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KO^{t}Bu-Mediated Highly Efficient Synthesis of Substituted Pyrimidines

Abstract

KO^{t}Bu-mediated tri- and tetra-merization of nitriles were observed under heating condition using catalytic amount of oxidant DTBP, which leads to formation of di substituted 4-aminopyrimidines and *N*-substituted pyrimidine. Multigram quantities of the corresponding have been prepared in high yields

Keywords: KO^{t}Bu, DTBP, one pot synthesis of pyrimidine derivatives)

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Introduction

Carbon-carbon and carbon-heteroatom bond formation is the key step in the synthetic organic chemistry and has numerous applications in synthetic chemistry especially for the development of molecules containing diverse heterocycles, biaryls moieties. Heterocycles are privilege structures with numerous applications in material, coordination, and biological chemistry. Also, heterocycles have attracted considerable interest in drug discovery as many novel heterocyclic rings successfully enter the drug discovery program annually. Pyrimidine motifs is an important class of heterocycles which has numerous application in biological sciences.[1-3]this core also present in biologically active substances such as vitamin B_1,[4] bacimethrin,[5] and chemotherapeutic agents.[6] Therefore, the development of novel efficient methods for synthesis of heterocycles particularly amino pyrimidine is highly desired.

Scheme 1 Cyclotri- and Tetra-Merization of Nitrile

Review of Literature

There are several routs available in literature showed the application of trimerization of nitrile for the synthesis of useful compounds such as s-triazines, aminopyrimidine etc. Cairns et al. has shown the cyclotrimerization of nitriles into s-triazines or pyrimidines under high pressure (5000-8000) × 105 Pa) in the presence of alcohols and amines[7,8]. Forsberg et al.found the trimerization of amide during the reactions between amines and nitriles.[9]Another alternative approach which involve the activation of nitriles having α-hydrogens by metal catalysts.[10,11]Recently Yadong et al. got success for synthesis of s-triazines and amino pyrimidines by cyclotrimerization of nitrile using Li_3N.[12]Moreover microwave assisted formation of 4-aminopyridine has been introduced by Ley et al.[13]

In continuation of our work towards the synthesis of biologically important heterocyclic molecules[14], here we present KO^{t}Bu (potassium tertiary butoxide)-mediated one pot synthesis of 4-amino pyrimidine and *N*-substituted pyrimidine amide by tri- and tetra-merization of nitrile, assisted by DTBP (Di-tertiary-butyl peroxide).

Aim of the Study

Amino-pyrimidines are core parts of many biologically and the rapeutically significant molecules in addition, pyrimidine and amino-pyrimidine scan also act as important herbicides and insecticides. Recently, pyrimidine derivatives have gathered much attention due to their liquid- crystalline and nonlinear optical properties. So the easy and convenient synthesis of pyrimidine derivatives is always required.

Experimental Analysis

All experimental analysis were performed by CIF division IISER Bhopal india, NMR experiments were carried out on Bruker 400 MHz spectrometer in $CDCl_3$ and NMR chemical shifts are reported in ppm referenced to the solvent peaks of $CDCl_3$ 7.26 ppm for ^1H and 77 (± 0.07) ppm for ^{13}C. The following abbreviations were used to indicate multiplicity: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) td (triplet of doublet) and m (multiplet). High resolution mass analysis was performed on quadrupole-time of flight Bruker MicroTOF-Q II mass spectrometer equipped with an ESI and APCI source. Single crystal X-ray data for compounds **2**, was collected on a Bruker D8 VENTURE diffractometer equipped with CMOS Photon 100 detector and Mo-Kα (λ = 0.71073 Å) radiation was used. Propiononitrile was purchased from Spectrochem Pvt. Ltd. India. HPLC grade acetonitrile was used for reaction and purchased from Merck. Silica gel (100-200 mesh size) was used for column chromatography purchased from RANKEM Pvt. Ltd. India. TLC analysis of reaction mixtures was performed using Merck silica gel (60 F_{254}) plates.

