JCRS

Journal of Chemical Reactivity and Synthesis 2021: 11(4) 264-270

Research Article

One pot synthesis of conjugated chalcone-quinoxalines using an organocatalyst under ultrasonic mediation

Kiana Darvishi

Department of Chemistry, Takestan Branch, Islamic Azad University, Takestan, Iran

ARTICLE INFO:

Received:
1 October 2021

Accepted:
8 December 2021

Available online:
10 December 2021

✉: K. Darvishi
kianadarvishi@yahoo.com

ABSTRACT

Ultrasonic irradiation was effectively used for the synthesis of one pot chalcon-quinoxaline derivatives with high efficiency and short time. The products are obtained by mixing parahydroxy acetophenone and various aldehydes or parahydroxy benzaldehyde with different ketones and then adding 2,6-dichloroquinoxaline, in the presence of catalytic amounts of pyrrolidine as a organocatalyst and DMF as a solvent. These conjugated chalcon-quinoxaline derivatives have been shown to have good anticancer activity.

Keywords: Ultrasonic mediation; Organocatalysts; Chalcone; Quinoxaline; Chalcon-quinoxaline

1. Introduction

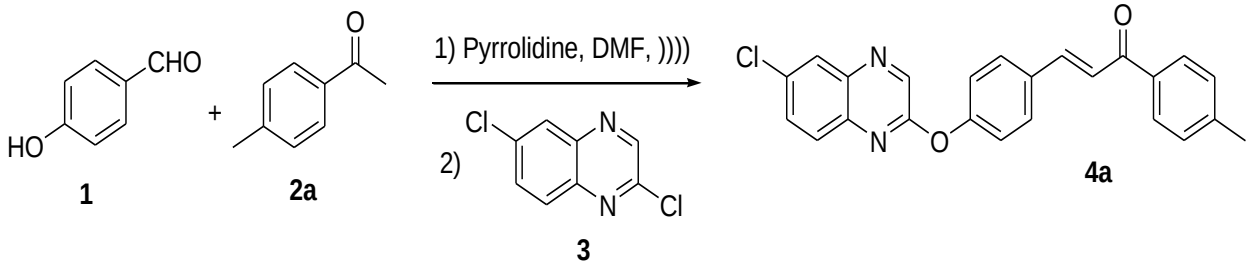
Chalcones are widely found in nature and have a variety of biological activities including antioxidants[1],hypnotics[2],anti-inflammatory[3], anti-obesity [4], antiviral [5] antimicrobial [6],antiprotozoal[7] and antitumor[8]. Quinoxaline is also a member of heterocyclic compounds with nitrogen at position 1, 4 on the ring. Quinoxaline derivatives also have a wide range of biological activities, such as anti-tuberculosis [9], antimicrobial [10], anti-inflammatory [11], antioxidants [12], anti-HIV [13], kinase inhibitors [14] and anti-cancer

[15]. Numerous reports have shown that conjugated quinoxaline and chalcones (chalcone-quinoxalins) show good anti-cancer activity [16-20].

