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A simple and rapid entry to 5-alkyl (aryl)-5-hydroxy-3,4-diarylfuranones and 3a-hydroxy-1-aryl-2,3a,4,5-tetrahydronaphthofuranones via a tandem esterification and oxidative cyclization process†

Srinivas Padakanti, Venugopal Rao Veeramaneni, Vijaya Raghavan Pattabiraman, Manojit Pal* and Koteswar Rao Yeleswarapu*

Chemistry-Discovery Research, Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500050, India

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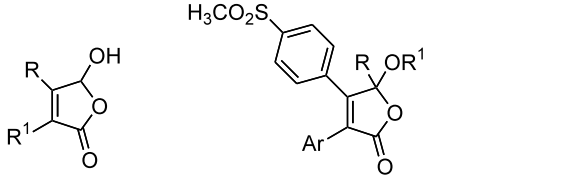
Abstract—A synthesis of 5-hydroxy-3,4-diarylfuranones and related derivatives is accomplished by the reaction of arylacetic acid with α-bromoketone in the presence of base and atmospheric oxygen. A variety of compounds were synthesized in good to excellent yield and many are of potential biological interest.

5-Hydroxyfuranones **1** (Fig. 1) are an integral part of many natural[1] and unnatural products,[2] including analgesic as well as the anti-inflammatory agent manoalide,[3a,b] endothelin-A (ET_A), the selective receptor antagonist PD-156707[3c] and a strong mutagen[4] in drinking water. They are valuable precursors for heterocycle synthesis as exemplified by the use of mucobromic acid **2** in pyrimidine synthesis. They are also useful as synthetic intermediates in the preparation of physiologically active compounds[5,6] such as pheromones, and selective COX-2 inhibitors[7,8] such as **3** (Fig. 1). 5-Hydroxyfuranone **4** (Fig. 1) has been detected as one of the major metabolites during the metabolism of rofecoxib.[9]

Because of their enormous importance in chemical as well as pharmaceutical research, a number of methods have been reported for the synthesis of **1** in the literature. Among the existing methods, the most useful routes involve photosensitized oxygenation of furans bearing a hydrogen or trialkylsilyl group at the α-position,[10,11] the oxidative cleavage of silyloxyfurans in the presence of dimethyldioxirane,[12] $Sn[Co(CO)_4]_4$-catalyzed double carbonylation of (2-bromoethyl)benzene,[13] the reaction of 5-halofuranones with water[14] or the reaction of maleic anhydride with Grignard reagents[15] and the treatment of diaryl-2(5*H*)-furanones with benzoylperoxide[16] or atmospheric oxygen in the presence of charcoal.[9b]

In connection with our studies on sulfonyl-substituted diarylheterocycles, the most widely used pharmacophore for the development of selective COX-2 inhibitors, we have reported the synthesis of 3,4-diaryl furanones,[8,17] 3,4-diarylmaleic anhydrides[18] and diphenyl-1,2,3-thiadiazole.[19] In pursuance of our research under the new drug discovery program we needed a wide variety of appropriately functionalized 5-hydroxy-3,4-diaryl furanones in order to generate a combinatorial library for a high throughput screen. We therefore required a rapid synthetic procedure for the synthesis of such compounds. The existing methods, however, were unattractive due to the lengthy synthetic procedures.[3c,10–15] We now wish to present here our exploratory work on the development of a general and convenient one-pot synthesis of 5-alkyl/aryl substituted



1
2 (R,R^1 = Br)

3
4 (R, R^1= H; Ar = C_6H_5)

Figure 1. Examples of some 5-hydroxyfuranones.

Keywords: 5-hydroxyfuranone; esterification; oxidative cyclization; phenylacetic acid; α-bromoketone.

