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A mild and general one-pot preparation of cyanoethyl-protected tetrazoles

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Dedicated to Professor John E. Sheats on the occasion of his retirement from Rider University

ABSTRACT

Described herein is a mild and general one-pot procedure for the conversion of cyanoethyl amides to cyanoethyl-protected tetrazoles with azidotrimethylsilane via the intermediacy of imidoyl chlorides generated in situ with phosphorus pentachloride. This synthetic sequence works well with sterically hindered amides and is compatible with acid sensitive functionality.

The employment of tetrazoles as isosteres of the carboxylic acid functionality has long been of interest to the medicinal chemistry community.[1] Tetrazoles have similar physicochemical properties to carboxylates, such as pK_a (Fig. 1) and aqueous solubility, yet are larger and tend to have greater lipophilicity.[1c] Tetrazoles can exhibit enhanced receptor binding compared to carboxylates, which has been attributed to their ability to form two hydrogen bonds.[1a,d–g] The successful replacement of carboxylates with tetrazoles in marketed drugs[1a] has driven the search for new methods for their synthesis.

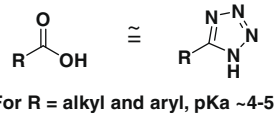
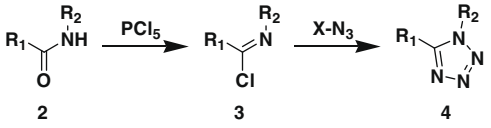


Figure 1.

Tetrazoles are commonly formed from nitriles and an azide source via a 1,3-dipolar cycloaddition.[1a,b] Amines, amides and aldehydes have also been employed, though to a lesser extent. Progress has been made in synthesizing tetrazoles without the use of toxic and/or explosive reagents such as azidotrimethylstannane or hydrazoic acid through the utilization of safer alternatives such as azidotrimethylsilane (TMS-N_3).[1a]

A general and efficient route to protected tetrazoles was required as part of a structure–activity relationship survey in a medicinal chemistry program. Tetrazoles protected by a cyanoethyl group were determined to be essential due to the mild conditions allowed for deprotection (aqueous hydroxide, rt).[2] One of the earliest methods for tetrazole formation involved the conversion of a secondary amide **2** to the corresponding imidoyl chloride **3** followed by treatment with sodium azide (Scheme 1, X = Na)[3a,b] or hydrazoic acid (Scheme 1, X = H)[3c,d] to afford the desired tetrazole **4**. More recently, the employment of azidotrimethylsilane in conjunction with imidoyl chlorides has been reported for the generation of *N*-alkyl and *N*-aryl tetrazoles.[4]



Scheme 1. Tetrazole synthesis via imidoyl chlorides.

One of the major drawbacks of accessing tetrazoles from amides via the intermediacy of imidoyl chlorides is the generation of hydrogen chloride as a by-product during imidoyl chloride formation. The hydrogen chloride can have obvious deleterious effects on acid sensitive functionality. For example, attempts to convert cyanoethyl amide **2a** to tetrazole **4a** using phosphorous pentachloride (1.5 equiv) and azidotrimethylsilane (4 equiv) successively at reduced or elevated temperature (40 °C) produced no desired product (Scheme 2).[4] At reduced temperature (−5 °C) amide **5** and tetrazole **6** were isolated in 65% and 23%, respectively (Table 1). At elevated temperature (40 °C), only amide **5** was produced in 71% yield. When the experiment at elevated temperature was repeated with excess pyridine present, the desired tetrazole **4a** was provided in good yield (83%).[5]

To determine the general applicability of this one-pot synthetic sequence, a series of aliphatic, aromatic, and hetero-aromatic cyanoethyl amides were prepared and subjected to the same tetrazole-forming reaction conditions.[6] The prerequisite cyanoethyl amides **2** were synthesized from the corresponding carboxylic acids **1**.[7,8] Treatment of the carboxylic acids with Vilsmeier reagent

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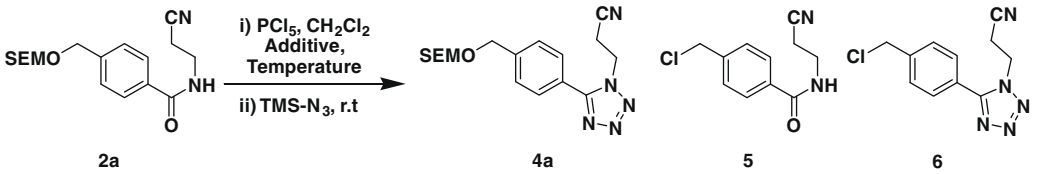


2a 4a 5 6

Scheme 2. Effect of pyridine on formation of tetrazole **4a**.

