"Dissemination of Education for Knowledge, Science and Culture"
Shikshanmaharshi Dr. Bapuji Salunkhe

KOLHAPUR

NAAC Re-Accredited 'A'

A Project Work

"Synthesis of Pyrano Pyrazole Derivatives By Using Multicomponent Reaction"

Submitted to,

DEPARTMENT OF CHEMISTRY

Vivekanand College, Kolhapur

For partial fulfillment of practical course for
The Award of M.Sc. Degree in Chemistry

By,

Miss.Kranti S Kachare, Miss.Poonam V Jagdale, Miss Anuja R Gurav & Mr.Pritam S Jadhav

GUIDE

Mr. S.S.Kadam

2018-2019

"Dissemination of Education for Knowledge, Science and Culture"
Shikshanmaharshi Dr. Bapuji Salunkhe

VIVEKANAND COLLEGE
KOLHAPUR

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DEPARTMENT OF CHEMISTRY

CERTIFICATE

This is to certify that Mr Pritam jadhav, miss Kranti Kachare, Miss Poonam V jagdale, Miss Anuja R Gurav of class M.Sc.2 has satisfactorily completed the project work on title "Synthesis of pyrano pyrazole derivatives by using multicomponent reactions" as a partial fulfillment of the practical course for the award of M.Sc. Degree in Chemistry by Shivaji University, Kolhapur.

Place: Kolhapur
Date: / /2019

Mr. S.S.Kadam
(Project Guide)

Examiner

Head of Department
Co-ordinator,
M. Sc. Organic Chemistry,
Vivekanand College, Kolhapur

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I extend my sincere thanks to all the faculty members as well as the non-teaching staff of the Chemistry Department for their Co-operation.

Lastly, thanks to all who have directly or indirectly involved in this project work.

Sr.No	*Name of Student*	Roll No.	Sign
1	Mr. Pritam Sarjerao Jadhav	152	
2	Miss. Poonam Vithal Jagdale	153	
3	Miss. Kranti Shahaji Kachare	154	
4	Miss. Anuja Rangrav Gurav		

DECLARATION

It is hereby declared that work reported in project entitled **"Synthesis of Pyrano Pyrazole derivatives by using multicomponent reactions "** is completed and written by us and has not copied from anywhere.

Place: Kolhapur

Date: / / 2019

Sr.No	*Name of Student*	Roll No.	Sign
1	Mr. Pritam Sarjerao Jadhav	152	
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4	Miss. Anuja Rangrav Gurav		

Introduction :

Multicomponent reactions (MCRs) are one of the most important processes for the preparation of highly functionalized organic compounds in modern synthetic chemistry [1]. Multicomponent reactions (MCRs) constitute one of the most efficient tools in modern synthetic organic chemistry, since they have all features that contribute to an ideal synthesis: high atom efficiency, quick and simple implementation, time and energy saving, environment-friendly and they offer a target and diversity-oriented synthesis [2] . Multicomponent reactions (MCRs) have attracted considerable attention because they are performed without need of isolation of any intermediate during the processes, which reduces time and saves both energy and raw materials.[3] Some popular MCRs include Strecker amino acid synthesis, Hantzsch, dihydropyridine synthesis, Biginelli reaction,Mannich reaction, Ugi-4-component condensation, Passerini-3-component reaction, Prins reaction, Gewald reaction etc.[4]

heterocycles are widely distributed in nature and play a vital role in metabolism because their structural subunits exist in many natural products, including vitamins, hormones, antibiotics, and alkaloids as well as pharmaceuticals, agrochemicals, dyes, and many others.[6] In addition to naturally occurring compounds, a large number of synthetic heterocyclic compounds with important physiological and pharmacological properties are also known.[7] These compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs.4 Moreover, compounds having heterocyclic moieties display enhanced solubility and salt-formation properties that enable their oral absorption and bioavailability.[8] Among heterocyclic compounds, nitrogen-containing heterocycls are the core structures of numerous biologically active compounds and exhibit numerous application in chemistry, biology and other sciences. They are the building blocks of life due to their wide occurrence in nature and central roles in the chemical reactions that occur in all organisms.[9]