2. Experimental

2.1. General Experimental Procedure for preparation of chalcon-quinoxalines

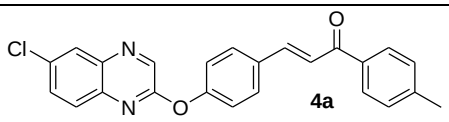
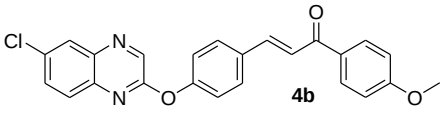
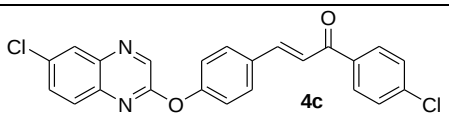
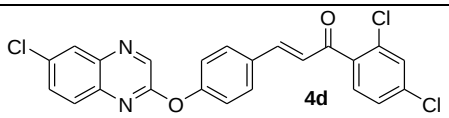
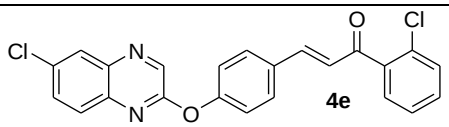
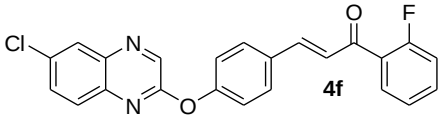
Pyrrolidine (0.5 mmol) in 3 ml DMF was added to a mixture of parahydroxy benzaldehyde **1** (1 mmol) and aromatic ketone **2** (1 mmol) or a mixture of parahydroxy acetophenone **5** (1 mmol) and aromatic aldehyde **6** (1 mmol) and was sonicated for a period of time. The progress of the reaction was monitored by TLC using petroleum ether/ethyl acetate (4: 1). Then 2,6-dichloroquinoxaline **3** (1 mmol) was added to the reaction vessel and sonicated. Completion of the reaction was followed by TLC. After completion of the reaction, cold water was added dropwise to the mixture and the formed solid was filtered and washed with cold water. The crude product was then recrystallized from methanol, washed and dried to give products **4a-f** and **7a-h**. All obtained products are known compounds [20] and were confirmed and identified by melting point.

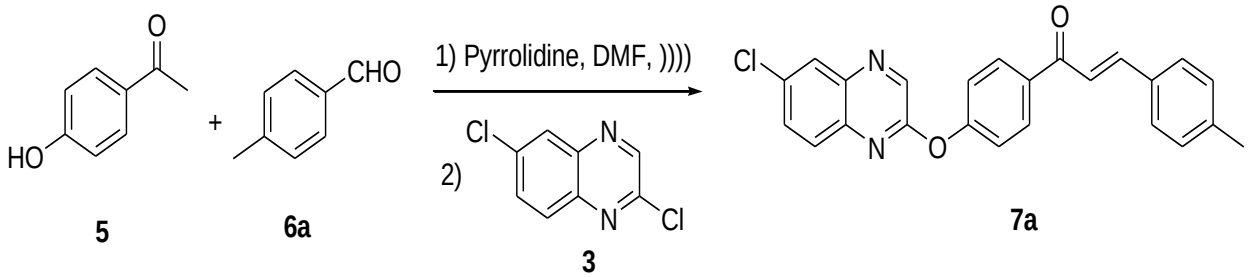


1 **2a** **3** **4a**

Scheme 1. Three-component synthesis of **4a**

Table 1. Reactions of parahydroxy benzaldehyde **1** with Aromatic ketones **2**

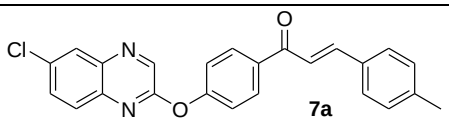
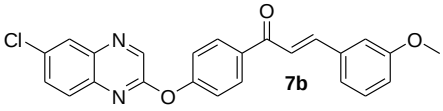
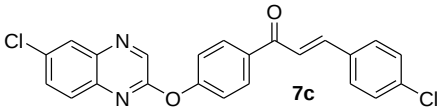
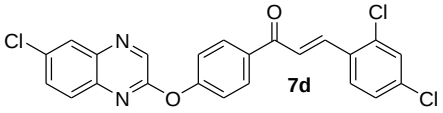
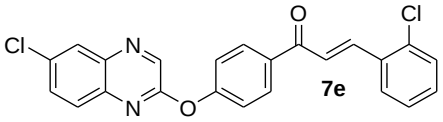
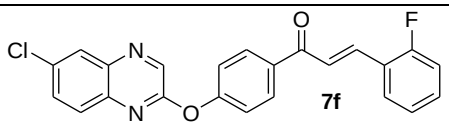
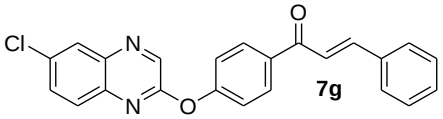
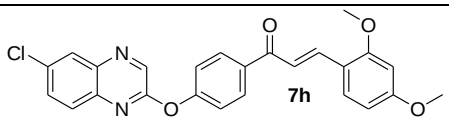
Entry	Ketone	Time (min)	Product	Yield (%)	m.p. (° C)
1	4-CH_3-C_6H_4	25	 **4a**	81	153-155
2	4-OCH_3-C_6H_4	20	 **4b**	86	145-148
3	4-Cl-C_6H_4	25	 **4c**	80	177-180
4	2,4-diCl-C_6H_3	30	 **4d**	82	154-155
5	2-Cl-C_6H_4	25	 **4e**	84	142-145
6	2-F-C_6H_4	25	 **4f**	78	148-150