Table 1
Effect of pyridine on formation of tetrazole **4a**

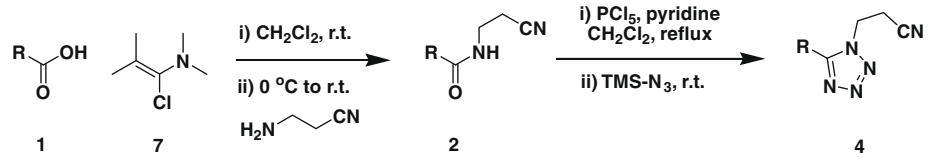
Temperature (°C)	Additive	% Yield **4a**	% Yield **5**	% Yield **6**
−5	None	0	65	23
40	None	0	71	0
40	Pyridine	83	0	0

7 resulted in clean and efficient acid chloride formation.[9] Addition of excess 3-aminopropanenitrile provided the desired amides **2a–h** in good to excellent yield (Table 2).

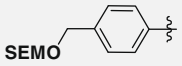
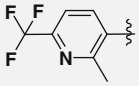
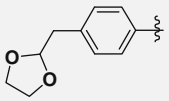
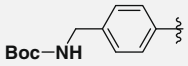
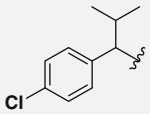
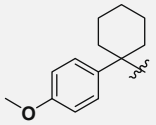
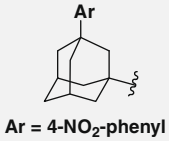
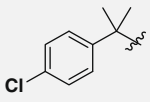
Conversion of amides **2a–h** to the corresponding tetrazoles **4a–h** using the previously described conditions proceeded efficiently (Table 2, entries 1–8).[10,11] The yield of the tetrazoles was reasonably consistent (73–86%) and the nature of the R-group appeared to have little impact. Sterically hindered aliphatic amides **2e–h** were converted as efficiently as their aromatic counterparts (**2a–d**). Functional groups such as methoxy and nitro, as well as SEM, Boc, and acetal protecting groups were unaffected by the transformation.

To further explore the ability of pyridine to protect acid sensitive functionality in this transformation, the reactions of amides

Table 2
Synthesis of cyanoethyl amides **2** and tetrazoles **4**



1 7 2 4

Entry	R	% Yield **2**	Tetrazole **4**	Method	% Yield **4**
1		86 (**2a**)	**4a**	A[a]	83
				B[b]	0
2		92 (**2b**)	**4b**	A	73
				B	26
3		98 (**2c**)	**4c**	A	76
				B	0
4		95 (**2d**)	**4d**	A	86
				B	21
5		95 (**2e**)	**4e**	A	85
6		98 (**2f**)	**4f**	A	73
7	 Ar = 4-NO_2-phenyl	99 (**2g**)	**4g**	A	81
8		99 (**2h**)	**4h**	A	77
				C[c]	0

[a] Method A: (i) PCl_5, pyridine, CH_2Cl_2, reflux; (ii) TMS-N_3, rt.
[b] Method B: (i) PCl_5, CH_2Cl_2, reflux; (ii) TMS-N_3, rt.
[c] Method C: diethylazodicarboxylate, triphenylphosphine, azidotrimethylsilane, THF, rt 16 h, then reflux 8 h.[2]

2b–d were repeated without pyridine. When the conversion of the nicotinamide **2b** to tetrazole **4b** was attempted without pyridine, product was isolated but the yield was dramatically reduced (26%, Table 2, entry 2, method B) compared to the identical reaction with pyridine (73%, Table 2, entry 2, method A).[12] Attempted conversion of amide **3c** to tetrazole **4c** without pyridine produced no desired product and completely decomposed starting amide **3c** (Table 2, entry 3, method B).[12] When amide **2d** was subjected to the reaction without pyridine, unreacted **2d** was recovered (11%) and product tetrazole **4d** was isolated in significantly reduced yield (21%, Table 2, entry 4, method B).[12] The presence of pyridine presumably had a protective effect for acid sensitive functionality by sequestering hydrogen chloride generated during imidoyl chloride formation.

