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Research Article

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One-pot three-component condensation for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles using cesium fluoride as an efficient catalyst

Vijay N. Bhosale*[1], Jaman A. Angulwar[2], Gopinath S. Khansole[1] and Gangadhar S. Waghmare[1]

[1]*P.G. Research centre, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded*
[2]*Dayanand Science College, Latur*

ABSTRACT

A clean and simple synthesis of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles was accomplished in good to excellent yields via the one-pot three component condensation of 3-methyl-1-phenyl- 2-pyrazolin-5-one, an aromatic aldehyde, and malononitrile catalysed by Cesium Fluoride in ethanol.

Keywords: Multi-component reactions, aromatic aldehyde, Cesium fluoride, malononitrile, fused pyrans, pyrazoles.

INTRODUCTION

Pyrano[2,3-*c*]pyrazole is a fused heterocycle comprised of pyrazole and pyran rings which are known as the sub-structural units of several biologically active compounds.[1,2] Polyfunctionalised benzopyrans have been widely used as medicinal intermediates due to their biological and pharmacological properties such as antibacterial, molluscicidal, anthelminitic, hypnotic and insecticidal activity.[3-9] Some 2-amino-4*H*-pyrans can be used as photoactive materials.[10] The 4*H*-pyran ring is also a structural unit of a number of natural products.[11-13]

1,4-Dihydropyrano[2,3-*c*]pyrazoles are generally prepared by one-pot three component condensations of malononitrile, aldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one using KF/Al_2O_3 in DMF at room temperature.[14] The utilisation of water as reaction medium for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles is demonstrated by using various phase transfer catalysts such as triethylbenzylammonium chloride (TEBA)[15] and hexadecyltrimethylammonium bromide (HTMAB).[16] Similarly, the use of the neutral organo-catalyst DL-proline using the grinding technique[17] and a surfactant such as *p*-dodecylbenzenesulfonic acid[18] (DBSA) has recently been demonstrated. Solvent-free reaction conditions along with microwave irradiation technique using piperidine as the base have also been introduced for the synthesis of 1,4- dihydropyrano[2,3-*c*]pyrazoles.[19]A clean and simple synthesis of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles was accomplished in good to excellent yields *via* the one-pot three component condensation of 3-methyl-1-phenyl-2-pyrazolin-5-one, an aromatic aldehyde, and malononitrile catalysed by sulfamic acid in ethanol. [20] In recent years, the catalytic activity of Cesium fluoride has emerged as a useful acid imparting high regio- and chemoselectivity in various chemical transformations.[21--24] The versatility of sulfamic acid because of its low cost, eco-friendly nature and ready availability as a common organic chemical encouraged us to explore it in various multi-component reactions under benign reaction conditions. Here we report another remarkable catalytic activity of cesium fluoride for the one-pot three-component condensation of malononitrile, an aromatic aldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one, to form a variety of 6-amino-4-aryl-3-methyl-1-phenyl-1,4- dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles**.**

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ using TMS as internal standard.

Typical experimental procedure:
A mixture of aromatic aldehyde (3 mmol), malononitrile (3 mmol), 3- Methyl-1-phenyl-2-pyrazolin-5-one and Cesium fluoride (5 mol%) in EtOH (20 ml) was refluxed for the time period as mentioned in Table 1. TLC monitored the progress of reaction. After the completion of reaction, it was cooled at room temperature and poured into crushed ice to get solid product which was filtered off. The crude products were recrystallised from EtOH to give pure 1,4-dihydropyrano[2,3-*c*]pyrazole in good to excellent yields.

