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One-Pot Synthesis of 2-Amino-4*H*-Pyrans and 2-Amino-Tetrahydro-4*H*-Chromenes Using *L*-Proline

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ABSTRACT

A one-pot procedure for the synthesis of 2-amino-4-aryl-4*H*-pyrans and 2-amino-tetrahydro-4*H*-chromenes via the multi-component reaction between aryl aldehydes, β-dicarbonyl compounds and malononitrile in the presence of *L*-proline-in ethanol under reflux conditions has been developed rapidly and smoothly in good to excellent yields.

Keywords: multicomponent; *L*-proline; 2-amino-4*H*-pyrans; chromenes; synthesis

1. INTRODUCTION

Multicomponent reactions have become very popular in the discovery of biologically active novel compounds due to its simple experimentation, atom economy and high yields of the products [1]. 2-Amino-4*H*-pyran derivatives represent an important class of compounds which are often used in cosmetics and pigments, and utilized as potentially biodegradable agrochemicals [2]. Polyfunctionalized 4*H*-pyrans also constitute a structural unit of many natural products [3] and biologically interesting compounds which possess various pharmacological activities, such as antiallergic, antitumor and antibacterial [4]. 4*H*-Pyran derivatives are also potential calcium channel antagonists [5] which are structurally similar to biologically active 1,4-dihydropyridines.

Generally, the conventional synthesis of benzopyran derivatives involves acid- as well as base-catalyzed condensation of the aldehydes with the active methylene compounds. 4*H*-benzo[b]pyran derivatives have been prepared with several catalysts, such as Na_2SeO_4 [6], tetra-methyl ammonium hydroxide (TMAH) [7], $CeCl_3$-$7H_2O$ [7], and organic solvents such as dimethylformamide (DMF) or acetic acid [9], but these solvents make the workup procedure complicated and lead to poor yields of products. However, some of the reported methods have their own merits but at least one of the limitations of poor yields, difficult-to-obtain reagent, long reaction times, effluent pollution, harsh reaction conditions, and expensive reagents. Therefore, the development of environmentally benign, efficient and economical methods for the synthesis of biologically interesting compounds remains a significant challenge in synthetic chemistry.

Our recent interest has been in the development of new synthetic methods on using *L*-proline as bio and recyclable catalyst [10,11]. In recent years, *L*-proline has gained importance as versatile catalyst for various organic transformations such as the synthesis of coumarins in ionic liquid [12] and α-aminoxylation of aldehydes [13]. Aso, *L*-proline and *L*-proline derivatives were successfully used as organo catalysts in asymmetric aldol and Michael addition reactions [14]. To the best of our knowledge in the open literature, one-

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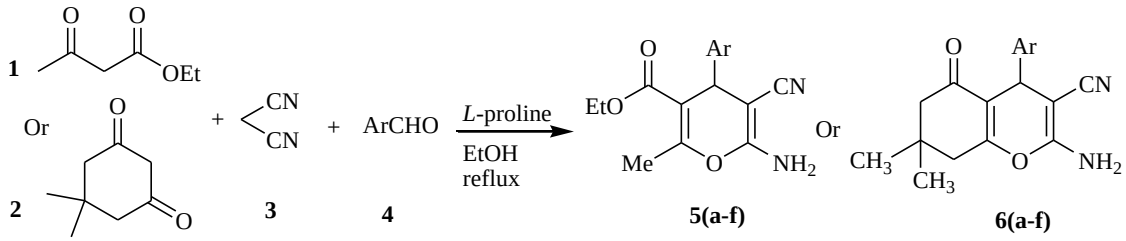
pot synthesis of 2-amino-4*H*-pyrans catalyzed by *L*-proline have not been reported. Therefore, we wish to report an efficient synthesis of 2-amino-4*H*-pyrans using of aromatic aldehydes, malononitrile and ethylacetoacetate or dimedone by *L*-proline in ethanol under reflux conditions (Scheme 1). The advantages of this method are high reaction yields, short reaction times and use of ethanol as an environmentally friendly solvent.



Scheme 1: Synthesis of 2-amino-4-aryl-4*H*-pyrans or 2-amino-tetrahydro-4*H*-chromenes using *L*-proline

2. EXPERIMENTAL

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Bruker FT-IR spectrometer did scanning between 4000–400 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker DRX-300 MHz AVANCE NMR instrument.