* Corresponding authors. Fax: 91-40-3045438/3045007; e-mail: manojitpal@drreddys.com; koteswarraoy@drreddys.com

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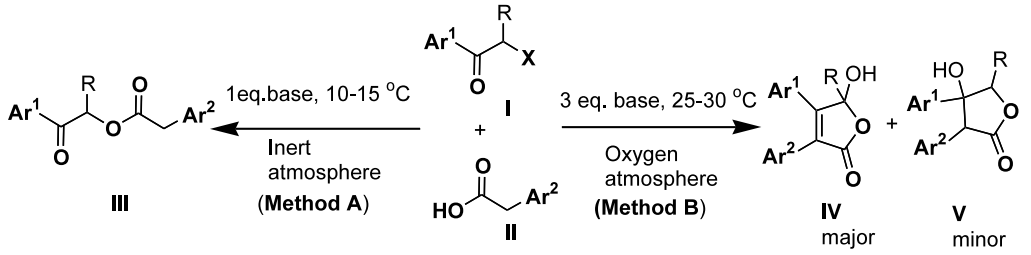
5-hydroxy-3,4-diarylfuranones starting from readily available starting materials.

The esterification of an arylacetic acid with an α-bromoketone in the presence of base under an inert atmosphere has been documented as the easiest protocol for accessing phenacyl esters **III**. The maximum yield of product was achieved when the reaction was carried out in the presence of 0.9–1.0 equiv. of base at 10–15°C for 20–25 min (Method A, Scheme 1). However, we observed that 5-hydroxy-3,4-diarylfuranones **IV** ($R \neq H$) were formed as the major product when the same reaction (when $R \neq H$ for **I**) was performed in the presence of 3 equiv. of base (with respect to the arylacetic acid) under an oxygen atmosphere at 25–30°C for a longer reaction time (Method B, Scheme 1). Our results are summarized in Table 1.

In a typical experiment, 4-methoxyphenylacetic acid (1.1 g, 6.61 mmol) in *N*,*N*-dimethyl formamide (DMF) (10 mL) was stirred along with potassium hydroxide (1.13 g, 20.17 mmol) and water (2 mL) for 0.5 h at 25°C to which was added a solution of 2-bromo-1-(4-methylsulfanylphenyl)-1-butanone (1.8 g, 6.59 mmol) in DMF (10 mL). The mixture was stirred for 6 h at 25°C in the presence of atmospheric oxygen and then poured into an ice-cold 3N HCl solution (30 mL) with stirring. The solid separated was filtered off and washed with water (2×15 mL) followed by petroleum ether (2×10 mL). The solid product was then analyzed.[20]

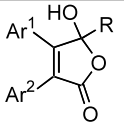
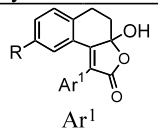
As can be seen from Table 1, a variety of α-bromoketones[21] **I** ($R \neq H$) and arylacetic acids **II** (obtained from the corresponding ketones via a Willgerodt reaction)[17a] were reacted to generate a number of 5-hydroxyfuranones **IV** (**5**–**15**) in good to excellent yields.

The reactions were usually carried out in the presence of potassium hydroxide or DBU. However, the use of other bases such as diisopropylamine and triethylamine was also investigated when phenacyl ester **III** was isolated as the sole product. In all the cases (entries 1–12, Table 1), the reaction proceeded well at 25–30°C leading to the formation of **IV** as the major product. However, another side product, i.e. 4-hydroxy-3,4-diaryltetrahydro-2-furanone **V** has been isolated as a minor product in many cases. Therefore, the effect of temperature and concentration of base (KOH) on product distribution has been investigated and is shown in Table 2.



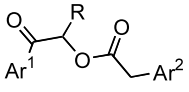
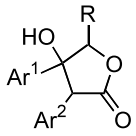
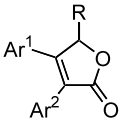
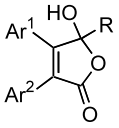
Scheme 1. Reaction of arylacetic acid with an α-bromoketone.

