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Synthesis of aminopyridine derivatives by four component reactions of naphtholes

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Abstract: An efficient, clean and one-pot procedure for the synthesis of 2-amino-4*H*-chromenes has been developed by three-component condensation of aldehyde derivatives, malononitrile, and 1- or 2-naphthol in the presence of aspartic acid as an amino acid and efficient catalyst under solvent-free and thermally conditions. Aspartic acid is one of two acidic amino acids. Aspartic acid is alanine with one of the β hydrogens replaced by a carboxylic acid group. The solvent-free conditions, a simple, efficient, and eco-friendly method, short reaction time and excellent yields of the products make this methodology highly significant.

Keywords:2-Amino-4*H*-chromenes, aspartic acid, malononitrile, solvent-free conditions, amino acid.

Introduction

The discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a focal point of research activity in the field of modern medicinal and combinatorial chemistry [1]. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product with the most of the atoms contained in the starting materials [2]. The rapid assembly of molecular diversity utilizing MCRs has received a great deal of attention, especially for the design and construction of elaborate heterocyclic frameworks possessing enhanced “drug-like” properties [3-5]. The chromene derivatives are widely present in natural alkaloids, flavonoids, tocopherols, and anthocyanins [6].Moreover, functionalized chromenes have played in ever-increasing role in the synthetic approaches to promising compounds in the field of medicinal chemistry [7].

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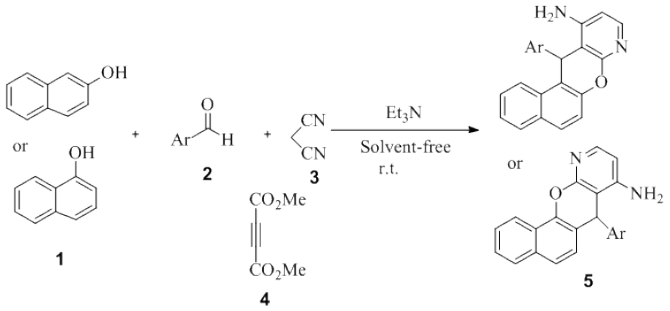
Among the different types of chromenesystems, 2-amino-4H-chromenes are of particular utilityas they belong to preferential medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced anticoagulant, diuretic, spasmolitic- and antianaphylactic activities [8-10].2-Amino-4*H*-chromenes are generally produced by refluxing active methylene compounds (e.g., malononitrile and cyanoacetic acid esters), with an aldehyde and an activated phenol in organic solvents such as ethanol and acetonitrile, and in the presence of catalyst for several hours [11–13].Heterocyclic compounds are very significant because of having inflexibility and important biological properties [14]. Further, this structure is displayed in the natural alkaloids, which is why synthesizing spiro heterocyclic compounds is both significant and interesting [15]. The heterocyclic compounds in among organic compounds have well-known position for showing many biological properties [16-23]. In our continuing interest in the development of one-pot multi-component reactions [24-27], we reported herein our results for the synthesis of chromene derivatives**5**scaffolds for the four-component solvent-free condensation of aromatic aldehydes**2**,