The synthesis of cyanoethyl tetrazoles possessing acid sensitive functionality (Boc-protected amines)[13] has been reported under Mitsunobu-like conditions (diethylazodicarboxylate, triphenylphosphine, azidotrimethylsilane).[2] However, this methodology can fail in sterically demanding systems. For example, when this synthetic sequence was applied to cyanoethyl amide **2h**, no desired product was detected at ambient or elevated temperature as analyzed by HPLC and LC–MS (Table 2, entry 8, method C).

In summary, a mild and general method for the conversion of cyanoethyl amides to the corresponding cyanoethyl-protected tetrazoles has been described. This procedure differs from other methods in that it employs pyridine to mitigate the negative effects of hydrogen chloride generated during imidoyl chloride formation with phosphorous pentachloride. This transformation is tolerated by a variety of functional groups, is amenable to use with acid-sensitive functionality, and efficiently converts sterically hindered amides. Furthermore, the reaction does not require hydrazoic acid or azide salts, and has the added advantage of being performed in a one-pot manner.

Acknowledgments

I would like to thank Scott A. Shaw, Bruce A. Ellsworth, Jeffrey A. Robl, and Jun Li for many helpful discussions.

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4. For examples of the synthesis of tetrazoles from amides using phosphorous pentachloride and azidotrimethylsilane, see: (a) Wu, S.; Fluxe, A.; Sheffer, J.; Janusz, J. M.; Blass, B. E.; White, R.; Jackson, C.; Hedges, R.; Murawsky, M.; Fang, B.; Fadayel, G. M.; Hare, M.; Djandjighian, L. *Biorg. Med. Chem. Lett.* **2006**, *16*, 6213; For examples involving tin(IV) chloride catalysis, see: (b) Boyko, V.; Rodik, R.; Danylyuk, O.; Tsymbal, L.; Lampeka, Y.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. *Tetrahedron* **2005**, *61*, 12282; (c) Yu, K. L.; Johnson, R. L. *J. Org. Chem.* **1987**, *52*, 2051.
5. (a) Elevated temperature (40 °C) was found to be optimal, compared to reduced or ambient temperature, for complete conversion of the starting amide to the corresponding imidoyl chloride; (b) Addition of 1–2 equiv of azidotrimethylsilane typically resulted in incomplete tetrazole formation.
6. All amide-forming reactions were performed on a 1–2 mmol scale. All tetrazole-forming reactions were performed on a 0.5 mmol scale. Reaction conditions are not optimized.
7. (a) All starting acids employed in this study were commercially available with the exception of **1a**. 3-Aminopropanenitrile was purchased stabilized over potassium carbonate. The Vilsmeier reagent **7** was purchased from Sigma–Aldrich; (b) *Preparation of acid* ***1a***: To a solution of methyl 4-(hydroxymethyl)benzoate (332 mg, 2.0 mmol), tetrabutylammonium iodide (148 mg,0.40 mmol), and triethylamine (558 μL, 4.0 mmol) in THF (4.0 mL) was added (2-(chloromethoxy)ethyl)trimethylsilane (706 μL, 4.0 mmol) dropwise over 2 min and the resulting mixture heated to 40 °C. After 6 h methanol (2 mL) was added. After 10 min aqueous lithium hydroxide (3.0 mL, 12.0 mmol, 4 M) was added and the resulting mixture stirred vigorously. After 20 min the reaction was cooled to room temperature and the pH adjusted to 2–3 with concentrated hydrochloric acid, then ethyl acetate/diethyl ether (1:1, 20 mL) was added. After 20 min the organic layer was separated, dried over sodium sulfate, and concentrated in vacuo. The resulting residue was purified via flash chromatography (SiO_2, 0–100% ethyl acetate/hexanes) to afford **1a** (348 mg, 62%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.79 (s, 2H), 4.69 (s, 2H), 3.68 (t, J = 8.6 Hz, 2H), 0.95 (t, J = 8.5 Hz, 2H), 0.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.82, 144.42, 130.35, 128.51, 127.39, 94.41, 68.68, 65.46, 18.08, −1.43. LC–MS: m/z calcd for $C_{14}H_{21}O_4Si$ $[M-H]^-$ 281.1; found: 281.3.
8. *Representative experimental procedure for cyanoethyl amides* **2a**–**h**: (a) *Amide* **2a**: To a solution of **1a** (282 mg, 1.0 mmol) in dichloromethane (5 mL) was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (**7**) (159 μL, 1.2 mmol) dropwise over 1 min. After 1 h the reaction mixture was cooled to 0 °C then 3-aminopropanenitrile (295 μL, 4.0 mmol) was added dropwise over 1 min, producing a white suspension. After 30 min the cooling bath was removed. After 1 h a 5% aqueous solution of citric acid (5 mL) was added and the resulting mixture stirred vigorously for 30 min. The organic phase was separated, dried over sodium sulfate, and concentrated in vacuo. The resulting residue was purified via flash chromatography (SiO_2, 0–100% ethyl acetate/hexanes) to afford **2a** (288 mg, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 6.52 (br s, 1H), 4.74 (s, 2H), 4.63 (s, 2H), 3.70 (q, J = 6.2 Hz, 2H), 3.64 (t, J = 8.2 Hz, 2H), 2.73 (t, J = 6.2 Hz, 2H), 0.93 (t, J = 8.6 Hz, 2H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.64, 142.55, 132.63, 127.72, 127.12, 118.26, 94.33, 68.53, 65.41, 36.10, 18.54, 18.11, −1.40. LC–MS: m/z calcd for $C_{17}H_{25}N_2O_3Si$ $[M-H]^-$: 333.2; found: 333.3; (b) *Amide* **2b** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 6.58 (br s, 1H), 3.71 (q, J = 6.1 Hz, 2H), 2.79 (t, J = 6.1 Hz, 2H), 2.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.93, 157.48, 148.73 (q, J = 35 Hz), 136.16, 133.40, 121.06 (q, J = 275 Hz), 117.89, 117.61, 36.13, 22.97, 18.39. LC–MS: m/z calcd for $C_{11}H_{11}N_3OF_3$ $[M+H]^+$: 258.1; found: 258.1; (c) *Amide* **2c** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 6.54 (br s, 1H), 5.09 (t, J = 4.7 Hz, 1H), 3.93–3.88 (m, 2H), 3.87–3.82 (m, 2H), 3.72 (t, J = 6.1 Hz, 2H), 3.03 (d, J = 4.4 Hz, 2H), 2.75 (t, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.82, 140.50, 131.77, 130.10, 126.96, 118.34, 103.99, 65.01, 40.52, 36.12, 18.46. LC–MS: m/z calcd for $C_{14}H_{17}N_2O_3$ $[M+H]^+$: 261.1; found: 261.1. (d) *Amide* **2d** (white solid): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.79 (t, J = 5.5 Hz, 1H), 7.80 