Published in final edited form as:

European J Org Chem. 2014 September 1; 2014(26): 5786–5792. doi:10.1002/ejoc.201402748.

Synthesis of Pyrrolidines and Pyrroles via Tandem Amination/Cyanation/Alkylation and Amination/Oxidation Sequences

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Abstract

Starting from a primary amine-tethered alkyne **1**, a copper-catalyzed three-component tandem amination/cyanation/alkylation sequence gives α -CN pyrrolidine **6** in good yield and regioselectivity. Also, a silver mediated tandem amination/oxidation of a secondary amine-tethered alkyne **7** produces functionalized pyrrole **8** in good yield. All reactions were conducted in one pot without any protection/deprotection steps.

Keywords

amination; tandem; pyrrolidines; pyrroles; cyanation

Introduction

N-heterocycles of different ring sizes and different substitution patterns are among the most common synthetic intermediates and the most important structural classes in medicinal chemistry.^[1] Although the synthesis of N-heterocycles has been around for over a century and a variety of well-established methods like cyclization of amine tethered C-C unsaturated system are available,^[2] there are still unmet needs to carry concise and efficient synthesis of structurally more complex N-heterocycles. The need to map new chemical spaces through tandem or cascade reactions^[3] in an atom economical fashion inspired us to develop a strategy to access heterocycles of different ring sizes, with different substitution patterns through cyclization triggered tandem reactions (Scheme 1). We applied this strategy successfully to tandem amination/alkynylation,^[4] tandem amination/cyanation,^[5] tandem amination/trifluoromethylation,^[5] and tandem amination/phosphorylation sequences^[6] (Scheme 1a).

Results and Discussion

We now report an expansion of our tandem strategy that includes primary amines tethered to alkynes and a new amination/oxidation sequence, both shown in Scheme 1b. This expansion led to a 3-component synthesis of α -CN pyrrolidines and a versatile synthesis of functionalized pyrroles (Scheme 1b). All these reactions were carried out in one pot without the need for protection/deprotection steps.

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Scanned copies of NMR spectroscopies for compounds **6** and **8** can be found in supporting information.

In our earlier work (Scheme 1a), the starting material used was a secondary amine-tethered alkyne, which cyclized via an enamine intermediate. When we started out with a primary amine-tethered alkyne, such as **1a**, the tandem amination/cyanation sequence, using our published conditions,^[5] gave only 46% of the desired product **4a** (Table 1, entry 1). The major byproduct of this reaction was imine **3a**. Increasing the amount of trimethylsilyl cyanide and changing the temperature did not improve the yield significantly (Table 1, entries 2–5). We also found that **4a** was unstable toward silica gel chromatography. We explained this result by invoking a thermodynamic equilibrium between **3a** and **4a** that prevented its complete conversion to **4a**.

We speculated that if the nitrogen in **4a** could be further substituted the resulting tertiary amine would be rendered more stable. This strategy succeeded using chloroacetonitrile **5a** as the alkylating reagent (Table 2, entry 1). And we also found that acetonitrile was a better solvent for this transformation (Table 2, entry 2). Reducing the amount of **5a** slightly increased the yield (Table 2, entry 3) and conventional heating also worked well (Table 2, entry 4), though longer reaction times were needed. Under the same optimized conditions, however, the reaction of the internal alkyne-tethered amine **1c** was sluggish (Table 2, entry 5), probably because the imine intermediate was less reactive. We solved this problem by adding a Lewis acid co-catalyst – Sc(OTf)₃, which is known to activate imines toward nucleophilic attack.^[7]

The reaction scope of our new three-component tandem reaction is tabulated in Table 3. A variety of alkylation reagents were compatible with our tandem reaction sequence (Table 3, entries 1–4, condition A). In general, the use of Sc(OTf)₃ as co-catalyst was helpful if the reaction was sluggish^[7] (Table 3, entries 5–9). Use of Sc(OTf)₃ can significantly increase rate of reactions and improve the chemical yields (Table 3, entries 5–9, condition B). **6f**, **6g** and **6h** were formed as closed to 1:1 mixtures of diastereoisomers.

