Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Chemoselective Esterification of Phenolic Acids in the Presence of Sodium Bicarbonate in Ionic Liquids

Ambika [a], Pradeep Pratap Singh [a] & S. M. S. Chauhan [a]
[a] Department of Chemistry, University of Delhi, Delhi, India

Available online: 22 Feb 2008

To cite this article: Ambika, Pradeep Pratap Singh & S. M. S. Chauhan (2008): Chemoselective Esterification of Phenolic Acids in the Presence of Sodium Bicarbonate in Ionic Liquids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:6, 928-936

To link to this article: http://dx.doi.org/10.1080/00397910701845480

Synthetic Communications®, 38: 928–936, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701845480

Chemoselective Esterification of Phenolic Acids in the Presence of Sodium Bicarbonate in Ionic Liquids

Ambika, Pradeep Pratap Singh, and S. M. S. Chauhan

Department of Chemistry, University of Delhi, Delhi, India

Abstract: Chemoselective esterification of phenolic acids with dialkyl sulphates or alkyl halides in the presence of sodium bicarbonate in 1,3-dialkylimidazolium ionic liquids is reported in excellent yields and less reaction time as compared to organic solvents.

Keywords: chemoselective esterification, ionic liquid, phenolic esters, sodium bicarbonate

INTRODUCTION

Natural phenolic acids and their esters are common plant constituents that possess antioxidant, anti-inflammatory, antimicrobial, antiallergic, antiviral, anti-carcinogenic and other biological activities.[1–5] Synthetic esters of phenolic acids are important intermediates for the synthesis of biologically active products.[6,7] Specific protection and deprotection methods have been employed for the synthesis of the phenolic esters.[5–7] Selected reagents such as diisopropyl azodicarboxylate/triphenylphosphine ($DIAD/PPh_3$),[3] cesium fluoride–celite,[8] lithium hydroxide monohydrate–dimethyl sulphate ($LiOH \cdot H_2O–Me_2SO_4$),[9] cesium fluoride–methyl iodide (CsF-MeI),[10] potassium bicarbonate in dimethyl formamide,[11] and trialkyl orthoacetates[12] have been used in chemoselective esterification of phenolic acids. The use of expensive reagents and catalysts, harsh reaction conditions,

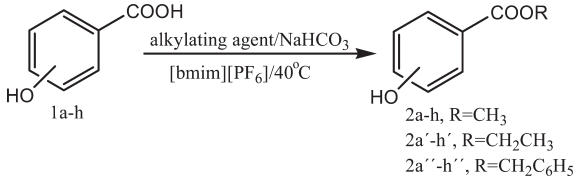
Received in India September 25, 2007
Address correspondence to S. M. S. Chauhan, Department of Chemistry, University of Delhi, Delhi 110007, India. E-mail: smschauhan@chemistry.du.ac.in

long reaction times, and relatively low yields are some of the limitations of these chemoselective methods.

Room-temperature ionic liquids (RTILs) are potential environmentally benign solvents for various organic and biochemical transformations.[13] The hydrophilicity, hydrophobicity, Lewis acidity, viscosity, and density have been altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion, and the length of the alkyl chain attached to the imidazolium ionic liquids.[13,14] The ionic liquids have been used in oxidation, reduction, hydrolysis, alkylation, protection, and deprotection and other reactions becasue of their reusability, potential to enhance reaction rates and selectivity, and easy separation of the products from the reaction mixture.[15] We report the chemoselective synthesis of phenolic esters from the corresponding phenolic acids with dialkyl sulphates or alkyl halides in the presence of $NaHCO_3$ in 1,3-dialkylimidazolium ionic liquids.

