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Intramolecular Imine Cross-Coupling in Dibenzylidine Sulfamides: Synthesis of Unsymmetrical 1,2-Diaryl Ethanediamines

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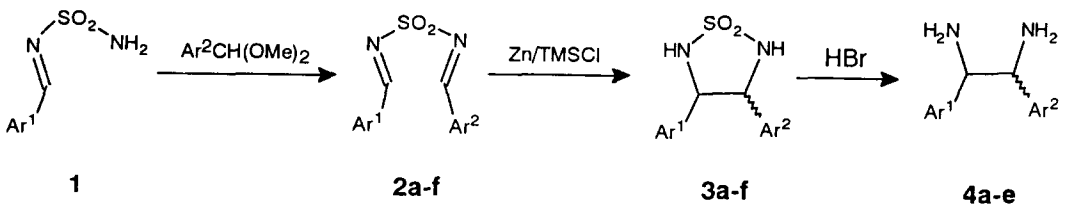
Abstract: Intramolecular reductive cross-coupling of unsymmetrical dibenzylidene sulfamides generates the corresponding cyclic sulfamides in good yield. These intermediates are readily converted to the free, unsymmetrical 1,2-diaryl ethanediamines. Copyright © 1996 Elsevier Science Ltd

Vicinal diamines are of interest due to their applications in asymmetric synthesis[1] and medicinal chemistry.[2] The synthesis of unsymmetrically substituted[3] as well as symmetrical[3a,4] vicinal diamines has therefore been intensively investigated in recent years. The reductive coupling of imines is the simplest approach to diaryl vicinal diamines and the intermolecular version of this reaction has been extensively studied.[5] This procedure, however, suffers from some drawbacks, the main one being its restriction to the homo-coupling mode. In contrast to the cross-coupling of carbonyl compounds,[6] a similar reaction involving two different imines has not been reported. Herein we describe preliminary results on a novel intramolecular cross-coupling of unsymmetrical diimines[7] as a new approach to chiral 1,2-diaryl ethanediamines.

For initial investigations we chose to prepare sulfamide derived diimines **2** (Scheme 1) since a) the precursor imine, monobenzylidene sulfamide **1** is readily prepared,[8] b) the reductive coupling to generate **3** may be expected to proceed with some element of stereocontrol and more importantly c) hydrolysis of **3** would lead directly to the free diamines **4**, an advantage not available with most of the conventional coupling procedures.[9]



1 **2a-f** **3a-f** **4a-e**

Scheme 1

Condensation of benzylidene sulfamide with *p*-tolualdehyde was attempted under a variety of conditions (benzene reflux, $SOCl_2$/THF reflux,[10a] $TiCl_4/CH_2Cl_2$[10b] rt.) all giving low yield of unsymmetrical diimine **2a** (Ar^1 = Ph, Ar^2 = 4MePh). The method of choice was reaction with *p*-tolualdehyde dimethylacetal in refluxing benzene[10c] to generate **2a** in 70% yield. The procedure is quite general and is applicable to a variety of aromatic aldehydes either in the arylidene sulfamide or the acetal component. Thus diimines **2a-e** were readily available in good yield (65-70% after recrystallization, quantitative yield of crude product). We next investigated the intramolecular reductive coupling of **2a**. Most of the reagents that successfully couple *N*-substituted arylimines[5] either failed to induce any coupling of **2a** or caused extensive decomposition (Al-Hg in moist ether did generate

3 in some cases but the reaction was capricious since **2** is readily hydrolysed by moisture). Although Zn metal in DMF or THF failed to yield **3a**, *in-situ* activation of the metal with TMSCl[11] was beneficial and yielded **3a** consistently as a ca. 2:1 mixture of *cis/trans* isomers. Attempts to improve the stereoselectivity of the process by lowering the temperature were unsuccessful since the coupling slowed down considerably. Although reaction of **2** with SmI_2 in THF[5d] at ambient temperature rapidly generated **3**, there was no significant improvement in yield or selectivity. Lowering the reaction temperature resulted in incomplete reaction with no change in stereoselectivity and the Zn mediated coupling procedure is therefore advantageous from a practical viewpoint. Thus, cyclic sulfamides **3** were readily available from **2** in good yield (63-85%).[12]

