Original Article: Meglumine Catalysed Green Synthesis of Ethyl-6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate Derivatives

Ganesh Baburao Pund[a] Sambhaji Tukaram Dhumal[b] |Madhav Janardan Hebade[c] |Mazahar Farooqui[d] |Bhagwansing Shivsing Dobhal[c,*]

[a]*Department of Chemistry, Dr. Rafiq Zakariya College for Women, Aurangabad (MS) India- 431001.*
[b]*Department of Chemistry, Ramkrishna Paramhansa Mahavidyalaya, Osmanabad (MS) India- 431501.*
[c]*Department of Chemistry, Badrinarayan Barwale Mahavidyalaya, Jalna (MS) India- 431213.*
[d]*Department of Chemistry, Maulana Azad College of Arts Science and Commerce, Aurangabad, (MS) India- 431001.*

Use your device to scan and read the article online

Citation G. B. Pund, S.T. Dhumal, M.J. Hebade, M. Farooqui, B.S. Dobhal*.**Meglumine Catalysed Green Synthesis of Ethyl-6-Amino-5-Cyano-2-Methyl-4-Phenyl-4*H*-Pyran-3-Carboxylate Derivatives**. *J. Appl. Organomet. Chem.*, **2022**, *2*(1), 15-23.

https://doi.org/10.22034/jaoc.2022.324493.1046

Article info:
Received: 14-02-2022
Accepted: 03-02-2022
Available Online: 05-03-2022
ID: JAOC-2201-1046
Checked for Plagiarism: Yes
Peer Reviewers Approved by:
Dr.SUNIL V. GAIKWAD
Editor who Approved Publication:
Professor Dr. AbdelkaderZarrouk

Keywords:
Meglumine; recyclable;Ethyl-6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylates; reusable; cyclocondensation

ABSTRACT

An efficient and simple one-pot synthetic protocol has been developed for the first time to synthesize the series of Ethyl-6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylates. This was achieved by the cyclocondensation of aromatic aldehydes, malononitrile, and ethylacetoacetate in the presence of the catalytic amount of Maglumine as a readily available, reusable,and biodegradable catalyst. This technique is very promising asit provides mild reaction conditions, an environmentally benign greener approach, easy workup process, high yield, less reaction time, low cost, and recycled up to five catalytic cycles without substantial loss of catalytic activity or product yield.

Introduction

One of the most important challenges in organic synthesis is to design easy synthetic pathways for commonly used organic molecules using easily available reagents. Single-step, one-pot, and three-component condensation reactions are now widely used for the synthesis of various heterocyclic compounds in synthetic organic chemistry.As compared to multistep techniques, one-pot protocols are more efficientasitoffers higher yield in shorter reaction time with easy workup processes.

4*H*-pyranare oxygen-containing heterocyclic moiety, with several biological properties including antibacterial,[1],[2] anticancer,[3]antiviral,[4]antitumor,[5]antifungal, antioxidant[6], [7], and antimicrobial activities[8]as well as shows anti-corrosion properties[9].Asillustrated in **Figure 1**, the

***Corresponding Author:** *Bhagwansing Shivsing Dobhal (drbsdobhal@gmail.com)*

pyran scaffold acts as asignificant structural motif in various bioactive compounds such as beta-lapachone,alpha-lapachone,zanamivir,laninamivir.
Correspondingly, derivatives of 4*H*-pyrans have been found as highly bioactive compounds because of their biodegradable abilities. They are alsofound in cosmetics, dyes, pigments,and agrochemicals[10].Consequently,the organic community has been encouraged to discover an excellent method for the synthesis of 4*H*-pyran.

