triazole derivatives **2**[a,b]

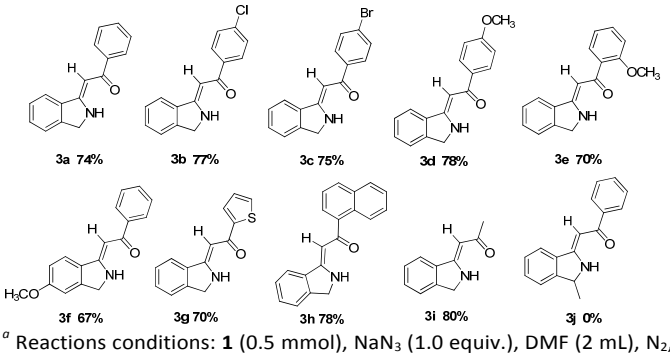


[a] Reactions conditions: 0.5 mmol of **1** and 0.6 mmol of sodium azide in 2 mL of DMF at 25 °C for 6 h.

[b] Isolated yield of pure product based on **1**.

Table 3 Substrate scope for the synthesis of isoindoline derivatives **3**[a,b]

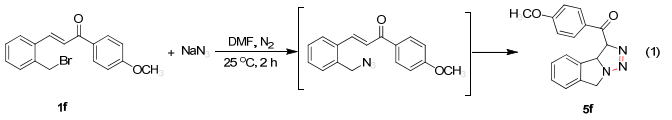




[a] Reactions conditions: **1** (0.5 mmol), NaN_3 (1.0 equiv.), DMF (2 mL), N_2, 10 °C for 3 h then rise to 60 °C for 1 h.

[b] Isolated yield of pure product based on **1**.

Under the optimal conditions as for **3a**, a range of reactions of selected benzyl bromides **1** and sodium azide were carried out, and the results are summarized in Table 3. Consistent with the results of fused 1,2,3-triazole synthesis, the substituent effect on the phenyl ring was not apparent, either with an electron-withdrawing (**3b** and **3c**) or an electron-donating group (**3d**, **3e** and **3f**), benzyl bromides **1** gave the corresponding isoindoline derivatives in good yields. Additionally, substrates bearing 2-thienyl (**3g**), 1-naphthyl (**3h**) and methyl (**3i**) groups were also transformed into the target compounds in similar satisfactory yields. Unfortunately, no desired product **3j** was obtained when treatment of the substituted benzyl bromide substrate ($R^2 = CH_3$) with sodium azide under these reaction conditions. In addition, the double bond in the products **3** were determined as *E*-configuration on the basis of their spectral and analytical data. For example, the ^1H NMR spectra of **3f** in $CDCl_3$ shows a broad absorption peak nearby 10.47 ppm, suggesting that there is a strong intramolecular hydrogen bonding between amine hydrogen and carbonyl oxygen atom[15] (see Figure S1 in the Supporting Information). The key NOESY correlation between CH-6 and CH-9 also confirmed this relative configuration of compound **3f** (see Figure S2 in the Supporting Information).



ESI/MS experiments were performed to gain evidence for the possible intermediates in the proposed mechanism. Under the atmosphere of nitrogen, a mixture of **1f** (0.5 mmol) and sodium azide (0.5 mmol) in DMF (2.0 mL) was reacted at 10 °C for 3 h [Eq. (1)] and 50 μL of the mixture was used for the ESI analysis in CH_3OH. The ESI/MS analyses showed a peak at m/z 294.1240, which was identified as a triazoline species **5f** (see the Supporting Information).

Conclusions

In summary, a convenient, efficient and regioselective method has been developed for the synthesis of fused 1,2,3-triazole and isoindoline derivatives using benzyl bromides bearing an ortho-substituted α, β-unsaturated ketone moiety under catalyst free conditions. The simple and mild conditions, broad substrate scopes, good to excellent yields and operational simplicity make this process very significant for academic research and practical applications. Further studies on the scope and synthetic applications of these reactions are currently in progress.