Typical Procedure for cyclotri- and tetra-merization of nitriles

To the stirring acetonitrile (4 mL) in a sealed tube, KO^{t}Bu (5 mmol) was added followed by the immediate addition of catalytic amount of DTBP, reaction vessel was placed in a pre-heated oil bath at 110 ^oC. for 5 h (for tetramerization after 5h, 1 mole KO^{t}Bu and 20 mole% DTBP added to reaction mixture and again heated for 3h). Progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was poured into water (15 mL), extracted with ethyl acetate (3 x 25 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Obtained crude product was purified by column chromatography

2,6-Dimethylpyrimidin-4-amine. ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 (s, 1H), 5.05 (brs, 2H), 2.43 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 165.7, 163.1, 100.6, 25.6, 23.8; GC-LRMS *m/z* calcd for $C_6H_9N_3$ [M^+] 123.08, found 123.01.

5-Ethyl-2,6-dipropylpyrimidin-4-amine^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (brs, 2H), 2.75 (t, *J* = 7.8 Hz, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 2.61 (q, *J* = 7.7 Hz, 2H), 1.70-1.85 (m, 4H), 1.20 (t, *J* = 7.7 Hz, 3 H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.99 ppm (t, *J* = 7.2 Hz, 3H) LRMS (ESI) *m/z* calcd for $C_{12}H_{21}N_3$ $[M+H]^+$ 208.18, found 208.17.

***N*-(2,6-Dimethylpyrimidin-4-yl)acetamide.** ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (brs, 1H), 7.80 (s, 1H), 2.54 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.0, 167.0, 156.9, 105.9, 25.6, 24.8, 24.4; LRMS (ESI) *m/z* calcd for $C_8H_{11}N_3O$ $[M+H]^+$ 165.09, found 165.02.

Figure1. **ORTEP view (40% probability) of*N*-(2,6-dimethylpyrimidin-4-yl)acetamide**

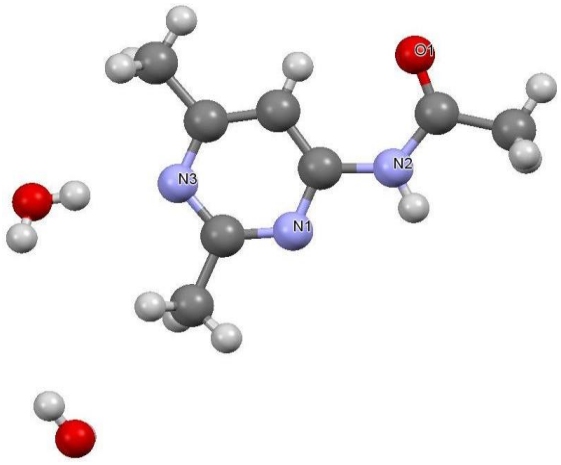
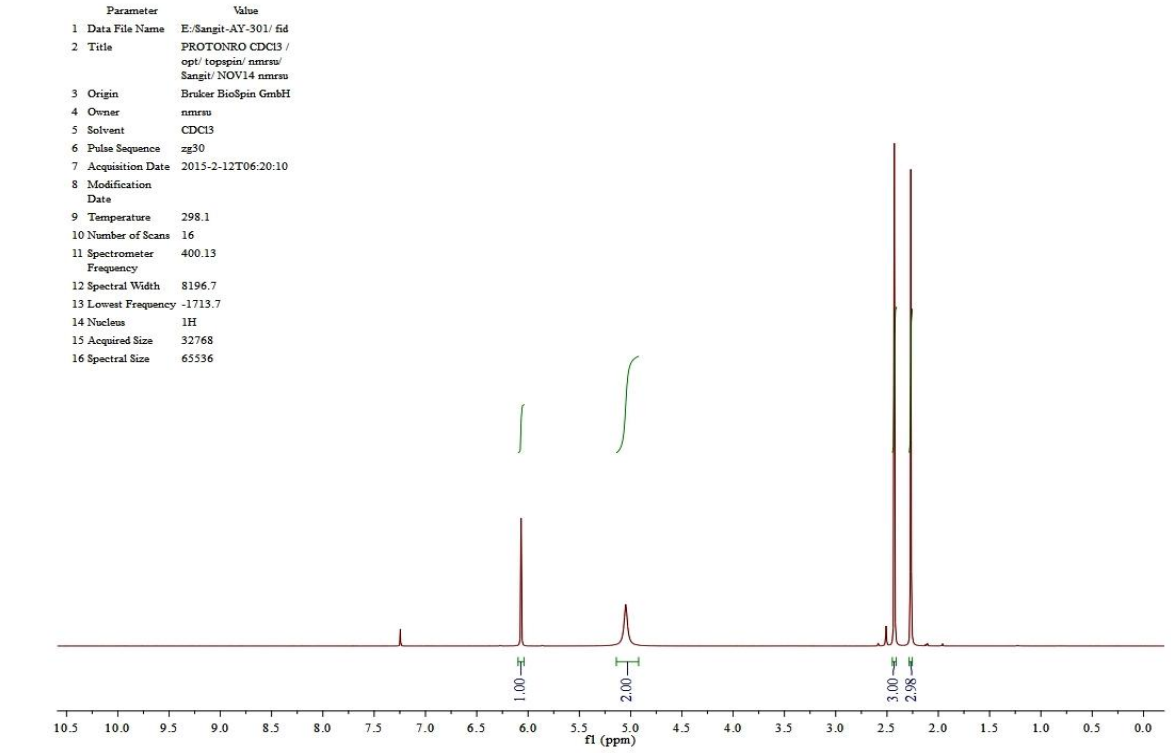