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 6.1 Hz, 1H), 7.32 (d, J = 8.3 Hz, 2H), 4.17 (d, J = 6.1 Hz, 2H), 3.48 (q, J = 6.1 Hz, 2H), 2.77 (t, J = 6.6 Hz, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.24, 155.70, 143.68, 132.22, 127.11, 126.63, 119.19, 77.80, 43.04, 35.33, 28.12, 17.41. LC–MS: m/z calcd for $C_{16}H_{21}N_3O_3$ $[M-H]^-$: 302.2; found: 302.4; (e) *Amide* **2e** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 4H), 5.96 (br s, 1H), 3.58–3.50 (m, 1H), 3.42–3.34 (m, 1H), 2.82 (d, J = 10.1 Hz, 1H), 2.69–2.61 (m, 1H), 2.56–2.49 (m, 1H), 2.41–2.32 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 7.2 Hz, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.69, 137.29, 133.11, 129.52, 128.68, 118.11, 60.91, 35.69, 31.61, 21.42, 20.21, 18.36. LC–MS: m/z calcd for $C_{14}H_{18}N_2OCl$ $[M+H]^+$: 265.1; found: 265.3; (f) *Amide* **2f** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.63 (br s, 1H), 3.81 (s, 3H), 3.36 (q, J = 6.2 Hz, 2H), 2.54 (t, J = 6.3 Hz, 2H), 2.24–2.18 (m, 2H), 2.07–1.99 (m, 2H), 1.64–1.55 (m, 2H), 1.53–1.42 (m, 4H), . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.23, 158.41, 134.40, 127.82, 117.96, 114.32, 55.27, 55.17, 50.23, 35.79, 34.22, 25.72, 22.61, 18.08. LC–MS: m/z calcd for $C_{17}H_{23}N_2O_2$ $[M+H]^+$: 287.2; found: 287.5; (g) *Amide* **2g** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 9.3 Hz, 2H), 6.09 (br s, 1H), 3.52 (q, J = 6.4 Hz, 2H), 2.65 (t, J = 6.1 Hz, 2H), 2.37–2.30 (m, 2H), 2.05–2.01 (m, 2H), 1.98–1.87 (m, 8H), 1.81–1.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.69, 157.09, 146.12, 125.88, 123.50, 118.16, 43.93, 41.66, 38.22, 37.33, 35.54, 35.28, 28.53, 18.31. LC–MS: m/z calcd for $C_{20}H_{24}N_3O_3$ $[M+H]^+$: 354.2; found: 354.3; (h) *Amide* **2h** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 4H), 5.65 (br s, 1H), 3.40 (q, J = 6.1 Hz, 2H), 2.59 (t, J = 6.3 Hz, 2H), 1.56 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.59, 124.95, 133.16, 128.94, 127.80, 117.88, 46.67, 35.86, 26.91, 18.00. LC–MS: m/z calcd for $C_{13}H_{16}N_2OCl$ $[M+H]^+$: 251.1; found: 251.1; (i) *Amide* **5**: (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 6.56 (br s, 1H), 4.62 (s, 2H), 3.73 (q, J = 6.4 Hz, 2H), 2.76 (t, J = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.37, 141.36, 133.39, 128.79, 127.47, 118.29, 45.25, 36.17, 18.46. LC–MS: m/z calcd for $C_{11}H_{12}N_2OCl$ $[M+H]^+$: 223.1; found: 223.1.
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10. *Representative experimental procedure for tetrazoles* **4a**–**h**: (a) *Tetrazole* **4a**: To a solution of amide **2a** (167 mg, 0.50 mmol) and pyridine (243 μL, 3.0 mmol) in dichloromethane (5 mL) was added phosphorous pentachloride (156 mg, 0.75 mmol) and the resulting mixture heated to reflux. After 3 h the reaction mixture was cooled to room temperature and azidotrimethylsilane (265 μL, 2.0 mmol) was added. After 16 h the reaction mixture was carefully quenched with freshly prepared saturated aqueous sodium bicarbonate (~200 μL), then