5 **6a** **3** **7a**

Scheme 2. Three-component synthesis of **7a**

Table 2. Reactions of parahydroxy acetophenone **5** with Aromatic aldehydes **6**

Entry	Aldehyde	Time (min)	Product	Yield (%)	m.p. (° C)
1	4-CH_3-C_6H_4	25	 **7a**	85	188-190
2	3-OCH_3-C_6H_4	20	 **7b**	90	138-140
3	4-Cl-C_6H_4	25	 **7c**	85	220-221
4	2,4-diCl-C_6H_3	25	 **7d**	86	138-140
5	2-Cl-C_6H_4	25	 **7e**	89	173-175
6	2-F-C_6H_4	30	 **7f**	83	167-169
7	C_6H_4	25	 **7g**	91	195-197
8	2,4-diOCH$_3$-C_6H_3	20	 **7h**	94	188-190

3. Results and discussion

First, the optimal conditions for one pot synthesis **4a** (Figure 1) from the three starting materials parahydroxy benzaldehyde **1**, 4-methyl acetophenon **2a** and 2,6-dichloro quinoxaline **3** were investigated in the presence of various catalysts, solvents and conditions, and the results showed that the shortest reaction time and highest efficiency were related to the use of pyrrolidine and dimethyl formamide under ultrasound radiation. For this purpose, triethyl amine, diethyl amine, morpholine and pyrrolidine organocatalysts were used under ultrasound. The reaction under reflux conditions was also investigated, which showed the heat causes more increase in by-products and a longer time than the same reaction under ultrasound radiation. Therefore, the products were obtained with less efficiency in reflux conditions. Solutions of dimethyl formamide, dimethyl sulfoxide, ethanol and water were also compared with each other to complete the optimization result. The optimization results are given in Table 3.

Table 3. Optimization of the reaction conditions for the synthesis of **4a**.

Entry	Organocatalyst	Condition	Solvent	Time (min)	Yield (%)
1	Et_3N	))))	DMF	60	7
2	Et_2NH	))))	DMF	60	13
3	Morpholine	))))	DMF	60	5
4	None	))))	DMF	60	0
5	Pyrrolidine	))))	DMF	25	81
6	Pyrrolidine	Reflux	DMF	60	45
7	Pyrrolidine	))))	DMSO	25	55
8	Pyrrolidine	))))	EtOH	25	30
9	Pyrrolidine	))))	H_2O	60	25
10	Pyrrolidine	None	DMF	60	0

4. Conclusions

The purpose of this article is to find an efficient method for the synthesis of chalcone-quinoxaline derivatives with anti-cancer properties. The single-vessel reaction makes the purification and separation processes with fewer steps and more ease. On the other hand,

using of pyrrolidine due to the benefits of organocatalyst was introduced. Ultrasound mediatin also shortens the reaction time and results in fewer by-products.

References:

[1] Polo, E.; Ibarra-Arellano, N.; Prent-Penaloza, L.; Morales-Bayuelo, A.; Henao, J. ; Gald_amez, A.; Guti_errez, M. *Bioorg. Chem*. 90 (2019) 103034.

[2] Cho, S.; Kim, S.; Jin, Z.; Yang, H.; Han, D.; Baek, N.-I.; Jo, J.; Cho, C.-W.; Park, J.-H.; Shimizu, M.; Jin, Y.-H. *Biochem. Biophys. Res. Commun.* 413 (2011) 637–642.

[3] Tang, Y.-L.; Zheng, X.; Qi, Y.; Pu, X.-J.; Liu, B.; Zhang, X.; Li, X.-S.; Xiao, W.-L.; Wan, C.-P.; Mao, Z.-W. *Bioorg. Chem.* 98 (2020) 103748.

