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## PYRIDINE METALLATIONS IN THE SYNTHESIS OF TRIAZOLE BASED NK-1 ANTAGONISTS

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**Abstract** – Regioselective pyridine metallation chemistry was used to produce *N*-(3-chloropyridin-4-ylmethyl)-*N*-methyl-1-(3,5-bis-trifluoromethylbenzyl)-5-phenyl-1*H*-[1,2,3]triazole-4-carboxamide (**9a**) and [1-(3,5-bis-trifluoromethylbenzyl)-5-morpholin-4-yl-1*H*-[1,2,3]triazol-4-yl]-[3-(3-chloropyridin-4-yl)-5-hydroxymethylisoxazol-4-yl]methanone (**16a**), which exhibit NK-1 antagonist activity.

In recent years, there has been significant interest in the discovery and development of NK-1 antagonists.<sup>1</sup> Currently, Merck's NK-1 antagonist (MK-869) is approved for the treatment of emesis.<sup>2</sup> NK-1 antagonists have been studied in the clinic as treatment for stress related disorders. We recently disclosed some of our work on a triazole based platform represented by compounds (**1**) and (**2**) (Figure 1).<sup>3</sup> These compounds demonstrated potent NK-1 antagonist activity in *in vitro* and *in vivo* models but issues of solubility and

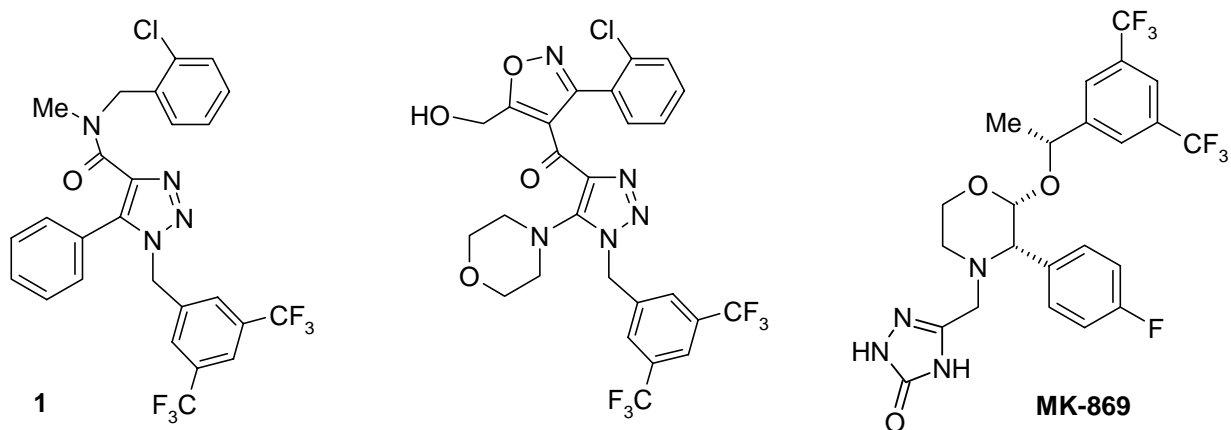
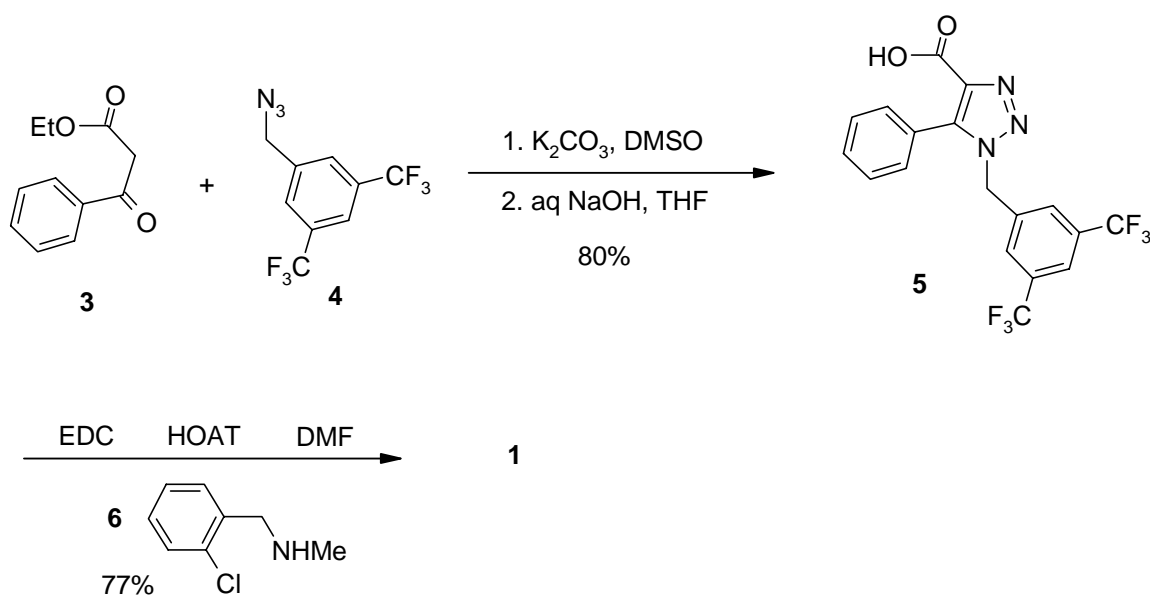


