A novel method for the synthesis of haloisoquinolines involving an electrophile-exchange process

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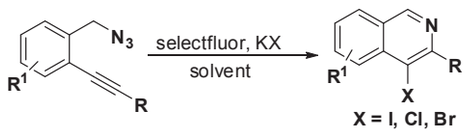
A synthesis of haloisoquinolines through electrophilic cyclisation involving an electrophilic-exchange process has been developed. A variety of 2-alkynyl benzyl azides are cyclised in the presence of KX (X = I, Br, Cl) and electrophilic fluoride reagents, to afford the corresponding haloisoquinolines in moderate to good yields. Reagents for electrophilic halogenation have been generated from their inorganic salts (M^+X^-) by oxidation with a Selectfluor reagent and reacted *in situ* with the substrates.

Keywords: haloisoquinolines; electrophilic-exchange process; electrophilic cyclisation; 2-alkynyl benzyl azides

Isoquinolines are present in a wide variety of biologically active compounds and pharmaceutical agents. Haloisoquinolins have recently attracted considerable attention from both industry and academia due to their therapeutic value in a variety of diseases, showing anti-HIV-1, anticancer, antimicrobial, and antifungal properties. Furthermore, functionalised isoquinolines have been shown to be organocatalysts and are recognised as useful tools for the highly enantioselective syntheses of chiral molecules. Because of their importance, the development of new synthetic approaches for their preparation remains an active research area. Among these methods, electrophilic cyclisation for accessing the haloisoquinoline skeleton has aroused considerable interest. For example, the Yamamto group[1,2] employed 2-alkynyl benzyl azides as the starting materials for haloisoquinolines using an electrophilic iodocyclisation process. Wu[3,4] prepared 4-haloisoquinolines *via* CuX_2-mediated cyclisation of 2-alkynylbenzaldehyde *O*-methyl oximes, and a three component reaction of 2-alkynylbenzaldoxime and carbodiimide with electrophile.[3,4] Another report by Li and co-workers[5] described the synthesis of iodoisoquinoline-fused benzimidazoles by a copper-promoted tandem cyclisation of 2-ethynylbenzaldehydes with *o*-benzenediamines and iodine.[5] Generally, all these procedures have focused on direct halogenation of the isoquinoline skeleton by using different halogenating species. Reagents for electrophilic halogenation are available in different forms varying from the diatomic elements to some fairly exotic halogen delivery reagents. Although most of these reagents can be prepared and isolated prior to use, the electrophiles are limited to halogens, such as ICl,[6,7] I_2,[8–10] NBS (*N*-bromo-succinimide),[11,12] and Br_2.[13,14] Some of these are relatively expensive, highly corrosive and toxic. Therefore, there is considerable interest in developing more efficient methods for electrophilic halogenation. Recently, it has been shown that Selectfluor reagent could not only be used as an electrophilic fluorination agent but also as an oxidising agent. A variety of Selectfluor reagents as new oxidisers have been used for the conversion of inorganic salts bearing halogen anions to active electrophilic halogenation species and have been successfully applied in introducing electrophiles into aromatic systems.[15,16] The results show that Cl^+ and Br^+ have been generated from their respective inorganic salts (M^+X^-) by oxidation with Selectfluor reagent, and then reacted *in situ* with aromatic substrates.

Recently, we reported the synthesis of 4-haloisoquinolines through the halopalladation cyclisation of alkynes with azides, and the results showed that 2-alkynyl benzyl azides were suitable for constructing the 4-haloisoquinoline skeleton.[17] A novel synthesis of spiro[4.5]decenones *via* electrophilic *ipso*-cyclisation involving an electrophile-exchange process was reported by Li and co-workers.[18] Accordingly, it occurred to us that alternative electrophilic cyclisation of 2-alkynyl benzyl azides including new electrophiles generated through the process involving electrophile-exchange with Selectfluor would give haloisoquinolines. Herein, we reported a new method for the synthesis of 4-haloisoquinolines from 2-alkynyl benzyl azides in the presence of KX and Selectfluor in DMF at 80 °C (Scheme 1).



