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A Synthon for the Convenient and Efficient Introduction of Tetrazolylmethyl Groups into Nucleophile-Bearing Compounds

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An activated synthon for the efficient introduction of a protected tetrazolylmethyl group into nucleophile-bearing compounds is presented. The β-cyanoethyl protecting group allows for very effective deprotection under mild basic conditions. The synthon can be prepared by a two-step procedure (42 %) starting from cheap starting material and can alkylate piperidine in 91 % yield. Even quadruple alkylation to form a protected version of the hexadentate ligand EDTT gives decent yields. Simultaneous removal of the four protecting groups furnishes the lithium salt of a formally zwitterionic ligand in 75 % yield. Finally, the synthon's performance has been assessed by comparison with its benzyl-protected counterpart and was found to be equally efficient in the alkylation of simple amines but superior in deprotection. For substrates bearing basic amine sites, the β-cyanoethyl group is largely preferable.

Introduction

Over the past few decades, the tetrazole functional group has attracted increasing interest in fields as diverse as drug discovery, organocatalysis, and coordination chemistry. In drug design in particular it is regarded as an isoster for the carboxylate group,[1] with the N–H acidity being remarkably close to the O–H acidity of the latter ($pK_a \approx 5.5$). The tetrazole moiety is also generally accepted to exhibit stronger resistance to in vivo metabolization than the carboxylate group, thus conferring to the corresponding drug longer lifetimes in blood.[2,3] In the field of organocatalysis, it is used as an attractive substitute for the carboxylic acid group to increase solubility in organic solvents.[4,5] Last but not least, the tetrazole group has been investigated for its coordination properties in metal complexes.[6] Here, it is regarded as a reasonably hard N ligand that can compensate positive charges stemming from the metal center so as to reduce the net charge of the resulting complex, a property that it shares with many other N–H "acidic" ligands found in metal complexes. However, those ligands almost exclusively show very high pK_a values and their acidity can be regarded as negligible compared with that of the tetrazole moiety. It is this property that places it in a rather unique position among N coordinating sites in multidentate ligands.

We have been interested in such N(x) ligands that can compensate the positive charges of metal centers to give electroneutral complexes for medical applications.[7] The value in using coordinating sites with a pK_a lower than physiological pH (7.4) has been recognized by experts for their ability to preserve high complex stability under these specific conditions.[8] They stressed the need to prevent competition between protonation and metal coordination of the coordinating site to avoid disruption of the metal-to-ligand bond. As seen with most other N donor moieties such as pyridyl or imidazolyl, tetrazolyl groups should be preferably introduced into multidentate ligands in such a fashion as to give 1,4-chelating motifs, leading to favorable five-membered chelate rings. This requires an extra chain member, usually a methylene group, to be placed between the tetrazole ring and the next coordinating heteroatom. Introduction of a tetrazolylmethyl group on to a heteroatom should thus be the focal point in ligand design.

The unprotected tetrazole moiety is commonly prepared from a nitrile using excess sodium azide (Scheme 1).[9,10] Coordination chemists have used this strategy to create tetrazoles in their multidentate ligands in the last step of the synthesis (Scheme 1).[11] Of course this strategy would not allow further synthetic manipulation without first protecting the N–H acidic sites, a measure that leads to unsatisfactory results (Scheme 2).[12] These drawbacks do not even address the challenge of introducing two to four protecting groups into the same molecule to furnish ligands displaying multiple tetrazole groups. We have therefore developed an alternative, highly convergent approach to introducing the tetrazolylmethyl group by using a regiochemically defined synthon bearing a benzyl protecting group and activated