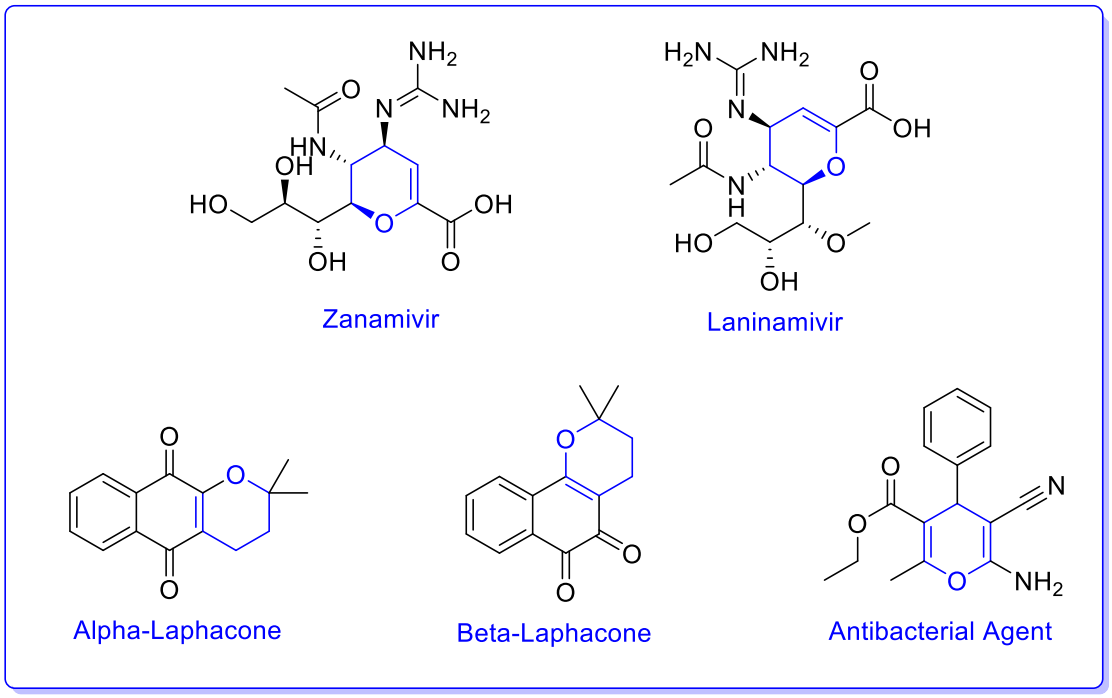


Figure 1. Some pharmacologically active derivatives of pyran

A review of the literature indicates that 4*H*-pyran could be synthesized by several different protocols, which includethe two-step approachas well as the one-pot three-component system.Mostly, 4*H*-pyrans are synthesized by a one-pot cyclocondensationreaction in betweenan aromatic aldehyde, malononitrile, and ethylacetoacetatein presence of a basic catalyst.This synthetic approachwas involved in presence of various catalysts such as $BaFe_{12}O_{19}$@IM,[11]PPh_3,[12]Potassium fluoride,[13]Mg/La mixed oxide,[14] tetramethylguanidine-[bmim][BF_4],[15]potassium phthalimide,[16]molecular sieve-supported zinc,[17]$BNFe_3O_4$,[18]Silica Supported V_2O_5,[19]thiourea dioxide[20]and Baker's yeast.[21]However, these above-mentioned protocols have one or more disadvantages, and the majority of therequired heating conditions and provide moderate yields even after a considerable reaction time. This clearly indicates that there is still scope for improvement in terms of developing an effective and environmentally friendly protocol for the synthesis of 4*H*-pyrans.

Hence, we have planned to synthesize Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylateby using Meglumine as a catalyst.The presence of hydroxyl groupsand an amino groupfrom the Meglumine tends to activate the nucleophilicas well as electrophilic centers, which helps inhydrogen bonding and electron donation.Meglumine shows fantastic propertiessuch as low toxicity, biodegradability, physiological inertness, reusability, low cost, and non-corrosion nature.Because of the above findings andour ongoing efforts [22-25] to developenvironment-friendly synthetic methods for various reactions, herein,we present Meglumine as a biodegradable catalyst

for one-pot synthesis of ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylatebyreactingaromatic aldehydes,malononitrile,andethylacetoacetatei n Ethanol:Water at room temperature.

