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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-trifluoromethyl-benzyl)-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.[1] Currently, Merck's NK-1 antagonist (MK-869) is approved for the treatment of emesis.[2] 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).[3] These compounds demonstrated potent NK-1 antagonist activity in *in vitro* and *in vivo* models but issues of solubility and

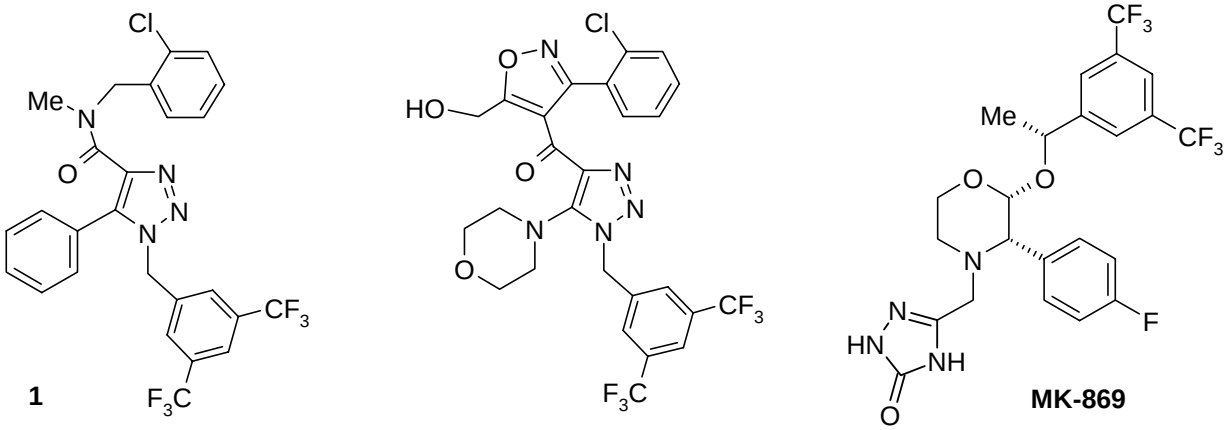
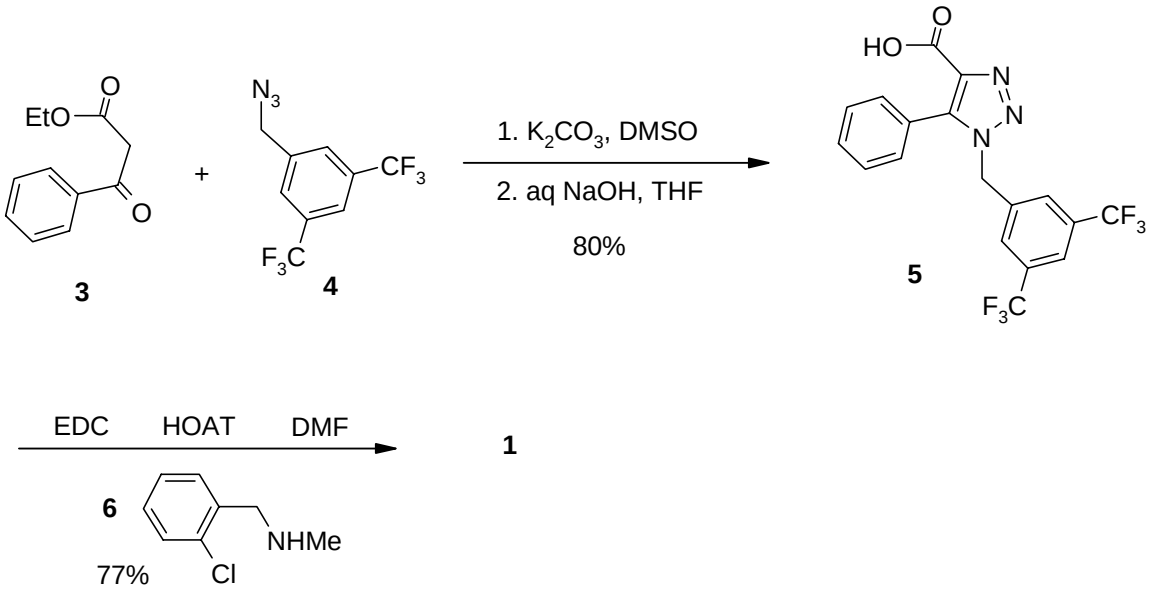


Figure 1

† *Dedicated to Professor Barry M. Trost on the occasion of his 65th 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 ß-keto ester (**3**) following the method of Cottrell.[4] 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.[5] 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.[5]