Some hetrocycles such as Pyrazoles are a key class of bioactive heterocycles that have become increasingly important to the pharmaceutical, chemical, and agricultural industries over recent decades.[10] .The pyrano[2,3c]pyrazole heterocyclic scaffold is an important substructure showing anticancer,[11],anti-HIV,[12],anti-inflammatory,[13],anti-microbial,[14].analgesic,[15] . it is also used in biodegradable agrochemicals.

Review of the relevant Literature:

Various references are found for the synthesis Pyranopyrazole derivatives in the heterocyclic compounds by using acid base catalysts .

Rajesh H Vekariya, and his groups [16] synthesized . 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives using starch solutionas a reaction media .via multicomponent reaction initiated by Knoevenagel condensation, subsequent Michael and finaly heterocyclization reactions of heteroaryl aldehyde, malononitrile,ethylacetoacetate and hydrazine and starch has been used as a catalyst.Short reaction time, environment friendly procedure and excellent yields are reported to bethe main advantagesof this procedure.

Rui-Yun Guo. And his groups[17] synteised 2-Amino-4H-pyrans by using of Benzaldehyde, 5,5-Dimethylcyclohexane-1,3-dione, and Malononitrile and A Novel and Efficient Catalyst meglumine. This methodology provides an alternative approach for rapid access to construct a diversity-oriented library of 4H-pyrans

Wenbo Li, . and his group[18] described One-pot synthesis of highly functionalized pyrano[2,3-c]pyrazole-4,4′-diacetate and 6-oxo-pyrano[2,3-c]pyrazole derivatives catalyzed by urea This transformation proceeds via a fourcomponent reaction of ethyl acetoacetate, a hydrazine, 3-oxo-pentanedioic acid dimethyl ester,and malononitrile. The bifunctional nature of urea means that it catalyzes many steps in this transformation, including domino Knoevenagel condensation, Michael addition, and ring opening and closing reactions. This synthetic method has several advantages, including good yield, simple work-up, harmless by-products, and simple purification

Manisha Bihani and his coworkers[19] synthesis dihydropyrano[2,3-c]pyrazoles by using a four-component reaction of a mixture of ethyl acetoacetate, hydrazine hydrate, aldehyde, and malononitrile in ethanol at room temperature in presence Amberlyst .as a catalyst The dihydropyrano[2,3-c]pyrazole compounds are versatile synthetic building blocks and the structural unit of a variety of therapeutic agents. The synthesis of dihydropyrano[2,3-c]-pyrazole derivatives is getting tremendous attention among synthetic chemists for their diverse bioactivity profiles,[20]. Amol B. Atar and his coworkers synthesis [21] of diversity-oriented 6-amino-2,4-dihydropyrano[2,3-c]pyrazol-5-carbonitriles derivatives via a four-component, one-pot cyclocondensation reaction of ethyl acetoacetate, hydrazine hydrate, aldehydes, and malononitrile using silica-supported tetramethylguanidine as a heterogeneous catalyst

Objectives:

multicomponent reactions (MCRs) are becoming powerful and valuable synthetic strategy in modern organic and medicinal chemistry because they make multistep synthesis to be conducted in a single procedural step to provide novel and highly functionalized organic molecules and biologically active heterocyclic compounds from simple and readily accessible starting materials. These reactions hold the possibility for convenient, safe, atom-economic, high-yielding, and environmentally benign procedures and reduce generation of chemical waste.[22-25] Pyrano pyrazole derivatives are one of the biologically important scaffolds because of their wide application in pharmaceuticals,and in organic synthesis as essential intermediates.[26]