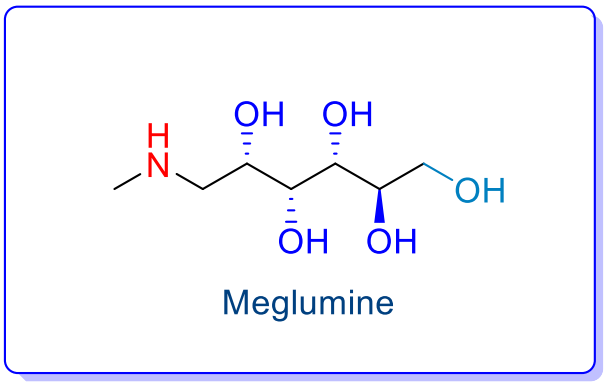
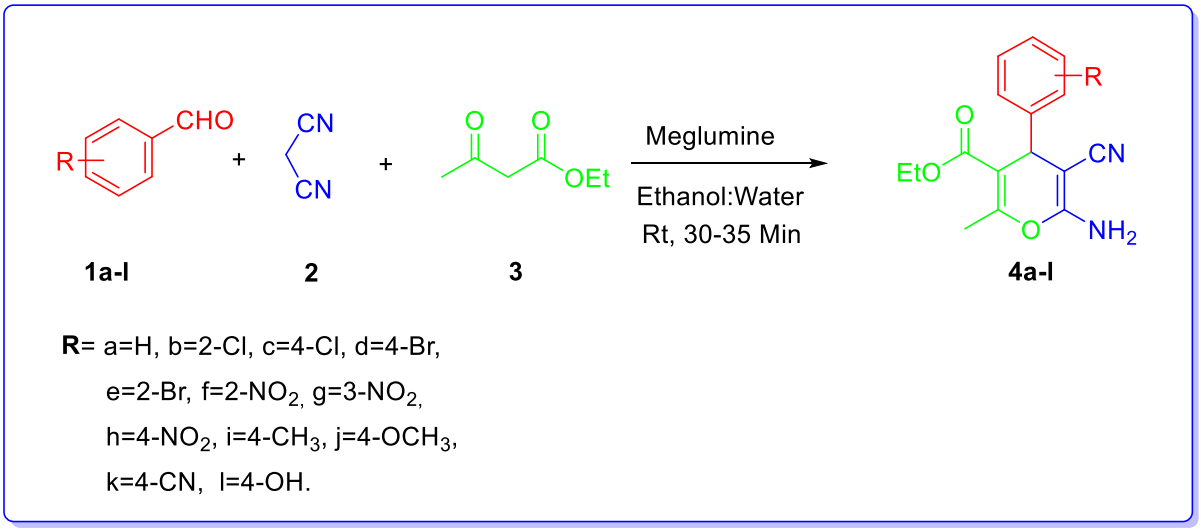


Figure 2. Structure of Meglumine Catalyst

Results and Discussion

The synthesis of Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylatederivativeswas achieved by reacting substituted aromatic benzaldehydes**(1a-l)** with malononitrile**(2)** and ethylacetoacetate**(3)**in ethanol:water in the presence of Meglumine as a catalyst. The product was obtained after stirring the reaction mixture for30-35 minutes at room temperature. Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylatederivatives**(4a-l)** were obtainedwith high purity and better toexcellent yields, as shown in **Scheme 1.**



Scheme 1. Synthesis of 4*H*-pyran using Meglumine catalyst

The structures of all the newly synthesized Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylates(**4a-l**) are depicted in **Figure 3.**

Optimization of the reaction parameters was performed bymodel reaction of benzaldehyde**(1a)**, malononitrile **(2)**, and ethylacetoacetate **(3)** as shown below.

