

watthe blo unications

Synthetic Communications An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Highly efficient one-pot synthesis of fused pyrimidones from 2-heteroaryl amines and Morita-Baylis-Hillman carbonates via intermolecular cyclocondensation

Surendra Babu Inturi, Biswajit Kalita & A. Jafar Ahamed

To cite this article: Surendra Babu Inturi, Biswajit Kalita & A. Jafar Ahamed (2018): Highly efficient one-pot synthesis of fused pyrimidones from 2-heteroaryl amines and Morita-Baylis-Hillman carbonates via intermolecular cyclocondensation, Synthetic Communications

To link to this article: https://doi.org/10.1080/00397911.2018.1479761



View supplementary material



Published online: 11 Jul 2018.



📝 Submit your article to this journal 🗹



則 🛛 View Crossmark data 🗹



Check for updates

Highly efficient one-pot synthesis of fused pyrimidones from 2-heteroaryl amines and Morita–Baylis–Hillman carbonates *via* intermolecular cyclocondensation

Surendra Babu Inturi^{a,b}, Biswajit Kalita^a and A. Jafar Ahamed^b

^aMedicinal Chemistry Division, Jubilant Biosys Ltd., Bangalore, India; ^bPost Graduate and Research Department of Chemistry, Jamal Mohamed College (Autonomous) affiliated to Bharathidasan University, Tiruchirappalli, India

ABSTRACT

A highly selective and efficient cyclocondensation reaction for construction of various 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones and related fused pyrimidones from allylic carbonates and 2-heteroaryl amines has been developed. The transformation involves one-pot sequential aza-Michael addition, intramolecular acyl substitution, and [1,3]-*H* shift. The method is catalyst free, eco-friendly, scalable, and completes within a short reaction time, with no work-up, no column purification, and demonstrate a broad functional group tolerance.

ARTICLE HISTORY

Received 11 April 2018

KEYWORDS

Cyclocondensation; fused pyrimidones; green chemistry; 2-heteroaryl amines; MBH carbonates

GRAPHICAL ABSTRACT



Introduction

Pyrimidine is an important structural motif and has appeared as one of the key pharmacophores in many bioactive molecules including DNA and RNA.^[1-2] The fused pyrimidone derivatives are one of the most promising and widely used heteroaromatic compounds across multiple therapeutic areas and target classes^[3] due to their unprecedented biological importance and have shown a wide range of biological activities that have led to the development of many marketed drugs.^[4] These derivatives, in particular, have been reported as G protein signaling (RGS) protein regulators,^[5] anticancer

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

B Supplemental data for this article can be accessed on the publisher's website.

© 2018 Taylor & Francis

CONTACT Biswajit Kalita Biswajit.kalita@jubilantbiosys.com Medicinal Chemistry Division, Jubilant Biosys Ltd, #96, Industrial Suburb, 2nd Stage, Yeshwanthpur, Bangalore 560022, Karnataka, India; A. Jafar Ahamed agjafar@ yahoo.co.in Post Graduate and Research Department of Chemistry, Jamal Mohamed College (Autonomous), affiliated to Bharathidasan University, Tiruchirappalli 620020, Tamil Nadu, India.



Figure 1. Selected biologically active compounds.

agents,^[6] HIV integrase inhibitors,^[7] estrogen-related receptors (ERR) agonists,^[8] anticoccidial agents,^[9] aldose reductase inhibitors,^[10] and antimalarial agents.^[11] A few of the biologically active fused pyrimidones were exemplified in Figure 1.^[3e,9] Because of their usefulness and importance, synthesis of this class of fused pyrimidones is one of the most attractive areas in organic and medicinal chemistry for several years.

