Selectfluor-mediated synthesis of isoindoline fused with triazoles under metal-free conditions

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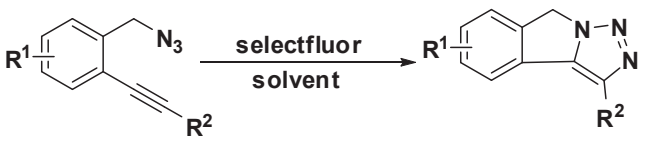
An efficient selectfluor-mediated cyclisation of 2-arylethynyl-benzyl azides at 80 °C in MeCN yielded 12 arylated triazolo-isoindoline derivatives (seven of which are novel). Products bearing either electron-donating or electron-withdrawing groups on the aromatic ring were formed in comparable yields.

Keywords: selectfluor, isoindoline fused with triazoles, metal-free, 2-alkynyl benzyl azides

1,2,3-Triazoles are heterocyclic compounds possessing effective biological properties with several pharmaceutical applications. Most research has focused on the synthesis and bioassay of 1,4- or 1,5-disubstituted 1,2,3-triazoles.[1] In recent years, fused triazoles as versatile synthetic intermediates have seen widespread use as precursors for drugs such as antiallergic agents[2] and potent glycosidase inhibitors.[3] Amongst them, an isoindoline fused with a triazole is considered an important building block (or novel pharmacophore).[4] Thus new methodologies for the synthesis of this skeleton are highly desirable. Although various strategies have been used for the synthesis of compounds containing fused triazoles,[5] the few approaches to isoindoline fused with triazoles that have been described were catalysed by transition metals such as Pd–Cu,[4] CuBTC–Pd MOF[6] or Pd–Cu/C.[7] For biological applications, the cytotoxicity of copper could represent an important constraint[8] and thus there is still a need for the development of copper-free protocols for the cycloaddition of alkyne-azides to isoindoline fused with 1,2,3-triazoles.

Selectfluor is a popular user-friendly electrophilic fluorinating reagent for electron-rich carbon centres, but its ability to act as mediator and catalyst for oxidative transformations other than fluorination is relatively less explored.[9] In a recent study,[10] we reported the cyclisation of 2−alkynyl-benzyl azides in the presence of KX (X=I, Br, Cl) and selectfluor reagents. The optimal conditions for the selectfluor-mediated cyclisation of 2−phenylethynyl benzyl azide to isoindoline fused with triazoles used MeCN as solvent. Encouraged by this result, we envisioned that this reagent and conditions could be used in the 1,3-dipolar cycloaddition of an alkyne-azide. We now report our preliminary results on the efficacy of a selectfluor-mediated approach for the preparation of isoindoline fused with 1,2,3-triazoles under metal-free conditions (Scheme 1). To our knowledge, studies exploiting this reagent for such transformations have not been reported previously.



Scheme 1 Selectfluor-mediated approach for isoindoline fused with triazoles.

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Results and discussion

Since in our previous study, isoindoline fused with triazoles were formed in MeCN solvent, 2−phenylethynyl benzyl azide **1a** was chosen as a model substrate and MeCN as solvent to carry out the desired 1,3-dipolar cycloaddition. In further support of our choice of reagent, we noted that selectfluor has been used successfully in the synthesis of a cyclohexanone ring fused with isoxazole derivatives from isoxazoline *N*-oxides.[11] Initially in our optimisation study, we evaluated three selectfluors, F1, F2 and F3 (Fig. 1).

As indicated in Table 1, among the various selectfluors tested, F2 promoted the reaction most effectively (entries 1–3). The desired product was formed only in moderate yield using selectfluor F3, and in poor yield using selectfluor F1, while no product was observed in the absence of F2 (entry 6). Then, the

Table 1 Optimisation of the conditions [a](temperature and duration of reaction) for the cyclisation of 2-phenylethynyl benzyl azide **1a** (R^1=H, R^2=Ph) to the tetracyclic product **2a** (R^1=H, R^2=Ph) (Scheme 1, solvent=MeCN) in the presence of selectfluors, F1, F2 or F3 (Fig. 1)

Entry	Selectfluor	Temp/°C	Time/h	Yield/%[b]
1	F1	80	22	35
2	F2	80	22	81
3	F3	80	22	62
4[c]	F2	80	24	58
5[d]	F2	80	20	78
6	–	80	22	Trace
7	F2	60	26	67
8	F2	100	20	76
9	F2	r.t.	30	20

[a]Reaction conditions: **1** (0.3 mmol), selectfluor (2 equiv.), and MeCN (3 mL).
[b]Isolated yield.
[c]F2 (1.2 equiv.).
[d]F2 (4 equiv.).