We also tested reaction primary amines with no geminal groups (**1d**, **1e**). Both of them didn't give the desired products under same condition in Table 3 (eqs 1–2), only a complex mixture was obtained. Changing to more powerful hydroamination catalyst (IPrAu-OTf) and using alkyl meslate instead of alkyl halide were not helpful also (eqs 3–4).

Our proposed mechanism for the formation of **6** is shown in Scheme 2. The alkylation step could occur in the beginning (pathway A) or in the last step of the reaction (pathway B). We favored pathway B because, as shown in Scheme 3, **1a** is known to cyclize to imine **3a** easily in the presence of a copper catalyst, due to Thorpe–Ingold effect or gem-dimethyl effect.^[8] And the isolated **3a** is prone to react with TMS-CN. Our unsuccessful attempts for reactions of primary amines with no geminal groups (**1d**, **1e**) can also be rationalized by pathway B. Cyclization of **1d** or **1e** is much slower and less selective than cyclization of **1a**. Indeed cyclization of **1d** gave a complex mixture (eq 5). Since corresponding imine cannot be formed selectively, according to pathway B, tandem cyanation/alkylation product can be obtained.

When the starting material was a mixture of **3a** and **4a**, we obtained the final product **6d** in good yield, using the same standard reaction conditions (Scheme 3).

We then turned our attention to the tandem amination/oxidation sequence. Knölker and coworkers have reported a silver(I)-promoted oxidative cyclization of homopropargylamines to yield pyrroles, but their method has only limited scope (only 2 substrates reported).^[9] Because we had already reported that hydroamination was a reversible process and the

migration of the triple bond was plausible,^[5] we were confident that homopropargylamines were not the only starting materials that could be employed in our protocol. Thus, we chose 5-yn-amine **7a**, where the N atom is separated from the alkyne carbon by a 4-carbon chain. Even though the most favored cyclization path for **7a** is the 6-exo-dig pathway,^[5] we did not observe the formation of a six-membered ring, rather, the pyrrole product **8a** was obtained in the presence of catalytic amounts of AgF (Table 4, entry 1), albeit the yield was very low (6%). A stoichiometric amount of silver was needed to increase the yield (Table 4, entry 2). The reaction was cleaner if it was conducted at room temperature (Table 4, entry 3). We also investigated the effect of different silver salts. Silver acetate exhibited the highest activity while other silver salts, such as silver nitrate, only generated trace amounts of product (Table 4, entries 3, 9 and 10). A screening of various solvents demonstrated that DCM was the most appropriate for the reaction (Table 4, entry 5). In general, 2 equivalent of silver acetate and longer reaction times gave better yields (Table 4, entries 7–8). Our attempt to reduce the amount of silver salt by using a catalytic amount of silver acetate in combination with an oxidant was unsuccessful (Table 4, entry 13).

The scope of our pyrrole synthesis is depicted in Table 5. This reaction worked well for both aliphatic and aromatic amines tethered to the alkyne starting material **7** when the carbon chain link between the amine and alkyne moieties is between 2–4 carbons. Typically, a silver fluoride salt furnished better yields when the starting material was a substituted aniline.

A reasonable mechanism for the formation of pyrrole **8a** is illustrated in Scheme 4. Hydroamination of 5-yn-amine **7a** produces a six-membered enamine **9** through a 6-exo-dig pathway.^[5] Migration of the double bond in enamine **9** yields **10**; hydroamination in the presence of a metal catalyst is a reversible process,^[5] therefore upon retro-hydroamination, **10** delivers alkyne **11**, which undergoes a second round of the hydroamination-migration protocol (i.e., **11** to **13**), similar to the one described from **7** to **10**. Oxidation or dehydrogenation of **13** with the silver oxidant furnishes the final pyrrole product **8a**.^[9]

Conclusions

In summary, our copper-catalyzed three-component tandem amination/cyanation /alkylation sequence gives α -CN pyrrolidine **6** in good yield and regioselectivity. Also, a silver mediated tandem amination/oxidation of a secondary amine-tethered alkyne **7** produces functionalized pyrrole **8** in good yields.

