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Research Article

Solvent-free Synthesis of Fused Pyrimidone Derivatives from Baylis-Hillman Acetates

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Abstract

By using the Baylis-Hillman acetates as the starting materials, an improved eco-friendly process for the synthesis of fused pyrimidone derivatives has been established. These reactions provide considerable yields (67-78%) of fused pyrimidone derivatives and are easily carried out under mild, solvent-free conditions.

Keywords

Solvent-free synthesis, fused pyrimidinone, Baylis-Hillman acetate, Eco-friendly reaction

Introduction

The development of more environmentally friendly, atom-efficient processes for the synthesis of various functionalized organic compounds with a broad variety of uses in both industry and academics has become a top priority for chemists in recent years.[1] With this goal in mind, it is now crucial to apply the concepts of green chemistry when creating and constructing innovative processes for the synthesis of compounds that are biologically significant. In this context, it has become standard procedure to either avoid using hazardous catalysts and solvents in many chemical processes or to substitute with environmentally friendly solvents.[2]

The creation of catalyst-free or solvent-free reactions has gained significant relevance in modern organic chemistry due to environmental concerns, as it decreases the usage of organic solvents and reduces the formation of other toxic by-products.[3]. Because many biologically active molecules contain heteroatoms, the synthesis of heterocyclic compounds using green chemistry principles has become an increasingly attractive and challenging work. Because of their biological properties and range of uses, pyrimidones and their derivatives have become highly significant among these heterocyclic compounds.[4] Figure 1 depicts a few of the pyrimidone derivatives that are significant as biologically active.

Numerous biological activities are demonstrated by pyrimidinedones, including anti-platelet,[5] anti-psychotic,[6] HIV-1 integrase inhibitors,[7] selective β3 adrenergic receptor agonist,[8] analgetic,[9] nonselective 5-HT/D2 antagonists,[10] anti-plasmodial,[11] inhibitors of dipeptidyl peptidase IV[12], and non-nucleoside reverse transcriptase inhibitors.[13]

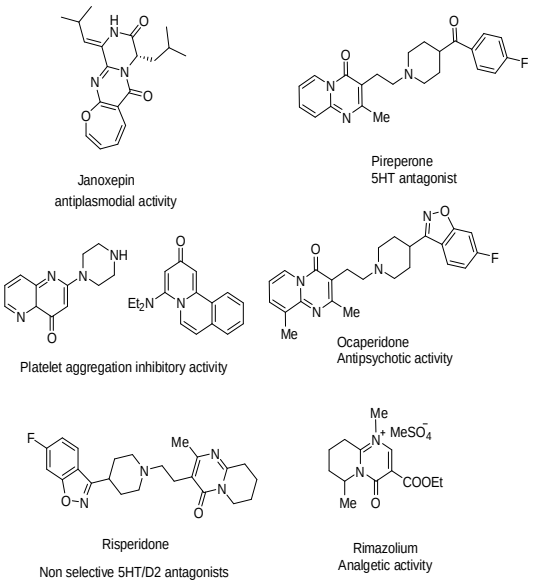


Fig. 1: Some biologically important fused pyrimidones

Because of these numerous uses, chemists are very interested in developing new synthetic techniques to create functionalized pyrimidones that have biological significance. Different approaches to the synthesis of pyrimidones and their derivatives have been documented.[14] Nonetheless, there is a need for the creation of straightforward, affordable, and environmentally friendly synthetic techniques.

The adaptable substrates known as Baylis-Hillman acetates are useful for building a variety of heterocyclic, carbocyclic, and natural compounds.[15] A facile technique for producing fused pyrimidones was described by Basavaiah and colleagues. It involved reacting derivatives of Baylis-Hillman acetates with 2-amino pyridine in an aqueous medium.[16] The synthesis of 5-benzoyl pyrimidine-2,4-diones was skillfully demonstrated by Kim and colleagues using the Baylis-Hillman adducts as the starting materials.[17] The present authors also recently made an attempt and succeeded in synthesizing fused pyrimidones by using ultrasound irradiation with excellent yields (75-88%).[18]

Thus, using Baylis-Hillman acetates as the starting materials, the authors herein attempted to develop an improved method for the titled compounds without the need for a catalyst or solvent in the construction of fused pyrimidone derivatives based on the expertise of the authors in green synthesis[19,20]. Recently, the authors also made a review on various synthetic methodologies pyrimidines[21].