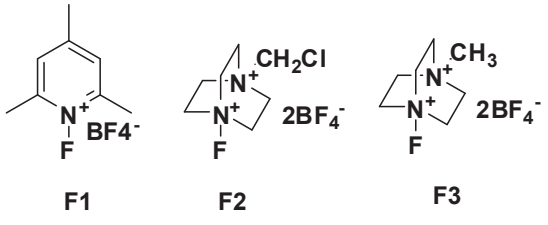

Fig. 1 Structures of three selectfluors. As indicated in Table 1, among the various selectfluors tested, **F2** promoted the reaction most effectively (entries 1–3). The desired product was formed only in moderate yield using selectfluor **F3**, and in poor yield using selectfluor **F1**, while no product was observed in the absence of **F2** (entry 6). Then, the optimal amount of **F2** was evaluated. The results showed that 2 equiv. of **F2** provided the best results, and produced 3-phenyl-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole **2a** in 81% yield (entries 2, 4 and 5). The yields were also significantly affected by the temperature, and the preferred temperature for the reaction was found to be 80 °C (entries 2 and 7–9).

Table 2 Yields/reaction times for the preparation, under the optimised conditions, of fused triazolo-isoindolines **2b–l** (Scheme 1, solvent = MeCN) mediated by selectfluor F2 (Fig. 1)[a]

Entry	R^1	R^2	Time/h	Yield/%[b]	M.p./°C	
					Found	Reported [ref]
1	H	4-Chlorophenyl	22	68 (**2b**)	151.2–152.9	
2	H	4-(Phenylethynyl)phenyl	22	82 (**2c**)	172.4–174.1	
3	H	4-Chloro–2–(methoxycarbonyl)phenyl	24	52 (**2d**)	191.5–193.3	
4	H	4-Nitrophenyl	24	58 (**2e**)	163.5–164.9	162–164 [13]
5	H	4-Methylphenyl	22	85 (**2f**)	160.4–161.7	160–162 [12,13]
6	H	5-Methylthiophen-2-yl	22	66 (**2g**)	183.1–184.7	
7	H	Octyl	22	76 (**2h**)	79.8–81.7	79–80 [12]
8[c]	H	H	22	74 (**2i**)	83.8–85.4	84–86 [14]
9	4-Methyl	Phenyl	28	83 (**2j**)	180.5–181.6	
10	4-Methyl	4-Methylphenyl	26	86 (**2k**)	185.5–187.1	
11	4-Methyl	4-Nitrophenyl	28	74 (**2l**)	191.2–192.4	

[a]Reaction conditions: **1** (0.3 mmol), selectfluor (2 equiv.), and MeCN (3 mL).
[b]Isolated yield.
[c]R^2 on substrate **1i** is TMS.

optimal amount of F2 was evaluated. The results showed that 2 equiv. of F2 provided the best results, and produced 3-phenyl-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole **2a** in 81% yield (entries 2, 4 and 5). The yields were also significantly affected by the temperature, and the preferred temperature for the reaction was found to be 80 °C (entries 2 and 7–9).

Under the optimised conditions, the selectfluor-mediated synthesis of variously substituted 1,2,2-triazolo-isoindolines was achieved, as illustrated by the examples in Table 2. Whether bearing either an electron withdrawing group (nitro and chloro) or an electron donating group (methyl) on the aromatic ring, the benzyl amide **1** reacted smoothly and furnished the corresponding isoindoline fused with a triazole in moderate to good yields (entries 1–5). Furthermore, a 2-heteroarylethynylbenzyl azide **1g** successfully underwent the cycloaddition to afford the fused triazole product **2g** in moderate yield (entry 6). Gratifyingly, the standard conditions were also successfully compatible with aliphatic alkyne substituents such as dec-1-ynyl (entry 7). Note that in the cyclisation of substrate [(2-(azidomethyl)phenyl)ethynyl] trimethylsilane **1i** desilylation occurred and the unexpected 8*H*-[1,2,3]triazolo[5,1-*a*]isoindole (**2i**) was produced in 74% yield (entry 8). Finally, we tested three substituents with methyl on the benzene ring of the azide derivatives. Gratifyingly, substrates **1k–l**, bearing either nitro or methyl group on the aromatic ring (or none), were tolerated without problems, giving the desired products in moderate to good yields (entries 10–12).