The reaction of salicylic acid (**1a**) with dimethyl sulphate in the presence of $NaHCO_3$ in 1-butyl-3-methyl-imidazoliumhexafluorophosphate, [bmim][PF_6], gave methyl salicylate (**2a**) in 94% yield (Scheme 1, Table 1). The reaction of **1a** in the absence of sodium bicarbonate in different ionic liquids gave **2a** in 5–10% yield (Table 1). The esterification of **1a** in the presence of $NaHCO_3$ proceeded much faster and more efficiently in different ionic liquids as compared to the conventional solvents such as dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF) (Table 1). The reaction of other phenolic acids (**1b**–**h**) with dimethyl sulphate in the presence of $NaHCO_3$ in [bmim][PF_6] gave the corresponding phenolic esters (**2b**–**h**) in good yields (Table 2). Further reaction of the phenolic acids (**1a**–**h**) with $(CH_3CH_2)_2SO_4$ and $C_6H_5CH_2Br$ in the presence of $NaHCO_3$ in ionic liquid gave the chemoselective products **2a′**–**h′** and **2a″**–**h″** respectively (Table 2). The nature and position of the groups in the aromatic ring have minor effect on the yields of esters of phenolic acids (Table 2).

Further, the recovery of the product is relatively simple in ionic liquids as compared to organic solvents. The esters are easily separated from the reaction mixture by simple extraction with ethyl acetate and purification by distillation and recrystallization with suitable solvents. The reaction of **1a** with dimethyl sulphate in the presence of $NaHCO_3$ in [bmim][PF_6] afforded **2a** in 94, 92, 87, and 83% yields by reuse of recovered ionic liquid in four cycles. Thus, the ionic liquids can be reused for several cycles without appreciable change in



Scheme 1.

Table 1. Effect of base and solvent on chemoselective esterification of salicylic acid (**1a**)

Solvents	Bases	Time (min)	(%) Yield[a]
[bmim][Br]	—	120	5
[bmim][BF_4]	—	120	8
[bmim][PF_6]	—	120	10
DMF	$NaHCO_3$	240	35
DMSO	$NaHCO_3$	240	40
THF	$NaHCO_3$	180	50
[bmim][Br]	$NaHCO_3$	40	88
[bmim][PF_6]	$NaHCO_3$	20	94
[bmim][BF_4]	$NaHCO_3$	20	90
[bmim][Br]	NaOH	20	45
[bmim][PF_6]	NaOH	20	50
[bmim][BF_4]	NaOH	20	48

Notes: All reactions were carried out using salicylic acid (**1a**, 1.0 mmol) and dimethyl sulphate (1.0 mmol).

[a]HPLC yields; [bmim][Br] = 1-butyl-3-methyl-imidazolium bromide, [bmim][BF_4] = 1-butyl-3-methylimidazolium tetrafluoroborate, and [bmim][PF_6] = 1-butyl-3-methyl-imidazolium hexafluoro-phosphate.

its reactivity. Similar yields and selectivity were obtained using the ionic liquids [bmim][BF_4] and [bmim][Br] (Table 1).

In summary, the chemoselective esterification of phenolic acids with dialkyl sulphates or alkyl halides in the presence of sodium bicarbonate in different ionic liquids is a simple and efficient method with shorter reaction times than other organic solvents.

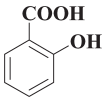
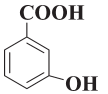
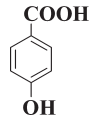
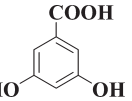
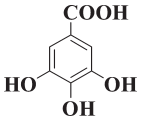
EXPERIMENTAL

All melting points were determined on a Thomas Hoover Unimelt melting-point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR 435 spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance 300 spectrometer using TMS as internal standard (chemical shift in parts per million). The symbols s, d, t, q, and m stand for singlet, doublet, triplet, quartet, and multiplet respectively. The electron spray ionization mass spectra (ESI-MS) were recorded on a Waters, LCT micromass instrument. High performance liquid chromatography (HPLC) analyses were performed on a Schimadzu LC 4A UV detector spectrophotometer.

