On water synthesis of 2-amino-tetrahydrobenzo[*b*]pyrans catalyzed by a green, efficient and simple organocatalyst

Mohammad Eslami, Mohammad G. Dekamin*, Ali Maleki

Department of Chemistry, Iran University of Science and Technology, Tehran 16846-13114, Iran.

E-mail: mdekamin@iust.ac.ir

Abstract:

An efficient and convenient method has been developed for the synthesis of 2-amino-4*H*-tetrahydrobenzo[*b*]pyrans derivatives *via* one-pot, three-component condensation of malononitrile or ethyl cyanoacetete, dimedone and different aldehydes in the presence of a catalytic amount of potassium phthalimide-*N*-oxyl (POPINO), as a new organocatalyst, in aqueous media. A variety of 2-amino-tetrahydrobenzo[*b*]pyrans derivatives were obtained in high to excellent yields within short reaction times.

Keywords: Multicomponent reaction, dimedone, on water synthesis, 2-amino-*4H-tetrahydrobenzo*[*b*]pyrans, potassium phthalimide-*N*-oxyl.

Introduction

Chromene and its derivatives belong to a major class of natural heterocyclic compounds, which they occur widely in edible vegetables and fruits [1,2]. They frequently expose a variety of biological and pharmacological activities [3]. Based on the extensive researches, it has been observed that chromene derivatives include biological activities such as antioxidant, spamolytic, anti-HIV, anticancer, anti-anaphylactic andantiba-cterialactiveity [4]. Furthermore, these compounds expose unique pharmacological activities such as the treatment of human inflammatory TNFa-mediated malady, Alzheimer's malady, amyotrophic lateral sclerosis, Huntington's malady, and Parkinson's malady. Moreover, functionally substituted chromenes appropriately 2-amino-4*H*-chromene derivatives have played important roles in synthetic approaches to promising compounds in the field of medicinal chemistry [5,6]. So that 2-amino-4*H*-chromenes bearing nitrile functionality arises from their potential application in the treatment

of psoriatic arthritis and rheumatoid, and in cancer therapy. In particular, some of their derivatives such as HA 14-1 and MX58151, are being developed as anticancer agents [7]. (Fig. 1).In previous decades, they have also been widely employed as potent biodegradable agrochemicals, pigments and cosmetics.

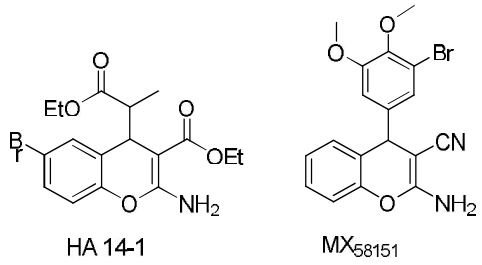
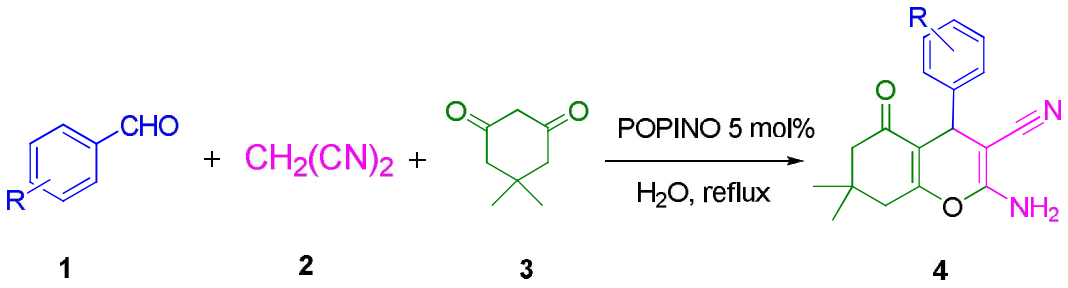


Figure 1.Examples of 2-amino-4*H*-chromene scaffold in HA-14-1 and MX58151 as anticancer agents

Due to their importance, the synthesis of these compounds has attracted a lot of interest; and several procedures have been described. Generally, 2-amino-4*H*-chromenes are synthesized by three-component reactions of dimedone or resorcinol with malononitrile and arylaldehydes. The cyclization reaction between dimedone and benzylidene malononitriles in the presence of a suitable base gives 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles. On the other hand, due to the steric hindrance between two hydroxyl groups, resorcinol reacted with benzylidene malononitriles at the position 6 rather than at the position 2 under above described conditions and further cyclization gives 2-amino-7-hydroxy-4*H*-chromenes [8]. Several catalytic reagent such asbasic alumina, piperidine, morphine, chitosan, Diammonium hydrogen phosphate, sodium carbonate, cetyltrimethyl-ammonium chloride (CTACl), [bmim]OH, DBU/microwave, K_2CO_3/microwave, $H_{14}[NaP_5W_{30}O_{110}]$ and lipase have been used as a catalyst in these reactions [9]. Most of these methods also involve using of volatile solvents; long reaction times and harsh work-up procedures.