The nature of the catalyst and solvent also play a crucial role in the determination of the product and selectivity. Therefore, development of an inexpensive, mild, and reusable catalyst for MCRs remains of interest to the synthetic organic chemist. We have demonstrated effectiveness of various catalysts in organic synthesis using MCRs strategy. [27]. We conceived that DMAP might be a better catalyst which can be explored further for multicomponent reactions for the synthesis of pyran annulated heterocycles. The significant features of the present protocol are simple, environmentally benign, high yields, non-aqueous work-up procedure, no chromatographic separation and recyclability of the catalyst.[28]

Methods and Materials:

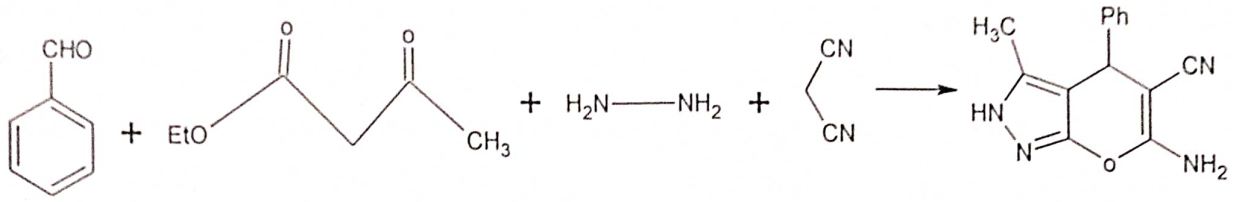
All solvents and chemicals were obtained commercially and were used as received. All known compounds were identified by comparison of their melting points with those in the authentic samples. Melting points were determined using an thiele tube apparatus and are uncorrected.

Procedure:

In a 50 ml flask equipped with a magnetic stirrer was charged with an equimolar amount of the following reagents:

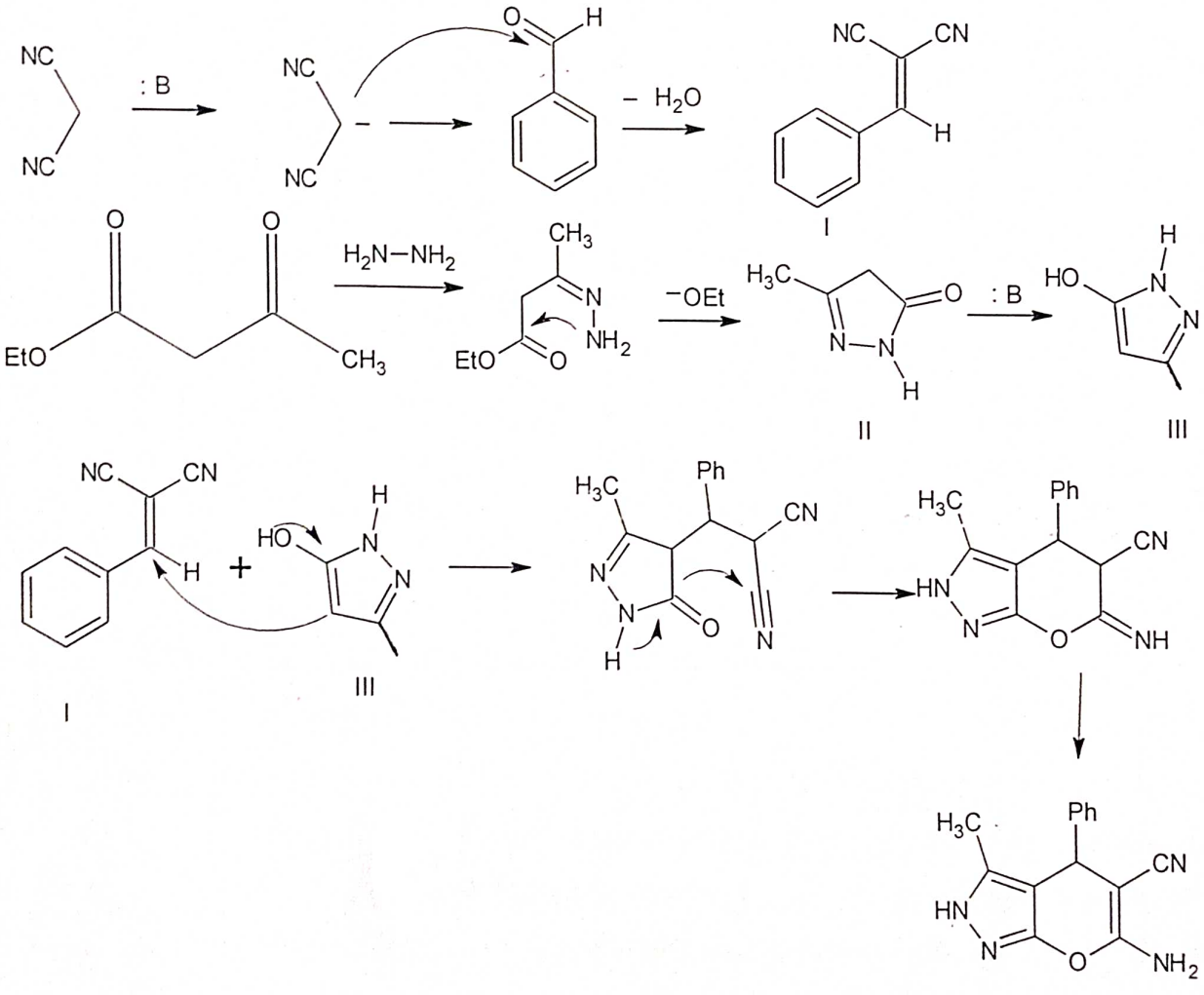
.Aldehydes (**1**, 1 mmol), hydrazine hydrate (**2**, 1mmol), malononitrile (**3**, 1 mmol), and β-keto ester (**4**, 1mmol) 4Dimethylaminopyridine (DMAP) (10 mol%) in EtOH-H2O (9:1, 2 ml). The resulting mixture was stirred at room temperature. After completion of the reaction (monitored by TLC), the precipitated product was filtered and washed with aqueous ethanol (5 ml). The crude product was purified by recrystallization from ethanol to afford the desired product. In order to recover the catalyst,the filtrate was dried under reduced pressure and recovered catalyst was washed with diethyl ether (2 ml) twice and reused after drying.

Reaction:



Benzaldehyde EAA Hydrazine Malononitrile pyrrole derivatives

Mechanism:



Plausible mechanism for synthesis of pyrrole derivatives IV

Results and discussion:

Initially, benzaldehydes, hydrazines,ethylacetoacetate and malenonitrile served as model substrates for optimization of reaction conditions. Some of the key results are summarized in Table 1. In the control experiments, no anticipated product was observed in the absence any catalyst Ceric ammonium nitrate (Table 1,entries1,2). Little product was obtained when the reaction was performed using nicotinamide as catalyst in a mixture of EtOH/H2O. When Sodium Lauryl Sulphate,ionic liquid, and Et3N was employed as the catalyst, the reaction took place, however, the yield of the compound was not satisfactory (entries 3-6). When the reaction was carried out in 4-Dimethylamino pyridine(DMAP) It was the best catalyst for this four-component reaction and afforded the desired product.

Entry No.	Catalyst	Time(Mins)	Yield %
1	None	360	0
2	CAN	360	0
3	nicotinamide	240	Trace
4	Ionic liquid	240	20
5	SLS	240	40
6	Et3N	240	52
7	DMAP	60	86

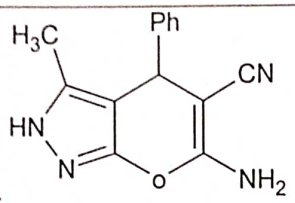
Subsequently, the reaction media, amounts of catalyst and reaction times were also examined. The reaction did not proceed satisfactorily in water, possibly due to incomplete homogeneity of the reaction mixture. Further studies showed that aqueous-ethanol (1:9, v/v) was the best choice of solvent for this transformation. The reaction was also carried out using different amounts of the catalyst and the results showed that 15 mol% of catalyst was the best choice. Decreasing the amount of catalyst to 10 mol% relative to substrate, the yield of product decreased. When the reaction was conducted with increasing amounts of DMAP or by prolonging the reaction times, the yield could not be further increased.