General Procedure

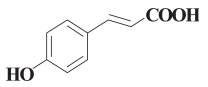
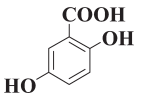
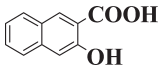
Ionic liquids based on 1-butyl-3-methyl-imidazolium (bmim) salts such as 1-butyl-3-methyl-imidazolium bromide [bmim][Br], 1-butyl-3-methylimidazolium

Table 2. Chemoselective esterification of phenolic acids (**1a**–**h**) using $NaHCO_3$/alkylating agent in [bmim][PF_6][a]

Entry	Substrate	Product	Alkylating agent	Time (min)	Yield (%)[b]	lit. Bp/mp (°C) Obs.	lit. Bp/mp (°C) Rep.
1a		2a	$(CH_3)_2SO_4$	20	94 (74)[c] (77)[e]	221–222[d]	223[17]
		2a′	$(CH_2CH_3)_2SO_4$	35	90	232[d]	231[17]
		2a″	$C_6H_5CH_2Br$	40	88	296–297[d]	—
1b		2b	$(CH_3)_2SO_4$	20	87	279–281[d]	280[17]
		2b′	$(CH_2CH_3)_2SO_4$	40	86	70–71	72–73[17]
		2b″	$C_6H_5CH_2Br$	25	88	69–70	68–69[21]
1c		2c	$(CH_3)_2SO_4$	20	90	126–128	127–129[17]
		2c′	$(CH_2\ CH_3)_2SO_4$	40	88	113–114	116[17]
		2c″	$C_6H_5CH_2Br$	25	86	118–119	119–121[19]
1d		2d	$(CH_3)_2SO_4$	25	87	163–165	163–164[17]
		2d′	$(CH_2\ CH_3)_2SO_4$	40	85	117–119	115–122[17]
		2d″	$C_6H_5CH_2Br$	35	84	130–132	132–133[19]
1e		2e	$(CH_3)_2SO_4$	25	84	155–156	157[17]
		2e′	$(CH_2\ CH_3)_2SO_4$	35	82	163–164	162[17]
		2e″	$C_6H_5CH_2Br$	35	80	148–149	145–149[19]

(*continued*)

Table 2. Continued

Entry	Substrate	Product	Alkylating agent	Time (min)	Yield (%)[b]	lit. Bp/mp (°C) Obs.	lit. Bp/mp (°C) Rep.
1f		2f	$(CH_3)_2SO_4$	20	88	140–141	139.5–141[18]
		2f′	$(CH_2CH_3)_2SO_4$	35	85	49–50	50–52[20]
		2f″	$C_6H_5CH_2Br$	35	86	92–93	92–93[12]
1g		2g	$(CH_3)_2SO_4$	20	92	86–87	88[16]
		2g′	$(CH_2\ H_3)_2SO_4$	30	90	75–77	77[16]
		2g″	$C_6H_5CH_2Br$	35	87	102–103	—
1h		2h	$(CH_3)_2SO_4$	15	80	74–77	75–76[16]
		2h′	$(CH_2CH_3)_2SO_4$	25	78	86–87	85[16]
		2h″	$C_6H_5CH_2Br$	35	84	86–87	—

[a]All reactions were carried out using phenolic acids (1.0 mmol), $NaHCO_3$ (1.2 mmol), dialkyl sulphate (1.0 mmol), or alkyl halide (1.5 mmol) in [bmim][PF_6].

[b]HPLC yields (μ-bond pack C-18 reverse phase column, acetonitrile, flow rate = 1 ml/min monitored at 232 nm).

[c]Yields using 0.5 eq. of DMS.

[d]Boiling point.

[e]Reaction was performed at room temperature.

tetrafluoroborate bmim][BF_4], and 1-butyl-3-methyl-imidazolium hexafluorophosphate [bmim][PF_6] were synthesized according to the modified literature procedure.[13] Phenolic acid (1.0 mmol) was dissolved in ionic liquid [bmim][PF_6] (2 ml), and $NaHCO_3$ (1.2 mmol) was added. The reaction mixture was stirred for 10–15 min. The dialkyl sulphate (1.0 mmol) or alkyl halide (1.5 mmol) was added dropwise to the suspension of the reaction mixture and stirred for 15–20 min at 40°C. The progress of the reaction was monitored by thin-layer chromatography (TLC), and after the completion of the reaction, the product was extracted with ethyl acetate (3 × 3 ml), and the organic layer was subsequently washed with 5% $NaHCO_3$ and 5% NaCl and dried (anhy. Na_2SO_4). The ethyl acetate layer was concentrated under reduced pressure to give the desired product. The remaining ionic liquid was dissolved in $CHCl_3$ and filtered to remove insoluble $NaHCO_3$ and precipitated sodium halides.