Scheme 1 Synthesis of haloisoquinolines promoted by Selectfluor involving an electrophile-exchange process.

Results and discussion

As shown in Table 1, 2-phenylethynyl benzyl azide (**1a**) was used as the model substrate to identify the optimal conditions. Initially, the effect of solvents on the reaction of azide **1a** was examined in the presence of 1.5 equiv. **F1**, 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, 3 equiv. KI (entries 1–5). DMF was superior to all the other solvents. The results revealed that solvent polarity played a significant role in the formation of haloisoquinoline. For example, the reactions proceeded in highly polar solvents such as MeCN and THF, although moderate yields of 68% and 66% were observed, respectively (entries 2 and 3), and a significantly lower yield was observed in 1,2-dichloroethane and toluene (entries 1 and 4). In addition, in the case of the electrophilic cyclisation of 2-phenylethynyl benzyl azide (**1a**), the cyclisation of **1a** afforded the corresponding product along with the 1,3-dipolar adduct **5** as a minor product in MeCN solvent. However, iodocyclisation *via* I^-/F^+ electrophile exchange procedure did not produce **5** at all (entry 2). The temperature also was evaluated, and the preferred temperature for the reaction was 80 °C (entries 5–8). Another electrophilic fluoride reagent **F2**, *N*-Fluoro-*N*′-(chloromethyl) triethylenediamine bis(tetrafluoroborate), was examined, but it was less effective than **F1** (entry 9). It was noteworthy that no reaction was observed without any electrophilic fluoride reagents (entry 10). Subsequently, the amount of both KI and **F1** was investigated. The results revealed that 3 equiv. of KI and 1.5 equiv. of **F1** provided the best results, and produced 4-iodo-3-phenylisoquinoline in 88% yield (entries 6, 11, and 12). Finally, a series of salts including KBr, KCl, NaCl and NH_4Cl were also examined by reacting with **1a** in the presence

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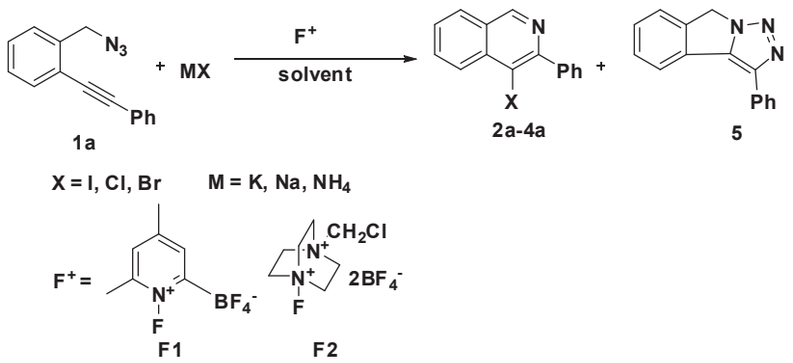
Table 1 Screening optimal conditions[a]



Entry	KX	Solvent	Selectfluor	Temperature/°C	Time /h	Yield /%[b]
1	KI	CH_2ClCH_2Cl	F1	80	22	22
2[c]	KI	MeCN	F1	80	22	68
3	KI	THF	F1	80	22	66
4	KI	Toluene	F1	80	24	18
5	KI	DMF	F1	80	22	88
6	KI	DMF	F1	100	20	76
7	KI	DMF	F1	60	26	54
8	KI	DMF	F1	r.t.	30	trace
9	KI	DMF	F2	80	22	68
10	KI	DMF	–	80	22	0
11[d]	KI	DMF	F1	80	22	81
12[e]	KI	DMF	F1	80	22	79
13	KBr	DMF	F1	80	23	80
14	KCl	DMF	F1	80	36	72
15	NaCl	DMF	F1	80	36	65
16	NH_4Cl	DMF	F1	80	36	60

[a]Reaction conditions: **1** (0.3 mmol), KX (3 equiv.), F^+ (1.5 equiv.), and DMF (3 mL).
[b]Isolated yield.
[c]1,3-dipolar adduct **5** in 15% yield was observed.
[d]F^+ (1.0 equiv.).
[e]KI (2 equiv.).

of the Selectfluor **F1** (entries 13–16). We observed that both KBr (**2b**) and KCl (**2c**) were highly reactive. The reactivity of the electrophiles generated from various potassium salts decreased in the order $I^+ > Br^+ > Cl^+$. It was found that using KCl was marginally more effective than that for NaCl and NH_4Cl. Thus, we chose the following reaction conditions as optimum for all subsequent cyclisations: 0.3 mmol of 2-alkynyl benzyl azides, 1.5 equiv. **F1**, and 3 equiv. KX in DMF stirred at 80 °C for an appropriate amount of time.

