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Unexpected products from the reaction of chalcones with cyanoguanidine

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ABSTRACT

A new series of unexpected dihydrochalcones DHCs attached with cyanoiminopyrimidine moiety in addition to expected cyanoaminopyrimidines CAMPs were synthesized by efficient and facile method via reaction of cyanoguanidine with chalcone derivatives in the presence of EtONa.

1. Introduction

Dihydrochalcones (DHCs) are one of the most important classes of flavonoid family, as a result of their wide distribution in nature and use as precursors for the synthesis of many natural products and pharmaceutical drugs.[1–4] Dihydrochalcones possess a broad spectrum of bioactivities, such as antioxidant,[5,6] anti-HIV-I protease,[7] anti-inflammatory,[8,9] antimalarial,[10] antiviral,[11] anti-leishmanial,[12] antidiabetic,[5,13] anticancer,[14,15] and anti-trypanosoma cruzi[16,17] activities. They also have significance for the treatment of human promyelotic leukemia HL-60 cells.[18] Therefore, the development methods to facilitate the synthesis of these compounds have attracted much attention in both the synthetic and medicinal chemistry communities.

From a chemical point of view, chalcones are very attractive starting compounds in organic chemistry; they are easily prepared with large variability at the two aromatic rings, and the enone provides a bifunctional site for 1,3-dinuclophiles affording several heterocyclic ring systems. Hence, in search of a simple method and readily available starting materials for the synthesis of dihydrochalcones containing a pyrimidine moiety, we turned our attention to chalcones and cyanoguanidine. For the first time, we envisioned that the reaction between chalcones and cyanoguanidine would be utilized in the synthesis of dihydrochalcones containing a pyrimidine moiety.

2. Results and discussion

Our synthetic approach to aryl-cyanoiminodihydropyrimidines (aryl-CIDHPMs) and cyanoaminopyrimidines (CAPMs) is shown in Scheme 1. Initial experiments established that the reaction of chalcone **1b** and commercially available cyanoguanidine in the presence of NaOH as basic catalyst at 79 °C afforded aryl-CIDHPM **2b** (5% yield) and CAPM **3b** (10% yield) after 18 h (Table 1, entry 1). The reaction was then optimized by changing various reaction parameters including the base, the time, the temperature and the equivalent amount of cyanoguanidine: the results are summarized in Table 1. The results of the base screening indicated that sodium ethoxide and sodium methoxide were the most effective bases for this reaction (Table 1, entries 3–13). It was shown that the cyano group in cyanoguanidine reduces the nucleophilicity of the guanidine fragment, and it cannot react with chalcones without a strong nucleophile such as methoxide or ethoxide anions (Table 1, entry 14).[19] The effect of temperature and time of the reaction was examined to improve the yields of **2b** and **3b**. For unexpected product **2b**, temperatures above 70 °C are not suitable (Table 1, entries 1 and 3), while by decreasing the temperature from 60 to 40 °C, the yield was improved to 25% (Table, entries 4–6). At room