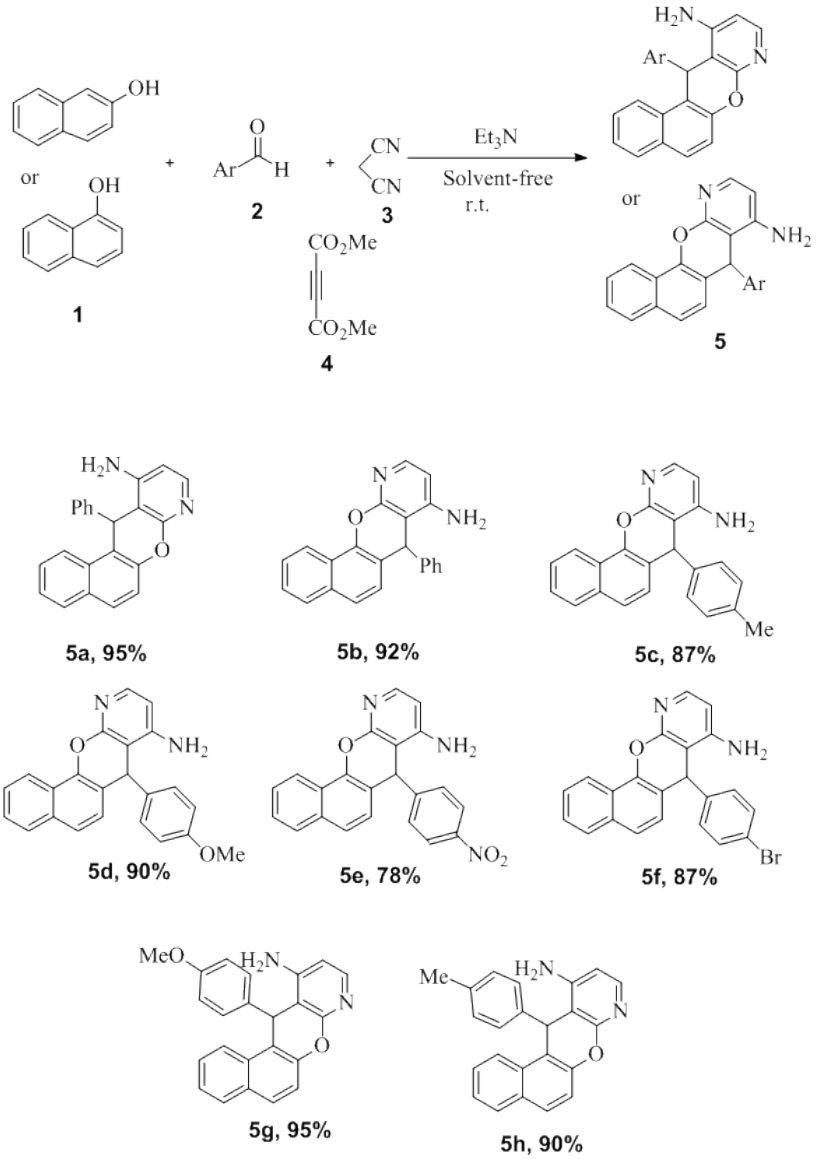
malononitrile**3**, 1- or 2-naphthol**1** and dimethyl acetylenedicarboxylate**4**in thermally conditions with excellent yields (Scheme **1**).



Scheme 1: Four component reaction of naphthols **5**

Result and Discussion

In this research, chromene derivatives **5** were prepared using four-component solvent-free condensation of aromatic aldehydes**2**, malononitrile**3**, 1- or 2-naphthol**1** and dimethyl acetylenedicarboxylate **4**in thermally conditions with excellent yields (Scheme **2**).



Scheme 2: Four component reaction of naphthols**5**

Another important factor for performing reaction and high yields of product is solvent. Table 1 demonstrates the solvent-free conditions as the beat conditions for conducting the sample reaction.

Table 1. Determination the best solvent in creation of **5a**

Entry	Solvent	Time (h)	Yield%[a]
1	EtOH	15	78
2	CH_2Cl_2	8	58
3	$CHCl_3$	5	62
4	H_2O	8	70
5	**Solvent-free**	**3**	**95**
6	DMF	12	----
7	toluene	12	74

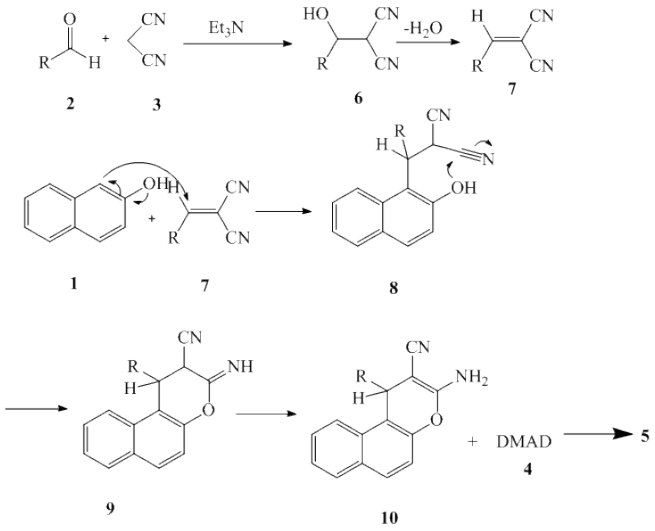
[a] Isolated Yields

After the purification of products, the constructions of prepared chromene derivatives **5** were specified via ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. Owing to the fact that the functional groups in all the synthesized compounds are similar, in this section the structure of compound **5a** as sample was investigated. In ^{1}H NMR spectra of compound **5a**, two singlets at 3.75 and 3.87 are for two methoxy groups one could find one singlet at 1.38 ppm for methyl protons, three singlets at 2.40, 3.63 and 3.73 ppm, one singlet at 5.21 was seen for methin proton and one singlet at 6.88 ppm for NH_2proton accompanied by signals for aromatic moiety at 7.14-7.92. In ^{13}C NMR spectra of compound **5a,** the three signals for carbonyl group at 168.7, 167.7 and 161.5 ppm were presented. Also, for confirmation of the carbonyl categories in the makeup of compound **5a**, the IR spectrum of **5a** was given. The all stages of prepared chromrne derivatives **5**were not specified and did not give any information about it but the proposed mechanism of these reactions could be explained in Scheme 2.

