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One-step synthesis of alkyl 2-chloropyrimido[1,2-*a*]benzimidazole-3-carboxylates under catalyst-free: combined experimental and computational studies

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ABSTRACT

An efficient method for the preparation of pyrimido[1,2-*a*]benzimidazole derivatives utilizing squaric acid dichloride has been developed at room temperature without catalyst. This method provided a rapid synthesis of pyrimido[1,2-*a*]benzimidazole system. The result indicates that those expeditious reactions could be carried out only in the presence of alcohols, affording the corresponding alkyl 2-chloropyrimido[1,2-*a*]benzimidazole-3-carboxylates. Furthermore, the yield of products seems to be closely relevant to the steric hindrance of the added alcohols. On the basis of experimental and theoretical analyses, a plausible mechanism has been proposed and corroborated through DFT calculations for exploring a practical way to efficiently synthesize those highly versatile substituted homologs.

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Introduction

As we all know, fused heterocyclic compounds[1] are often of much greater interest and application than the constituent monocyclic systems[2] in the aspect of various chemistry fields including functional materials,[3] molecular recognition[4] medicinal chemistry,[5] and coordination chemistry.[6] Among those heterocycles, the N-based heteroaromatic pyrimido[1,2-*a*]benzimidazole has been widely applied[7] and functionalized in view of their particular privileged structures[8] and wide spectrum of biological activity.[9] In fact, almost all the reported pyrimido[1,2-*a*]benzimidazoles, known as effective pharmacophores possess antibiotic[10] and anti-arrhythmic[11] activity, substance p receptor-binding activity,[12] as well as promising antineoplastic activity,[13] are highly substituted by various effective groups inherited from the reaction precursors. For instance, Matthew's group[14] utilized pyrimido[1,2-*a*]benzimidazole structure as a central skeleton to study the treatment of T-cell-mediated autoimmune and inflammatory disorder and organ transplant, and they found that those highly modified derivatives exhibited potent inhibition of lymphocyte specific kinase activity.

Currently, pyrimido[1,2-*a*]benzimidazole tricyclic systems are prepared by condensation of 1*H*-benzimidazol-2-amine with a series of electron-deficient reactants like enaminones,[15] acetylenic aldehydes,[16] tetracyanoethylene,[17] α,β-unsaturated ketones/esters,[18] etc. Recently, one-pot synthetic approaches utilizing aromatic aldehydes[19] for substituted pyrimido[1,2-*a*]-benzimidazoles have also been reported. And also, Pozharskii and his coworkers[20] utilized an aldehyde derivative to react with 2-aminobenzimidazole to synthesize the substance with the pyrimido[1,2-*a*]benzimidazole structure. However, these methods often need a suitable metallic catalyst or longtime refluxing at high temperature. Therefore, developing a synthetic method in a straightforward manner is to be extremely desired for medicinal chemists.

In this Letter, we provide an efficient method that can be conducted at the room temperature and under metal-free condition. The synthesis is based on 3,4-dichlorocyclobut-3-ene-1,2-dione (squaric acid dichloride) for synthesizing a series of novel pyrimido[1,2-*a*]benzimidazole derivatives. Laboratory findings reveal that the present system could be rapidly operated only in the presence of alcohols and the obtained products are assigned to be the corresponding Cl-substituted carboxylic esters. Interestingly, the product yields are inversely proportional to the steric hindrance of the hydroxy group of the added alcohols. To explore the reason for the phenomena observed, underlying reaction mechanisms were calculated in detail and compared employing density functional theory (DFT), a method of choice for the cost-effective treatment of large chemical systems with high accuracy.[21–23] The B3LYP

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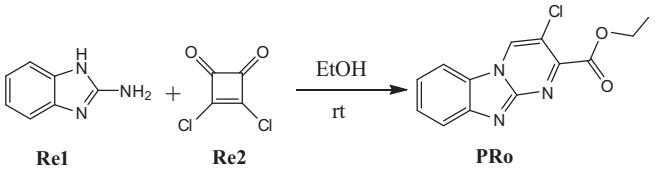


Scheme 1. The synthesis of compound **PRo**.