Table 1. Crystal data and structure refinement for N-(2,6-dimethylpyrimidin-4-yl)acetamide

Identification code	N-(2,6-dimethylpyrimidin-4-yl)acetamide	
Empirical formula	C8 H15 N3 O3	
Formula weight	201.23	
Temperature	105(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 15.654(5) Å	α= 90°.
	b = 9.402(3) Å	β= 102.349(10)°.
	c = 7.384(2) Å	γ = 90°.

Volume	1061.6(5) Å^3

^{1}H NMR spectra of2,6-Dimethylpyrimidin-4-amine



Parameter	Value
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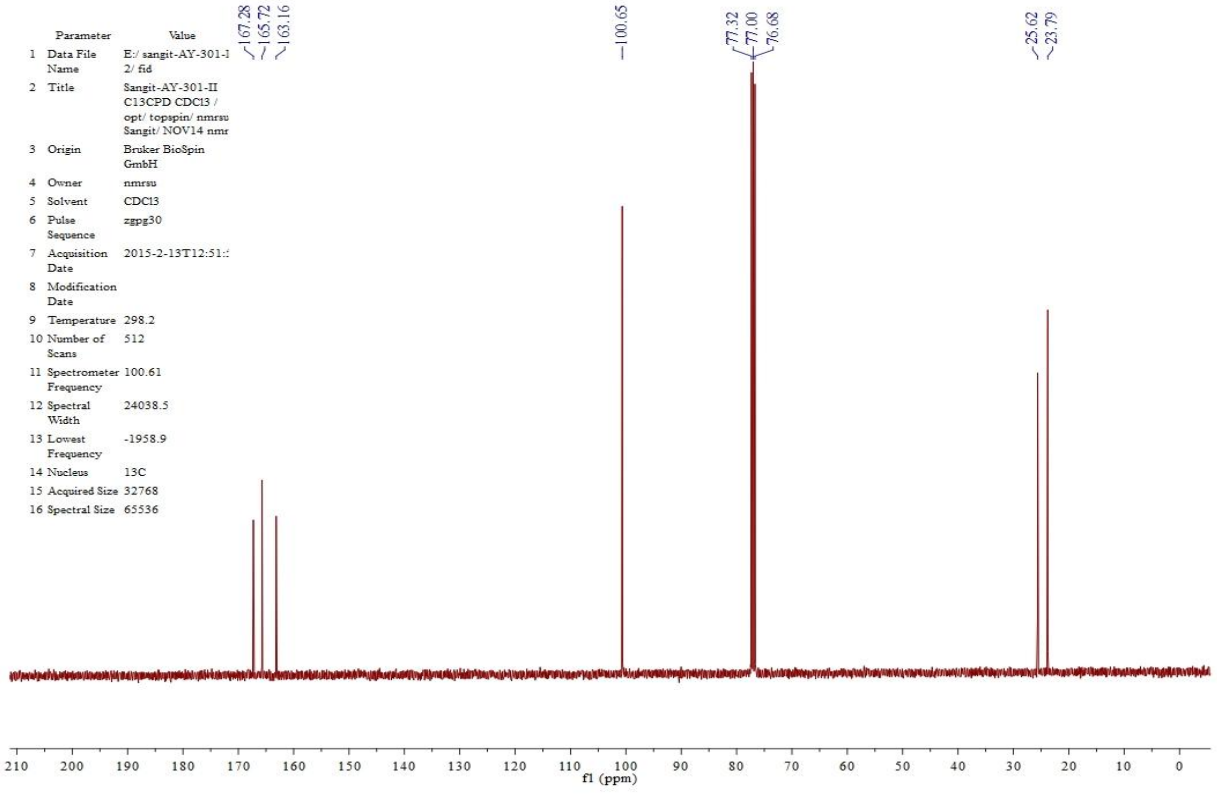
4 Owner	nmrsu
5 Solvent	CDCl3
6 Pulse Sequence	zg30
7 Acquisition Date	2015-2-12T06:20:10
8 Modification Date	
9 Temperature	298.1
10 Number of Scans	16
11 Spectrometer Frequency	400.13
12 Spectral Width	8196.7
13 Lowest Frequency	-1713.7
14 Nucleus	1H
15 Acquired Size	32768
16 Spectral Size	65536