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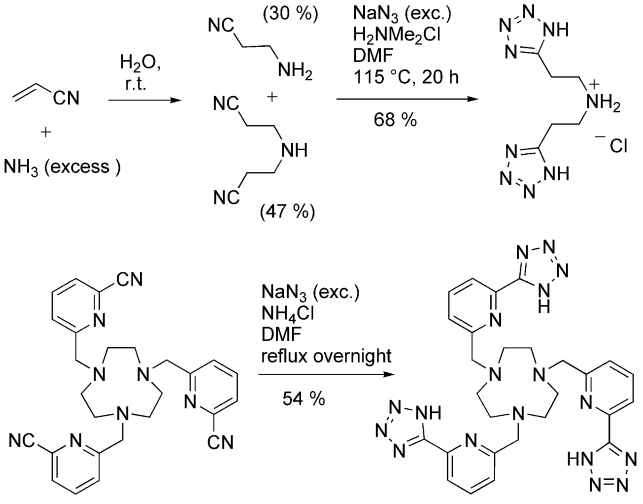
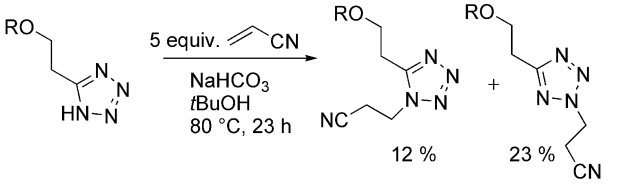
for nucleophilic attack (Scheme 3).[13] This strategy is analogous to many other strategies such as the grafting of *tert*-butyl-protected acetate groups onto nucleophile-bearing compounds. Synthon **1**[14] was thus applied to the straightforward synthesis of the tetrakis-tetrazolyl analogue of EDTA, namely EDTT.[13] No ligand displaying multiple units of free tetrazoles has been synthesized by using a preprotected tetrazole synthon before. However, its synthesis was hampered in the last step by the requirement of large amounts of palladium/carbon to remove four units of the benzyl protecting group. Thus, we describe an alternative synthon bearing a protecting group with properties orthogonal to those of the benzyl group. The scope of both our synthons is demonstrated through a few syntheses as examples.

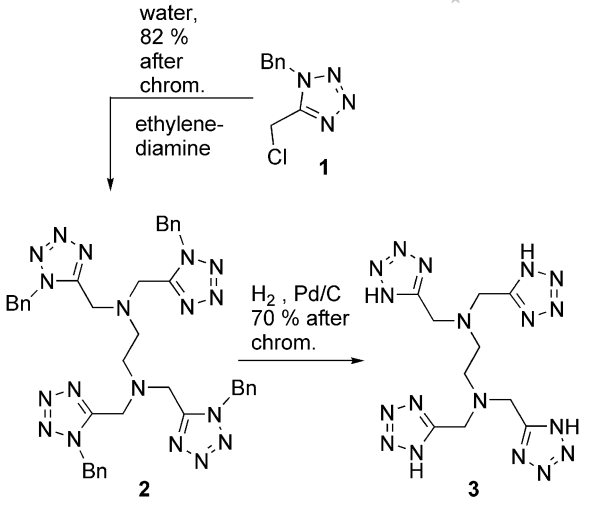


Scheme 1. Examples of tetrazole syntheses from nitriles.[9–11]

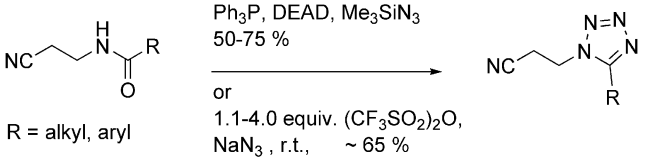


Scheme 2. Regioisomers formed when protecting free tetrazoles.[12]

In the field of medicinal chemistry, the creation of β-cyanoethyl (BCE)-protected tetrazole rings is now a fairly established procedure.[15–19] The BCE group can be cleaved under comparatively mild conditions by the use of LiOH or DBU in a retro-hetero-Michael reaction releasing acrylonitrile. On the other hand, the BCE-protected tetrazole moiety is exclusively synthesized from the corresponding BCE-substituted carboxamide (Scheme 4). Costly commercial reagents are required and the transformations give moderate yields and large amounts of waste material (Scheme 4).[20–26]