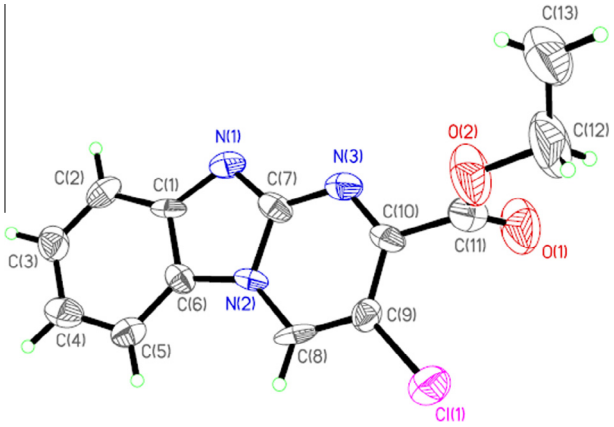
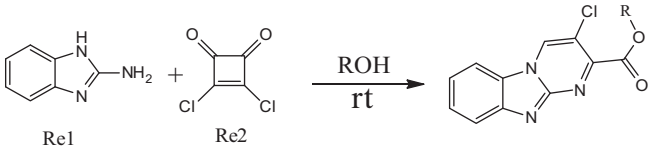


Figure 1. ORTEP diagram of the product.

method together with the standard 6-311G(d,p) basis were used in all calculations under the Gaussian 09 program.[24]

As reported, we firstly attempted to react 1*H*-benzimidazol-2-amine with diethyl squarate for synthesizing squaramide derivatives, but the results, unexpectedly, showed that the reaction only gave the starting materials even if refluxing for 24 h in EtOH (determined with TLCs). Several other solvents (DMF, CH_3CN, and DMF) were subsequently tried but the results remained. Considering the activity, we improved the project by adding a saturated EtOH solution of equivalent 2-aminobenzimidazole into fresh squaric acid dichloride under vigorous stirring (Scheme 1). To our great surprise, the reaction mixtures turned into orange-red immediately accompanied by white smoke as well as heat release, then a large amount of solid precipitated out after a further 20 min stirring at room temperature. The yellow fluorescent product was isolated in 46% yield and crystallized by the slow evaporation method. Surprisingly, the X-ray diffraction analysis showed that the product was assigned to be the alkyl 2-chloropyrimido[1,2-*a*]benzimidazole-3-carboxylates (**PRo**) (Fig. 1) instead of squaramide derivatives. Meanwhile, compound **PRo** was characterized by ^1H and ^{13}C NMR spectroscopy, FT-IR and elemental analysis (see Supporting information).

Curiously, the EtOH in the magical system above was replaced by a series of alcohols and several other common solvents in the laboratory. As shown in Scheme 2, the reactions could be rapidly operated in the presence of any tested alcohols and the products were assigned to be the corresponding alkyl 2-chloropyrimido[1,2-*a*]benzimidazole-3-carboxylates confirmed by NMR analyses (see Supporting information). On the contrary, the mixtures turned into jelly-like substance instantly after adding the other solvents (CH_3CN, THF, and DMF) of 1*H*-benzimidazol-2-amine into fresh squaric acid dichloride under vigorous stirring. Unfortunately, we failed to isolate any pure product because of the extreme instability in the presence of ambient moisture. Addition with equivalent stilled EtOH, noteworthily, the intractable intermediate in mixtures will immediately dissolve and afforded the corresponding **P2** under the same conditions. The



Scheme 2. The reaction between 1*H*-benzimidazol-2-amine (**Re1**) and squaric acid dichloride (**Re2**).

Table 1
The reaction of 1*H*-benzimidazol-2-amine and squaric acid dichloride in various solvents

Entry	Solvent	R	Time[b]	Product	Yield[c] (%)
1	MeOH	CH_3	20	P1	52
2	EtOH	CH_2CH_3	20	P2	46
3	*n*-PrOH	$(CH_2)_2CH_3$	20	P3	41
4	*i*-PrOH	$CH(CH_3)_2$	40	P4	Trace[a]
5	*n*-BuOH	$(CH_2)_3CH_3$	20	P5	38
6	*t*-BuOH	$C(CH_3)_3$	60	P6	Trace
7	Phemethylol	$PhCH_2$	20	P7	35
8	CH_3CN + EtOH[d]	CH_2CH_3	20 + 40	P2	25
9	THF + EtOH[d]	CH_2CH_3	20 + 40	P2	26
10	DMF + EtOH[d]	CH_2CH_3	20 + 40	P2	23

[a] Compared with obtained product by TLC.
[b] Times are in minute.
[c] The isolated yield of spectroscopically pure product.
[d] The reactions were operated in CH_3CN, THF or DMF (5 ml) for 20 min followed by additional EtOH (5 ml) for another 40 min.