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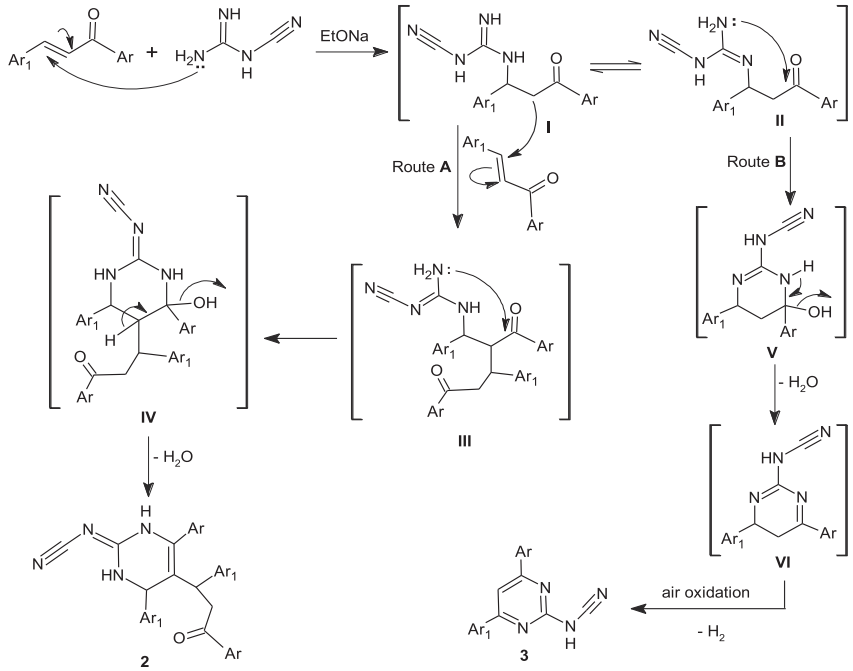
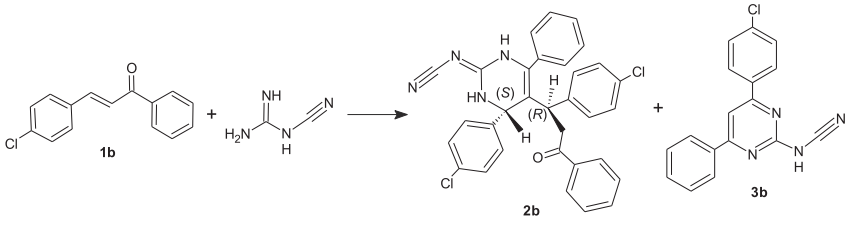


Scheme 1. Reaction mechanism for the formation of **aryl-CIDHPMs 2** and **CAPMs 3.**

temperature 25 °C, however, the yield decreased again (Table 1, entry 7, 10%). By increasing reaction time to 60 h, the yield was further improved to 29% (Table 1, entry 8). Finally, optimization of the amount of cyanoguanidine required was screened, and it was found that increasing the concentration of cyanoguanidine to 2.5 mol increased the reaction yield (39%). Over 2.5 mol there was no improvement of the reaction yield (Table 1, entries 8–11).

Using the optimized conditions (Table 1, entry 10), various substituted chalcones were reacted with cyanoguanidine to afford the corresponding aryl-CIDHPMs **2a-g** and CAPMs **3a-g** in

Table 1
Optimization of the synthesis of aryl-CIDHPM **2b** and CAPM **3b**.



Entry	Base[a]	Solvent	Cyanoguanidine (n equiv)	Temp. [°C]	Time (hrs)	Yield %	
						3b	**2b**
1	NaOH	EtOH/H_2O[b]	1.0	79	18	10	5[c]
2	NaOH	EtOH/H_2O[b]	2.5	40	60	15	13
3	EtONa	EtOH	1.0	79	18	13	7[c]
4	EtONa	EtOH	1.0	60	18	17	12
5	EtONa	EtOH	1.0	50	18	18	16
6	EtONa	EtOH	1.0	40	18	20	25
7	EtONa	EtOH	1.0	25	18	12	10
8	EtONa	EtOH	1.0	40	60	22	29
9	EtONa	EtOH	1.5	40	60	25	33
10[d]	**EtONa**	**EtOH**	**2.5**	**40**	**60**	**28**	**39**
11	EtONa	EtOH	3.0	40	60	26	38
12	MeONa	MeOH	2.5	64	18	16	11[c]
13	MeONa	MeOH	2.5	40	60	24	32
14	–	EtOH	2.5	40	60	–	–

Bold signifies the optimized condition.
[a] 3 Equivalents of base used.
[b] EtOH:H_2O in the ratio 80:20.
[c] Separated as a resin, by column chromatography (Al_2O_3, eluent $CHCl_3$:MeOH as 10:1).
[d] Optimized conditions.