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Three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide, α,β-unsaturated carbonyl compound, with bromine

Hui Ren [a], Shengqing Ye [a], Fen Liu [b], Jie Wu [a,*]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China
[b] Key Laboratory of Radioactive Geology and Exploration Technology Fundamental Science for National Defense, East China Institute of Technology, Fuzhou, Jiangxi 344000, China

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ABSTRACT

Different outcomes were generated under different conditions for the three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide, α,β-unsaturated carbonyl compound, with bromine. 6-Bromo*H*-pyrazolo[5,1-*a*]isoquinoline was obtained when the reaction was performed in NMP at 70 °C in the presence of DABCO as base, while 6-bromo-1,2,3,10*b*-tetrahydropyrazolo[5,1-*a*]isoquinoline was afforded when the reaction occurred in DMAc at 10 °C in the presence of K_3PO_4 as the base.

1. Introduction

It is well recognized that the combination of methodology development and library approaches is an efficient device for the discovery of small-molecule enzyme inhibitors or receptor ligands.[1] Usually, the natural product-like compounds with privileged scaffolds are considered as an important source of small molecules. Among the skeletons, isoquinoline is a subunit in numerous naturally occurring alkaloids that exhibit a wide range of biological acitivities,[2,3] such as inhibitor of human topoisomerase I[4] and anti-HIV activity.[5] In continuation of our interest in the synthesis of bioactive heterocycles using tandem reactions,[6] we became interested to construct a focused library of isoquinolines. Recently, we have discovered several efficient strategies for the isoquinolines generation.[7,8] Among the compounds synthesized, *H*-pyrazolo[5,1-*a*]isoquinolines are more attractive[8] since in our preliminary biological assays, these particular analogues show promising activity as PTP1B inhibitor. In order to search better hits, we need to rapidly prepare the diverse *H*-pyrazolo[5,1-*a*]isoquinolines. The synthetic route should have considerable flexibility to introduce a diversity of functionalities in a high-throughput manner.

As mentioned above, we reported an efficient approach for generation of *H*-pyrazolo[5,1-*a*]isoquinolines via silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and α,β-unsaturated carbonyl compound.[8d] In this reaction process, 2-alkynylbenzaldehyde condensed with sulfonohydrazide firstly to afford the *N*′-(2-alkynylbenzylidene)hydrazide, which then underwent *endo*-cyclization catalyzed by AgOTf to furnish the isoquinolinium-2-yl amide. After [3+2] cycloaddition of α,β-unsaturated carbonyl compound and aromatization, *H*-pyrazolo[5,1-*a*]isoquinoline would be afforded. Inspired by this result, we envisioned that an electrophile might be involved in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide with α,β-unsaturated carbonyl compound. As expected, the 6-bromo*H*-pyrazolo[5,1-*a*]isoquinoline would be produced, which could be further elaborated using palladium-catalyzed cross-coupling reactions to introduce more diversity into the *H*-pyrazolo[5,1-*a*]isoquinoline scaffold. Herein, we would like to disclose our recent efforts for the three-component reaction[9] of *N*′-(2-alkynylbenzylidene)hydrazide, α,β-unsaturated carbonyl compound, with bromine. Interestingly, different outcomes were generated under different conditions. The desired 6-bromo*H*-pyrazolo[5,1-*a*]isoquinoline was obtained when the reaction was performed in NMP at 70 °C in the presence of DABCO, while 6-bromo-1,2,3,10*b*-tetrahydropyrazolo[5,1-*a*]isoquinoline was afforded when the reaction occurred in DMAc at 10 °C in the presence of K_3PO_4.

* Corresponding author. Tel.: +86 21 6510 2412; fax: +86 21 6564 1740; e-mail address: jie_wu@fudan.edu.cn (J. Wu).