In summary, we report the first use of selectfluor as an efficient, mild, and straightforward reagent for the synthesis of isoindoline derivatives fused with triazoles in good yields under metal-free conditions. The scope of this transformation is broad, and substrates bearing electron-donating or electron-withdrawing groups on the aromatic ring afforded several structurally intriguing skeletons.

Experimental

NMR spectra were obtained on a Bruker AMX-500 spectrometer (^{1}H NMR at 500 Hz, ^{13}C NMR at 125 Hz) in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. 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. Variously substituted benzyl azides were prepared according to the published method.[20] Other reagents and chemically were obtained from the Alfa Aesar or TCI companies.

CAUTION: Many low-molecular-weight azides are known to be explosive. In this laboratory, no problems have been encountered, 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; an increase in the scale of these reactions will decrease the efficiency of heat dissipation and explosions may result.

*Synthesis of 3-phenyl-8*H*-[1,2,3]triazolo[5,1-*a*] isoindole; general procedure*

Azide **1** (0.3 mmol), selectfluor (2 equiv.) and MeCN (5 mL) were added to a flame-dried Schlenk tube equipped with a magnetic stir bar. The reaction mixture was stirred at 80 °C for 22 h until complete consumption of the starting material had occurred as monitored by TLC and GC–MS analysis. After completion of the reaction, the solvent was removed under reduced pressure, the residue was mixed with H_2O (30 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried with anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel (100–200 mesh) column chromatography (EtOAc–hexane) to afford the corresponding products **2a–l**.

All compounds were characterised by their physical and spectral properties and, if novel, a HRMS was determined.

*3-Phenyl-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole* (**2a**):[12] Pale brown solid; yield 81%; m.p. 153.5–154.9 °C (lit.[12] 152–154 °C) (uncorrected) ^{1}H NMR: δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 1H),7.53 (t, *J* = 7.5 Hz, 3H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.44–7.40 (m, 2H), 5.37 (s, 2H); ^{13}C NMR: δ 141.1, 139.3, 139.0, 131.2, 128.9, 128.7, 128.4, 128.1, 127.0, 124.2, 121.2, 50.9; LRMS (EI, 70 eV) *m/z* (%): 235 (M^++2, 21), 233 (M^+, 7), 205 (54), 204 (100).

*3-(4-Chlorophenyl)-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole* (**2b**): White solid; yield 68%; m.p. 151.2–152.9 °C (uncorrected). ^{1}H NMR: δ 7.87–7.86 (m, 2H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.50–7.47 (m, 3H), 7.46–7.42 (m, 1H), 5.37 (s, 2H); ^{13}C NMR: δ 196.9, 136.9, 136.6, 136.3, 133.4, 132.2, 131.9, 130.0, 129.0, 128.7, 128.4, 127.3, 89.1, 53.6; LRMS (EI, 70 eV) *m/z* (%): 269 (M^++2, 13), 267 (M^+, 24), 232 (–Cl, 28), 177 (41), 128 (100).

*3-(4-(Phenylethynyl)phenyl)-8*H*-[1,2,3]triazolo[5,1-*a*]isoindole* (**2c**): White solid; yield 82%; m.p. 172.4–174.1 °C (uncorrected) ^{1}H NMR: δ 7.91 (d, *J* = 7.5 Hz, 3H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.56–7.55 (m, 3H),7.51 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.39–7.35 (m, 3H), 5.39 (s, 2H); ^{13}C NMR: δ 141.2, 139.3, 138.8, 132.1, 131.6, 131.1, 128.9, 128.6, 128.4, 128.0, 126.8, 124.3, 123.1, 122.9, 121.4, 90.3, 89.2, 50.9; LRMS (EI, 70 eV) *m/z* (%): 335 (M^++2, 13), 333 (M^+, 24), 256 (32), 156 (46), 142 (100); HRMS (EI) for $C_{23}H_{15}N_3$ (M^+): calcd 333.1334, found 333.1328.

