One Pot “Click” Synthesis of 1-N-alkyl-4-Aryl-1,2,3-triazoles From Protected Arylalkynes and Alkyl Bromides.

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Experimental section

General Procedures

Commercial chemicals were used as supplied. All experiments were carried out with freshly distilled anhydrous solvents obtained from a Pure Solv™ solvent purification system from Innovative Technologies except where specifically mentioned. N,N,N-Triethylamine (Et₃N), N,N-diisopropylamine (iPr₂NH) were distilled over CaH₂ under a nitrogen atmosphere. Solvents employed for the Click reaction were used without further purification; lab grade methanol was purchased and deionised water was accessible within the laboratory. 1-Bromo-4-methoxybenzene,⁠¹ 4-bromo-N,N-dimethylaniline,⁠¹ 2-bromo-5-iodopyridine,⁠¹ and 5-bromo-2-iodopyridine² were prepared following literature procedures and their characterization corresponds to that found in the literature.

All reactions were performed using standard Schlenck techniques under an inert (N₂) atmosphere, save for the Click reactions. Flash column chromatography was performed using silica gel (Silia-P from Silicycle, 60 Å, 40-63μm). Analytical thin layer chromatography (TLC) was performed with silica plates with aluminum backings (250 μm with indicator F-254). Compounds were visualized under UV light. ¹H and ¹³C NMR spectra were recorded on either a Brucker Avance spectrometer at 400 MHz and 100 MHz, respectively or a Brucker Avance spectrometer 300 MHz and 75MHz, respectively. The following abbreviations have been used for multiplicity assignments: “s” for singlet, “d” for doublet, “t” for triplet, “m” for multiplet, and “br” for broad. Deuterated cholorform (CDCl₃) was used as the solvent of record except where noted below. Spectra were referenced to the solvent peak. Melting points (Mp’s) were recorded using open-end capillaries on a Meltemp melting point apparatus and are uncorrected. GC-MS samples were separated on a Shimadzu HP5-MS 30 m x 0.25 mm ID x 0.25 μm film thickness column. High resolution mass spectra were recorded on a VG Micromass ZAB-2F at the Université de Sherbrooke.
Synthesis.

**General procedures for formation of arylethynyltrimethylsilanes:**

**Procedure A:**
Palladium (0) tetrakistriphenylphosphine (0.5 mol%) and Cu(I) (1.0 mol%) were degassed in a flame-dried RBF. Triethylamine (0.3 to 0.4 M) was added with the desired bromoarene, (1.00 equiv.). The solution was degassed again and then trimethylsilyl acetylene (TMSA) was added (1.50 equiv.). The reaction mixture was heated to reflux for a 24 h period and then allowed to cool to room temperature. The black solution was diluted with DCM and then treated with 0.1 N HClaq until the aqueous layer was at pH = 1. The aqueous solutions were extracted multiple times with DCM. All organic phases were combined, dried with anhydrous magnesium sulfate, filtered on a Celite ® plug and concentrated under reduced pressure to obtain the crude product. The product was purified via flash column chromatography using silica gel as stationary phase and hexanes or a mixture of hexanes and EtOAc to obtain the final product. All products obtain by this method were characterized by $^1$H and $^{13}$C NMR, GC-MS, LR-MS and HR-MS and Mp, when applicable. Compound characterization matched those found in the literature. For detailed references see below.

**Trimethyl(phenylethynyl)silane (1a):**

\[
\begin{align*}
\text{TMS} & \\
\text{C} & \equiv \text{C} \\
\end{align*}
\]

Clear Oil (99 %). The compound characterization is in agreement with that previously reported.3

**((2,4-Difluorophenyl)ethynyl)trimethylsilane (1g):**

\[
\begin{align*}
\text{F} & \\
\text{C} & \equiv \text{C} \\
\end{align*}
\]

Clear Oil (95 %). $R_f$: 0.38 (Hexanes). $^1$H NMR (CDCl₃) $\delta$ (ppm) : 7.17 (dd, J = 8.1, 15.2 Hz, 1H), 6.55 (dd, J = 5.1, 12.8 Hz, 2H), 0.00 (s, 9H). $^{13}$C NMR (CDCl₃) $\delta$ (ppm) : 164.5 (dd, J = 11.8, 66.0 Hz), 162.0 (dd J = 11.8, 63.7 Hz), 135.0 (dd, J = 2.6, 9.8 Hz),
111.6 (dd, J = 3.8, 21.4 Hz), 108.3 (dd, J = 4.0, 16.0 Hz), 104.4 (t, J = 25.4 Hz), 100.0 (s), 97.0 (s), 0.01 (s). GC-MS (m/z): 100% = 210 (7.49 min). LR-MS (EI, 70eV) (m/z): 210 (M+), 195, 133, 77. HR-MS: Found: 210.0679; Calculated: (C₁₁H₁₂F₂Si) 210.0676.