2.1. Synthesis of 2-amino-4*H*-pyrans or 2-amino-tetrahydro-4*H*-chromenes using *L*-proline.

General procedure: A mixture of aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol, 0.066 g), ethyl acetoacetate (1.0 mmol, 0.13 g) or dimedone (1.0 mmol, 0.14 g) and *L*-proline (10 mol%) was refluxed in ethanol (10 mL). After completion of the reaction, as indicated by TLC, the solvent was evaporated and the crud product was extracted from ethyl acetate and water. The organic layer was dried with Na_2SO_4 and the solvent was evaporated to obtain the crude product. Thus the residue was recrystallized from methanol (Table 3). All products are known and characterized with those of authentic sample in literature.

2.2 Reusability of the catalyst:

L-Proline was also resulted by evaporation of the aqueous layer, then it was used for four runs. In this case, it found reusable *L*-proline act as well as fresh *L*-proline (Table 1)

Table 1: Reusability of the catalyst

Entry	Runs	Yield%[a]
1	1st	84
2	2nd	77
3	3th	72
4	4th	70

[a]Reaction conditions: Benzaldehyde (1.0 mmol, 0.106 g), ethylacetoacetate (1.0 mmol, 0.13 g), molononitrile (1.0 mmol, 0.066 g) and *L*-proline (10 mol%) in ethanol (10 mL) under reflux conditions at 1.0 h.

3. RESULTS AND DISCUSSION

Firstly, the model reaction was simply carried out by mixing benzaldehyde, malononitrile, ethylacetoacetate and *L*-proline in ethanol under reflux conditions. The corresponding ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate **5a** was obtained in high yield. The effect of catalyst amount and different solvents such as ethanol, chloroform and water on the yield of product was evaluated (Table 2, 3).

Table 2: Solvent effecting on the synthesis of methyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate

Entry	Solvent(10 ml)	Yield%
1	CH_3Cl	55
2	C_2H_5OH	93
3	H_2O	88
4	C_2H_5OH:H_2O (1:1)	80
5	Solvent-free	68

[a]Reaction conditions: Benzaldehyde (1.0 mmol, 0.106 g), ethylacetoacetate (1.0 mmol, 0.13 g), malonitrile (1.0 mmol, 0.066 g) and *L*-proline (10 mol%) under reflux conditions at 1.0 h.

As indicated in Table 2, the polar solvents such as ethanol were found much better than the non-polar solvents like chloroform. The results could be interpreted with the much better solubility the reactants in polar solvents. Thus in present study has been used only ethanol, which is relatively benign organic solvent and 10 mol% of *L*-proline as a reusable organocatalyst.

Table 3: The effect of catalyst amount on the synthesis of methyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate

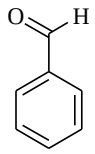
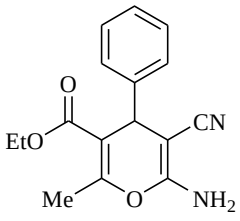
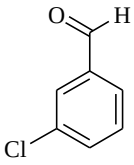
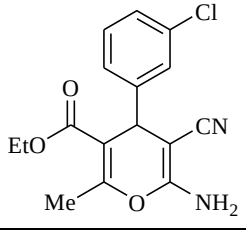
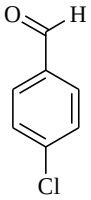
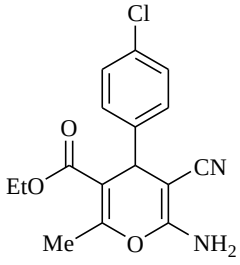
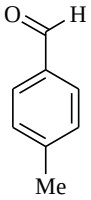
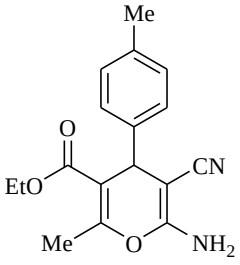
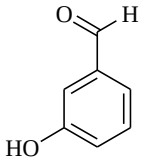
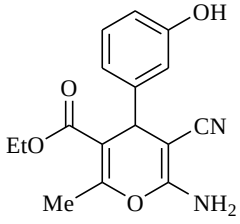
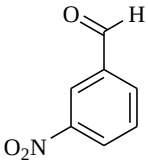
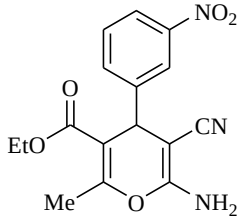
Entry	Catalyst (mol %)	Yield%[a]
1	Free	10
2	5	75
3	10	93
4	15	93

[a]Reaction conditions: Benzaldehyde (1 mmol, 0.106 g), ethylacetoacetate (1 mmol, 0.13 g), malononitrile (1 mmol, 0.066 g) and *L*-proline (10 mol%) in ethanol (10 mL) under reflux conditions at 1.0 h.

