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Highly Convenient One-Pot Conversion of Aryl Acylals or Aryl Aldehyde Bisulfites into Dihydropyrimidones Using $Bi(NO_3)_3 \cdot 5H_2O$

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ABSTRACT: *A new, facile, and efficient one-pot deprotection–cyclocondensation method is presented for the Biginelli reaction from aryl acylals or aryl aldehyde bisulfites in the presence of catalytic amounts of $Bi(NO_3)_3 \cdot 5H_2O$ under solvent-free conditions. In addition, high levels of chemoselectivity for this synthesis have been achieved.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:684–687, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20352

INTRODUCTION

The increasing attention during the last decades for environmental protection has influenced both modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost while using nontoxic reagents, catalysts and solvents, or even better without solvents. One of the tools to combine economic aspects with the environmental ones is the multicomponent reaction strategy; this process consists of two or more synthetic steps, which are carried out without isolation of any intermediates thus reducing time, saving energy, and raw materials. As part of our program aimed at developing new selective and environment friendly methodologies for the preparation of fine chemicals, another catalytic 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) synthesis is reported.

RESULT AND DISCUSSION

The synthesis of DHPMs remains a great interest due to wide applications of such heterocycles in the pharmacological and biological sciences. Antihypertensive agents [1], calcium channel blockers [2], α-adrenergic [3], and neuropeptide Y antagonists [4] antitumor, antibacterial, and anti-inflammatory [5] behaviors are the properties of some DHPM derivatives. Recently, batzelladine alkaloids containing a dihydropyrimidinone-5-carboxylate core [6] have been found to be potent HIV-gp-120-CD4 inhibitors [7]. In addition, because these compounds are important as synthons in organic synthesis, the development of facile and environment friendly synthetic methods for dihydropyrimidones is an active area of investigation in organic synthesis. The most well-known route to DHPMs is the Biginelli method that involves the direct condensation of aldehydes with β-dicarbonyls and urea under Lewis acid conditions [8–14].

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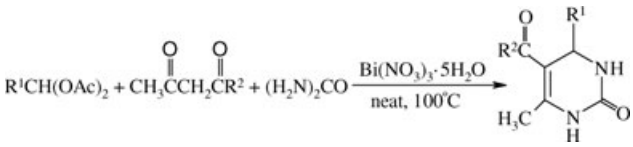
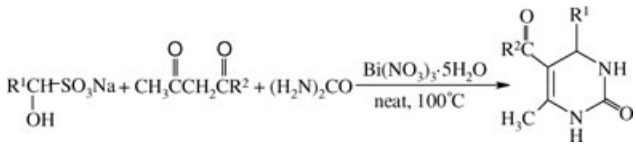


SCHEME 1



SCHEME 2

Acylals (geminal diacetates), because of their remarkable stability toward a variety of reaction conditions, have become important in organic synthesis as an alternative to acetals for the protection of aldehydes [15]. The majority of studies have aimed at their deprotection [16]; however, there are no reports on the deprotection–cyclocondensation reaction of acylals.

In many recent papers, the use of bismuth compounds in organic transformations is described as ecological friendly compounds [17]. In addition, bismuth derivatives have been widely used in medicine [18]. Most of bismuth salts have attracted attention because of their low toxicity, ease of handling, low cost, and relative insensitivity to air and small amounts of moisture [19]. In the course of our research on catalysis by Bi(III) salts [20], we report herein, for the first time, an efficient and environmentally benign method for the one-pot synthesis of 3,4-dihydropyrimidin-2-ones from aryl acylals, β-dicarbonyl compounds, and urea under solvent-free conditions (Scheme 1).

The experimental procedure for the synthesis of these compounds is straightforward and involves stirring of acylals with β-dicarbonyl compounds and urea in the presence of $Bi(NO_3)_3 \cdot 5H_2O$ at 100°C. Various substituted aromatic acylals reacted well to give the corresponding dihydropyrimidinones in 64–97% yields (Table 1). Interestingly, aromatic acylals with electron-donating groups gave comparatively better yields and reaction times than those with electron-withdrawing groups. Aliphatic acylals, such as 1,1-diacetoxypropane, did not give any products with the above-mentioned catalyst even after 3 h (Table 1, entry 20). Acid-sensitive substrates, such as cinnamyl acylals, reacted in high yields without the formation of any side products (Table 1, entry 7). This methodology is also compatible in the presence of other functional groups such as methoxy and nitro groups and alkene double bonds.

Bisulfite addition products are widely used for protection and purification of aldehydes, and the regeneration of the aldehyde can be performed by treatment of the addition product with mineral acid or base [21,22]. To extend the scope of $Bi(NO_3)_3 \cdot 5H_2O$ as a catalyst, the reaction with aldehyde bisulfites, as another protected form of aldehydes, was also investigated (Scheme 2).