Conversion of **3** to the free diamines **4** proved challenging. Initial investigations were conducted with **3g**, which was found to be inert to most reagents that reductively cleave sulfoxides[13] or reduce sulfones to sulfides,[14] for eg. Ra-Ni/EtOH, Mg/EtOH, Mg(Hg), Na(Hg), Al(Hg), LAH/THF reflux and SmI_2 at ambient temperature. Treatement with excess SmI_2 at elevated temperature caused decomposition. Acid mediated cleavage[15] studies of **3g** indicated that it was inert to refluxing HBr or HCl, whereas heating in HBr/AcOH or AcOH/$HClO_4$ caused decomposition. However, heating **3g** in HBr with added phenol for solubilization[16] generated the free diamine **4g** in 63% yield. Similarly, diamines **4a-e** were obtained in 52-75% yield. The reaction sequence constitutes a new synthesis of unsymmetrical 1,2-diaryl ethanediamines involving a novel cross-coupling of imines. The results for the reductive coupling of **2** and the generation of free diamines **4** are summarized in Table 1.

Some of the substrates exhibit a preference for the *cis* coupling[12] mode, and introduction of an *ortho* substituent into one of the aryl groups causes an increase in the amount of the *trans* product. (cis/trans = 2/1 for **3a**, and 1/1 for **3b**). It is noteworthy in this regard that the symmetrical substrate **2j**[10] ($Ar^1 = Ar^2$ = 2-naphthyl) furnished only *N,N'*-methyl-2-naphthyl sulfamide (reduction product) and reductive coupling was not observed, presumably due to steric crowding in the transition state leading to **3**. However, a distinct trend in such steric effects and an explanation of the observed stereoselectivity is not obvious at present (eg. cis/trans = 2.5/1 for **3c** and 1/1 for **3h**).[17]

Table 1. Reductive coupling of arylidenesulfamides **2** and hydrolysis of **3**.

Compound	Ar^1, Ar^2	Reagent	Solvent	Yield% 3	3 cis/trans[c]	Yield% 4[a]
2a	Ph, 4MePh	Zn/TMSCl	DMF	85[a]	2/1	52
		SmI_2	THF	95[b]	3/1	
2b	Ph, 2MePh	Zn/TMSCl	DMF	63[a]	1/1	67
		SmI_2	THF	75[b]	1/1	
2c	2MePh, 4MePh	Zn/TMSCl	DMF	72[a]	2.5/1	52
		SmI_2	THF	75[b]	2/1	
2d	Ph, 2naphthyl	Zn/TMSCl	DMF	75[a]	1/1	58
2e	Ph, *p*ClPh	Zn/TMSCl	DMF	71[a]	1.2/1	75
		SmI_2	THF	60[b]	-	-
2f	Ph, 4MeOPh	Zn/TMSCl	DMF	55[a]	2/1	-
2g	Ph, Ph	Zn/TMSCl	DMF	72[a]	3/1	63
2h	4MePh, 4MePh	Zn/TMSCl	DMF	70[a]	1/1	51
2i	4MeOPh, 4MeOPh	Zn/TMSCl	DMF	90[b]	3/1	-
2j	2naph., 2naph.	Zn/TMSCl	DMF	d	-	-

a: Isolated yields. b: Yield estimated by ^1H NMR of crude product. c: Ratio determined by ^1H NMR and/or ^{13}C NMR. d: not obtained.

In conclusion, we have developed a novel synthesis of a new class of chiral 1,2-diaryl ethanediamines employing an intramolecular reductive cross-coupling of electronically similar imines as the key step. Current efforts focus on studying the factors influencing the stereoselectivity of the coupling reaction and application to intramolecular reactions of related unsymmetrical substrates.