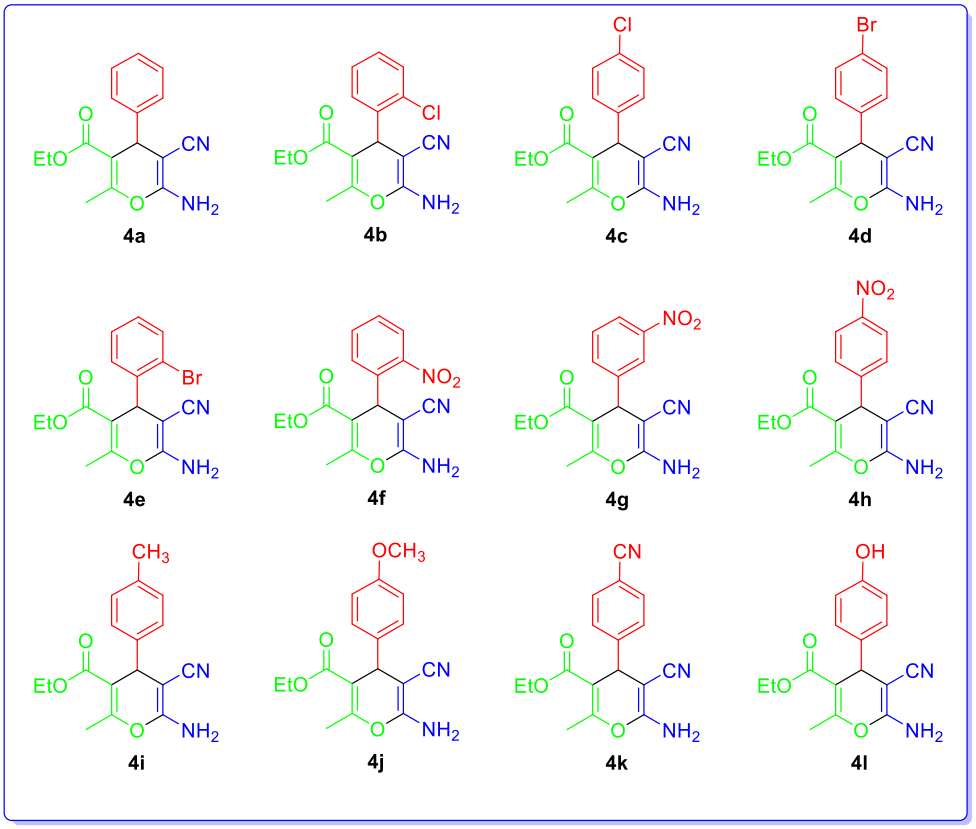
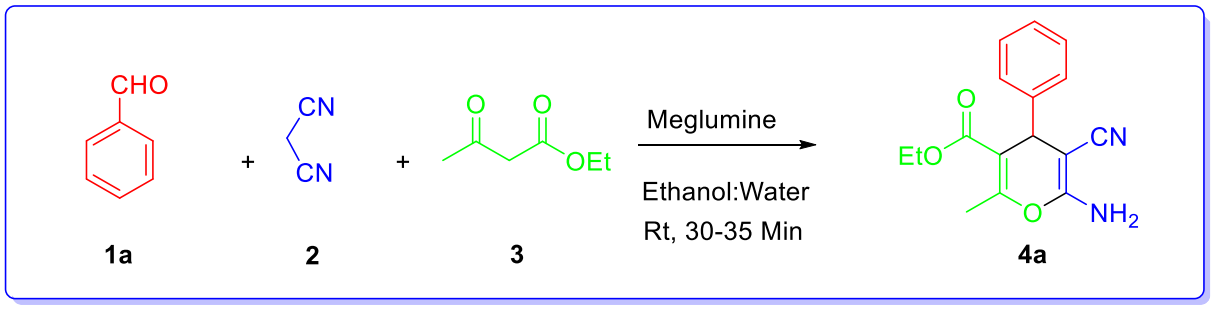


Figure 3. Structures of the synthesized Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate derivatives (**4a-l**)



Scheme 2. Model reaction for Synthesis of 4*H*-pyran

Firstly, we have considered solvent parameters and observed reactions in different solvents like water, methanol, PEG-400, and ethanol as protic solvents as well as DCM, DMF, and acetonitrile as aprotic solvents. We observed that the solvent has an important role in the progress of the reaction. The reaction with ethanol:water gave the corresponding product in good yields, whereas the findings with other solvents such as DCM, DMF, and acetonitrile, yielded the product **4a** in fewer quantities, neither PEG-400 nor water were particularly given good results.Further,it has beendecided the impressive and ideal solvent for this conversion was aqueous ethanol (water:ethanol, 9:1, v/v).

Table 1. Screening of reaction conditions with respect to solvent and catalyst loading **4a**[a]

Entry	Solvent	Catalyst(mol%)	Yield[b](%)
1	Water	10% Meglumine	N R
2	Methanol	10% Meglumine	74
3	Ethanol	10% Meglumine	79
4	PEG-400	10% Meglumine	58
5	DCM	10% Meglumine	26
6	DMF	10% Meglumine	29
7	Acetonitrile	10% Meglumine	31
8	Ethanol:Water(1:1)	10% Meglumine	79
9	Ethanol:Water(9:1)	5% Meglumine	90
10	Ethanol:Water(9:1)	10% Meglumine	96
11	Ethanol:Water(9:1)	15% Meglumine	93
12	Ethanol:Water(9:1)	No catalyst	09

[a]**Reactionconditions:**Benzaldehyde (1mmol), Malononitrile (1mmol), Ethylacetoacetate(1mmol), 10mol% Meglumine in 5 mL ethanol:water, at room temperature for 30-35 min.[b]Isolated yields, NR: No Reaction

However, in the model reaction, the influence of catalyst loading was also investigated. The results revealed that a catalyst concentration of 10mol% was a great choice for this process. Increasing the catalyst concentration 10 to 15mol% resulted in a low effect on yield and not be further increased.When the reaction was conducted with reducing amounts of catalyst, the yield of **4a** could not be further increased.Under optimized conditions when the standard reaction was performed in absence of Megluminethere was less conversion of reactants to products after stirring at room temperature(**Table 1**, entry 12).

