Base-promoted synthesis of 1*H*, 3*H*-pyrrolo[1, 2-*c*]thiazol-3-imine derivatives *via* [3+2] annulation of 2-alkynylpyrroles with isothiocyanates

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Abstract: Base-promoted [3+2] annulation of 2-alkynyl pyrrole with isothiocyanate affording 1*H*, 3*H*-pyrrolo[1, 2-*c*]thiazol-3-imine derivatives has been developed. The control experiments suggest that the reaction proceeds via simple nucleophilic attack followed by intramolecular addition. The present cascade reaction provides a facile one-pot synthesis of 1*H*, 3*H*-pyrrolo[1, 2-*c*]thiazol-3-imine derivatives under mild conditions with good yields and high regioselectivity.
Keywords: 2-alkynylpyrrole, annulation, isothiocyanate.

1. Introduction

Pyrrolo[1, 2-*c*]thiazoles and their derivatives have attracted immense attention due to their profound physiological and pharmacological properties.[1-4] The 1*H*,3*H*-pyrrolo[1, 2-*c*]thiazole skeletons are found in many synthesized drugs or pro-drug molecules possessing various biological activities, such as, anti-leukemic activity,[1] PAF-antagonist,[2] anti-inflammatory[3] and anti-tumor activity.[4] Besides, the 1*H*,3*H*-pyrrolo[1, 2-*c*]thiazoles are reactive and versatile motifs in construction of complicated pyrrolocycles. It is a simple and direct method to construct pyrrolo[1,2-c]thiazole skeleton in one pot. However, pyrrolo[1,2-c]thiazole synthesized by this way is hard to functionalization further as all sites in pyrrolo[1,2-*c*]thiazole skeleton are occupied by specific substituents.

It is a powerful strategy to synthesize carbocycles and heterocycles via annulation of difunctional aromatic compounds containing alkynyl group.[5] Very recently, we have reported two examples of *o*-alkynylacetophenones participating in construction of carbocycles.[6] In addition, we are also interested in developing synthetic methods of *N*-heterocycles *via* annulation process using alkynes as one of the reactants,[7] In continuation of our previous work on the synthesis and transformation of pyrroles.[8] Therefore, in this work we design a [3+2] annulation of 2-alkynylpyrroles as a difunctional aromatic compound with isothiocyanates to construct pyrrolo[1, 2-*c*]thiazol-3-imine skeleton in the presence of base in one-pot manner.

2. Experimental (or Theoretical)

All commercial reagents are analytically pure and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded using $CDCl_3$ as solvent at 298 K. ^{1}H NMR (400 MHz) chemical shifts (δ) were referenced to internal standard TMS (for ^{1}H, δ = 0.00 ppm). ^{13}C NMR (101 MHz) chemical shifts were referenced to internal solvent $CDCl_3$ (for ^{13}C, δ = 77.16 ppm). HRMS experiments were performed on a high resolution magnetic sector mass spectrometer.

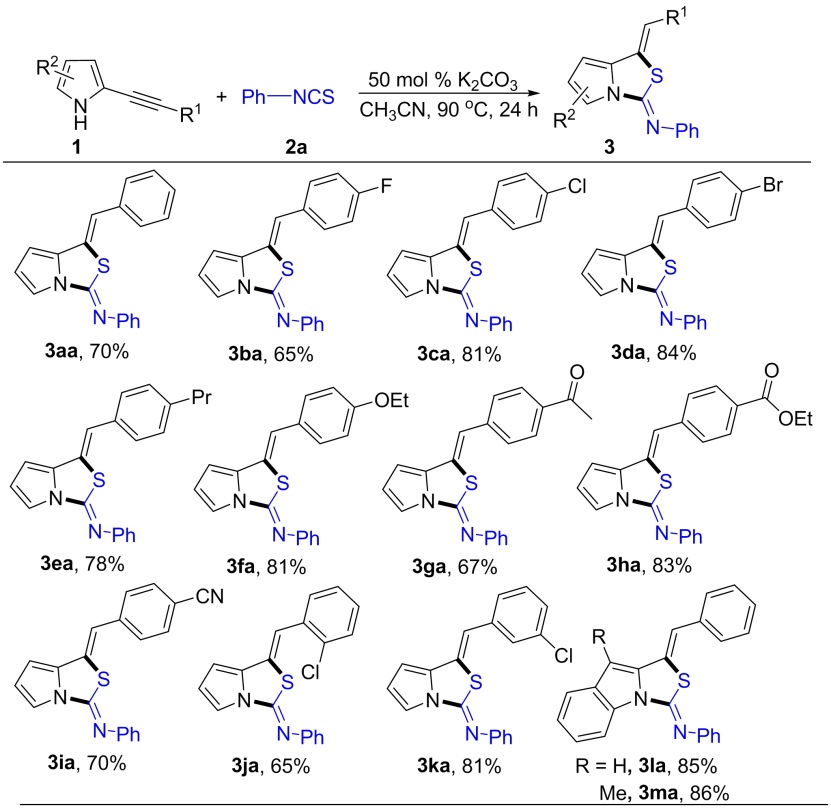
To a 25-mL tube equipped with a magnetic stirrer, **1f** (211.0 mg, 0.5 mmol), K_2CO_3 (35 mg, 0.5 equiv), **1a** (101.0 mg, 0.75 mmol) and CH_3CN (2 mL) were added sequentially. The tube was sealed and stirred at 90 °C in an oil bath for 24 h. After removal of the solvent under reduced pressure, purification was performed by flash column chromatography on silica gel with petroleum ether/ethyl acetate as eluent to afford **3fa** in 81% yield (140.0 mg).