Experimental Section

Compounds **1a–c** were synthesized using a literature method.^[10] **7** was synthesized using our previous published method.^[5]

General procedure for synthesis of **6**

Amino alkyne **1a** (43 mg, 0.25 mmol), trimethylsilyl cyanide (99 mg, 1.0 mmol), dioxane (1 mL) and water (4.5 mg, 1.0 equiv) were charged into a microwave tube reactor, and CuBr (1.8 mg, 5% equiv) was added to the mixture under stirring. After all the starting materials

were dissolved, the microwave tube reactor was flushed with argon. Then the reaction mixture was heated to 100°C under microwave irradiation for 0.5 h. The resulting reaction mixture was directly concentrated in a rotary evaporator and purified by silica gel flash chromatography (4:1 hexane:ether) to give a yellow liquid **4a** (48 mg, 95%).

General procedure for synthesis of **8**

Amino alkyne **7a** (61 mg, 0.25 mmol) and silver acetate (63 mg, 0.375 mmol) and DCM (1 mL) were added to a glass vial. The mixture was stirred for 40 h at room temperature and was concentrated immediately after in a rotary evaporator and purified by silica gel flash chromatography (5:1 hexane:ether) to give a yellow liquid **8a** (45 mg, 74%).

5-Methyl-3,3-diphenyl-3,4-dihydro-2H-pyrrole (3a)—Yellow solid. IR (KBr disk): 3289, 3065, 2949, 2865, 1644, 1602, 1495, 1448, 1378, 1304, 1033, 754, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 2.08 (s, 3H), 3.20 (s, 2H), 4.45 (s, 2H), 7.08–7.33 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 20.2, 52.6, 56.3, 73.1, 126.2, 127.0, 128.4, 147.9, 174.4. ESI-HRMS (ESI+): m/z calcd. for C₁₇H₁₇N (M⁺ + H) 236.1434, found 236.1431.

1-(Cyanomethyl)-2-methyl-4,4-diphenylpyrrolidine-2-carbonitrile (6a)—Yellow oil (70.1 mg, 93% yield); IR (neat): 3457, 3027, 2970, 2810, 2215, 1739, 1446, 1366, 1217, 734, 695 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.56 (s, 3H), 2.69 (d, *J* = 11.2 Hz, 1H), 3.35 (d, *J* = 7.6 Hz, 1H), 3.44 (d, *J* = 11.2 Hz, 1H), 3.55 (d, *J* = 13.6 Hz, 1H), 3.79 (d, *J* = 13.6 Hz, 1H), 4.12 (d, *J* = 7.6 Hz, 1H), 7.17–7.41 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 24.5, 37.3, 51.7, 52.4, 60.6, 64.4, 115.7, 119.2, 126.5, 126.6, 126.9, 127.0, 128.6, 128.7, 145.3, 150.0; ESI-HRMS (ESI+): m/z calcd. for C₂₅H₂₄N₂ (M⁺ - CN) 326.1908, found 326.1906.

2-(2-Cyano-2-methyl-4,4-diphenylpyrrolidin-1-yl)acetamide (6b)—Brown solid (73.5 mg, 92% yield). Mp 151.2 – 154.7 °C. IR (neat): 3446, 3210, 3170, 2960, 2920, 2875, 2234, 1679, 1648, 1451, 1218, 1114, 705 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.57 (s, 3H), 2.94 (d, *J* = 14.4 Hz, 1H), 3.18 (d, *J* = 16.8 Hz, 1H), 3.24 (d, *J* = 14.4 Hz, 1H), 3.37 (d, *J* = 10 Hz, 1H), 3.45 (d, *J* = 17.2 Hz, 1H), 3.83 (d, *J* = 10 Hz, 1H), 5.98 (s, 1H), 6.24 (d, 1H), 7.14–7.32 (m, 10H). ¹³C NMR (100 MHz, CDCl₃): δ 24.4, 51.1, 52.5, 52.6, 60.8, 64.6, 120.4, 126.4, 126.7, 126.8, 126.8, 128.7, 145.8, 147.4, 172.6. ESI-HRMS (ESI+): m/z calcd. for C₂₀H₂₁N₃O (M⁺ - CN) 293.1654, found 293.1652.

