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Effect of Sulfonyl Protecting Groups on the Neighboring Group Participation Ability of Sulfonamido Nitrogen

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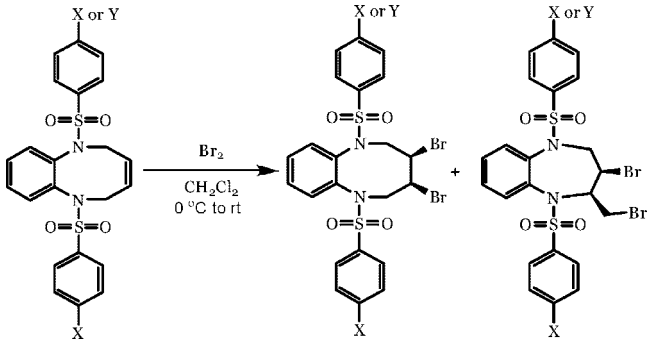
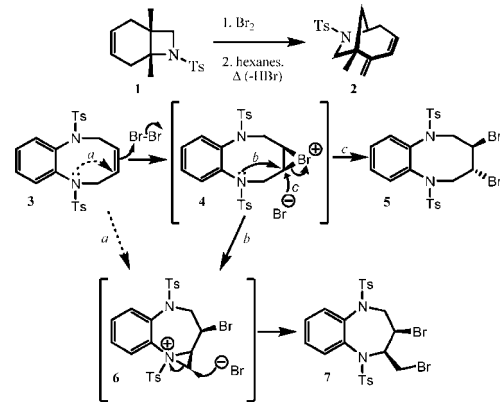
Received January 12, 2009



The addition of elemental bromine dissolved in CH_2Cl_2 to para-disubstituted benzodiazocines where X is the same (H, CH_3, Br, OMe, NO_2) or a different substituent as X and Y (CH_3, Br; OMe, NO_2) has been found to proceed in most cases with competition between two pathways. While conventional trans-1,2-addition operates predominantly, electron-releasing groups also foster a ring-contraction process with ultimate 1,3-positioning of the pair of bromine atoms. The observed regio- and stereoselectivities, confirmed where necessary by X-ray crystallographic analysis, establish the capability of sulfonamide nitrogen centers to engage in neighboring group participation.

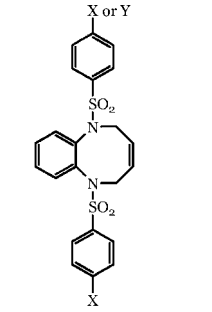
According to classical opinion, neighboring group participation is a phenomenon defined by three criteria: rate enhancements, abnormal stereochemical outcomes, and the isolation of isomeric products.[1] While the capacity of ether, hydroxyl, thioether, amino, and amido groups for nucleophilic involvement in such processes has been extensively reported, examples of comparable participation by the electron pair of sulfonamido nitrogen centers are much less well documented. The conversions of **1** to **2**[2] and of **3** to **7**[3] under bromination conditions represent two uncommon examples. For **3**, the initial generation of bromonium ion **4** has been advanced in light of the coformation of the trans vicinal dibromide **5**. The possibility exists, however, that the pathway involving the direct conversion

SCHEME 1



of **3** to aziridinium ion **6** may also be operational (Scheme 1). Presently, added insight into the electron movement available to benzo-fused 1,4-diazocines related to **3** has been examined from two perspectives.

In the first, the *p*-aryl substituents **X** in **8a**−**e** were altered in pairwise fashion with maintenance of molecular C_s symmetry. The objective here was to learn if distribution of the isomeric products related to **5** and **7** is altered as a function of the electron-donating or electron-withdrawing nature of **X** in **8**. Adherence to a Hammett-type relationship would reflect the relative importance of neighboring group participation in routes *a* and *b* in Scheme 1. On the other hand, the presence of two different substituents as in **8f** and **8g** sets the stage for direct intramolecular competition involving the sulfonamide nitrogen electron pairs.



8a, X=CH_3
8b, X=NO_2
8c, X–Br
8d, X–H
8e, X=OMe
8f, X–CH_3, Y–Br
8g, X–OMe , Y–NO_2

Preparative Considerations. In light of the prior report detailing the successful disulfonylation of the *o*-phenylenediamine (**9**) with tosyl chloride,[4] comparable conditions were evaluated for the close analogues. The protocol consisted of the slow addition of a solution of the sulfonyl chloride in pyridine to **9** in the same solvent at 0 °C. Unexpectedly, only very low yields were realized. Recourse was therefore made to the methodology developed by Massacret.[5] Under these experi-

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(2) Paquette, L. A.; Kelly, J. F. *J. Org. Chem.* **1971**, *36*, 442.
(3) Proust, N.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **2008**, *73*, 6279.
(4) (a) Van Otterlo, W. A. L.; Morgans, G. L.; Khanye, S. D.; Aderibigbe, B. A.; Michael, J. P.; Billing, D. G. *Tetrahedron Lett.* **2004**, *45*, 9171. (b) Acheson, R. M. *J. Chem. Soc.* **1956**, 4731.
(5) Massacret, M.; Lhoste, P.; Sinou, D. *Eur. J. Org. Chem.* **1999**, 129.