However, the scope and generality of this three-component one-pot synthesis of 2-amino-4*H*-pyrans have been illustrated with different aldehydes and the results have been summarized in Table 4. This method has the ability to tolerate a variety of other functional groups such as hydroxyl, methyl, nitro, and chloro under the reaction conditions. Both, the electron-rich and electron-deficient aldehydes worked well, leading to high yields of products **5a-f**.

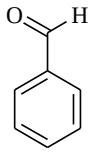
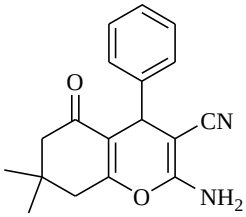
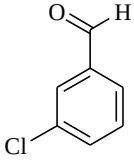
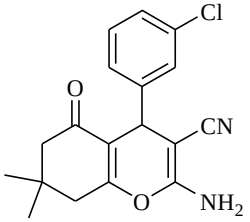
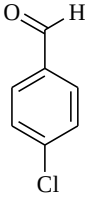
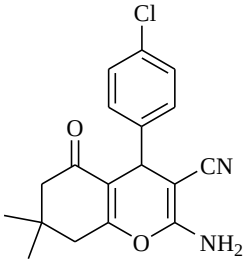
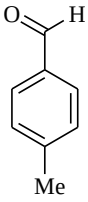
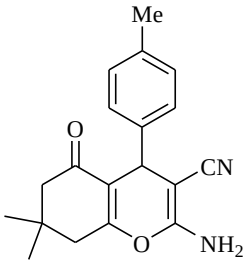
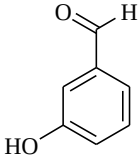
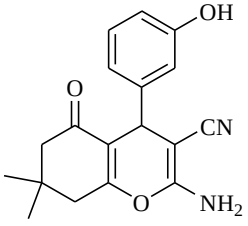
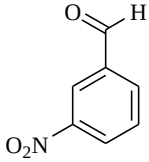
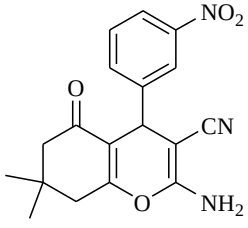
Also, in a series of reactions, dimedone was employed instead of ethyl acetate under reaction condition to give the corresponding or 2-amino-tetrahydro-4*H*-chromenes. In these cases, the reactions were then evaluated using a variety of structurally diverse aldehydes (Table 5). Three component condensation of dimedone with various aromatic aldehydes bearing electron withdrawing groups such as nitro or electron releasing groups such as methyl and malononitrile was carried out in the presence of *L*-proline as a catalyst. The yields obtained were good-to-excellent. The results obtained in the current method are illustrated in Table 5 (**6a-f**). In each case, the reaction profile is clean and this one-pot three-component procedure presents some improvements and advantages over existing methods. One of the major advantages of this protocol is the isolation and purification of the products, which have been achieved by simple washing and crystallization of the crude products. All the products were identified by comparison of analytical data with those of authentic samples.

Table 4: Synthesis of 2-amino-4*H*-pyrans using *L*-proline

Entry	ArCHO	Product	Time(h)	Yield%	M.p.(°C) Found	M.p.(°C) Reported
1		 **5a**	1.0	84	194 -195	195-196[17]
2		 **5b**	2.0	78	152-154	153-156 [4]
3		 **5c**	2.0	72	170-171	172-174[16]
4		 **5d**	2.45	59	172-175	177-179 [16]
5		 **5e**	1.25	71	163-165	164-165 [16]
6		 **5f**	2.0	78	177-179	182-183 [4]

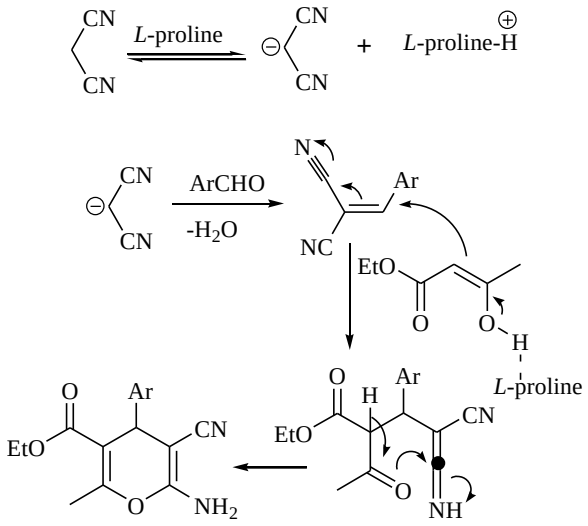
[a]Reaction conditions: Aryl aldehyde (1.0 mmol), ethylacetoacetate (1.0 mmol, 0.13 g), mononitrile (1.0 mmol, 0.066 g) and *L*-proline (10 mol%) in ethanol (10 mL) under reflux conditions.

