

Regioselective Synthesis of 3-Aminoimidazo[1,2- α]pyrimidines Under Continuous Flow Conditions

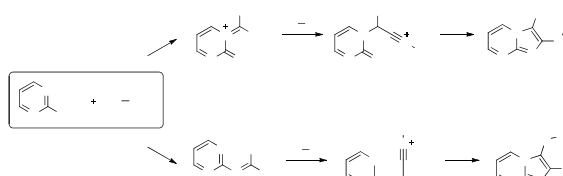
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Introduction

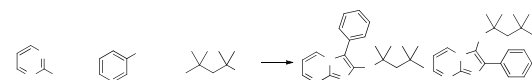
Multicomponent synthesis of fused imidazoles from an aldehyde, an isocyanide and a 2-aminoazine has been widely studied.¹ When 2-aminopyrimidine is used, a regioisomeric mixture of products is produced.² In addition to the expected 3-aminoimidazo[1,2- α]pyrimidines, the corresponding 2-amino products are also formed, this mixture arising *via* the possibility of initial imine formation through either the exocyclic amino-group, or one of the ring nitrogen atoms (Scheme 1).



Scheme 1. Regioisomers formed via different mechanisms.

Project Aims

The aim of our work is to improve the yield and regioselectivity of the above reaction by using continuous flow conditions. Two Lewis acids, scandium triflate and zirconium chloride, will be screened as they are known to catalyse the reactions being studied³.



Yields in the batch reaction are 50 % of the 3-isomer and 16 % of the 2-isomer after 2 days

In order to optimise the continuous flow conditions, the temperature, reaction duration and Lewis acid were screened. Reactions were performed using a Vapourtec R series™ flow reactor. Solutions of 0.02 mol dm⁻³ concentration were used throughout with the amine, aldehyde and Lewis acid in one flask and the isocyanide in another flask. All yields were calculated using HPLC unless stated. The results of these experiments are shown:

Batch Reaction

Many groups have performed this reaction with varying results, so several batch reactions were performed to determine the appropriate catalyst and solvent conditions:

T, /hr	Solvent	Catalyst	2-amino	3-amino	2 / 3
3	MeOH:CH ₂ Cl ₂ (1:3)	ZrCl ₄ (10%)	4	39	1:10
24	MeOH:CH ₂ Cl ₂ (1:3)	ZrCl ₄ (10%)	13	71	1:5
24	PEG 400	ZrCl ₄ (10%)	1	67	1:67
24	MeOH:CH ₂ Cl ₂ (1:3)	ZrCl ₄ (2.5%)	14	43	1:3
24	MeOH:CH ₂ Cl ₂ (1:3)	Sc(OTf) ₃ (2.5%)	27	25	1:1
24	MeOH	ZrCl ₄ (10%)	13	14	1:1

Unfortunately PEG 400 is too viscous to be used under flow, so methanol/dichloromethane solvent with zirconium chloride catalyst was chosen.

Temperature

The next stage in optimising the conditions was to alter the temperature of the reaction and quantity of the catalyst. It was found that a plateau is reached at 70 °C, with any increase in yield at higher temperature offset by problems with flow rate due to developing gas bubbles in the tubing:

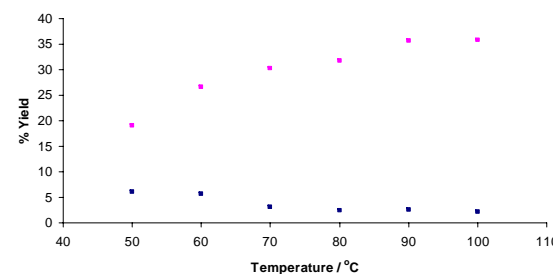


Table 2. Reaction yields with 10 mol % zirconium chloride, a residence time of 20 mins and with varying temperature (3-isomer in pink, 2-isomer in blue)

Residence Time

With the Lewis acid and temperature optimised for the reaction, the final factor to screen was residence time. The data shows a plateau is reached at 50 mins with a yield of 63 % of the 3-isomer:

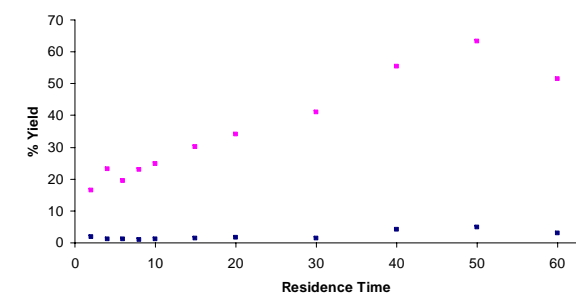


Table 1. Reaction yields and regioselectivity at 70 °C with 10 mol % zirconium chloride with changing residence time. (3-isomer in pink, 2-isomer in blue)

Conclusions

Three-component synthesis of 3-aminoimidazo[1,2- α]pyrimidines under continuous flow conditions gives comparable yields and improved regioselectivity with a dramatic decrease in reaction time when compared to batch conditions.

Further investigation with different reagents is underway in order to improve the scope of this chemistry.

References

- (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661-663; (b) Bienaymé, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234-2237; (c) Blackburn, C.; Guan, B.; Fleming, P.; Siosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635-3638.
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