2-((Trimethylsilyl)ethynyl)pyridine (1n):

Brown oil (86 %). The compound characterization is in agreement with that previously reported.⁴

Trimethyl(naphthalen-1-ylethynyl)silane (1m):

Black oil (90 %). The compound characterization is in agreement with that previously reported.⁵

Trimethyl((4-nitrophenyl)ethynyl)silane (1i):

Beige solid (48 %). The compound characterization is in agreement with that previously reported.⁶

Trimethyl((2-nitrophenyl)ethynyl)silane (1k):

Beige solid (59 %). The compound characterization is in agreement with that previously reported.⁷

Trimethyl((3-nitrophenyl)ethynyl)silane (1j):
White solid (83 %). The compound characterization is in agreement with that previously reported. \(^8\)

**Trimethyl(thiophen-2-ylethynyl)silane (1o):**

\[
\text{S} \quad \equiv \quad \text{TMS}
\]

Brown oil (75 %). The compound characterization is in agreement with that previously reported. \(^9\)

**Methyl 4-((trimethylsilyl)ethynyl)benzoate (1h):**

\[
\text{MeO} \quad \equiv \quad \text{TMS}
\]

Beige solid (91 %). The compound characterization is in agreement with that previously reported. \(^10\)

**2,5-bis((trimethylsilyl)ethynyl)pyridine (1q):**

\[
\text{TMS} \quad \equiv \quad \text{N} \quad \equiv \quad \text{TMS}
\]

Beige solid (93 %). The compound characterization is in agreement with that previously reported. \(^11\)

**((4-Bromophenyl)ethynyl)trimethylsilane (1f):**

\[
\text{Br} \quad \equiv \quad \text{TMS}
\]

Beige solid (52 %). The compound characterization is in agreement with that previously reported. \(^12\)

**5-Bromo-2-((trimethylsilyl)ethynyl)pyridine (1p):**

\[
\text{Br} \quad \equiv \quad \text{TMS}
\]

Beige solid (97 %). The compound characterization is in agreement with that previously reported. \(^13\)

**5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (1r):**
Brown solid (94%). \textbf{Rf}: 0.38 (10\% EtOAc/Hexanes). \textbf{Mp}: 53-55 ^\circ\text{C}. \textit{Litt.}: 45-46 ^\circ\text{C}.\textsuperscript{14}

\textbf{1H NMR (300 MHz, CDCl}_3\textbf{)} \: \delta \textbf{(ppm)}: 8.73 (d, \textit{J} = 1.8 Hz, 1H), 8.68 (d, \textit{J} = 4.3 Hz, 1H), 8.38 (dd, \textit{J} = 11.7, 8.1 Hz, 2H), 7.87 (dd, \textit{J} = 8.3, 2.2 Hz, 1H), 7.85 - 7.77 (m, 1H), 7.32 (ddd, \textit{J} = 7.3, 4.7, 0.9 Hz, 1H), 0.28 (s, 9H).

\textbf{13C NMR (75 MHz, CDCl}_3\textbf{)} \: \delta \textbf{(ppm)}: 155.6, 155.1, 152.2, 149.4, 139.9, 137.1, 124.1, 121.5, 120.3, 101.9, 99.3, -0.02. \textbf{LR-MS (EI, 70eV)) m/z): 252 (M^+), 237, 221. \textbf{HR-MS (EI, 70eV)}: \textit{Calculated}: 252.1083 \textbf{Found}: 252.1088. The \textbf{1H NMR} spectrum is in agreement with that previously reported.\textsuperscript{14} but the \textbf{13C NMR} spectrum was found to be different.