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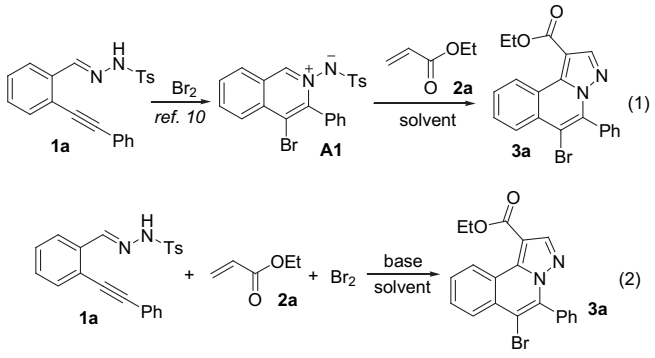
2. Results and discussion

As described previously, *N*′-(2-alkynylbenzylidene)hydrazide could be easily transferred to bromo-containing isoquinolinium-2-yl amide in the presence of bromine.[10] In order to simplify the reaction optimization process, initial studies were carried out for the reaction of bromo-containing isoquinolinium-2-yl amide **A1** with ethyl acrylate **2a** (Scheme 1, Eq. 1). The reaction was complicated when MeCN was used as the solvent at 70 °C. To our delight, the result could be improved dramatically when the reaction occurred in DMAc, which afforded the desired product **3a** in 63% yield. Higher yield was obtained when DMF was utilized as a replacement in the reaction (73% yield). Gratifyingly, compound **3a** was isolated in 90% yield when the reaction took place in NMP. With this promising result in hand, we started to explore the three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a**, ethyl acrylate **2a**, with bromine (Scheme 1, Eq. 2). Since HBr would be generated during the reaction process, a base was added as a scavenger. After screening different bases (LiOH, K_3PO_4, DABCO, KOAc, Na_2CO_3, Et_3N) for the above reaction in NMP at 70 °C, we realized that the reaction proceeded the most efficiently in the presence of 2.0 equiv of DABCO, leading to the desired product **3a** in 65% yield.

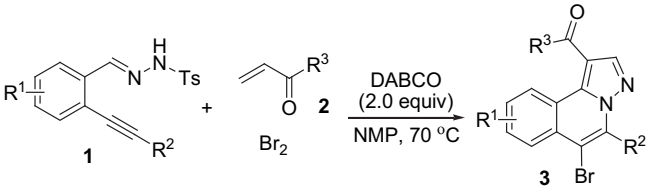


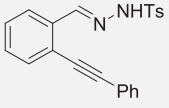
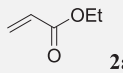
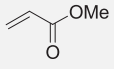
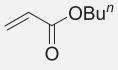
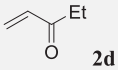
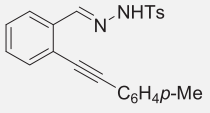
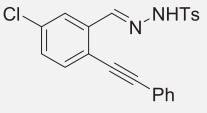
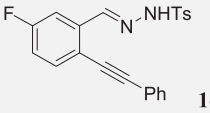
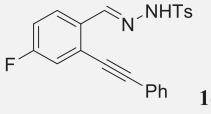
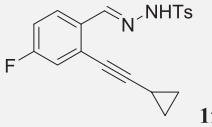
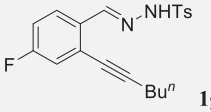
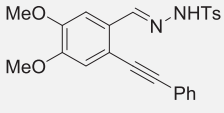
Scheme 1. Initial studies for the three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a**, ethyl acrylate **2a**, with bromine.

The optimized reaction condition mentioned above (DABCO 2.0 equiv in NMP at 70 °C) led us to examine the generality of the reaction for the synthesis of 6-bromo*H*-pyrazolo[5,1-*a*]isoquinolines (Table 1). As shown in Table 1, similar results were generated when methyl acrylate **2b** or *n*-butyl acrylate **2c** was employed as the substrate in the three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** with bromine (Table 1, entries 2 and 3). When pent-1-en-3-one **2d** was used as a partner in the above reaction, the corresponding product **3d** was obtained in 55% yield (Table 1, entry 4). Reactions of chloro- or fluoro-substituted *N*′-(2-alkynylbenzylidene)hydrazides **1** with ethyl acrylate **2a** and bromine were examined meanwhile, which gave rise to the desired products in moderate yields (Table 1, entries 6–10). Substrates with alkyl (*n*-butyl and cyclopropyl) groups attached to the triple bond of *N*′-(2-alkynylbenzylidene)hydrazides **1** also worked well in the transformation (Table 1, entries 9–10). However, *N*′-(2-alkynylbenzylidene)hydrazide with electron-donating groups attached on the aromatic backbone effected the reaction remarkably, resulting in diminished reactivity. For instance, only a trace amount of product was detected when compound **1h** was employed in the reaction of ethyl acrylate **2a** and bromine (Table 1, entry 11).