The spectroscopic data including IR, NMR, and mass spectra of the products were identical to those of authentic samples. The physical data are given in Table 2, and the spectroscopic data of selected phenolic esters (**2a**″–**h**″) are given as follows.

Data

Benzyl 2-hydroxybenzoate (2a″): IR (nujol, cm^{-1}): 3392, 1670, 1639, 1580, 1325, 1232, 1110; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 5.50 (s, 2H, -CH_2), 7.05–7.30 (m, 3H, H-3 to H-5), 7.34–7.59 (m, 6H, H-6, H-2a′ to H-6a′), 9.80 (s, 1H, OH); ESI-MS: 229.2479 (M + 1).

Benzyl 3-hydroxybenzoate (2b″): IR (nujol, cm^{-1}): 3395, 1696, 1612, 1350; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 5.39 (s, 2H, -CH_2), 5.82 (s, 1H, OH), 7.08 (m, 1H, H-4), 7.28–7.48 (m, 5H, H-2a′ to H-6a′), 7.30 (t, 1H, J = 8.2 Hz, H-5), 7.62 (m, 1H, H-2), 7.68 (m, 1H, H-6); ESI-MS: 252.2378 (M + Na).

Benzyl 4-hydroxybenzoate (2c″): IR (nujol, cm^{-1}): 3425, 1712, 1270, 1160; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 5.40 (s, 2H, -CH_2), 6.96 (d, J = 8.6 Hz, 2H, H-3 & H-5), 7.34–7.45 (m, 5H, H-2a′ to H-6a′), 8.15 (d, J = 8.6 Hz, 2H, H-2 & H-6); ESI-MS: 229.2482 (M + 1).

Benzyl 3,5-dihydroxybenzoate (2d″): IR (nujol, cm^{-1}): 3392, 1696, 1611, 1337; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 5.34 (s, 2H, -CH_2), 6.60 (d, 1H, J = 2.5 Hz, H-4), 7.05 (d, 2H, J = 2.5 Hz, H-2 & H-6), 7.31–7.53 (m, 5H, H-2a′ to H-6a′), 8.58 (s, 2H, OH); ESI-MS: 267.0632 (M + Na).

Benzyl 3,4,5-trihydroxybenzoate (2e″): IR (nujol, cm^{-1}): 3369, 1690, 1605, 1339 1235; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 5.32 (s, 1H, -CH_2), 7.20

(s, 2H, H-2 & H-6), 7.32–7.47 (m, 5H, H-2a′ to H-6a′), 9.09 (s, 3H, OH); ESI-MS: 261.2471 (M + 1).

Benzyl 4-hydroxycinnamate (2f″): IR (KBr, cm^{-1}): 3470, 2950, 1717, 1630, 1220, 1170, 1080, 1027; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 5.27 (s, 2H, -CH_2), 6.13 (s, 1H, OH), 6.44 (d, $J = 16.0$ Hz, 1H, =CHAr), 6.92 (d, $J = 8.1$ Hz, 2H, H-3 & H-5), 7.31–7.44 (m, 7H, H-2 & H-6, H-2a′ to H-6a′), 7.62 (d, $J = 16.0$ Hz, 1H, =CHCO); ESI-MS: 277.3080 (M + Na).

Benzyl 2,5-dihydroxybenzoate (2g″): IR (KBr, cm^{-1}): 3388, 1668, 1637, 1575, 1319, 1228, 1103; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 4.80 (s, 1H, OH), 5.54 (s, 2H, -CH_2), 6.95 (d, $J = 8.4$ Hz, 1H, H-3), 7.08 (dd, $J = 2.5$, 8.2 Hz, 1H, H-4), 7.20 (d, $J = 2.5$ Hz, 1H, H-6), 7.44–7.53 (m, 5H, H-2a′ to H-6a′), 10.40 (s, 1H, OH); ESI-MS: 245.2496 (M + 1).