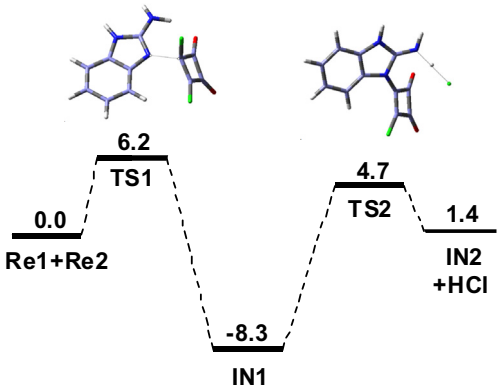
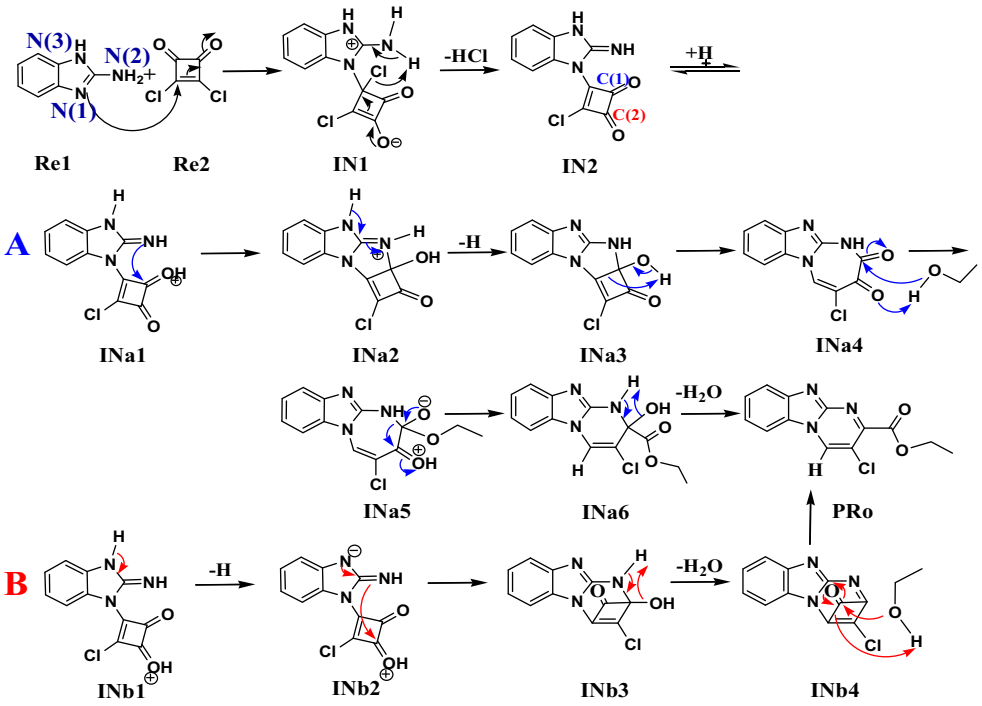


Figure 2. The potential energy profile of the process from **Re1** to **IN2** (energies are in kcal·mol^{-1}).

yields of the reactions operating in various solvents are summarized in Table 1. It is interesting to find that the yield of products seems to be closely relevant to the nature of the added alcohols. As shown below, the yield undergoes an insignificant decrease from 52% to 35% after addition with primary alcohols. The yields are nearly trace after addition with the secondary (*i*-PrOH) or tertiary alcohol (*t*-BuOH). That is, the yield goes down with the increase of steric hindrance of alcohol (see Fig. 2).

On the basis of theoretical analyses, there are two possible mechanisms for the reaction between **Re1** and **Re2** in EtOH solution. As shown in Scheme 3, the N(1) atom of **Re1** firstly attacks the carbon atom linked to Cl atom of the electron-deficient four-membered ring of **Re2**. This classical Michael addition involves a low energy barrier of 6.2 kcal·mol^{-1} and affords the intermediate **IN1** via a transition state **TS1** (Fig. 3). After that, compound **IN1** eliminates a HCl molecule with an energy barrier of 13.0 kcal·mol^{-1} and forms the intermediate **IN2**. Additionally, this



Scheme 3. Overall reaction mechanisms for the reaction between 1*H*-benzimidazol-2-amine and squaric acid dichloride in EtOH.

