Tetrahedron Letters 51 (2010) 2745–2747

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The combination of $TsNBr_2/TsNH_2$ as the nitrogen/halo source for the aminobromination of β-methyl-β-nitrostyrenes catalyzed by $Mn(OAc)_2$

Sanjun Zhi [a,b], Guanghui An [b], Hao Sun [b], Jianlin Han [b,*], Guigen Li [c,*], Yi Pan [b,*]

[a] Jiangsu Key Laboratory for the Chemistry of Low-Dimensional Materials, Huaiyin Normal University, Huaian 223300, PR China
[b] School of Chemistry and Chemical Engineering, Nanjing University, State Key Laboratory of Coordination, Nanjing, 210093, China
[c] Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

ARTICLE INFO

Article history:
Received 5 January 2010
Revised 9 March 2010
Accepted 16 March 2010
Available online 19 March 2010

ABSTRACT

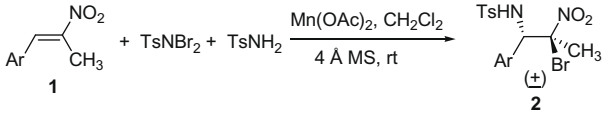
The combination of *N*,*N*-dibromo-*p*-tolunesulfonamide (4-$TsNBr_2$) and $TsNH_2$ was found to be an efficient halogen/nitrogen source for the aminohalogenation of β-methyl-β-nitrostyrenes with manganese (II) acetate as the catalyst in the presence of 4 Å molecular sieves. The reaction results in vicinal bromoamino nitroalkanes with the opposite regioselectivity comparing with those reported, which was also confirmed by X-ray structural analysis.

Vicinal haloamines are important building blocks in organic and medicinal chemistry,[1] because they can be easily converted into numerous useful functional groups by replacement of the halogen in both intramolecular and intermolecular reactions.[2] Aminohalogenation of functionalized olefins provides an easy route to vicinal haloamines.[3–6] In recent years, the catalytic aminohalogenation of alkenes has received many attentions. A variety of nitrogen/halogen sources such as *N*,*N*-dichloro-2-nitrobenzenesulfonamide,[2c,7] $TsNCl_2$,[8] *N*,*N*-dichlorobenzenesulfonamide,[5c,9] 4-$TsNBr_2$,[10] *N*,*N*-dibromobenzenesulfonamide,[11a–c] chloramine-T[11d,11e,16a], and 4-$TsNH_2$/NBS[12] have been used in the reactions. Some of the reactions gave the corresponding haloamines with good chemical yields and stereoselectivities. Although several functionalized olefins, including α,β-unsaturated carboxylic esters,[8c–e] α,β-unsaturated ketones,[13] vinylidenecyclopropanes[14], and α,β-unsaturated nitriles,[15] have been used in the aminohalogenation reactions,[16–19] the reaction of nitro-substituted olefins receives little attention until we reported that the reaction of β-nitrostyrenes with $TsNCl_2$ offers a specific 1,2-vicinal dichloroamino products.[20]

As the formed vicinal dihaloamino nitroalkanes could be converted into diamine and other useful compounds,[21] we continued our investigations on the aminohalogenation reaction of nitro-substituted olefins. Herein, we reported our preliminary results on the aminohalogenation reaction of β-methyl-β-nitrostyrenes. We found that the reaction of β-methyl-β-nitrostyrenes with $TsNBr_2$ and $TsNH_2$ as halo/nitrogen source catalyzed by $Mn(OAc)_2$ proceeds smoothly offering new vicinal mono-bromoamination products with opposite regioselectivity comparing with aminohalogenation of regular electron-deficient olefins(Scheme 1).[16–19]