1-Benzyl-2-methyl-4,4-diphenylpyrrolidine-2-carbonitrile (6c)—Yellow oil (66.8 mg, 79% yield). IR (neat): 3061, 3033, 2832, 2222, 1714, 1597, 1495, 1448, 1210, 1145, 1038, 907, 758, 698 cm⁻¹. Yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.60 (s, 3H), 2.54 (d, *J* = 14 Hz, 1H), 3.02 (d, *J* = 10.8 Hz, 1H), 3.43 (d, *J* = 14 Hz, 1H), 3.49 (d, *J* = 13.2 Hz, 1H), 3.71 (d, *J* = 10 Hz, 1H), 4.10 (d, *J* = 13.6 Hz, 1H), 7.11–7.39 (m, 15H); ESI-HRMS (ESI+): m/z calcd. for C₂₀H₁₉N₃ (M⁺ - CN) 275.1548, found 275.1553.

1-(2-Chloroethyl)-2-methyl-4,4-diphenylpyrrolidine-2-carbonitrile (6d)—Yellow oil (80.4mg, 99% yield). IR (neat): 3024, 2988, 2768, 2107, 1685, 1395, 1039, 785 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.44 (s, 3H), 2.46 (d, *J* = 14 Hz, 2H), 2.73–2.88 (m, 1H), 3.02–

3.11 (m, 2H), 3.31 (d, $J = 13.6$ Hz, 1H), 3.59–3.64 (m, 2H), 3.95 (d, $J = 10$ Hz, 1H), 7.05–7.38 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.8, 42.5, 51.5, 51.8, 52.5, 61.8, 64.9, 120.3, 126.1, 126.6, 126.9, 127.3, 128.2, 128.6, 145.9, 149.7. ESI-HRMS (ESI⁺): m/z calcd. for $\text{C}_{20}\text{H}_{21}\text{ClN}_2$ ($\text{M}^+ - \text{CN}$) 298.1362, found 298.1359.

1-(Cyanomethyl)-2,4-dimethyl-4-phenylpyrrolidine-2-carbonitrile (6f)—Yellow oil (54.4mg, 91% yield). **6f** was obtained as a mixture of two diastereoisomers in ratio of (1:1). IR(neat): 3047, 2963, 2879, 2119, 1602, 1495, 1448, 1257, 1029, 907, 763, 735 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.54 (s, 3H), 1.56 (s, 3H), 2.34 (d, $J = 13.6$ Hz, 1H), 2.55 (d, $J = 13.6$ Hz, 1H), 2.93 (d, $J = 9.2$ Hz, 1H), 3.50 (d, $J = 16.8$ Hz, 1H), 3.67 (d, $J = 9.6$ Hz, 1H), 3.74 (d, $J = 16.8$ Hz, 1H), 7.16–7.28 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 23.9, 28.5, 37.2, 42.5, 55.3, 60.6, 66.5, 117.6, 119.4, 125.2, 126.4, 128.6, 144.3. ESI-HRMS (ESI⁺): m/z calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_3$ ($\text{M}^+ - \text{CN}$) 213.1392, found 213.1389.