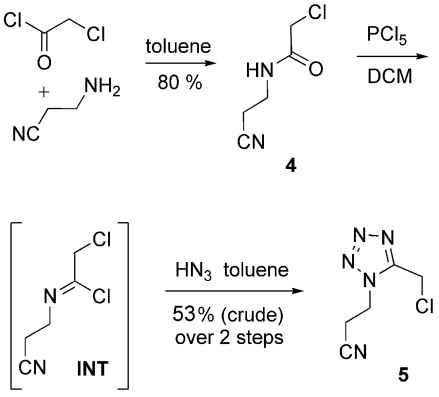
Scheme 3. Our strategy of employing a preprotected synthon, applied to the exemplary synthesis of EDTA-analogous ligand **3**.[13]



Scheme 4. Synthesis of the BCE-protected tetrazole moiety, as used in the field of medicinal chemistry.

Results and Discussion

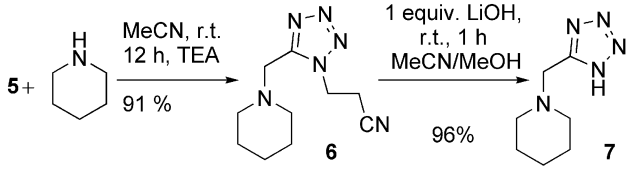
The classic conditions using hydrazoic acid (HN_3) introduced by von Braun[27] (see also ref.[28]) have served well to synthesize large quantities of synthon **1**. The protocol for the synthesis of BCE derivative **5** is similar to that of the benzyl derivative **1** that we developed[13] based on the original report by Harvill et al.[14] Economic β-aminopropionitrile is treated with chloroacetyl chloride to give solid *N*-cyanoethylchloroacetamide (**4**) in good yield (80%, Scheme 5). Great care is crucial for the success of the next two steps: The transformation to the chloroimine intermediate (**INT**) by use of PCl_5 requires the removal of all HCl generated in the process.[36]



Scheme 5. Preparation of new BCE-protected tetrazole synthon **5**.

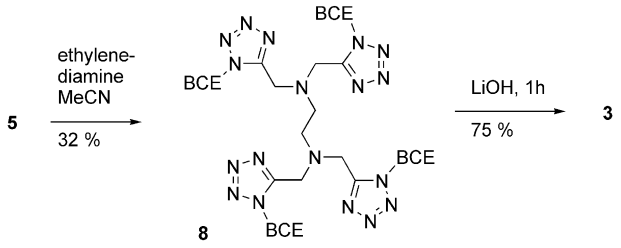
Thorough degassing limits the presence of **4** in the final product **5** to less than 5% after treatment of the chloroimine **INT** with a toluene solution of hydrazoic acid (HN_3) and a yield of crude **5** of 72% can be reliably attained. Silica gel chromatography then removes residual **4** and phosphoryl chloride ($POCl_3$) to give pure **5** as a colorless oil in 42% yield over three steps, and this on the gram scale. The presence of polar **4** exceeding 5% will greatly compromise the success of this purification step. Synthon **5** is soluble in most organic solvents, sparely soluble in water, and totally soluble in hot water. It can be kept for months without taking particular precautions.