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REFERENCES AND NOTES

1. Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 497-526.
2. Michalson, E. T.; Smuszkovicz, J. *Prog. Drug Res.* **1989**, 33, 135.
3. a) Ricardson, P. F.; Nelson, L. T. J.; Sharpless, K. B. *Tetrahedron Lett.* **1995**, 36, 9241-9244. b) Asaro, M. F.; Nakayama, I.; Wilson, R. B. *J. Org. Chem.* **1992**, 57, 778-782. c) Reetz, M. T.; Jaeger, R, Drewlies, R.; Hubel, M. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 103-106. d) Katritzky, A. R.; Fan, W.-Q.; Fu, C. *J. Org. Chem.* **1990**, 55, 3209-3213.
4. a) Corey, E. J.; Lu, D. -H.; Sarshar, S. *Tetrahedron Asymmetry*, **1995**, 6, 3-6. b) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, 35, 3391-3394 and references therein.
5. For leading references see: a) Cuvinot, D.; Mangeney, P.; Alexakis, A.; Normant, J. -F. *J. Org. Chem.* **1989**, 54, 2420-2425. b) Betschart, C. A.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta.* **1988**, 71, 1999-2021. c) Kalyanam, N.; Rao, G. V. *Tetrahedron Lett.* **1993**, 34, 1647-1648. d) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141-1142.
6. a) Robertson, G. M. in *'Comprehensive Organic Synthesis'*, Trost, B. M. Ed. Pergamon Press 1991, Vol. 3, pg. 563. b) Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990**, 55, 5924-5926.
7. Intramolecular coupling of symmetrical aryldiimines has been studied, see ref. 4b and Shono, T.; Kise, N.; Oike, H.; Yoshimoto, M.; Okazaki, E. *Tetrahedron. Lett.* **1992**, 38, 5559-5562.
8. Yamaguchi, H.; Hatakeyama, K. *Hiroshima Daigaku Kogakubu Kenkyu Hokoku* **1973**, 22, 27-34, (CA80:132955b). Typically, a solution of benzaldehyde (2.0 ml, 20.8 mmol) and sulfamide (1.0 g, 10.4 mmol) in methanol (made acidic with 20% HCl (10 µl)) was heated to reflux for 18h. Concentration followed by partitioning in ether/water gave the product imine **1** (Ar^1 = Ph, 1.52 g, 80%) which was used further without purification.
9. The $NbCl_4(THF)_2$ or low valent titanium mediated silylimine coupling are exceptions, Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, 109, 3152-3154, and ref. 5b.
10. a) The procedure for the preparation of dibenzylidene sulfamide was adapted, see: Knollmuller, M.; Reich, K. R. *Monatsh.* **1975**, 106, 1095-1102. The symmetrical substrates **2g-j** were similarly prepared from sulfamide and the aryl aldehyde. b) Jennings, W. B.; Lovely, C. J.; *Tetrahedron Lett.* **1988**, 29, 3725-3728. c) Davis, F. A.; Lamendola, Jr., J. F.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimera, M. *J. Am. Chem. Soc.* **1980**, 102, 2000-2005.
11. a) Shono, T.; Kise, N.; Nomura, R.; Yamanami, A. *Tetrahedron Lett.* **1993**, 34, 3577-3580. b) Cosio, F. P.; Odriozola, J. M..; Oiarbide, M.; Palomo, C. *J. Chem. Soc. Chem. Commun.* **1989**, 74-76.
12. All crude product mixtures were analysed for diastereomer composition by ^{1}H NMR (200 MHz) and/or ^{13}C NMR (50.3 MHz). The stereochemistry of the major isomer in **3** was determined to be *cis* by comparison of the chemical shifts for the methine proton bearing carbons to those of **3g**, for which the major isomer (NCH upfield) yielded the *meso* 1,2-diphenylethanediamine whose stereochemistry was confirmed

according to the known procedure, see supplementary material in ref. 9. Satisfactory ^{1}H NMR, and IR spectral data were obtained for all diimines **2**.