Initially, the reaction of β-methyl-β-nitrostyrene (**1a**) with $TsNBr_2$ was conducted under previous catalytic conditions with dichloromethane as solvent, DMAP as the catalyst in the presence of 4 Å molecular sieves at room temperature.[20] No desired dibromoamino product was observed and most of the starting materials remained even after the reaction time was extended to 72 h and the temperature was increased to 50 °C. We next investigated the reaction by using $TsNH_2$ as a co-additive. Pleasingly, a new product was observed with 30% yield after 48 h. The new product was carefully isolated and characterized. ^{1}H NMR analysis of the compound (**2a**) revealed that the product was not the expected dibromoamine product. X-ray crystal structure analysis revealed that the product is monohaloamine with bromo moiety attached to the α-carbon atom of nitro group, and not to β-position (Fig. 1). This regioselectivity was opposite to that of previously reported.[16–19]

In order to improve the chemical yield, a series of metal salts were tried (Table 1). As shown in Table 1, $Mn(OAc)_2$ was found to be the best catalyst and can catalyze the reaction to complete within 48 h resulting in the vicinal haloamine **2a** with 78% chemical yield (Table 1, entry 6). DMAP, the most effective catalyst for β-nitrostyrenes,[20] was not a good catalyst for the current system



Scheme 1. Reaction of β-methyl-β-nitrostyrenes with $TsNBr_2/TsNH_2$.

* Corresponding authors. Tel.: +86 25 83592846; fax: +86 25 83309123 (J.H.).
E-mail addresses: molab@nju.edu.cn (J. Han), guigen.li@ttu.edu (G. Li), yipan@nju.edu.cn (Y. Pan).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.03.060

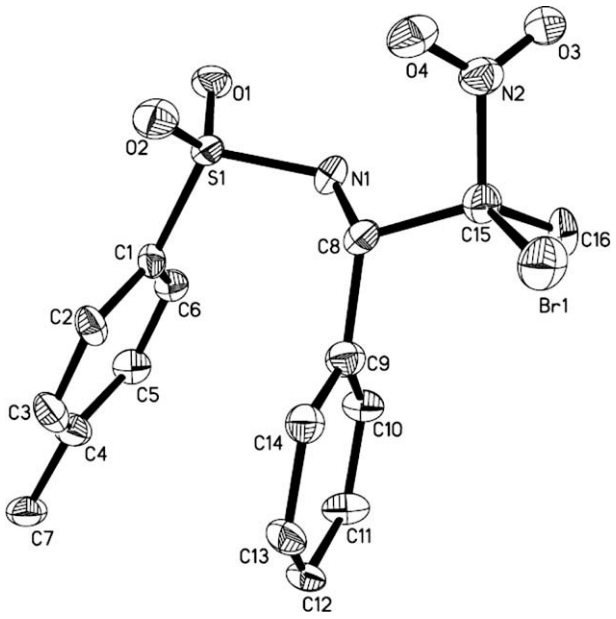
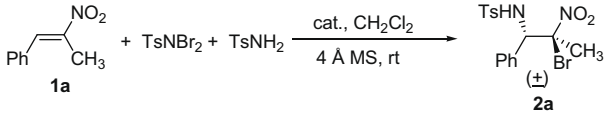


Figure 1. ORTEP diagram showing **2a**.

Table 1
Aminohalogenation reaction of β-methyl-β-nitrostyrene with $TsNBr_2/TsNH_2$[a]



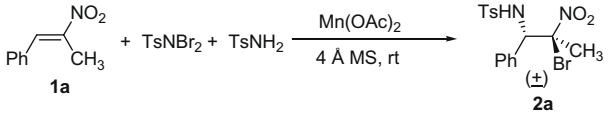
Entry	Catalysts	Yield[b] (%)
1	DMAP	30
2	$MnSO_4$	40
3	$Cu(OAc)_2$	56
4	AgOAc	30
5	$Ni(OAc)_2$	61
6	$Mn(OAc)_2$	78
7	AgOTs	45
8	CuI	<5
9	CuCl	<5
10	CuOTf	<5
11	$CuCl_2$	<5

[a] Condition: **1a** (1.0 mmol), $TsNBr_2$ (2.0 mmol), $TsNH_2$ (2.0 mmol), catalysts (20 mol %), and 4 Å molecular sieves (500 mg) in CH_2Cl_2 (5.0 mL) at room temperature under N_2.
[b] Isolated yields.