Acknowledgements

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Notes and references

1 For some reviews, see: (a) W. R. J. D. Galloway, A. Isidro-Llobet and D. R. Spring, *Nature Commun.*, 2010, **1**, 80; (b) C. J.

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DOI: 10.1039/C6GC01553K

O'Connor, H. S. G. Beckmann and D. R. Spring, *Chem. Soc. Rev.,* 2012, **41**, 4444.
2 Representative reports on intramolecular azide-alkene cascade reaction: (a) R. Ducray, and M. A. Ciufolini, *Angew. Chem., Int. Ed.,* 2002, **41**, 4688; (b) S. Kim, Y. M. Lee, J. Lee, T. Lee, Y. Fu, Y. Song, J. Cho and D. Kim, *J. Org. Chem.,* 2007, **72**, 4886; (c) Y. Zhou and P. V. Murphy, *Org. Lett.,* 2008, **10**, 3777; (d) B. W. Q. Hui and S. Chiba, *Org. Lett.,* 2009, **11**, 729; (e) I. de Miguel, M. Velado, B. Herradón and E. Mann, *Adv. Synth. Catal.,* 2013, **355**, 1237.
3 (a) L. S. Kallander, Q. Lu, W. Chen, T. Tomaszek, G. Yang, D. Tew, T. D. Meek, G. A. Hofmann, C. K. Schulz-Pritchard, W. W. Smith, C. A. Janson, M. D. Ryan, G.-F. Zhang, K. O.Johanson, R. B. Kirkpatrick, T. F. Ho, P. W. Fisher, M. R. Mattern, R. K. Johnson, M. J. Hansbury, J. D. Winkler, K. W. Ward, D. F. Veber and S. K. Thompson, *J. Med. Chem.,* 2005, **48**, 5644; (b) H. Y. Hsieh, W. C. Lee, G. C. Senadi, W. P. Hu, J. J. Liang, T. R. Tsai, Y. W. Chou, K. K. Kuo, C. Y. Chen and J. J. Wang, *J. Med. Chem.,* 2013, **56**, 5422; (c) P. J. Snyder, J. Werth, B. Giordani, A. F. Caveney, D. Feltner and P. Maruff, *Hum. Psychopharmacol.,* 2005, **20**, 263; (d) K. Tatsuta, Y. Ikeda and S. Miura, *J. Antibiot.,* 1996, **49**, 836.
4 For some reviews, see: (a) P. L. Golas and K. Matyjaszewski, *Chem. Rev.,* 2010, **39**, 1338; (b) J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302; (c) L. Liang and D. Astruc, *Chem. Rev.* 2011, **255**, 2933. For recently selected examples, see: (a) Y. M. A. Yamada, S. M. Sarkar and Y. Uozumi, *J. Am. Chem. Soc.*, 2012, **134**, 9285; (b) Z.-J. Cai, X.-M. Lu, Y. Zi, C. Yang, L.-J. Shen, J. Li, S.-Y. Wang and S.-J. Ji, *Org. Lett.*, 2014, **16**, 5108; (c) S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov and V. V. Fokin, *Org. Lett.*, 2010, **12**, 4217; (d) Y. Jiang, C. Kuang, Q. Yang, *Synthesis*, 2010, 4256.
5 J.-M. Ferland, C. A. Demerson and L. G. Humber, *Can. J. Chem.,* 1985, **63**, 361.
6 Z. P. Zhuang, M. P. Kung, M. Mu and H. F. Kung, *J. Med. Chem.,* 1998, **41**, 157.
7 T. R. Belliotti, W. A. Brink, S. R. Kesten, J. R. Rubin, D. J. Wustrow, K. T. Zoski, S. Z. Whetzel, A. E. Corbin, T. A. Pugsley, T. G. Heffner and L. D. Wise, *Bioorg. Med. Chem. Lett.,* 1998, **8**, 1499.
8 (a) I. Pendrak, S. Barney, R. Wittrock, D. M. Lambert and W. D. Kingsbury, *J. Org. Chem.,* 1994, **59**, 2623; (b) E. De Clercq, *J. Med. Chem.,*1995, **38**, 2491.
9 (a) E. C. Taylor, P. Zhou, L. D. Jennings, Z. Mao, B. Hu and J.-G. Jun, *Tetrahedron Lett.,* 1997, **38**, 521; (b) C. Riedinger, J. A. Endicott, S. J. Kemp, L. A. Smyth, A. Watson, E. Valeur, B. T. Golding, R. J. Griffin, I. R. Hardcastle, M. E. Noble and J. M. McDonnell, *J. Am. Chem. Soc.,* 2008, **130**, 16038.
10 (a) Y. Y. Xie, Y. C. Wang, H. E. Qu, X. C. Tan, H. S. Wang and Y. M. Pan, *Adv. Synth. Catal.,* 2014, **356**, 3347; (b) Y. Wang, J. Li, Y. He, Y. Xie, H. Wang and Y. Pan, *Adv. Synth. Catal.,* 2015, **357**, 3229; (c) J. Li, Y. Wang, W. Li, H. Wang, D. Mo and Y. Pan, *Chem. Commun.,* 2015, **51**, 17772.
11 D. S. Reddy, W. R. Judd and J. Aubé, *Org. Lett.,* 2003, **5**, 3899.
12 (a) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey and G. P. Nowack, *J. Am. Chem. Soc.,*1965, **87**, 306; (b) D. B. Ramachary and A. B. Shashank, *Chem. Eur. J.,* 2013, **19**, 13175.
13 (a) C. K. Sha, S. L. Ouyang, D. Y. Hsieh, R. C. Chang and S. C. Chang, *J. Org. Chem.,* 1986, **51**, 1490; (b) A. G. Schultz and W. G. McMahon, *J. Org. Chem.*, 1984, **49**, 1676; (c) G. A. Molander and C. T. Bibeau, *Tetrahedron Lett.*, 2002, **43**, 5385; (d) J. Li, Y. Fu, Q. X. Guo, *Tetrahedron*, 2008, **64**, 11167.
14 (a) S. Allemann and P. Vogel, *Synthesis*, 1991, 923; (b) R. S. Dahl and N. S. Finney, *J. Am. Chem. Soc.,* 2004, **126**, 8356.
15 (a) F. Xiao and J. Wang, *J. Org. Chem.*, 2006, **71**, 5789; (b) C.-H. Lin, R.-R. Chuang, P.-Y. Kuo and D.-Y. Yang, *Tetrahedron Lett.*, 2013, **54**, 2431.