Recently, we have reported the first catalytic cyclotrimerization of aryl and alkyl isocyanates using PPINO [10]. On the basis of our previous results and to develop the catalytic scope of the phthalimide-*N*-oxyl nucleophile, we decided to examine the feasibility and efficiency of POPINO in the preparation of 2-amino-tetrahydrobenzo[*b*]pyrans. Herein, we wish to report a facile, three-component method for the synthesis of 2-amino-4*H*-tetrahydrobenzo[*b*]pyrans

derivatives using (**4**) dimedone (**3**), various aromatic aldehydes (**1**) and malononitrile (**2**) in the presence of PPINO under reflux conditions (**Scheme 1**).



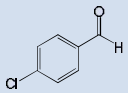
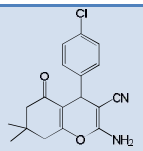
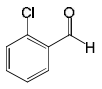
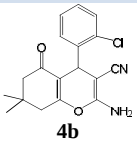
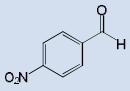
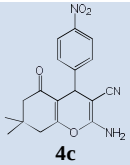
Scheme 1.Three-component synthesis of 2-amino-4*H*-chromenes

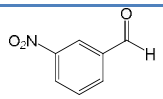
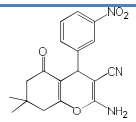
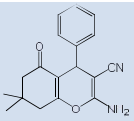
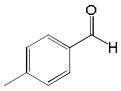
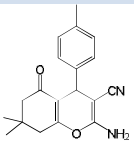
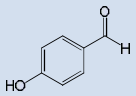
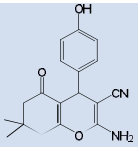
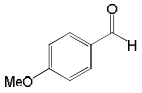
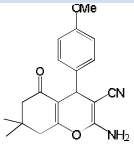
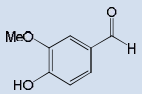
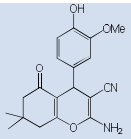
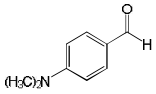
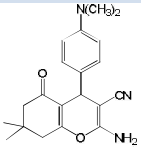
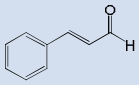
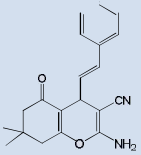
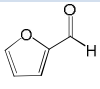
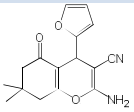
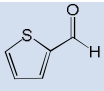
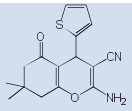
Results and Discussion

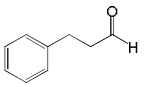
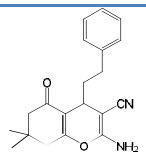
The results have been summarized in Table 1 which clearly show that all substrates react smoothly under optimal conditions to give the direct products in high yields. Subsequently, we demonstrated that benzaldehyde and the aromatic aldehydes bearing electron-withdrawing groups (such as nitro or halogens) require a shorter reaction time and give better yields than those bearing electron-donating groups (such as methoxy or methyl).

Table 1

Synthesis of different derivatives of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran *via* condensation of malononitrile, dimedone and aldehydes in the presence of POPINO

Entry	RCHO (3)	Product[b]	Time (min)	Yield[c] %	Mp (Obsd) (^{o}C)
1	 **1a**	 **4a**	15	95	216-218
2	 **1b**	 **4b**	20	98	214-215
3	 **1c**	 **4c**	15	88	180-182

4	 **1d**	 **4d**	10	92	217-219
5	 **1e**	 **4e**	15	95	234-236
6	 **1f**	 **4f**	20	94	219-221
7	 **1g**	 **4g**	20	92	226-228
8	 **1h**	 **4h**	25	89	201-203
9	 **1i**	 **4i**	40	98	240-242
10	 **1j**	 **4j**	30	95	210-212
11	 **1k**	 **4k**	25	93	183-185
12	 **1l**	 **4l**	20	96	220-222
13	 **1m**	 **4m**	30	95	226-228

14	 **1n**	 **4n**	35	88	203-205

[a] Reaction conditions: dimedone (1 mol), aldehyde (1 mol), malononitrile (1.1 mol), water (2 mL, reflux), POPINO (5 mol%).

[b] All compounds are known and their structures were established from their spectral data and melting points as compared with literature values.

[c] The yields refer to Isolated products.