(Table 1, entry 1). $MnSO_4$, $Cu(OAc)_2$, AgOAc, $Ni(OAc)_2$, and AgOTs can also catalyze the reaction but offer lower chemical yields (Table 1, entries 2–5 and 7). Almost no desired product was detected when CuI, CuCl, CuOTf, or $CuCl_2$ was employed as catalysts in the reactions (Table 1, entries 8–11), and most of the starting materials remained.

Effect of solvents on the reaction was also checked (Table 2). As revealed in Table 2, CH_2Cl_2 was the best choice for this reaction and the highest chemical yield was obtained (Table 2, entry 1). Other solvents such as CH_3CN, $CHCl_3$, toluene, and CCl_4, gave lower yields (Table 2, entries 2–5). No desired product was obtained at all when the reaction was performed in THF or DMF (Table 2, entries 6 and 7). Interdiction effect of THF or DMF to the reaction may be due to their coordinative capability to the metal center, lowering catalytic activity of the catalyst. The reaction completed usually within 48 h (Table 2, entry 8). Extending the reaction time to 72 h did not give any improvement on the chemical yield (79%, Table 2, entry 9), and

Table 2
Optimization of reaction conditions for β-methyl-β-nitrostyrenes[a]



Entry	Solvents	Time (h)	Cat. (mol %)	Yield[b] (%)
1	CH_2Cl_2	48	20	78
2	CH_3CN	48	20	45
3	$CHCl_3$	48	20	40
4	PhMe	48	20	55
5	CCl_4	48	20	30
6	THF	48	20	<5
7	DMF	48	20	<5
8	CH_2Cl_2	24	20	75
9	CH_2Cl_2	72	20	79
10	CH_2Cl_2	48	10	30

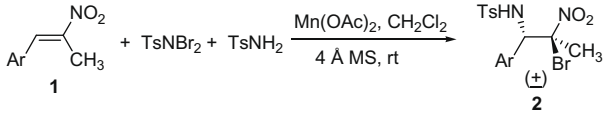
[a] Condition: **1a** (1.0 mmol), $TsNBr_2$ (2.0 mmol), $TsNH_2$ (2.0 mmol), $Mn(OAc)_2$, and 4 Å molecular sieves (500 mg) in solvent (5.0 mL) under N_2.
[b] Isolated yields.

a slightly lower yield would be found when the reaction was stopped at 24 h (75%, Table 2, entry 8). Meanwhile, 20 mol % loading amount of $Mn(OAc)_2$ was necessary for the catalytic system. The yield will decrease to 30% when 10 mol % of $Mn(OAc)_2$ was used in the reaction (Table 2, entry 10).

After optimizing the reaction conditions, a series of β-methyl-β-nitrostyrene derivatives were employed to examine the substrate scope of the current catalytic system (Table 3).[22] As shown in Table 3, several β-methyl-β-nitrostyrenes were suitable olefin substrates for this reaction to give moderate to good yields (40–79%). For the substrate with *para*-MeO, a strong electron-donating group, on the aromatic ring, the highest yield was observed (79%, Table 3, entry 3). Nitro substitution on the aromatic ring lowers the yield substantially even after the reaction time was extended to 72 h (Table 3, entry 7). All the reactions showed good to excellent stereoselectivities with ratios ranging from 10:1 to 20:1, and all the reactions gave only one regioisomer.