The essence of this work resides in the comparison of the performances of the synthons **1** and **5** in the alkylation of nucleophile-bearing compounds and the deprotection of the resulting species. We were not surprised to find that monoalkylation of a simple substrate with **5** is highly effective. In fact, with rare exceptions,[21] most drug targets only sport one tetrazole moiety, a statement that holds true also for organocatalysts. Although an initial test of **5** with piperidine in acetonitrile at reflux gave crude **6** along with side-products (70% yield after chromatography), its transformation over 12 h with the same slight excess (1.07 equiv.) of piperidine, but at room temperature, gave pure solid **6** in 91% yield without further purification (Scheme 6). Neither the presence of an excess of TEA as helper base nor the presence of piperidine appeared to endanger the BCE group. According to Biot et al.,[26] LiOH in acetonitrile proved to be the most effective base for removing the BCE group, whereas organic bases such as DBU/TBAF in DCM produced free tetrazoles of lower purity. In our hands, the application of 1.05 equiv. of LiOH in mixtures of acetonitrile and methanol indeed gave very satisfactory results. Reactions at room temperature were complete after 1 h (NMR) and a simple work-up involving evaporating the mixture to dryness and washing the residue with acetonitrile gave excellent yields of the free tetrazole **7** (Scheme 6).



Scheme 6. Performance of BCE-protected synthon **5** during the monoinstallation of a tetrazolylmethyl unit onto a nucleophile-bearing compound.

As described in Scheme 3, we recently reported the application of benzyl-protected synthon **1** in the exemplary preparation of the EDTA analogue EDTT (**3**).[13] We now wished to determine whether the use of BCE-protected synthon **5** would approach the remarkably efficient four-fold alkylation of ethylenediamine that we observed for **1** (Scheme 7). The driving force responsible for the almost quantitative yields of **2** was its precipitation in water even at 70 °C. Unfortunately, we were not able to develop such favorable conditions when using **5**. Whereas **1** is a crystalline colorless solid that melts and gives a white emulsion at 70 °C in water, resin-like **5** dissolves in water above 50 °C. According to LCMS/UV-monitoring, the reaction never went to completion and partially alkylated species were always detected, no matter what conditions were used. Both 2,6-lutidine and triethylamine were tested as helper bases, and water, acetonitrile, THF, and toluene as solvents. The results of these experiments revealed the optimal procedure to involve heating the mixture at 50 °C for 4 days in acetonitrile whereupon the mixture is concentrated in vacuo and the resultant resin washed with DCM and water to give already pure **8** (yield 32%). The presence of lutidine did not seem to have an adverse effect on the base-sensitive BCE protective group.



Scheme 7. Performance of BCE-protected synthon **5** in the synthesis of EDTA analogue EDTT (**3**).

We then reexamined the deprotection conditions of benzylated **2**[13] to decide on the overall performance of the two strategies. Two flaws in the hydrogenative debenzylation of this particular compound can be identified: (1) The need for large amounts and a high quality/freshness of the Pd/C catalyst and (2) LCMS-monitoring to pinpoint the moment at which work-up should be launched. Indeed, Sajiki and Hirota described how they could control the performance of the catalyst towards hydrogenation or hydrogenolysis of aliphatic or aromatic benzyl ethers by poisoning the catalyst with ammonia or more sophisticated nitrogen bases.[29] Ethylenediamine or diethylenetriamine showed the "best" results. They concluded that the important criterion for good Pd/C poisoning is a 1,4-didentate coordinating motif giving five-membered chelates with palladium. In addition, from their results they proposed a two-step coordination process with a fast first step in which a loose interaction between ethylenediamine and Pd/C is formed, and a second step that may take more than 30 h in which the chelate is formed. This may then be at the root of the hydrogenation problems described above, especially in view of the facts that (1) we have reported the deprotection of **1** under "truly catalytic conditions"[13] and (2) the reaction time for **2** should not exceed 2 days (point 2 from above) to avoid losses due to excessive absorption.[13] Other research teams similarly observed that the debenzylation of tetrazoles requires excessive amounts of palladium catalyst.[21,30–32] Surfraz et al., who tried to deprotect aminocyclitols bearing two benzylated secondary alcohol groups, noticed that the presence of a secondary or tertiary nitrogen atom prevented hydrogenolysis altogether (0% yield) whereas its absence allowed smooth deprotection under truly catalytic conditions (quantitative yield)![33]