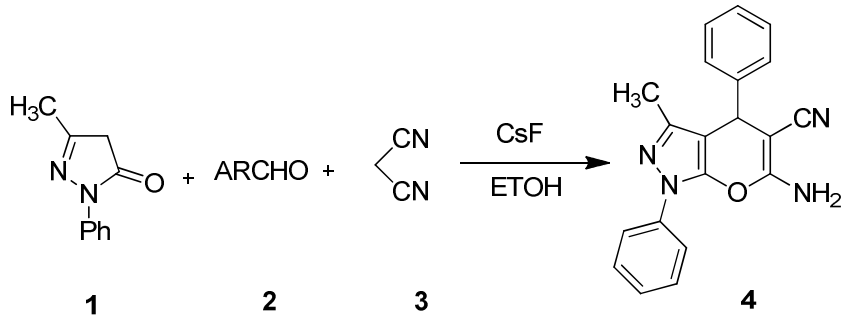
The physical details and spectral analysis for the new product are given below:
6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4d**): Yellow crystalline solid,m.p. 191–193°C. IR (KBr): τmax 3490, 3330, 3017, 2937, 2896, 2198,1666, 1589, 1381,1242,1122, 882 cm‑1. NMR ($CDCl_3$): δ 1.92 (s, 3H,CH_3), δ 3.81 (s, 3H, OCH_3), δ 3.83 (s, 3H, OCH_3), δ 4.67 (s, 1H, ArCH),δ 6.33 (s, 2H, br., NH_2), 6.88 (s, 1H, ArH), 6.72 (d, *J* = 8.28 Hz, 1H, ArH), 6.79 (d, *J* = 8.28 Hz, 1H, ArH), 7.29–7.37 (m, 5H, ArH). Anal.Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96; found: C, 67.29;H, 4.83; N, 14.99%.

RESULTS AND DISCUSSION

Initially, we examined the model reaction of benzaldehyde (3 mmol), malononitrile (3 mmol) and 3-methyl-1-phenyl-2- pyrazolin-5-one (3 mmol) in ethanol (20 ml) using cesium fluoride as the catalyst. When cesium fluoride (5 mmol%) was added to the above stirred reaction mixture at room temperature, a red brown colour is observed. The room-temperature stirring of the reaction mixture for 3–5 h did not result in the formation of the expected product. Therefore we carried out the reaction by heating under reflux for 7–13 h, using TLC to monitor progress. When the reaction was complete, the mixture was cooled to room temperature and a solid product was precipitated. The entire reaction mixture was poured onto crushed ice and the solid was filtered off. The crude product was recrystallised from ethanol to afford analytically pure product in 82% yield. The reaction did not proceed in the absence of cesium fluoride . The optimum yield of the product was obtained when 5 mol% of cesium fluoride was employed.

The scope of this three-component condensation was then extended using a range of aromatic aldehydes, and the results are summarised in Table 1. Thus the methoxy substituted aromatic aldehydes (Table 1, entries b–d) underwent a clean three component condensation to form the corresponding 1,4-dihydropyrano[2,3-*c*]pyrazoles in excellent yields. Other aromatic aldehydes (Table 1, entries e–i) with electron releasing and withdrawing substituents produced 1,4-dihydropyrano[2,3-*c*] pyrazole in good yields. However, *p*-dimethylamino benzaldehyde (Table 1, entry 10) failed to produce any 1,4-dihydropyrano[2,3-*c*] pyrazole. A similar failure was reported earlier.[18] The isolated pyrano[3,2-*c*] pyrazole derivatives **4a–j** were completely characterised by IR and ^{s}H NMR, and the melting points of known compounds were consistent with those of the references reported. For example, the IR spectra for **4a** exhibited sharp bands at 3471, 3257 cm–1 due to NH_2 and 2198 cm–1 due to CN. The ^{1}H NMR spectrum of **4a** exhibited a characteristic peak at δ = 4.62 ppm for H-4 and a broad singlet peak at δ = 6.71 ppm due to the NH_2 group.