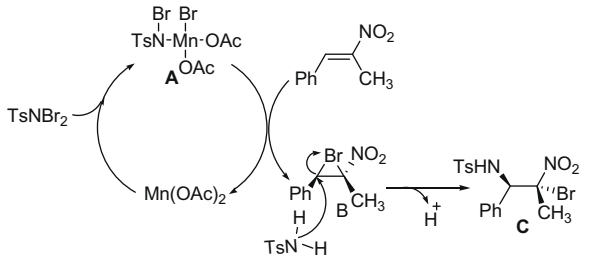
For aminohalogenation, the reaction mechanism should involve the formation of aziridinium intermediates[7,8,13–15,21] or chloronium intermediate.[20] Based on the resulting regio- and stereochemistry of the current aminohalogenation system, a mechanism involving predominant formation of bromonium intermediates was suggested (Scheme 2). As shown in Scheme 2, the first step involves that the catalyst $Mn(OAc)_2$ activates the N–Br bond of

Table 3
Results of the reaction between β-methyl-β-nitrostyrenes and $TsNBr_2/TsNH_2$[a]



Entry	Ar	Products	Stereoselectivity (*anti*:*syn*)[b]	Yield[c] (%)
1	Ph	**2a**	1:15	78
2	4-CH_3–C_6H_4	**2b**	1:12	75
3	4-CH_3O–C_6H_4	**2c**	1:12	79
4	4-Cl–C_6H_4	**2d**	1:15	72
5	4-F–C_6H_4	**2e**	1:10	45
6	2-Cl–C_6H_4	**2f**	1:20	54
7	4-NO_2–C_6H_4	**2g**	1:18	40

[a] Condition: **1** (1.0 mmol), $TsNBr_2$ (2.0 mmol), $TsNH_2$ (2.0 mmol), $Mn(OAc)_2$ (20 mol %) and 4 Å molecular sieves (500 mg) in CH_2Cl_2 (5.0 mL) under N_2.
[b] The selectivity of *anti*:*syn* was detected by crude ^1H NMR.
[c] Isolated yields.



Scheme 2. Suggested mechanism for the reaction.

$TsNBr_2$ to generate a new intermediate **A**. At the second step, 'Br^+' is delivered from intermediate **A** to the C=C double bond of β-methyl-β-nitrostyrene to give the bromonium intermediate **B**. The positively charged bromonium intermediate **B** is opened by *p*-toluenesulfonamide on its α-position which is more positively charged than its β-position, giving the final vicinal bromoamine product **C**. The regio- and stereoselectivity of this reaction can be explained well on the basis of this mechanistic hypothesis involving the key halonium intermediate.

In conclusion, a novel regio- and stereoselective aminobromination of β-methyl-β-nitrostyrenes using $TsNBr_2/TsNH_2$ as a halo/nitrogen source catalyzed by $Mn(OAc)_2$ has been developed. The reaction was carried out at room temperature, and the new method provides an easy route to vicinal bromoamino nitroalkanes with opposite regioselectivity compared to that of previously reported. Moderate to good chemical yields and excellent regio- and stereoselectivity have been obtained. The structure and stereochemistry of the product were confirmed by X-ray analysis.

Acknowledgments

We gratefully acknowledge National Natural Science Foundation of China (Grant Nos. 20772056 and 20932004) and Jiangsu 333 program (for Pan) for the generous financial support. This work was also partially supported by the Jiangsu Key Laboratory for the Chemistry of Low-Dimensional Materials (No. JSKC09069).

