HETEROCYCLES, Vol. 65, No. 4, 2005, pp. 767 - 773
Received, 22nd October, 2004, Accepted, 7th February, 2005, Published online, 8th February, 2005

A ONE-POT SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2-(1*H*)-ONES FROM PRIMARY ALCOHOLS PROMOTED BY $Bi(NO_3)_3.5H_2O$ IN TWO DIFFERENT MEDIA: ORGANIC SOLVENT AND IONIC LIQUID

Ahmad R. Khosropour,* Mohammd M. Khodaei,* Mojtaba Beygzadeh, and Mahbubeh Jokar

Department of Chemistry, Faculty of Science, Razi University, Kermanshah 67149, Iran Tel.: +98-831-427-4559; fax: +98-831-427-4559; e-mail: arkhosropour@razi.ac.ir or mmkhoda@razi.ac.ir

Abstract – A new, simple and efficient procedure for the one-pot conversion of alcohols instead of aldehydes to the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) with $Bi(NO_3)_3.5H_2O$ as a commercially available, inexpensive, stable and non-toxic reagent in two media, acetonitrile (as an organic solvent) and tetrabutylammonium bromide (as an ionic liquid) is described. This one-pot oxidation-cyclocondensation reaction is performed without isolation of any intermediate (aldehyde) and thus reducing time, saving energy and raw materials. On the other hand treatment of primary alcohols with this new one-pot method produce the dehydropyrimidinones in higher yields than those are obtained in the traditional method.

INTRODUCTION

One of the strategies for combination of economic aspects with the environmental ones is the multicomponent reaction. This process consists of two or more synthetic steps, which are performed without isolation of any intermediates thus reducing time, saving energy and raw materials. In the past decade there have been tremendous developments in three and four component reactions and great efforts have been and still are being made to find and develop new multicomponent reactions.[1] One of the most attractive three component condensation is Biginelli reaction that has been widely used for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives[2] with important therapeutic and pharmacological behaviors such as HIV gp-120-CD4 inhiditors,[3] calcium channel blockers, α-adrenergic and neuropeptide Y antagonists,[4] antihypertensive agents,[5] antitumor, antibacterial and anti-inflammatory activity.[6] The scope of this pharmacophore has been further increased by the identification of monastrol as a novel

cell-permeable lead molecule for the development of new anticancer drugs that containing a dihydropyrimidinone core.[7] Thus the development of facile and environmentally friendly synthetic methods towards dihydropyrimidinones, constitutes an active area of investigation in organic synthesis. The most well-known method for the preparation of these compounds (Biginelli reaction) limits to the direct condensation of aldehydes as a precursor with β-dicarbonyls and urea in the presence of different Lewis acids.[8-10] Therefore, expansion of this method which can be applied to a number of substrates with different natures, from the viewpoint of total synthesis for the preparation of new dihydropyrimidinone derivatives, is highly desirable.

RESULTS AND DISCUSSION

In 1985, Ireland and co-worker reported a one-pot scheme in which an aldehyde was generated using Swern oxidation conditions from alcohols and trapped in situ by the Wittig reagent.[11] This procedure alleviated the necessity of isolating the intermediate aldehyde and vastly improved the yield. In the course of our work on the ability of Bi(III) salts,[12] we found the oxidative[13] and catalytic behaviors[14] of $Bi(NO_3)_3$. $5H_2O$ in organic transformations. These results prompted us to focus our work on the using of primary alcohols instead of aldehyde in Biginelli reaction.

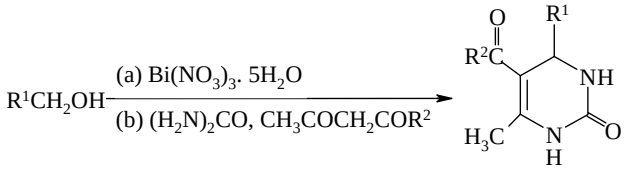
Two paths can be considered for the conversion of primary alcohols to their dihydropyrimidinones: **Path 1** (traditional manner) that containing of: (1) oxidation of the alcohols to their aldehydes (2) isolation of the aldehydes (3) purification of the aldehydes and (4) utility of the aldehydes in the condensation reaction.