4-((Trimethylsilyl)ethyl)ynyl)phenyl acetate (4):

Beige solid (86 \%). \textbf{Rf}: 0.52 (20\% EtOAc/Hexanes). \textbf{Mp}: 73\textdegree\text{C}. \textbf{1H NMR (400 MHz, CDCl}_3\textbf{)} \: \delta \textbf{(ppm)}: 7.47 (d, \textit{J} = 8.8 Hz, 2H), 7.03 (d, \textit{J} = 8.8 Hz, 2H), 2.29 (s, 3H), 0.24 (s, 8H). \textbf{13C NMR (101 MHz, CDCl}_3\textbf{)} \: \delta \textbf{(ppm)}: 169.1, 150.6, 133.2, 121.6, 120.9, 104.2, 94.4, 21.2, 0.0. \textbf{LR-MS (EI, 70eV)) m/z): 232 (M^+), 217, 190, 175, 146, 115, 105. \textbf{HR-MS (EI, 70eV)}: \textit{Calculated}: 232.0920 \textbf{Found}: 232.0925.

**Procedure B:**

Palladium (II) Acetate trimer (3.0 mol\%), tri-\textit{tert}-butylphosphonium tetrafluoroborate (6.0 mol\%) and Cu(I)I (0.60 mol\%) were degassed in a flame-dried RBF. A triethylamine / diisopropylamine (1/1) (0.3 to 0.4 M in total) mixture was added with the desired bromoarene (1.00 equiv.). The solution was degassed and the TMSA was added (1.50 equiv.). The reaction mixture was heated to reflux for a 24 h period and progression of the reaction was followed by GC-MS. The reaction mixture was cooled to room temperature. The black solution was diluted with DMC and treated with 0.1 \textit{N HCl} \textit{aq} until the aqueous layer was at pH = 1. The aqueous solutions were extracted multiple times with DCM. All organic phases were combined, dried with anhydrous magnesium sulfate, filtered onto a Celite ® plug and concentrated under reduced pressure to obtain the crude product. The product was purified via flash column chromatography using silica gel as
stationary phase and hexanes or a mixture of hexanes and EtOAc to obtain the final product. All products obtained by this method were characterized by $^1$H and $^{13}$C NMR, GC-MS, LR-MS and HR-MS and Mp, when applicable. Compound characterization matched those found in the literature. For detailed references see below.

((4-Methoxyphenyl)ethynyl)trimethylsilane (1c):

Yellow oil (93 %). The compound characterization is in agreement with that previously reported.$^9$

((3-Methoxyphenyl)ethynyl)trimethylsilane (1d):

Brown oil (92 %). R$_f$: 0.47 (Hexanes). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) : 7.20 (t, $J = 8.0$ Hz, 1H), 7.07 (dt, $J = 7.6$, 1.2 Hz, 1H), 6.99 (dd, $J = 2.6$, 1.4 Hz, 1H), 6.87 (ddd, $J = 8.4$, 2.7, 1.1 Hz, 1H), 3.80 (s, 3H), 0.26 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm): 159.3, 129.4, 124.7, 124.2, 116.6, 115.5, 105.1, 55.4, 0.11. LR-MS (EI, 70eV) (m/z): 204 (M$^+$), 289, 146. HR-MS (EI, 70eV): Calculated: 204.0970 Found: 204.0975. The compound characterization for $^1$H NMR is in agreement with that previously reported.$^{15}$

N,N-Dimethyl-4-((trimethylsilyl)ethynyl)aniline (1e):

Yellow solid (87 %). The compound characterization is in agreement with that previously reported.$^{10}$

Miscellaneous syntheses

General procedure for synthesis of 5,5'-disubstituted-2,2'-bipyridines by Negishi coupling:

\[
\begin{array}{c}
\text{TMS} \quad \text{Br}
\end{array}
\text{a) BuLi, THF, -78°C}
\begin{array}{c}
\text{ZnCl$_2$, THF, -78°C to r.t.}
\end{array}
\begin{array}{c}
Pd(PPh$_3$)$_4$, THF, reflux
\end{array}
\begin{array}{c}
\text{TMS} \quad \text{R}
\end{array}
\begin{array}{c}
\text{R} = H, \text{TMS} \quad \text{Br}
\end{array}
\]

S7
To a degassed solution of 1p (1.00 equiv.) in 0.1 M THF at -78 °C was added n-BuLi (1.82 M solution in hexanes, 2.00 equiv.) over 30 minutes. The solution was then allowed to stir at -78 °C for a further 20 minutes. To this solution was added via cannula a 0.4 M THF solution of anhydrous ZnCl₂ at RT (2 equiv.). After the addition, the blackish reaction mixture was allowed to slowly warm to RT. The resulting zincate was cannulated into a degassed solution of the desired 2-bromo-5-R₁-pyridine (1.00 equiv.) and Pd(PPh₃)₄ (5.0 mol%) in THF (0.1 M). The solution was again degassed and heated to reflux for 18 h. The reaction mixture was cooled then diluted with DCM and the crude solution was treated with a basic saturated EDTA solution (EDTAₐq and NaHCO₃ₐq). The resulting mixture was extracted 2x with DCM. The combined organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure and then in vacuo. The products were purified by flash chromatography on silica gel using DCM as mobile phase.