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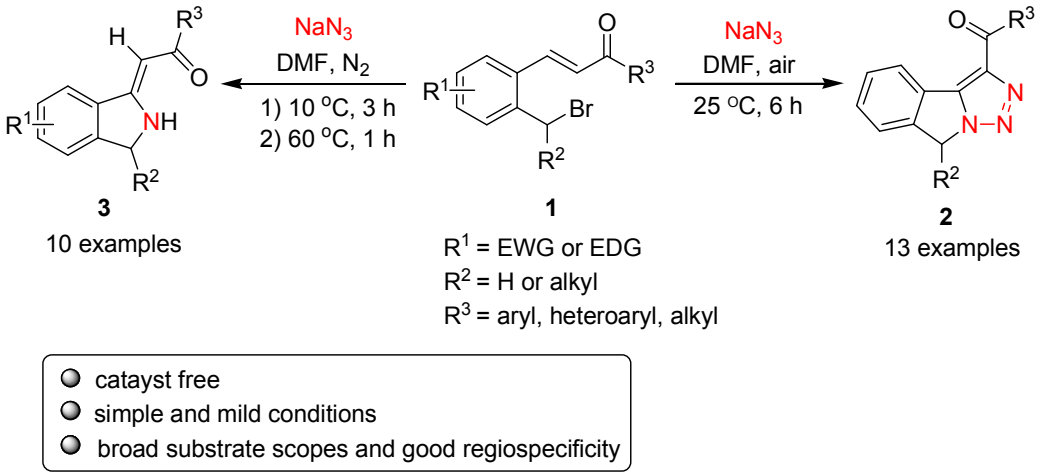

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