Similar to our previous report,[8d] for the reaction process we conceived that the bromine-mediated 6-*endo*-cyclization would occur firstly to generate the key intermediate isoquinolinium-2-yl amide **A**. After [3+2] cycloaddition reaction with α,β-unsaturated carbonyl compound **2**, compound **4** would be afforded. Subsequent release of tosyl group and aromatization would produce 6-bromo*H*-pyrazolo[5,1-*a*]isoquinoline **3** (Scheme 2). To support the mechanistic proposal and illustrate the reaction process, reaction of bromo-containing isoquinolinium-2-yl amide **A1** with ethyl acrylate **2a** in different solvent was re-investigated. Indeed, under the standard conditions shown in Table 1, during the reaction process a new compound, which might be the key intermediate **4** could be

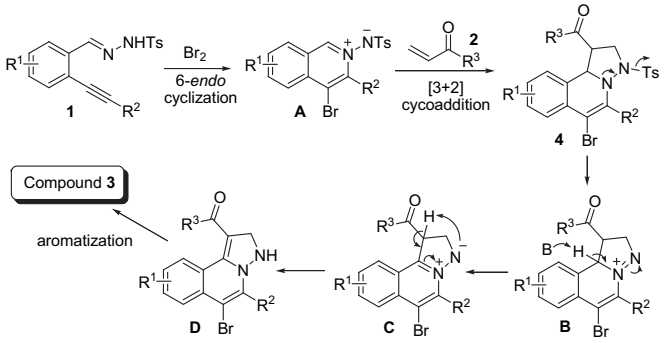
Table 1
Synthesis of 6-bromo*H*-pyrazolo[5,1-*a*]isoquinoline **3** via three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1**, α,β-unsaturated carbonyl compound **2**, with bromine



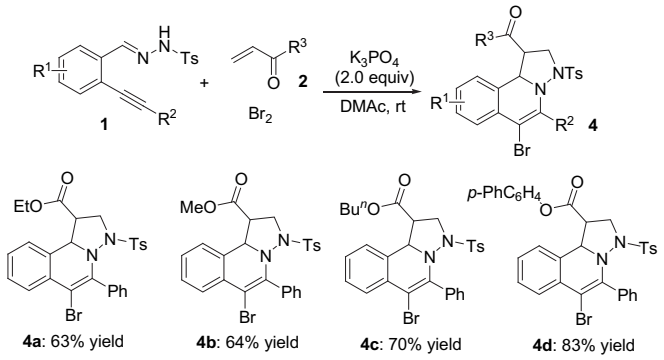
Entry	Compound **1**	Compound **2**	Yield[a] (%)
1	 **1a**	 **2a**	65 (**3a**)
2	**1a**	 **2b**	61 (**3b**)
3	**1a**	 **2c**	60 (**3c**)
4	**1a**	 **2d**	55 (**3d**)
5	 **1b**	**2a**	63 (**3e**)
6	 **1c**	**2a**	53 (**3f**)
7	 **1d**	**2a**	50 (**3g**)
8	 **1e**	**2a**	52 (**3h**)
9	 **1f**	**2a**	31 (**3i**)
10	 **1g**	**2a**	55 (**3j**)
11	 **1h**	**2a**	Trace

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

detected. However, the effort for separation of the compound was difficult since the compound was disappeared fast at 70 °C. We reasoned that the key intermediate might be isolated at lower temperature. To our delight, we observed the formation of compound **4a** with a 92% isolated yield when the reaction was performed in DMAc at 10 °C. In addition, we found that three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1**, α,β-unsaturated carbonyl compound **2**, with bromine in the presence of K_3PO_4 as a base in DMAc at 10 °C proceeded efficiently to afford compound **4** in good yields (Scheme 3). However, compound **4** was not stable, which was easily decomposed after several minutes of storage.



Scheme 2. Possible mechanism for the three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide, α,β-unsaturated carbonyl compound, with bromine.



