

One-pot synthesis of ynamines from employing multicomponent reaction of isothiocyanate

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Abstract: An efficient one-pot synthesis of functionalized ynamines is described. This involves the multicomponent reaction of ammonium thiocyanate, benzoyl chlorides, and secondary amines in the presence of dialkylacetylenedicarboxylates in acetone at reflux conditions.

Keywords: Multicomponent reaction; Ynamine; Benzoyl chloride; Activated acetylenes.

Introduction

Disubstituted-1-alkynylamines, the common name “ynamines”, are regarded as the alkynes activated through the interaction of the amino group linked directly to a triple bond, and thereby liable to undergoing the reaction with a variety of electrophiles [1-5]. During recent decades, the preparation and synthetic utility of ynamines in organic and related fields have been explored [6]. However, synthetic application of ynamines remained relatively limited because of the difficulty experienced in their preparation and handling, due to their high reactivity and sensitivity toward hydrolysis. Thus, modification to thermally stable ynamines without decreasing the reactivity afforded a challenging approach to improve their synthetic utility. An important example of this approach includes functionalized acetylenes containing “push-pull” systems, with an electron-donating group at one end and an electron-withdrawing group at the other end of the triple bond, as pioneered in Hsung and Ishihara [7]. As part of our current studies on the development of new routes in organic synthesis [8], we report an efficient synthesis of ynamine derivatives.

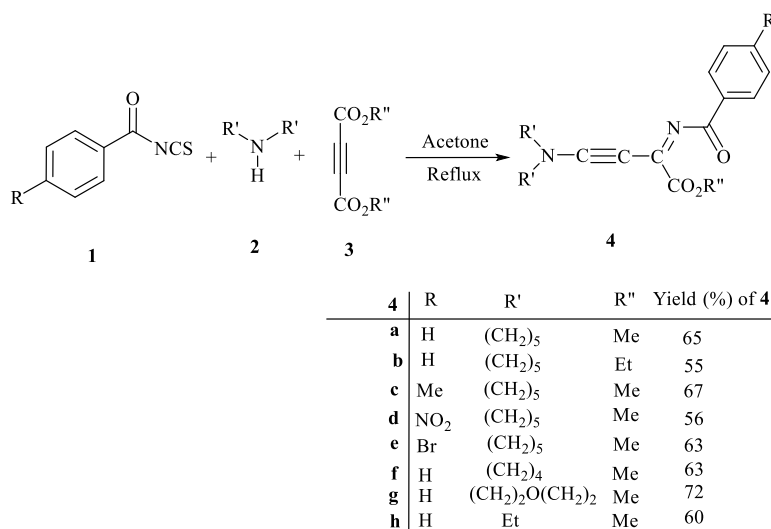
Results and Discussion

Thus, the reaction of aryl isothiocyanates **1**, and secondary amines **2** in the presence of dialkyl acetylenedicarboxylates **3** led to alkyl 2-[(benzoyl)imino]-4-dialkylamino-3-butynoate **4** in good yields (Scheme 1).

