



Original article

Highly efficient one-pot, three-component synthesis of 1,5-benzodiazepine derivatives



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ARTICLE INFO

Article history:

Received 17 July 2013

Received in revised form 30 October 2013

Accepted 6 November 2013

Available online 27 November 2013

Keywords:

One-pot

Synthesis

1,5-Benzodiazepine derivative

ABSTRACT

A general, mild and efficient protocol for the synthesis of ethyl 4-methyl-2-(thiophen-2,5-dihydro-1,5-benzodiazepine-3-carboxylate is achieved for first time using $H_3PMo_{12}O_{40}$ in ethanol at 0 °C by a one-pot, three-component condensation of various thiophene aldehydes, substituted *o*-phenylenediamines and ethyl acetoacetate. Compared with the conventional synthesis method, this procedure has the advantages of convenient operation, excellent yields, and environmentally benign. A plausible formation mechanism has been proposed. The structure of the products is characterized by 1H NMR, IR, MS and elemental analysis.

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1. Introduction

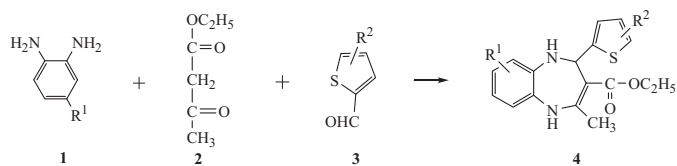
Benzodiazepines play a unique role in drug discovery programs because of their wide spectrum of biological activities, such as antibacterial, analgesic, anticonvulsant, antidepressive and hypnotic properties [1]. In the last decade, 1,5-benzodiazepines have been used in the treatment of several diseases, such as cancer, viral infections and cardiovascular disorders [2]. Particularly, 1,5-benzodiazepines are useful precursors for the synthesis of some fused ring benzodiazepine derivatives, such as triazoloto-, oxadiazolo-, oxazino-, or furano benzodiazepines [3]. Considering their wide range of applications in biological and industrial synthetic organic chemistry, the development of mild and efficient protocols for the synthesis of 1,5-benzodiazepine analogs continues to be a challenging endeavor [4]. Such synthesis is traditionally performed through a sequence of separate reaction steps. After the completion of each step, the solvent and waste products are removed and discarded, and then the intermediate products are separated and purified. These considerations prompt us to develop new methodologies for preparing these important compounds. Presently, the design, development, and utilization of efficient and environmentally benign synthetic processes have become the conscientious choice of synthesis chemists [5]. One attractive strategy is to design and develop novel, one-pot, multistep syntheses that can help simplify reaction handling and product purification, improve synthesis efficiency, as well as reduce solvent consumption and thereby disposal. Consequently, the

consumption of natural resources is reduced, the potential harmful impact of various chemicals on the environment is minimized, and sustainability is ultimately improved [6].

Our group has been interested in 1,5-benzodiazepine derivatives for a few years and prepared several series of 1,5-benzodiazepines. Synthesis methods have been developed and the biological activities of these compounds have been investigated. Recently, *N*-heterocyclic compounds containing the thiophene ring with high biological and pharmacological activities have also been reported [7]. Previous studies have indicated that a free $COOCH_2CH_3$ group at different positions on the 1,5-benzodiazepine nucleus enhances pharmacological properties by increasing solubility in lipid materials and fat deposits in the body. And one-pot, three-component reaction of aromatic aldehydes, 1,2-phenylenediamine, and β -ketoesters producing ethyl 2-(4-(2-thiophenyl)-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-ylidene)acetate in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing 1,2-dichloroethane (DCE) has been described [8]. However, the reported method has some disadvantages. Firstly, this reaction mainly involves the γ -selective C–C bond formation of β -keto esters and produced 2-(4-(2-thiophenyl)-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-ylidene)acetate, but had no detailed study for the α -selective C–C bond analog produced during the synthesis of this compound. Secondly, the product is a mixture of the two isomers, and yields are unsatisfactory (33–68%). As a consequence, it lacks the application value of a one-step multicomponent method for the synthesis of these compounds. Finally, this method involves the toxic reagent, DCE, which has potential carcinogenic effects. Based on their extensive applications, it is necessary to further develop an efficient and convenient method to construct such significant heterocyclic compounds.

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Scheme 1. One-pot synthesis of 1,5-benzodiazepine derivatives **4**.

Accordingly, we developed an efficient, general, and convenient protocol for the one-pot synthesis of a novel series of 1,5-benzodiazepine derivatives containing thiophene and COOCH₂CH₃ groups. The reaction proceeded by a three-component condensation of substituted thiophene aldehydes, *o*-phenylenediamine (*o*-PDA) and ethyl acetoacetate utilizing phosphomolybdic acid (PMA) in ethanol at 0 °C (Scheme 1). The advantages of the program are mild reaction conditions (ethanol as a green solvent, simple ice-water bath), and in the process, the absence of γ -selected products produced, so the yields of α -selected compounds are very high (85–90%). This reaction also discussed the regioselectivity between the thiophene aldehyde and ethyl acetoacetate when employing the unsymmetrical *o*-PDA, and proposed the plausible formation mechanism.