Scheme 3. Generation of 6-bromo-1,2,3,10*b*-tetrahydropyrazolo[5,1-*a*]-isoquinoline **4** via three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1**, α,β-unsaturated carbonyl compound **2**, with bromine.

3. Conclusions

In summary, we have described a three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide, α,β-unsaturated carbonyl compound, with bromine, which affords different results under different conditions. 6-Bromo*H*-pyrazolo[5,1-*a*]isoquinoline is generated when the reaction is performed in NMP at 70 °C in the presence of DABCO, while 6-bromo-1,2,3,10*b*-tetrahydropyrazolo [5,1-*a*]isoquinoline is obtained when the reaction occur in DMAc at 10 °C in the presence of K_3PO_4. This temperature-controlled result also gives us hits for the understanding of reaction process.

4. Experimental section

4.1. General procedure for synthesis of 6-bromo*H*-pyrazolo-[5,1-*a*]isoquinoline 3 via three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide 1, α,β-unsaturated carbonyl compound 2, with bromine

A mixture of *N*′-(2-alkynylbenzylidene)hydrazide **1** (0.2 mmol) and bromine (0.24 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was stirred at room temperature under air atmosphere for 10 min. Then the temperature was elevated to 70 °C, and DABCO (0.3 mmol, 1.5 equiv) and α,β-unsaturated carbonyl compound (0.4 mmol, 2.0 equiv) were added into the reaction mixture. After completion of the reaction as indicated by TLC, the reaction was quenched with saturated NH_4Cl (aq), extracted with ethyl acetate (10 mL×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired product **3**.

*4.1.1. Ethyl 6-bromo-5-phenylpyrazolo[5,1-a]isoquinoline-1-carboxylate (**3a**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97–9.94 (m, 1H), 8.38 (s, 1H), 8.33–8.30 (m, 1H), 7.77–7.73 (m, 2H), 7.62–7.57 (m, 3H), 7.51–7.49 (m, 2H), 4.43 (q, *J*=7.3 Hz, 2H), 1.43 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 163.7, 145.4, 138.4, 137.6, 134.1, 130.2, 130.0, 129.7, 129.6, 129.4, 128.7, 127.9, 127.4, 123.8, 112.0, 108.1, 60.6, 14.4. HRMS (ESI) calcd for $C_{20}H_{15}BrN_2O_2$: 417.0215 (M+Na^+), found: 417.0204.

*4.1.2. Methyl 6-bromo-5-phenylpyrazolo[5,1-a]isoquinoline-1-carboxylate (**3b**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95–9.93 (m, 1H), 8.37 (s, 1H), 8.32–8.28 (m, 1H), 7.78–7.73 (m, 2H), 7.62–7.57 (m, 3H), 7.51–7.49 (m, 2H), 3.95 (s, 3H). ^{13}C NMR (100 MHz) δ 164.1, 145.4, 138.5, 137.6, 134.0, 130.3, 130.0, 129.7, 129.6, 128.7, 128.4, 127.9, 127.4, 123.7, 112.1, 107.7, 51.8. HRMS (ESI) calcd for $C_{19}H_{13}BrN_2O_2$: 403.0058 (M+Na^+), found: 403.0050.

*4.1.3. Butyl 6-bromo-5-phenylpyrazolo[5,1-a]isoquinoline-1-carboxylate (**3c**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97–9.94 (m, 1H), 8.37 (s, 1H), 8.31–8.28 (m, 1H), 7.76–7.75 (m, 2H), 7.62–7.57 (m, 3H), 7.51–7.49 (m, 2H), 4.37 (t, *J*=6.6 Hz, 2H), 1.83–1.76 (m, 2H), 1.54–1.44 (m, 2H), 0.99 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 163.9, 145.5, 138.6, 137.8, 134.2, 130.4, 130.2, 129.8, 129.7, 128.8, 128.7, 128.1, 127.5, 124.0, 112.1, 108.3, 64.7, 30.9, 19.5, 13.9. HRMS (ESI) calcd for $C_{22}H_{19}BrN_2O_2$: 445.0528 (M+Na^+), found: 445.0510.