10.1021/jo900065q CCC: $40.75 © 2009 American Chemical Society
Published on Web 03/10/2009

SCHEME 2

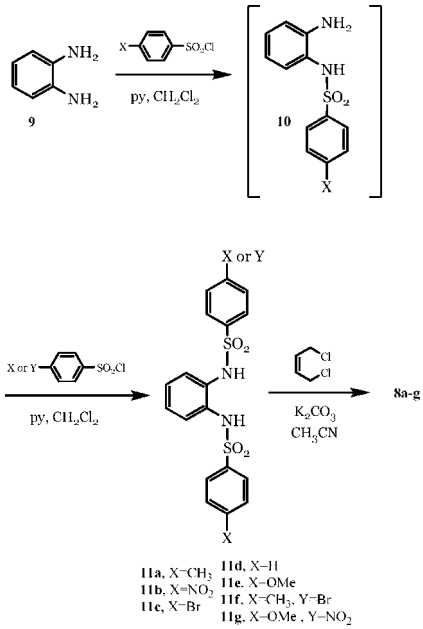


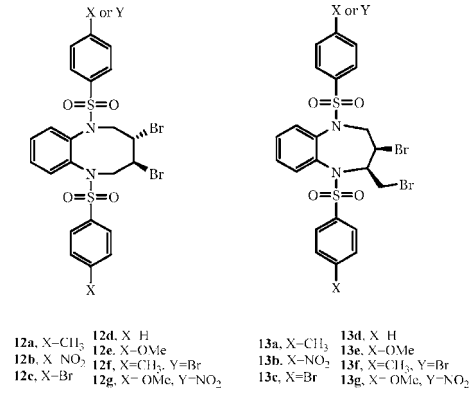
TABLE 1. Selectivity of the Dibromination Reaction

entries	substrate **8**	*trans*-dibromides **12** (%)	rearranged dibromides **13** (%)
1	**b**, NO_2/NO_2	>99	trace
2	**c**, Br/Br	>97	<3
3	**d**, H/H	73	27
4	**a**, CH_3/CH_3	82	18
5	**e**, OMe/OMe	64	36
6	**f**, CH_3/Br	68	32
7	**g**, NO_2/MeO	81	19

mental conditions, **9** was dissolved in cold (0 °C) CH_2Cl_2 and treated sequentially with pyridine (2.0 equiv) and the sulfonyl chloride (2.0 equiv). The reaction mixture was then warmed to rt where it was maintained until complete reaction was realized (TLC analysis). The yields of **11** were in excess of 75% in all cases.

Relevantly, the mixed derivatives **11f** and **11g** were prepared in a single flask by the preliminary addition of 1 equiv of the first sulfonyl chloride and subsequent introduction of an equivalent of the second sulfonyl chloride after 4 h at rt (Scheme 2). For arrival at the benzodiazocines, the diprotected phenylenediamines were dissolved in CH_3CN, admixed with K_2CO_3 and *cis*-1,4-dichloro-2-butene, and heated at reflux overnight.[6] Ultimate purification by flash chromatography on silica gel afforded pure samples of **8a**−**g**.

Formation of the Dibromides. The addition of elemental bromine to the five symmetrically difunctionalized benzodiazocines **8a**−**e** in CH_2Cl_2 at 0 °C to rt under standardized conditions led quantitatively to the formation of **12a**−**e** and **13a**−**e** in the ratios compiled for entries 1−5 in Table 1. No additional products were isolated, thereby demonstrating the consistency of the chemical response of these medium-ring heterocycles. When the observations were made that the more electronically deactivated diazocines **8b** and **8c** did not proceed to completion even after several days at rt, the decision was made to employ an excess of the halogen in the preparative scale experiments. For convenience, the subsequent quantitative bromination studies were performed under standard conditions with 5.0 equiv of Br_2.



The ^1H NMR spectra of **12b**−**g** were expectedly very similar to those of **12a**, whose trans geometry had been previously defined by X-ray crystallography.[3] The cis relative configuration of the Br and CH_2Br substituents in **13b**−**g** could be similarly deduced by spectral comparison with **13a** and three-dimensional structure analysis.[3] However, definition of the regiochemical course of this ring contraction required independent verification of the exact placement of the para substituents **X** and **Y** when different (**13f** and **13g**).