1-Benzyl-2,4-dimethyl-4-phenylpyrrolidine-2-carbonitrile (6g)—Yellow oil (64.6 mg, 89% yield). IR (neat): 3061, 2972, 2800, 2154, 1665, 1606, 1499, 1443, 1373, 1127, 1033, 762, 698, 549 cm^{-1} . **6g** was obtained as a mixture of two diastereoisomers in ratio of (1:1). ^1H NMR (400 MHz, CDCl_3): δ 1.50 (s, 3H), 1.61 (s, 3H), 2.16 ($J = 13.6$ Hz, 1H), 2.55 (d, $J = 13.2$ Hz, 1H), 2.84 (d, $J = 9.6$ Hz, 1H), 3.02 (d, $J = 9.6$ Hz, 1H), 3.49 (d, $J = 13.6$ Hz, 1H), 4.09 (d, $J = 13.2$ Hz, 1H), 7.31–7.43 (m, 5H). ESI-HRMS (ESI⁺): m/z calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2$ ($\text{M}^+ - \text{CN}$) 264.1572, found 264.1569.

1-(2-Chloroethyl)-2,4-dimethyl-4-phenylpyrrolidine-2-carbonitrile (6h)—Yellow oil (61.1 mg, 93% yield). IR (neat): 3033, 2983, 2835, 2100, 1665, 1443, 1273, 1225, 1033, 762, 736, 570 cm^{-1} . **6h** was obtained as a mixture of two diastereoisomers in ratio of (1:1). ^1H NMR (400 MHz, CDCl_3): δ 1.51 (s, 3H), 1.57 (s, 3H), 2.09 (d, $J = 14.0$ Hz, 1H), 2.47 (d, $J = 14.0$ Hz, 1H), 2.74 (d, $J = 9.6$ Hz, 1H), 2.79–2.84 (m, 1H), 3.07–3.18 (m, 1H), 3.26 (d, $J = 7.2$ Hz, 1H), 3.57–3.66 (m, 2H), 7.21–7.47 (m, 5H). ESI-HRMS (ESI⁺): m/z calcd. for $\text{C}_{15}\text{H}_{19}\text{ClN}_2$ ($\text{M}^+ - \text{CN}$) 236.1206, found 236.1201.

1-(Cyanomethyl)-2-ethyl-4,4-diphenylpyrrolidine-2-carbonitrile (6i)—Yellow oil (63.8 mg, 81% yield). IR (neat): 3069, 2963, 2874, 2229, 1681, 1446, 1220, 1145, 987, 725, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 0.93 (t, $J = 6$ Hz, 3H), 1.26–1.55 (m, 2H), 2.64 (d, $J = 14$ Hz, 1H), 3.26 (d, $J = 10.4$ Hz, 1H), 3.32 (d, $J = 13.6$ Hz, 1H), 3.49 (d, $J = 17.6$ Hz, 1H), 3.76 (d, $J = 16.8$ Hz, 1H), 4.13 (d, $J = 10$ Hz, 1H), 7.13–7.33 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 18.1, 37.5, 39.3, 50.2, 51.6, 64.4, 65.2, 115.7, 118.6, 126.4, 126.6, 126.8, 127.0, 128.5, 128.7, 145.3, 148.1. ESI-HRMS (ESI⁺): m/z calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_3$ ($\text{M}^+ - \text{CN}$) 289.1705, found 289.1711.

1-Benzyl-2-hexyl-1H-pyrrole (8a)—Yellow oil (44.6 mg, 74% yield). IR (neat): 2930, 2851, 1658, 1518, 1248, 1033, 837, 698 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 0.78 (t, $J = 7.2$ Hz, 3H), 1.05–1.28 (m, 6H), 1.41–1.53 (m, 2H), 2.36 (d, $J = 8.0$ Hz, 2H), 4.95 (s, 2H), 5.88 (s, 1H), 6.05 (t, $J = 2.4$ Hz, 1H), 6.53, 6.86–6.96 (m, 2H), 7.11–7.27 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 22.6, 26.2, 28.8, 29.1, 31.6, 50.2, 105.8, 107.0, 120.7,

126.3, 127.3, 128.6, 133.7, 138.6. ESI-HRMS (ESI+): m/z calcd. for $C_{17}H_{23}N$ ($M^+ + H$) 242.1903, found 242.1905.

