Silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated carbonyl compound†

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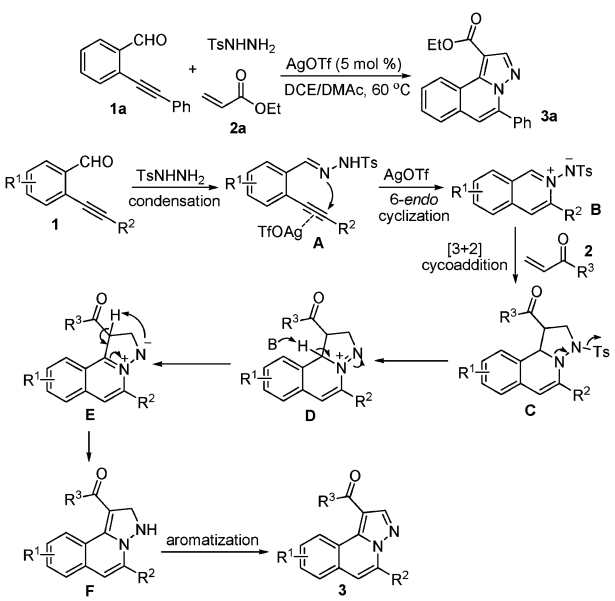
A highly efficient silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated carbonyl compound is reported, which affords *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylates in good yield.

The development of efficient strategies for nitrogen-containing heterocycles formation continues to be of major importance in synthetic organic chemistry. Among the approaches utilized, multi-component reactions are very attractive since this method can create novel products while increasing the efficiency and modularity of the reactions by reducing the number of chemical transformations and chemical waste.[1] Especially, the MCRs are ideally suited for the construction of natural product-like compounds in the field of combinatorial chemistry prone to display biological activity.[2]

Since the isoquinoline ring system is present in numerous naturally occurring alkaloids, the synthesis of isoquinolines and related compounds has received considerable attention.[3–5] Among the isoquinoline family, the fused isoquinoline such as lamellarin alkaloid is an attractive scaffold due to its promising biological activities.[6] In order to build up a focused library of fused isoquinolines for our biological assays, development of efficient synthetic methodologies is extremely important to ensure diversity-oriented synthesis.

Recently, 2-alkynylbenzaldehyde has been discovered as a useful building block for construction of heterocycles.[7] We also developed tandem reactions[8] of *N*′-(2-alkynylbenzylidene)-hydrazide, which was derived from 2-alkynylbenzaldehyde.[9] During the studies, we recognized that *N*′-(2-alkynylbenzylidene)-hydrazide could be easily cyclized to isoquinolinium-2-yl amide *via* 6-*endo*-cyclization in the presence of silver salts or electrophiles. Thus, further cycloadditions might occur under suitable conditions. Indeed, dimethyl acetylenedicarboxylate has been successfully employed as a partner in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide,[9b] since 1,3-dipolar cycloaddition of ylidic species is a powerful method for the construction of complex *N*-heterocycles.[10] Prompted by these results and the advancement of multicomponent reactions, we envisioned that three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated esters or ketones might be a good vehicle for the fused isoquinoline generation.

As mentioned previously, isoquinolinium-2-yl amide **B** could be easily generated *via* 6-*endo*-cyclization of *N*′-(2-alkynylbenzylidene)hydrazide in the presence of silver triflate.[9] In order to simplify the optimization process, our initial studies were performed for the reaction of isoquinolinium-2-yl amide **B** (R^1 = H, R^2 = Ph) with ethyl acrylate **2a** in the presence of different bases and solvents (Scheme 1, for details, please see ESI†). Gratifyingly, we observed the formation of a product (21% yield) when the reaction was carried out with DABCO in THF. However, structural identification revealed the product was *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylate **3a**, instead of the expected product **C** (R^1 = H, R^2 = Ph). The structure was also confirmed by X-ray diffraction analysis (Fig. 1). The ^{1}H NMR data indicated that presumably there is a space effect of the carbonyl group to one of the aromatic protons. Subsequently, a variety of bases and solvents were examined. Compound **3a** could be isolated in 73% yield when DMF was utilized as the solvent as well as a base.[11] With this promising result in hand, we started to explore the



Scheme 1 Initial studies for the three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and acrylate.

