Cascade Enantioselective Synthesis of 3-Arylphthalides Using Chiral Auxiliary Route

Anil V. Karnik,* Suchitra S. Kamath

Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai 400098, India
Fax +91(22)26528547; E-mail: avkarnik@chem.mu.ac.in

Received 16 November 2007; revised 13 March 2008

Abstract: An enantioselective synthesis of 3-arylphthalides was achieved using (*S*)-1-phenylethylamine as a chiral auxiliary. Reduction of chiral keto amides of 2-aroylbenzoic acids followed by acid-catalyzed lactonization yielded (*S*)-3-arylphthalides with 75–85% ee.

Key words: enantioselective synthesis, (*S*)-1-phenylethylamine, chiral auxiliary, reduction, 3-arylphthalides

Chiral 3-substituted phthalide moieties are found in a large number of natural products and biologically active compounds, such as 3-*n*-butylphthalide, (–)-hydrastine, (–)-narcotine),[1] (–)-typhaphthalide,[2] vermistatin,[3] alcyopterosin E,[4,5] and cytosporone E.[6] Some members of this group are cytotoxic (vermistatin, alcyopterosin E), antibacterial (cytosporone E), show anticonvulsant,[7] antiasthmatic[8] and antitumor properties,[9] increase the duration of anesthesia,[10] and exhibit cerebral anti-ischemic action (3-*n*-butylphthalide).[11] They also compose part of the structure of several complex alkaloids (e.g., the convulsant alkaloid bicuculline)[12] and serve as intermediates for their synthesis.

The precise biological activity of 3-substituted phthalides is often crucially dependent on their configuration. Efficient and stereoselective synthetic routes to these products in enantiomerically pure form are therefore highly desirable.

One of the approaches for the preparation of nonracemic 3-substituted phthalides involves enantioselective reduction of 2-acylbenzoic acids and their derivatives followed by lactonization. Noyori et al. introduced a BINAP-Ru(II) catalyzed enantioselective hydrogenation of 2-acylbenzoic esters giving a straightforward entry to optically active 3-substituted phthalides in very high enantioselectivity.[13] Brown et al. reported a convenient and general synthesis of chiral 3-substituted phthalides with equally high enantioselectivity via intramolecular asymmetric reduction of 2-acylbenzoic acids by diisopinocampheylborane and intermolecular asymmetric reduction of 2-acylbenzoates with (–)-*B*-chlorodiisopinocampheylborane.[14] Asymmetric transfer hydrogenation methodology using chiral Ru complexes has been employed for the preparation of 3-substituted phthalides.[15] In addition to the asymmetric reduction of 2-acylbenzoic acid derivatives, some other useful methodologies have been reported for the preparation of chiral 3-substituted phthalides.[16,17]

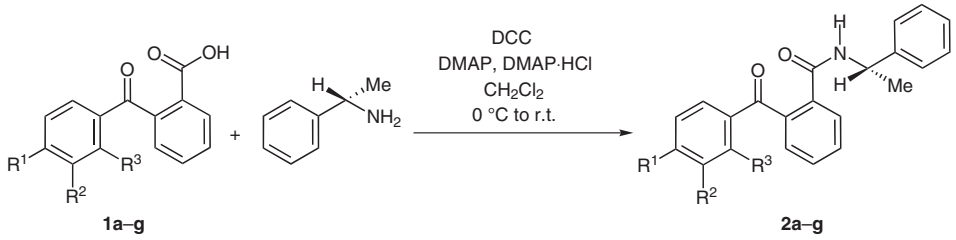
A chiral auxiliary approach has been used effectively for the enantioselective synthesis of γ-substituted-γ-lactones by many groups,[18,19] including a contribution from our group.[20] The presence of the same basic structural unit in 3-substituted phthalides made us consider the chiral auxiliary approach for the synthesis of nonracemic 3-substituted phthalides. We initially carried out the synthesis of racemic 3-arylphthalides by reduction of 2-aroylbenzoates followed by acid-catalyzed lactonization.[21] It was reasoned that the use of a chiral auxiliary in the process would result in the formation of nonracemic 3-arylphthalides. It was also expected that the forced proximity between the prochiral centre and the chiral auxiliary would result in better stereoselectivity than in the previous series of synthesis of nonracemic γ-substituted-γ-lactones.

