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COMMUNICATION

A copper-mediated cyclization reaction of hydrazine with enediynones providing pyrazolo[1,5-*a*]pyridines[†]

Hung-Chou Wu,^a Long-Chih Hwang^a and Ming-Jung Wu^{*b}

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2,7-Disubstituted pyrazolo[1,5-*a*]pyridines were synthesized in good chemical yields by the reaction of enediynones with hydrazine, followed by addition of copper chloride. This reaction can tolerate many functional groups.

Molecules that contain the pyrazolo[1,5-a]pyridine substructure exhibit a broad spectrum of biological activities. For instance, the 3-carboxypyrazolo[1,5-a]pyridines have been shown to be potent and selective 5HT₃-antagonists in vitro and in vivo.¹ The 2,3-disubstituted pyrazolo[1,5-a]pyridines were evaluated as potent p38 kinase inhibitors and exhibit good anti-inflammatory activity² while other substituted pyrazolo[1,5-a]pyridines exhibit anti-herpetic activity³ and a series of aminomethyl-substituted pyrazolo[1,5-a]pyridines were recently reported to be high affinity D₄ receptor ligands.⁴ However, synthetic methods to construct the pyrazolo[1,5-a]pyridine skeleton are still limited. The most general method is the regioselective [3+2] cycloaddition of Naminopyridines with alkenes⁵ or alkynes.⁶ Another method is the thermal cyclization of pyridinyl aziridines.^{2a,7} In a continuation of our study on the cyclization of enediynes to heterocycles,8 we report herein a new method for the synthesis of pyrazolo[1,5a]pyridines by the reaction of enediynones with hydrazine mediated by copper chloride.

The synthesis of enediynone **1a** starting from commercially available *cis*-1,2-dichloroethylene (2) is outlined in Scheme 1. The palladium-catalyzed coupling reaction of **2** with 1-octyne (**3a**) under reaction conditions reported in the literature⁹ gave vinyl chloride **4a** in 62% yield. Compound **4a** was then coupled with propargyl alcohol **5a** under the same reaction conditions to give enediynol **6a** in 88% yield. Finally, oxidation of **6a** with MnO₂ gave enediynone **1a** in 92% yield. Our first attempt at the cyclization of enediynone **1a** was the treatment of **1a** with five equivalents of hydrazine in the presence of one equivalent of hydrogen chloride in methanol at room temperature for six hours. The cyclization product that was obtained was eneynylpyrazine **7a** in 90% yield.



(eqn (1)) None of the expected pyrazolo[1,5-*a*]pyridine adduct **8a** was observed. When the same reaction mixture was heated at reflux with stirring for six days, pyrazolo[1,5-*a*]pyridine **8a** was isolated in 14% yield along with **7a** in 73% yield. (eqn (2)) Although the yield of the desired product is low, this result encouraged us to continue the investigation of this cyclization reaction.

It has been demonstrated that copper(I) can catalyze the intramolecular hydroamidation of alkynes.¹⁰ Therefore the copper(I) catalysis of the cyclization of the enynylpyrazine 7a to the cascade product 8a was investigated. Copper iodide has little effect on the reaction, however copper chloride provided much more promising results. When the reaction mixture of 1a and five equivalents

^aDepartment of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan

^bDepartment of Chemistry, National Sun Yat-sen University, Kaohsiung, Taiwan. E-mail: mijuwu@faculty.nsysu.edu.tw; Fax: +886-7-5253909

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of hydrazine along with four equivalents of copper chloride were heated in refluxing acetonitrile for one day, pyrazolo[1,5*a*]pyridine **8a** was obtained in 53% yield along with **9a** in 32% yield. (eqn (3)) The structure of **9a** was unambiguously determined by X-ray crystallography. (Fig. 1) This structure presented another example of an (η^2 -alkyne)-copper complex¹¹ and it is apparently the intermediate to the final product **8a**. We therefore dissolved **9a** in acetonitrile and heated the reaction mixture at reflux for 30 h. This led to the virtually complete conversion of **9a** to **8a**. (eqn (4)) We then treated **1a** with five equivalents of hydrazine and four equivalents of copper chloride in refluxing acetonitrile for 30 h to give **8a** in 90% yield.



Fig. 1 ORTEP drawing of complex 9a.