We found that treatment of both electron-rich and electron-deficient aryl aldehyde bisulfite adducts with β-dicarbonyl compounds and urea in the presence of catalytic amounts of $Bi(NO_3)_3 \cdot 5H_2O$ provided the corresponding DHPMs in good to excellent yields (74–99%). The reaction time was usually short (10–45 min), and isolation of the product was straightforward (Table 2, entries 1–21). However, aliphatic bisulfites did not form the product under similar experimental conditions and remained unchanged (Table 2, entry 22). The experimental results show that electron-deficient aryl aldehyde bisulfites

TABLE 1 Formation of Dihydropyrimidinones[a] from Acylals Catalyzed by $Bi(NO_3)_3 \cdot 5H_2O$ under Solvent-Free Conditions

Entry	R^1	R^2	*Time (min)*	*Yield (%)*[b]
1	C_6H_5	OEt	10	97
2	4-$CH_3C_6H_4$	OEt	10	93
3	4-$CH_3OC_6H_4$	OEt	10	94
4	2,4-$(CH_3O)_2C_6H_3$	OEt	15	88
5	4-$(CH_3)_2NC_6H_4$	OEt	20	92
6	α-Naphthyl	OEt	20	95
7	$C_6H_5CH{=}CH$	OEt	30	91
9	4-ClC_6H_4	OEt	120	83
10	2,4-$Cl_2C_6H_3$	OEt	150	85
11	2-$NO_2C_6H_4$	OEt	180	66
12	3-$NO_2C_6H_4$	OEt	120	64
13	4-$NO_2C_6H_4$	OEt	100	68
14	4-$CH_3C_6H_4$	OMe	15	96
15	4-ClC_6H_4	OMe	120	70
16	C_6H_5	Me	20	85
17	4-$CH_3OC_6H_4$	Me	15	87
18	4-$NO_2C_6H_4$	Me	120	69
19	2-$NO_2C_6H_4$	Me	180	64
20	$CH_3CH_2CH_2$	OEt	180	0

[a]All products were characterized by comparison of their physical and spectral data with those of authentic samples.
Analytical data for 5-(ethoxycarbonyl)-6-methyl-4-styryl-3,4-dihydropyridin-2(1*H*)-one (entry 7): mp 233–234°C; ν_{max} (KBr): 3240, 1700, 1648 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.10 (s, 1H, NH), 7.50 (d, J = 1.9 Hz, 1H, NH), 7.18–7.43 (m, 5H, Ar), 6.34 (d, J = 15.9 Hz, 1H, H—C═CH), 6.18 (dd, J = 15.8, 6.0 Hz, 1H, CH═C—H), 4.73 (d, J = 5.80 Hz, 1H, CH), 4.06 (m, 2H, OCH_2), 2.18 (s, 3H, CH_3), 1.17 (t, J = 7.0 Hz, 3H, CH_3); δ_c (50 MHz, $CDCl_3$) 165.3, 152.4, 148.5, 136.0, 130.0, 128.5, 128.0, 127.3, 126.2, 97.7, 59.2, 51.7, 17.7, 14.2; HRMS calcd. for $C_{16}H_{18}N_2O_3$ 286.1346; found 286.1317.
[b]Isolated yields.

TABLE 2 Formation of Dihydropyrimidinones[a] from Aldehyde Bisulfites Catalyzed by $Bi(NO_3)_3{\cdot}5H_2O$ under Solvent-Free Conditions

Entry	R^1	R^2	*Time (min)*	*Yield (%)*[b]
1	C_6H_5	OEt	10	99
2	4-$CH_3C_6H_4$	OEt	20	86
3	4-$CH_3OC_6H_4$	OEt	10	96
4	2,4-$(CH_3O)_2C_6H_3$	OEt	10	93
5	4-$(CH_3)_2NC_6H_4$	OEt	15	97
6	2-HOC_6H_4	OEt	25	86
7	α-Naphthyl	OEt	25	84
9	$C_6H_5CH{=}CH$	OEt	35	83
10	4-FC_6H_4	OEt	20	92
11	4-ClC_6H_4	OEt	25	89
12	2,4-$Cl_2C_6H_3$	OEt	45	82
13	2-$NO_2C_6H_4$	OEt	25	83
14	3-$NO_2C_6H_4$	OEt	20	90
15	4-$NO_2C_6H_4$	OEt	10	94
16	4-$CH_3C_6H_4$	OMe	15	86
17	4-$NO_2C_6H_4$	OMe	15	91
18	C_6H_5	Me	20	84
19	4-$CH_3OC_6H_4$	Me	20	82
20	4- $NO_2C_6H_4$	Me	20	84
21	2- $NO_2C_6H_4$	Me	35	74
22	$CH_3CH_2CH_2$	OEt	180	3

[a]All products were characterized by comparison of their physical and spectral data with those of authentic samples.
[b]Isolated yields.

are more reactive than the corresponding acylals and work better in terms of reaction times and yields.