The Morita–Baylis–Hillman (MBH) adducts are synthetically important synthons for constructing a wide range of densely functionalized cyclic and heterocyclic skeletons.^[12] Consequently, several methods were known to synthesize fused pyrimidones over the years.^[13] Notably, Basavaiah et al. and the other leading groups have reported the synthesis of 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones and related fused pyrimidones in a one-pot protocol from 2-aminopyridine and MBH derived acetates at room temperature under solvent and solvent-free conditions.^[14] Satyanarayana et al. have reported the solvent-free microwave assisted reaction to synthesize this class of fused pyrimidones using the same starting materials.^[15] Recently, Alsharif et al. reported hexafluoroisopropanol (HFIP) mediated synthesis of 3-substituted-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones from MBH alcohols and 2-aminopyridines under thermal condition.^[16]

Although these methods are efficient to form 3-substituted-2H-pyrido[1,2-a]pyrimidin-2-ones and related fused pyrimidones, however, these reactions involve in long reaction time and the use of microwaves irradiations that impose a limitation on scalability. HFIP is a corrosive and hazardous liquid. Guided by the reactivity of the MBH carbonates and its affinity for cyclocondensation, we sought to develop a one-pot reaction strategy that would fulfill the large scope of this class of compound synthesis with a broad substrate variety.

In this study, we report a novel methodology that employs a variety of allylic carbonates in a one-pot reaction system to give a diverse range of 3-substituted-2H-pyrido[1,2-a]pyrimidin-2-ones and related fused pyrimidones in good to excellent yields. To the best of our knowledge, use of allylic carbonates in the synthesis of this class of fused heterocycles has never been previously reported.

Results and discussion

We initially began our investigation reaction between pyridin-2-amine (1) and ethyl 2-(((tert-butoxycarbonyl)oxy)(phenyl)methyl)acrylate (2a) in 1,4-dioxane at room temperature (Table 1, entry 1). To our delight, the desired product 3a was obtained in 20% yield over a period of 16 h along with 50% of ethyl 2-(phenyl(pyridin-2-ylamino)methyl)-acrylate(4) (confirmed by ¹H & ¹³C NMR, see supporting information), which is possible *via* nucleophilic allylic amination of MBH carbonate 2a. Our study began by screening of solvents such as ACN, THF, DMF, and EtOH (Table 1, entries 2–5). The optimization

	OBoc NH ₂ + Ph	$CO_2Et \xrightarrow{Solvent} N$	Et Solvent T (°C), Time	
	1 2a	3a	Ph4	
Entry	Solvent	Temperature (°C)	Time	Yield 3a/4 (%) ^b
1	1,4-dioxane	25	16 h	20/50
2	MeCN	25	16 h	40/25
3	THF	25	16 h	46/20
4	DMF	25	16 h	25/15
5	EtOH	25	5 h	85/trace
6	EtOH	65	15 min	94/0
7	MeOH	65	15 min	75/0
8	<i>i</i> -PrOH	65	15 min	78/0
9	-	65	15 min	60/0
3 -				

Table 1. Optimization of reaction conditions^a.

^aReaction conditions: 1 (0.5 mmol), 2a (0.53 mmol), solvent (0.8 mL), 25–65 °C, under air.

^bIsolated yields based on **1**.

The significance of bold value indicates the best optimized condition and was taken forward.

results are summarized in Table 1. From these screening results, we found that under an un-optimized condition, ethanol was superior to all other solvents that we had tested giving 85% yield of the corresponding 3-benzyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**3a**) along with trace of **4** (Table 1, entry 5). Based on these initial outcomes, we planned to further optimize the reaction condition to reduce the reaction time and to improve yield. It was noteworthy to mention that increasing the reaction temperature up to $65 \,^{\circ}$ C, the desired product **3a** was achieved in 94% isolated yield within 15 min (Table 1, entry 6). During the course of the reaction, product **3a** was precipitated which was then diluted with diethyl ether (4 mL) and filtered to get the pure product **3a** confirmed by ¹H, ¹³C NMR, and MS that match with the reported literature values.^{14a} The reaction proceeded less efficiently in other solvents such as methanol and isopropyl alcohol (Table 1, entries 7 and 8). A reduction in yield of **3a** was observed while removing solvent from the reaction (Table 1, entry 9). Thus, the optimized reaction condition was established as: **1** (1 equiv.) and **2a** (1.05 equiv.) in EtOH at 65 °C for 15 min (Table 1, entry 6).