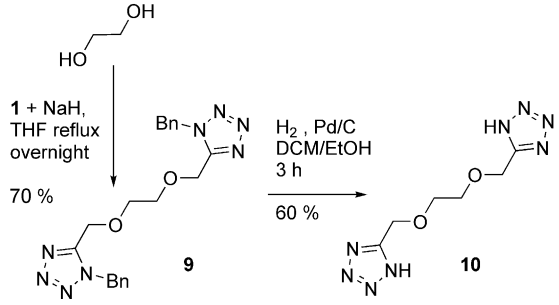
The report by Sajiki and Hirota,[29] that the poisoning effect of nitrogen bases can be repressed by the presence of strong acids, prompted us to investigate the effect of trifluoroacetic acid (TFA) on the deprotection of **2** (Table 1). All in all, the best yield of **3** was achieved with 300 wt.-% of 5% Pd/C in TFA (which corresponds to 1 equiv. based on Pd) for 48 h (84%). This can be compared with the yield of 70% achieved in DCM/EtOH and in the absence of TFA for the same duration.[38]

Table 1. Hydrogenation conditions and results for the deprotection of **1**, **2**, and **9**.

	Solvent	Reaction time [h]	Pd/C(% w/w)	Isolated yield [%]
1	EtOH	24	20	99[a]
1	EtOH	1	100	99[b]
2	DCM/EtOH 1:1	48	600	70[c]
2	DCM/EtOH 1:1 + 10 equiv. TFA	–	600	–[d]
2	TFA (neat)	48	300	84[e]
2	DCM/EtOH 1:1	48	300	21
9	DCM/EtOH 1:1	12	250	–[f]
9	DCM/EtOH 1:1	3	500	60

[a] Not isolated, hydrogenation also resulted in partial loss of the chlorine atom and formation of a methyl group (40%). [b] Not isolated, hydrogenation also resulted in partial loss of the chlorine atom and formation of a methyl group (66%). [c] See ref.[13]. [d] Reaction stopped midway. [e] Approximate yield. [f] Not determined because reaction still not complete.

Finally, we wished to assess the influence of tetrazoles on catalyst performance and synthesized the model compound **10**. The double alkylation of ethylene glycol with benzylated synthon **1** in THF at reflux and in the presence of sodium hydride was straightforward (Scheme 8). Dibenzylated **9** turned out to be remarkably polar, but could be purified on silica gel with up to 5% MeOH, albeit containing residual polar impurities (70% yield). The speed of hydrogenative deprotection of **9** was again very much dependent on the quality (batch) of the (commercial) palladium catalyst. The conditions that we were able to reproduce several times comprised 500 wt.-% of 5% Pd/C (0.5 equiv. per benzyl moiety), that is, as much as was used to deprotect **2**, but **10** was furnished in a sixteenth of the time (3 h) found for **3** (Table 1). Free bis-tetrazole **10** is a colorless resin that slowly precipitates as a powder from an acetonitrile solution. The yield of 60% combined with that of the previous double alkylation step leads to an overall yield of 42% starting from ethylene glycol, a decent performance.



Scheme 8. Satisfactory performance of the installation and deprotection of benzylated synthon **1** on compounds bearing nucleophiles other than amine groups.

Conclusions

We have prepared a BCE-protected tetrazolylmethyl synthon (**5**) and assessed its merits in the installation of one or four units of the free tetrazolylmethyl group into nucleophile-bearing compounds by comparison with its benzylated analogue (**1**). The removal of the benzyl group from those compounds resulting from the use of synthon **1** is severely hampered by the presence of chelating units; the presence of acid may mitigate catalyst poisoning to some extent. Even compounds displaying ether moieties instead of aliphatic amines appear to impair catalyst performance. We therefore cannot but conclude that tetrazoles that are part of chelating motifs may interact detrimentally with Pd/C. On the other hand, benzylated tetrazoles that are not part of such a motif appear to react with truly catalytic amounts of catalyst.