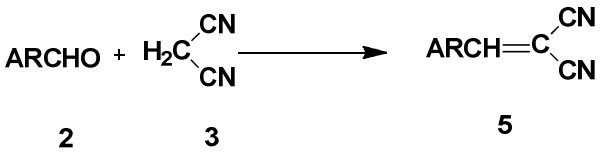
A tentative reaction mechanism for the three-component synthesis of 6-amino-4-aryl-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles is shown in **Scheme 2**. The aromatic aldehyde **2** can react with malononitrile **3** to form the dicyano-olefin **5** through Knoevenagel condensation. 3-Methyl-1-phenyl-2-pyrazolin-5-one **1** can then react with **5** via a Michael-type addition to form **6** which may undergo cyclisation via **7** to form the final product **4**. In summary, a highly efficient methodology for the synthesis of 1,4-dihydropyrano[2,3‑*c*]pyrazole-5-carbonitriles by one-pot three component condensation of aromatic aldehydes, malononitrile and 3- methyl-1-phenyl-2-pyrazolin-5-one in the presence of catalytic quantity of cesium fluoride is reported. This one-pot synthesis is characterised by mild reaction conditions, broad scope, high yields, and preparative simplicity.



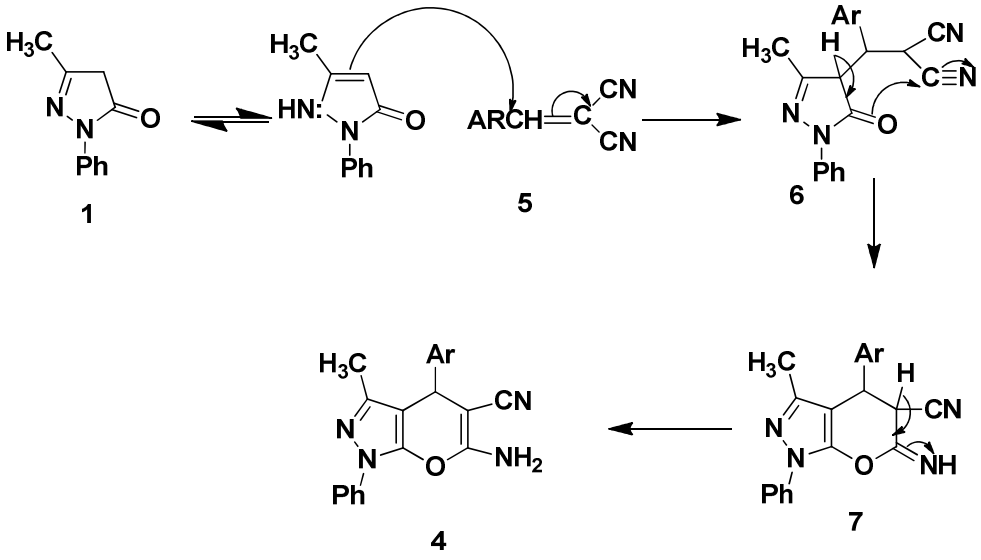
1 2 3 4

Scheme 2

Mechanism for the preperation of dihydro-pyrano pyrazoles:



2 3 5



1 5 6 7 4

Scheme 2

Entry	Ar	Reaction time/h	Product	Yield /%	Melting-point/°C Found	Melting-point/°C reported[16,18]
4a	C_6H_5	6	White	70%	167-168	168-170
4b	$4CH_3C_6H_5$	8	White	80%	168-170	168-170
4c	$4ClOC_6H_5$	5	Yellow	80%	175-177	175-177
4d	$4OHC_6H_5$	5	White	80%	208-209	208-209
4e	$4NO_2OC_6H_5$	5	Cream	60%	185-187	185-187
4f	$2ClOC_6H_5$	4	Green	70%	178-180	178-180
4g	$3,4(CH_3O)_2C_6H_5$	3	White	70%	191-193	191-193
4h	$4CH_3OC_6H_5$	4	White	80%	167-170	167-170
4i	$2OHOC_6H_5$	9	White	60%	168-171	168-171
4j	OSC_5H_4	9	White	64%	220-223	220-223
4k	4-Br C_6H_5	1	White	66%	198-200	198-200
4l	4-Br C_6H_5	10	White	64%	155-156	155-156
4m	4-F C_6H_5	1	White	69%	163-164	163-164
4n	$4\text{-}NO_2C_6H_5$	10	White	70%	235-238	235-238
4o	$4\text{-}C_6H_5N$	10	White	78%	267-270	267-270
4p	$3\text{-}OH,4\text{-}OCH_3\,C_6H_5$	10	Yellow	68%	280-284	280-284
4q	$3\text{-}OHC_6H_5$	10	White	65%	295-297	295-297
4r	$2\text{-}C_4H_4O$	10	White	58%	289-291	289-291