Experimental

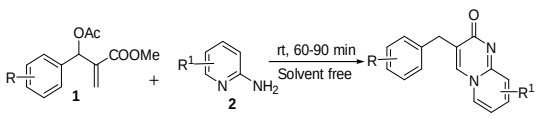
***General procedure for the synthesis of (3a-i)*:** For thirty minutes, a mixture of 2-amino pyridine derivative **2** (1 mmol) and Baylis-Hillman acetate **1** (1 mmol) is stirred at room temperature without the use of a solvent. The crude reaction mixture was crystallized from methanol to produce the pure pyrimidone derivatives (**3a–i**) after the reaction was completed as indicated by TLC. Finally, the pure products were well characterized by comparing the spectral data with our earlier report[18].

Results and Discussion

We anticipated that the Baylis-Hillman acetates on reaction with 2-amino pyridine derivatives would yield the fused pyrimidones under environmentally acceptable conditions, keeping in mind the need for a solvent-free and catalyst-free reaction. As a result, we have created three substituted Baylis-Hillman acetate derivatives by using the methods described in published works.[22]

With the synthesized derivatives of the Baylis-Hillman acetates **1a-c** in hand, we conducted a pilot experiment as shown in **Scheme 1** in which we stirred a combination of **1a** (1 mmol) and 2-amino pyridine **2a** (1 mmol) at room temperature in solvent free conditions.The reaction progress was then monitored by the use of Thin Layer Chromatography.

The reaction mixture was then solidified and the TLC showed that the reaction was finished after 60 minutes of stirring at room temperature. After completing crystallization in methanol solvent, the crude reaction mixture produced 3-benzyl-2H-pyrido[1,2-a]pyrimidin-2-one **3a** with an isolated yield of 77% (**Table 1**, entry 1).

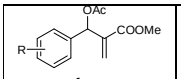
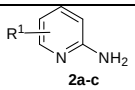
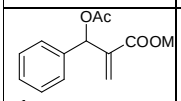
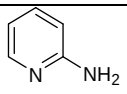
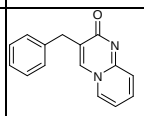
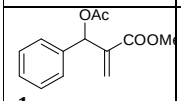
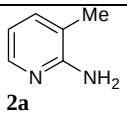
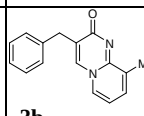
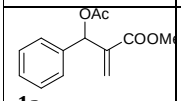
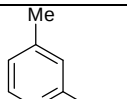
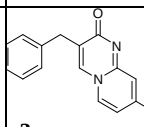
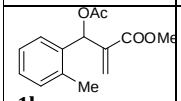
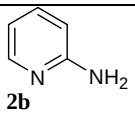
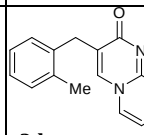
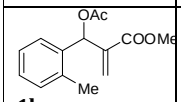
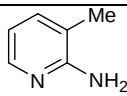
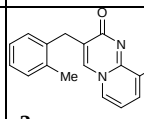
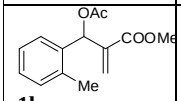
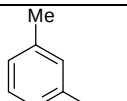
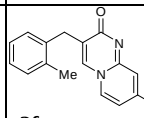
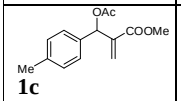
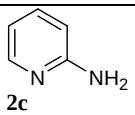
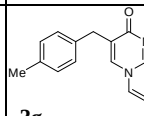
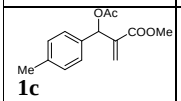
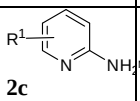
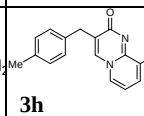
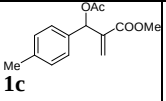
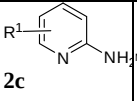
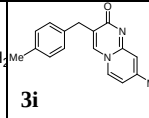


Scheme 1: Solvent free synthesis of fused pyrimidones

Motivated by the initial outcome, we continued to examine in the present approach with

the reactivity of 2-amino pyridine derivatives and substituted Baylis-Hillman acetates.

Table 1: Synthesis of fused pyrimidone derivatives

 **1a-c**	 **2a-c**	**Product (3a-i)**	**Yield** (%)
 **1a**	 **2a**	 **3a**	77
 **1a**	 **2a**	 **3b**	72
 **1a**	 **2a**	 **3c**	75
 **1b**	 **2b**	 **3d**	76
 **1b**	 **2b**	 **3e**	67
 **1b**	 **2b**	 **3f**	74
 **1c**	 **2c**	 **3g**	78
 **1c**	 **2c**	 **3h**	73
 **1c**	 **2c**	 **3i**	75

For this purpose, we have employed the Baylis-Hillman acetates methyl 2-(acetoxy(*o*-tolyl)methyl)acrylate (**1b**) and methyl 2-(acetoxy(*p*-tolyl)methyl)acrylate (**1c**) as shown in **Scheme 1** and we have chosen 2-amino pyridine, 3-methyl 2-amino pyridine, 4-methyl 2-amino pyridine for our study in the current optimized protocol.