^{13}C NMR spectra of2,6-Dimethylpyrimidin-4-amine



Parameter	Value
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4 Owner	nmrsu
5 Solvent	CDCl3
6 Pulse Sequence	zgpg30
7 Acquisition Date	2015-2-13T12:51::
8 Modification Date	
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11 Spectrometer Frequency	100.61
12 Spectral Width	24038.5
13 Lowest Frequency	-1958.9
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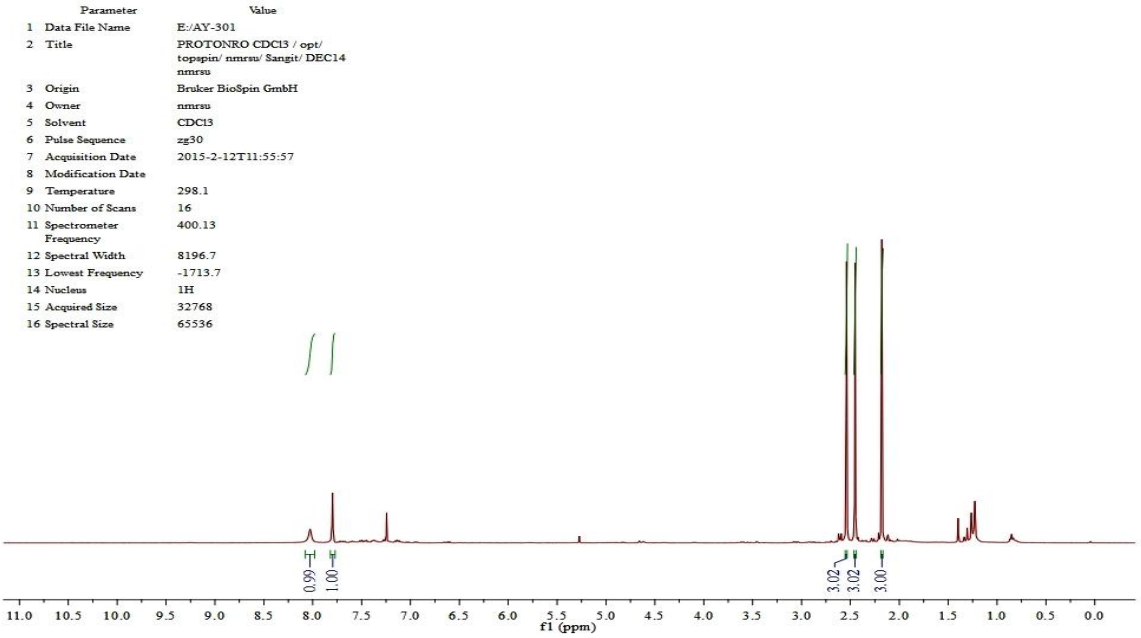
