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Synthesis of 3-(5*H*-Pyrazolyl)cyclobutanone Derivatives

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A 3-(5*H*-pyrazolyl)cyclobutanone derivative was synthesized *via* two different optimized routes. In the first route, the substitutional pyrazole olefins was prepared as a precursor, the target molecule was synthesized *via* [2 + 2]-cycloaddition by using pyrazols olefins and ketene in total yield of 3 %. In the second route, the four-member ring cyclobutanone fragment was made first, then the pyrazole ring was obtained through cyclization, offering the target molecule with a yield of 8.6 %.

Keywords: Pyrazoles, Cyclobutanone, Synthesis.

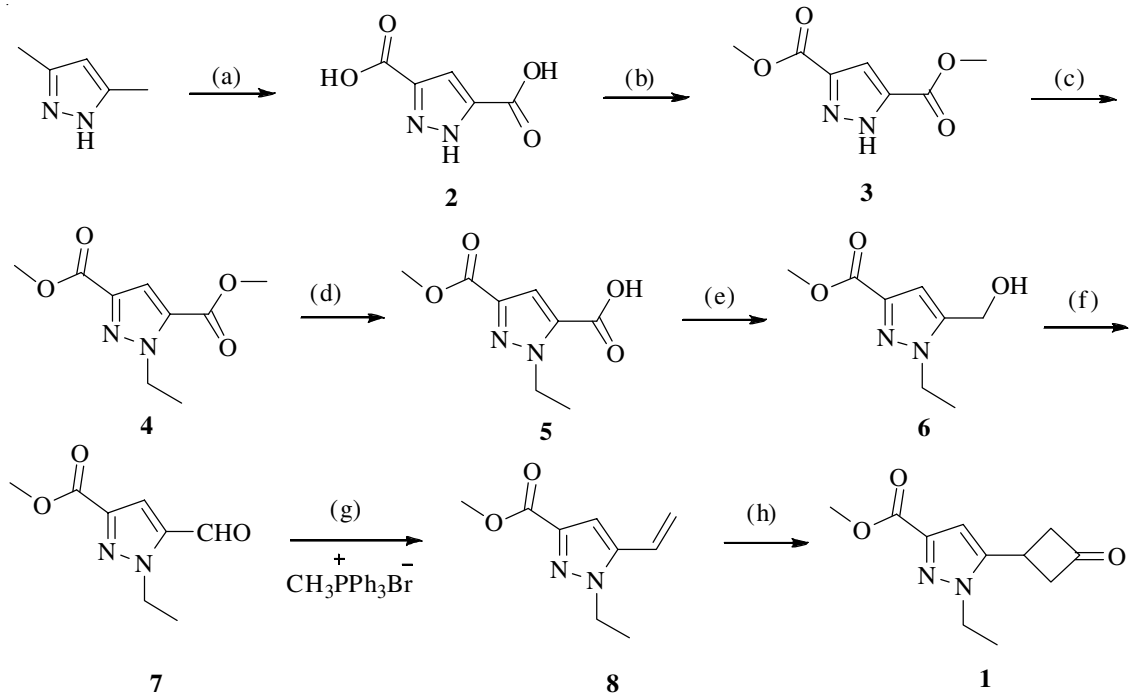
INTRODUCTION

Functionalized pyrazoles and their derivatives were potentially valuable and attractive compounds for a variety of organic reactions. Pyrazole derivatives were reported to possess various biological activities such as reducing inflammation, antifungal, antiviral, antitumor and so on[1]. Cyclobutanones constitute another important class of synthetic building block, widely used for construction of biologically active carbocyclic and heterocyclic compounds[2]. In addition, certain cyclobutanones themselves have been shown to possess interesting biological properties such as serine protease and β-lactamase inhibitions[3,4]. The inherent driving force of their special structures offers a new strategy for the synthesis of some natural products and biologically active compounds. Therefore, more attention was paid to prazole-cyclobutanone combinations because of their biological activity and unique reactivity resulting from the presence of these two unique groups. They have emerged as significant compounds because of their biological and pharmaceutical activity[5]. However, few methods for their synthesis were reported. We herein report a facile route to prepare prazole-cyclobutanone.