Table 1. Synthesis of 5-hydroxy-3,4-diarylfuranones **IV**[a]

Entry No.				Compd. No.[b]	Yield of **IV** (%)[c]
	Ar^1	Ar^2	R		
1	Phenyl	4-Methylsulfanylphenyl	Ethyl	**5**	77
2	Phenyl	Phenyl	Ethyl	**6**	81
3	4-Fluorophenyl	4-Methylsulfanylphenyl	Ethyl	**7**	83
4	4-Methoxyphenyl	4-Methylsulfanylphenyl	Ethyl	**8**	79
5	4-Methylsulfanylphenyl	4-Methylsulfonylphenyl	Phenyl	**9**	88
6	4-Methylsulfanylphenyl	Phenyl	Phenyl	**10**	72
					
	Ar^1		R		
8	4-Methylsulfanylphenyl		H	**11**	63
9	4-Methylsulfanylphenyl		Methyl	**12**	71
10	4-Methylsulfonylphenyl		H	**13**	48
11	4-Methylsulfonylphenyl		Methyl	**14**	54
12	4-Methylsulfinylphenyl		H	**15**	47

[a]Reactions were carried out using **I** (6.6 equiv), **II** (6.6 equiv) and KOH (20 equiv) in DMF (10 mL). [b]Identified by ^{1}H NMR, IR, and mass spectroscopy. [c] Isolated yields.

Table 2. Effect of reaction conditions on product distribution[a]

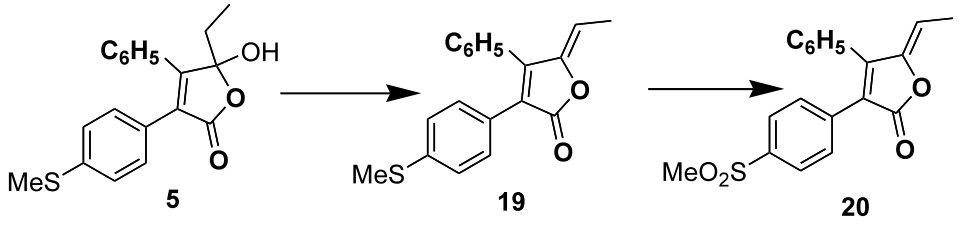
Entry	Arylacetic acid (**II**): Base (KOH) (molar ratio)	Temp. (°C)	Conv.[b] (%)	Product Distribution[c] (%) (Ar^1= 4-Methoxyphenyl; Ar^2= 4-Methylsulfanyl; R = Ethyl)			
							
				16	**17**	**18**	**8**
1	1: 0.5	10-15	59	100	0	0	0
2	1: 0.5	25-30	77	100	0	0	0
3	1:1	10-15	91	96	traces	n.d	n.d.
4	1:1	25-30	98	83	11	n.d.	n.d.
5	1:2	10-15	92	80	14	n.d.	n.d.
6	1:2	25-30	95	45	25	11	traces
7	1:3	10-15	90	traces	64	17	13
8	1:3	25-30[d]	-	n.d.	38	19	41
9	1:3	25-30	98	0	16	traces	79
10	1:3	25-30[e]	-	0	11	17	67

[a]The reaction was carried out in DMF under oxygen atmosphere for 6 hours. [b]Conversion was determined on the basis of the isolated yield of product and recovered starting material. [c]Product distributions were calculated based on the isolated yield of each product. [d]The reaction was carried out in DMF under oxygen atmosphere for 2 hours. [e]DBU was used as base. n.d.= not detected.