*4.1.4. 1-(6-Bromo-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)propan-1-one (**3d**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08–10.06 (m, 1H), 8.39 (s, 1H), 8.32–8.30 (m, 1H), 7.78–7.73 (m, 2H), 7.62–7.59 (m, 3H), 7.51–7.48 (m, 2H), 3.06 (q, *J*=7.3 Hz, 2H), 1.30 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 195.3, 145.0, 137.8, 137.4, 134.1, 130.6, 130.0, 129.8, 129.7, 128.7, 128.6, 128.1, 127.3, 124.1, 116.6, 112.8, 34.7, 8.7. HRMS (ESI) calcd for $C_{20}H_{15}BrN_2O$: 401.0265 (M+Na^+), found: 401.0247.

*4.1.5. Ethyl 6-bromo-5-p-tolylpyrazolo[5,1-a]isoquinoline-1-carboxylate (**3e**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97–9.94 (m, 1H), 8.38 (s, 1H), 8.32–8.29 (m, 1H), 7.77–7.74 (m, 2H), 7.42–7.38 (m, 4H), 4.43 (q, *J*=6.9 Hz, 2H), 2.49 (s, 3H), 1.44 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz) δ 163.8, 145.4, 139.7, 138.5, 137.8, 131.2, 130.2, 129.9, 129.7, 129.5, 128.6, 127.9, 127.4, 123.8, 112.0, 108.1, 60.6, 21.6, 14.4. HRMS (ESI) calcd for $C_{21}H_{17}BrN_2O_2$: 431.0371 (M+Na^+), found: 431.0352.

*4.1.6. Ethyl 6-bromo-9-chloro-5-phenylpyrazolo[5,1-a]isoquinoline-1-carboxylate (**3f**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05–10.04 (m, 1H), 8.38 (s, 1H), 8.24–8.21 (m, 1H), 7.70–7.68 (m, 1H), 7.60–7.58 (m, 3H), 7.50–7.47 (m, 2H), 4.44 (q, *J*=7.3 Hz, 2H), 1.44 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz) δ 163.4, 145.5, 137.9, 137.3, 134.8, 133.7, 130.6, 130.0, 129.8, 128.9, 128.7, 128.0, 127.2, 124.6, 111.2, 108.6, 60.8, 14.4. HRMS (ESI) calcd for $C_{20}H_{14}BrClN_2O_2$: 429.0005 (M+H^+), found: 428.9992.

*4.1.7. Ethyl 6-bromo-9-fluoro-5-phenylpyrazolo[5,1-a]isoquinoline-1-carboxylate (**3g**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83–9.80 (m, 1H), 8.38 (s, 1H), 8.33–8.30 (m, 1H), 7.62–7.58 (m, 3H), 7.52–7.47 (m, 3H), 4.44 (q, *J*=7.3 Hz, 2H), 1.44 (t, *J*=7.4 Hz,

3H). ^{13}C NMR (100 MHz) δ 163.5, 162.0 (d, $J_{(C,F)}$=247.9 Hz), 145.4, 137.7, 137.1, 133.8, 130.0, 129.9, 129.8, 128.7, 126.3, 125.2 (d, $J_{(C,F)}$=11.4 Hz), 118.9 (d, $J_{(C,F)}$=23.8 Hz), 113.5 (d, $J_{(C,F)}$=26.7 Hz), 111.3, 108.5, 60.8, 14.4. HRMS (ESI) calcd for $C_{20}H_{14}BrFN_2O_2$: 435.0120 (M+Na$^+$), found: 435.0114.

*4.1.8. Ethyl 6-bromo-8-fluoro-5-phenylpyrazolo[5,1-a]isoquinoline-1-carboxylate (**3h**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08–10.05 (m, 1H), 8.37 (s, 1H), 7.99–7.96 (m, 1H), 7.60–7.48 (m, 6H), 4.42 (q, J=6.9 Hz, 2H), 1.43 (t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz) δ 163.7, 163.2 (d, $J_{(C,F)}$=248.9 Hz), 144.9, 138.9, 138.1, 132.4, 132.3, 130.9 (d, $J_{(C,F)}$=9.5 Hz), 130.0, 129.9, 128.8, 119.9, 116.5 (d, $J_{(C,F)}$=22.9 Hz), 112.3 (d, $J_{(C,F)}$=25.7 Hz), 110.7, 107.4, 60.6, 14.4. HRMS (ESI) calcd for $C_{20}H_{14}BrFN_2O_2$: 435.0120 (M+Na$^+$), found: 435.0103.