2-Hexyl-1-phenyl-1H-pyrrole (8b)—Yellow oil (40.4mg, 71% yield). IR (neat): 2963, 2930, 2860, 1709, 1667, 1457, 1294, 1168, 1075, 1033, 693 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, $J = 6.8$ Hz, 3H), 1.14–1.30 (m, 6H), 1.44–1.55 (m, 2H), 2.51 (t, $J = 8$ Hz, 2H), 6.05 (s, 1H), 6.20 (s, 1H), 6.73 (d, $J = 1.2$ Hz, 1H), 7.18–7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 26.7, 29.0, 29.1, 31.5, 106.6, 107.8, 121.4, 126.1, 127.0, 129.0, 134.3, 140.5. ESI-HRMS (ESI+): m/z calcd. for $C_{16}H_{21}N$ ($M^+ + H$) 228.1747, found 228.1745.

2-Hexyl-1-(4-methoxyphenyl)-1H-pyrrole (8c)—Yellow oil (39.3 mg, 62% yield). IR (neat): 2930, 2857, 1688, 1514, 1463, 1302, 1247, 1040, 838, 709, 607 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 0.768 (t, $J = 6.6$ Hz, 3H), 1.12–1.23 (m, 6H), 1.33–1.47 (m, 2H), 2.39 (t, $J = 7.6$ Hz, 2H), 3.77 (d, $J = 1.2$ Hz, 3H), 5.95 (s, 1H), 6.11 (s, 1H), 6.61 (d, $J = 1.2$ Hz, 1H), 6.84–6.88 (m, 2H), 7.10–7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 26.6, 29.0, 29.1, 31.6, 55.5, 106.1, 107.4, 114.1, 121.6, 127.4, 133.8, 134.6, 158.5. ESI-HRMS (ESI+): m/z calcd. for $C_{17}H_{23}NO$ ($M^+ + H$) 258.1852, found 228.1855.

1-Benzyl-2-butyl-1H-pyrrole (8e)—Yellow oil (46.3 mg, 80% yield). IR (neat): 2961, 2924, 2855, 1698, 1603, 1497, 1322, 1078, 755, 695 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 0.884 (t, $J = 7.6$ Hz, 3H), 1.24–1.40 (m, 2H), 1.49–1.61 (m, 2H), 2.50 (t, $J = 8$ Hz, 2H), 5.04 (s, 2H), 5.97 (s, 1H), 6.14 (t, $J = 2.4$ Hz, 1H), 6.62 (s, 1H), 7.00 (m, 2H), 7.22–7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 25.9, 31.0, 50.2, 105.8, 107.0, 120.7, 126.3, 127.3, 128.7, 133.7, 138.6. ESI-HRMS (ESI+): m/z calcd. for $C_{15}H_{19}N$ ($M^+ + H$) 214.1590, found 213.1591.

2-butyl-1-phenyl-1H-pyrrole (8f)—Yellow oil (73% yield). The spectroscopic data is consistent with literature report.^[11]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of Health for financial support (NIGMS-1R15GM101604-01). We acknowledge the support provided by the CREAM Mass Spectrometry Facility (University of Louisville) funded by NSF/EPSCoR grant # EPS-0447479.

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a) previous work

b) this work

Scheme 1.

Synthesis of N-heterocycles *via* cyclization triggered tandem reactions.

Scheme 2.
Proposed mechanism for the formation of **6**.

Scheme 3.
Mechanistic investigation for the formation of **6**.

Scheme 4.
Proposed mechanism for the formation of **8**.

Table 1

Using a primary amine-tethered alkyne **1a** as starting material.

entry	TMS-CN 2a	condition	time	4a ^a
1	4 equiv	mw / 100 °C	30 min	46 %
2	4 equiv	mw / 100 °C	60 min	42 %
3	2 equiv	mw / 100 °C	30 min	32 %
4	8 equiv	100 °C	20 h	50%
5	8 equiv	rt	20 h	50%

^a¹H-NMR yield.