We report here for the first time the formation of nonracemic 3-arylphthalides using chiral auxiliary approach, without involvement of organometallics or chiral catalyst. The main strategy adapted by us to prepare nonracemic 3-arylphthalide was the reduction of chiral amide of 2-aroylbenzoic acid followed by acid-catalyzed lactonization, which involved the use of (*S*)-1-phenylethylamine as a chiral auxiliary. The choice of (*S*)-1-phenylethylamine was on the basis of its easy accessibility, cost effectiveness, and wide utility in asymmetric synthesis.[22–24] The synthesis of chiral keto amides of 2-aroylbenzoic acids and (*S*)-1-phenylethylamine and their utility in the preparation of nonracemic 3-arylphthalides are discussed. (*S*)-2-Aroyl-*N*-(α-phenylethyl)benzamides **2a**–**g** were prepared from 2-aroylbenzoic acids **1a**–**g** and (*S*)-1-phenylethylamine using DCC as the coupling reagent (Scheme 1).

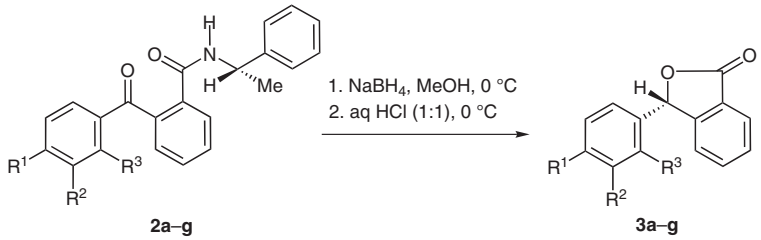
Arriving at this stage, the next step was the enantioselective synthesis of 3-arylphthalides. This was achieved in a one-pot reaction by $NaBH_4$ reduction of (*S*)-2-aroyl-*N*-(α-phenylethyl)benzamides **2a**–**g** followed by acid-catalyzed lactonization (Scheme 2).

Chiral identities of 3-arylphthalides **3a**–**g** were established by comparison of their optical rotations with that of authentic compounds reported in the literature.[14,25] The enantiomeric excesses of (*S*)-3-arylphthalides **3a**–**g** (Table 1) were determined by HPLC using a chiral stationary phase (Chiralcel OD-H, *n*-hexane–*i*-PrOH, 98:2).

SYNTHESIS 2008, No. 12, pp 1832–1834
Advanced online publication: 16.05.2008
DOI: 10.1055/s-2008-1067098; Art ID: T17607SS



Scheme 1 Synthesis of novel chiral keto amides



Scheme 2 Enantioselective synthesis of (*S*)-3-arylphthalides

Table 1 Enantioselective Synthesis of (*S*)-3-Arylphthalides

Entry	Product	R^1	R^2	R^3	Yield (%)	ee (%)
1	**3a**	H	H	H	57	75
2	**3b**	Me	H	H	58	81
3	**3c**	OMe	H	H	58	85
4	**3d**	Me	Me	H	59	85
5	**3e**	Me	H	Me	57	81
6	**3f**	Cl	H	H	55	76
7	**3g**	Br	H	H	54	78

In summary, the synthesis of novel chiral keto amides of 2-aroylbenzoic acids and the utility of these compounds in enantioselective synthesis of 3-arylphthalides have been demonstrated. (*S*)-3-Arylphthalides were obtained in a one-pot reaction by $NaBH_4$ reduction of (*S*)-2-aroyl-*N*-(α-phenylethyl)benzamides followed by acid-catalyzed lactonization with 75–85% ee. The chemical yields are reasonable and enantioselectivities observed are satisfactory to good. The methodology also allows the use of very mild reaction conditions and inexpensive reagents.

Optical rotations were measured with Jasco DIP-1000 digital polarimeter. Enantiomeric excesses were determined on HPLC Thermo Finnigan spectra system using Daicel Chiralcel OD column with UV detector. IR spectra were recorded on Shimadzu FTIR-4200 spectrometer. ^{1}H NMR spectra were scanned in $CDCl_3$ on Bruker (300 MHz) and Varian Mercury Plus (400 MHz) spectrometers with TMS as an internal standard. Elemental analyses were carried on Carlo Enra instrument EA-1108 Elemental analyzer. Mass spectra were obtained in ESI mode. All melting points are uncorrected. Boiling point of the petroleum ether (PE) used was in the range of 60–80 °C.