A general trend for the bromination reaction was observed, as electron-withdrawing groups tended to decrease the amount of rearranged dibromide generated during the reaction (Table 1, entries 1 and 2), whereas electron-donating groups showed enhancement of the amount of rearranged dibromide (entries 4 and 5). As a result, the ratios of trans dibromides to rearranged dibromides at the time of reaction completion were concluded to be directly related to the nucleophilicity of the sulfonamide nitrogens and, hence, to the nature of the para substituents in the particular sulfonamide.

The two nonsymmetric substrates **8f** and **8g** were investigated to shed added insight into this trend by way of intramolecular competition. Diazocine **8f** reacted with Br_2 to give *trans*-dibromide **12f** as well as a mixture of two rearranged dibromides, **13f** and its regioisomer (X = Br, Y = CH_3) in a 2:1 ratio, respectively. In contrast, diazocine **8g** reacted with Br_2 to generate *trans*-dibromide **12g** and the unique rearranged dibromide **13g**, whose structure could be determined by high-field NMR analysis and X-ray crystallography (see the Supporting Information for an ORTEP diagram of **13g**).

In both cases (**8f** and **8g**), we observed that the sulfonamido nitrogen linked to the electron-donating group displayed enhanced nucleophilicity as demonstrated by the regioselectivity of the rearrangement of the diazocine upon bromination. As a consequence, we concluded that electron-withdrawing groups reduce the nucleophilicity of the nitrogen, which in turn decreases neighboring group participation of this nitrogen in the bromination reaction. Conversely, electron-donating groups enhance the nucleophilicity of the sulfonamide nitrogen, which increase its neighboring group participation.

Concurrently, we evaluated the influence of the para substituents of the sulfonyl protecting group on the reactivity of the double bond of the diazocines toward bromine. This was achieved via high-field ^1H NMR monitoring of the reaction progress. Diazocines **8a**−**g** were dissolved in $CDCl_3$ at rt, placed in NMR tubes, and treated with Br_2 (5.0 equiv) in one portion.

(6) (a) Malhas, R. N.; Ibrahim, Y. A. *Synthesis* **2006**, 3261. (b) Proust, N.; Preston, A.; Paquette, L. A. *Heterocycles* **2009**, *77*, 163.

TABLE 2. Reactivity of the Double Bond

entries	substrate **8**	completion time (min)	**1**/time (min^{-1})
1	**b**, NO_2/NO_2	1020	9.8
2	**c**, Br/Br	520	19.2
3	**d**, H/H	165	60.6
4	**a**, Me/Me	75	133.3
5	**e**, OMe/OMe	75	133.3
6	**f**, CH_3/Br	555	18.0
7	**g**, NO_2/MeO	600	16.7

The NMR tubes were then loaded into a 400 MHz NMR spectrometer, and spectra of the reaction mixtures were collected until completion of the reaction was established. Each substrate was noted to require a different time to reach complete reaction (Table 2). Concluded from these data is the fact that electron-withdrawing groups (such as NO_2 or Br) on the sulfonyl protecting group appreciably decrease the reactivity of the double bond of the diazocine (entries 1, 2, 6, and 7). On the other hand, electron-donating groups (such as CH_3 or MeO) dramatically increase the reactivity of the double bond of the diazocine as demonstrated by the shorter time needed to bring about complete conversion to products (entries 4 and 5). These observations highlight the long-range inductive effect of para substituents of the sulfonyl protecting groups on the electronic profile of the diazocine double bond.

Experimental data gleaned from ^{1}H NMR monitoring of the bromination of substrates **8a**−**g** have led us to conclude that substituents para to the sulfonyl protecting groups have a marked influence on both the nucleophilicity of the sulfonamide nitrogens and the reactivity of the double bond of the diazocines. Electron-withdrawing groups greatly decrease the reactivity of the diazocine double bond as well as the nucleophilicity of the sulfonamido nitrogens. Electron-donating groups exhibit the opposite effect and lead to shorter reaction times and enhanced amounts of rearranged dibromides.