By contrast, the new β-cyanoethyl-protected synthon **5** performs superbly under very mild conditions during monoalkylation and subsequent deprotection to the free tetrazole compound. Even in the challenging case of quadruple alkylation the yield of the hexadentate ligand is acceptable and its mild deprotection to a difficult-to-handle zwitterionic system gives very satisfactory yields.

Experimental Section

Caution: *Experimentation with sodium azide and hydrazoic acid can be hazardous.* Safety precautions should include working in a properly working fume hood and wearing gloves and safety glasses. Azides of heavy metals can be explosive and thus contact with heavy metals must be avoided. Contact of azides with chlorinated solvents should also be avoided, as should any unnecessary scale-up of the described reactions.[34,35]

***N*-Cyanoethylchloroacetamide (4):** Chloroacetyl chloride (7 mL, 89 mmol) was added dropwise to a vigorously stirred solution of aminopropionitrile (13 mL, 180 mmol, 2 equiv.) in toluene (50 mL) at 0 °C using a mechanical stirrer. A colorless precipitate formed immediately and the suspension thickened progressively, thus potentially requiring the addition of further toluene. Once the addition of the reactant was complete, stirring was continued for 20 min before quenching the reaction with water (100 mL). The addition of ethyl acetate (50 mL) caused the solid to dissolve completely. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 × 50 mL), dried with Na_2SO_4, filtered, and concentrated. *N*-Cyanoethylchloroacetamide (**4**) was thus obtained as a colorless solid (10.07 g, 79%). ^{1}H NMR ($CDCl_3$, 300 K, 200 MHz): δ = 4.08 (s, 2 H), 3.59 (q, J = 6.4 Hz, 2 H), 2.37 (t, J = 6.4 Hz, 2 H) ppm.

1-Cyanoethyl-5-chloromethyltetrazole (5). Step 1: Phosphorus pentachloride (16.8 g, 81 mmol) was added portionwise to a vigorously stirred suspension of *N*-cyanoethylchloroacetamide (**4**; 10.2 g, 70 mmol) in dichloromethane (250 mL) at 0 °C. The reaction mixture was raised to ambient temperature and thoroughly degassed for at least 2 h to remove all HCl. Extra dichloromethane was

added sporadically to avoid drying of the reaction mixture. The solution of crude *N*-cyanoethyl-1,2-dichloroacetylimine thus obtained was then used directly in the next step.

Step 2: Under a properly operating fumehood, a solution of concentrated sulfuric acid (25 mL) was added dropwise under cooling to a gently stirred solution of sodium azide (15 g, 0.35 mol) in water (15 mL) overlaid by toluene (60 mL). The phases were separated and the aqueous layer was extracted with toluene (2 × 20 mL). The combined extracts were dried with Na_2SO_4. This hydrazoic acid (HN_3) solution was slowly added to the cooled chloroimine solution from step 1 and stirred overnight at room temperature; over time a red-brown resin precipitated from the mixture. The excess of HN_3 was removed under reduced pressure (under a well operating fumehood) followed by removal of the dichloromethane and eventually toluene. The proportion of residual **4** in the green resin obtained was assessed by NMR spectroscopy. The latter is dissolved in chloroform/ethyl acetate (9:1; to separate an orange insoluble) and purified by silica gel chromatography (9:1 to 6:4) to give pure **5** (6.4 g, 53%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 K, 200 MHz): δ = 4.94 (s, 2 H), 4.75 (t, J = 6.7 Hz, 2 H), 3.15 (t, J = 6.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 300 K, 50 MHz): δ = 151.9, 116.0, 43.5, 31.2, 18.7 ppm. HRMS: calcd. for $C_5H_6ClN_5Na$ [M + Na]$^+$ 194.0209; found 194.0215.