Figure 1

<sup>†</sup> Dedicated to Professor Barry M. Trost on the occasion of his 65<sup>th</sup> birthday.

metabolism limited drugability. Our goal was to improve the aqueous solubility of these compounds by replacing the chloro-phenyl moiety with a chloro-pyridyl moiety without reducing intrinsic NK-1 antagonist activity.

Synthesis of the triazole template is accomplished regioselectively through the condensation of an azide (**4**) with an appropriately substituted  $\beta$ -keto ester (**3**) following the method of Cottrell.<sup>4</sup> Base-catalyzed hydrolysis provided the desired triazole acid (**5**). Coupling of the triazole acid (**5**) with (2-chlorobenzyl)-methylamine (**6**) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxy-7-azabenzotriazole (HOAT) in DMF provided compound (**1**) (Scheme 1).



### Scheme 1

In order to prepare the appropriately substituted pyridines we took advantage of the directing ability of halogen to selectively metallate halopyridines. We used LDA/THF deprotonation conditions to achieve “thermodynamic” lithiation as described by Queguiner.<sup>5</sup> Quench of the anions with DMF produced the desired aldehydes (**7a-c**). Our results metallating chloropyridines to produce pyridyl aldehydes (**7a-c**) are summarized in Figure 2 and parallel results described by Queguiner using fluoro pyridines.<sup>5</sup>

