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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.

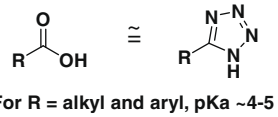
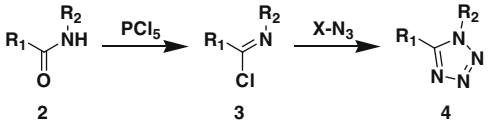


Figure 1.

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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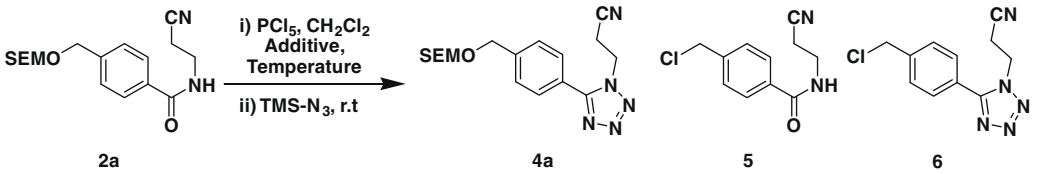


2a 4a 5 6

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

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

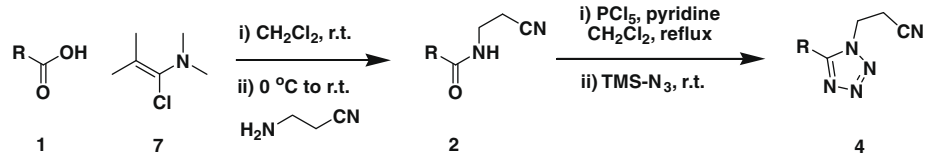
Temperature (°C)	Additive	% Yield **4a**	% Yield **5**	% Yield **6**
−5	None	0	65	23
40	None	0	71	0
40	Pyridine	83	0	0

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).

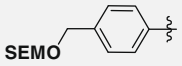
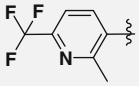
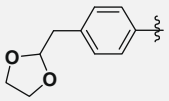
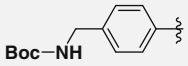
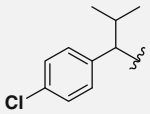
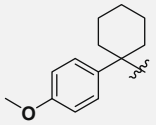
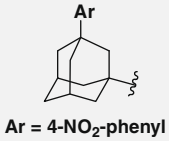
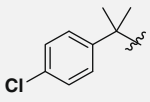
Conversion of amides **2a–h** to the corresponding tetrazoles **4a–h** using the previously described conditions proceeded efficiently (Table 2, entries 1–8).[10,11] The yield of the tetrazoles was reasonably consistent (73–86%) and the nature of the R-group appeared to have little impact. Sterically 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]