[4] El Sayed Aly, M. R.; Abd El Razek Fodah, H. H.; Saleh, S. Y. *Eur. J. Med. Chem.* 76 (2014) 517–530.

[5] Gan, X. H.; Hu, D. Y.; Wang, Y. J.; Yu, L.; Song, B. A. *J. Agric. Food Chem.* 65 (2017) 4367–4377.

[6] Xia, R.; Guo, T.; He, J.; Chen, M.; Su, S.; Jiang, S.; Tang, X.; Chen, Y.; Xue, W. *Monatsh. Chem.* 150 (2019) 1325–1334.

[7] Hayat, F.; Moseley, E.; Salahuddin, A.; Van Zyl, R. L.; Azam, A. *Eur. J. Med. Chem*. 46 (2011) 1897–1905.

[8] Cong, H.; Zhao, X.; Castle, B. T.; Pomeroy, E. J.; Zhou, B.; Lee, J.; Wang, Y.; Bian, T.; Miao, Z.; Zhang, W.; et al. *Mol. Pharm*. 15 (2018) 3892–3900.

[9] Ramalingam, P.; Ganapaty, S.; Rao, C. B. *Bioorg. Med. Chem. Lett*. 20 (2010) 406–408.

[10] Patel, H. M.; Bhardwaj, V.; Sharma, P.; Noolvi, M. N.; Lohan, S.; Bansal, S.; Sharma, A. *J. Mol. Struct.* 1184 (2019) 562–568.

[11] Ruiz-Alcaraz, A. J.; Trist_an-Manzano, M.; Guirado, A.; G_alvez, J.; Mart_ınez-Esparza, M.; Garc_ıa-Pe~narrubia, P. *Eur. J. Pharm. Sci*. 99 (2017) 292–298.

[12] Saravana Mani, K.; Murugesapandian, B.; Kaminsky, W.; Rajendran, S. P. *Tetrahedron Lett.* 59 (2018) 2921–2929.

[13] Patel, S. B.; Patel, B. D.; Pannecouque, C.; Bhatt, H. G. *Eur. J. Med. Chem.* 117 (2016) 230–240.

[14] Kim, S. C.; Boggu, P. R.; Yu, H. N.; Ki, S. Y.; Jung, J. M.; Kim, Y. S.; Park, G. M.; Ma, S. H.; Kim, I. S.; Jung, Y. H. *Bioorg. Med. Chem. Lett.* 30 (2020) 127189.

[15] Ghanbarimasir, Z.; Bekhradnia, A.; Morteza-Semnani, K.; Rafiei, A.; Razzaghi-Asl, N.; Kardan, M. Design, *Spectrochim Acta A Mol. Biomol. Spectrosc*. 194 (2018) 21–35.

[16] (a) Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: A *Chem. Rev*. 117 (2017) 7762–7810. (b) Tariq, S.; Somakala, K.; Amir, M. Quinoxaline: An Insight into the Recent Pharmacological Advances. *Eur. J. Med. Chem*. 143 (2018) 542–557. (c) Kaushal, T.; Srivastava, G.; Sharma, A.; Negi, A. S. *Bioorg. Med. Chem*. 27 (2019) 16–35.

[17] Mielcke, T. R.; Mascarello, A.; Filippi-Chiela, E.; Zanin, R. F.; Lenz, G.; Leal, P. C.; Chiaradia, L. D.; Chirardia, L. D.; Yunes, R. A.; Nunes, R. J.; et al. *Eur. J. Med. Chem*. 48 (2012) 255–264.

[18] Desai, V.; Desai, S.; Gaonkar, S. N.; Palyekar, U.; Joshi, S. D.; Dixit, S. K. *Bioorg. Med. Chem. Lett.* 27 (2017) 2174–2180.

[19] Alswah, M.; Bayoumi, A. H.; Elgamal, K.; Elmorsy, A.; Ihmaid, S.; Ahmed, H. E. A. *Molecules*. 23 (2017) 48-57.

[20] Ma, X.; Wang, D.; Wei, G.; Zhou, Q.; & Gan, X. *Synth. Commun.* 51 (2021) 1363-1372.