This result motivates us to investigate the methods for synthesis of Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylates from substituted benzaldehydes,malononitrile, and ethylacetoacetate using a 10mol%Meglumine catalyst and ethanol:water as a solvent in an optimized reaction condition.

The recyclability of the meglumine catalyst was further examined for the standard reaction of benzaldehyde (**1a**), malononitrile (**2**), and ethylacetoacetate(**3**) in ethanol:water solvent at room temperature for 30-35 minutes. The results are shown in **Figure 4**.

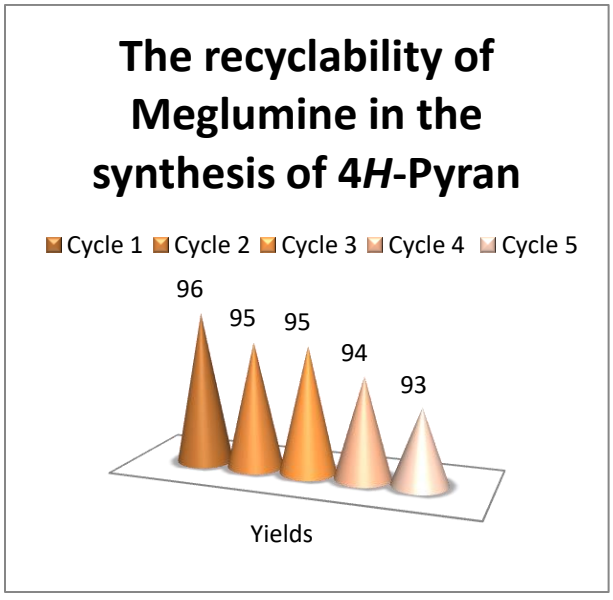
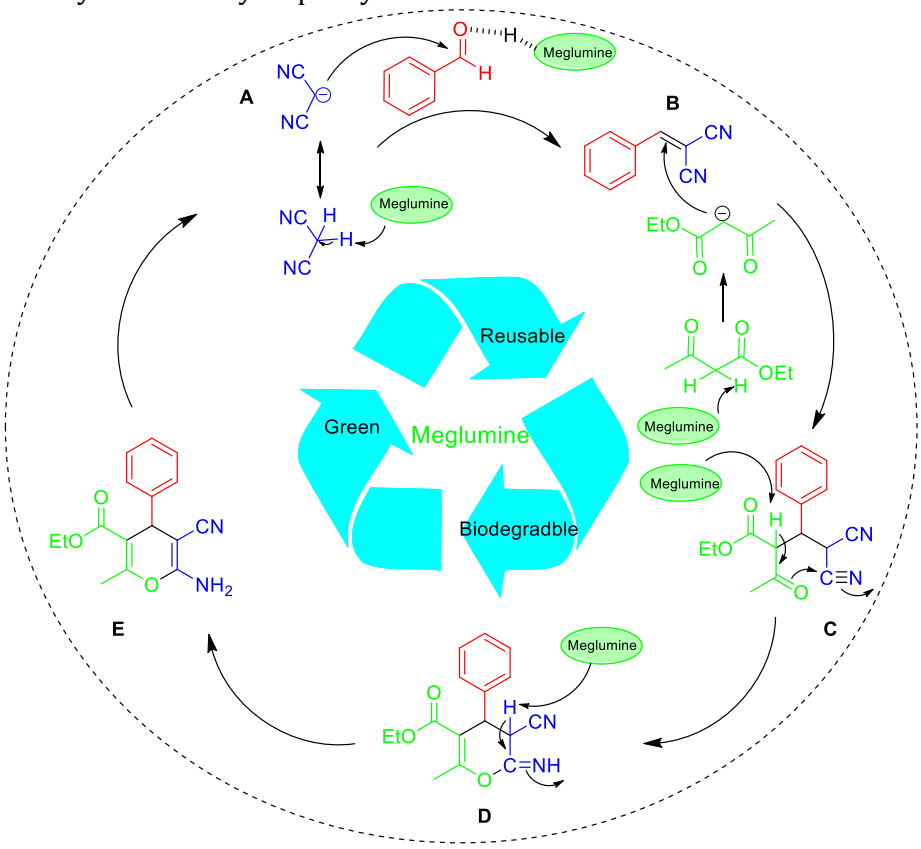


Figure 4. The recyclability of Meglumine[a] in the synthesis of 4*H*-pyran

After the completion of the reaction, the catalyst was recovered andthe filtrate was dried. The recovered catalyst was reused after drying for the next run. The catalyst was reused for four runs, and the target compounds were formed in yields (96% to 94%) in their corresponding reaction periods in each and every reaction.