A mixture of furanone **18**, 5-hydroxyfuranone **8** along with 4-hydroxyfuranone **17** was isolated when the reaction was carried out at a lower temperature in the presence of 3 equiv. of KOH (entry 7, Table 2). On the other hand decomposition of the products was observed when the reaction temperature was increased. It is evident from Table 2 that the base has a crucial role in the formation of product **8**. Phenacyl ester **16** was isolated as the sole product even when the reaction was carried out in the presence of oxygen using a lesser amount of KOH (entries 1 and 2, Table 2). Indeed, ester **16** was isolated as the major product in most of the cases (entries 3–6, Table 2). However, 4-hydroxyfuranone **17** was detected along with the furanone **18** in appreciable quantity when the reaction time was restricted to 2 h instead of 6 h (entry 8 versus 9, Table 2). All these observations indicated that the ester, 4-hydroxyfuranone and furanone are possible sequential intermediates formed during the course of the reaction,[22] whereas the most effective molar ratio of arylacetic acid **II** to base was found to be 1:3 to give a high yield of product **IV**. Thus, the temperature, base and oxygen have combined influences on the nature of the product formed in this tandem esterification–oxidative cyclization reaction.

5-Hydroxy-3,4-diarylfuranones **5**–**10** and 3a-hydroxy-2,3a,4,5-tetrahydronaphthofuranones **11**–**15** have been synthesized using a single-step operational procedure in the presence of atmospheric oxygen. Many of these compounds showed biological activity[23] when tested in vitro[24] against the cyclooxygenase (COX) enzyme. A few of them showed strong inhibition[23b] against both of its isoforms (COX-1 and COX-2). Compound **5** was dehydrated (using *p*-toluene sulfonic acid in benzene) and then oxidized (using oxone in acetone) to the corresponding 5-alkylidenefuranone **20** which has potential biological interest (Scheme 2).[8]

In conclusion, we have demonstrated a distinctly mild and efficient one-pot procedure (a single-step operation) for the synthesis of 5-alkyl/aryl substituted 5-hydroxyfuranones starting from readily available starting materials. We have also described the first synthesis of 3a-hydroxy-1-aryl-2,3a,4,5-tetrahydronaphthofuranones using this two-component coupling process. The present protocol certainly has distinct advantages over the existing methods in terms of time, operational simplicity and environmental drawbacks. As 5-hydroxyfuranones are of great interest due to their interesting biological activities, the present protocol will



Scheme 2. Synthesis of a compound of potential biological importance.

find wide usage both in organic and medicinal chemistry.