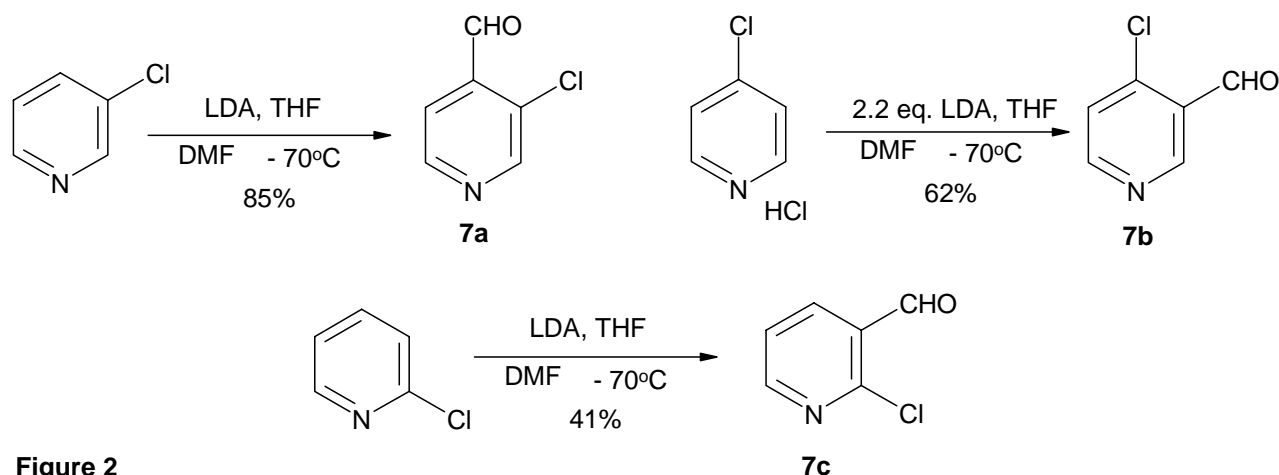
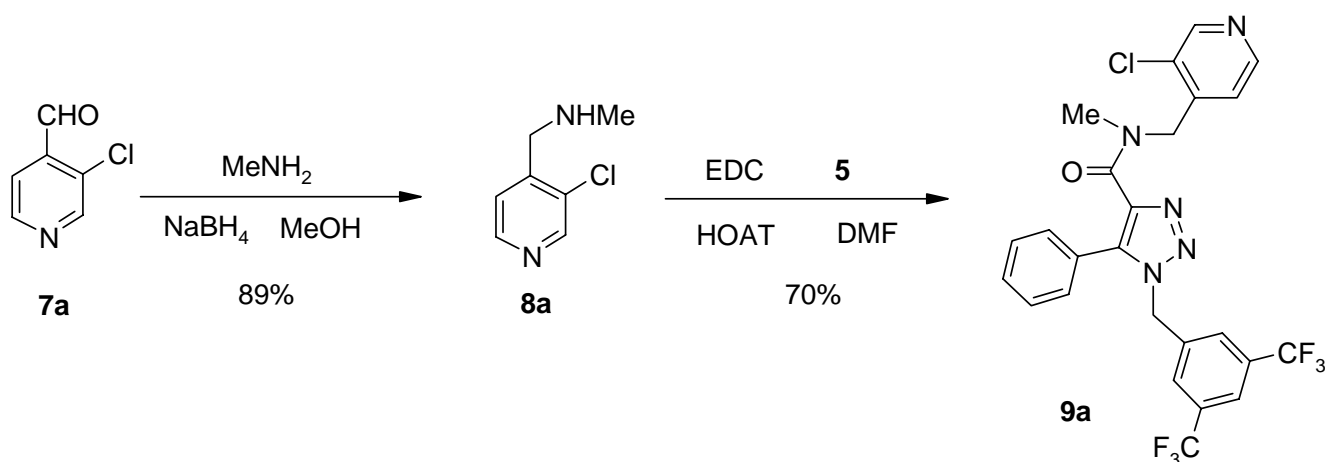