The plausible mechanism for the synthesis of Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate(**4a**)as shown in **Scheme 3**, involves the proton abstraction of the active methylene group of malononitrile by the Meglumineindicated as **A**, later it reacts with benzaldehyde involves the dehydration resulting in the formation of **B**, which on the attack of active methylene group of ethylacetoacetateto form **C**, after that abstraction of hydrogen by Meglumine from **C** and **D** to form desired product **E**.



Scheme 3. Plausible mechanism for the synthesis of Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylatederivative(**4a**)

Conclusion

Finally, by utilizing Meglumine as a green and recyclable catalyst, we designed a mild, rapid, and environmentally sustainable synthesis process for Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate **(4a-l)** from aromatic benzaldehyde, malononitrile, and ethylacetoacetate.Simple reaction conditions, no side reactions, and high yield product formation are all essential features of the technique. For the synthesis of Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate, the current technique is an alternative to traditional methods. The catalyst was retrieved several times without losing catalytic activity, resulting in a cost-effective method.

Experimental

General experimental procedure for the synthesis of ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate

In a dry and clean 50mL round bottom flask, a mixture of substituted benzaldehyde (1 mmol), malononitrile (1mmol), and ethylacetoacetate(1mmol) was stirred in 5 mL ethanol:water as a solvent along with Meglumine(10 mole%) as a catalyst at room temperature for 30-35 min. The progress of the reaction was monitored by thin-layer chromatography. After the completion of the reaction, the reaction mixture was poured oncrushed ice, which was then filtered. The crude product was crystallized using ethanol to yield pure 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate.The melting points of the products are in good agreement with those described in the literature[26-32].

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (4a)

The compound **(4a)** was synthesized with Megluminecatalyzed reaction in betweenbenzaldehyde**(1a)**,malononitrile**(2)**an dethylacetoacetate**(3)** aswhite solid; yield 96%; Mp 190-192°C; ^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm):1.00-1.03 (t, 3H, CH_3-CH_2-), 2.31 (s, 3H, CH_3), 3.92-3.99 (m, 2H, CH_2-CH_3), 4.37 (s, 1H, pyran-H), 4.40 (s, 2H, NH_2), 7.12-7.24 (m, 5H, Ar-H).;^{13}C NMR (75 MHz, $CDCl_3$)δ (ppm) :12.86, 17.37, 37.74, 59.65, 76.00, 106.98, 117.80, 126.17, 126.49, 127.56, 142.73, 155.76, 156.39, 164.84.; LCMS (ESI$^+$) calcd. for $C_{16}H_{16}N_2O_3$(M+H)$^+$: 285.12; found 285.14.

Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4H-pyran-3-carboxylate (4c)

The compound **(4c)** was synthesized with Megluminecatalyzed reaction in between4-chlorobenzaldehyde**(1c)**,malononitrile**(2)**andet hylacetoacetate**(3)** as light yellow solid; yield 94%; mp 138-139°C;^{1}H-NMR (300 MHz, $CDCl_3$)δ (ppm) :1.03-1.05(t, 3H,CH_3-CH_2-), 2.30 (s, 3H,CH_3), 3.96-4.00 (q, 2H,CH_2-CH_3), 4.36 (s, 1H,pyran-H), 4.49 (s, 2H,NH_2), 7.06-7.08 (d, 2H, Ar-H), 7.19-7.20 (d, 2H, Ar-H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) :12.77, 17.30, 37.16, 59.62, 75.88, 106.46, 117.52, 127.59, 127.76, 131.80, 141.24, 155.90, 156.37, 164.49.; LCMS (ESI$^+$) calcd. for $C_{16}H_{15}ClN_2O_3$(M+H)$^+$: 319.08; found 319.09.