*4.1.9. Ethyl 6-bromo-5-cyclopropyl-8-fluoropyrazolo[5,1-a]isoquinoline-1-carboxylate (**3i**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97–9.94 (m, 1H), 8.46 (s, 1H), 7.93 (dd, J=7.8, 2.8 Hz, 1H), 7.39–7.34 (m, 1H), 4.41 (q, J=7.3 Hz, 2H), 2.38–2.33 (m, 1H), 1.45–1.35 (m, 3H), 1.26–1.24 (m, 4H). ^{13}C NMR (100 MHz) δ 163.8, 163.3 (d, $J_{(C,F)}$=249.8 Hz), 145.0, 139.0, 138.2, 132.5, 131.1, 131.0, 119.9, 116.6 (d, $J_{(C,F)}$=22.9 Hz), 112.4 (d, $J_{(C,F)}$=25.8 Hz), 107.6, 60.6, 31.4, 30.2, 14.4, 10.4. HRMS (ESI) calcd for $C_{17}H_{14}BrFN_2O_2$: 399.0120 (M+Na$^+$), found: 399.0111.

*4.1.10. Ethyl 6-bromo-5-butyl-8-fluoropyrazolo[5,1-a]isoquinoline-1-carboxylate (**3j**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96–9.93 (m, 1H), 8.45 (s, 1H), 7.86 (dd, J=8.2, 2.3 Hz, 1H), 7.36–7.33 (m, 1H), 4.42 (q J=7.3 Hz, 2H), 3.53 (t, J=7.8 Hz, 2H), 1.78–1.73 (m, 2H), 1.54 (q, J=7.4 Hz, 2H), 1.45 (t, J=7.4 Hz, 3H), 1.00 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 163.8, 163.4 (d, $J_{(C,F)}$=249.8 Hz), 145.3, 140.6, 137.9, 132.1, 131.2, 131.1, 119.9, 116.4 (d, $J_{(C,F)}$=21.9 Hz), 112.3 (d, $J_{(C,F)}$=24.5 Hz), 109.6, 107.8, 60.7, 32.1, 28.9, 14.5, 14.0. HRMS (ESI) calcd for $C_{18}H_{18}BrN_2O_2$: 393.0614 (M+H$^+$), found: 393.0615.

4.2. General procedure for generation of 6-bromo-1,2,3,10*b*-tetrahydropyrazolo[5,1-*a*]isoquinoline 4 via three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide 1, α,β-unsaturated carbonyl compound 2, with bromine

A mixture of *N*′-(2-alkynylbenzylidene)hydrazide **1** (0.2 mmol) and bromine (0.24 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was stirred at room temperature under air atmosphere for 10 min. Then K_3PO_4 (0.3 mmol, 1.5 equiv) and α,β-unsaturated carbonyl compound (0.2 mmol, 1.0 equiv) were added into the reaction mixture. The reaction mixture was stirred at 10 °C until completion of the reaction. The mixture was then quenched with saturated NH_4Cl (aq), extracted with ethyl acetate (10 mL×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired product **4**.

*4.2.1. Ethyl 6-bromo-5-phenyl-3-tosyl-1,2,3,10b-tetrahydropyrazolo-[5,1-a]isoquinoline-1-carboxylate (**4a**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.47 (m, 1H), 7.44–7.43 (m, 1H), 7.39–7.37 (m, 2H), 7.36–7.30 (m, 2H), 7.28–7.20 (m, 2H), 7.16–7.13 (m, 3H), 6.95 (t, J=7.8 Hz, 1H), 6.40 (d, J=7.8 Hz, 1H), 5.14 (d, J=8.7 Hz, 1H), 4.17–4.10 (m, 1H), 3.73–3.63 (m, 3H), 3.59–3.53 (m, 1H), 2.44 (s, 3H), 0.78 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 171.6, 145.3, 144.6, 136.3, 133.0, 129.6, 129.4, 129.3, 129.0, 128.7, 127.9, 127.8, 127.6, 127.2, 126.1, 101.3, 65.1, 61.4, 52.7, 47.1, 21.8, 13.6. HRMS (ESI) calcd for $C_{27}H_{25}BrN_2O_4S$: 575.0616 (M+Na$^+$), found: 575.0596.