Experimental

A mixture of aromatic aldehyde (1 mmol), malononitrile (1.1mmol), dimedone (1 mmol) and POPINO as a catalyst (5 mol%) in H_2O (2 mL) was stirred under reflux conditions for appropriate time. After completion of the reaction, which was monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was collected by filtration, washed with water to give the pure products. All products were identified by comparing their physical and spectral data with authentic literature data.

Conclusions

In conclusion, we have developed an efficient procedure for the synthesis of 4*H*-chromene, which are often encountered in biologically active compounds. This method was simple, mild, and efficient and the reaction products were isolated by easy work-up procedure and do not need any further purification steps. Therefore, POPINO as a green and environmentally benign organocatalyst is an efficient catalyst for this multi-component reaction in aqueous media.

Acknowledgment

This research was supported by the Research Council of Iran University of Science and Technology (IUST).

References

[1] Z. Dua, W. Y. Siau, J. Wang, *Tetrahedron Lett.* 52 (2011) 6137–6141.

[2] L. Moafi, S. Ahadi, A. Bazgir, *Tetrahedron Lett.* 51 (2010) 6270–6274.

[3] a) L. Bonsignore, G. Loy, D.Secci, A.Calignano,*Eur. J. Med. Chem.* 28(1993)517; b) K.Terao,E. Niki, *J. Free Radical Biol. Med.* 2(1986) 193;c) J. Z. Deng, D. A. Sun, S. R, Starck,S.M. Hecht, R. L. Cerny, J. R. Engen,*J. Chem. Soc.,Perkin Trans.* 1(1999) 1147;

d) D. J. Maloney,S. M. Hecht. *Org. Lett.*7 (2005) 4297; e) Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagishi, T. Fujioka, K. Mihashi, K. Mizuki, L. M. Cosentino, K. Fowke, S. L. Morris-Natschke, K. H. Lee, *Tetrahedron* 57 (2001) 1559.

[4]a) L. Bonsignore, G. Loy, D. Secci, A.Calignano, *Eur. J. Med. Chem*. 28(1993) 517; b) J. Z. Deng, D. A. Sun, S. R. Starck, S. M. Hecht, R. L.Cerny, J. R. Engen, *J. Chem. Soc., Perkin Trans*. 1(1999) 1147.

[5] M. N. Elinson, A. S. Dorofeev, F. M. Miloserdov, A. I. Iloaisky, S, K, Feducovich, P. A. Belyakov, G. I.Nikishina, *Adv. Synth.Catal*. 350(2008) 591.

[6] A. Shaabani, R. Ghadari, A. Sarvary, A. H. Rezayan, *Org. Chem.74(*2009) 4372.

[7] a) W. Kemnitzer, S. Kasibhatla, S. Jiang, H. Zhang, J. Zhao, S. Jia, L. Xu, C. Crogan-Grundy, R.Denis, N. Barriault, L. Vaillancourt, S. Charron, J. Dodd, G. Attardo, D. Labrecque, S. Lamothe, H. Gourdeau, B. Tseng,J. Drewe, S. X. Cai, *Bioorg. Med. Chem. Lett.*15(2005) 4745; b) S. Kasibhatla, H. Gourdeau, K.Meerovitch, J. Drewe, S. Reddy, L. Qiu, H. Zhang, F. Bergeron, D. Bouffard, Q. Yang, J. Herich, S. Lamothe, S. X. Cai, B. Tseng, *Mol. Cancer Ther*. 3(2004) 1365.

[8]S. R. Kolla, Y. R. Lee, *Tetrahedron.* 67(2011) 8271-8275.

[9] a)J. Zheng, Y. Li,*Mendeleev Commun.*21(2011) 280–281; b) M. R. Naimi-Jamal, S. Mashkouri, A. Sharif-i,*Mol Divers.* 14(2010) 473–477; c) J.Ch. Xu, W.M. Li, H. Zheng, Y.F. Lai, P.F. Zhang, *Tetrahedron.* 67(2011) 9582-9587; d) M. M. Heravi,Kh.Bakhtiari, V.Zadsirjan, F. F. Bamoharramb,O. M. Heravi, *Bioorganic & Medic-inal Chemistry Lett*17 (2007) 4262–4265.

[10]M.G. Dekamin, F.M. Moghaddam, H. Saiedian, S. Mallakpour, *Monatsh. Chem.* 137(2006) 1591–1595.

[11] Sh. Gao, Ch. H. Tsai, Ch. Tseng, Ch-Fa. Yao, *Tetrahedron.* 64(2008) 9143–9149.

[12] D. Kumar , V. B. Reddy , Sh. Sharad , U. Dube , S. Kapur, *European Journal of Medicinal Chemistry*. 44(2009) 3805–3809.

[13] T. S. jin, A. Q. Wang, X. Wang, J. S. Zhang, T. S. Li, *Synlett*. (2004) 871-873.