excess saturated aqueous sodium bicarbonate (~2 mL) was added and the resulting mixture stirred vigorously for 15 min. The organic layer was separated, dried over sodium sulfate, and concentrated in vacuo. The resulting residue was purified via flash chromatography (SiO_2, 0–100% ethyl acetate/hexanes) to furnish tetrazole **4a** (149 mg, 83%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 4.81 (s, 2H), 4.72 (s, 2H), 4.68 (t, J = 6.9 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 3.14 (t, J = 7.2 Hz, 2H), 0.97 (t, J = 8.3 Hz, 2H), 0.04 (s, 9H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.72, 142.47, 128.96, 128.48, 121.96, 115.45, 94.43, 68.35, 65.49, 43.25, 18.51, 18.08, −1.43. LC–MS: m/z calcd for $C_{17}H_{26}N_5O_2Si$ $[M+H]^+$: 360.2; found: 360.5; (b) *Tetrazole* **4b** (colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 4.53 (t, J = 6.3 Hz, 2H), 3.14 (t, 6.3 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.30, 152.63, 150.31 (q, J = 35 Hz), 139.82, 121.66, 120.93 (q, J = 275 Hz), 118.07, 115.51, 43.18, 22.95, 18.82. LC–MS: m/z calcd for $C_{11}H_{10}N_6F_3$ $[M+H]^+$: 283.1; found: 283.2; (c) *Tetrazole* **4c** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.3 Hz, 2H), 7.52 (d, 8.3 Hz, 2H), 5.13 (t, J = 4.7 Hz, 1H), 4.68 (t, J = 7.2 Hz, 2H), 3.99–3.84 (m, 4H), 3.13 (t, J = 7.2 Hz, 2H), 3.08 (d, J = 4.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.82, 140.45, 131.04, 128.74, 121.10, 115.48, 103.84, 65.05, 43.23, 40.52, 18.48. LC–MS: m/z calcd for $C_{14}H_{16}N_5O_2$ $[M+H]^+$: 286.1; found: 286.4; (d) *Tetrazole* **4d** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 5.04 (br s, 1H), 4.67 (t, J = 6.9 Hz, 2H), 4.43 (d, J = 6.1 Hz, 2H), 3.14 (t, J = 6.9 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.96, 154.67, 143.41, 129.09, 128.13, 121.63, 115.55, 79.88, 44.04, 43.23, 28.33, 18.46. LC–MS: m/z calcd for $C_{16}H_{21}N_6O_2$ $[M+H]^+$: 329.2; found: 329.4; (e) *Tetrazole* **4e** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2H), 7.24–7.20 (m, 2H), 4.49–4.33 (m, 2H), 3.74 (d, J = 9.6 Hz, 1H), 2.99–2.91 (m, 1H), 2.81–2.66 (m, 2H), 1.05 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.56, 136.12, 134.06, 129.68, 129.41, 115.62, 48.28, 42.34, 33.08, 21.57, 20.50, 18.40. LC–MS: m/z calcd for $C_{14}H_{17}N_5Cl$ $[M+H]^+$: 290.1; found: 290.3; (f) *Tetrazole* **4f** (white solid): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 9.3 Hz, 2H), 4.07 (t, J = 7.4 Hz, 2H), 3.81 (s, 3H), 2.53–2.44 (m, 2H), 2.38 (t, J = 7.4 Hz, 2H), 2.20–2.08 (m, 2H), 1.76–1.61 (m, 5H), 1.50–1.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.83, 158.84, 135.01, 127.42, 25.44, 22.48, 17.27. LC–MS: m/z calcd for $C_{17}H_{22}N_5O$ $[M+H]^+$: 312.2; found: 312.2; (g) *Tetrazole* **4g** (white solid): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.17 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 4.88 (t, J = 6.3 Hz, 2H), 3.22 (t, J = 6.3 Hz, 2H), 2.30–2.24 (m, 2H), 2.23–2.20 (m, 2H), 2.15–2.08 (m, 4H), 2.06–1.98 (m, 2H), 1.95–1.87 (m, 2H), 1.86–1.79 (m. 1H), 1.78–1.71 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d6): δ = 160.01, 157.32, 145.66, 126.54, 123.27, 117.94, 44.04, 43.89, 50.40, 38.12, 37.06, 34.27, 28.02, 18.26 . LC–MS: m/z calcd for $C_{20}H_{23}N_6O_2$ $[M+H]^+$: 379.2; found: 379.3; (h) *Tetrazole* (white solid) **4h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 3.95 (t, J = 7.2 Hz, 2H), 2.78 (t, J = 6.9 Hz, 2H), 1.86 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.66, 142.17, 134.02, 129.72, 126.96, 115.38, 43.45, 38.45, 28.86, 17.45. LC–MS: m/z calcd for $C_{13}H_{15}N_5Cl$ $[M+H]^+$: 276.1; found: 276.1; (i) *Tetrazole* **6** (colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 4.69 (t, J = 6.5 Hz, 2H), 4.67 (s, 2H), 3.15 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.46, 141.36, 129.62, 129.34, 122.87, 115.45, 45.05, 43.33, 18.56. LC–MS: m/z calcd for $C_{11}H_{11}N_5Cl$ $[M+H]^+$: 248.1; found: 248.1.

11. In an attempt to limit the potential formation of hydrazoic acid during work-up, the reactions were quenched with aqueous sodium bicarbonate. Throughout the course of this study it was found that a freshly prepared solution of sodium bicarbonate (pH ~8) was optimal to work up the reactions. Sodium bicarbonate solution becomes more basic over time (to pH ~10), which can lead to partial cleavage of the cyanoethyl-protecting group (5–10%).
12. Numerous unidentified species were observed via HPLC and LC–MS analysis.
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