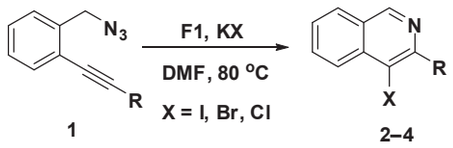
With the standard reaction conditions in hand, we then used the KX/**F1** system to explore the scope of azides (Table 2). The results showed that azides attached to various aryl group at the terminal alkyne were tolerated well in the presence of 3 equiv. KX and 1.5 equiv. **F1** and afforded the corresponding haloisoquinolines in moderate to good yield, respectively (entries 1–9). Substrates with an electron-withdrawing group also reacted (entries 1, 2, 3, 7, 8 and 9). The standard conditions were also compatible with both aliphatic and vinyl alkynes **1e**–**g** (entries 10–18). Substrate **1g** with a cyclohexenyl group, for instance, gave the desired product **4g** in 88% yield (entry 16). However, the annulation of aliphatic alkynes **1e**–**g** afforded 4-bromo-1,2-dihydro-isoquinolines **3e**–**g** using KBr/**F1** system (entries 11, 14 and 17). A thiophen-2-yl substrate **1h** was perfectly tolerated. For example, in the presence of 3 equiv. KX (X=I, Br) and 1.5 equiv. **F1**, treatment of 2-((2-(azidomethyl)phenyl)ethynyl)-5-methylthiophene (**1h**) gave the corresponding haloisoquinolines **3h** and **4h** in 82% and 84% yield, respectively. It was interesting that an unexpected dichloro-addition product **2h** was obtained in KCl/**F1** system. The result was in accordance with our previous reports on halopalladation of 2-alkynyl benzyl azides.[17]

In conclusion, we have developed a novel and flexible approach to highly haloisoquinolines through electrophilic cyclisation involving an electrophile-exchange procedure. In the presence of KX (X=I, Br, Cl) and electrophilic fluoride reagents, a variety of 2-alkynyl benzyl azides were cyclised to afford the corresponding haloisoquinolines in moderate to excellent yields. Importantly, a halide is introduced into the products, which can then be further functionalised, making the methodology more attractive for organic synthesis.

Experimental

NMR spectroscopy was performed on AMX-500 (Bruker) spectrometer, operating at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). TMS was used an internal standard and $CDCl_3$ was used as the solvent. Mass spectrometric analysis was performed on a GC-MS instrument (Shimadzu GCMS-QP2010 plus). Melting points were recorded on an Electrothermal type 9100 melting point apparatus. All melting points are uncorrected. Benzyl azides were prepared according to the published method.[20] Other reagents which were commercially available were obtained from the Alfa Aesar and TCI companies.

Table 2 Synthesis of haloisoquinolines with azides and electrophiles[a]