First, in the presence of Et_3N, aldehydes**2** react with malononitrile**2** andproduced intermediate **7** by elimination of water. Compound **1** react with intermediate **7** and produced intermediate **8** which by intermolecular cyclization produced intermediate **10** and react with DMAD and produced compounds **5**.

Conclusion

In summary, we report an eco-friendly and straightforward one-pot condensation for the synthesis of aminopyridine derivatives in good yields in the presence of Et3N at room temperature under solvent-free conditions. Moreover, this method has several other advantages such as, operational simplicity, ecofriendly, high yields, and solvent-free conditions, which makes it a useful and attractive process for the synthesis of a wide variety of biologically active compounds.



Scheme 3: Proposed mechanism for synthesis of 2-amino-4*H*-chromene derivatives

Experimental

All reagents were purchased from Merck (Darmastadt, Germany) and Fluka (Buchs, Switzerland) and used without further purification. Melting points and IR spectra of all the compounds were measured on an Electro Thermal 9100 apparatus and FT-IR-JASCO-460 plus spectrometer. ^{1}H and ^{13}C NMR spectra of known compounds were recorded on a Bruker DRX-400 Avance instrument in DMSO at 400 MHz and 100 MHz. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure for synthesis of 2-amino-4H-chromenes

A mixture of malononitrile (1 mmol), benzaldehyde derivatives (1 mmol), 2-naphthol (1 mmol), and Et_3N (1mmol) was mixed in room temperature under solvent-free conditions and maintained for an appropriate time. The DMAD (1 mmol) was added to previous mixture and mixed for 3 h. After completion of the reaction as indicated by TLC, the residue was washed with water (3 × 10 mL) and recrystallized from ethanol to afford aminopyridine derivatives in exellent yields. The pure product was characterized by

conventional spectroscopic methods. Spectral data for the selected compounds are given below:

3-amino-1-phenyl-1H-benzo[f]chromene-2-carbonitrile (5a):

Yellow Solid; FT–IR (KBr) (νmax, cm-1): 3430 and 3336 (NH2), 2183 (C≡N), 1650 (C=C, vinylnitrile), 1589 (C=C, aromatic); 1H NMR (DMSO-d6, 400 MHz), δ (ppm): 7.14-7.92 (m, 11H, Ar-H), 6.88 (br, s, 2H, NH2), 5.21 (s, 1H, CH).

3-amino-1-(4-chlorophenyl)-1H-benzo[f]chromene-2-carbonitrile (5b):

White Solid; FT–IR (KBr) (ν_{max}, cm^{-1}): 3458 and 3350 (NH_2), 2180 (C≡N), 1660 (C=C, vinylnitrile), 1564 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.25-7.89 (m, 10H, Ar-H), 7.18 (d, 2H, J=8.1 Hz, Ar-H), 7.12 (d, 2H, J=8.1 Hz, Ar-H), 7.01 (s, 2H, NH_2), 5.11 (s, 1H, CH).

3-amino-1-(4-methoxyphenyl)-1H-benzo[f]chromene-2-carbonitrile (5c):

Pale yellow solid; FT–IR (KBr) (ν_{max},cm^{-1}): 3415 and 3365 (NH_2), 2168 (C≡N), 1636 (C=C, vinylnitrile), 1554 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.05-7.92 (m, 10H, Ar-H), 6.98 (br, s, 2H, NH_2), 4.89 (s, 1H, CH), 3.84 (s, 3H, OCH_3).