Although we have accomplished a cascade cyclization reaction of enediynone 1a to pyrazolo[1,5-a]pyridine 8a in good chemical yield, a liability of this process is the large amounts of hydrazine and copper chloride that are needed. It is known that copper(I) or (II) may form a complex with hydrazine and further decomposition to copper particles.¹² It is possible that this happens under the previous conditions. In order to reduce the amount of hydrazine and copper used in this reaction, we revised the reaction process by addition of two equivalents of hydrazine to the acetonitrile solution of **1a** and heating the reaction mixture to 60 °C. This reaction was monitored by TLC and was found that 1a was completely converted to 7a within one hour. One equivalent of copper chloride was added into the reaction mixture and it was stirred at reflux temperature for 30 h. The pyrazolo[1,5-a]pyridine 8a was obtained in 75% yield after column chromatography on silica gel. (Table 1, entry 1)

After optimizing the reaction conditions, attention was turned to the scope and limitations of the method. Thus, eneynones **1b–m** were prepared according to the procedure outlined in Scheme 1. All of the enynones were employed in the cascade cyclization reaction under the optimal reaction conditions. The results are summarized in Table 1. When enediynones containing a straight chain alkyl group on the terminus of the alkyne, such as compounds **1b** and **1c**, pyrazolo[1,5-*a*]pyridines **8b** and **8c** were

Ph NH₂NH₂ (2 equiv) CH₃CN, 60 °C, 1h then CuCl (1 equiv) reflux, 30 h R 1 8 Entry Enediynones Products/yields (%) **1a**, $\mathbf{R} = \mathbf{C}_6 \mathbf{H}_{13}$ 8a/75 1 2 **1b**, $R = C_4 H_9$ 8b/80 3 1c, $R = C_5 H_{11}$ 8c/74 4 1d, R = iso-butyl 8d/75 5 1e, R = tert-butyl 8e/13 (9e/72) 6 1f, $R = C_6 H_5$ 8f/69 7 1g, $R = o - CH_3C_6H_4$ 8g/61 8 **1h**, $R = m - CH_3C_6H_4$ 8h/46 9 1i, $R = p - CH_3C_6H_4$ 8i/63 10 1j, R = o-CH₃OC₆H₄ 8i/73 11 $\mathbf{1}\mathbf{k}, \mathbf{R} = m - CH_3 OC_6 H_4$ 8k/45 12 **11**, $R = p - CH_3OC_6H_4$ 81/73 13 1m, $R = p - NO_2C_6H_4$ 8m/45

Cascade cyclization of enediynones to pyrazolo[1,5-a]pyridines

Table 1

8a-m

obtained in 80% and 74%, respectively. Compound 1d, which contains a more sterically hindered *iso*-butyl group provided product 8d in 75% yield.

However when the substituent on the terminal alkyne is a tert-butyl group, the yield of product 8e drops to 13%. The major product isolated in this reaction is complex 9e. (Table 1, entry 5). The structure of 9e was unambiguously determined by X-ray crystallography as shown in Fig. 2. Unlike the complex 9a, complex 9e is a complex of a 1:1 ratio of copper with enynylpyrazine. We also find that complex 9e is very stable. Heating a solution of 9e in acetonitrile for two days led to very little conversion to 8e and about 90% of 9e remains unchanged. On the other hand, 2,7-diarylpyrazolo[1,5-a]pyridines 8f-m were also prepared in modest to good yields (Table 1, entries 6-13). When a phenyl ring bearing an electron-withdrawing group is on the terminus alkyne, such as compound 1m, the desired pyrazolo[1,5*a*]pyridine **8m** was obtained in 45% yield. (Table 1, entry 13) The lower yield in this case could be due to the low electron density of the triple bond to disfavor the formation of the (η^3 -alkyne)-copper complex.



Fig. 2 ORTEP drawing of complex 9e.

The substituent effects on the other phenyl ring were also examined. Enediynones **1n–r** were synthesized using the procedure

 Table 2
 Cascade cyclization of enediynones to pyrazolo[1,5-a]pyridines

 8n-r



used for the preparation of **1a–m**. (Scheme 2) Vinyl chlorides **4c**, **4f**, **4l** and **4n** were coupled with propargyl alcohols **5b** and **5c** using palladium as the catalyst to give enediynols **6n–r** in 60–77% yields. Oxidation of **6n–r** with MnO₂ gave enediynones **1n–r** in 88– 95% yields. Treatment of **1n–r** with two equivalents of hydrazine, followed by one equivalent of copper chloride under the optimized reaction conditions provided pyrazolo[1,5-*a*]pyridines **8n–r** in 42– 74% isolated yields. (Table 2) Once again, when the phenyl ring had an electron-withdrawing group, the reactions led to decreased yield of product. (Table 2, entries 4 and 5)



Scheme 2

In summary, we have developed a new synthetic method for 2,7disubstituted pyrazolo[1,5-*a*]pyridines in good chemical yields by the reaction of enediynones with hydrazine promoted by copper chloride. This reaction can tolerate many functional groups. Since pyrazolo[1,5-*a*]pyridines are important heterocycles in both pharmaceutical science and materials chemistry, we believe the synthetic method described here may have a strong impact in those areas.

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