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References

1. (a) He, H.; Kulanthaivel, P.; Baker, B. J. *Tetrahedron Lett*. **1994**, *35*, 7189–7192; (b) Schmidt, E. W.; Faulkner, D. *Tetrahedron Lett*. **1996**, *37*, 3951–3954; (c) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc*. **1996**, *118*, 8759–8760.
2. (a) Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M.; Grast, M. E. *J. Org. Chem*. **1991**, *56*, 7007–7014; (b) Doherty, A. M. *Drug Discovery Today* **1996**, *1*, 60–70.
3. (a) de Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett*. **1980**, *21*, 1611–1614; (b) Potts, B. C. M.; Faulkner, D. J.; De Carvalho, M. S.; Jacobs, R. S. *J. Am. Chem. Soc*. **1992**, *114*, 5093–5100; (c) Doherty, A. M.; Patt, W. C.; Edmunds, J. J.; Berryman, K. A.; Reisdorph, B. R.; Plummer, M. S.; Shahripour, A.; Lee, C.; Cheng, X.-M.; Walker, D. M.; Haleen, S. J.; Keiser, J. A.; Flynn, M. A.; Welch, K. M.; Hallak, H.; Taylor, D. G.; Reynolds, E. E. *J. Med. Chem*. **1995**, *38*, 1259–1263.
4. (a) Suzuki, N.; Nakaniski, J. *Chemosphere* **1990**, *21*, 387–392; (b) Jinqu, Z.; Zhen, Z.; Huixian, Z.; Minmin, Y. *Synth. Commun*. **1995**, *25*, 3401–3405.
5. Takabe, K.; Yoda, H.; Iwabuchi, M.; Tanaka, M. Jpn. Kokai Tokkyo Koho JP 02218673, 31 Aug 1990, 5 pp. *Chem. Abstr*. 114:61913.
6. Takabe, K.; Yoda, H. Jpn. Kokai Tokkyo Koho JP 02311471, 27 Dec 1990, 5 pp. *Chem. Abstr*. 115:29102.
7. Black, C.; Grimm, E.; Wang, Z.; Leger, S. World Patent WO 9636623 A1, 21 Nov 1996, *Chem. Abstr*. 126:89250.
8. Pal, M.; Rao, Y. K.; Rajagopalan, R.; Misra, P.; Kumar, P. M.; Rao, C. S. World Patent WO 01/90097, 29 Nov 2001, *Chem. Abstr*. 2002, *136*, 5893.
9. (a) Halpin, R. A.; Geer, L. A.; Zhang, K. E.; Marks, T. M.; Dean, D. C.; Jones, A. N.; Melillo, D.; Doss, G.; Vyas, K. P. *Drug Metab. Dispos*. **2000**, *28*, 1244–1254; (b) Nicoll-Griffith, D. A.; Yergey, J. A.; Trimble, L. A.; Silva, J. M.; Li, C.; Chauret, N.; Gauthier, J. Y.; Grimm, E.; Leger, S.; Roy, P.; Therien, M.; Wang, Z.; Prasit, P.; Zamboni, R.; Young, R. N.; Brideau, C.; Chan, C.-C.; Mancini, J.; Riendeau, D. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2683–2686.
10. Kernan, M. R.; Faulkner, D. J. *J. Org. Chem*. **1988**, *53*, 2773–2776.
11. (a) Pommier, A.; Kocienski, P. J. *Chem. Commun*. **1997**, 1139–1140; (b) Soriente, A.; De Rosa, M.; Scettri, A.; Sodano, G. *Tetrahedron Lett*. **1996**, *37*, 8007–8010; (c) Piers, E.; Wai, J. S. M. *Can. J. Chem*. **1994**, *72*, 146–157; (d) Katsumura, S.; Inagaki, Y.; Tsujino, K.; Han, Q. *Chem. Lett*. **1993**, 351–352.
12. Boukouvalas, J.; Lachance, N. *Synlett* **1998**, 31–32.
13. Monflier, E.; Pellegrini, S.; Mortreux, A.; Petit, F. *Tetrahedron Lett*. **1991**, *32*, 4703–4704.
14. Takabe, K.; Yoda, H.; Tanaka, M.; Sugimoto, M.; Ishioka, T.; Miyazaki, A. Jpn. Kokai Tokkyo Koho JP 02218672, 31 Aug 1990, 5 pp. *Chem. Abstr*. 114:42558.
15. Lardelli, G.; Dijkstra, P.; Harkes, D.; Boldingh, J. *Rec. Trav. Chim*. **1966**, *85*, 43.
16. Black, C.; Grimm, E.; Wang, Z.; Leger, S. World Patent WO 9636623, 21 Nov 1996, 109 pp., *Chem. Abstr*. 126:89250.
17. (a) Pal, M.; Rao, V. V.; Srinivas, P.; Murali, N.; Akhila, V.; Premkumar, M.; Rao, C. S.; Misra, P.; Ramesh, M.; Rao, Y. K. *Indian J. Chem*. **2002**, in press; (b) Srinivas, P.; Pal, M.; Rao, Y. K. *Synth. Commun*., submitted.
18. Pattabiraman, V. R.; Padakanti, P. S.; Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. *Synlett* **2002**, 947–951.