*Methyl-2-(8*H*-[1,2,3]triazolo[5,1-*a*]isoindol-3-yl)-5-chlorobenzoate* (**2d**): White solid; yield 52%; m.p. 191.5–193.3 °C (uncorrected)

^{1}H NMR: δ 7.96 (s, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 7.60 (d, *J*=8.5 Hz, 1H), 7.54–7.52 (m, 1H),7.46–7.43 (m, 1H), 7.42–7.29 (m, 2H), 5.39 (s, 2H), 3.67 (s, 3H); ^{13}C NMR: δ 166.9, 141.1, 140.3, 136.4, 134.4, 132.0, 131.8, 130.4, 129.7, 128.7, 128.5, 127.9, 124.1, 121.1, 52.5, 51.1; LRMS (EI, 70 eV) *m/z* (%): 327 (M^++2, 21), 325 (M^+, 17), 310 (25), 290 (–Cl, 24), 231 (46), 156 (58), 116 (100); HRMS (EI) for $C_{17}H_{12}ClN_3O_2(M^+)$: calcd 325.0634, found 325.0611.

*3-(4-Nitrophenyl)-8*H-*[1,2,3]triazolo[5,1-*a*]isoindole* (**2e**):[13] Light yellow solid; 58% yield; m.p. 163.5–164.9 °C (lit.[13] 162–164 °C) (uncorrected). ^{1}H NMR: δ 8.51 (d, *J*=6.0 Hz, 2H), 8.00 (d, *J*=8.0 Hz, 1H), 7.89 (t, *J*=8.0 Hz, 1H), 7.82 (d, *J*=8.5 Hz, 2H), 7.57–7.54 (m, 2H), 5.55 (s, 2H); ^{13}C NMR: δ 144.5, 142.8, 141.6, 138.1, 134.3, 133.3, 130.9, 129.9, 128.8, 126.5, 125.4, 53.3; LRMS (EI, 70 eV) *m/z* (%): 280 (M^++2, 17), 278(M^+, 34), 232 (31), 188 (57), 128 (100).

*3-(4-Methylphenyl)-8*H-*[1,2,3]triazolo[5,1-*a*]isoindole* (**2f**):[12,13] White solid; yield 85%; m.p. 160.4–161.7 °C (lit.[12,13] 160–162 °C) (uncorrected) ^{1}H NMR: δ 7.97 (d, *J*=8.0 Hz, 1H), 7.90 (d, *J*=9.0 Hz, 2H), 7.83 (d, *J*=8.0 Hz, 1H), 7.71–7.67 (m, 1H), 7.54–7.44 (m, 1H), 7.36 (d, *J*=9.0 Hz, 2H), 5.51 (s, 2H), 2.40 (s, 3H); ^{13}C NMR: δ 144.8, 140.6, 140.2, 139.7, 131.3, 130.9, 130.4, 130.1, 129.3, 128.8, 126.5, 122.4, 52.3, 22.1; LRMS (EI, 70 eV) *m/z* (%): 249 (M^++2, 11), 247 (M^+, 56), 232 (23), 219 (100).

*3-(5-Methylthiophen-2-yl)-8*H-*[1,2,3]triazolo[5,1-*a*]isoindole* (**2g**): Yellow solid; 66% yield; m.p. 183.1–184.7 °C (uncorrected) ^{1}H NMR: δ 7.52 (d, *J*=8.0 Hz, 1H), 7.48 (d, *J*=8.0 Hz, 1H), 7.43–7.39 (m, 3H), 6.82 (s, 2H), 5.35 (s, 2H); ^{13}C NMR: δ 147.8, 140.6, 137.7, 133.3, 131.0, 130.0, 129.2, 128.8, 127.5, 125.4, 125.3, 123.0, 119.3, 53.3; LRMS (EI, 70 eV) *m/z* (%): 255 (M^++2, 11), 253 (M^+, 26), 238 (52), 177 (32), 156 (100); HRMS (EI) for $C_{14}H_{11}N_3S(M^+)$: calcd 253.0734, found 253.0728.

*3-Octyl-8*H-*[1,2,3]triazolo[5,1-*a*]isoindole* (**2h**):[12] Pale yellow solid; yield 76%; m.p. 79.8–81.7 °C (lit.[12] 79–80 °C) (uncorrected) ^{1}H NMR: δ 7.61 (d, *J*=7.5 Hz, 1H), 7.51–7.45 (m, 2H), 7.38 (t, *J*=7.5 Hz, 1H), 5.30 (s, 2H), 2.94 (t, *J*=7.5 Hz, 2H), 1.82–1.77 (m, 2H), 1.42 (t, *J*=4.0 Hz, 2H), 1.39 (d, *J*=7.0 Hz, 2H), 1.34–1.25 (m, 6H), 0.87 (t, *J*=7.0 Hz, 3H); ^{13}C NMR: δ 140.6, 139.4, 139.3, 128.7, 128.5, 127.7, 124.1, 120.8, 50.9, 31.8, 29.6, 29.5, 29.3, 29.2, 29.1, 22.6, 14.1; LRMS (EI, 70 eV) *m/z* (%): 271 (M^++2, 24), 269(M^+, 33), 254 (12), 198 (31), 179 (46), 132 (100).