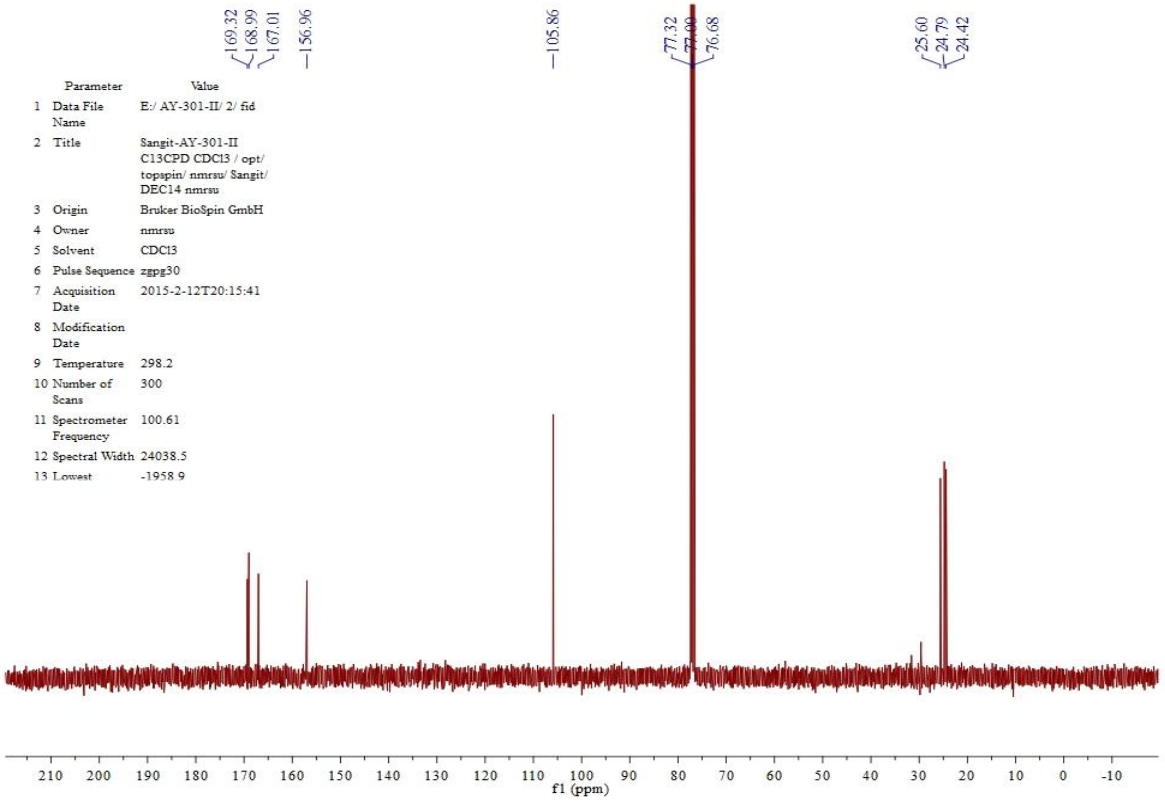
16 Spectral Size	65536

^{1}H NMR spectra of*N*-(2,6-Dimethylpyrimidin-4-yl)acetamide



^{13}C NMR spectra of*N*-(2,6-Dimethylpyrimidin-4-yl)acetamide



LRMS spectra of*N*-(2,6-Dimethylpyrimidin-4-yl)acetamide

Display Report

Analysis Info

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Sample Name	AY-301-II	Instrument	micrOTOF-Q II 10330
Comment			