Reactions of **1a** with 3-methyl 2-amino pyridine and 4-methyl 2-amino pyridine proceeded smoothly under normal circumstances, yielding the corresponding products in 72% (**3b**) and 75% (**3c**) yields, respectively (**Table 1**, entry 2,3).

The Baylis-Hillman acetate containing 2-Me substituent **1b** was also treated to the reaction with 2-amino pyridine, 3-methyl 2-amino pyridine and 4-methyl 2-amino pyridine under the similar conditions. It was observed that each reaction proceeded with efficiency and produced the corresponding products **3d–f** with yields of 76%, 67%, and 74%, respectively.

Additionally, we investigated the reactivity of Baylis-Hillman acetate bearing 2-Me substituent as given for **1c** with 2-amino pyridine, 3-methyl 2-amino pyridine, and 4-methyl 2-amino pyridine in the current strategy. The corresponding products **3g-i** were obtained in 78%, 73%, and 75% yields, respectively, and the results are summarized in **Table 1** as entries 7,8,9.

Using contemporary analytical procedures, every product obtained is thoroughly characterized. Further, it is to note that all the reactions were carried out with Baylis-Hillman acetates **1**(1 mmol) and 2-amino pyridine derivatives (1 mmol) under solvent free conditions about 60-90 min of stirring at room temperature and the yields of pure products obtained and reported in the Table 1 are only after recrystallization from methanol solvent.

An examination of the previous reports of the same compounds[18] it was found that the yields obtained (67-78%) were somewhat less compared to the reactions conducted under ultrasound radiation(75-88%) but not much difference. However, the reaction times were high for solvent free reactions (60-90 min) compared to the same ultrasound reactions (30 min)[18] may be because of energy requirements for the reactions to complete.

Conclusions

In conclusion, we have developed an improved method that eliminates the need for a solvent and catalyst in the synthesis of fused pyrimidone derivatives. The present protocol is gentle, effective, easy to follow, and environmentally friendly. The method offers a simple way to produce large yields of differently substituted fused pyrimidone derivatives.

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Conflicts of interest

The authors declare no potential conflicts of interests on the present work.