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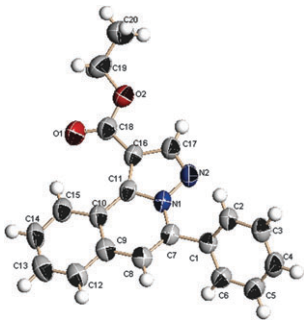


Fig. 1 ORTEP illustration of compound **3a** (30% probability ellipsoids).

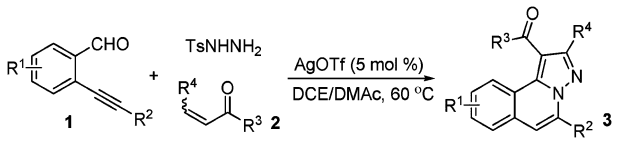
three-component reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide, and ethyl acrylate **2a** (Scheme 1). Finally, we realized that the reaction worked most efficiently (88% yield) in the presence of AgOTf (5 mol%) as catalyst in DCE/DMAc at 60 °C.

For the possible mechanism, we reasoned that after condensation of 2-alkynylbenzaldehyde **1** with sulfonohydrazide, *N*′-(2-alkynylbenzylidene)hydrazide **A** would be obtained. In the presence of AgOTf, the triple bond would be activated and then the 6-*endo*-cyclization occurred to afford the isoquinolinium-2-yl amide **B**. Subsequently, acrylate would be involved in the [3 + 2] cycloaddition process to generate the intermediate **C**. After release of tosyl group and aromatization, *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylate **3** was then afforded (Scheme 1).

To establish the scope of this reaction, the effects of changing the α,β-unsaturated carbonyl compounds and the substituents at the 2-alkynylbenzaldehydes were tested under the optimized conditions (AgOTf (5 mol%), DCE/DMAc, 60 °C) (Table 1). This silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde **1**, sulfonohydrazide, and α,β-unsaturated carbonyl compound **2** occurred smoothly to generate the desired *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylates **3** in good yields (Table 1). For instance, 2-alkynylbenzaldehyde **1a** reacted with sulfonohydrazide and methyl acrylate **2b**, leading to the corresponding product **3b** in 85% yield (entry 2). Similar yield (82%) was obtained when n-butyl acrylate **2c** was employed in the above reaction (entry 3). With respect to the but-3-en-2-one **2d** and cyclohex-2-enone **2e**, the expected *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylates resulting from reactions of 2-alkynylbenzaldehyde **1a** with sulfonohydrazide were obtained and isolated in moderate yields (entries 4 and 5). This methodology could also be extended to the reactions of 2-alkynylbenzaldehyde with cyclopropyl or n-butyl group attached to the C≡C triple bond, and all reactions proceeded smoothly to afford the corresponding products in good yields (entries 6–11). Other substrates were examined as well and this three-component reaction was found to be workable with 2-alkynylbenzaldehydes **1d–1n** with electron-withdrawing and -donating substituents on the aromatic backbone.

In conclusion, we have developed a simple, practical, and novel approach to various functionalized *H*-pyrazolo[5,1-*a*]-isoquinoline-1-carboxylates *via* silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated carbonyl compound. The starting materials

Table 1 Silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated carbonyl compound