(*S*)-2-Aroyl-*N*-(α-phenylethyl)benzamides 2a–g, General Procedure

To a stirred solution of 2-aroylbenzoic acid **1a–g** (4.9 mmol), (*S*)-1-phenylethylamine (0.52 mL, 4.1 mmol), DMAP (0.1 g, 0.83 mmol), and DMAP·HCl (0.13 g, 0.83 mmol) in anhyd CH_2Cl_2 (50 mL) at 0 °C was added DCC (0.84 g, 4.1 mmol). The mixture was stirred at r.t. for 12 h, filtered, and the residue washed with CH_2Cl_2 (10 mL). The combined filtrates were washed first with dilute aq HCl (1:1, 20 mL) and then with aq 5% Na_2CO_3 (20 mL). The organic phase was dried (Na_2SO_4) and evaporated. The crude product was crystallized from $CHCl_3$–PE to give **2a–g** as colorless crystals.

(*S*)-2-Benzoyl-*N*-(α-phenylethyl)benzamide (2a)

Yield: 0.87 g (65%); mp 121–123 °C; $[\alpha]_D^{19}$ –45.8 (*c* 1.00, MeOH).

IR (KBr): 3328, 3066, 3033, 2969, 2929, 2850, 1669, 1626, 1601, 1573, 1495, 1468, 1449 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.75–7.73 (m, 1 H), 7.57 (d, *J* = 7.2 Hz, 1 H), 7.43–7.40 (m, 3 H), 7.35–7.33 (m, 1 H), 7.24–7.16 (m, 6 H), 7.07–7.05 (m, 2 H), 6.33 (s, 1 H), 4.76 (q, *J* = 7.2 Hz, 1 H), 1.77 (d, *J* = 7.2 Hz, 3 H).

MS: *m*/*z* = 328.64 [M$^+$].

Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.24; H, 5.78; N, 4.26. Found: C, 80.32; H, 5.82; N, 4.15.

(*S*)-2-(4′-Methylbenzoyl)-*N*-(α-phenylethyl)benzamide (2b)

Yield: 0.94 g (67%); mp 142–143 °C; $[\alpha]_D^{19}$ –45.7 (*c* 1.00, MeOH).

IR (KBr): 3324, 3034, 2974, 2935, 1664, 1626, 1601, 1513, 1495, 1469 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.76–7.75 (m, 1 H), 7.50–7.46 (m, 6 H), 7.25–7.18 (m, 6 H), 6.55 (s, 1 H), 4.76–4.70 (m, 1 H), 2.24 (s, 3 H), 1.77 (d, *J* = 7.4 Hz, 3 H).

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.47; H, 6.12; N, 4.08. Found: C, 80.56; H, 6.05; N, 4.04.

(*S*)-2-(4′-Methoxybenzoyl)-*N*-(α-phenylethyl)benzamide (2c)

Yield: 0.99 g (68%); mp 185–187 °C; $[\alpha]_D^{19}$ –66.4 (*c* 1.00, MeOH).

IR (KBr): 3325, 3178, 3036, 2928, 2850, 1665, 1626, 1609, 1576, 1512, 1467 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.78–7.76 (m, 1 H), 7.46–7.44 (m, 2 H), 7.20–7.12 (m, 10 H), 6.73 (s, 1 H), 4.80–4.78 (m, 1 H), 3.77 (s, 3 H), 1.79 (d, *J* = 7.3 Hz, 3 H).

Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.88; H, 5.85; N, 3.90. Found: C, 76.76; H, 5.94; N, 3.83.

(*S*)-2-(3′,4′-Dimethylbenzoyl)-*N*-(α-phenylethyl)benzamide (2d)
Yield: 0.99 g (68%); mp 142–144 °C; $[\alpha]_D^{19}$ –41.8 (*c* 1.00, MeOH).

IR (KBr): 3323, 2974, 2928, 1673, 1626, 1573, 1494, 1469 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.76–7.74 (m, 1 H), 7.59 (d, *J* = 7.3 Hz, 1 H), 7.44–7.41 (m, 2 H), 7.26–7.11 (m, 6 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 6.85 (s, 1 H), 4.74 (q, *J* = 7.3 Hz, 1 H), 2.24 (s, 3 H), 2.03 (s, 3 H), 1.79 (d, *J* = 7.3 Hz, 3 H).