Antibacterial activity:

The synthesized compounds were evaluated for their antibacterial activity against gram positive species S. aureus and B. substilis and gram negative species E. coli and S. typhi by paper disc diffusion method. All the synthesized compounds were dissolved in dimethyl sulphoxide. The synthesized compounds exhibited zone of inhibition of 07-14mm in diameter where as standard Norfloxin exhibited zone of inhibition of 14 and 24 in diameter against S. aureus and B. substilis and 20 and 16mm in diameter against E. coli and S. typhi respectively where as Streptomycin exhibited zone of inhibition of 16 and 18 in diameter against S. aureus and B. substilis and 20 and 18mm in diameter against E. coli and S. typhi respectively . Amongst the synthesized compounds, Compounds (2,3,4) showed higher zone of inhibition against S. aureus, Compounds (1,3,4),showed higher zone of inhibition against E.Coli ,Compounds(3,4) showed higher zone of inhibition against B.Substilis and Compounds (3) showed higher zone of inhibition against S.Typhi as compared to other compounds.

Table: Antimicrobial activity of compound (1-18)

Entry no.	R	Diameter in mm of zone of inhibition			
		S. Aureus	*B. Substilis*	*E. Coli*	*S. Typhi*
1	C_6H_5	08	09	12	05
2	$4CH_3C_6H_5$	10	06	09	07
3	$4ClOC_6H_5$	10	14	12	10
4	$4OHC_6H_5$	11	09	12	06
5	$4NO_2OC_6H_5$	07	08	11	08
6	$2ClOC_6H_5$	09	10	10	06
7	$3,4(CH_3O)_2C_6H_5$	09	08	14	08
8	$4CH_3OC_6H_5$	14	24	20	16
9	$2OHOC_6H_5$	16	18	20	18
10	OSC_5H_4	08	09	12	05
11	4-Br C_6H_5	10	06	09	07
12	4-Br C_6H_5	10	14	12	10
13	4-F C_6H_5	11	09	12	06
14	$4\text{-}NO_2C_6H_5$	07	08	11	08
15	$4\text{-}C_6H_5N$	09	10	09	06
16	$3\text{-}OH,4\text{-}OCH_3\,C_6H_5$	09	06	10	08
17	$3\text{-}OHC_6H_5$	14	24	20	16
18	$2\text{-}C_4H_4O$	16	18	20	18
	Norfloxin	14	24	20	16
	Streptomycin	16	18	20	18

CONCLUSION

In conclusion, the present procedure is of the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles by one-pot three component condensation of aromatic aldehydes, malononitrile and 3- methyl-1-phenyl-2-pyrazolin-5-one in the presence of catalytic quantity of cesium fluoride is reported.reaction. Most significantly,this process of three

component condensation throws a challenge to the existing procedures which use volatile and hazardous solvents and toxic catalysts, and in general, leads to a new direction in organic synthesis. We believe this will find useful applications as a practical alternative for the synthesis of dihdropyrimidinone.