Entry	R^1, R^2	R^3, R^4	Product	Yield (%)[a]
1	H, C_6H_5 (**1a**)	OEt, H (**2a**)	**3a**	88
2	H, C_6H_5 (**1a**)	OMe, H (**2b**)	**3b**	85
3	H, C_6H_5 (**1a**)	O^{n}Bu, H (**2c**)	**3c**	82
4	H, C_6H_5 (**1a**)	Me, H (**2d**)	**3d**	54
5	H, C_6H_5 (**1a**)	–$(CH_2)_3$– (**2e**)	**3e**	56
6	H, cyclopropyl (**1b**)	O^{n}Bu, H (**2c**)	**3f**	85
7	H, cyclopropyl (**1b**)	Me, H (**2d**)	**3g**	55
8	H, cyclopropyl (**1b**)	–$(CH_2)_3$– (**2e**)	**3h**	54
9	H, *n*-Bu (**1c**)	O^{n}Bu, H (**2c**)	**3i**	84
10	H, *n*-Bu (**1c**)	Me, H (**2d**)	**3j**	62
11	H, *n*-Bu (**1c**)	–$(CH_2)_3$– (**2e**)	**3k**	50
12	4-F, C_6H_5 (**1d**)	O^{n}Bu, H (**2c**)	**3l**	81
13	4-F, C_6H_5 (**1d**)	Me, H (**2d**)	**3m**	72
14	4-F, C_6H_5 (**1d**)	–$(CH_2)_3$– (**2e**)	**3n**	51
15	4-F, cyclopropyl (**1e**)	O^{n}Bu, H (**2c**)	**3o**	74
16	4-F, *n*-Bu (**1f**)	O^{n}Bu, H (**2c**)	**3p**	80
17	5-Cl, C_6H_5 (**1g**)	O^{n}Bu, H (**2c**)	**3q**	90
18	5-Cl, C_6H_5 (**1g**)	Me, H (**2d**)	**3r**	82
19	5-Cl, cyclopropyl (**1h**)	O^{n}Bu, H (**2c**)	**3s**	83
20	5-Cl, *n*-Bu (**1i**)	O^{n}Bu, H (**2c**)	**3t**	81
21	4,5-$(OMe)_2$, cyclopropyl (**1j**)	O^{n}Bu, H (**2c**)	**3u**	52
22	4,5-$(OMe)_2$, *n*-Bu (**1k**)	O^{n}Bu, H (**2c**)	**3v**	60
23	4-Me, C_6H_5 (**1l**)	O^{n}Bu, H (**2c**)	**3w**	88
24	4-Me, C_6H_5 (**1l**)	Me, H (**2d**)	**3x**	62
25	4-Me, cyclopropyl (**1m**)	O^{n}Bu, H (**2c**)	**3y**	80
26	4-Me, *n*-Bu (**1n**)	O^{n}Bu, H (**2c**)	**3z**	77

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

are readily available and this reaction proceeds with wide scope under mild conditions with high efficiency and excellent selectivity. Well tolerated functional groups at different positions of the substrates are demonstrated. The focused library construction is currently in progress, which will be directly used for different biological assays.

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Notes and references

1 For selected examples of multi-component reactions, see: (*a*) *Multicomponent Reactions*, ed. J. Zhu and H. Bienayme, Wiley-VCH, Weinheim, Germany, 2005; (*b*) D. J. Ramon and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602; (*c*) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekenth and L. Balagopal, *Acc. Chem. Res.*, 2003, **36**, 899; (*d*) R. V. A. Orru and M. D. Greef, *Synthesis*, 2003, 1471; (*e*) G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem.*, 2003, 4101; (*f*) A. Domling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (*g*) H. Bienayme, C. Hulme, G. Oddon and P. Schmitt, *Chem.–Eur. J.*, 2000, **6**, 3321; (*h*) L. Weber, K. Illgen and M. Almstetter, *Synlett*, 1999, 366; (*i*) I. Ugi, A. Domling and B. Werner, *J. Heterocycl. Chem.*, 2000, **37**, 647; (*j*) J. Zhu, *Eur. J. Org. Chem.*, 2003, 1133; (*k*) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51; (*l*) L. Weber, *Curr. Med. Chem.*, 2002, **9**, 1241.

2 A. Ulaczyk-Lesanko and D. G. Hall, *Curr. Opin. Chem. Biol.*, 2005, **9**, 266.

3 (*a*) Q. Huang and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 980; (*b*) G. Dai and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 920; (*c*) G. Dai and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 7042; (*d*) Q. Huang, J. A. Hunter and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 3437; (*e*) K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 86; (*f*) K. R. Roesch, H. Zhang and R. C. Larock, *J. Org. Chem.*, 2001, **66**, 8042; (*g*) K. R. Roesch and R. C. Larock, *Org. Lett.*, 1999, **1**, 553; (*h*) G. Dai and R. C. Larock, *Org. Lett.*, 2001, **3**, 4035.