5,5'-bis((trimethylsilyl)ethyl)-2,2'-bipyridine (1s):

\[
\text{TMS} = \begin{array}{c}
\text{N} \\
\text{Br}
\end{array} \quad \text{a) BuLi, THF, -78°C} \\
\begin{array}{c}
\text{TMS} \\
\text{Br}
\end{array} \quad \text{b) ZnCl₂, THF, -78°C to r.t.} \\
\begin{array}{c}
\text{Br} \\
\text{TMS}
\end{array} \quad \text{c) Pd(PPh₃)₄, THF, reflux}
\]

Light brown solid (35 %). The compound characterization is in agreement with that previously reported.¹⁶

5-((trimethylsilyl)ethyl)-2,2'-bipyridine (5):

\[
\begin{array}{c}
\text{N} \\
\text{Br}
\end{array} \quad \text{a) BuLi, THF, -78°C} \\
\begin{array}{c}
\text{N} \\
\text{Br}
\end{array} \quad \text{b) ZnCl₂, THF, -78°C to r.t.} \\
\begin{array}{c}
\text{Br} \\
\text{N}
\end{array} \quad \text{c) Pd(PPh₃)₄, THF, reflux}
\]

Light brown solid (60 %). The compound characterization is in agreement with that previously reported.¹⁷
Miscellaneous syntheses

Synthesis of 4-((Trimethylsilyl)ethynyl)phenol (1b):

\[
\text{HO-} - \text{TMS} \quad \rightarrow \quad \text{OH}
\]

The corresponding acetate 4 (498.4 mg, 2.14 mmol, 1.00 equiv.) was dissolved in a mixture of THF, methanol and water (15ml; 1/1/1) to obtain a concentration of ca. 0.15 M. The solution was cooled to 0°C and lithium hydroxide monohydrate (185.4 mg, 4.42 mmol, 2.05 equiv.) was added. The solution was stirred for 30 min and the reaction progression was followed by TLC. The reaction mixture was diluted in 1N HCl_aq (50 mL) and was extracted with Et_2O. All organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to obtain a brown oil. The crude product was purified by flash chromatography column using a gradient of 10 to 15% EtOAc in hexanes. White solid (347.0 mg; 85%). The characterization was found to be different than that found in the literature.\textsuperscript{18} \textbf{Rf:} 0.25 (20% Et_2O/Hexanes). \textbf{Mp :} 63-64 °C. \textbf{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\textsuperscript{)} \delta (ppm): 7.36 (d, \textit{J} = 8.8 Hz, 2H), 6.75 (d, \textit{J} = 8.8 Hz, 2H), 5.24 (s, 1H), 0.24 (s, 9H). \textbf{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\textsuperscript{)} \delta (ppm): 155.8, 133.8, 115.6, 115.5, 115.5, 105.3, 92.8, 0.2. \textbf{LR-MS (EI, 70eV) (m/z):} 190 (M\textsuperscript{+}), 175, 115, 87. \textbf{HR-MS (EI, 70eV): Calculated:} 190.0814 \textbf{Found:} 190.0817.