Experimental Section

General Method for the Preparation of the Diprotected *o*-Phenylenediamines. To an ice-cold solution of *o*-phenylenediamine (2.00 g, 18.5 mmol, 1.0 equiv) and pyridine (2.0 equiv) in CH_2Cl_2 (50 mL) was added portionwise the desired sulfonyl chloride (2.0 equiv). The reaction mixture was warmed and maintained at rt until completion of the reaction (TLC analysis). Water (50 mL) was next introduced, causing the product to precipitate. (When no precipitation was observed, the products were extracted into CH_2Cl_2. The CH_2Cl_2 layer was dried and evaporated to give a residue, which was recrystallized from ethanol.) The reaction mixture was filtered and the cake was washed with H_2O. The orange-red solid so obtained was recrystallized from EtOH to afford a pale yellow to white crystalline product.

***p*-Br/*p*-CH_3 derivative 11f:** 7.0 g, 79%; mp 200−201 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.49−7.39 (m, 6H), 7.11−7.08 (m, 2H), 7.03−6.81 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 144.4, 137.7, 134.9, 132.2, 131.2, 130.0, 129.7, 129.1, 128.3, 127.8, 127.6, 127.3, 126.5, 125.7, 21.6; HRMS (ES) calcd for $[C_{19}H_{17}BrN_2O_4S_2 + Na]^+$ 504.9682, found 504.9685.

***p*-NO_2/*p*-MeO derivative 11g:** 6.6 g, 60%; mp 204−205 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.56 (br s, 1H), 8.38 (m, 2H), 7.97 (m, 2H), 7.58 (m, 2H), 7.27−6.91 (m, 6H), 3.85 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 163.5, 150.5, 144.6, 131.3, 130.9, 129.9, 129.5, 128.9, 127.9, 127.5, 127.3, 126.4, 126.1, 126.0, 124.4, 124.3, 114.2, 55.3; HRMS (ES) calcd for $[C_{19}H_{17}N_3O_7S_2 + Na]^+$ 486.0400, found 486.0386.

General Method for the Preparation of the Diazocines. A solution of the *N*,*N*′-disulfonyl-1,2-diaminobenzene (1.0 g) and *cis*-1,4-dichloro-2-butene (1.0 equiv) in acetonitrile (100 mL) over K_2CO_3 (5.0 equiv) was heated at reflux for 24 h. At the end of this period, the reaction mixture was cooled to rt, filtered, and freed of solvent under reduced pressure. The resulting pale yellow solid was purified over silica gel by flash chromatography (CH_2Cl_2/EtOAc, 98:2) to provide the desired diazocine as a white powder.

***p*-Br/*p*-CH_3 derivative 8f:** 1.55 g, 70%; mp 197−199 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69−7.66 (m, 6H), 7.40−7.10 (m, 6H), 5.67−5.60 (m, 2H), 4.36 (d, J = 6.0 Hz, 2H), 4.19 (d, J = 4.8 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.0, 137.6, 136.3, 135.7, 132.4, 132.3, 129.9, 129.8, 129.7, 129.3, 129.2, 128.4, 128.2, 128.1, 127.9, 127.7, 48.4, 47.1, 21.6; HRMS (ES) calcd for $[C_{23}H_{21}BrN_2O_4S_2 + Na]^+$ 556.9999, found 556.9979.

***p*-NO_2/*p*-MeO derivative 8g:** 0.76 g, 68%; mp 213.8−214.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (m, 2H), 8.02 (m, 2H), 7.63 (m, 2H), 7.58 (m, 1H), 7.31 (m, 1H), 7.18 (m, 1H), 6.98 (m, 2H), 6.83 (m, 1H), 5.70−5.64 (m, 2H), 5.60−5.55 (m, 2H), 4.58 (d, J = 7.6 Hz, 2H), 4.07 (dd, J = 4.8, 0.8 Hz, 2H), 3.9 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.3, 150.3, 143.9, 136.9, 135.3, 130.5, 130.2, 130.1, 129.6, 128.7, 128.0, 127.7, 126.6, 124.3, 114.3, 55.7, 49.4, 46.3; HRMS (ES) calcd for $[C_{23}H_{21}N_3O_7S_2 + Na]^+$ 538.0713, found 538.0722.

General Method for Dibromination with a Large Excess of Br_2. 3,4-Dibromo-1,6-bis(X-4-sulfonyl)-1,2,3,4,5,6-hexahydrobenzo[*b*] [1,4]diazocine and 3-bromo-2-bromomethyl-1,5-bis(X-4-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine (X = NO_2, Br, H, CH_3, MeO). In a 50 mL flask was loaded diazocine **8** (100 mg, 2.14 mmol) dissolved in CH_2Cl_2 (5 mL) at rt. The resulting mixture was cooled to 0 °C in an ice bath when Br_2 (10.0 equiv) was added dropwise. Each reaction mixture was slowly warmed and maintained at rt until completion was reached (reactions were followed by TLC analysis, CH_2Cl_2). Saturated aqueous $NaHSO_3$ solution was added to quench the excess bromine, CH_2Cl_2 and water were added, and the CH_2Cl_2 layer was separated, dried, and evaporated under reduced pressure to afford an off-white solid. The solid was analyzed by ^{1}H NMR and shown to consist of the normal *trans*-dibromide **12** and the rearranged dibromides **13**, which could be separated by chromatography on silica gel using CH_2Cl_2 as the eluent.

