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Indium-mediated tandem dimerization and cyclization of nitrqones and aldimines to 3-arylaminodihydrobenzofurans under aqueous conditions

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Abstract—Nitrones undergo deoxygenative reductive coupling and subsequent cyclization to 3-arylamino-2,3-dihydrobenzofuran derivatives in the presence of indium under aqueous conditions at ambient temperature in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

Indium mediated carbon–carbon bond-forming reactions have commanded considerable attention because of the high efficiency with which indium promotes these processes in water.^{1–3} Reductive dimerization of imines offers attractive possibilities for direct access to vicinal diamines.^{4–8} A variety of reductants including active metals have been developed for this purpose. Indium mediated allylation⁹ of aldimines and its novel reductive coupling¹⁰ have been documented. Indium exhibits, in general, a low heterophilicity in organic reactions. Thus, oxygen and nitrogen containing functional groups are usually tolerated within the molecule. Indium with chloromethylsilane has been shown¹¹ to deoxygenate aryl ketones and *sec*-benzylic alcohols. Very recently, deoxygenation of nitrones and *N*-oxides for diastereoselective (dl) formation of vicinal diamines using indium has been reported.¹² The preparation of *meso* isomers for use as imprint molecules for studying applications of molecularly imprinted polymers was conceived. However, during the course of our studies on the reductive dimerization of imines by the reported procedures,^{4,7} we found the formation of dihvdrobenzofurans 3 in trace amounts. Further studies revealed that nitrones and aldimines could be converted directly into 3-arylaminodihydrobenzofurans 3 by indium in aqueous medium. To the best of our knowledge, tandem dimerization and cyclization of nitrones or aldimines that are substituted with groups amenable to cyclization has not vet been achieved. This tandem reaction offers a simple method for the generation of compounds 3. No reports on the synthesis of 3 are available to date. The results are provided in Scheme 1 and Table 1.



Scheme 1.

Keywords: tandem dimerization and cyclization; vicinal diamines; diastereomers; deoxygenative reductive coupling. * Corresponding author. Tel.: 886-3-5721484; fax: 886-3-5711082; e-mail: ycling@mx.nthu.edu.tw

Entry	R ¹	R ²	Yield (%) ^a of 3 using indium		Yield (%) ^b of 3 and 4 using zinc	
			From nitrone	From aldimine	From nitrone	From aldimine
1a, 2a, 3a, 4a	-H	-H	88	61	49 (34)	42 (30)
1b, 2b, 3b, 4b	-CH ₃	-H	72	58	41 (30)	38 (34)
1c, 2c, 3c, 4c	-CH ₂ CH ₃	-H	70	59	44 (35)	23 (36)
1d, 2d, 3d	-CH(CH ₃) ₂	-H	67	53	_	-
1e, 2e, 3e, 4e	-Cl	-H	18	12	10 (57)	8 (56)
1f, 2f, 3f	-Br	-H	12	6	_ ` `	
1g, 2g, 3g	-CH ₃	-Br	52	38	_	_
1h, 2h, 3h	-CH ₂ CH ₃	-Cl	45	34	_	_

^a Isolated yields.

^b Yields based on PMR analysis.

All nitrones and aldimines except 1e, 1f and 2e, 2f afforded 3 in moderate to good yields; the formation of vicinal diamines was not observed. It is known that the chemistry of indium partly resembles that of zinc and tin. However, the reaction of nitrones or aldimines with zinc yielded a mixture of dihydrobenzofurans and secondary amines 4 (resulting from the reduction of nitrones and aldimines). The close $R_{\rm f}$ values of 3 and 4 made their separation tedious by column chromatography. The formation of 4 was not observed while using indium. Our qualitative observations suggest the possibility of the intermediacy of vicinal diamines. Halogen substituted nitrones (1e and 1f) afforded 3 in lower yields, but dl vicinal diamines¹² in 69–71% yields. This could be attributed to the stability of the dl isomer by strong hydrogen bonding.13 The higher yield of 3 and the absence of vicinal diamines with other substituents could be rationalized by subsequent conversion of diamines to dihydrobenzofurans. Further mechanistic studies, that is the sequence of coupling and deoxygenation, oxidation of 3, and the extension of this protocol to the synthesis of arylaminobenzothiopenes and indoles are in progress.

General procedure: Indium (2–3 mmol) was added in one portion to an ethanol (3 mL)–water (3 mL containing 1 mmol NH₄Cl) system containing nitrone (1 mmol). The mixture was heated to reflux for approx. 16 h until the completion of the reaction, as shown by TLC. Dilution with ethyl acetate, filtration through a Celite bed, followed by concentration and column chromatographic purification afforded **3**.

Representative spectral and analytical data (**3c**). ¹H NMR (300 MHz, CDCl₃) δ 1.18 (t, 3H, *J*=7.6 Hz), 2.54 (q, 2H, *J*=7.6 Hz), 5.26 (d, 1H, *J*=8.3 Hz), 5.61 (d, 1H, *J*=8.3 Hz), 6.77 (d, 2H, *J*=8.5 Hz), 6.83–6.97 (m, 4H), 7.05–7.12 (m, 3H), 7.19–7.27 (m, 2H), 7.45 (dd, 1H, *J*=1.6 Hz, 8.6 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 15.68, 27.99, 65.11, 86.85, 110.69, 116.72,

117.12, 120.28, 121.51, 124.76, 125.32, 125.79, 128.15, 128.90, 129.22, 130.06, 137.19, 143.07, 154.16, 159.26. MS m/z 331 (M⁺), HRMS calcd for $C_{22}H_{21}NO_2$ 331.1572; found 331.1574.

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