With the optimized condition in hand, we decided to evaluate the efficiency and versatility of this methodology. As shown in Table 2, this was generalized using various aromatic, heteroaromatic, and aliphatic aldehyde derived MBH carbonates as electrophiles (2a-2p) with 2-aminopyridine (1). A range of functional groups was tolerated with good to excellent yields and selectivity. It was found that halogen, electron-donating groups (EDG), and electron-withdrawing groups (EWG), such as *p*-Br, *p*-MeO, *p*-CF₃, *m*-Cl, *m*-CN, *o*-F, *o*-Cl, and *o*-Me were very well tolerated under the reaction condition, leading to the corresponding products 3b-3i in 70–98% yields. Polysubstituted allylic carbonates 2j and 2k gave the corresponding cycloadducts 3j and 3k in yields of 75 and 87%, respectively. Also, other heterocycles like pyridine (2l), *N*methyl pyrazole (2m), thiophene (2n), and thiazole (2o) at R were very well tolerated to give desired products (3l-o) in excellent yields (70–82%). It is noteworthy to mention that several MBH carbonates having heteroaryls (2l-o) worked highly efficiently under the reaction condition and provide first-in-class examples in this area. In addition, the

4 👄 S. B. INTURI ET AL.

Table 2. Substrate scope of diverse MBH carbonates^{a,b}.



^aReaction conditions: 1 (0.5 mmol) and 2a-p (0.53 mmol) in EtOH (0.8 mL) at 65 °C for 15 min.
^bIsolated yields based on 1.

^cThis reaction was performed on a 1.0 g scale.

^dReaction was continued at 65 °C for 4 h.

scope of this methodology worked well with cycloalkyl MBH carbonate (2p) giving the desired fused pyrimidine compound (3p) in 65% yield. The reaction performed on a 1g scale with 2f was reproducible and yielded 95% of 3f.

To further explore the synthetic potential of this protocol, several substituted 2-aminopyridines (1a-1k), 3-aminopyridazines (11 and 1m) and 8-aminonapthridine (1n) based substrates as nucleophiles were investigated under the optimized reaction condition. The results of our studies are summarized in Table 3. Importantly, the pyridine ring bearing halogen substituents such as F (1h) and Br (1d, 1i) groups were compatible with this reaction, leading to the corresponding fused pyrimidones 5h, 5d, and 5i in 60–74% yields, which provide an access for further modifications. 2-Aminopyridine ring bearing EDG (-Me, -OMe) reacted efficiently with electrophile (2a) to give the desired products 5a-5c, 5f and 5g in 68-90% yields, respectively. Subsequently, EWG (-COOEt, -COOMe) on 2-aminopyridine ring (1e and 1j) could react with MBH carbonate (2a) smoothly to generate the desired products 5e and 5j in moderate yields. Disubstitueed





 a Reaction conditions: 1a–n (0.5 mmol) and 2a (0.53 mmol) in EtOH (0.8 mL) at 65 $^\circ C$ for 15 min. b Isolated yields based on 1.

2-aminopyridine (1k) was converted to the desired product 5k in 70% yield. Furthermore, the reaction of substituted 3-aminopyridazine as nucleophile (1l and 1m) with allylic carbonate (2a) proceeded very well and generated the desired products 5l and 5m in 72 and 70% yields, respectively. It is worth noting that 1,7-naphthyridin-8-amine (1n) can be tolerated in this reaction affording product (5n) in 45% yield.

The advantage of the described method compared to the reported ones in the literature was summarized in Table 4. The careful comparison between the yields derived from using MBH acetates^[14a,b,15] versus MBH carbonates revealed that the Boc group facilitated the reaction in a much better way than the acetate group.

To further evaluate the scope of this reaction, diversely substituted nucleophiles (1e, 1i, 1k, 1l, and 1o) with the MBH derived Michael acceptors (2l-o) were examined under the standard condition as shown in Table 5. Particularly these derivatives (Table 5, 6a-h) can be used as excellent precursors for bioactive molecules.