Acquisition Parameter

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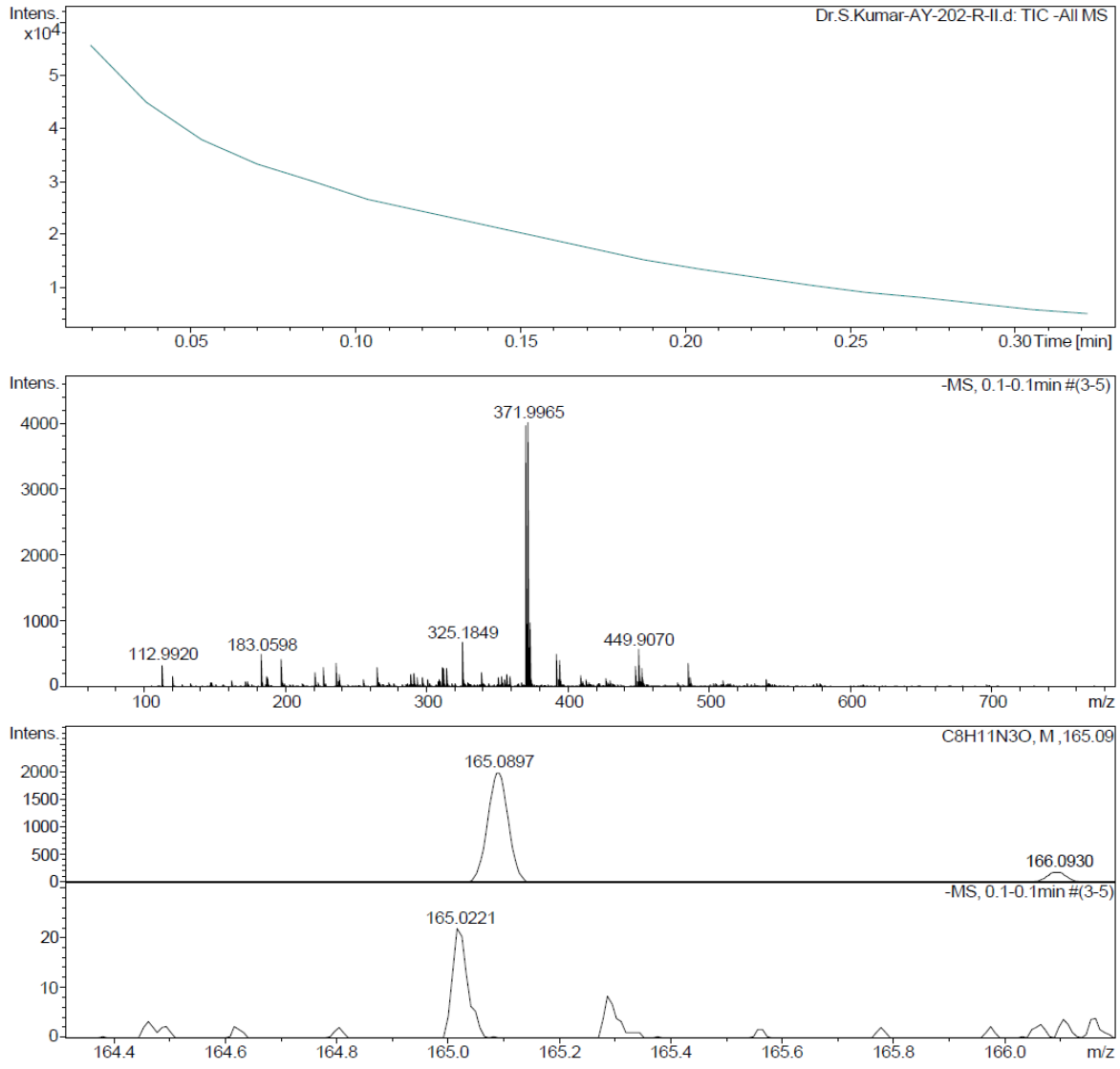
Scan End	3000 m/z	Set Collision Cell RF	130.0 Vpp	Set Divert Valve	Waste



Conclusions

We have developed a simple and scaleable method for the synthesis of 4-aminopyrimidines and pyrimidine amide via tri- and tetra-merization of nitriles respectively.

Acknowledgements

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