2. Experimental

We studied the influence of the solvent, catalyst, temperature, and reaction time of the experiment to obtain the optimum experimental conditions. Subsequently, the three-component reaction of *o*-PDA **1** (R=H) (1 mmol), ethyl acetoacetate **2** (1 mmol), and 2-thiophene aldehyde **3a** (1 mmol) was conducted as the model reaction to optimize the reaction condition. Since, the reaction medium is one of the most important factors influencing any process, several solvents including acetonitrile, dichloromethane, chloroform, methanol, ethanol, benzene and toluene were tested. The same high yield of the target product **4a** can be obtained both by using methanol and ethanol as a solvent. However, ethanol is deemed to be the preferred solvent for this one-pot transformation considering the requirements of green chemistry. Other solvents, such as acetonitrile, dichloromethane, chloroform, benzene and toluene, produced lower yields. Therefore, ethanol was selected as the reaction solvent in this study. Among the existing methods, the acid-catalyzed condensation of *o*-PDA and carbonyl complexes is one of the most simple and direct approaches to the synthesis of 1,5-benzodiazepine derivatives. Thus, some solid organic acids, like *p*-TsOH, protic acids [e.g. acetic acid (HOAc)]; heteropolyacids (HPAs) [e.g. silicotungstic acid (STA, H₄SiW₁₂O₄₀) and PMA (H₃PMo₁₂O₄₀)]; and Lewis acids [e.g. CeCl₃·7H₂O, NiCl₂·6H₂O and I₂], were used to determine the appropriate catalyst. A comparative study was then conducted in the presence of these materials as catalyst. The samples were produced under conventional conditions at 0 °C in the presence of each catalyst. The corresponding results are summarized in Table 1.

Table 1
Screening of catalysts and optimization of reaction conditions.^a

Entry	Catalyst ^b	Time (h)	Yield ^c (%)
1	<i>p</i> -TsOH	8	85
2	HOAc	6.5	79
3	STA	12	70
4	PMA	7	89
5	CeCl ₃ ·7H ₂ O	10	85
6	NiCl ₂ ·6H ₂ O	10	86
7	I ₂	7	75
8	Catalyst free	14	–

^a Solvent: EtOH, temperature: 0 °C.

^b 10 mmol%.

^c Isolated yield.

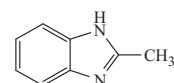


Fig. 1. Structures of benzimidazole.

Table 1 shows that only a trace amount of the product was obtained when the reaction was conducted in the absence of catalyst even after 14 h. Conversely, all tested acid catalysts had catalytic effects on the three-component condensation reaction with the yields of the target product **4a** also found to be high. Under the same experimental conditions, we found that entry 2, catalyzed by HOAc, can be completed within the shortest time, but the yield of product **4a** was not the highest. The catalyst PMA was found to be the prominent catalyst and provided the highest yield for the transformation (entry 4, 89%). Therefore, PMA was the most effective catalyst in obtaining the yield of 1,5-benzodiazepine **4a**. Moreover, HPAs are economically attractive, environmentally benign, possess very high Brønsted acidity, involve a mobile ionic structure and absorb polar molecules easily in the bulk forming a 'pseudo liquid phase'. As a result, both the surface protons and the bulk protons of HPAs participate in their catalytic activity, which significantly enhances the reaction rate, even at relatively low temperatures [9]. Thus, PMA was selected for subsequent experiments.

The reactions at different temperatures were then examined to determine the effects on the reaction. Results showed that the yield of the target product **4a** was lower when the temperature was higher, such as in refluxing ethanol conditions. Under ethanol reflux in the three-component reaction system, it was easier to form the isomer, ethyl 2-(4-(2-thiophenyl)-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-ylidene)acetate, which was also reported in the document [8]. Conversely, the yield of product **4a** was higher when the temperature was lower, such as in an ice-water bath (0 °C), even when the reaction time was prolonged. We also conducted the reaction in an ice-salt bath (<–10 °C) and found that the reaction time was the longest, but the product yield was similar to the reaction in ice-water bath. Thus, we conducted the reaction in an ice-water bath and the reason was as follows.

The efficiency of the reaction is mainly affected by the amount of catalyst and temperature. Several side reactions occur when the reaction is changed either by adding excessive catalyst, or by increasing the temperature. For instance, adding excessive catalyst (>10 mmol%) or increasing the temperature (>0 °C) promotes the formation of the by-product benzimidazole (Fig. 1). The structure of this by-product was isolated and characterized by IR, ¹H NMR and elemental analysis. In our study, benzimidazole and the target product (1,5-benzodiazepine **4**) were found to be competitive products, and benzimidazole was more stable than 1,5-benzodiazepine containing a seven membered ring. The high reaction temperature and stronger acidic conditions promote the formation of the benzimidazole by-product which reduced the yields of the target products. Thus, we synthesized 1,5-benzodiazepine **4a** using PMA as catalyst in ethanol at 0 °C by a one-pot, three-component condensation of 2-thiophene aldehyde, *o*-PDA and ethyl acetoacetate.

Under the optimized conditions described above, the reactions of substituted *o*-PDA **1**, ethyl acetoacetate **2** and a group of thiophene aldehydes **3a–3g** were examined. In most cases, the substrates smoothly underwent the one-pot reaction to afford the corresponding products **4a–4u** in good yields (Table 2, entries 1–21). As shown in Table 2, we synthesized 21 novel kinds of compounds. The characterization data are listed in Supporting information.

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