However, in **path 2**, these steps can be done in one-pot transformation (a short cut manner) and the intermediate aldehyde trapped without isolation. This procedure alleviated the necessity of isolating the intermediate aldehyde and vastly improved the yield.

To investigate the utility of $Bi(NO_3)_3.5H_2O$ in a one-pot reaction, benzyl alcohol was treated with $Bi(NO_3)_3.5H_2O$ followed immediately by addition of ethyl acetoacetate and urea at reflux conditons. Regardless of reaction times, no dihydropyrimidinone was achieved.

However, the alcohol with $Bi(NO_3)_3.5H_2O$ in acetonitrile in a traditional manner could be converted to the corresponding DHPM in 40 % yield (path 1). Next, with further investigation we found that true one-pot reaction was also possible. Benzyl alcohol was treated with $Bi(NO_3)_3.5H_2O$ in acetonitrile and allowed to react at reflux conditions. Once the oxidation was complete, as determined by TLC, the mixture of ethyl acetoacetate and urea was added and allowed to stir at 70 °C (path 2). Treatment of the alcohol with this new one-pot oxidation-cyclocondensation procedure led to a dramatic doubling of the yield (82 %) of the DHPMs as compared to the overall yield obtained in the traditional process where after oxidation of the alcohol, the aldehyde is isolated and purified before the subsequent cyclocondensation.

Therefore, we now report the development of methodology utilizing $Bi(NO_3)_3.5H_2O$ in the one-pot oxidation-cyclocondensation of alcohols to their DHPMs in acetoniltrile (Scheme 1, Method A).



R^1 = Alkyl or Aryl
$R^2 = CH_3$ or OC_2H_5
Method A = CH_3CN as solvent
Method B = TBAB as solvent

Scheme 1

To the best of our knowledge no report is available in the literature using primary alcohols as precursors for Biginelli reaction. The generality of this process was demonstrated by the wide range of primary alcohols. This method is a short cut for conversion of primary alcohols to their dihydropyrimidinones (Table 1).

Table 1. Formation of dihydropyrimidinones[a] from primary alcohols with $Bi(NO_3)_3.5H_2O$ in CH_3CN (Method A)

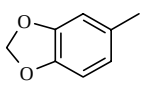
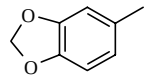
Entry	R^1	R^2	Time(min)[b]	Yield /%	Ref.
1	C_6H_5	OC_2H_5	40	82	14
2	*p*-$CH_3OC_6H_4$	OC_2H_5	30	91	14
3	*m*-$CH_3OC_6H_4$	OC_2H_5	85	79	9
4	*p*-HOC_6H_4	OC_2H_5	90	81	9
5	*o*-HOC_6H_4	OC_2H_5	100	78	9
6	*m*- HOC_6H_4	OC_2H_5	80	79	14
7	*p*- FC_6H_4	OC_2H_5	40	83	14
8	*p*- ClC_6H_4	OC_2H_5	100	89	14
9	*o*- ClC_6H_4	OC_2H_5	60	80	8
10	*o*- BrC_6H_4	OC_2H_5	90	77	8
11	2,4-$Cl_2C_6H_3$	OC_2H_5	100	84	14
12	*m*- $NO_2C_6H_4$	OC_2H_5	190	77	14
13	*p*- $NO_2C_6H_4$	OC_2H_5	210	76	14
14		OC_2H_5	105	70	9
15		OC_2H_5	100	80	8
16		OC_2H_5	140	78	9
17	C_6H_5	CH_3	45	83	14
18	*p*-$CH_3OC_6H_4$	CH_3	30	82	14

Table 1. (continued)

Entry	R^1	R^2	Time(min)[b]	Yield /%	Ref.
19	*m*-$CH_3OC_6H_4$	CH_3	40	70	9
20	*p*-HOC_6H_4	CH_3	40	72	9
21		CH_3	60	84	9
22	*p*- FC_6H_4	CH_3	40	89	9
23	*o*- ClC_6H_4	CH_3	65	70	9
24	*o*- BrC_6H_4	CH_3	30	91	9
25	2,4-$Cl_2C_6H_3$	CH_3	60	79	9
26	$CH_3(CH_2)_3CH_2$	CH_3	30	90	9
27	$CH_3(CH_2)_2CH_2$	CH_3	30	92	9
28	$CH_3(CH_2)_3CH_2$	OC_2H_5	25	93	9
29	$CH_3(CH_2)_2CH_2$	OC_2H_5	30	91	9