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REFERENCES

[1] M.H. Elnagdi, M.R.H. Elmoghayar and G.E.H. Elgemeie, *Adv.Heterocyclic Chem*., **1987**, 41, 319.
[2] M.H. Elnagdi, M.R.H. Elmoghayar and K.U. Sadek, *Adv. HeterocyclicChem*., **1990,** 48, 223.
[3] S. G. Kuo, L. J. Huang and H. Nakamura, *J. Med. Chem.* **1984,** 27, 539.
[4] L. L. Adreani and E. Lapi, *Boll. Chim. Farm.* 1960, **99**, 583; *Chem. Abstr*.**1961,** 55, 2668d.
[5] Y. L. Zhang, B. Z. Chen, K. Q. Zheng, M. L. Xu and X. H. Lei, *ActaPharm. Sinica*, 1982, **17**, 17; *Chem. Abstr*. **1982**, 96, 135 383e.
[6] L. Bonsignore, G. Loy, D. Secci and A. Calignano, *Eur. J. Med. Chem.***1993**, 28, 517.
[7] E.C. Witte, P. Neubert and A. Roesch, *Ger. Offen. DE* 1986, 3 427 985;*Chem. Abstr*. **1986**, 104**,** 224 915f.
[8] J.L. Wang, D. Liu, Z.J. Zhang, S. Shan, X. Han, S.M. Srinivasula,C.M. Croce, E.S. Alnemri and Z. Huang, *Proc. Natl. Acad. Sci. U.S.A.*,**2000**, 97, 7124.
[9] Y.A. Mohamed, M.A. Zahran, M.M. Ali, A.M. El-Agrody and U.H. El-Said, *J. Chem. Res. (S)*, **1995**, 322.
[10] D. Armesto, W.M. Horspool, N. Martin, A. Ramos and C. Seoane, *J. Org.Chem.* **1989**, 54, 3069.
[11] S. Hatakeyama, N. Ochi, H. Numata and S. Takano, *J. Chem. Soc., Chem.Commun.* **1988,** 1202.
[12] R. Gonzalez, N. Martin, C. Seoane and J. Soto, *J. Chem. Soc., PerkinTrans. 1*, **198**5, 202.
[13] Kamaljit Singh, Jasbir Singh and Harjit Singh, *Tetrahedron*, **1996**, 52,14273.
[14] X.S. Wang, D.Q. Shi, L.C. Rong, C.S. Yao and G.Y. Dai, *Jiego Huaxue***,2003**, 22, 331.
[15] D.Q. Shi, S. Zhang, Q.Y. Zhuang, S.J. Tu and H.W. Hu, *Chin. J. Org.Chem*., **2003**, 23, 1314.
[16] T.S. Jin, A.Q. Wang, Z.L. Cheng, J.S. Zhang and T.S. Li, *Synth. Commun*.**,2005**, 35, 137.
[17] S.B. Guo, S.X Wang and J.T. Li, *Synth. Commun.*, **2007**, 37, 2111.
[18] T.S. Jin, R.Q. Zhao and T.S. Li, *Arkivoc*, **2006,** xi, 176.
[19] J.F. Zhou, S.J. Tu, Y. Gao and M. Ji, *Chinese J. Org. Chem*., **2001**,**21**,742.
[20] Sandeep V. Shinde, Wamanrao N. Jadhav, Jeevan M. Kondre, Sumit V. Gampawar and Nandkishor N. Karade *Journal of Chemical Research.*,**2008**,08,5203,278.
[21] T.S. Jin, G. Sun, Y.W. Li and T.S. Li, *Green Chem.,* **2002**, 4, 255.
[22] W. Bo, Y.L. Ming and S.J. Shuan, *Tetrahedron Lett.*, **2003,** 44, 5037.
[23] B. Wang, Y.L. Gu, C. Luo, T. Yang, L.M. Yang and J.S. Suo, *Tetrahedron Lett.*, **2004**, **45**, 3369.
[24] P.R. Singh, D.U. Singh and S.D. Samant, *Synlett*, **2004**, 11, 1909.