Table 5: Synthesis of 2-amino-tetrahydro-4*H*-chromenes using *L*-proline

Entry	ArCHO	Product	Time(h)	Yield%	M.p.(°C)	
					Found	Reported
1		 **6a**	1.0	93	222-224	226-228 [4]
2		 **6b**	1.45	91	221-224	223-225[15]
3		 **6c**	1.5	87	199-202	202-203[16]
4		 **6d**	2.5	65	210	209-211[16]
5		 **6e**	2.0	79	219-221	224-226[16]
6		 **6f**	2.3	88	201-203	201-205[16]

[a]Reaction conditions: Aryl aldehyde (1.0 mmol), dimedone (1.0 mmol, 0.14 g), malononitrile (1.0 mmol, 0.066 g) and *L*-proline (10 mol%) in ethanol (10 mL) under reflux conditions.

Mechanistically, the initial condensation of aromatic aldehyde with malononitrile in the presence of *L*-proline leads to the formation of arylidenemalononitrile with the loss of a water molecule. The nucleophilic addition of the enolizable ethylacetoacetate to arylidene malononitrile followed by intramolecular cyclization of the resulting species produce the 2-amino-4*H*-pyrans (Scheme 2).



Scheme 2: Purposed mechanism for synthesis of 2-amino-4-aryl-4*H*-pyrans or 2-amino-tetrahydro-4*H*-chromenes using *L*-proline

4. CONCLUSION

In this paper, a facile, convenient and environmentally benign one-pot synthesis of 2-amino-4*H*-pyrans and 2-amino-tetrahydro-4*H*-chromenes have developed using *L*-proline-in ethanol under reflux conditions. The desired products can be also obtained in high yields and purities without further chromatographic purification. Finally, the recovered *L*-proline can be reused in another cycle without losing its activity.

Spectra data

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (5a): IR (KBr / cm^{-1}): 3404, 3330 (NH_2), 2190 (CN), 1693 (C=O), 1211 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.31-7.19 (m, 5H), 4.44 (s, 2H), 4.43 (s, 1H), 4.06-4.0 (m, 2H), 2.38 (s, 3H), 1.09 (t, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 167, 159, 156, 142, 128, 125, 117, 107, 61, 58, 38, 15, 14.

Ethyl 6-amino-4-(3-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (5b): IR (KBr / cm^{-1}): 3347, 3257 (NH_2), 2190 (CN), 1683 (C=O), 1215 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.28-7.12 (m, 4H), 4.55 (s, 2H), 4.40 (s, 1H), 4.08-4.0 (m, 2H), 2.35 (s, 3H), 1.09 (t, 3H) .^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 167, 159, 156, 143, 134, 130, 128, 127, 125, 117, 107, 61, 58, 38, 15, 14.

Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (5c): IR (KBr / cm^{-1}): 3394, 3321 (NH_2), 2192 (CN), 1682 (C=O), 1213 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.25 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 5.93 (s, 2H), 4.38 (s, 1H), 4.06-4.0 (m, 2H), 2.36 (s, 3H), 1.12 (t, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 167, 159, 156, 131, 130, 128, 124, 117, 107, 61, 58, 38, 15, 14.

Ethyl 6-amino-4-(4-methylphenyl)-5-cyano -2-methyl -4*H*- pyran-3-carboxylate (5d): IR (KBr / cm^{-1}): 3382, 3316 (NH_2), 2192 (CN), 1682 (C=O), 1213 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.07 (s, 4H), 5.80 (s, 2H), 4.35 (s, 1H), 4.03-4.01 (m, 2H), 2.35 (s, 3H), 1.09 (t, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 167, 159, 156, 139, 135, 129, 124, 117, 107, 61, 58, 38, 24,15, 14.