Entry	R	KX	Time /h	Yield/%[b,f]	M.p./°C	
					Found	Reported [ref.]
1		KCl	24	70 (**2b**)	140.2–141.1	
2	4-Chlorophenyl (**1b**)	KBr	22	79 (**3b**)	142.8–143.6	
3		KI	22	80 (**4b**)	145.5–146.4	
4		KCl	24	74 (**2c**)	77.5–77.8	77.6–77.8[17]
5	4-Methoxyphenyl (**1c**)	KBr	22	82 (**3c**)	109.6–110.8	109.8–110.9[17]
6		KI	20	86 (**4c**)	113.6–114.4	113–115[19]
7		KCl	36	35 (**2d**)	154.4–155.7	154.6–155.8[17]
8	4-Nitrophenyl (**1d**)	KBr	30	44 (**3d**)	158.6–159.4	
9		KI	26	56 (**4d**)	154.6–155.8	
10		KCl	24	77 (**2e**)		
11	Pentyl (**1e**)	KBr	22	87 (**3e**)[c]		
12		KI	22	90 (**4e**)		
13		KCl	24	66 (**2f**)		
14	Octyl (**1f**)	KBr	22	81 (**3f**)[d]		
15		KI	22	85 (**4f**)		
16		KCl	30	73 (**2g**)		
17	1-Cyclohexenyl (**1g**)	KBr	24	82 (**3g**)[e]		
18		KI	24	88 (**4g**)		
19		KCl	34	71 (**2h**)[f]	77.6–78.8	
20	5-Methylthiophen-2-yl (**1h**)	KBr	22	82 (**3h**)	80.5–81.2	
21		KI	22	84 (**4h**)	89.6–90.9	

[a]Reaction conditions: **1** (0.3 mmol), KX (3 equiv.), F1 (1.5 equiv.), and DMF (3 mL) at 80 °C.
[b]Isolated yield.
[c]**3e** is 4-bromo-3-pentyl-1,2-dihydroisoquinoline.
[d]**3f** is 4-bromo-3-octyl-1,2-dihydroisoquinoline.
[e]**3g** is 4-bromo-3-cyclohexenyl-1,2-dihydroisoquinoline.
[f]**2h** is 4-chloro-3-(3-chloro-5-methylthiophen-2-yl)isoquinoline.
[g]Products were characterised by ^{1}H NMR and ^{13}C NMR spectroscopy.

Synthesis of haloisoquinolines; general procedure

A flame-dried Schlenk tube with a magnetic stirring bar containing the azide **1** (0.3 mmol), Selectfluor (1.5 equiv.), KX (3 equiv.) and DMF (3 mL) was stirred at 80 °C until the complete consumption of the starting material was observed (monitored by TLC and GC-MS analysis). After the reaction was finished, the mixture was poured into ethyl acetate, washed with brine (3 × 10 mL). The combined organic layers were dried by anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford the desired product.

4-Chloro-3-(4-chlorophenyl)isoquinoline (**2b**): Yield 70%; white solid, m.p. 140.2–141.1 °C. (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.34 (d, *J*=8.5 Hz, 1H), 8.03 (d, *J*=8.0 Hz, 1H), 7.86 (t, *J*=8.5 Hz, 1H), 7.77 (t, *J*=8.0 Hz, 2H), 7.70 (t, *J*=8.5 Hz, 1H), 7.48 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 148.7, 137.4, 134.6, 131.8, 131.4, 128.6, 128.3, 128.1, 127.7, 125.9, 124.1; LRMS (EI, 70 eV) *m/z* (%): 275 (M^++2, 5), 273 (M^+, 15), 238 (–Cl, 69), 203 (–2Cl, 34); HRMS (EI) for $C_{15}H_9Cl_2N$ (M^+): calcd 273.0112, found 273.0110.

4-Chloro-3-(3-chloro-5-methylthiophen-2-yl)isoquinoline (**2h**): Yield 71%; orange solid, m.p. 77.6–78.8 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.35 (d, *J*=8.5 Hz, 1H), 7.99 (s, 1H), 7.96 (d, *J*=8.0 Hz, 1H), 7.82 (t, *J*=7.5 Hz, 1H), 7.63 (t, *J*=7.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 135.7, 135.0, 131.9, 129.0, 128.1, 127.8, 127.7, 124.0, 13.1; LRMS (EI, 70 eV) *m/z* (%): 297 (M^++4, 52), 295 (M^++2, 100), 293 (M^+, 13), 258 (–Cl, 11), 223 (–2Cl, 20); HRMS (EI) for $C_{14}H_9Cl_2NS$ (M^+): calcd 292.9833, found 292.9828.