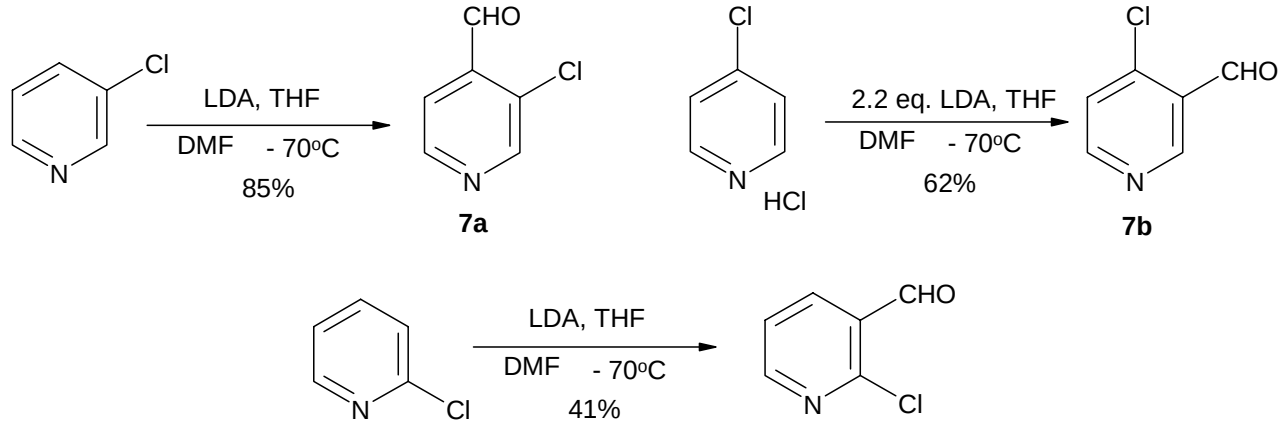
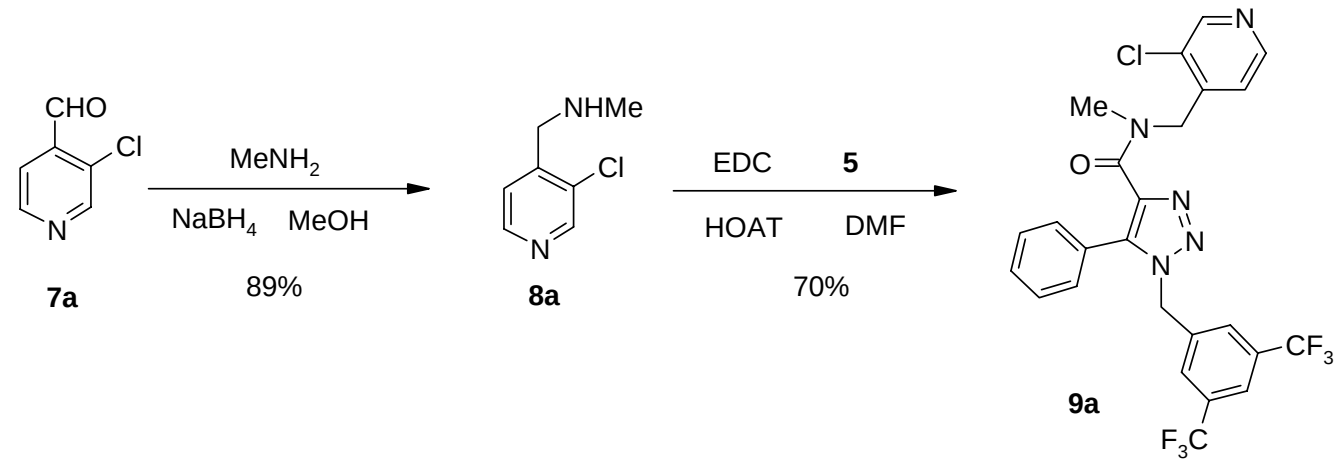