Benzyl-3-hydroxy-2-naphthoate (2h″): IR (KBr, cm^{-1}): 3418, 1651, 1517, 1404, 1317, 1210, 1022; ^{1}H NMR (300 MHz, δ ppm, $CDCl_3$): 5.52 (s, 2H, -CH_2), 7.43 (s, 1H, H-4), 7.49–7.53 (m, 5H, H-2a′ to H-6a′), 7.65–7.72 (m, 4H, H-5 to H-8), 7.90 (s, 1H, H-1), 11.80 (s, 1H, OH); ESI-MS: 279.3080 (M + 1).

REFERENCES

1. Silva, F. A. M.; Borges, F.; Guimaraes, C.; Lima, J. L. F.C.; Matos, C.; Reis, S. Phenolic acids and derivatives: studies on the relationship among structure, radical scavenging activity, and physicochemical parameters. *J. Agri. Food. Chem.* **2000**, *48*, 2122–2126.
2. Kawabata, J.; Okamoto, Y.; Kodama, A.; Makimoto, T.; Kasai, T. Oxidative dimers produced from protocatechuic and gallic esters in the DPPH radical scavenging reaction. *J. Agri. Food. Chem.* **2002**, *50*, 5468–5471.
3. Appendino, G.; Minassi, A.; Daddario, N.; Bianchi, F.; Tron, G. C. Chemoselective esterification of phenolic acids and alcohols. *Org. Lett.* **2002**, 3839–3841.
4. Golden, R.; Gandy, J.; Vollmer, G. A review of the endocrine activity of parabens and implications for potential risks to human health. *Crit. Rev. Toxicol.* **2005**, *35*, 435–458.
5. Tillekeratne, L. M. V.; Sherette, A.; Grossman, P.; Hupe, L.; Hupeb, D.; Hudsona, R. Simplified catechin-gallate inhibitors of HIV-1 reverse transcriptase. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2763–2767.
6. Xu, G.; Hartman, T. L.; Wargo, H., Jr.; Turpin, A.; Buckhert, R. W.; Cushman, M. Synthesis of alkenyldiarylmethane (ADAM) non-nucleoside HIV-1 reverse transcriptase inhibitors with non-identical aromatic rings. *Bioorg. Med. Chem.* **2002**, *10*, 283–290.
7. Burke, T. R., Jr.; Fesen, M. R.; Mazumder, A.; Wang, J.; Carothers, A. M.; Grunberger, D.; Driscoll, J.; Kohn, K.; Pommier, Y. Hydroxylated aromatic inhibitors of HIV-1 integrase. *J. Med. Chem.* **1995**, *38*, 4171–4178.