4-Bromo-3-(4-chlorophenyl)isoquinoline (**3b**): yield 79%; orange solid, m.p. 142.8–143.6 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.32 (d, *J*=8.5 Hz, 1H), 8.00 (d, *J*=8.5 Hz, 1H), 7.84 (t, *J*=7.5 Hz, 1H), 7.70–7.67 (m, 3H), 7.46 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 151.1, 139.1, 136.0, 134.4, 132.0, 131.4, 128.7, 128.2, 128.1, 127.7, 127.0, 118.3; LRMS (EI, 70 eV) *m/z* (%): 319 (M^++2, 45), 317 (M^+, 47), 238 (–Br, 62), 203 (–(Br+Cl), 41); HRMS (EI) for $C_{15}H_9{}^{79}BrClN$ (M^+): calcd 316.9607, found 316.9604.

4-Bromo-3-(4-nitrophenyl)isoquinoline (**3d**): Yield 44%; yellow solid, m.p. 158.6–159.4 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.33 (d, *J*=8.5 Hz, 2H), 7.90 (d, *J*=8.0 Hz, 1H), 7.76 (d, *J*=8.0 Hz, 2H), 7.48 (t, *J*=7.5 Hz, 1H), 7.32 (d, *J*=7.5 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 135.1, 132.9, 131.3, 131.2, 131.0, 129.5, 129.2, 127.3, 124.5, 124.1, 122.5, 100.0, 29.7; LRMS (EI, 70 eV) *m/z* (%): 329 (M^++2, 33), 327 (M^+, 100), 249 (–Br, 25); HRMS (EI) for $C_{15}H_9{}^{79}BrN_2O_2$ (M^+): calcd 327.9843, found 327.9840.

4-Bromo-3-(5-methylthiophen-2-yl)isoquinoline (**3h**): Yield 82%; orange solid, m.p. 80.5–81.2 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.31 (d, *J*=8.0 Hz, 1H), 8.02 (d, *J*=8.5 Hz, 1H,), 7.93 (d, *J*=7.5 Hz, 1H), 7.79 (t, *J*=7.5 Hz, 1H), 7.61 (t, *J*=7.5 Hz, 1H), 6.85–6.84 (m 1H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8,

143.4, 141.3, 136.5, 131.9, 129.7, 128.0, 127.8, 127.5, 126.0, 115.3, 15.4; LRMS (EI, 70 eV) *m/z* (%): 307 (M^++4, 52), 305 (M^++2, 100), 303 (M^+, 23), 224 (–Br, 31); HRMS (EI) for $C_{14}H_{10}BrNS$ (M^+): calcd 302.9721, found 302.9718.

4-Iodo-3-(4-chlorophenyl)isoquinoline (**4b**): Yield 80%; yellow solid, m.p. 145.5–146.4 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.20 (d, *J*=8.5 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 1H), 7.83 (d, *J*=8.5 Hz, 1H), 7.81 (d, *J*=6.5 Hz, 1H), 7.68 (t, *J*=7.5 Hz, 2H), 7.47 (t, *J*=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 152.1, 142.0, 138.5, 134.3, 132.3, 131.3, 128.2, 128.1, 128.0, 127.9, 98.0; LRMS (EI, 70 eV) *m/z* (%): 367 (M^++2, 5), 365 (M^+, 25), 238 (–I, 60), 203 (–(Cl+I), 31); HRMS (EI) for $C_{15}H_9ClIN$ (M^+): calcd 364.9468, found 364.9463.

4-Iodo-3-(4-nitrophenyl)isoquinoline (**4d**): Yield 56%; yellow solid, m.p. 154.6–155.8 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.36 (d, *J*=6.0 Hz, 2H), 8.24 (d, *J*=8.5 Hz, 1H), 8.00 (d, *J*=8.0 Hz, 1H), 7.89 (t, *J*=8.0 Hz, 1H), 7.82 (d, *J*=8.5 Hz, 2H), 7.75 (t, *J*=7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 152.3, 149.7, 147.5, 138.3, 132.7, 132.4, 131.1, 128.8, 128.3, 128.1, 123.2, 98.0; LRMS (EI, 70 eV) *m/z* (%): 378 (M^++2, 33), 376 (M^+, 100), 249 (–I, 25); HRMS (EI) for $C_{15}H_9IN_2O_2$ (M^+): calcd 375.9704, found 375.9701.