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.67; H, 6.44; N, 3.92. Found: C, 80.74; H, 6.50; N, 3.85.

(*S*)-2-(2′,4′-Dimethylbenzoyl)-*N*-(α-phenylethyl)benzamide (2e)
Yield: 0.98 g (68%); mp 141–142 °C; $[\alpha]_D^{19}$ –47.1 (*c* 1.00, MeOH).

IR (KBr): 3328, 3068, 3027, 2977, 2934, 1674, 1626, 1570, 1494, 1468 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.13 (d, *J* = 7.8 Hz, 1 H), 7.77–7.75 (m, 1 H), 7.47–7.42 (m, 2 H), 7.19–7.02 (m, 8 H), 6.59 (s, 1 H), 4.60 (q, *J* = 7.3 Hz, 1 H), 2.44 (s, 3 H), 2.32 (s, 3 H), 1.85 (d, *J* = 7.3 Hz, 3 H).

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.67; H, 6.44; N, 3.92. Found: C, 80.62; H, 6.54; N, 3.99.

(*S*)-2-(4′-Chlorobenzoyl)-*N*-(α-phenylethyl)benzamide (2f)
Yield: 0.97 g (66%); mp 164–165 °C; $[\alpha]_D^{19}$ –45.2 (*c* 1.00, MeOH).

IR (KBr): 3321, 2972, 2932, 2850, 1668, 1626, 1577, 1491, 1469 cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.73–7.71 (m, 1 H), 7.56–7.50 (m, 2 H), 7.28–7.21 (m, 3 H), 7.20–7.16 (m, 4 H), 7.13–7.07 (m, 3 H), 6.21 (s, 1 H), 4.63 (q, *J* = 7.3 Hz, 1 H), 1.86 (d, *J* = 7.3 Hz, 3 H).

Anal. Calcd for $C_{22}H_{18}ClNO_2$: C, 72.63; H, 4.95; Cl, 9.77; N, 3.85. Found: C, 72.75; H, 4.88; Cl, 9.83; N, 3.80.

(*S*)-2-(4′-Bromobenzoyl)-*N*-(α-phenylethyl)benzamide (2g)
Yield: 1.05 g (63%); mp 146–148 °C; $[\alpha]_D^{19}$ –42.8 (*c* 1.00, MeOH).

IR (KBr): 3321, 3033, 2970, 2851, 1680, 1628, 1602, 1575, 1486, 1469 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.73–7.72 (m, 1 H), 7.54–7.43 (m, 6 H), 7.32–7.10 (m, 6 H), 6.25 (s, 1 H), 4.72–4.69 (m, 1 H), 1.78 (d, *J* = 6.0 Hz, 3 H).

Anal. Calcd for $C_{22}H_{18}BrNO_2$: C, 64.71; H, 4.41; Br, 19.61; N, 3.43. Found: C, 64.74; H, 4.35; Br, 19.71; N, 3.36.

(*S*)-3-(2′,4′-Dimethylphenyl)phthalide (3e); Typical Procedure
To a stirred solution of chiral keto amide **2e** (714 mg, 2 mmol) in MeOH (30 mL) at 0 °C was added $NaBH_4$ (76 mg, 2 mmol) in portions and the mixture was stirred for 8 h at the same temperature. The mixture was then treated with cold aq 1:1 HCl (100 mL) and stirred for further 12 h at 0 °C. The mixture was extracted with $CHCl_3$ (3 × 20 mL); the combined $CHCl_3$ extracts were washed with aq 5% Na_2CO_3 (20 mL), dried (Na_2SO_4), and evaporated. The crude product was crystallized from EtOH to give **3e** as white crystals; yield: 0.27 g (57%); mp 72–73 °C; $[\alpha]_D^{19}$ +26.4 (*c* 0.5, $CHCl_3$).

IR (KBr): 2957, 2926, 1759, 1612, 1503, 1463 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.2 Hz, 1 H), 7.65 (t, *J* = 7.3 Hz, 1 H), 7.54 (t, *J* = 7.3 Hz, 1 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.06 (s, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.77 (d, *J* = 7.8 Hz, 1 H), 6.63 (s, 1 H), 2.44 (s, 3 H), 2.31 (s, 3 H).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.67; H, 5.88. Found: C, 80.74; H, 5.84.

The analytical data of compounds **3a–g** were in accord with the literature values.[26]

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