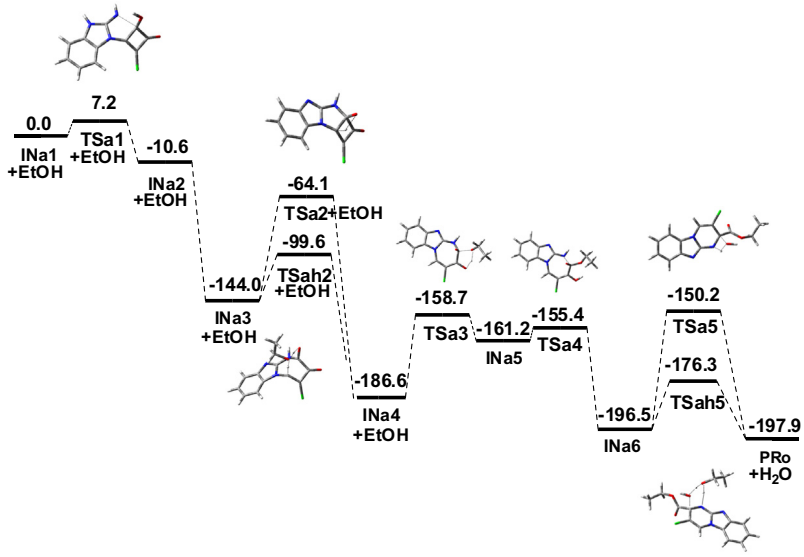


Figure 3. The potential energy profile of route A (energies are in kcal·mol^{-1}).

reaction is an endothermic process with the energy of 1.4 kcal·mol^{-1}. Theoretically, the N atom of secondary amino-group in **IN2** undergoes an intramolecular nucleophilic addition instantly by attacking the carbon atom linked to the oxygen atom. There are two possible attacking ways which are defined as route A and route B, with the corresponding active sites labeled C(1) and C(2) atoms, respectively.

In route A, the first step involves a transition state **TSa1** with an energy barrier of 7.2 kcal mol^{-1} and affords a fused-heterocycle **INa2**, which can easily lose a proton to form **INa3** directly without extra energy. Because of the tensile force, the four-membered ring of **INa3** tends to break to form a loose plane seven-membered ring in **INa4** which accompanies intramolecular proton transfer. However, this synergistic step holds a high energy barrier of 79.9 kcal·mol^{-1} (**TSa2**) without considering the solvent effect, which means that this step is not able to occur at the room temperature. Then we introduce the solvent effect of EtOH to assist the proton transfer. As expected, the energy barrier sharply decreases to 44.4 kcal·mol^{-1} (**TSah2**) which is the rate-determining step in route A (see Figs. 4 and 5).

Whereafter, the O atom of EtOH molecule attacks the carbon atom of carbonyl group bonded with N(2) atom in **INa4**, which involves a transition state **TSa3** to form **INa5** with an energy barrier of 27.9 kcal·mol^{-1}. Then, compound **INa5** encounters an intramolecular rearrangement to form a more stable six-membered ring intermediate **INa6**, which will eliminate a

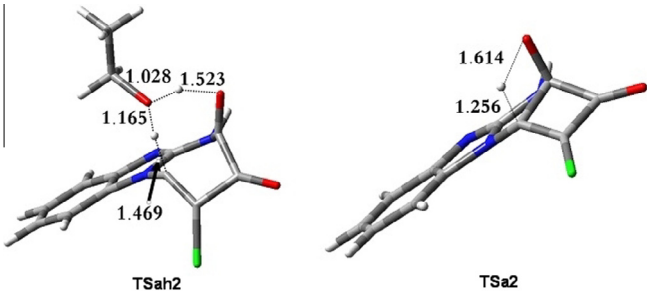


Figure 4. The optimization structure of transition states **TSah2** and **TSa2** (bond lengths are in Å).

