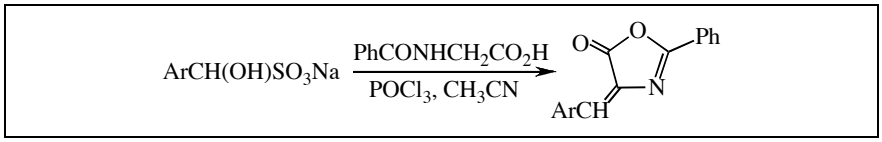
A New, Efficient and Chemoselective One-Pot Protocol for Synthesis of 4-Arylidene-2-phenyl-5(4*H*)-oxazolones from Aryl Aldehyde Bisulfite Adducts Promoted by $POCl_3$

Ahmad R. Khosropour,*[a] Mohammad M. Khodaei,[b] and Seyed J. Hoseini Jomor[b]

[a]Catalysis Division, Department of Chemistry, University of Isfahan, Isfahan 81746-73441, Iran
[b]Department of Chemistry, Faculty of Science, Razi University, Kermanshah 67149, Iran

Received March 5, 2007



A one-pot procedure for the synthesis of 4-arylidene-2-phenyl-5(4*H*)oxazolones directly from aryl aldehyde bisulfite adducts in the absence of Ac_2O in good to excellent yields using phosphoryl chloride is reported. In addition, the observed chemoselectivity can be considered as a noteworthy advantage of this method.

J. Heterocyclic Chem., **45**, 683 (2008).

INTRODUCTION

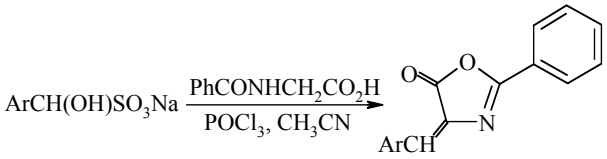
4-Arylidene-2-phenyl-5(4*H*)oxazolones (azlactones) and their derivatives, occupy an important place in the realm of biological and pharmaceutical sciences. They have served as versatile substrates to a variety of synthetic targets such as synthesis of peptides [1] and amino acids [2] or antitumor [3], antimicrobial [4], biosensor [5] or new heterocyclic compounds [6]. Hence, synthesis of this heterocyclic nucleus is of continuing interest.

The simple and direct method for the synthesis of the azlactones involves the one-pot condensation of an aldehyde and hippuric acid using anhydrous sodium acetate as a basic catalyst in acetic anhydride [7]. Alternative catalysts, including inorganic or organometallic compounds such as SO_3 in DMF [8], $Pb(OAc)_4$ [9], PPA [10], Al_2O_3-H_3BO_3 [11], supported KF [12], $ZnCl_2$ [13], $Bi(CH_3CO_2)_3$ [14] and $Ca(OAc)_2$ [15] were applied to improve the yield of the process. Also, we recently reported a practical procedure for the synthesis of azlactones catalyzed by $BiCl_3$, $Bi(TFA)_3$, and $Bi(NO_3)_3$ [16]. Although each of these methods has its own merit, the presence of acetic anhydride may cause side reactions such as esterification or acylation. Therefore replacement of acetic anhydride by other reagents is required. Aldehydes hold a central position in synthesis and sometimes they are difficult to isolate due to their volatility or sensitivity (hydrolyzation or polymerization) [17]. The exchange of this functional group for a more stable one is therefore desirable. Aldehyde bisulfite adducts are frequently used as protecting groups for aldehydes under basic conditions and due to their highly crystalline forms are extensively utilized [18]. Thus using these masked aldehyde forms directly could allow for more substituent variation.