Ethyl 6-amino-5-cyano-2-methyl-4-(2-nitrophenyl)-4H-pyran-3-carboxylate (4f)

The compound **(4f)** was synthesized with Meglumine catalyzed reaction in between2-nitrobenzaldehyde**(1f)**, malononitrile**(2)**andethylacetoacetate**(3)** as yellowish solid; yield 94%;Mp 178-179°C; ^{1}H NMR (300 MHz, $CDCl_3$)δ (ppm) :0.88-0.91 (t, 3H, CH_3-CH_2-), 2.31 (s, 3H,CH_3), 3.85-3.87 (q, 2H, CH_2-CH_3), 4.56 (s, 2H, NH_2), 5.16 (s, 1H, pyran-H), 7.17–7.72 (m, 4H, Ar-H).; ^{13}C NMR (75 MHz, $CDCl_3$)δ (ppm):12.51, 17.30, 31.83, 59.79, 75.61, 106.15, 117.00, 122.91, 126.76, 129.46, 132.08, 137.95, 147.95, 156.91, 157.09, 163.89;LCMS (ESI$^+$) calcd. for $C_{16}H_{15}N_3O_5$(M+H)$^+$: 330.31; found 330.35.

Supporting Information

Full experimental detail, LCMS, ^{1}H, and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

Acknowledgments

The author G.B.P. is very much thankful to the Council for Scientific and Industrial Research (CSIR), New Delhi, for theaward senior research fellowship. File No. 08/613(0005)/2018-EMR-I

Conflict of Interest

The authors declare no conflict of interest.

Orcid:

Ganesh Baburao Pund
https://orcid.org/0000-0003-1560-6171
Sambhaji Tukaram Dhumal
https://orcid.org/0000-0003-3018-6179
Madhav Janardan Hebade
https://orcid.org/0000-0003-0008-8834
Mazahar Farooqui

https://orcid.org/0000-0003-2236-6639
Bhagwansing Shivsing Dobhal
https://orcid.org/0000-0002-9469-3869