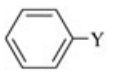
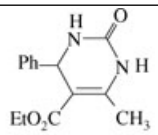
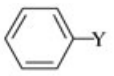
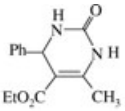
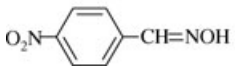
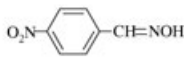
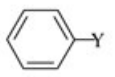
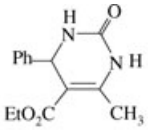
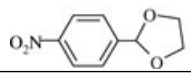
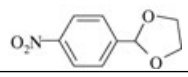
To explore further the synthetic utility of this procedure, the competitive deprotection–cyclocondensation of aryl acylals and aldehyde bisulfites in the presence of sensitive functional groups was also investigated (Table 3).

The net result was that the sensitive groups such as acetals, oximes, and aliphatic aldehydes were mostly intact and were stable under the described reaction conditions (Table 3, entries 1–3). In summary, we have demonstrated a new, efficient, and environment friendly method for the one-pot preparation of DHPMs from aryl acylals and aryl bisulfites with $Bi(NO_3)_3{\cdot}5H_2O$ as a low toxic, inexpensive, oxygen and moisture tolerant catalyst under solvent-free conditions. In addition, the high levels of chemoselectivity described in this report are another merit of this method.

GENERAL EXPERIMENTAL PROCEDURE

To a solution of aryl acylal or aryl bisulfite (1 mmol) and urea (1.5 mmol) in β-ketoester or β-diketone (2 mmol), $Bi(NO_3)_3{\cdot}5H_2O$ (0.25 mmol) was added. The

TABLE 3 Competitive Deprotection–Cyclocondensation of Aryl Acylals and Aryl Aldehyde Bisulfites in the Presence of $Bi(NO_3)_3{\cdot}5H_2O$[a] under Solvent-Free Conditions

			Yield (%)[b] */Time (min)*	
Entry	R^1	*Product*	*Y = CH(OAc)₂*	*Y = CH(OH)SO₃Na*
1			91 (10 min)	90 (10 min)
	$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2CHO$	100	100
2			95 (10 min)	92 (10 min)
			100	100
3			90 (10 min)	87 (10 min)
			100	97

[a]0.25 mmol.
[b]Isolated yields.

reaction mixture was stirred at 100°C for the appropriate time as described in Tables 1 and 2. After completion of the reaction, as indicated by TLC, ethanol (20 mL) was added, the mixture was filtered and cooled until the product crystallized. The product was washed with a mixture of (1:1) water/ethanol and then was dried. Pure product was obtained by recrystallization from ethanol in 64–99% yields.

REFERENCES

[1] Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. J Cardiovasc Pharmacol 1995, 26, 289.

[2] Ronyar, G. C.; Kinball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. J Med Chem 1995, 38, 119.

[3] (a) Nagarathnam, D.; Wong, W. C.; Miao, S. W.; Patance, M. A.; Gluchowski, C. PCT Int Appl WO 97 17 969, 1997; (b) Sidler, D. R.; Larsen, R. D.; Chartrain, M.; Ikemoto, N.; Roberg, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. PCT Int Appl WO 99 07 695, 1999.

[4] Bruce, M. A.; Pointdexter, G. S.; Johnson, G. PCT Int Appl WO 98 33 791, 1998.

[5] Kappe, C. O. Tetrahedron 1993, 49, 6937 and references cited therein.

[6] (a) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. J Am Chem Soc 1995, 117, 2657; (b) Snider, B.; Shi, Z. J Org Chem 1993, 58, 3828.

[7] (a) Snider, B.; Chen, J.; Patil, A. D.; Freyer, A. Tetrahedron Lett 1996, 37, 6977; (b) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Ports, B. C. M. J Org Chem 1995, 6, 1182.

[8] (a) Rama Rao, A. V.; Gujar, M. K.; Vasudevan, J. J Chem Soc Chem Commun 1995, 1369; (b) Snider, B. B.; Chen, J.; Patai, A. D.; Freyer, A. Tetrahedron Lett 1996, 37, 6977; (c) Kappe, C. O.; Falsone, S. F. Synlett 1998, 718.