RESULTS AND DISCUSSION

Recently, one-pot multicomponent reactions have attracted a great deal of interest due to the possibility of generating molecular diversity in a minimum number of steps [19]. As a part of our continuous interest directed towards the development of new methodologies for the synthesis of heterocyclic compounds [20], we report in preliminary form the results of our recent efforts devoted to the synthesis of functionalized azalactones. In this manuscript, we wish to report a new and efficient method for the one-pot synthesis of azalactones using aryl aldehyde bisulfite adducts in the presence of $POCl_3$ in the absence of acetic anhydride (Scheme I).

Scheme I



1 **2**

In order to determine the optimum reaction conditions, benzaldehyde bisulfite and hippuric acid were treated with phosphoryl chloride under various conditions (Table 1). Thus, treatment of 1 equiv. of benzaldehyde bisulfite with 1.1 equiv. of hippuric acid and 2 equiv. of $POCl_3$ in acetoniltrile (2 mL) for 20 min under reflux, resulted in the formation of the corresponding azlactone in 86% yield, with high purity.

Under similar conditions various substituted aromatic aldehyde bisulfite adducts carrying either electron-donating or –withdrawing substituents were converted to

Table 1

Reaction of Benzaldehyde Bisulfite Adduct and Hippuric Acid with Phosphoryl Chloride Under Various Conditions.

Entry	Solvent/Conditions	Equivalent of $POCl_3$	Time(min)	Yield (%)
1	Solvent-free/Δ	2	120	Nil
2	$CHCl_3$/reflux	2	120	4
3	CH_3CN/r.t.	2	120	9
4	CH_3CN/reflux	2	5	53
5	CH_3CN/reflux	2	10	74
6	CH_3CN/reflux	2	20	86
7	CH_3CN/reflux	1.5	60	69
8	CH_3CN/reflux	2.5	20	87

the azalactones in good to excellent yields and the results are summarized in Table 2.

In all cases, the reactions proceeded rapidly (7-30 min) with high efficiency (Table 2). The products were characterized from their ^{1}H-NMR, IR and mass spectra and also by comparison with authentic samples [7-15]. This method is clean and free from the side products which are normally observed under Bi(III) catalysts [16]. To the best of our knowledge, this is the first report of the preparation of azalactones in the absence of acetic anhydride. It is noteworthy that the existence of activated substitutents on the aromatic ring that in the traditional methods (using of catalyst/acetic anhydride system) may give a mixture of side products that were not detected under these reaction conditions while at the same time the purification of product were simplified.

Interestingly, we found that under the same reaction conditions, aryl aldehydes reacted sluggishly and the yield of products was much lower than those obtained with aryl aldehyde bisulfite adducts (Table 2, entries 1 and 9). On the other hand, aliphatic aldehyde bisulfites are inert toward $POCl_3$ during this transformation. For example, bisulfite of 2-phenylethanal did not provide the desired azalactone under similar reaction conditions. It seems necessary that the aldehyde bisulfite group should be activated by its α-substituents such as the phenyl ring for reaction to take place. The proposed mechanism of this process is shown in Scheme II.

This method was found to be highly chemoselective. In a binary mixture of aryl bisulfite adduct and aryl aldehydes or other protecting forms of aldehydes like acetals or acylals the aryl bisulfites were quantitatively converted to their azalactones while the aryl aldehydes, acetals or acylals remained intact (Table 3).

Table 2

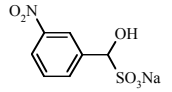
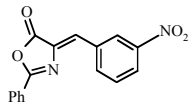
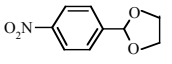
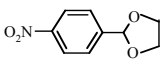
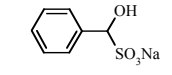
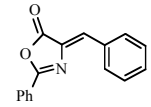
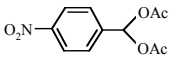
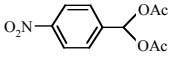
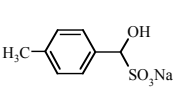
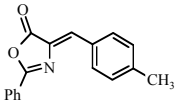
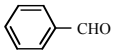
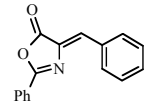
Synthesis of 4-arylidene-2-phenyl-5(4*H*)oxazolones from aryl aldehyde bisulfite adducts in the presence of $POCl_3$