4 For selected examples, see: (*a*) M. Balasubramanian and J. G. Keay, *Isoquinoline Synthesis*, in *Comprehensive Heterocyclic Chemistry II*, ed. A. E. McKillop, A. R. Katrizky, C. W. Rees and E. F. V. Scrivem, Elsevier, Oxford, 1996, vol. 5, p. 245; (*b*) For a review on the synthesis of isoquinoline alkaloid, see: M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341; (*c*) Y.-N. Niu, Z.-Y. Yan, G.-L. Gao, H.-L. Wang, X.-Z. Shu, K.-G. Ji and Y.-M. Lang, *J. Org. Chem.*, 2009, **74**, 2893; (*d*) Y.-Y. Yang, W.-G. Shou, Z.-B. Chen, D. Hong and Y.-G. Wang, *J. Org. Chem.*, 2008, **73**, 3928; (*e*) D. Fischer, H. Tomeba, N. K. Pahadi, N. T. Patil, Z. Huo and Y. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 15720; (*f*) M. Movassaghi and M. D. Hill, *Org. Lett.*, 2008, **10**, 3485; (*g*) T. Blackburn and Y. K. Ramtohul, *Synlett*, 2008, 1159; (*h*) G. Pandey and M. Balakrishnan, *J. Org. Chem.*, 2008, **73**, 8128; (*i*) S. Su and J. A. Porco, *Org. Lett.*, 2007, **9**, 4983; (*j*) M. Mori, H. Wakamatsu, K. Tonogaki, R. Fujita, T. Kitamura and Y. Sato, *J. Org. Chem.*, 2005, **70**, 1066; (*k*) Z. Xiang, T. Luo, K. Lu, J. Cui, X. Shi, R. Fathi, J. Chen and Z. Yang, *Org. Lett.*, 2004, **6**, 3155; (*l*) B. K. Ghorai, S. Duan, D. Jiang and J. W. Herndon, *Synthesis*, 2006, 3661; (*m*) F. Palacios, C. Alonso, M. Rodríguez, E. Martinez de Marigorta and G. Rubiales, *Eur. J. Org. Chem.*, 2005, 1795; (*n*) F. Palacios, C. Alonso, G. Rubiales and M. Villegas, *Tetrahedron*, 2005, **61**, 2779; (*o*) T. K. Sarkar, N. Panda and S. Basak, *J. Org. Chem.*, 2003, **68**, 6919; (*p*) P. R. Carly, T. C. Govaerts, S. L. Cappelle, F. Compernolle and G. J. Hoornaert, *Tetrahedron*, 2001, **57**, 4203; (*q*) T. K. Sarkar, S. K. Ghosh and T. J. Chow, *J. Org. Chem.*, 2000, **65**, 3111; (*r*) P. R. Carly, S. L. Cappelle, F. Compernolle and G. J. Hoornaert, *Tetrahedron*, 1996, **52**, 11889.

5 (*a*) Z. Chen, X. Yu, M. Su, X. Yang and J. Wu, *Adv. Synth. Catal.*, 2009, **351**, 2702; (*b*) Q. Ding, Z. Wang and J. Wu, *J. Org. Chem.*, 2009, **74**, 921; (*c*) Q. Ding and J. Wu, *Adv. Synth. Catal.*, 2008, **350**, 1850; (*d*) Q. Ding, Z. Wang and J. Wu, *Tetrahedron Lett.*, 2009, **50**, 198.

6 (*a*) M. V. R. Reddy, M. R. Rao, D. Rhodes, M. S. T. Hansen, K. Rubins, F. D. Bushman, Y. Venkateswarlu and D. J. Faulkner, *J. Med. Chem.*, 1999, **42**, 1901; (*b*) A. Aubry, X.-S. Pan, L. M. Fisher, V. Jarlier and E. Cambau, *Antimicrob. Agents Chemother.*, 2004, **48**, 1281; (*c*) E. Marco, W. Laine, C. Tardy, A. Lansiaux, M. Iwao, F. Ishibashi, C. Bailly and F. Gago, *J. Med. Chem.*, 2005, **48**, 3796; (*d*) C. Bailly, *Curr. Med. Chem.: Anti-Cancer Agents*, 2004, **4**, 363.