Figure 2

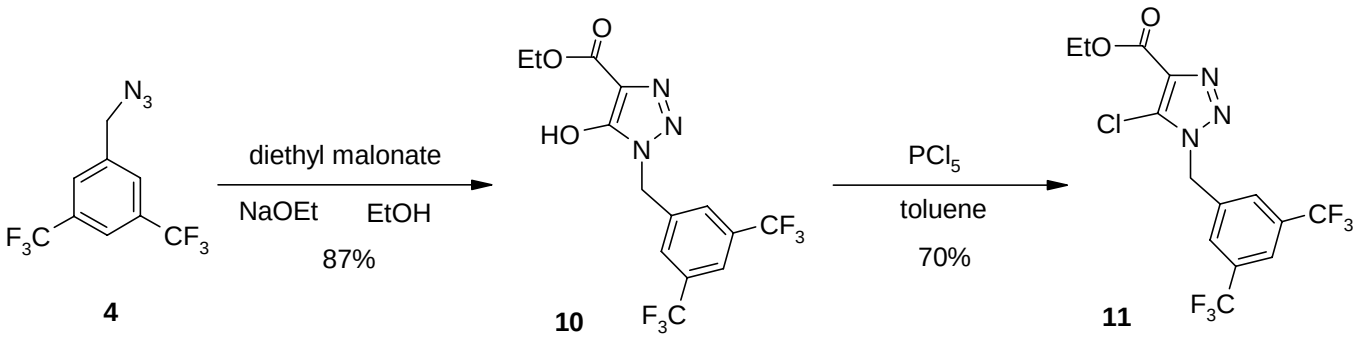
To complete construction of the desired pyridyl amide derivatives, for example, pyridyl aldehyde (**7a**) was subjected to reductive amination conditions with methylamine to produce the amine (**8a**) (Scheme 2). Subsequent amide coupling to the previously described triazole acid (**5**) provided the 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).[6,8]



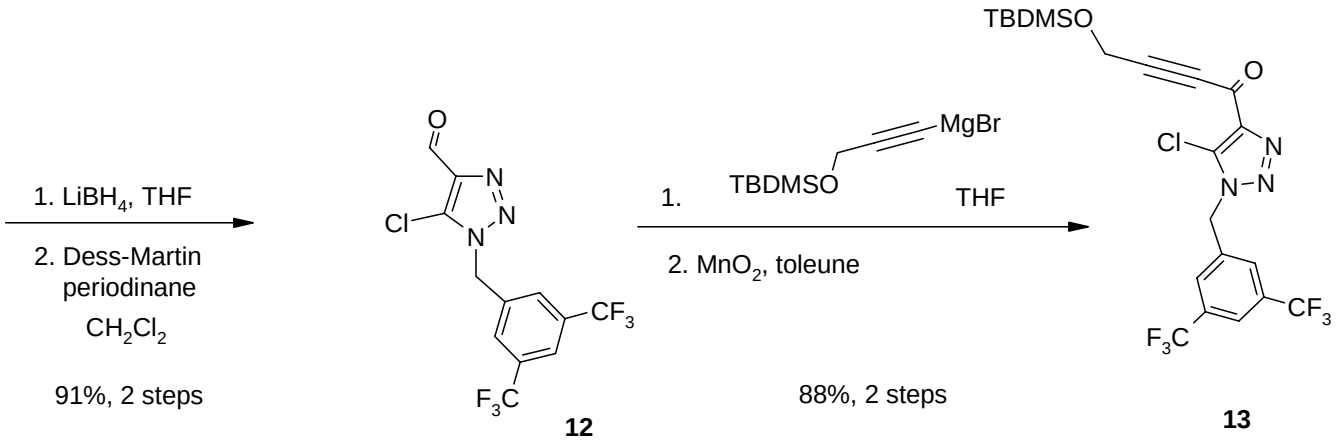
7a **8a** **9a**

Scheme 2

Another aspect of our investigation involved the use of isoxazoles as potentially more metabolically stable amide isosteres. Using the method of Buckle,[7] reaction of an azide (**4**) with diethyl malonate produced the 5-hydroxytriazole derivative (**10**). Conversion to the 5-chlorotriazole derivative (**11**) using 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 $LiBH_4$ in THF followed by Dess-Martin oxidation to the triazole aldehyde (**12**). Alkynyl Grignard addition to the triazole aldehyde (**12**) followed with MnO_2 oxidation in toluene produced the keto alkyne intermediate (**13**).