[a] All products were characterized with ^1H NMR, ^{13}C NMR, IR spectra and comparison of their physical and spectral data with those samples in the literatures; [b] Total time (oxidation + cyclocondensation reactions)

As shown in Table 1, one-pot treatment of a variety of primary alkyl or aryl alcohols with $Bi(NO_3)_3.5H_2O$ in acetonitrile afforded the corresponding DHPMs in good to high yields. The use of large amounts of $Bi(NO_3)_3.5H_2O$ is also found to be not fruitful and does not increase the yields.

In this procedure several functional groups like chloro, bromo, hydroxyl, methoxy and nitro on aryl alcohols do survive during the course of the reaction (Table 1, Entries 1-25). Acid sensitive alcohols such as piperonyl alcohol also work well without the formation of any side products (Table 1, Entries 14, 21).

Interestingly we found that primary aliphatic alcohols were produced DHPMs in excellent yields (Table 1, Entries 26-29) against to the alkyl aldehydes that we did not achieve these products previously.[14]

Due to the growth in interest for using of ionic liquid as novel reaction media,[15] and as a part of our research on utility of tetrabutyl ammonim bromide (TBAB) as an ionic liquid in organic transformation,[18] we were also interested to carry out this reaction in a one-pot manner using $Bi(NO_3)_3.5H_2O$ immobilized on TBAB (Scheme 1, Method B).

The experimental procedure for this transformation is remarkably straightforward and does not require the use of toxic organic solvents or inert atmospheres. We have found that treatment of primary benzyl alcohols, carrying either electron-withdrawing or electron-donating groups, afforded the dihydro-pyrimidinones in high yields in short reaction times (Table 2). Another important aspect is that various functionalities such as ether, halide, nitro, etc., survived under the present reaction conditions. On the other hand acid-sensitive groups such as cinnamyl alcohol are also reacted in high yields without the formation of any side products (Table 2, Entry 6). However, under the same reaction conditions, primary aliphatic alcohols such as 1-propanol reacted sluggishly and the product yield was much lower than those obtained with benzylic alcohols (Table 2, Entry 20). Also it was found that $Bi(NO_3)_3.5H_2O$-TBAB (Method

B) was a more effective (both in reaction times and yields of the products) than $Bi(NO_3)_3.5H_2O$-CH_3CN (Method A) in the one-pot transformation of benzyl alcohols to their DHPMs.

Table 2. Formation of dihydropyrimidinones[a] from primary alcohols with $Bi(NO_3)_3.5H_2O$-TBAB (Method B)

Entry	R^1	R^2	Time (min)[b]	Yield /%	Ref.
1	C_6H_5	OC_2H_5	20	97	14
2	*p*-$CH_3C_6H_4$	OC_2H_5	20	96	14
3	*p*-$CH_3OC_6H_4$	OC_2H_5	20	94	14
4	*p*-HOC_6H_4	OC_2H_5	22	84	9
5	*o*-HOC_6H_4	OC_2H_5	65	80	9
6	$C_6H_5CH=CH$	OC_2H_5	30	85	14
7	*p*- FC_6H_4	OC_2H_5	30	93	14
8	*p*- ClC_6H_4	OC_2H_5	30	86	14
9	*o*- ClC_6H_4	OC_2H_5	55	80	8
10	*o*- BrC_6H_4	OC_2H_5	50	79	8
11	2,4-$Cl_2C_6H_3$	OC_2H_5	55	84	14
12	*p*- $NO_2C_6H_4$	OC_2H_5	100	93	14
13	*m*- $NO_2C_6H_4$	OC_2H_5	115	82	14
14	*o*- $NO_2C_6H_4$	OC_2H_5	135	80	14
15	*p*-$CH_3C_6H_4$	OCH_3	20	92	14
16	*p*- FC_6H_4	OCH_3	32	88	9
17	*p*- ClC_6H_4	OCH_3	33	81	14
18	2,4-$Cl_2C_6H_3$	OCH_3	60	76	9
19	*p*- $NO_2C_6H_4$	OCH_3	100	86	14
20	$CH_3(CH_2)_2CH_2$	OCH_3	150	12	9