In this report, two different routes for synthesis of compound **1** were investigated. In the first route (**Scheme-I**), the substituted pyrazole olefins were first prepared and then the target compound **1** was synthesized *via* [2 + 2]-cycloaddition[6-8] by using pyrazole olefins and ketene. In the second route (**Scheme-II**), the four-member ring cyclobutanone fragment was made first and then the pyrazole ring was obtained through cyclization, offering compound **1**.

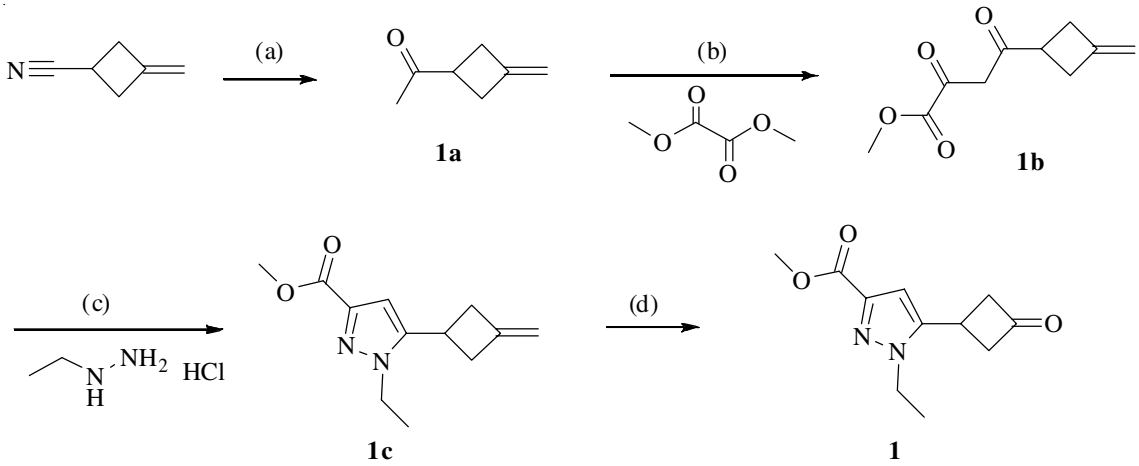
EXPERIMENTAL

In **Scheme-I**, starting with 3,5-dimethyl-1*H*-pyrazole, the diacid compound **2** was prepared through potassium permanganate oxidation[9]. Then, compound **2** was treated with thionyl chloride and methylation in MeOH, affording diester compound **3**. *N*-Alkylation of compound **3** was performed by using iodoethane in weak base condition[10]. In order to selectively hydrolyze one of the ester groups in compound **4**, one equivalent of potassium hydroxide in MeOH was allowed to react for 24 h under 20 ºC. The reaction mixture was evaporated and the residue was dissolved in water. The pH was then adjusted to 3 with HCl slowly. Monoacid compound **5** was crystallized as a white solid. In order to reduce acid compound **5** to alcohol **6**, BH_3·THF was selected as the reducing agent. After several experimental investigations, 0.1 equivalent of the BH_3·THF was used and subsequently 1 equivalent of BH_3·SMe_2 was added to produce compound **6** in high yield. Oxidizing compound **6** to aldehyde **7** with active manganese dioxide was performed at 0 ºC. Olefin **8** was obtained *via* Witting reaction from aldehyde **7**. However, synthesis of the target compound **1** from compound **8** encountered difficulties. We tried three kinds of different reaction conditions. The first one was to use trichloro-acetyl chloride with active zinc powder in anhydrous ether and tetrahydrofuran. Olefins **8** was added and the reaction was allowed to proceed for 2 h at room temperature *via* [2 + 2]-cycloaddition to get the intermediate methyl 5-(2,2-dichloro-3-oxocyclobutyl)-1-ethyl-1*H*-prozole-3-carboxylate[11]. However, analysis by LC-MS showed that no product was obtained. The reason may be that the steric hindrance of olefins blocked the above-



Reagents and conditions: (a) $KMnO_4$, H_2O, 95 °C, 4 h, 88.0%; (b) $SOCl_2$, MeOH, 0 °C, then 65 °C, 15 h, 90.0%; (c) CH_3CH_2I, K_2CO_3, DMF, 90 °C, 2 h, 74.7%; (d) MeOH, KOH, 20 °C, 10 h, 38%; (e) BH_3 THF, THF, 0 °C, 4 h; BH_3 SMe_2, rt, 12 h, then, 60 °C, 2 h, 70.8%; (f) MnO_2, CH_2Cl_2, rt, 20 h, 78.1%; (g) *n*-BuLi, -78 °C, 2 h, then rt, 1 h, 57.1%; (h) Tf_2O, $ClCH_2CH_2Cl$, DMAC, -15 °C, 10 min; Collidine, $ClCH_2CH_2Cl$, -20 °C, then 90 °C, 15 h; H_2O, 100 °C, 2 h, 36.0%.