	Ar [a]	Time min	Yield [b]	Mp (°C)	Mp (°C) [16]
2a	C_6H_5	20 (120) [c]	86 (5) [c]	165	168
2b	*p*-$CH_3C_6H_4$	10	89	141	143
2c	2,4-$(CH_3)_2C_6H_3$	10	88	149	152
2d	*p*-$CH_3OC_6H_4$	10	73	155	156
2e	2,5-$(CH_3O)_2C_6H_3$	25	85	170	167
2f	2,4-$(CH_3O)_2C_6H_3$	10	82	174	172
2g	*p*-$(CH_3)_2NC_6H_4$	7	96	210	213
2h	*o*-HOC_6H_4	30	68	173	171
2i	*p*-ClC_6H_4	15(120) [c]	95 (8) [c]	186	185
2j	*m*-ClC_6H_4	15	90	148	147
2k	2,4-$Cl_2C_6H_3$	20	89	188	189
2l	*o*-$O_2NC_6H_4$	15	91	152	152
2m	*m*-$O_2NC_6H_4$	15	96	164	165
2n	*p*-$O_2NC_6H_4$	15	90	238	241

[a] All products were characterized by ^{1}H-NMR, ^{13}C-NMR, IR and comparison of their physical and spectral data with those of literature samples [16]. [b] Isolated yield. [c] Achievement from aldehyde form.

Table 3

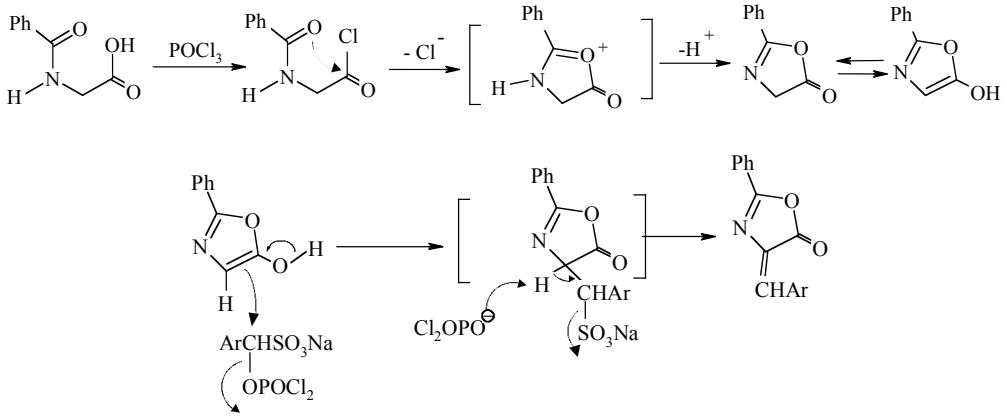
Competitive azlactone synthesis with aryl aldehyde bisulfite adducts in the presence of $POCl_3$

Entry	Substrates	Products	Yields (%) [a]
1 [b]			96
			100
2 [c]			86
			100
3 [d]			86
			0

[a] Isolated yield. [b] After 20 min. [c] After 25 min. [d] After 15 min.

In conclusion, we have demonstrated a new, clean, simple and chemoselective one-pot conversion of aryl aldehyde bisulfite adducts to their azlactones in good to excellent yields. Moreover, this procedure uses advantageously a more stable substrate than an aldehyde and replaces acetic anhydride by phosphorus oxychloride in traditional methods for azalactone synthesis.