3-amino-1-(2-hydroxy-4-nitrophenyl)-1H-benzo[f] chromene-2-carbonitrile (5d):

Yellow solid; FT–IR (KBr) (ν_{max}, cm^{-1}): 3422 and 3346 (NH_2), 2197 (C≡N), 1657(C=C, vinylnitrile), 1590 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 11.01 (s, 1H, OH), 7.49-8.16 (m, 6H, Ar-H), 7.23 (s, 2H, NH_2), 7.26-7.41 (m, 3H, Ar-H), 5.36 (s, 1H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 58.36,97.61, 106.52, 113.01, 119.45, 121.86, 122.09, 122.13, 122.64, 124.07, 126.56, 130.14, 131.27, 131.72, 133.90, 143.88, 149.32, 158.92. Anal.Calcd for $C_{20}H_{13}N_3O_4$ (359.34): C, 66.85; H, 3.65; N, 11.69%; Found: C, 66.92; H, 3.67; N, 11.73%.

References

[1] Nefzi, A.; Ostresh, J. M.; Houghten, R.A. *Chem. Rev.* **1997**, *97*, 449.

[2] Weber, L.; *Drug Discovery Today*. **2002**, *7*, 143.

[3] Orru, R.V.A.; de Greef, M. *Synthesis*. **2003**, 1471.

[4] Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem*. **2002**, *10*, 2415.

[5] Kappe, C. O. *QSAR Comb. Sci*. **2003,** *22*,630.

[6] Harborne, J. B.; Mabry, T.J. *The Flavanoids-Advances in Research*, eds., Chapman & Hall, London, **1982**.

[7] Sun, W.; Cama, L. J.; Birzin, E. T.; Warrier, S.; Locco, L.; Mosley, R.; Hammond, M. L.; Rohrer, S. P. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1468.

[8] Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem*. **1993**, *28*, 517.

[9] Kumar, D.; Reddy, V. B.; Mishra, B. K. Rana, G. R. Mallikarjuna, N. Nadagouda, R. Varma, S. *Tetrahedron*. **2007**, *63*, 3093.

[10] Maggi, R.; Ballini, R.; Sartori, G. *Tetrahedron Lett*. **2004,** *45*, 2297.

[11] Anderson, D. R.; Hegde, S.; Reinhard, E.; Gomez, L.; Vernier, W.F.; Lee, L.; Liu, S.; Sambandam, A.; Snider, P. A.; Masih, L. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1587.

[12] Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrecque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2005,** *15*, 4745.

[13] Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2004,** *47*, 6299.

[14] Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacanni, A.; Righi, P.; Sartori, G. *Tetrahedron*, **2001**, *57*, 1395.

[15] Jin, T. S.; Xiao, J. C.; Wang, S. J.; Li, T. S. *Ultrason. Sonochem*. **2004**, *11*, 393.

[16] Ballini, R.; Bigi, F.; Conforti, M. L. *Catal. Today*. **2000**, *60*, 305.

[17] Wang, X.; Shi, D.; Tu, S. *Synth. Commun*. **2004**, *34*, 509.

[18] Sunil Kumar, B.; Srinivasulu, N.; Udupi, R.; Rajitha, B.; Thirupathi Reddy, Y.; Narsimha Reddy, P.; Kumar, P. *Russ. J. Org. Chem*. **2006,** *4*, 1813.

[19] Shestopalov, A. M.; Emelianova, Y. M. *Russ. Chem. Bull*. **2002**, *51*, 2238.

[20] Heravi, M. M.; Bakhtiari, Kh.; Zadsirjan, V.; Bamoharram, F. F.; Heravi, M. O. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4262.

[21] Gong, K.; Wang, H. L.; Fang Liu, Z-L. *Catal Commun*. **2008**, *9*, 650.

[22] Ren, Y. M.; Cai, Ch. *Catal Commun*. **2008**, *9*, 1017.
[23] Khandan-Barani, K.; Kangani, M.; Mirbaluchzehi, M.; Siroos, Z. *Inorg. Nano-Metal Chem*. **2017**, *5*, 751.
[24] Khandan-Barani, K.; Maghsoodlou, M.T.; Hassanabadi, A.; Hosseini-Tabatabaei, M. R.; Saffari, J.; Kangani, M. *Res. Chem. Intermed*. **2015,** *41*, 3011.
[25] Motamedi-Asl, A.; Khandan-Barani, K. *Iran J. Catal*. **2015**, *5*, 339.
[26] Maghsoodlou, M. T.; Khandan-Barani, K.; Hazeri, N.; Habibi-Khorassani, S. M.; Willis, A. C. *Res. Chem. Intermed*. **2014,** *40*, 779.
[27] Maghsoodlou, M. T.; Hazeri, N.; Khandan-Barani, K.; Habibi-Khorassani, S. M.; Abedi, A. *J. Heterocycl. Chem*. **2014**, *51*, E152.