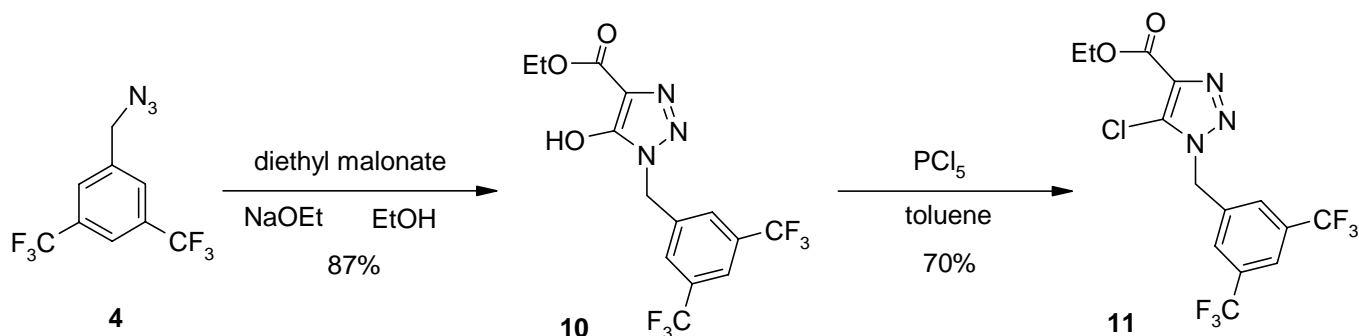
Figure 2

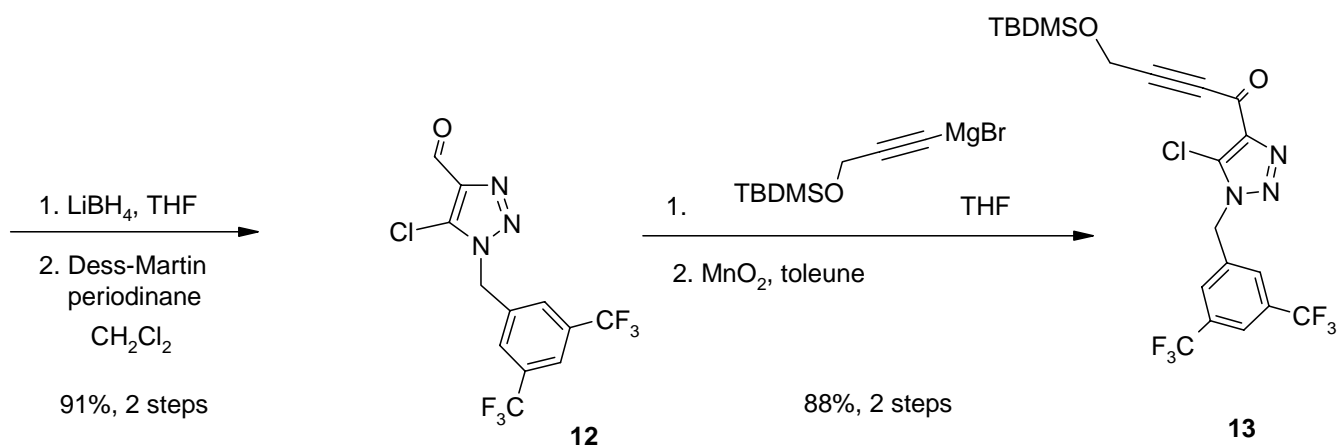
To complete construction of the desired pyridyl amide derivatives, for example, pyridyl aldehyde (**7a**) was subjected to reductive amination conditions with methylamine to produce the amine (**8a**) (Scheme 2). Subsequent amide coupling to the previously described triazole acid (**5**) provided the desired chloropyridyl-triazole amide (**9a**). This sequence was successfully accomplished with aldehydes (**7b**) and (**7c**) to provide the regioisomeric pyridyl amide derivatives (**9b**) and (**9c**). We were pleased to find that the pyridyl analogs displayed improved aqueous solubility and retained their activity as NK-1 receptor antagonists (compound **9a**,  $K_i = 0.10$  nM; compound **9b**,  $K_i = 50.80$  nM; compound **9c**,  $K_i = 2.90$  nM).<sup>6,8</sup>