3. Results and discussion

We first investigated the substitution effect of 2-alkynylpyrroles. As showed in Table 2,2-(phenylethynyl)-pyrrole **1a** could react with isothiocyanatobenzene **2a** to afford the corresponding product **3aa** in 70% yield. The 2-(phenylethynyl)-pyrrole bearing halogen (F, Cl and Br), electron-donating groups (Pr, and OEt), and electron-withdrawing groups (COMe, COOEt and CN) at *para*-position of phenyl could provide the corresponding product in modest to excellent yield. The results above indicated the electron effect trend of substituents on the phenyl ring of substrate **1** was not apparent. In addition, *ortho*-substituted

(**3ja**, 65%) and *meta*-substituted (**3ka**, 81%) 2-(phenylethynyl)-pyrrole could also underwent the present reaction smoothly, affording corresponding products in good yields. Notably, 2-alkynyl indoles were compatible in the reaction system as well (**3la**, 85%; **3ma**, 86%). Therefore, it provided a new method to construct thiazolo[3,4-a]indole skeleton with high yield and high atom economy at the same time.

Table 1. Scope of 2-alkynylpyrroles for the synthesis of pyrrolo[1, 2-*c*]thiazol-3-imines[a].



[a] The reactions were performed with **1** (0.5 mmol), **2a** (0.75 mmol) and K_2CO_3 (0.25 mmol) in 2 mL of CH_3CN, isolated yield.

4. Conclusions

In conclusion, we have developed a new synthetic method access to 1*H*, 3*H*-pyrrolo[1, 2-*c*]thiazol-3-imine derivatives in moderate to good yields with high atom economy and high regioselectivity *via* a K_2CO_3-promoted [3+2] annulation of 2-alkynylpyrroles with isothiocyanates, which are easily available starting materials.

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References

1. Anderson, W. K.; Mach, R. H. *J. Med. Chem.* , *30*(**1987**)2109.
2. Pinquier, J. L.; Sedivy, P.; Bruno, R.; Bompart, F.; Gregoire, J.; Strauch, G.; Gaiilot, J.; Clucas, A. *Eur. J. Clin. Pharmacol.* , *41(***1991**)141.
3. Fabre, J.-L.; Farge, D.; James, C.; Lavé, D.Asao, N. U.S. Patent 4529728(1985).
4. Soares, M. I. L.; Brito, A. F.; Laranjo, M.; Paixão, J. A.; Botelho, M. F.; Pinho e Melo, T. M. V. D. *Eur. J. Med. Chem.* , *60*(**2013)**254.
5. Pan, X.; Luo, Y.; Kuang, Y.; Li, G.; Org. Biomol. Chem. , 12(2014)5861.
6. Guo, B.; Hua, R., Tetrahedron , 72(2016)4608.
7. Su, J.; Liu, H.; Hua, R. Int. J. Mol. Sci. , 16(2015) 3599.
8. Zheng, Q.; Hua, R.; Jiang, J.; Zhang, L. Tetrahedron, 70(2014) 8252.