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NA

References

1. Tanaka, K.; Toda, F. *Chem. Rev.*, **2000**, *100(3)*, 1025.
2. (a) Sarkar, A.; Santra, S.; Kundu, S. K.; Hajra, A.; Zyryanov, G. V.; Chupakhin, O. N.; Charushin, V. N.; Majee, A. *Green Chem.*, **2016**, *18*, 4475. (b) Azizi, N.; Aryanasab, F.; Saidi, M. R. *Org. Lett.*, **2006**, *2(3)*, 5275.
3. (a) Zangade, S.; Patil P. *Curr. Org. Chem.* **2019**, *23*, 2295. (b) Tanaka K.; Toda, F. *Chem. Rev.* **2000**, *100(3)*, 1025.
4. Hill, P. J.; Abibi, A.; Albert, R.; Andrews, B.; Gagnon, M. M.; Gao, N.; Grebe, T.; Hajec, L. I.; Huang, J.; Livchak, S.; Lahiri, S. D.; McKinney, D. C.; Thresher, J.; Wang, H.; Olivier, N.; Buurman, Ed T. *J. Med. Chem.*, **2013**, *56(18)*, 7278.
5. Roma, G.; Cinone, N.; Di Braccio, M.; Grossi, G.; Leoncini, G.; Signorello, M. G.; Carotti, A. *Bioorg. Med. Chem* , **2000**, *8(4)*, 751.
6. Ravina, E.; Casariego, I.; Masaguer, C. F.; Fontenla, J. A.; Montenegro, G. Y.; Rivas, M. E.; Loza, M. I.; Enguix, M. J.; Villazon, M.; Cadavid, M. I.; Demontis, G. C. *J. Med. Chem.*, **2000**, *43(24)*, 4678.
7. Yu, S.; Sanchez, T. W.; Liu, Y.; Yin, Y.; Neamati, N.; Zhao, G. *Bioorg. Med. Chem. Lett.*, **2013**, *23(22)*, 6134.
8. Edmondson, S. D.; Zhu, C.; Kar, N. F.; Salvo, J. D.; Nagabukuro, H.; Sacre-Salem, B.; Dingley, K.; Berger, R.; Goble, S. D.; Morriello, G.; Harper, B.; Moyes, C. R.; Shen, D.-M.; Wang, L.; Ball, R.; Fitzmaurice, A.; Frenkl, T.; Gichuru, L. N.; Ha, S.; Hurley, A. L.; Jochnowitz, N.; Levorse, D.; Mistry, S.; Miller, R. R.; Ormes, J.; Salituro, G. M.; Sanfiz, A.; Stevenson, A. S.; Villa, K.; Zamlynny, B.; Green, S.; Struthers, M.; Weber, A. E. *J. Med. Chem.*, **2016**, *59(2)*, 609.
9. Hermecz, I.; Vasvdri-Debreczy, L.; Horvdth, A.; Balogh, M.; Kokosi, J.; DeVos, C.; Rodriguez, L. *J. Med. Chem.*, **1987**, *30(9)*, 1543.
10. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.*, **2000**, *2(23)*, 3679.
11. Sprogoe, K.; Manniche, S.; Larsen, T. O.; Christopherse, C. *Tetrahedron*, **2005**,61, 8718.
12. Zhang, Z.; Wallace, M. B.; Feng, J.; Stafford, J. A.; Skene, R. J.; Shi, L.; Lee, B.; Aertgeerts, K.; Jennings, A.; Xu, R.; Kassel, D. B.; Kaldor, S. W.; Navre, M.; Webb, D. R.; Gwaltney, S. L. *J. Med. Chem.*, **2011**, *54(2)*, 510.
13. Mai, A.; Artico, M.; Sbardella, G.; Quartarone, S.; Massa, S.; Loi, A. G.; De Montis, A.; Scintu, F.; Putzolu, M.; La Colla, P. *J. Med. Chem.*, **1997**, *40(10)*, 1447.
14. (a) Sukach, V. A.; Resetnic, A. A.; Tkachuk, V. M.; Lin, Z.; Kortz, U.; Vovk, M. V.; Roschenthaler, G. V. *Eur. J. Org. Chem.*, **2015**, *2015(6)*, 1290. (b) Lemrova, B.; Soural, M. *Eur. J. Org. Chem.*, **2015**, *2015(9)*, 1869.(c) Sukach, V. A.; Tkachuk, V. M..; Shoba, V. M.; Pirozhenko, V. V.; Rusanov, E. B.; Chekotilo, A. A.; Röschenthaler, G.-V.; Vovk, M. V. *Eur. J. Org. Chem.*, **2014**, *2014(7)*, 1452. (d) Weng, Y. Y.; Ying, L. M.; Chen, Q. X.; Su, W. K. *Chin. Chem. Lett.*, **2012**, *23(8)*, 911. (e) Beaume, A.; Courillon, C.; Derat, E.; Malacria, M. *Chem. Eur. J.*, **2008**, *14(4)*, 1238. (f) Cebasek, P.; Bevk, D.; Pirc, S.; Stanovnik, B.; Svete, J. *J. Comb. Chem.*, **2006**, *8(1)*, 95.
15. (a) Santos, M. S.; Coelho, F.; Lima-Junior, C. G.; Vasconcellos, M. L. A. A. *Curr. Org. Synth.*, **2015**, *12(6)*, 830. (b) Wei, Y.; Shi, M. *Acc. Chem. Res.*, **2010**, *43(7)*, 1005. (c) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.*, **2010**, *110(9)*, 5447. (d) Singh, V.; Batra, S. *Tetrahedron*, **2008**, *64*, 4511.
16. (a) Sreevani, R.; Manjula, A.; Rao, B. V. *J. Heterocyc. Chem.*, **2011**, *48(3)*, 586. (b)

Basavaiah, D.; Satyanarayan, T. *Tetrahedron Lett.*, **2002**, *43(24)*, 4301.
17. Kim, J. M.; Kim, E. S.; Kim, J. N. *Bull. Korean Chem. Soc.*, **2009**, *30(4)*, 938.
18. Santha Kumari, M.; Sivarama Krishna Reddy, V.; Hari Babu, B.; V. V. Satyanarayana, P. *Indian J. Heterocycl. Chem.*, **2022**, *32*, 119.
19. Hari Babu, B.; Vijay, K.; Bala Murali Krishna, K.; Sharmila, N.; Baby Ramana, M. .*J. Chem. Sci.*, **2016**, *28(9)*, 1475.
20. Mule, S. R.; Satyanarayana, P. V. V.; Bollikolla, H. B. *Lett. Org. Chem.*, **2012,** *9(10)*, 739.
21. Hari Babu, B.; Dhayanidhi, S.; Laxmi Prasanna, Y.; Surendranatha Reddy, O.; Srinivasa Rao, A.; Basavaiah, C.; Lakshmi, G J V S N D.; Ravi, V. *Carib. J. Sci. Tech.*, **2023**, *11(1)*, 01.
22. (a) Inturi, S. B.; Kalita, B.; Ahamed, A. J. *Synth. Commun.* **2018**, *48(16)*, 2037.(b) Shahrisa, A.; Ghasemi, Z. *Chem. Heterocycl. Comp*, **2016**, *46(1)*, 30. (c) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.*, **2012**, *14(17)*, 4580. (d) Kim, J. M.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28(12)*, 2505.