**Scheme 2**

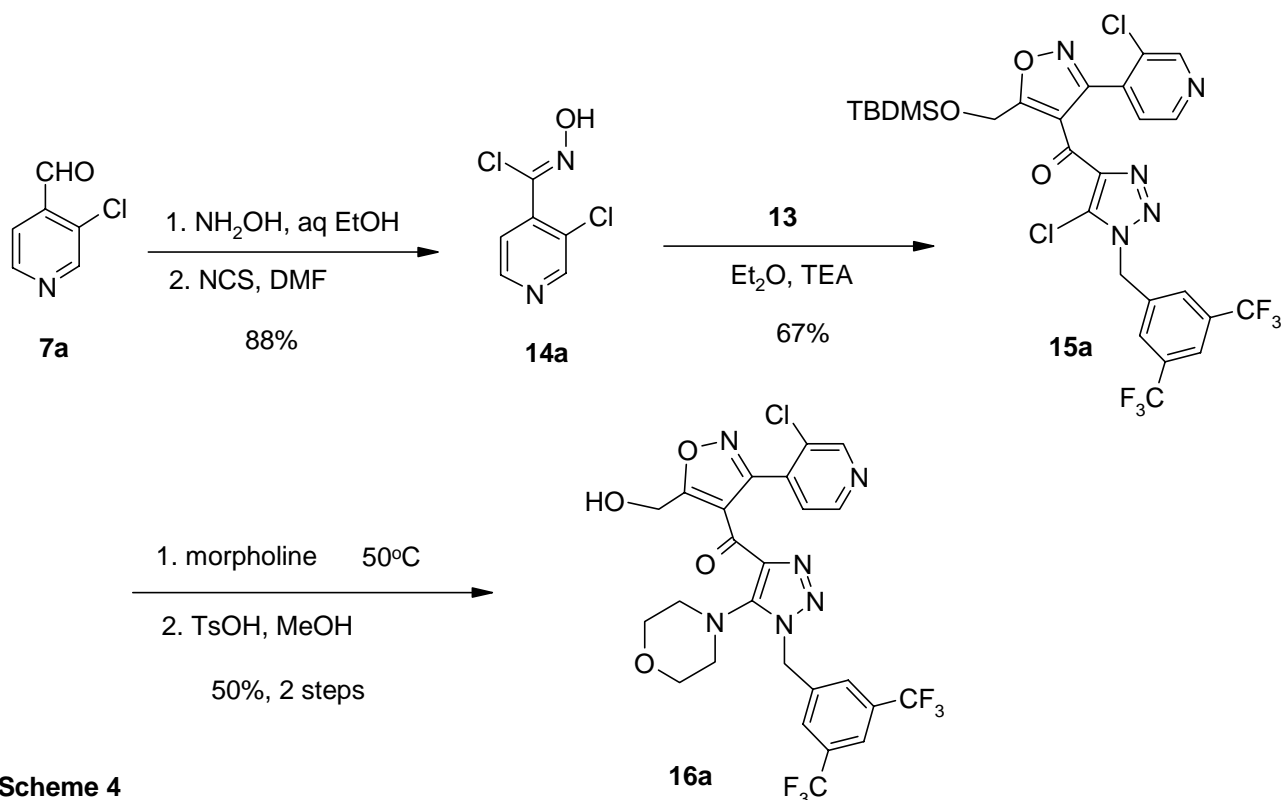
Another aspect of our investigation involved the use of isoxazoles as potentially more metabolically stable amide isosteres. Using the method of Buckle,<sup>7</sup> reaction of an azide (**4**) with diethyl malonate produced the 5-hydroxytriazole derivative (**10**). Conversion to the 5-chlorotriazole derivative (**11**) using  $\text{PCl}_5$  in toluene set the molecule up for late stage substitution at the triazole C-5 position (Scheme 3). In preparation for isoxazole construction, the 5-chlorotriazole ester (**11**) was reduced with  $\text{LiBH}_4$  in THF followed by Dess-Martin oxidation to the triazole aldehyde (**12**). Alkynyl Grignard addition to the triazole aldehyde (**12**) followed with  $\text{MnO}_2$  oxidation in toluene produced the keto alkyne intermediate (**13**).





### Scheme 3

To prepare for cycloaddition with the keto alkyne (**13**), the pyridyl-substituted nitrile oxide precursor (**14**) was produced by conversion of the pyridyl aldehyde (**7a**) to the oxime followed by oxidation with *N*-chlorosuccinimide (Scheme 4). Reaction of **14a** with the keto alkyne intermediate (**13**) in diethyl ether using triethylamine (TEA) as base resulted in formation of the desired isoxazole ring (**15a**). Substitution at C-5 of the triazole was accomplished, for example, by heating the 5-chlorotriazole derivative (**15a**) with morpholine followed by acid catalyzed hydrolysis of the silyl ether protecting group to give the desired pyridyl-isoxazole-triazole-ketone (**16a**) (Scheme 4). Similarly this sequence was carried out with each of the pyridyl aldehydes (**7b-c**). These compounds demonstrated good NK-1 antagonist activity (analog **16a**,  $K_i = 0.16$  nM; analog **16b**,  $K_i = 2.59$  nM; analog **16a**,  $K_i = 0.24$  nM)<sup>6,8</sup> as well as improved solubility and metabolic properties.



### Scheme 4

In conclusion, we have used directed pyridine metallation chemistry to produce various pyridyl triazole amides and pyridyl isoxazole-triazole-ketones. These derivatives demonstrated comparable biological activity to the phenyl substituted analogs (1) and (2). Further disclosure of additional aspects of our triazole based structure activity relationships will occur in due course.

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