***N*,*N*,*N*′,*N*′-Tetrakis[(1-cyanoethyltetrazol-5-yl)methyl]-1,2-ethanediamine (8):** A solution of ethylenediamine (1 equiv., 0.36 mmol) was prepared by combining a stock solution of ethylenediamine (6 mL, 60 mM) in acetonitrile with 2,6-lutidine (0.17 mL, 4.2 equiv., 1.5 mmol). The resulting solution was treated with **5** (0.26 g, 4.2 equiv., 1.5 mmol). The mixture was heated at 50 °C and after 1 day at 60 °C. The pH was adjusted to 8 by regular addition of 2,6-lutidine. The reaction was monitored by LC–MS, a white solid precipitated, and the solution turned from yellow to red. After 4 d, the acetonitrile was evaporated and the resulting dark-red resin was washed with dichloromethane and water to yield pure **8** (70 mg, 32%). ^{1}H NMR (CD_3CN, 300 K, 200 MHz): δ = 4.65 (t, J = 6.6 Hz, 8 H), 4.14 (s, 8 H), 3.07 (t, J = 6.7 Hz, 8 H), 2.90 (s, 4 H) ppm. ^{13}C NMR (CD_3CN, 300 K, 50 MHz): δ = 152.3, 117.4, 51.1, 46.3, 43.2, 18.2 ppm.

***N*,*N*,*N*′,*N*′-Tetrakis[(tetrazol-5-yl)methyl]-1,2-ethanediamine (3). Lithium Salt (obtained from 8):** A solution of $LiOH·H_2O$ (1 mL, 4.1 equiv., 26.7 mg, 0.64 mmol) was added to a stirred solution of **8** (93 mg, 0.16 mmol) in acetonitrile (5 mL) under argon. After 20 min a creamy red solid began to precipitate and the reaction was carried on for another 1.5 h. The solvents were evaporated under reduced pressure and the light-red solid obtained was washed with dichloromethane and acetonitrile to yield pure **3** (45 mg, 73%). ^{1}H NMR (D_2O, 300 K, 200 MHz): δ = 3.96 (s, 8 H), 2.76 (s, 4 H) ppm. ^{13}C NMR (D_2O, 300 K, 50 MHz): δ = 159.1, 50.2, 47.3 ppm.

***N*-[(1-Cyanoethyltetrazol-5-yl)methyl]piperidine (6):** A basic solution of piperidine (1 equiv., 1.6 mmol) was prepared by combining a stock solution of piperidine (0.32 M, 5 mL) in acetonitrile with triethylamine (1 mL, 4.5 equiv.). The resulting solution was treated with **5** (0.25 g, 0.94 equiv., 1.5 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After 12 h, acetonitrile was evaporated under reduced pressure and water (20 mL) was added. The mixture was extracted with chloroform (2 × 50 mL). The organic phases were combined, dried with Na_2SO_4, and concentrated to dryness to give **6** as a colorless solid (300 mg, 91%). ^{1}H NMR ($CDCl_3$, 300 K, 200 MHz): δ = 4.75 (t, J = 6.8 Hz, 2 H), 3.80 (s, 2 H), 3.06 (t, J = 6.8 Hz, 2 H), 2.35 (m, 4 H), 1.47 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 300 K, 50 MHz): δ = 152.8, 116.4, 54.7, 51.5, 43.2, 25.9, 23.7, 18.5 ppm.

***N*-[(Tetrazol-5-yl)methyl]piperidine (7). Lithium Salt:** The same procedure as applied to **8** was applied to **6** (254 mg, 1 equiv., 1.2 mmol) by using $LiOH·H_2O$ (51 mg, 1.05 equiv., 1.2 mmol). The desired **7** was obtained as a colorless solid (190 mg, 96%). ^{1}H NMR (D_2O, 300 K, 200 MHz): δ = 3.53 (s, 2 H), 2.17 (m, 4 H), 1.25–1.05 (m, 6 H) ppm. ^{13}C NMR (D_2O, 300 K, 50 MHz): δ = 158.2, 52.8, 51.2, 24.8, 23.0 ppm. HRMS: calcd. for $C_7H_{13}N_5Na$ [M + Na]$^+$ 190.1069; found 190.1074.