References

[1]R.R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari, D. Sriram, *Bioorganic Med. Chem. Lett.*,**2007**, *17*,6459–6462. [Crossref], [Google Scholar], [Publisher]
[2]D. Kumar, V.B. Reddy, S. Sharad, U. Dube, S. Kapur, *Eur. J. Med. Chem.*, **2009**, *44*, 3805–3809. [Crossref], [Google Scholar], [Publisher]
[3]W. Kemnitzer, J. Drewe, S. Jiang, H. Zhang, C. Crogan-Grundy, D. Labreque, M. Bubenick, G. Attardo, R. Denis, S. Lamothe, H. Gourdeau, B. Tseng, S. Kasibhatla, S.X. Cai, *J. Med. Chem.*,**2008**, *51*,417–423. [Crossref], [Google Scholar], [Publisher]
[4]P.G. Wyatt,B.A. Coomber, D.N. Evans, T.I. Jack, H.E. Fultone, A.J. Wonacott, P. Colman, J. Varghese, *Bioorganic Med. Chem. Lett.*,**2001**,*11*, 669–673. [Crossref], [Google Scholar], [Publisher]
[5]M. Kidwai, S. Saxena, M.K.R. Khan, S.S. Thukral, *Bioorganic Med. Chem. Lett.*,**2005**, *15*,4295–4298.[Crossref], [Google Scholar], [Publisher]
[6]L. Moafi, S. Ahadi, A. Bazgir, *Tetrahedron Lett.*,**2010**, *51*,6270–6274.[Crossref], [Google Scholar], [Publisher]
[7]M.G. Dekamin, M. Eslami, A. Maleki, *Tetrahedron*,**2013**, *69*,1074–1085.[Crossref], [Google Scholar], [Publisher]
[8]C.B. Sangani, D.C. Mungra, M.P. Patel, R.G. Patel, *Chinese Chem. Lett.*,**2012**,*23*, 57–60. [Crossref], [Google Scholar], [Publisher]
[9]A. El Hattak, S. Izzaouihda, Z. Rouifi, F. Benhiba, S. Tabti, A. Djedouani, N. Komiha, H. Abou El Makarim, R. Touzani, H. Oudda, I. Warad, A. Zarrouk, *Chem. Data Collect.*,**2021**, *32*, 100655.[Crossref], [Google Scholar], [Publisher]
[10] E. Abdel, A. Hafez, M.H.Elnagdi,*Heterocycles*,**1987**,*26*,903–907.[Crossref], [Google Scholar], [Publisher]
[11] S. Amirnejat, A. Nosrati, R. Peymanfar, S. Javanshir, *Res. Chem. Intermed.*,**2020**, *46*, 3683–3701.[Crossref], [Google Scholar], [Publisher]
[12] S.S. Ramadoss, H. Kiyani, H. Mansoor,*Iran. J. Chem. Chem. Eng*.,2017, 36,19–26.[Crossref], [Google Scholar], [Publisher]
[13] B. Maleki, S. Sheikh, *Org. Prep. Proced. Int.*,**2015**, *47*, 368–378. [Crossref], [Google Scholar], [Publisher]
[14] N. Seshu Babu, N. Pasha, K.T. Venkateswara Rao, P.S. Sai Prasad, N. Lingaiah, *Tetrahedron Lett.*,**2008**, *49*, 2730–2733. [Crossref], [Google Scholar], [Publisher]
[15] Y. Peng, G. Song, F. Huang, *Monatshefte fur Chemie*,**2005**, *136*,727–731.[Crossref], [Google Scholar], [Publisher]
[16] H. Kiyani, F. Ghorbani, *J. Saudi Chem. Soc.*,**2014**, *18*, 689–701.[Crossref], [Google Scholar], [Publisher]
[17] A. Magyar, Z. Hell,*Green Process. Synth.*,**2018**, *7*,316–322.[Crossref], [Google Scholar], [Publisher]
[18] A. Molla, S. Hussain, *RSC Adv.*, **2016**, *6*,5491–5502.[Crossref], [Google Scholar], [Publisher]
[19] E.A. Mostafa, T.K. Khatab, *Org. Chem. An Indian J. Res.*,**2018**, *14*, 2–7. [Crossref], [Google Scholar], [Publisher]
[20] S.S. Mansoor, K. Logaiya, K. Aswin, P.N. Sudhan,*J. Taibah Univ. Sci.*,**2015**, *9*,213–226. [Crossref], [Google Scholar], [Publisher]
[21] U.R. Pratap, D.V. Jawale, P.D. Netankar, R.A.Mane, *Tetrahedron Lett.*, **2011**,*52*, 5817–5819.[Crossref], [Google Scholar], [Publisher]
[22] M.J. Hebade, R.D. Kamble, S.V. Hese, P.P. Mogle, A.N. Ambhore, S.N. Kadam, B.S. Dawane, *Phosphorus, Sulfur Silicon Relat. Elem.*,**2016**, *191*, 1155–1159.[Crossref], [Google Scholar], [Publisher]
[23] S.N. Kadam, A.N. Ambhore, M.J. Hebade, R.D. Kamble, S.V. Hese, M.V. Gaikwad, P.D. Gavhane, B.S. Dawane, *Synlett*,**2018**, *29*, 1902–1908.[Crossref], [Google Scholar], [Publisher]
[24] S.T. Dhumal, A. Deshmukh, K.R. Kharat, B.R. Sathe, R.A.Mane,*New J. Chem.*, **2019**, 1–27. [Crossref], [Google Scholar], [Publisher]
[25] M.J. Hebade, T.R. Deshmukh, S.T. Dhumal, *Synth. Commun.*,**2021**, *51*, 2510–2520. [Crossref], [Google Scholar], [Publisher]
[26] P.B. Hiremath, K. Kantharaju, *ChemistrySelect*, **2020**, *5*, 1896–1906. [Crossref], [Google Scholar], [Publisher]

[27] M. Kamalzare, M. Bayat, A. Maleki, *R. Soc. Open Sci.*,**2020**, *7*,200385.[Crossref], [Google Scholar], [Publisher]
[28] A. Sanchez, F. Hernandez, P.C. Cruz, Y. Alcaraz, J. Tamariz, F. Delgado, M.A. Vazquez, *J. Mex. Chem. Soc.*, **2012**, *56*, 121–127. [Crossref], [Google Scholar], [Publisher]
[29] A.M. Zonouz, D. Moghani, *Commun. Catal.*,**2018**, *1*,13–20. [Crossref], [Google Scholar], [Publisher]
[30] B. Chowhan, M. Gupta, N. Sharma, *ChemistrySelect*,**2019**, *4*, 12689–12700. [Crossref], [Google Scholar], [Publisher]
[31] A. Moshtaghi Zonouz, D. Moghani, S. Okhravi, *Curr. Chem. Lett.*,**2014**, *3*, 71–74. [Crossref], [Google Scholar], [Publisher]
[32] R. Smits, S. Belyakov, A. Plotniece, G. Duburs, *Synth. Commun.*,**2013**, *43*, 465–475. [Crossref], [Google Scholar], [Publisher]