[9] (a) Ranu, B. C.; Hajra, A.; Jana, U. J Org Chem 2000, 65, 6270; (b) Yun, M.; Changtao, Q.; Limin, W.; Min, Y. J Org Chem 2000, 65, 3864; (c) Lin, H.; Ding, J.; Chen, X.; Zhang, Z. Molecules 2000, 5, 1240; (d) Lu, J.; Ma, H. Synlett 2000, 63; (e) Yadav, J. S.; Subba, B. V.; Reddy, E.; Reddy, J.; Ramalingam, T. J Chem Res (S) 2000, 354; (f) Stefani, H. A.; Gatti, P. M. Synth Commun 2000, 30, 2165.

[10] (a) Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Venugopal, C.; Ramalingam, T. Synthesis 2001, 1341; (b) Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. Tetrahedron Lett 2001, 42, 7873; (c) Peng, J.; Deny, Y. Tetrahedron Lett 2001, 42, 5917; (d) Dondoni, A.; Massi, A. Tetrahedron Lett 2001, 42, 7975.

[11] Fan, X.; Zhang, X.; Yongmin, Z. J Chem Res (S) 2002, 436.

[12] (a) Reddy, Ch. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. Tetrahedron Lett 2002, 43, 2657; (b) Lu, J.; Bai, Y. Synthesis 2002, 466; (c) Jin, T.; Zhang, S.; Guo, J.; Li, T. J Chem Res (S) 2002, 37.

[13] Varala, R.; Alam, M. M.; Adapa, S. R. Synlett 2003, 67.

[14] Kiran, K.; Reddy, G. S.; Srinivas Reddy, Ch.; Yadav, J. S.; Sabitha, G. Synlett 2003, 858.

[15] Kochhar, K. S.; Bal, B. S.; Deshpande, R. P.; Rajadhyaksha, S. N.; Pinnick, H. W. J Org Chem 1983, 48, 1765.

[16] (a) Zhang, Z. H.; Li, T. S.; Fu, C. G. J Chem Res (S) 1997, 174; (b) Li, T. S.; Zhang, Z. H.; Gao, Y. J. Synth Commun 1998, 28, 4665; (c) Karimi, B.; Maleki, J. J Org Chem 2003, 68, 4952.

[17] (a) Cunha, S. B.; Lima, R.; Souza, A. R. Tetrahedron Lett 2002, 43, 49; (b) Keramane, E. M.; Boyer, B.; Roque, J. P. Tetrahedron 2001, 57, 1909; (c) Keramane, E. M.; Boyer, B.; Roque, J. P. Tetrahedron Lett 2001, 42, 855; (d) Laurent-Robert, H.; Dubac, J. Synlett 1998, 1138; (e) Anderson, A. M.; Blazek, J. M.; Garg, P.; Payne, B. J.; Mohan, R. S. Tetrahedron Lett. 2000, 41, 1527.

[18] Wilkinson, G.; Gillard, R. D.; McCleverty, J. A. (Eds.) Comprehensive Coordination Chemistry; Pergamon Press: London, 1987; Vol. 3, pp. 292–313.

[19] (a) Reglinski, J. In Chemistry of Arsenic, Antimony and Bismuth; Norman, N. C. (Ed.); Blackie Academic and Professional: New York, 1998; pp 403–440; (b) Marshall, J. A. Chemtracts 1997, 1064; (c) Suzuki, H.; Ikegami, T.; Matano, Y. Synthesis 1997, 249; (d) Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. J Org Chem 2000, 65, 8399; (e) Srivastava, N.; Banik, B. K. J Org Chem 2003, 68, 2109.

[20] (a) Mohammadpoor-Baltork, I.; Khosropour, A. R. Monatsh Chem 2002, 133, 189; (b) Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. Tetrahedron 2001, 57, 5851; (c) Mohammadpoor-Baltork, I.; Khosropour, A. R. Molecules 2001, 6, 996; (d) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Aliyan, H. J Chem Res (S) 2001, 780; (e) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Aliyan, H. Synth Commun 2001, 22, 3411; (f) Mohammadpoor-Baltork, I.; Khodaei, M. M.; Nikoofar, K. Tetrahedron Lett 2003, 44, 591.

[21] (a) Vogel, A. I. Textbook of Practical Organic Chemistry, 4th ed.; ELBS and Longman: London, 1978; pp 761; (b) Soffer, M. D.; Bellis, M. P.; Gellerson, H. E.; Stewart, R. A. Org Synth; Wiley: New York, 1992; Vol. 4, p. 903.

[22] (a) Kjell, D. P.; Slattery, B. J.; Semo, M. J. J Org Chem 1999, 64, 5722; (b) Mitra, A. K.; Aparna, D.; Karchaudhuri, N. J Chem Res (S) 1999, 560.