[a] All products were characterized with ^1H NMR, ^{13}C NMR, IR spectra and comparison of their

In conclusion, we have demonstrated for the first time a new, straightforward, efficient and environmentally friendly procedure for the one-pot conversion of primary alcohols to their dihydropyrimidinones under neutral conditions in two media. The reaction can be carried out conveniently and proceeds with good to high yield and purity. In addition, high chemoselectivity, easy work-up and using of low cost, low toxicity and easy handling of reagent, specially in the case of $Bi(NO_3)_3.5H_2O$-TBAB as a new and environmentally friendly oxidative-catalytic media, are worthy advantages of this method. On the other hand, this procedure would expand the tools available to chemists to perform Biginelli reactions on sensitive or volatile aldehydes.

EXPERIMENTAL

General Procedure for the Conversion of Primary Alcohols to Their Dihydropyrimidinones in Acetonitrile Promoted by $Bi(NO_3)_3.5H_2O$ (Method A)

To a solution of primary alcohol (1 mmol) in acetonitrile (2 mL) was added $Bi(NO_3)_3.5H_2O$ (0.63 g, 1.3 mmol) and the mixture was allowed to stir under reflux conditions as verified by TLC (usually 2-8 h). After the reaction was completed, urea (0.09 g, 1.5 mmol) and the β-dicarbonyl compound (2 mmol) were added and the reaction mixture was stirred under reflux conditions for the appropriate time according to Table 1. The progress of the reaction was monitored by TLC and after completion hot ethanol (10 mL) was added. The mixture was filtered and the filterate was cooled until the product was crystallized. The product was washed with a cooled mixture of (1:1) water/ethanol and then dried. The pure product was purified by recrystallization from ethanol (95%) in 70-93 % yields.

General Procedure for the Conversion of Primary Alcohols to Their Dihydropyrimidinones in Molten TBAB Promoted by $Bi(NO_3)_3.5H_2O$ (Method B)

To the mixture of primary alcohol (1 mmol) in molten TBAB (0.16 g, 0.5 mmol), $Bi(NO_3)_3.5H_2O$ (0.53 g, 1.1 mmol) was added. The reaction mixture was stirred at 50 ^oC for 5 min. After completion of the oxidation step, the β-dicarbonyl compound (1.2 mmol) and urea (0.09 g, 1.5 mmol) were added and the mixture was stirred magnetically at 90 ^{o} C for 15 min (the progress of the reaction was followed by TLC). When the reaction was completed, hot ethanol (20 mL) was added and the suspension was filtered. The filtrate was cooled until the product was crystallized. The solid product was separated and recrystallised from ethanol (95%) to afford the pure product (12-97%).

ACKNOWLEDGEMENTS

The authors thank the Razi University Research Council for the support of this work.

REFERENCES

1. H. Z. S. Huma, R. Halder, S. S. Kalra, J. Das, and J. Iqbal, *Tetrahedron Lett.*, 2002, **43**, 6485; M. C. Bagley, J. W. Cale, and J. Bower, *Chem. Commun.*, 2002, 1682; D. Dallinger, N. Y. Gorobets, and C. O. Kappe, *Org. Lett.*, 2003, **5**, 1205; U. Bora, A. Saikia, and R. C. Boruah, *Org. Lett.*, 2003, **5**, 435;
2. P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360; P. Wipf and A. Cunningham, *Tetrahedron. Lett.* 1995, **36**, 7819; A. Studer, P. Jeger, P. Wipf, and D. P. Curran, *J. Org. Chem.*, 1997, **62**, 2917; C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879.
3. B. Snider, J. Chen, A. D. Patil, and A. Freyer, *Tetrahedron Lett.*, 1996, **37**, 6977; A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertzberg, R. K. Johnson, J. W. Westley, and B. C. M. Potts, *J. Org. Chem.*,

1995, **60**, 1182.

