Synthesis of 6-trifluoromethylindolo[1,2-*c*]quinazolines and related heterocycles using *N*-(2-iodophenyl)trifluoroacetimidoyl chlorides as starting material *via* C–H bond functionalization†

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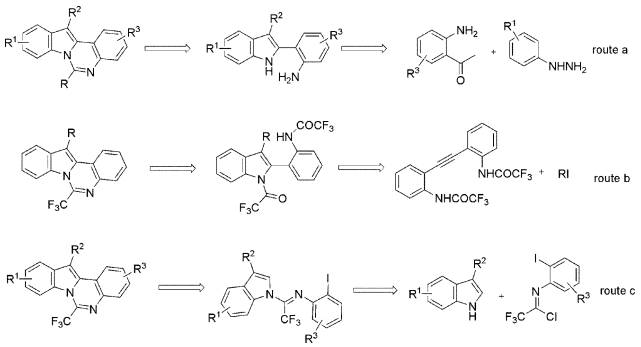
A mild, two-step reaction for the synthesis of 6-trifluoromethylindolo[1,2-*c*]quinazolines from readily available indoles and *N*-(2-iodophenyl)trifluoroacetimidoyl chlorides *via* addition–elimination/arylation is described. An array of aza-fused trifluoromethylated heterocycles can be easily assembled *via* Friedel–Crafts reaction/C–H bond activation by this methodology.

Indole scaffolds are one of the most extensively studied class of heterocyclic compounds, and have been increasingly attracting attention as bioactive natural products and their pharmaceutical implications.[1] Moreover, fused indole derivatives such as indolocarbazoles,[2] indoloisoquinolines,[3] indoloquinolines,[4] and indoloquinazolines[5] display a number of interesting pharmacological properties. Among them, indolo[1,2-*c*]quinazolines show potent activity against bacterial and fungal strains.[6] It's a known fact that the trifluoromethyl group can dramatically influence the properties of organic molecules, thereby increasing their applicability as pharmaceuticals, agrochemicals, or building blocks for synthetic materials.[7] Recently, our group has focused on the syntheses of fluorinated heterocycles by using *N*-phenyltrifluoroacetimidoyl halides as starting materials.[8] Here, we report a straightforward procedure to synthesize 6-trifluoromethyl indolo[1,2-*c*]quinazolines *via* palladium-catalyzed C–H functionalization of intermediary 1-(*N*-arylimino)indoles complexes, which can be easily prepared by addition–elimination reaction of *N*-phenyltrifluoroacetimidoyl chlorides with indoles. This strategy can also lead to the formation of other related trifluoromethylated heterocycles *via* Friedel–Crafts reaction/C–H bond activation.

6-Methyl- and 6-benzylindolo[1,2-*c*]quinazolines were synthesized by reacting acetyl and benzoyl chlorides with 2-(2′-amino)phenylindole, which was obtained by Fisher indole cyclization from the hydrazone of 2-aminophenyl ethyl ketone and phenylhydrazine condensation (route a, Scheme 1).[9] Trifluoro-methylated analogues were prepared by palladium-catalyzed reaction of readily available bis(*o*-trifluoroacetimidophenyl)acetylene with aryl or vinyl halides, followed by cyclization of the resultant derivatives (route b, Scheme 1).[10] These reported methods suffered from either limited availability of starting material or required multiple steps. Inspired by recent advances in the direct arylation of pyrroles and indoles with aryl halides,[11,3a] we designed another approach to construct 6-trifluoromethylindolo[1,2-*c*]quinazolines *via* palladium-catalyzed intramolecular cyclization of 1-(*N*-arylimino)indole derivatives, which can be easily assembled by reacting *N*-phenyltrifluoroacetimidoyl chlorides with indoles *via* the addition/elimination process (route c, Scheme 1).



Scheme 1 Methods for synthesis of indolo[1,2-*c*]quinazolines.