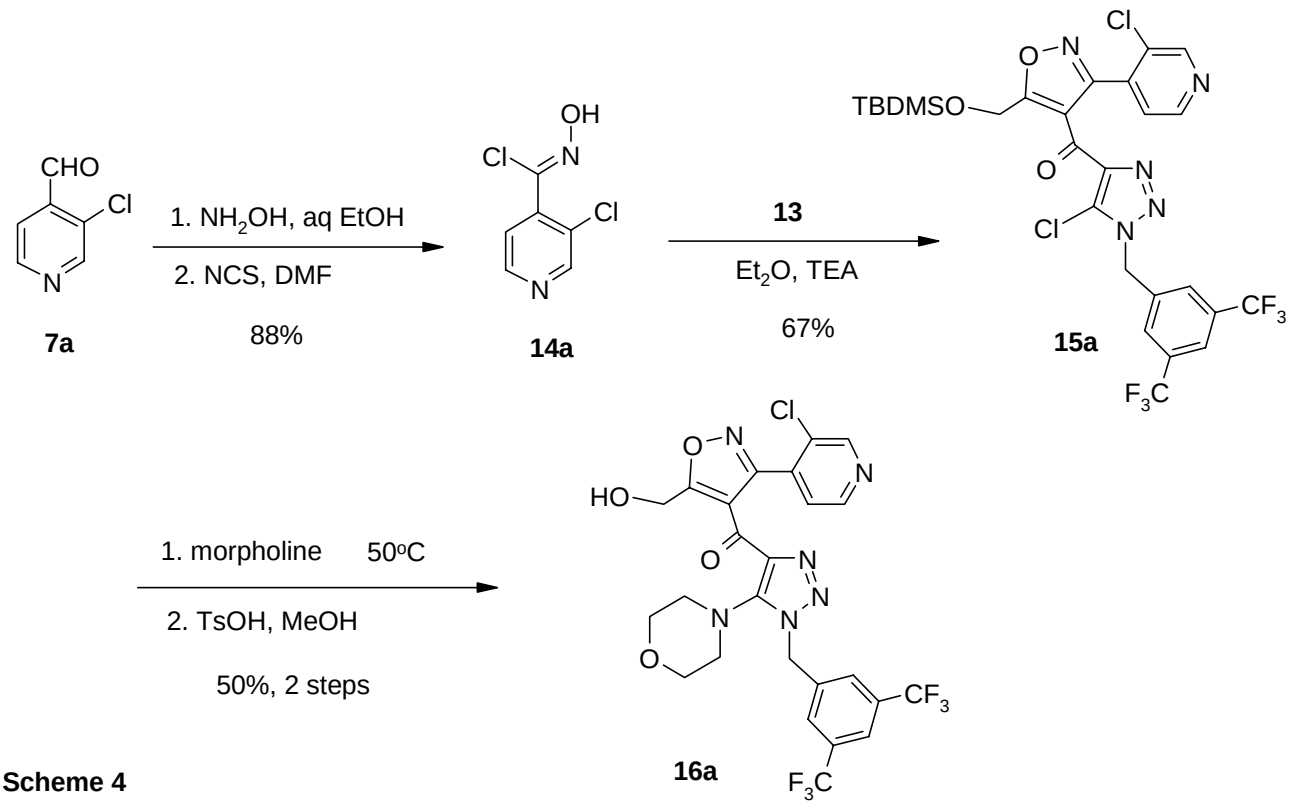


4 **10** **11**



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)[6.8] 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.

REFERENCES

1. J. Humphrey, *Curr Topics in Med Chem*., 2003, **3**, 1423.
2. D. Campos, J. Rodrigues Pereira, R. Reinhardt, C. Carracedo, S. Poli, C. Vogel, J. Martinez-Cedillo, A. Erazo, J. Wittreich, L. Eriksson, A. Carides, and B. Gertz, *J. Clin. Oncology*, 2001, **19**, 1759; J. Hale, S. Mills, M. MacCoss, P. Finke, M. Cascieri, S. Sadowski, E. Ber, G. Chicchi, M. Kurz, J. Metzger, G. Eiermann, N. Tsou, D. Tattersall, N. Rupniak, A. Williams, W. Rycroft, R. Hargreaves, and D. MacIntyre, *J. Med. Chem*., 1998, **41**, 4607.
3. A. Amegadzi, K. Gardinier, E. Hembre, J. Hong, L. Jungheim, B. Muehl, D. Remick, M. Robertson, and K. Savin, *Chem. Abstr*., 2003, **139**, 364938.
4. I. Cottrell, P. Hands, P. Houghton, G. Humphrey, and S. Wright, *J. Heterocycl. Chem*., 1991, **28**, 301.
5. F. Marsais and G. Queguiner, *Tetrahedron*, 1983, **39**, 2009.
6. Unpublished results from D. Schober and D. Gehlert, Lilly Research Laboratories.
7. D. Buckle and R. Rockell, *J. Chem Soc., Perkin Trans. I*, 1982, 627.
8. Satisfactory spectral data were obtained for all new compounds. Structure and purity determinations were based upon TLC, EA, NMR and mass spectroscopy measurements.