Scheme II



EXPERIMENTAL

General Procedure for the Synthesis of 4-arylidene-2-phenyl-5(4*H*)oxazolones from aryl aldehyde bisulfite adducts in the presence of $POCl_3$. A mixture of aryl bisulfite **1** (1 mmol), phosphorus oxychloride (0.306 g, 2 mmol) and hippuric acid (0.197 g, 1.1 mmol) in CH_3CN (2 mL) was stirred and heated to reflux for the specified time (see Table II). After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and ethanol (5 mL) was added to it. It was stirred for 10 min until a yellow solid precipitated. The mixture was allowed to stand overnight, and then it was cooled in an ice bath. The crude azalactones were obtained after filteration and washing with hot water. Recrystalisation from aceton/water afforded the pure product in 68-96% yields.

4-Benzylidene-2-phenyloxazole-5(4*H*)-one (2a). solid, mp 165 °; ir (KBr): 3075, 1790, 1650, 1160, 760, 690 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.62 (m, 6H), 8.25 ppm (m, 4H). *Anal*. Calcd. for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.44; N, 5.61. Found: C, 76.60; H, 4.80 ; N, 5.49.

4-(4'-Methylbenzylidene)-2-phenyloxazole-5(4*H*)-one (2b). solid, mp 141 °; ir (KBr): 3060, 2925, 1795, 1650, 1600, 1160, 860, 820, 765, 695 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.29 (m, 3H), 7.54 (m, 3H), 8.19 (m, 4H). *Anal*. Calcd. for $C_{17}H_{13}NO_2$: C, 77.25; H, 5.34; N, 5.30. Found: C, 77.05; H, 5.77; N, 5.30.

4-(2',4'-Dimethoxybenzylidene)-2-phenyloxazole-5(4*H*)-one (2f). solid, mp 174 °; ir (KBr): 3020, 2920, 1775, 1640, 1600, 1270, 1160, 850, 765, 695 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 3.9 (s, 6H), 6.53 (s, 1H), 6.69 (m, 1H), 7.61 (m, 3H), 7.88 (s, 1H), 8.25 (m, 2H), 8.95 (m, 1H). *Anal*. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.65; H, 5.28; N, 4.51.

4-(4'-*N*,*N*-Dimethylaminobenzylidene)-2-phenyloxazole-5(4*H*)-one (2g). solid, mp 210 °; ir (KBr): 3060, 2920, 1760, 650, 1600, 1530, 1370, 1160, 810,690 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 3.08 (s, 6H), 6.74 (d, J = 4.2, 2H), 7.20 (s, 1H), 7.45 (m, 3H), 8.15 (m, 4H). *Anal*. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.62; H, 5.74; N, 9.51.

Acknowledgement. We are thankful to the Isfahan University and Razi University Research Councils for partial support of this work.

REFERENCES

[1] (a) Mitra, S. N.; Dey, S.; Karthikeyan, S.; Singh, T. P. *Biopolymers*, **1997**, *41*, 1997; (b) Cavalier, F.; Verducci, J. *Tetrahedron Lett*., **1995**, *36*, 4425.

[2] (a) Bautista, F. M.; Campelo, J. M.; Garcia, D. L. ; Marinas, J. M. *Amino Acids* **1992**, *2*, 87. (b) Cativela, C.; Diaz-de-Villegas, M. D.; Garcia, J. I.; Jimenez, A. I. *Tetrahedron* **1997**, *53*, 4479. (c) Meiwes, J.; Schudock, M.; Kretzschmar, G. *Tetrahedron Asymmetry* **1997**, *8*, 527. (d) Gootwald, K.; Seebach, D. *Tetrahedron* **1999**, *55*, 723. (e) Konkel, J. T.; Fan, J.; Jayachandran, B.; Kirk, K. L. *J. Fluorine Chem*. **2002**, *115*, 27.

[3] Abd-el-Rahm, A. H.; Kandeel, E. M.; Abdel-Razik, E. A.; El-Ghamry, I. A. *An. Quim*. **1993**, *89*, 237.

[4] Gelmi, M. L.; Clerici, F.; Melis, A. *Tetrahedron* **1997**, *53*, 1843.