4-Iodo-3-pentylisoquinoline (**4e**): Yield 90%; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.10 (d, *J*=8.5 Hz, 1H), 7.87 (d, *J*=8.0 Hz, 1H), 7.75 (t, *J*=7.5 Hz, 1H), 7.59 (t, *J*=7.5 Hz, 1H), 3.25 (t, *J*=8.0 Hz, 2H), 1.83–1.77 (m, 2H), 1.49–1.37 (m, 4H), 0.93 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 152.0, 138.3, 131.8, 131.4, 127.8, 127.7, 127.1, 98.8, 42.5, 31.8, 29.2, 22.6, 14.1; LRMS (EI, 70 eV) *m/z* (%): 327 (M^++2, 9), 325 (M^+, 7), 254 (23), 177 (100); HRMS (EI) for $C_{14}H_{16}IN$ (M^+): calcd 325.0327, found 325.0323.

4-Iodo-3-octylisoquinoline (**4f**): Yield 85%; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.09 (d, *J*=8.5 Hz, 1H), 7.86 (d, *J*=8.0 Hz, 1H), 7.74 (t, *J*=7.5 Hz, 1H), 7.58 (t, *J*=7.5 Hz, 1H), 3.25 (t, *J*=8.0 Hz, 2H), 1.82–1.76 (m, 2H), 1.48–1.43 (m, 2H), 1.30–1.27 (m, 6H), 0.87 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 152.0, 138.3, 131.7, 131.4, 127.8, 127.7, 127.1, 98.8, 42.5, 31.9, 29.6, 29.5, 29.4, 29.3, 22.7, 14.1; LRMS (EI, 70 eV) *m/z* (%): 369 (M^++2, 4), 367 (M^+, 10), 240 (–I, 28), 177 (100); HRMS (EI) for $C_{17}H_{22}IN$ (M^+): calcd 367.0797, found 367.0793.

4-Iodo-3-(5-methylthiophen-2-yl)isoquinoline (**4h**): Yield 84%; orange solid, m.p. 89.6–90.9 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.21 (d, *J*=9.0 Hz, 1H), 7.87 (d, *J*=8.0 Hz, 1H), 7.82 (t, *J*=11.5 Hz, 1H), 7.78–7.73 (m, 1H), 7.61 (t, *J*=7.5 Hz, 1H), 6.86 (t, *J*=2.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 150.0, 143.1, 139.0, 133.7, 132.2, 129.9, 127.7, 126.4, 15.4; LRMS (EI, 70 eV) *m/z* (%): 353 (M^++2, 32), 351 (M^+, 16), 224 (–I, 21), 127 (20); HRMS (EI) for $C_{14}H_{10}INS$ (M^+): calcd 350.9579, found 350.9576.

3-Phenyl-8H-[1,2,3]triazolo[5,1-a]isoindole (**5**):[21] White solid, 151.6–152.9 °C (lit.[21] 152–154 °C)(uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J*=8.0 Hz, 2H), 7.90 (d, *J*=7.5 Hz, 1H), 7.53 (t, *J*=7.5 Hz, 3H), 7.48 (t, *J*=7.5 Hz, 1H), 7.44–7.40 (m, 2H), 5.37 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 139.3, 139.0, 131.2, 128.9, 128.8, 128.4, 128.2, 128.1, 127.0, 124.1, 121.2; LRMS (EI, 70 eV) *m/z* (%): 235 (M^++2, 28), 233 (M^+, 16), 126 (24).

CAUTION: Many low-molecular-weight azides are known to be explosive. In this lab, no problems have been encountered in this work, but great caution should be exercised when heating compounds of this type, especially neat. The reactions described here were run on only a few grams; but an increase in the scale of these reactions will decrease the efficiency of heat dissipation and explosions may result.

The authors thank the major project in institutions of higher education of Hunan province (No. 14A133), Hunan provincial natural Science Foundation (No. 14JJ7076), and Scientific and Technological Innovative team of Shaoyang University (2012) for financial support.

Received 17 August 2014; accepted 20 October 2014
Paper 1402836 doi: 10.3184/174751914X14140703941872
Published online: 13 November 2014

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