The cyclization precursor **2a** was typically prepared from reacting *N*-(2-iodophenyl)trifluoroacetimidoyl chloride **1a** with 3-methylindole by the addition/elimination process in the presence of butyllithium in THF at −78 °C in good yield. We subsequently investigated different palladium sources to identify an optimum catalyst for intramolecular cyclization of **2a**. We have studied palladium sources, such as $PdCl_2(PPh_3)_2$, Pd_2dba_3, $Pd(PPh_3)_4$, $Pd(OAc)_2/PPh_3$, and found that the $Pd(OAc)_2/PPh_3$ system was a desirable catalyst for this transformation. Optimization on the reaction was also performed against various bases and reaction media, the results were summarized in Table 1. It showed that the yields were nearly quantitative when bases like KOAc, K_3PO_4 and K_2CO_3 were used while Cs_2CO_3 only afforded the desired product in moderate yield (entries 1, 5–7, Table 1). It was found that DMF was the optimal solvent for this reaction, while other solvents (DMSO, CH_3CN, and toluene) resulted in lower yields (entries 2–4, Table 1).

The scope and limitation of the palladium-catalyzed cyclization reaction was explored by employing various indoles and *N*-aryltrifluoroacetimidoyl chlorides **1** containing a wide range of functional groups. *N*-Aryltrifluoroacetimidoyl chlorides **1** containing both electron-withdrawing and electron-donating groups were suitable substrates and gave the corresponding products in excellent yields (entries 5–11, Table 2). Electron-rich indoles showed better reactivity and

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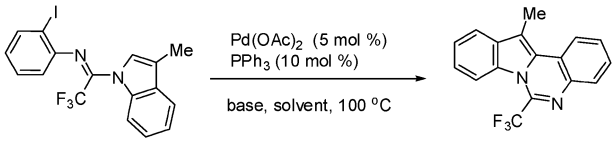
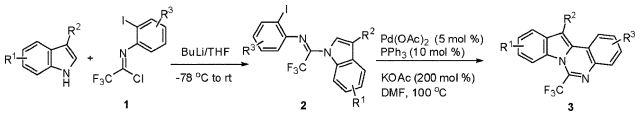
Table 1 Optimization of reaction conditions[a]



Entry	Base	Solvent	Time	Yield[b] (%)
1	KOAc	DMF	15 min	100 (96)
2	KOAc	DMSO	15 min	87
3	KOAc	CH_3CN	3 h	74
4	KOAc	toluene	3 h	34
5	K_2CO_3	DMF	15 min	97
6	K_3PO_4	DMF	15 min	100
7	Cs_2CO_3	DMF	15 min	60

[a] Conditions: **2a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), base (200 mol%), solvent (2 mL), 100 °C. [b] The yield was determined by ^{19}F NMR; isolated yield in parentheses.

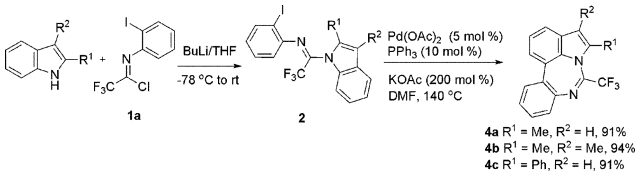
Table 2 Synthesis of various 6-trifluoromethylindolo[1,2-*c*]quinazolines[a]



Entry	R^1	R^2	R^3	Yield[c] (%)
1	H	H	H	**3b**/86
2	H	Ph	H	**3c**/88
3	H	Et	H	**3d**/90
4	H	Pr	H	**3e**/92
5	H	Me	3-OMe	**3f**/97
6	9-Me	H	2-Me	**3g**/87
7	H	Me	2-Me	**3h**/97
8	H	Me	2-F	**3i**/75
9	H	Me	2-Cl	**3j**/86
10	H	Me	2-CF_3	**3k**/96
11[b]	H	Me	2-NO_2	**3l**/67
12[b]	10-OMe	H	H	**3m**/88
13	8-Me	H	H	**3n**/92
14	11-Cl	H	H	**3o**/67
15	9-F	H	H	**3p**/58
16[b]	9-Cl	H	H	**3q**/54
17[b]	10-NO_2	H	H	**3r**/38
18[b]	10-Br	H	H	**3s**/50

[a] Conditions: **2** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), KOAc (200 mol%), DMF (2 mL), 15 min, 100 °C. [b] The reaction temperature was elevated to 140 °C. [c] Yields of isolated products.