6 🕒 S. B. INTURI ET AL.

Entry	Compound	MBH acetate/ Yield (literature reported) (%)	MBH carbonate/ Yield (current method) (%)
1	3a	77 ^{14a}	94
2	3b	86 ^{14b}	89
3	3с	56 ^{14a}	84
4	3i	79 ^{14a}	96
5	5a	86 ¹⁵	90
6	5i	68 ^{14b}	74

Table 4. Yield comparison between MBH acetates and MBH carbonates.







^cThis reaction was performed on a 1.0 g scale.

These results indicate that the reaction underwent smoothly to generate the desired fused pyrimidone products 6a-h in excellent yields.

In Scheme 1, it is proposed that the Michael addition of pyridine nitrogen of 2-aminopyridine (1) onto the olefinic double bond of allylic carbonate (2) generates the transient intermediate A, which undergoes an elimination of carbon dioxide and *tert*-butanol *via* intermediate B to give the iminopyridine acrylate C. A subsequent intramolecular acyl substitution followed by 1,3-hydrogen shift would give the desired fused pyrimidone G.



Scheme 1. Proposed reaction pathway for the formation of fused pyrimidones.

Conclusion

In summary, we have developed a highly efficient one-pot cyclocondensation reaction for synthesis of structurally diverse 3-substituted-2H-pyrido[1,2-a]pyrimidin-2-ones and related fused pyrimidone derivatives. The reaction is environmentally benign, operationally simple, cost-effective, diverse, and have broad functional group tolerance giving good to excellent yields and selectivity. Importantly, the reaction can be readily scaled up to gram quantities, offering good practicality.

Experimental

General experimental methods

All chemicals and solvents were purchased from commercial suppliers and used without further purification. Solvents were used without drying. The MBH carbonates **2** were synthesized according to the reported procedure.^[17] ¹H and ¹³C NMR spectra were recorded at 400 and 100.5 MHz on Varian NMR spectrometer with DMSO- d_6 as solvent. Chemical shifts were reported in δ ppm using residual solvent protons as internal standard (δ 2.48 ppm for DMSO- d_6 in ¹H-NMR and δ 40.0 ppm for DMSO- d_6 in ¹³C-NMR). Coupling constants (J) were reported in Hz and refer to apparent peak multiplicity. The peak splitting patterns were indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; td, triplet of doublets; and tt, triplet of triplets. High resolution mass spectra were obtained on WATERS Q-TOF Premier-HAB213 spectrometer in ESI mode. Melting points were recorded using Buchi melting point apparatus and temperatures were uncorrected. Thin layer chromatography was performed on aluminum plates coated with silica gel 60 with F254 indicator.

General procedure for the synthesis of compounds 3a-3p, 5a-5n, and 6a-6h

To a stirred solution of 2-heteroaryl amine (0.5 mmol, 1 equiv.) and MBH carbonate (0.53 mmol, 1.05 equiv.) in ethanol (0.8 mL) was heated at $65 \degree$ C for 15 min. During the

8 🕒 S. B. INTURI ET AL.

course of the reaction, product was precipitated which was then diluted with diethyl ether (4 mL) and filtered to get the pure product.

In case of **3p**, reaction was continued to stir at $65 \,^{\circ}$ C for 4 h. After this time, ethanol was evaporated under reduced pressure; the obtained solid was diluted with diethyl ether (2 mL) and filtered to get the pure product.

3-Benzyl-2H-pyrido[1,2-a]pyrimidin-2-one (3a)^[14a]

White solid; Yield: 111 mg, 94%; M.p.: 219–221 °C (lit: 218–220 °C); ¹H NMR (400 MHz, DMSO- d_6): δ 8.19 (s, 1H), 8.14 (d, J=6.4 Hz, 1H), 7.63 (tt, J=6.8, 2.0 Hz, 1H), 7.30–7.25 (m, 4H), 7.21–7.16 (m, 1H), 7.13 (d, J=9.2 Hz, 1H), 6.91 (td, J=6.4, 0.8 Hz, 1H), 3.72 (s, 2H); ¹³C NMR (100.5 MHz, DMSO- d_6): δ 167.6, 151.1, 139.2, 136.8, 136.6, 134.4, 129.3, 128.7, 127.9, 126.6, 122.9, 113.0, 34.1. ESI-MS [M+H]⁺ m/z 237.1. All other characterization data and spectra of compounds are given in supplementary data.