Scheme-I: Preparation of compound **1**



Reagents and conditions: (a) MeLi, THF, -15 °C, 15 min; H_2SO_4, rt, 4 h, 27.3%; (b) Na, EtOH, 0 °C, then 80 °C, 12 h, 85%; (c) CF_3CH_2OH, rt, 4 h, 62%; (d) $RuCl_3$, $NaIO_3$, Bu_4NCl, $CH_2Cl_2/CH_3CN/H_2O$=1.5/1/1, rt, 8 h, 62%.

Scheme-II: Preparation of compound **1**

mentioned intermediate formation. Therefore we tried the second method[12]. Olefins **8** was dissolved in anhydrous ether and the solution was cooled to 0 °C. Trichioro-acetyl chloride and phosphorus oxychloride in anhydrous ether was added sequentially in a dropwise manner. After addition of zinc-copper, the mixture was heated 40 °C overnight. Unfortunately, analysis by LC-MS showed no existence of the intermediate. Finally, we tried the third method and succeeded[13]. To a solution of *N*,*N*-dimethylacetamide (7 mmol) in 1,2-dichloroethane (40 mL) under nitrogen atmosphere, trifluoromethane-sulfonic anhydride (8.4 mmol) was added dropwise around -15 °C. The mixture was stirred at -15 °C for 10 min, then, a solution of alkene **8** (2.4 mmol) and sym-collidine (9.3 mmol) in 1,2-dichloroethane (10 mL) was added dropwise. After completion of the addition, the cooling bath was removed and the mixture was warmed to room temperature. The reaction was allowed

to proceed for another 15 h at 90 °C. The reaction mixture was cooled to room temperature and water (20 mL) was added. The mixture was stirred at 100 °C for 2 h. After cooling to room temperature, the product was extracted from diluted aqueous $NaHCO_3$ solution with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried with Na_2SO_4, filtered and concentrated to give a brown oil. Purification by flash chromatography (PE: EtOAc = 1:1) gave target compound **1** (192 mg, 36 %) as a yellow oil. $C_{11}H_{14}N_2O_3$ (222.24). HPLC-MS (ESI+): t_R = 3.22, 223 $[M + H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.80 (s, 1H); 3.78-3.83 (q, 2H); 3.76 (s, 3H); 3.75-3.73 (m, 1H); 3.56-3.48 (m, 2H); 3.34-3.26 (m, 2H); 1.28 (t, 3H).

In **Scheme-II**, we tried to synthesize target compound **1** with another route. The commercially available methylene-cyclobutane carbonitrile was converted into ketone **1a** by using methyl lithium[14]. Then, Claisen condensation was carried out in ethanol using freshly prepared sodium alcoholate solution, offering compound **1b** as a yellow oil. Compound **1b** was reacted with ethyl hydrazine hydrochloride salt in trifluoroethanol at room temperature to perform the cyclization, producing the pyrazole compound **1c** as a pale yellow oil. Finally, the terminal double bond of pyrazole derivative (**1c**) was cleaved with ruthenium tetroxide[15]. The ruthenium tetroxide was generated from ruthenium(III) chloride and sodium periodate in the presence of dichloromethane and water, catalyzed by tetrabutylammonium chloride at room temperature. Target compound **1** was obtained as a yellow oil with a yield of 8.6 %.

RESULTS AND DISCUSSION

Two synthetic routes were investigated, of which one is construction of cyclobutanone and another is construction of pyrazole ring. In the first route, the pyrazole ring is available and the starting material is low-cost and can be obtained easily. But this synthetic route is longer and the total yield is only 3 %. For these reasons, it is not suitable for large scale preparation. The second route is based on the materials commercially available. Although the starting material is more expensive, the reaction involves 4 steps. The total yield was up to 8.6 %. This synthetic route not only saves the time but lowers the cost for manufacture. In summary, both synthetic routes successfully provided a strategy for synthesis of pyrazole cyclobutanone derivatives.

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