[5] (a) Penalba, J.; Puchades, R.; Maquieira, A.; Gee, S.; Hammock, B. D. *Biosens. Bioelectron*. **2000**, *15*, 99. (b) Chikere, A. C.; Galunsky, B.; Schünemann, V.; Kasche, V. *Enzyme. Microb. Technol.* **2001**, *28*, 168.

[6] (a) Bossio, R.; Marcaccini, S.; Pepino, R.; Paoli, P. J. *Heterocycl. Chem*. **1994**, *31*, 729. (b) Cannella, R.; Clerici, F.; Gelmi, M. L.; Penso, M.; Pocar, D. *J. Org. Chem*. **1996**, *61*, 1854. (c) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Tetrahedron Lett*. **2002**, *43*, 4167.

[7] (a) R. Filler, *Advances in Heterocyclic Chemistry*, A. R. Katritzky, A. J. Boulton, and J. M. Lagowski (eds.), Vol. 4, Academic Press, New York (1965), p. 75. (b) R. Filler and Y. S. Rao, *Advances in Heterocyclic Chemistry*, A. R. Katritzky and A. J. Boulton (eds.), Vol. 21, Academic Press, New York (1977), p. 198. (c) Y. S. Rao and R. Filler, *Oxazoles*, edited by I. J. Turchi, John Wiley and Sons, New York (1986), p. 361.

[8] Baltazzi, E.; Davis, E. A. *Chem. Ind. (London)* **1962**, 929.

[9] (a) Cativiela, C.; Melendez, E. *Synthesis* **1978**, 832. (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron Lett*. **1999**, *40*, 1027.

[10] Rao, Y. S. *J. Org. Chem*. **1976**, *41*, 722.

[11] Kashyap, J.; Chetry, A. B.; Das, P. J. *Synth. Commun*. **1998**, *28*, 4187.

[12] Bautista, F. M.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M.; Romero, A. A. *J. Chem. Soc. Perkin Trans 2*, **2002**, 227.

[13] (a) Rao, P. S.; Venkatratnam, R. V. *Indian J. Chem*. **1994**, *33B*, 984. (b) Kidwai, M.; Kumar, R.; Kumar, P. *Indian J. Chem*. **1996**, *35B*, 1004.

[14] Monk, K. A.; Sarapa, D.; Mohan, R. S. *Synth. Commun*. **2000**, *30*, 3167.

[15] Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Tetrahedron Lett*.

2004, *45*, 425.

[16] Khodaei, M. M.; Khosropour, A. R.; Hoseini Jomor, S. J. *J. Chem. Res.(S)* **2003**, 638.

[17] Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815.

[18] (a) Vogel, A. I. *Textbook of Practical Organic Chemistry*, London, ELBS and Longman, **1978**, p. 761. (b) Khusid, A. Kh.; Chizhova, N. V. *J. Org. Chem. USSR (Engl. Transl.)* **1985**, *21*, 37. (c) Mitra, A. K; De, A.; Karchaudhuri, N. *J. Chem. Res.(S)* **1999**, 560. (d) Kjell, D. P.; Slattery, B. J.; Semo, M. *J. Org. Chem.* **1999**, *64*, 5722.

[19] (a) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485. (b) Bagley, M. C.; Cale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682. (c) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205. (d) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435.

[20] (a) Khodaei, M. M.; Khosropour, A. R.; Beygzadeh, M. *Synth. Commun.* **2004**, *34*, 1551. (b) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Catal. Commun.* **2007**, *8*, 200. (c) Khosropour, A. R.; Mohammadpoor-Baltork, I.; Khodaei, M. M.; Ghanbary, P. *Z. Naturforsch. B*, **2007**, *62b*, 537. (d) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Monatshefte für Chemie* **2007**, *138*, 663. (e) Khosropour, A. R.; Khodaei, M. M.; Beygzadeh, M.; *Heteroatom Chem.* **2007**, *18*, 684.