General procedure for reductive coupling of diimines 2: To a solution of the diimine in anhydrous DMF was added activated Zn dust (325 mesh, Sisco Research Laboratories, Bombay, India). The stirred mixture was cooled to 0 °C and TMSCl was added slowly (exotherm). The mixture was then stirred at room temperature for 12-14 h and the reaction was monitored by TLC. Saturated $NaHCO_3$ solution was added and the mixture filtered. The filtrate was extracted with EtOAc to furnish the crude product which was purified by flash chromatography on silica gel. Thus, reaction of **2a** (1.1 g, 3.85 mmol) with Zn (1.31 g, 20 mmol) and TMSCl (2.54 ml, 20 mmol) in DMF (60 ml) for 14 h gave after purification 946 mg (85%, 96 mg *trans*, 640 mg *cis* and 210 mg mixture of *cis* and *trans*) of **3a**. Data for *cis* **3a**: mp. 117-120 °C. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.2-7.1 (m, 4 H, Ar*H*), 7.0-6.8 (m, 5 H, Ar*H*), 5.20-5.10 (m, 1 H, C*H*), 5.1-4.90 (m, 2 H, N*H*), 2.25 (s, 3 H, CH_3). IR (Nujol): 3250, 1460, 1380, 1360, 1300, 1270, 1240, 1170, 710 cm^{-1}. ^{13}C NMR (75.5 MHz, $CDCl_3$+d6-DMSO): δ 136.0, 135.3, 135.2, 132.1, 132.0, 127.4, 126.7, 126.6, 126.5 (Ar*C*), 63.5 (*C*H), 63.3 (*C*H), 20.0 (CH_3). MS (EI, 70 eV) m/z 65 (12), 77 (25), 91 (30), 106 (100), 118 (94), 120 (70), 289 (M+1). TLC: R*f* 0.28 (SiO_2, pet. ether/EtOAc, 7/3). Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.06, H, 5.72; N, 9.51. *Trans* **3a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-7.25 (m, 4 H, Ar*H*), 7.15 (s, 5 H, Ar*H*), 5.1-4.95 (m, 2 H, N*H*), 4.8-4.7 (m, 2 H, C*H*), 2.35 (s, 3 H, CH_3). IR ($CHCl_3$): 3260, 1510, 1400, 1320, 1170, 1050, 950 cm^{-1}. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 138.5, 136.1, 133, 132.9, 129.4, 128.6, 127.1 (Ar*C*), 67.5, 67.3 (*C*H), 20.9 (CH_3). MS (EI, 70 eV) m/z 65 (15), 77 (18), 91 (38), 106 (100), 118 (90), 120 (93), 289 (M+1). TLC: R*f* 0.31 (SiO_2, pet. ether/EtOAc, 7/3).

General procedure for cleavage of cyclic sulfamides 3: A mixture of **3** and phenol in HBr (aqueous, 48%) was heated at 130-140 °C for 20 min., cooled to room temperature and the solution extracted with EtOAc to remove phenol. The aqueous phase was made basic with solid NaOH and the diamine isolated by extraction with EtOAc. Thus, reaction of *cis* **3a** (230 mg, 0.8 mmol) in HBr (5 ml) and phenol (0.35 ml, 4 mmol) furnished *R*S** **4a** (96 mg, 52%) that was pure by ^{1}H NMR (200 MHz). Data for **4a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-7.0 (m, 9 H, Ar*H*), 4.0-3.85 (m, 2 H, NC*H*), 2.25 (s, 3 H, CH_3), 1.8-1.6 (br s, 4 H, NH_2). IR ($CHCl_3$): 3300, 1600 (br), 1520, 1500, 1460, 1220 cm^{-1}. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 142.5, 139.2, 137.1, 129.1, 128.3, 127.5, 127.4, 126.9 (Ar*C*), 62.4, 62.1 (*C*H), 21 (CH_3).

13. Hayakawa, K.; Takewaki, M.; Fujimoto, I.; Kanematsu, K. *J. Org. Chem.* **1986**, *51*, 5100-5105.
14. a) Lee, G.H.; Choi, E.B.; Pak, C. S. *Tetrahedron Lett.* **1994**, 35, 2195-2196. b) Akgun, E.; Mahmood, K.; Mathis, C. A. *J. Chem. Soc. Chem. Commun.* **1994**, 761-762.
15. a) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, 53, 2367-2371. b) Kudav, D. P.; Samant, S. P.; Hosangadi, B. D. *Synth. Commun.* **1987**, 17, 1185-1187 and references therein.
16. This is a modification of a procedure for the cleavage of benzenesulfonamides, see: Snyder, H, R.; Heckert, R. E. *J. Am. Chem. Soc.* **1952**, 74, 2006-2009.
17. Coupling of symmetrical **2** derived from 2-methyl benzaldehyde gives cis **3** as the major product (*cis*/*trans* = 5/1). This result is contrasteric and a simple explanation is not apparent. Stereoselectivity in intramolecular reductive coupling of symmetrical diimines leading to macrocycles is reported to depend on the electronic nature of the aryl group (*trans*/*cis* ratio is higher with *p*-electron donating substituents, see ref. 7.). No distinct electronic effects are seen in the present study.

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