Ethyl 6-amino-4-(3-hydroxyphenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (5e): IR (KBr / cm^{-1}): 3452, 3414 (NH_2, OH), 2199 (CN), 1651 (C=O), 1215, (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 8.85 (s, 1H), 7.07 (t, 1H), 6.67-6.64 (m, 3H), 5.74 (s, 2H), 4.31 (s, 1H), 4.05-4.02 (m, 2H), 2.35 (s, 3H), 1.13 (t, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 167, 159, 156, 143, 130, 124, 121, 117, 114, 112, 107, 61, 58, 39, 15, 14.

Ethyl 6-amino-4-(3-nitrophenyl)-5-cyano-2-methyl -4*H*-pyran-3-carboxylate (5f): IR (KBr / cm^{-1}): 3429, 3334 (NH_2), 2186 (CN), 1680 (C=O), 1210 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.86-7.83 (d, 1H), 7.81 (s, 1H), 7.47-7.26 (m, 2H), 5.65 (s, 2H), 4.32 (s, 1H), 3.86-3.78 (q, 2H), 2.18 (s, 3H), 0.89 (t, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 167, 159, 156, 148, 143, 135, 129, 124, 117, 107, 61, 58, 37, 15, 14.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6a): IR (KBr / cm^{-1}): 3395, 3324 (NH_2), 2199 (CN), 1680 (C=O), 1214 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.28-7.10 (m, 5H), 5.93 (s, 2H), 4.14 (s, 1H), 2.26-2.20 (d, 1H), 2.10-2.05 (d, 1H), 2.28 (s, 2H), 1.01 (s, 3H), 0.93 (s, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 198, 159, 155, 142, 128, 125, 117, 113, 58, 51, 44, 37, 30, 27.

2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6b): IR (KBr / cm^{-1}): 3347, 3257 (NH_2), 2190 (CN), 1683 (C=O), 1215 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.80-7.12 (m, 2H), 7.43-7.58 (m, 2H), 5.14 (s, 2H), 4.28 (s, 1H), 2.27 (s, 2H), 2.20-2.17(d, 1H), 2.10-2.05 (d, 1H), 1.05 (s, 3H), 0.96 (s, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 198, 159, 155, 143, 134, 130, 128, 127, 117, 113, 58, 51, 44, 37, 30, 27.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6c): IR (KBr / cm^{-1}): 3394, 3321 (NH_2), 2192 (CN), 1682 (C=O), 1213 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.24 (d, 2H), 7.18 (d, 2H), 5.79 (s, 2H), 4.33 (s, 1H), 2.46 (s, 2H), 2.24 (d, 1H), 2.16 (d, 1H), 1.11 (s,

3H), 1.02 (s, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 198, 159, 155, 140, 131, 130, 128, 121, 117, 113, 58, 51, 44, 37, 30, 27.

2-Amino-7,7-dimethyl-5-oxo-4-p-tolyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6d): IR (KBr / cm^{-1}): 3382, 3316 (NH_2), 2192 (CN), 1682 (C=O), 1213 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 7.70-7.11 (m, 4H), 5.60 (s, 2H), 4.30 (s, 1H), 2.46 (s, 2H), 2.28 (s, 3H), 2.19 (d, 1H), 2.16 (d, 1H), 1.10 (s, 3H), 1.03 (s, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 198, 159, 155, 139, 135, 129, 121, 117, 113, 58, 51, 44, 37, 30, 27, 24.

2-Amino-4-(3-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6e): IR (KBr / cm^{-1}): 3452, 3414 (NH_2, OH), 2199, (CN), 1651 (C=O), 1215 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 6.65 (d, 2H), 6.92 (d, 2H), 6.93 (brs, 2H), 4.06 (s, 1H), 2.5 (brs, 2H), 2.25 (d, 1H), 2.10 (d,1H), 1.04 (s, 3H), 0.96 (s, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 198, 159, 158, 155, 143, 130, 121, 118, 117, 113, 58, 51, 44, 37, 30, 27.

2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6f): IR (KBr / cm^{-1}): 3429, 3334 (NH_2), 2186 (CN), 1680 (C=O), 1210 (C-O). ^{1}HNMR ($CDCl_3$ / 300 MHz / δ ppm): 8.05 (d, 1H), 7.95 (s, 1H), 7.65-7.57 (m, 2H), 7.17 (s, 2H), 4.39 (s, 1H), 2.27-2.22 (d, 1H), 2.11-2.06 (d, 1H), 2.48 (s, 2H), 1.02 (s, 3H), 0.93 (s, 3H). ^{13}CNMR ($CDCl_3$ / 300 MHz / δ ppm): 198, 159, 155, 148, 143, 135, 129, 124, 118, 117, 113, 58, 51, 44, 36, 30, 27.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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