4. G. C. Ronyar, S. D. Kinball, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang, and S. Moreland, *J. Med. Chem.*, 1995, **38**, 119.
5. G. J. Grover, S. Dzwonczyk, D. M. McMullen, C. S. Normadinam, P. G. Sleph, and S. J. Moreland, *J. Cardiovasc. Pharmacol.*, 1995, **26**, 289.
6. C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937 and references cited therein.
7. T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, and T. J. Mitchison, *Science*, 1999, **286**, 971.
8. X. Fan, X. Zhang, and Z. Yongmin, *J. Chem. Res. (S)*, 2002, 436; Ch. V. Reddy, M. Mahesh, P. V. K. Raju, T. R. Babu, and V. V. N. Reddy, *Tetrahedron Lett.*, 2002, **43**, 2657; J. Lu and Y. Bai, *Synthesis*, 2002, 466; T. Jin, S. Zhang, J. Guo, and T. Li, *J. Chem. Res. (S)*, 2002, 37.
9. P. Salehi, M. Dabiri, M. A. Zolfigol, and M. A. Bodagh Ford, *Tetrahedron Lett*., 2003, **44**, 2889; R. Varala, M. M. Alam, and S. R. Adapa, *Synlett*, 2003, 67; K. Kiran, G. S. Reddy, Ch. Srinivas Reddy, J. S. Yadav, and G. Sabitha, *Synlett*, 2003, 858. A. S. Paraskar, G. K. DewKar, and A. Sudalai, *Tetrahedron Lett.*, 2003, **44**, 3305; D. Subhas Bose, L. Fatima, and H. B. Mereyala, *J. Org. Chem.*, 2003, **68**, 587; K. R. Reddy, Ch. V. Reddy, M. Mahesh, P. V. K. Raju and V. V. N. Reddy, *Tetrahedron Lett*., 2003, **44**, 8173.
10. S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang, and Q. Zhuang, *Synlett*, 2004, 537; M. Gohain, D. Prajapati and J. S. Sandhu, *Synlett*, 2004, 235; D. S. Bose, R. K. Kumar, and L. Fatima, *Synlett*, 2004, 279.
11. R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198.
12. I. Mohammadpoor-Baltork, H. Aliyan, and A. R. Khosropour, *Tetrahedron*, 2001, **57**, 5851; I. Mohammadpoor-Baltork and A. R. Khosropour, *Monatsh. Chem.*, 2002, **133**, 189; M. M. Khodaei, A. R. Khosropour, and S. J. Hoseini Jomor, *J. Chem. Res. (S)*, 2003, **10**, 638; A. R. Khosropour, M. M. Khodaei, and K. Ghozati, *Chem. Lett*., 2004, 304; A. R. Khosropour, M. M. Khodaei, and M. Kookhazadeh, *Tetrahedron Lett.*, 2004, **45**, 1725.
13. M. M. Khodaei, I. Mohammadpoor-Baltork, and K. Nikoofar, *Bull. Korean Chem. Soc.*, 2003, **24**, 885.
14. M. M. Khodaei, A. R. Khosropour, and M. Beygzadeh, *Synth. Commun*., 2004, **34**, 1551.
15. A. R. Khosropour, M. M. Khodaei, and K. Ghozati, *Chem. Lett*., 2004, 1378; J. S. Yadav, B. V. S. Reddy, A. K. Basak, and A. Venkat Narsaiah, *Tetrahedron Lett*., 2003, **44**, 1047; B. Ganchegui, S. Bouquillon, F. Henin, and J. Muzart, *Tetrahedron Lett.*, 2002, **43**, 6641; B. C. Ranu, A. Das, and S. Samanta, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1520; K. Selvakumar, A. Zapt, and M. Beller, *Org. Lett.*, 2002, **4**, 3031.
16. M. M. Khodaei, A. R. Khosropour, and K. Ghozati, *Tetrahedron Lett.*, 2004, **45**, 3525; M. M. Khodaei, A. R. Khosropour, and M. Kookhazadeh, *Synlett*, 2004, 1980.