Tetrahedron Letters 59 (2018) 2426–2429

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# A simple and efficient synthesis of new fluorophore 4-hydroxy pyrazolo[1,5-a]pyridines through a tandem reaction

Peiling Yan [a], Guiyun Duan [b], Ruixue Ji [b], Yanqing Ge [b,*]

[a] College of Chemistry and Chemical Engineering, Qingdao University, Qingdao, Shandong 266071, PR China
[b] School of Chemistry and Pharmaceutical Engineering, Taishan Medical University, Taian, Shandong 271016, PR China

ARTICLE INFO

*Article history:*
Received 18 March 2018
Revised 19 April 2018
Accepted 11 May 2018
Available online 12 May 2018

*Keywords:*
Cascade
Pyrazolo[1,5-a]pyridine
Pyrazole
Fluorescence

ABSTRACT

The cascade reaction of ethyl pyrazole-5-carboxylate with α, β-unsaturated ester leading to 4-hydroxy pyrazolo[1,5-a]pyridine derivatives has been developed. A possible mechanism is proposed. The resulting pyrazolo[1,5-a]pyridines present strong fluorescence in solutions.



## Introduction

Pyrazolo[1,5-a]pyridines[1], as a class of fused heteroaromatic bicyclic compounds, have been of interest for their pharmacological and biological activities. They are used as dopamine $D_2/D_3/D_4$ antagonists[2], anti-herpetic agents[3], p38 kinase inhibitors[4], PI3 kinase inhibitors[5], antitubercular agent[6], EP1 receptor antagonists[7], $5HT_3$-antagonists[8], melatonin receptor ($MT_1/MT_2$) ligands[9], Mcl-1Bcl-xL dual inhibitors[10], and the corticotropin-releasing factor 1 antagonists[11]. However, they have not been explored extensively due to difficult syntheses.

The most commonly used method for their preparation involves the regioselective [3 + 2] cycloaddition of *N*-aminopyridines with alkenes or alkynes, and the thermal cyclization of pyridinyl aziridines[12]. These transformations are high yielding but require several synthetic steps for the synthesis of starting substrates like *N*-aminopyridine derivatives which are commercially not available. Hence it hampers the efficiency of the process. With an expectation for the discovery of lead compounds, methods development for the efficient synthesis of diverse pyrazolo[1,5-a]pyridines is in great demand.

On the other hand, due to its high sensitivity and great applicability, the fluorescence phenomenon has received more attention in the modern scientific fields of chemistry, biology, materials science, biomedical science, and their interfaces[13]. Many studies have been pursued to deeper understand the structure-photophysical property relationship of organic fluorophores for the development of better fluorescent probes, but the existing organic fluorophores are limited to some restricted dyes such as rhodamine, BODIPY, fluorescein, coumarin, naphthalimide, and cyanine derivatives. Thus, it is a great challenge to design and synthesize new fluorophores with high quantum yield.

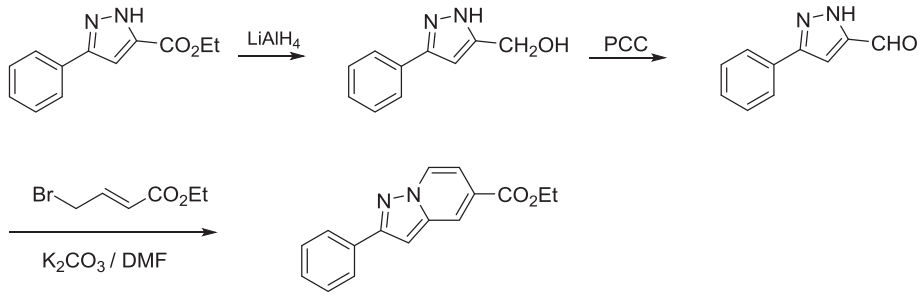
Tandem reactions have attracted greater attention in organic synthesis in recent years. These processes enable the construction of complex molecules in an efficient manner[14]. As part of our cell imaging effort to prepare new fluorophores[15–25], we sought to synthesize pyrazolo[1,5-a]pyridines. Previously, we successfully synthesized a series of pyrazolo[1,5-a]pyridines via a tandem reaction (Scheme 1) [26]. However, it still needs two steps (reduction and oxidation) to prepare the starting material pyrazole aldehyde. In the need for a shorter and convenient route to pyrazolo[1,5-a]pyridines, we envisioned that the commercially accessible pyrazole ester **1** may react with α, β-unsaturated ester **2** in one step to form pyrazolo[1,5-a]pyridine (Scheme 2, this work). Herein, we report the results of this effort.