***O*,*O*′-Bis[(1-benzyltetrazol-5-yl)methyl]-1,2-ethanediol (9):** A stock solution of ethylene glycol (5 mL, 1 equiv., 2.3 mmol, 0.46 M) was added dropwise under argon to a cooled and stirred suspension of sodium hydride (previously washed with petroleum ether) in THF (5 mL) in a two-necked round-bottomed flask equipped with a condenser. Under continued cooling, **1** (1.0 g, 2.1 equiv., 4.8 mmol) in THF (5 mL) was added dropwise. The solution was raised to room temperature and heated at reflux overnight. The orange suspension obtained was quenched under cooling with water (15 mL) and extracted with DCM (3 × 70 mL). After evaporation under reduced pressure a yellow resin was obtained and purified by silica gel chromatography (ethyl acetate/petroleum ether, 50:50, to pure ethyl acetate) to give reasonably pure **9** (700 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 K, 200 MHz): δ = 7.31–7.19 (m, 2 H), 2.17 (m, 10 H), 5.54 (s, 4 H), 4.65 (s, 4 H), 3.47 (s, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 300 K, 50 MHz): δ = 151.4, 133.3, 129.2, 129.1, 127.9, 70.0, 61.5, 51.5 ppm. HRMS: calcd. for $C_{20}H_{22}N_8O_2Na$ [M + Na]$^+$ 429.1763; found 429.1764.

***O*,*O*′-Bis[(tetrazol-5-yl)methyl]-1,2-ethanediol (10):** A solution of **9** (0.27 g, 0.67 mmol) in a 1:1 mixture of DCM/EtOH (20 mL) was treated with 5% palladium on carbon ("Degussa" quality) (1.4 g, 1 equiv., 500 wt.-%). The stirred solution was saturated with hydrogen, the flask sealed with a septum and the gas phase purged with hydrogen, and finally placed under 1 atm. of hydrogen. Stirring was continued at room temperature for 3 h. The mixture was filtered through Celite, washed with ethanol, and concentrated to give the crude product as a colorless oil. Acetonitrile was added to the oil and the mixture was stored in the fridge until the precipitation of colorless **10** was complete. Decantation and drying yielded 90 mg of **9** (60%). ^{1}H NMR (D_2O, 300 K, 200 MHz): δ = 4.82 (s, 4 H), 3.69 (s, 4 H) ppm. ^{13}C NMR (D_2O, 300 K, 50 MHz): δ = 154.2, 70.2, 61.4 ppm. HRMS: calcd. for $C_6H_{10}N_8O_2Na$ [M + H]$^+$ 249.0824; found 249.0831.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra.

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[36] By NMR monitoring we demonstrated that after the addition of nearly equimolar amounts of PCl_5 and degassing for 2 h, which requires the addition of extra DCM to avoid too high a concentration of the mixture, no starting material **1** is left in the **INT** sample. Should one omit degassing and leave the mixture overnight, one may discover only starting material **1** in the mixture the following day. Note that we did not detect any trace of an amidine-like condensation product resulting from the tautomerization of **INT** and its reaction with another molecule of **INT**, as has been described by Harvill et al. for aliphatic chloroimines.[14,37]
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[38] To remove the TFA component from the initially obtained hydrotrifluoroacetate, we resorted to a precipitation approach that involved adjusting the pH to 13 with a solution of NaOH and then adding a mixture of MeCN/MeOH (9:1) to induce precipitation. Our published preparation of **2**[13] was subsequently reproduced several times with yields of around 65% after reversed-phase cartridge purification and the resulting free zwitterion was obtained in pure quality (according to NMR and LC–MS analyses) ready for metal complexation experiments.

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