Entry.No	Catalyst loading(mole%)	Solvent	Time(mins)	Yield%
1	10	no	120	0
2	10	H2O	120	10
3	10	PrOH	120	71
4	10	MeOH	120	74
5	10	EtOH	60	77
6	1	EtOH:H_2O(9:1)	60	79
7	5	EtOH:H_2O(9:1)	60	80
8	10	EtOH:H_2O(9:1)	60	82
9	**15**	EtOH:H_2O(9:1)	60	**86**
10	20	EtOH:H_2O(9:1)	60	81

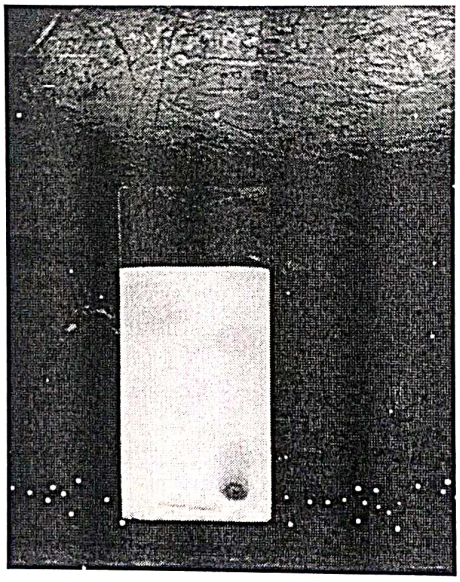
Aldehyde change:

Entry No	Aldehyde	Yield(%)	M.P(^{0}C)
1	PhCHO	86	220^0
2	2-ClC_6H_4CHO	88	240^0
3	4-FC_6H_4CHO	87	230^0
4	4-$NO_2C_6H_4CHO$	86	160^0
5	4-$OEtC_6H_4CHO$	84	240^0
6	4-MeC_6H_4CHO	83	220^0

Characterization data:

Sr. No	Compound	Spectral Data
1		White solid.m.p.220°C. IR (KBr): 3428, 3362 (NH2), 3305 (-NH-), 3168, (Aromatic), 2876 (-CH3), 2188.73(-CN), 1390 cm−1 (-NH-); 1H NMR (400 MHz,DMSO-*d*6): δH (ppm) 1.77 (s, 3H, CH3), 4.56 (s, 1H, 4*H*), 6.57 (s, 2H, NH2), 7.14-7.32 (m, 5H, Ar-H), 12.03 (s, 1H, NH);