furnished the desired products in good yields (entries 12 and 13, Table 2). In agreement to previous reports,[12] the reaction of other electron-deficient indoles gave the indolo[1,2-*c*]quinazolines in moderate yields, which was in accordance with the mechanism of the electrophilic aromatic substitution at the palladium center (S_EAr) (entries 14–18, Table 2). Other halide substitutions (*e.g.*, Cl, Br) survived under our optimal reaction conditions, providing a useful handle for further cross-coupling reactions (entries 9, 14, 16, and 18, Table 2). 3-Substituted indoles (*e.g.*, 3-ethyl, 3-phenyl and 3-propyl) could be effectively converted to the corresponding products (entries 2–4, Table 2). *N*-(2-Bromophenyl)trifluoroacetimidoyl chloride afforded product **3a** in 78% yield although an elevated temperature of 140 °C was needed in order to drive the reaction



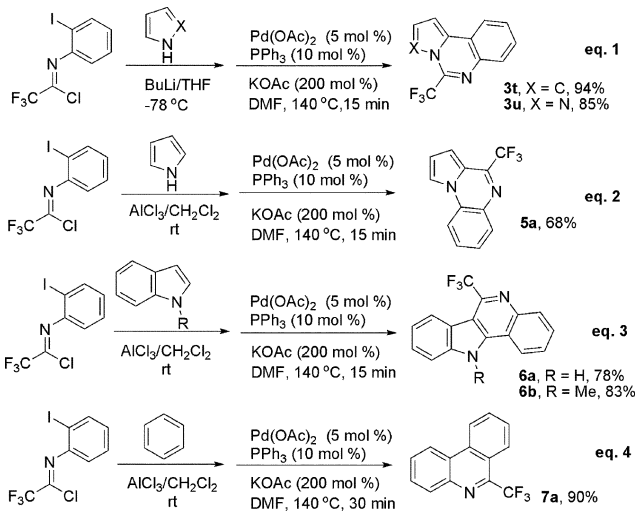
Scheme 2 Formation of an expanded seven-membered ring.

to completion. However, only a trace amount of the desired product **3a** was detected when *N*-(2-chlorophenyl)trifluoroacetimidoyl chloride was used, even under prolonged heating at the above temperature. The polycyclic products **3** were fully characterized by ^1H and ^{13}C NMR methods and mass spectroscopic data. The structure of product **3i** was further confirmed by X-ray crystallographic analysis.†

When the 2-position of the indole moiety was blocked by a methyl or phenyl group, an expanded seven-membered fused ring product **4** was obtained in excellent yields at 140 °C (Scheme 2). The structure of **4c** was unambiguously confirmed by X-ray analysis.† The formation of the seven-membered ring *via* palladium-catalyzed direct arylation is uncommon hence rarely reported.[13]

The reaction was then successfully extended to pyrrole and pyrazole, affording pyrrolo[1,2-*c*]quinazoline **3t** and pyrazolo-[1,5-*c*]quinazoline **3u** in good yields (eqn (1), Scheme 3). We also explored *N*-(2-iodophenyl)trifluoroacetimidoyl chlorides with indoles, pyrrole and benzene *via* Friedel–Crafts reaction to acquire the corresponding intermediate for the direct arylation. By this methodology, some other related trifluoromethylated heterocycles, such as pyrrolo[1,2-*a*]quinoxaline **5a** (eqn (2), Scheme 3), indolo[3,2-*c*]quinolines **6a** and **6b** (eqn (3), Scheme 3), and 6-(trifluoromethyl)phenanthridine **7a** (eqn (4), Scheme 3), were obtained in moderate to good yields.

In conclusion, we have developed an efficient two-step reaction for the synthesis of substituted 6-trifluoromethylindolo [1,2-*c*]quinazolines from *N*-(2-iodophenyl)trifluoroacetimidoyl chlorides and indoles *via* addition–elimination and subsequent palladium-catalyzed arylation. When the 2-position of indole was blocked by substitutions, a seven-membered ring was formed instead. The applicability of the methodology has been



Scheme 3 Synthesis of other related trifluoromethylated heterocycles.

demonstrated by a rapid synthesis of other trifluoromethylated polyheterocycles *via* Friedel–Crafts reaction/C–H bond functionalization using *N*-(2-iodophenyl)trifluoroacetimidoyl chlorides as building blocks.

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