7 Selected examples for metal-catalyzed cyclization of 2-alkynylbenzaldehyde: (*a*) A. B. Beeler, S. Su, C. A. Singleton and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2007, **129**, 1413, and references cited therein; (*b*) N. Asao, *Synlett*, 2006, 1645; (*c*) I. Nakamura, Y. Mizushima, I. D. Gridnev and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9844; (*d*) N. Kim, Y. Kim, W. Park, D. Sung, A.-K. Gupta and C.-H. Oh, *Org. Lett.*, 2005, **7**, 5289; (*e*) K. Sato, N. Asao and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 8977; (*f*) N. Asao, K. Sato, Menggenbateer and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 3682; (*g*) H. Kusama, H. Funami, J. Takaya and N. Iwasawa, *Org. Lett.*, 2004, **6**, 605; (*h*) N. Asao, H. Aikawa and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 7458; (*i*) N. Asao, H. Aikawa and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 7458; (*j*) Q. Ding and J. Wu, *Org. Lett.*, 2007, **9**, 4959; (*k*) K. Gao and J. Wu, *J. Org. Chem.*, 2007, **72**, 8611; (*l*) W. Sun, Q. Ding, X. Sun, R. Fan and J. Wu, *J. Comb. Chem.*, 2007, **9**, 690; (*m*) Q. Ding, B. Wang and J. Wu, *Tetrahedron*, 2007, **63**, 12166; (*n*) Y. Ohta, Y. Kubota, T. Watabe, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2009, **74**, 6299.

8 For selected examples, see: (*a*) J. Montgomery, *Angew. Chem., Int. Ed.*, 2004, **43**, 3890; (*b*) E. Negishi, C. Coperet, S. Ma, S. Y. Liou and F. Liu, *Chem. Rev.*, 1996, **96**, 365; (*c*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*d*) R. Grigg and V. Sridharan, *J. Organomet. Chem.*, 1999, **576**, 65; (*e*) T. Miura and M. Murakami, *Chem. Commun.*, 2007, 217; (*f*) M. Malacria, *Chem. Rev.*, 1996, **96**, 289; (*g*) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.*, 2003, 551; (*h*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*i*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*j*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2006.

9 (*a*) Z. Chen, X. Yang and J. Wu, *Chem. Commun.*, 2009, 3469; (*b*) Z. Chen, Q. Ding, X. Yu and J. Wu, *Adv. Synth. Catal.*, 2009, **351**, 1692; (*c*) X. Yu, X. Yang and J. Wu, *Org. Biomol. Chem.*, 2009, **7**, 4526; (*d*) Z. Chen, M. Su, X. Yu and J. Wu, *Org. Biomol. Chem.*, 2009, **7**, 4641; (*e*) X. Yu, Q. Ding, Z. Chen and J. Wu, *Tetrahedron Lett.*, 2009, **50**, 4279; (*f*) X. Yu, Z. Chen, X. Yang and J. Wu, *J. Comb. Chem.*, 2010, **12**, 374.

10 For recent reviews on the [3+2] cycloaddition reaction: (*a*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765; (*b*) C. Najera and J. M. Sansano, *Angew. Chem., Int. Ed.*, 2005, **44**, 6272; (*c*) C. Najera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105.

11 For selected examples, see: (*a*) S. Kobayashi and K. Nishio, *J. Org. Chem.*, 1994, **59**, 6620; (*b*) C. Ogawa, M. Sugiura and S. Kobayashi, *Chem. Commun.*, 2003, 192; (*c*) S. Kobayashi and R. Hirabayashi, *J. Am. Chem. Soc.*, 1999, **121**, 6942; (*d*) R. Hirabayashi, C. Ogawa, M. Sugiura and S. Kobayashi, *J. Am. Chem. Soc.*, 2001, **123**, 9493; (*e*) C. Ogawa, M. Sugiura and S. Kobayashi, *J. Org. Chem.*, 2002, **67**, 5359; (*f*) J. Wu, X. Sun and H.-G. Xia, *Eur. J. Org. Chem.*, 2005, 4769.