*8*H-*[1,2,3]Triazolo[5,1-*a*]isoindole* (**2i**):[3] Black solid; yield 74%; m.p. 83.8–85.4 °C (lit.[14] 84–86 °C) (uncorrected) ^{1}H NMR: δ 7.84 (s, 1H), 7.66 (d, *J*=7.5 Hz, 1H), 7.54 (t, *J*=7.5 Hz, 1H), 7.48 (t, *J*=7.5 Hz, 1H), 7.42 (t, *J*=7.5 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR: δ 141.9, 140.2, 128.9, 128.4, 124.2, 124.1, 121.7, 51.0; LRMS (EI, 70 eV) *m/z* (%): 159 (M^++2, 16), 157(M^+, 31), 129 (100).

*5-Methyl-3-phenyl-8*H-*[1,2,3]triazolo[5,1-*a*]isoindole* (**2j**): Brown solid; yield 83%; m.p. 180.5–181.6 °C. ^{1}H NMR: δ 7.84 (d, *J*=8.0 Hz, 2H), 7.78 (s, 1H), 7.42 (t, *J*=7.5 Hz, 2H), 7.33 (t, *J*=7.5 Hz, 2H), 7.12 (s, 2H), 5.66 (s, 2H), 2.34 (s, 3H); ^{13}C NMR: δ 147.9, 140.8, 133.5, 130.9, 130.4, 130.1, 128.9, 128.7, 128.0, 125.6, 123.2, 119.7, 53.5, 20.7; LRMS (EI, 70 eV) *m/z* (%): 249 (M^++2, 18), 247(M^+, 23), 232 (23), 155 (35), 115(100); HRMS (EI) for $C_{16}H_{13}N_3(M^+)$: calcd 247.1134, found 247.1131.

*5-Methyl-3-*p*-tolyl-8*H-*[1,2,3]triazolo[5,1-*a*]isoindole* (**2k**): Brown solid; yield 86%; m.p. 185.5–187.1 °C. ^{1}H NMR: δ 7.69 (t, *J*=8.5 Hz, 3H), 7.17 (d, *J*=8.0 Hz, 2H), 7.04 (s, 2H), 5.57 (s, 2H), 2.33 (s, 3H), 2.28 (s, 3H); ^{13}C NMR: δ 147.8, 140.6, 137.7, 133.3, 130.9, 129.9, 129.3, 128.8, 127.5, 125.4, 125.3, 123.0, 119.3, 53.3, 21.1, 20.6; LRMS (EI, 70 eV) *m/z* (%): 263 (M^++2, 21), 261 (M^+, 32), 231 (23), 203 (25), 129 (100); HRMS (EI) for $C_{17}H_{15}N_3(M^+)$: calcd 261.1325, found 261.1321.

*5-Methyl-3-(4-nitrophenyl)-8*H-*[1,2,3]triazolo[5,1-*a*]isoindole* (**2l**): Yellow solid; 74% yield; m.p. 191.2–192.4 °C. ^{1}H NMR: δ 8.23 (d, *J*=8.0 Hz, 2H), 7.97 (t, *J*=8.0 Hz, 2H), 7.46 (s, 1H), 7.20 (d, d, *J*=7.5 Hz, 1H), 7.14 (d, d, *J*=7.5 Hz, 1H), 5.69 (s, 2H), 2.34 (s, 3H); ^{13}C NMR: δ 147.1, 145.6, 141.2, 136.7, 133.7, 130.5, 129.1, 126.0, 124.1, 123.5, 121.2, 53.8; LRMS (EI, 70 eV) *m/z* (%): 294 (M^++2, 11), 292 (M^+, 34), 277(18), 246 (24), 155 (32), 127 (100); HRMS (EI) for $C_{16}H_{12}N_4O_2(M^+)$: calcd 292.1034, found 292.1031.

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