***p*-MeO Derivatives. 12e:** mp 192−195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87−7.83 (m, 4H), 7.31 (s, 4H), 7.03−6.99 (m, 4H), 4.24−4.21 (m, 2H), 4.08−4.01 (m, 4H), 3.88 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 136.8, 130.6, 130.2, 129.6, 129.1, 114.4, 55.7, 54.8, 51.5; HRMS (ES) calcd for $[C_{24}H_{24}Br_2N_2O_6S_2 + Na]^+$ 682.9315, found 682.9281.

13e: mp 118−120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94−7.91 (m, 2H), 7.88−7.84 (m, 2H), 7.54 (d, J = 8 Hz, 1H), 7.44−7.38 (m, 2H), 7.33−7.31 (m, 1H), 7.06−7.00 (m, 4H), 4.68−4.63 (m,1H), 4.39 (dd, J = 15.2, 3.6 Hz, 1H), 4.32 (dt, J = 12.0, 4.0 Hz, 1H), 3.90 (m, 6H), 3.83 (dd, J = 11.2, 2.4 Hz, 1H), 3.04 (dd, J = 14.8, 12.4 Hz, 1H), 2.50 (t, J = 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 163.4, 138.9, 132.2, 131.7, 131.2, 131.0, 130.3, 130.2, 129.5, 128.9, 128.3, 114.6, 114.2, 60.7, 55.7, 55.6, 48.7, 48.1, 26.7; HRMS (ES) calcd for $[C_{24}H_{24}Br_2N_2O_6S_2 + Na]^+$ 682.9315, found 682.9292.

***p*-NO_2/*p*-MeO Derivatives. 12g:** mp 170−171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (dd, J = 2.0, 7.2 Hz, 2H), 8.14 (dd, J = 2.0, 7.3 Hz, 2H), 7.78 (dd, J = 2.0, 7.2 Hz, 2H), 7.59 (dd, J = 1.2, 8.4 Hz, 1H), 7.41 (dt, J = 1.2, 7.6 Hz), 7.35 (dt, J = 1.2, 7.6 Hz, 1H), 7.03 (dd, J = 2.1, 7.0 Hz, 2H), 6.98 (dd, J = 1.2, 7.6 Hz, 1H), 4.62−4.59 (m, 1H), 4.35 (dd, J = 5.6, 14.4 Hz, 1H), 4.28−4.24 (m, 1H), 4.06−3.96 (m, 2H), 3.91 (s, 3H), 3.87−3.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6, 150.5, 150.4, 144.1, 137.8, 130.9, 130.4, 129.9, 129.8, 129.7, 129.0, 124.4, 114.5, 60.4, 55.7, 55.1, 21.0, 14.2; HRMS (ES) calcd for $[C_{23}H_{21}Br_2N_3O_7S_2 + Na]^+$ 697.9060, found 697.9078.

13g: mp 218−220 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36−8.35 (m, 2H), 8.07−8.04 (m, 2H), 7.82−7.78 (m, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.48−7.44 (m, 1H), 7.40−7.38 (m, 1H),

7.02−6.99 (m, 2H), 4,74−4.70 (m, 1H), 4.43−4.36 (m, 2H), 3.90 (s, 3H), 3.79−3.76 (m, 1H), 3.15 (dd, J = 12.4, 15.6, 1H), 2.43 (t, J = 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6, 150.5, 145.0. 137.6, 133.5, 132.8, 131.2, 130.7, 130.3, 130.0, 129.7, 129.3, 124.8, 114.3, 60.4, 55.7, 49.0, 47.5, 26.4; HRMS (ES) calcd for $[C_{23}H_{21}Br_2N_3O_7S_2 + Na]^+$ 697.9060, found 697.9087.

Quantitative Bromination Studies. Each experiment was performed under standardized conditions with 5 equiv of bromine dissolved in CH_2Cl_2 in the temperature range 0 °C to rt. The product distributions (see Table 1) were determined after workup with the NMR data provided above as reference.

Acknowledgment. We thank The Ohio State University for partial financial support and Dr. Jeanette Krause of the University of Cincinnati for the crystallographic data collection.

Supporting Information Available: Experimental data, details of the X-ray crystallographic analysis of **13f**, and copies of the ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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