

Ugi Reaction of Natural Amino Acids Promoted by NbCl₅

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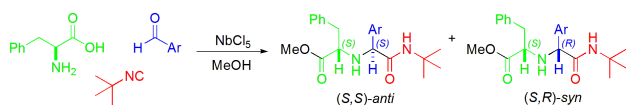
INTRODUCTION

Multicomponent Reactions (MCR) are useful reactions to obtain complex products by a simple mixture of 3 or more reactants.¹ Classic Ugi reaction (4-UCR) involves a mixture of an amine, aldehyde, isocyanide and a carboxylic acid giving peptoides as products. Some modifications on the components such as the use of amino acids and Lewis acids like titanium (IV) chloride have been reported to induced stereoselectivity in good ratio.²

Niobium (V) pentachloride have been reported as an efficient Lewis acid to promote several organic reactions.³ This led us to investigate the use of NbCl₅ as Lewis acid and its ability to induce the new chiral center formed in the Ugi reaction using natural amino acids, aldehyde, isocyanide and methanol as a fourth component.

RESULTS AND DISCUSSION

A mixture of 1 mmol of amino acid and 1 mmol of aldehyde in anhydrous methanol was stirred for 30 minutes at room temperature. After this time, 1 mmol of *tert*-butylisocyanide and 0.3 mmol of NbCl₅ were added and stirred for 72 h (Scheme 1).



Scheme 1. Ugi reaction of amino acids mediated by NbCl₅.

The products were isolated by column chromatography and the yields ranged from 40 to 50% in a moderate diastereoselectivity (3-4:1) in favor of the (S,S)-isomer (Table 1).

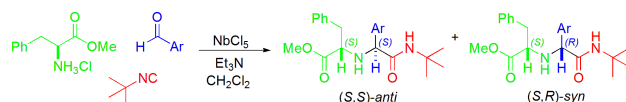
Table 1. Results of Modified Ugi Reactions using NbCl₅.

Entry	Ar	Ratio (S,S):(S,R) ^a	Yield (%) ^b
1	3-NO ₂ Ph	4:1	40
2	4-NO ₂ Ph	3:1	42
3	4-Cl-Ph	3:1	50

a) Calculated by ¹H-NMR spectroscopic data from crude product.
b) After purification on column chromatography.

Initial results were not satisfactory and could be attributed to the complexation of niobium and isocyanide, decreasing its nucleophilicity and leading to moderate yields.

The reaction using amino ester instead of amino acids was also investigated in an attempt to increase the product yields (Scheme 2).



Scheme 2. Ugi reaction of amino ester mediated by NbCl₅.

The reaction was carried out in dry dichloromethane and an equimolar amount of Et₃N. In this conditions, the product was isolated in only 35% yield.

Several modifications are being made to increase the yields and diastereoselectivities such as changes in the Lewis acids, solvents, temperatures and substrates.

CONCLUSION

Preliminary results showed the efficiency of NbCl₅ as Lewis Acid despite the moderate yields and poor selectivity. Some modifications on the methodology are being investigated to improve both yields and diastereoselectivities.

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