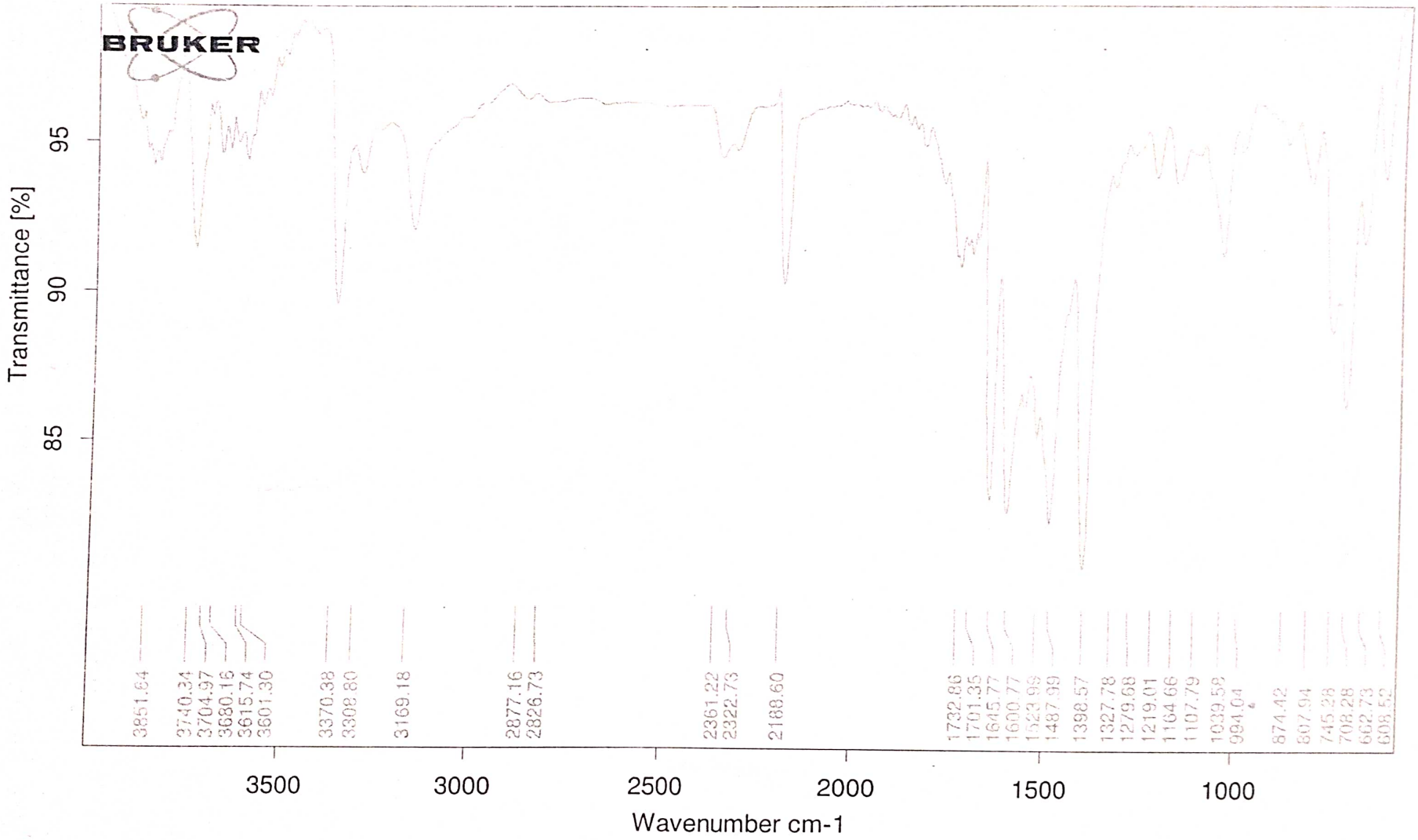
TLC Report:



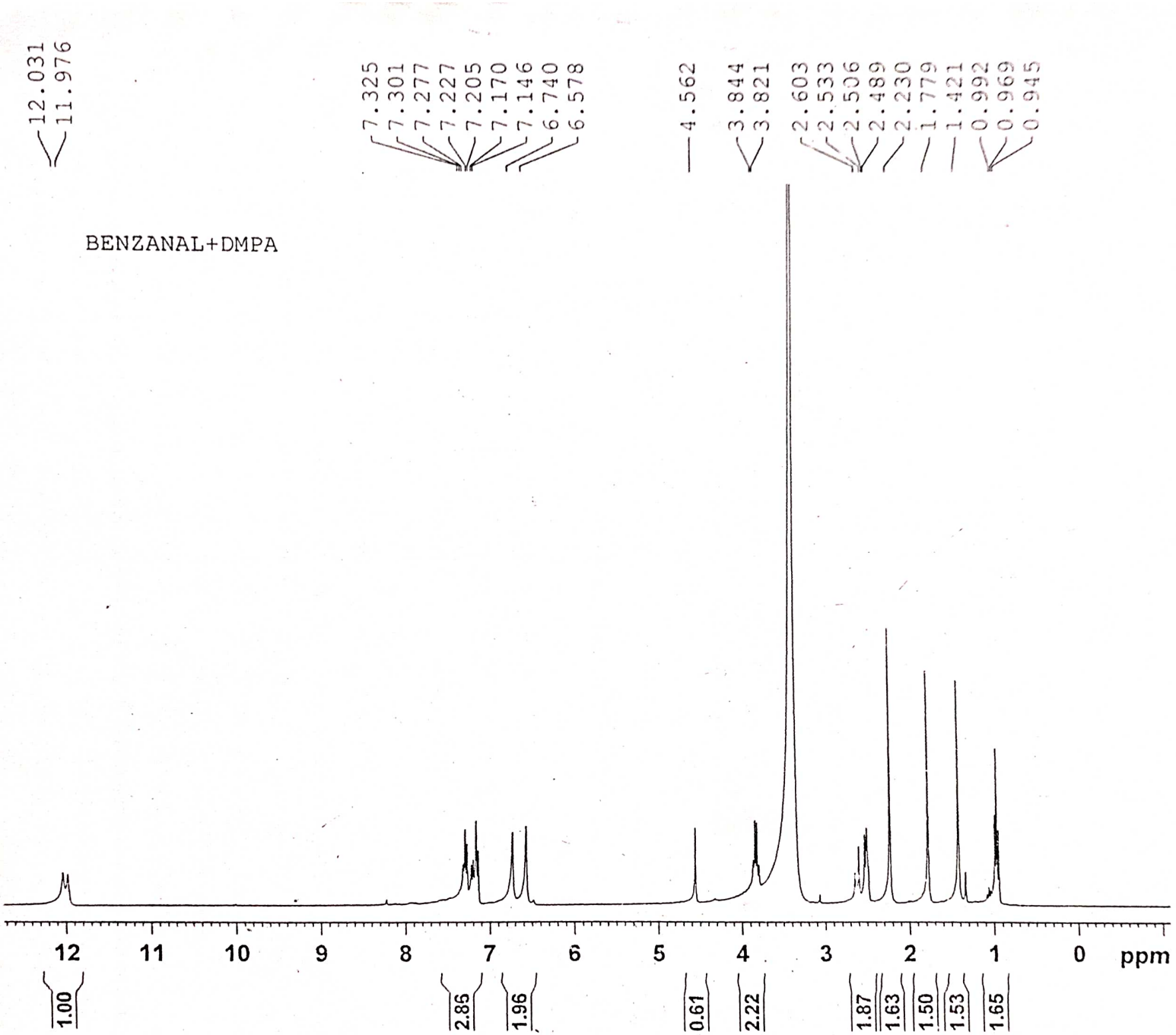
(TLC was developed in iodine chamber)

Solvent system –Petether : Ethylacetate

8 ml : 10 ml



D:\FTIR DATA\AgPm\DMAP.0	DMAP	Instrument type and / or accessory	3/5/2019



BRUKER

NAME	SPATIL
EXPNO	1542
PROCNO	1
Date_	20190317
Time	16.41
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	6188.119 Hz
FIDRES	0.094423 Hz
AQ	5.2953587 sec
RG	114
DW	80.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	11.50 us
PL1	0.00 dB
PL1W	10.72575474 W
SFO1	300.1316534 MHz
SI	32768
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Conclusion:

In summary, we have developed a highly efficient and greener approach for the one-pot, four-component synthesis of pyranopyrazole derivatives using DMAP as an inexpensive, biodegradable and reused catalyst. The merits for the presented methodology are its efficient, generality, wide scope of substrates, high yield, short reaction time,simplicity, no elevated temperature, ease of product isolation, cleaner reaction profile, evasion of hazardous catalysts or solvents, and agreement with the green chemistry protocols, which make it a useful and attractive process for the synthesis of pyranopyrazoles

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