## Results and discussion

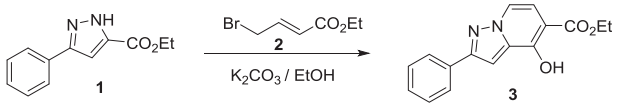
First, in an attempt to improve the reaction yield, the effects of the solvent and base were performed using ethyl 3-phenyl-1*H*-pyrazole-5-carboxylate **1b** and ethyl 4-bromobut-2-enoate **2**. The results are shown in Table 1. We performed the reaction of 3-phenyl-1*H*-pyrazole-5-carboxylate **1b** (1.00 equiv.) and (E)-ethyl

* Corresponding author.
*E-mail address:* geyanqing2016@126.com (Y. Ge).

https://doi.org/10.1016/j.tetlet.2018.05.022
0040-4039/




**Scheme 1.** Previous synthetic route of pyrazolo[1,5-a]pyridines.

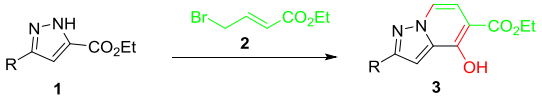



**Scheme 2.** New synthetic route of pyrazolo[1,5-a]pyridines.

4-bromobut-2-enoate **2** (2.00 equiv.), $K_2CO_3$ (2.05 equiv.) as a catalyst at room temperature in $C_2H_5OH$, but no product formation was observed (Table 1, entry 1). When the same reaction was performed at 78 °C, **3b** was obtained in 60% yield. It was also noted that protic and strong polar aprotic solvents were significantly preferred over weak aprotic solvents and the best bases were potassium carbonate. Therefore, the optimum conditions set for the present protocol are as follows: $C_2H_5OH$ as solvent, 78 °C, potassium carbonate as base, 8 h reaction time (Table 1, entry 3).

Second, under this set of optimized conditions, the scope of the tandem reaction was investigated where various 3-substituted pyrazole **1a-f** were reacted with brominated α, β-unsaturated compounds **2** using potassium carbonate in $C_2H_5OH$. The results are summarized in Table 2. The presence of electron-donating/withdrawing groups in the benzene moieties at the para position could be tolerated and the desired products **3a-3f** were obtained in 42–60% yield. The structures of adducts **3a-f** were characterized by spectroscopic methods ($^1$H NMR, $^{13}$C NMR and HRMS).

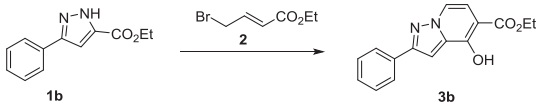
**Table 2**
Synthesis of pyrazolo[1,5-a]pyridine derivatives from pyrazole-5-carboxylate.




| Entry | R | Product | Isolated Yield (%) |
|---|---|---|---|
| 1 | Methyl | **3a** | 42 |
| 2 | Phenyl | **3b** | 60 |
| 3 | 4-methylphenyl | **3c** | 48 |
| 4 | 4-fluorophenyl | **3d** | 44 |
| 5 | 4-chlorophenyl | **3e** | 57 |
| 6 | 4-bromophenyl | **3f** | 50 |

Based upon the above observation, we proposed the reaction mechanism in Scheme 3. Firstly, pyrazole-5-carboxylate **1** reacts with ethyl 4-bromobut-2-enoate **2** through an intermolecular $S_N2$ reaction and generates the intermediate **4**. Subsequently, intermediate **4** is deprotonated by the existing base to form a γ-carbanion of the ester, and in turn the electron pair transfers from the γ position to α position. Then the formed β,γ-unsaturated α-carbanion of ester **5** cyclizes with the pyrazole ester group by intramolecular nucleophilic substitution to afford intermediate **6**.

**Table 1**
Optimization survey for the reaction of **1b** and **2**.




| Entry | Solvent | Temp (°C) | Time (h) | Base | Yield (%) |
|---|---|---|---|---|---|
| 1 | $C_2H_5OH$ | 20 | 24 | $K_2CO_3$ | – |
| 2 | $C_2H_5OH$ | 78 | 2 | $K_2CO_3$ | 10 |
| 3 | $C_2H_5OH$ | 78 | 8 | $K_2CO_3$ | 60 |
| 4 | $C_2H_5OH$ | 78 | 12 | $K_2CO_3$ | 61 |
| 5 | 2-Propanol | 82 | 8 | $K_2CO_3$ | 51 |
| 6 | *n*-Propanol | 97 | 8 | $K_2CO_3$ | 36 |
| 7 | DMF | 80 | 8 | $K_2CO_3$ | 52 |
| 8 | DMSO | 80 | 8 | $K_2CO_3$ | 51 |
| 9 | $CH_3CN$ | 78 | 8 | $K_2CO_3$ | 58 |
| 10 | Acetone | 56 | 8 | $K_2CO_3$ | 23 |
| 11 | $CH_2Cl_2$ | 40 | 8 | $K_2CO_3$ | – |
| 12 | $CHCl_3$ | 61 | 8 | $K_2CO_3$ | 16 |
| 13 | THF | 66 | 8 | $K_2CO_3$ | 34 |
| 14 | $C_2H_5OH$ | 78 | 12 | $Cs_2CO_3$ | 56 |
| 15 | $C_2H_5OH$ | 78 | 12 | $Na_2CO_3$ | 24 |
| 16 | $C_2H_5OH$ | 78 | 12 | Pyridine | 50 |
| 17 | $C_2H_5OH$ | 78 | 12 | Triethylamine | 52 |
| 18 | $C_2H_5OH$ | 78 | 12 | Piperidine | 49 |
| 19 | $C_2H_5OH$ | 78 | 12 | KOH | 41 |
| 20 | $C_2H_5OH$ | 78 | 12 | NaOH | 45 |