19. Pal, M.; Rao, V. V.; Rao, Y. K. Presented at the symposium on *Current Perspectives in Organic Chemistry (CPOC-2002)*, Indian Association for the Cultivation of Science, Kolkata, India, 24–25 January, 2002; Paper number 6.
20. All new compounds were characterized by ^{1}H NMR, IR, Mass and C, H, N microanalyses; some selected analytical data are listed below: Spectral data for **6**: mp 94–95°C (1:9 EtOAc–hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.26 (m, 10H, ArH), 2.09–2.02 (m, 2H, $C\underline{H}_2CH_3$), 0.87 (t, J=7.4 Hz, 3H, $CH_2C\underline{H}_3$); IR (KBr, cm^{-1}) 3319 (bs, OH), 1739 (C=O). Mass (EI) m/z 280 (M^+, 11), 262 (93), 178 (100). Elemental analysis found: C, 77.24; H, 5.73; $C_{18}H_{16}O_3$ requires C, 77.13; H, 5.75%.
Spectral data for **7**: mp 121–122°C (2:8 EtOAc–hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56–7.0 (m, 8H, ArH), 2.48 (s, 3H, $SC\underline{H}_3$), 2.05–1.86 (m, 2H, $C\underline{H}_2CH_3$), 0.87 (t, J=7.3 Hz, 3H, $CH_2C\underline{H}_3$); IR (KBr, cm^{-1}) 3455 (bs, OH), 1741 (C=O). Mass (EI) m/z 344 (M^+, 6), 326 (100). Elemental analysis found: C, 66.30; H, 4.97; $C_{19}H_{17}FO_3S$ requires C, 66.26; H, 4.98%.
Spectral data for **12**: mp: 227–229°C (MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.25 (m, 5H, ArH), 7.08 (s, 1H, ArH), 6.89 (d, J=7.89 Hz, 1H, ArH), 3.31–2.90 (m, 3H, one is D_2O exchangeable, OH and CH_2), 2.80–2.60 (m, 1H, $\underline{H}$-CH-), 2.55 (s, 3H, SCH_3), 2.35 (s, 3H, CH_3), 2.25–2.10 (m, 1H, $\underline{H}$-CH-); IR (KBr, cm^{-1}) 3329, 1742. Mass (CI, *i*-butane) m/z 339 (M^+, 43), 321 (100). Elemental analysis found: C, 70.89; H, 5.37; $C_{20}H_{18}O_3S$ requires C, 70.98; H, 5.36%.
21. α-Bromoketones were prepared via Friedel–Crafts acylation of the appropriate arene followed by bromination of the resulting ketone according to the similar procedure described in the literature. See for example: (a) Giordano, C.; Casagrande, F. Ger. Offen. DE 3006277, 4 Sep 1980, 26 pp, *Chem. Abstr*. 94:30372; (b) Carter, J. S.; Rogier, D. J.; Graneto, M. J.; Seibert, K.; Koboldt, C. M.; Zhang, Y.; Talley, J. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1167–1170.; (c) Almansa, C.; de Arriba, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; Merlos, M.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem*. **2001**, *44*, 350–361.
22. Mechanistically, the reaction proceeds via in situ generation of the phenacyl ester followed by an intramolecular aldol-type condensation leading to the formation of the corresponding furanone, which subsequently can react with molecular oxygen to yield the product. See for example: Ref. 18.

23. (a) A separate account of the biological activities of the compounds described here will be communicated soon; (b) Compounds **11** and **12** showed ~20-fold selectivity in COX-2 inhibition over COX-1 when tested against recombinant human COX-2 (expressed in sf9 insect cells using baculovirus) and COX-1 (Ram Seminal vesicles) enzyme in vitro[24] (% inhibition was recorded @10 μM concentration of the drug). Selective inhibition of COX-2 over COX-1 is beneficial for the treatment of inflammatory diseases with reduced ulcerogenic side effects. See: Jackson, L. M.; Hawkey, C. J. *Expert Opin. Invest. Drugs* **1999**, *8*, 963–971.
24. Brideau, C.; Kargman, S.; Liu, S.; Dallob, A. L.; Ehrich, E. W.; Rodger, I. W.; Chan, C.-C. *Inflamm. Res.* **1996**, *45*, 68–74.