*4.2.2. Methyl 6-bromo-5-phenyl-3-tosyl-1,2,3,10b-tetrahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4b**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.49 (m, 1H), 7.43–7.37 (m, 2H), 7.35–7.29 (m, 3H), 7.29–7.21 (m, 2H), 7.14 (d, J=8.3 Hz, 3H), 6.96 (t, J=7.8 Hz, 1H), 6.40 (d, J=7.8 Hz, 1H), 5.17 (d, J=8.7 Hz, 1H), 4.20 (dd, J=9.2, 3.6 Hz, 1H), 3.72 (dd, J=7.3, 5.1 Hz, 1H), 3.64–3.60 (m, 1H), 3.23 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz) δ 172.1, 145.1, 144.6, 136.3, 133.0, 130.8, 129.6, 129.4, 129.0, 128.7, 127.8, 127.7, 127.6, 126.1, 101.4, 65.1, 52.9, 52.1, 47.0, 21.8. HRMS (ESI) calcd for $C_{26}H_{23}BrN_2O_4S$: 561.0460 (M+Na$^+$), found: 561.0422.

*4.2.3. Butyl 6-bromo-5-phenyl-3-tosyl-1,2,3,10b-tetrahydropyrazolo-[5,1-a]isoquinoline-1-carboxylate (**4c**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 1H), 7.47–7.45 (m, 1H), 7.41–7.40 (m, 2H), 7.37–7.29 (m, 3H), 7.24–7.22 (m, 1H), 7.18–7.16 (m, 3H), 6.98 (t, J=7.3 Hz, 1H), 6.44 (d, J=7.4 Hz, 1H), 5.17 (d, J=8.2 Hz, 1H), 4.20 (dd, J=8.7, 3.7 Hz, 1H), 3.75–3.66 (m, 2H), 3.62–3.52 (m, 2H), 2.47 (s, 3H), 1.36–1.28 (m, 2H), 0.94–0.87 (m, 2H), 0.83–0.79 (m, 3H). ^{13}C NMR (100 MHz) δ 171.8, 145.2, 144.5, 136.3, 133.0, 130.8, 129.6, 129.4, 129.3, 129.0, 128.7, 127.9, 127.8, 127.7, 127.6, 127.2, 126.1, 101.3, 65.3, 65.1, 52.8, 47.2, 30.1, 21.8, 19.0, 13.7. HRMS (ESI) calcd for $C_{29}H_{29}BrN_2O_4S$: 603.0929 (M+Na$^+$), found: 603.0924.

*4.2.4. Biphenyl-4-yl 6-bromo-5-phenyl-3-tosyl-1,2,3,10b-tetrahydropyrazolo[5,1-a]isoquinoline-1-carboxylate (**4d**).* White solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.59 (m, 1H), 7.47–7.45 (m, 2H), 7.43–7.37 (m, 7H), 7.37–7.36 (m, 1H), 7.31–7.27 (m, 3H), 7.26–7.21 (m, 2H), 7.18–7.16 (m, 2H), 6.96 (dt, J=7.4, 0.9 Hz, 1H), 6.44 (m, 3H), 5.35 (d, J=9.2 Hz, 1H), 4.31 (dd, J=8.7, 3.7 Hz, 1H), 3.89–3.83 (m, 1H), 3.79–3.75 (m, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz) δ 171.0, 149.6, 145.4, 144.8, 140.3, 139.2, 136.2, 133.0, 130.8, 129.7, 129.5, 129.4, 128.9, 128.6, 128.2, 127.9, 127.7, 127.6, 127.5, 127.3, 127.2, 126.4, 121.4, 101.3, 65.4, 52.8, 47.5, 21.8. HRMS (ESI) calcd for $C_{37}H_{29}BrN_2O_4S$: 699.0929 (M+Na$^+$), found: 699.0923.

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Supplementary data

Experimental procedures, characterization data, ^{1}H, and ^{13}C NMR spectra of compounds **3** and **4**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.08.052.

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