Table 2

Optimization of the tandem amination/ cyanation sequence using a primary amine.

entry	1	2a	5a	co-catalyst	solvent	condition	6
1	1a	1 equiv	4 equiv	-	dioxane	mw /100°C / 30 min	80%
2	1a	4 equiv	4 equiv	-	acetonitrile	mw /100°C / 30 min	87%
3	1a	4 equiv	2 equiv	-	acetonitrile	mw / 90°C / 30 min	93%
4	1a	4 equiv	2 equiv	-	acetonitrile	100°C / 12h	85%
5	1c	4 equiv	2 equiv	-	acetonitrile	mw /100°C / 30 min	trace
6	1c	4 equiv	2 equiv	Sc(OTf) ₃ (5 %)	acetonitrile	100°C / 12h	85%

Table 3

Scope of three-component tandem amination/cyanation/ alkylation.

$ \begin{array}{c} \text{R}^6 \\ \\ \text{R}^7 - \text{C} - \text{CH}_2\text{NH}_2 \\ \\ \text{C} \equiv \text{C} - \text{R}^5 \\ \mathbf{1} \end{array} + \text{R}^8\text{Cl} \quad \mathbf{5} \xrightarrow[\text{CH}_3\text{CN, mw, 90}^\circ\text{C, 40 min}]{\text{CuBr (5\%), TMSCN (4 equiv)}} \begin{array}{c} \text{R}^6 \\ \\ \text{R}^7 - \text{C} - \text{CH}_2\text{N}(\text{R}^8) \\ \\ \text{C} \equiv \text{C} - \text{R}^5 \\ \mathbf{6} \end{array} $					
entry	1	R ⁸ Cl (5)	condition ^a	6	isolated yield (%)
1			A		93
2	1a		A		92
3	1a		A		79
4 ^b	1a		A		99
5 ^c	1a		B		42
6			B		91
7	1b		B		89
8 ^b	1b		B		93
9			B		81

^a **Condition A:** amino alkyne **1** (0.25 mmol), TMSCN (1 mmol) alkylation reagent (0.5 mmol), water (1.0 equiv), CuBr (5 mol%), acetonitrile (1 mL), microwave / 90°C, 40 min; **Condition B:** same as condition except use of co-catalyst Sc(OTf)₃ (2%).

^b Reaction was conducted in DCE;

^c 40 equiv of 1-pentyl chloride was used.

Table 4Optimization of pyrrole **8a** via tandem amination/ oxidation.

entry	[Ag]	solvent	condition	8a^a
1	AgF (0.1 equiv)	dioxane	90°C / 12 h	6%
2	AgF (1.0 equiv)	dioxane	90°C / 12 h	22%
3	AgF (1.0 equiv)	dioxane	rt / 12 h	31%
4	AgOAc (1.0 equiv)	dioxane	rt / 24 h	40%
5	AgOAc (1.0 equiv)	DCM	rt / 24 h	52%
6	AgOAc (1.5 equiv)	DCM	rt / 24 h	66%
7	AgOAc (2.0 equiv)	DCM	rt / 24 h	62%
8	AgOAc (2.0 equiv)	DCM	rt / 40 h	81% (74%^b)
9	AgNO ₃ (2.0 equiv)	DCM	rt / 24 h	trace
10	AgCO ₃ (2.0 equiv)	DCM	rt / 24 h	no rxn
11	CuBr (0.1 equiv)	DCM	rt / 24 h	complex
12	CuBr (1.0 equiv)	DCM	rt / 24 h	complex
13	AgOAc (1.0 equiv)/DDQ (1.1 equiv)	DCM	rt / 40 h	trace

^a NMR yield;^b isolated yield.

Table 5

Reaction scope for synthesis of pyrrole **8** via tandem amination/ oxidation.^a

entry	7	8	yield ^c
1	7a	8a	74%
2 ^b	7b	8b	71%
3 ^b	7c	8c	62%
4 ^b	7d	8d	0%
5	7e	8e	80%
6 ^b	7f	8f	73%

^aReaction condition: amino alkyne (0.25mmol), silver acetate (0.375 mmol), DCM (1 mL), rt, 40 h;^bsilver fluoride (0.375 mmol) was used;

^cisolated yields.