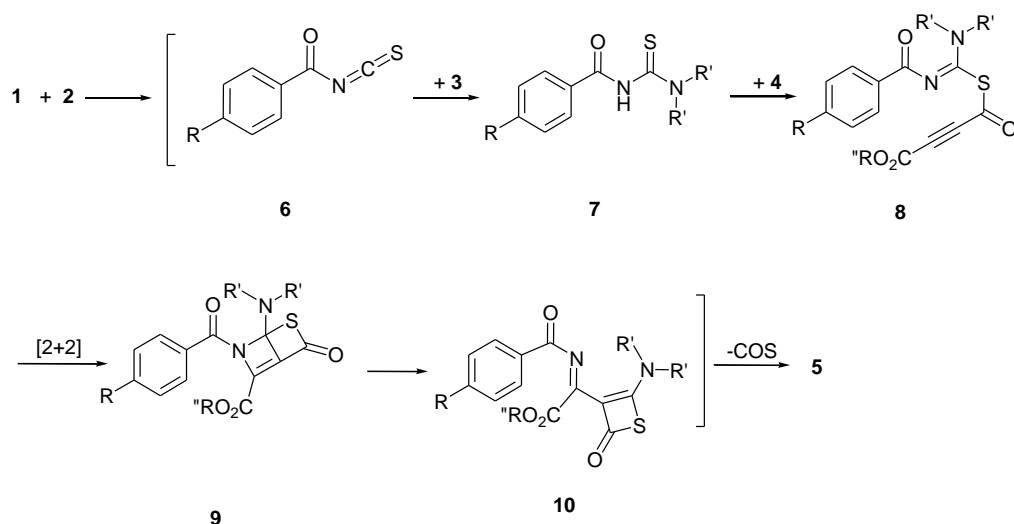
Structures of compounds **4a-4h** were assigned by IR, ^1H NMR, ^{13}C NMR and mass spectral data. For example, the ^1H NMR spectrum of **4a** exhibited two broad multiplets ($\delta = 1.73$ and 3.61) for pentamethylene, a singlet ($\delta = 3.76$) for methoxy, and characteristic multiplets ($\delta = 7.39-7.76$) for the aromatic protons. The ^{13}C NMR spectrum of **4a** shows carbonyl ($\delta = 162.4$ and 170.8), imine ($\delta = 160.2$), and acetylenic ($\delta = 59.5$ and 109.1) carbons, in agreement with the ynamine structure. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 298$. Mechanistically, the benzoyl isothiocyanate **1**, followed by addition of amine **3** to generate the benzoylthiourea derivative **6** [10]. Subsequent nucleophilic attack of **6** to acetylenic compound **3** yields the 1:1 adducts **7**, which undergoes an intramolecular [2+2] cycloaddition [11] to produce the strained intermediate **8**. Electrocyclic ring opening [12]

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of **8** leads to **9**, which is finally converted to **4** by elimination of COS [13] (Scheme 2).



Scheme 1: synthesis of ynamines **4**



Scheme 2: Proposed mechanism for the synthesis of ynamines **4**

Conclusion

In conclusion, we have described a convenient route to functionalized ynamines from the four-component reaction of aryleisothiocyanates, and secondary amines, in the presence of dialkylacetylenedicarboxylates. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The simplicity of the present procedure makes it an interesting alternative to other approaches. The procedure described here

provides an acceptable one-pot method for the preparation of functionalized ynamines.

References

- [1] Collard-Motte, J.; Janousek, Z. *Top. Curr. Chem.* **2009**, *130*, 89.
- [2] Ficini, J. *Tetrahedron* **2020**, *32*, 1449.
- [3] Viehe, H. G. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **2003**; Ch 12, pp 861–912.
- [4] Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2014**, *63*, 1455.

- [5] Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **2020**, 6, 767.
- [6] (a) Furber, M. In *Comprehensive Organic Functional Group transformations*; Katritzky, A. R.; Mett-Cohn, O.; Rees, C. W. Eds.; Pergamon: Oxford, **2008**; 1, 997. (b) Ficini, J. *Tetrahedron*, **2021**, 32, 1449. (c) Collard-Motte, J.; Janousek, Z. *Top. Current Chem.* **2003**, 130, 89. (d) Zificask, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. *Tetrahedron* **2001**, 57, 7575. (e) Tanaka, K.; Takeishi, K., *Synthesis* **2007**, 18, 2920.
- [7] Mantani, T.; Ishihara, T.; Konno, T.; Yamanaka, H. *J. Fluorine Chem.* **2001**, 108, 229.
- [8] (a) Yavari, I.; Sabbaghan, M.; Hossaini, Z. *Synlett.* **2006**, 2501. (b) Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2006**, 47, 2953. (c) Yavari, I.; Moradi, L. *Tetrahedron Lett.* **2006**, 47, 1627.
- [9] a) Yavari, I.; Hossaini, Z.; Sabbaghan, M. *Tetrahedron Lett.* **2006**, 47, 6037. b) Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2015**, 46, 7491.
- (10) Scriven, E. F.V., *Org. Synth. Coll.* **2001**, 3, 735.
- (11) (a) Lee C. C., Leung M. K., Lee G. H., Liu Y. H., and Peng S. M., *J. Org. Chem.* **2006**, 71, 8417; (b) Zhang L., *J. Am. Chem. Soc.* **2005**, 127, 16804.
- (12) (a) Murakami, M.; Miyamoto, Y.; and Ito, Y. *J. Am. Chem. Soc.* **2001**, 123, 6441. (b) Grieco, P. A.; Takigawa, T.; Schillinger, W. J., *J. Org. Chem.* **1980**, 45, 2247.
- (13) Padwa A., Flick A. C., and Lee H. I., *Org. Lett.* **2005**, 7, 2925.