Synthesis of 6-iodohexanol (6):

\[
\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}
\]

A DCM solution (ca. 0.50 M) of 1,6-hexanediol (1.50 g, 12.7 mmol, 1.00 equiv.) was prepared in a RBF covered with aluminum foil. Imidazole (957.3 mg, 14.1 mmol, 1.10 equiv.), triphenylphosphine (3.68 g, 14.0 mmol, 1.10 equiv.) and iodine (3.26 g, 12.7 mmol, 1.00 equiv.) were respectively added to the previous solution at room temperature. The reaction mixture was left for 4 h until reaction completion was obtained as determined by TLC. The reaction mixture was diluted with water and the layers were separated. The organic layer was washed 2x with a saturated sodium thiosulfate. The aqueous layers were combined and extracted with DCM. The organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure to afford a white solid. This crude product was purified via a flash column chromatography
using a gradient of 20 to 40% EtOAc in hexanes. Yellow oil (1.14 g, 39%). The compound characterization is in agreement with that previously reported.\textsuperscript{19}

**Synthesis of 1,3,5-tris(bromomethyl)benzene (7):**

To a suspension of LiAlH\textsubscript{4} (900 mg, 23.7 mmol, 3.30 equiv.) in THF (120 mL) cooled to 0°C was added dropwise benzene-1,3,5-tricarboxylic acid (1.50 g, 7.14 mmol, 1.00 equiv.) in THF (60 mL). The mixture was stirred for 0.5 h after the addition and then was heated to reflux for 20 h. The reaction was cooled to room temperature. To the mixture was added water (3 mL) and the reaction mixture was stirred for 1 h. The solvents were evaporated to dryness. To the crude salt was added an aqueous solution of HBr (48% wt, 45 mL) and benzene (75 mL). The mixture was heated to reflux for 2 days. The reaction was followed by TLC until 100% conversion was observed. The reaction mixture was cooled to room temperature. The benzene layer was separated and the aqueous phase was washed with Et\textsubscript{2}O (3 x 50 mL). The organic phases were combined and dried over MgSO\textsubscript{4}. The organic phase was filtered and then concentrated under reduced pressure to yield a white solid (2.20 g, 88%). The compound characterization is in agreement with that previously reported.\textsuperscript{20}
Spectra:

((2,4-Difluorophenyl)ethynyl)trimethylsilane (1g):
5-((trimethylsilyl)ethynyl)-2,2'-bipyridine (1r):
4-((Trimethylsilyl)ethynyl)phenyl acetate (4):
((3-Methoxyphenyl)ethynyl)trimethylsilane (1d):
4-((Trimethylsilyl)ethynyl)phenol (1b):
1-benzyl-4-phenyl-1H-1,2,3-triazole (2a) and 1-benzyl-5-phenyl-1H-1,2,3-triazole (3a) mixture:
1-benzyl-4-phenyl-1H-1,2,3-triazole (2a):
1-benzyl-4-(2,4-difluorophenyl)-1H-1,2,3-triazole (2g):
2-(1-benzyl-1H-1,2,3-triazol-4-yl)pyridine (2n):
1-benzyl-4-(naphthalen-1-yl)-1H-1,2,3-triazole (2m):
1-benzyl-4-(4-nitrophenyl)-1H-1,2,3-triazole (2i):
1-benzyl-4-(2-nitrophenyl)-1H-1,2,3-triazole (2k):
1-benzyl-4-(3-nitrophenyl)-1H-1,2,3-triazole (2j):
1-benzyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole (2c):
4-(1-benzyl-1H-1,2,3-triazol-4-yl)-N,N-dimethylaniline (2e):
Mixture of 1-benzyl-4-(thiophen-2-yl)-1H-1,2,3-triazole (2o) and 1-benzyl-5-(thiophen-2-yl)-1H-1,2,3-triazole (3o):
methyl 4-(1-benzyl-1H-1,2,3-triazol-4-yl)benzoate (2h):
1-benzyl-4-(3-methoxyphenyl)-1H-1,2,3-triazole (2d):
1-benzyl-4-(4-bromophenyl)-1H-1,2,3-triazole (2f):
5-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-bromopyridine (2p):
2,5-bis(1-benzyl-1H-1,2,3-triazol-4-yl)pyridine (2q):
4-(1-benzyl-1H-1,2,3-triazol-4-yl)phenol (2b):
1-benzyl-4-o-tolyl-1H-1,2,3-triazole (2l):
5-(1-benzyl-1H-1,2,3-triazol-4-yl)-2,2'-bipyridine (2r):
5,5'-bis(1-benzyl-1H-1,2,3-triazol-4-yl)-2,2'-bipyridine (2s):
4-(4-methoxyphenyl)-1-methyl-1H-1,2,3-triazole (2t):
1-allyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole (2x):
1-hexyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole (2v):
[Image of a graph or diagram with chemical structures and data points]
6-(4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl)hexan-1-ol (2w) :
1,3,5-tris((4-(2,4-difluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)benzene (2y):
References