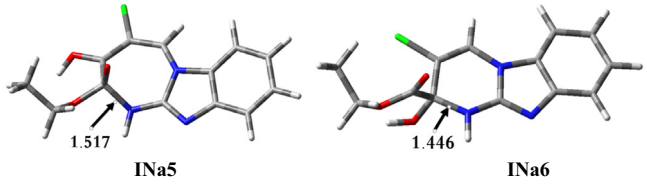


Figure 5. The optimization structure of intermediates **INa5** and **INa6** (bond lengths are in Å).

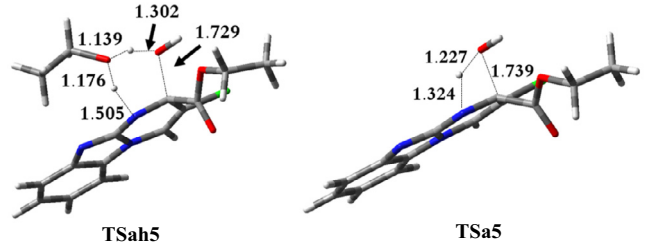


Figure 6. The optimization structure of transition states **TSah5** and **TSa5** (bond lengths are in Å).

H_2O molecule to afford the target product **PRo**. The energy barrier for this step is 20.2 kcal·mol^{-1} (**TSa5**) which is lack of the solvent effect and 5.8 kcal·mol^{-1} (**TSah5**) assisted in EtOH, respectively (see Figs. 6 and 7).

For route B, the proton on the N(3) atom firstly breaks away to form a more stable intermediate **INb2**, which is 114.9 kcal·mol^{-1} lower than **INb1**. Then N(2) atom attacks the protonated carbonyl at C(2) atom to afford **INb3** via **TSb2** with an energy barrier of 38.7 kcal·mol^{-1}. Comparing with route A, this step encounters a more apparent distortion. After that, in the rate-determining step, the **INb3** eliminates H_2O with a high energy barrier of 56.4 kcal·mol^{-1}, which affords intermediate **INb4** with great tensile force. That means it is difficult for the formation of **INb4**. In the next step, the four member cycle of the unstable **INb4** is easily attacked by EtOH to afford the **PRo**. The energy barrier of this step is only 1.8 kcal·mol^{-1} and the exothermicity is 103.9 kcal·mol^{-1}.

Based on the above computational analyses, the path A is the more favorable reaction route both thermodynamically and kinetically. Notably, the EtOH plays not only as a solution but also as an essential cocatalyst and a reactant in the reaction. In route A, the process in which the EtOH helps open the ring is the rate-determining step, which means the stereochemical structure of the added alcohols greatly affects the yield of the product.

In summary, we have developed here a one-pot system that provides a facile, efficient, and original approach for synthesizing

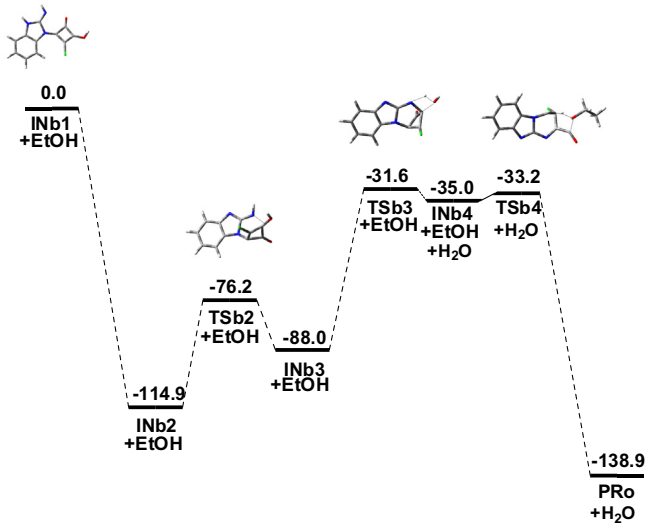


Figure 7. The potential energy profile of route B (energies are in kcal·mol^{-1}).

a series of Cl-substituted pyrimido[1,2-*a*]benzimidazole carboxylic esters at the room temperature under metal-free conditions. Furthermore, the underlying mechanism in the present system is particularly depicted by means of experimental and DFT theoretical analyses. Results reveal that the expeditious procedure could be carried out only in the presence of alcohols with an energy barrier of 44.4 kcal·mol^{-1}. The expansion of the magic system and the pharmacodynamic screening of these heteroaromatic derivatives will be reported in the future.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.050.

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