Acknowledgments

The authors sincerely thank the Senior Management of Jubilant Biosys Ltd. for providing the facilities to conduct this research work and also thankful to the Management of Jamal Mohamed College.

Disclosure statement

The authors declare no competing financial interest.

References

- (a) Khorana, H. G. Chemical Biology; World Scientific: London, 2000; Vol. 5, Chapter 2, pp 31–41. (b) Jezewski, A.; Jurczak, J.; Lidert, Z.; Tice, C. M. J. Heterocycl. Chem 2001, 38, 645–648. (c) Seager, S. L.; Slabaugh, M. R. Chemistry for Today: General, Organic and Biochemistry, 4th ed.; Brooks/Cole: UK, 2000; pp 649–681. (d) Mai, A.; Artico, M.; Sbardella, G.; Quartarone, S.; Massa, S.; Loi, A. G.; Montis, A. D.; Scintu, F.; Putzolu, M.; Colla, P. L. J. Med. Chem. 1997, 40, 1447–1454.
- [2] (a) Jeanmart, S.; Edmunds, A. J.; Lamberth, C.; Pouliot, M. Bioorg. Med. Chem. 2016, 24, 317–341. (b) Chen, D. C.; Su, S. J.; Cao, Y. J. Mater. Chem. C. 2014, 2, 9565–9578. (c) Li, J. J. Heterocyclic Chemistry in Drug Discovery; John Wiley & Sons: Hoboken, N.J., 2013. (d) Liu, M.; Su, S. J.; Jung, M. C.; Qi, Y. B.; Zhao, W. M. Kido. J. Chem. Mater. 2012, 24, 3817–3827.
- [3] (a) Yu, G.; Zhou, G.; Zhu, M.; Wang, W.; Zhu, T.; Gu, Q.; Li, D. Org. Lett. 2016, 18, 244–247. (b) Rebhun, J. F.; Roloff, S. J.; Velliquette, R. A.; Missler, S. R. Fitoterapia. 2015, 101, 57–63. (c) Huang, G.; Roos, D.; Stadtmüller, P.; Decker, M. Tetrahedron Lett. 2014, 55, 3607–3609. (d) Schramm, A.; Hamburger, M. Fitoterapia. 2014, 94, 127–133. (e) Rapolu, S.; Alla, M.; Ganji, R. J.; Saddanapu, V.; Kishor, C.; Bommena, V. R.; Addlagatta, A. Med. Chem. Commun. 2013, 4, 817–821.
- [4] (a) Smith, R. L.; Barrett, R. J.; Sanders-Bush, E. J Pharmacol. Exp. Ther. 1995, 275, 1050–1057. (b) Matsutani, S.; Mizushima, Y. Eur. Pat. Appl. EP 89–102635 19890216, 1989. (c) Yanagihara, Y.; Kasai, H.; Kawashima, T.; Shida, T. Jpn. J. Pharmacol. 1988, 48, 91–101. (d) Awouters, F.; Vermeire, J.; Smeyers, F.; Vermote, P.; Van Beek, R.; Niemegeers, C. J. E. Drug Dev. Res. 1986, 8, 95–102. (e) Gohda, T.; Ra, C.; Hamada, C.;

Tsuge, T.; Kawachi, H.; Tomino, Y. Arzneimittelforschung. 2008, 58, 18–23. (f) Corena-McLeod, M. Drugs R&D. 2015, 15, 163–174.