8. Lee, J. C.; Choi, Y. An improved method for preparation of carboxylic esters using CsF-celite/alkyl halide/CH_3CN combination. *Synth. Commun.* **1998**, *28*, 2021–2026.
9. Chakraborti, K.; Basak, A.; Grover, V. Chemoselective protection of carboxylic acid as methyl ester: A practical alternative to diazomethane protocol. *J. Org. Chem.* **1999**, *64*, 8014–8017.
10. Sato, T.; Otera, J.; Nazaki, H. CsF-promoted esterification of carboxylic acids: a practical alternative to the diazomethane method and direct conversion of organotin carboxylates. *J. Org. Chem.* **1992**, *57*, 2166–2169.
11. Lee, J. C.; Goul Song, I.; Park, J. Y. Microwave-promoted facile synthesis of methyl and ethyl carboxylates. *Synth. Commun.* **2002**, *32*, 2209–2213.
12. Guo, W.; Li, J.; Fan, N.; Wu, W.; Zhou, P.; Xia, C. A simple and effective method for chemoselective esterification of phenolic acids. *Synth. Commun.* **2005**, *35*, 145–152.
13. Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. Chemical and biochemical transformations in ionic liquids. *Tetrahedron* **2005**, *61*, 1015–1060.
14. Handy, S. T. Room temperature ionic liquids: different classes and physical properties. *Curr. Org. Chem.* **2005**, *9*, 959–988.
15. (a) Srinivas, K. A.; Kumar, A.; Chauhan, S. M. S. Epoxidation of alkenes with hydrogen peroxide catalyzed by iron(III) porphyrins in ionic liquids. *Chem. Commun.* **2002**, *20*, 2456–2457; (b) Chauhan, S. M. S.; Kumar, A.; Srinivas, K. A. Oxidation of thiols with molecular oxygen catalyzed by cobalt(II) phthalocyanines in ionic liquid. *Chem. Commun.* **2003**, *9*, 2348–2349; (c) Kumar, A.; Jain, N.; Chauhan, S. M. S. Oxidation of benzylic alcohols to carbonyl compounds with potassium permanganate in ionic liquids. *Synth. Commun.* **2004**, *34*, 2835–2842; (d) Kumar, A.; Jain, N.; Chauhan, S. M. S. Biomimetic oxidation of veratryl alcohol with H_2O_2 catalyzed by iron(III) porphyrins and horseradish peroxidase in ionic liquid. *Synlett* **2007**, *3*, 411–414; (e) Howarth, J.; James, P.; Ryan, R. Sodium borohydride reduction of aldehydes and ketones in the recyclable ionic liquid [bmim]PF_6. *Synth. Commun.* **2001**, *31*, 2935–2938; (f) Chauhan, S. M. S.; Jain, N.; Kumar, A.; Srinivas, K. A. Copper(I) chloride–catalyzed synthesis of diaryl ethers in ionic liquids under mild conditions. *Synth. Commun.* **2003**, *33*, 3607–3614; (g) Angrish, C.; Kumar, A.; Chauhan, S. M. S. Microwave-assisted aromatic nucleophilic substitution reaction of chloronitrobenzenes with amines in ionic liquids. *Ind. J. Chemun. Sec. B: Org. Med. Chem.* **2005**, *44*, 515–1518; (h) Jain, N.; Kumar, A.; Chauhan, S. M. S. Metalloporphyrin and heteropoly acid to catalyzed oxidation of C═NOH bonds in an ionic liquid: Biomimetic models of nitric oxide synthase. *Tetrahedron. Lett.* **2005**, *46*, 2599–2602; (i) Kumar, A.; Jain, N.; Rana, S.; Chauhan, S. M. S. Ytterbium(III) triflate–catalyzed conversion of carbonyl compounds into 1,3-oxathiolanes in ionic liquids. *Synlett* **2004**, *15*, 2785–2787; (j) Jain, N.; Kumar, A.; Chauhan, S. M. S. Synthesis of transition metal porphyrins from free-base 5,10,15,20-tetraarylporphyrins under microwave irradiation in ionic liquids. *Synth. Commun.* **2005**, *35*, 1223–1230.
16. Buchingham, J.; Donaghy, S. M. *Dictionary of Organic Compounds*, 6th edn.; Chapman and Hall: London, 1982.
17. Parmar, V. S.; Kumar, A.; Bisht, K. S.; Mukherjee, S.; Prasad, A. K.; Sharma, S. K.; Wengel, J.; Olsen, C. E. Novel chemoselective de-esterification of esters of polyacetoxy aromatic acids by lipases. *Tetrahedron* **1997**, *53*, 2163–2176.

18. Helm, R. F.; Ralpht, J. Lignin-hydroxycinnamyl model compounds related to forage cell wall structure, 1: Ether-linked structures. *J. Agri. Food. Chem.* **1992**, *40*, 2107–2175.
19. Rivero-Cruz, B.; Rivero-Cruz, I.; Rodriguez-Sotres, R.; Mata, R. Effect of natural and synthetic benzyl benzoates on calmodulin. *Phytochemistry* **2007**, *68*, 1147–1155.
20. Patel, C. K.; Owen, C. P.; Gyamfi, K. A.; Ahmed, S. Structure–activity relationship determination study of a series of novel compounds as potential inhibitors of the enzyme estrone sulfatase (ES). *Lett. Drug Des. Dis.* **2004**, *1*, 35–44.
21. Laursen, B.; Denieul, M. P.; Skrydstrup, T. Formal total synthesis of PKC inhibitor, balanol: Preparation of the fully protected benzophenone. *Tetrahedron* **2002**, *58*, 2231–2238.