- [5] Blazer, L. L.; Roman, D. L.; Chung, A.; Larsen, M. J.; Greedy, B. M.; Husbands, S. M.; Neubig, R. R. Mol. Pharmacol. 2010, 78, 524–533.
- [6] Ni, J.; Liu, Q. S.; Xie, S. Z.; Carlson, C.; Von, T.; Vogel, K.; Riddle, S.; Benes, C.; Eck, M.; Roberts, T.; et al. *Cancer Discov.* 2012, *2*, 425–433.
- [7] Le, G.; Vandegraaff, N.; Rhodes, D. I.; Jones, E. D.; Coates, J. A.; Lu, L.; Li, X.; Yu, C.; Feng, X.; Deadman, J. J. Bioorg. Med. Chem. Lett. 2010, 20, 5013–5018.
- [8] Peng, L.; Gao, X.; Duan, L.; Ren, X.; Wu, D.; Ding, K. J. Med. Chem. 2011, 54, 7729-7733.
- [9] Silpa, L.; Niepceron, A.; Laurent, F.; Brossier, F.; Penichon, M.; Enguehard-Gueiffier, C.; Abarbri, M.; Silvestre, A.; Petrignet, J. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 114–120.
- [10] La Motta, C.; Sartini, S.; Mugnaini, L.; Simorini, F.; Taliani, S.; Salerno, S.; Marini, A. M.; Da Settimo, F.; Lavecchia, A.; Novellino, E.; et al. *J. Med. Chem.* 2007, 50, 4917–4927.
- [11] (a) Mane, U. R.; Mohanakrishnan, D.; Sahal, D.; Murumkar, P. R.; Giridhar, R.; Yadav, M. R. *Eur. J. Med. Chem.* 2014, 79, 422–435. (b) Mane, U. R.; Li, H.; Huang, J.; Gupta, R. C.; Nadkarni, S. S.; Giridhar, R.; Naik, P. P.; Yadav, M. R. *Bioorg. Med. Chem.* 2012, 20, 6296–6304.
- [12] (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. Chem. Rev. 2010, 110, 5447-5674. (b) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. Bull. Korean Chem. Soc. 2005, 26, 1481-1490. (c) Kim, J. N.; Lee, K. Y. Curr. Org. Chem. 2002, 6, 627-645. (d) Basavaiah, D.; Dharma Rao, P.; Hyma, R. S. Tetrahedron. 1996, 52, 8001-8062.
- [13] (a) Katritzky, A. R.; Rogers, J. W.; Witek, R. M.; Nair, S. K. Arkivoc. 2004, 2004, 52-60.
 (b) Chichetti, S. M.; Ahearn, S. P.; Adams, B.; Rivkin, A. Tetrahedron Lett. 2007, 48, 8250-8252. (c) Weng, Y. Y.; Ying, L. M.; Chen, Q. X.; Su, W. K. Chin. Chem. Lett. 2012, 23, 911-914. (d) Alanine, T. A.; Galloway, W. R.; Bartlett, S.; Ciardiello, J. J.; McGuire, T. M.; Spring, D. R. Org. Biomol. Chem. 2016, 14, 1031-1038.
- [14] (a) Basavaiah, D.; Satyanarayana, T. Tetrahedron Lett. 2002, 43, 4301–4303. (b) Sreevani, R.; Manjula, A.; Rao, B. V. J. Heterocycl. Chem. 2011, 48, 586–591. (c) Shahrisa, A.; Ghasemi, Z. Chem. Heterocycl. Compd. 2010, 46, 30–36.
- [15] Satyanarayana, S.; Praveen Kumar, K.; Lakshmi Reddy, P.; Narender, R.; Narasimhulu, G.; Subba Reddy, B. V. *Tetrahedron Lett.* 2013, 54, 4892–4895.
- [16] Alsharif, Z.; Ali, M. A.; Alkhattabi, H.; Jones, D.; Delancey, E.; Ravikumar, P. C.; Alam, M. A. New J. Chem. 2017, 41, 14862–14870.
- [17] Roy, S. J. S.; Mukherjee, S. Chem. Commun. (Camb). 2014, 50, 121-123.