References and notes

1. Qui, J.; Silverman, R. B. *J. Med. Chem.* **2000**, *43*, 706.
2. (a) Chen, D.; Timmons, C.; Guo, L.; Xu, X.; Li, G. *Synthesis* **2004**, 2749; (b) Chen, D.; Kim, S. H.; Hodges, B.; Li, G. *ARKIVOC* **2003**, 56; (c) Chen, D.; Guo, L.; Liu, J.; Kirtane, S.; Cannon, J. F.; Li, G. *Org. Lett.* **2005**, *7*, 921.
3. Kemp, J. E.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 469–513.
4. (a) Yeung, Y. Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644; (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863; (c) Driguez, H.; Vermes, J. P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119; (d) Lessard, J.; Driguez, H.; Vermes, J. P. *Tetrahedron Lett.* **1970**, *11*, 4887.
5. (a) Daniher, F. A.; Butler, P. E. *J. Org. Chem.* **1968**, *33*, 4336; (b) Daniher, F. A.; Butler, P. E. *J. Org. Chem.* **1968**, *33*, 2637; (c) Daniher, F. A.; Melchior, M. T.; Butler, P. E. *Chem. Commun.* **1968**, 931; (d) Orlek, B. S.; Stemp, G. *Tetrahedron Lett.* **1991**, *32*, 4045.
6. (a) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618; (b) Danielec, H.; Klugge, J.; Schlummer, B.; Bach, T. *Synthesis* **2006**, 551; (c) Xu, L.; Du, H. F.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 7038; (d) Du, H. F.; Yuan, W. C.; Zhao, B. G.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496; (e) Du, H. F.; Zhao, B. G.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762.
7. (a) Li, G.; Kim, S. H.; Wei, H. *Tetrahedron Lett.* **2000**, *41*, 8699; (b) Liu, J.; Wang, Y.; Li, G. *Eur. J. Org. Chem.* **2006**, 3112; (c) Rozentsveig, I. B.; Levkovskaya, G. G.; Rybalova, T. N.; Mirskova, A. N. *Russ. J. Org. Chem.* **2001**, 87.
8. (a) Li, G.; Wei, H. X.; Kim, S. H.; Neighbors, M. *Org. Lett.* **1999**, *1*, 395; (b) Xin, X.; Kotti, S.; Liu, Y.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 4881; (c) Chen, D.; Timmons, C.; Chao, S.; Li, G. *Eur. J. Org. Chem.* **2004**, *12*, 3097; (d) Wei, H. X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 3869; (e) Kotti, S.; Xu, X.; Wang, Y.; Headley, A. D.; Li, G. *Tetrahedron Lett.* **2004**, *45*, 7209; (f) Han, J.; Li, Y.; Zhi, S.; Pan, Y.; Timmons, C.; Li, G. *Tetrahedron Lett.* **2006**, *47*, 7225.
9. (a) Ueno, Y.; Takemura, S.; Ando, Y.; Terauchi, H. *Chem. Pharm. Bull.* **1965**, *13*, 1369; (b) Levkovskaya, G. G.; Rudyakova, E. V.; Rozentsveig, I. B.; Mirskova, A. N.; Albanov, A. I. *Russ. J. Org. Chem.* **2000**, *36*, 1338.
10. (a) Yamasaki, A.; Terauchi, H.; Takemura, S. *Chem. Pharm. Bull.* **1976**, *24*, 2841; (b) Terauchi, H.; Yamasaki, A.; Takemura, S. *Chem. Pharm. Bull.* **1975**, *23*, 3162; (c) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811; (d) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9526; (e) Revesz, L.; Blum, E.; Wicki, R. *Tetrahedron Lett.* **2005**, *46*, 5577.
11. (a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444; (b) Terauchi, H.; Kowata, K.; Minematsu, T.; Takemura, S. *Chem. Pharm. Bull.* **1977**, *25*, 556; (c) Shen, R.; Huang, X. *J. Org. Chem.* **2007**, *72*, 3961; (d) Minakata, S.; Yoneda, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2006**, *8*, 967; (e) Wang, G. W.; Wu, X. L. *Adv. Synth. Catal.* **2007**, *349*, 1977.
12. (a) Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861; (b) Wu, X. L.; Xia, J. J.; Wang, G. W. *Org. Biomol. Chem.* **2008**, *6*, 548; (c) Wei, J. F.; Zhang, L. H.; Chen, Z. G.; Shi, X. Y.; Cao, J. J. *Org. Biomol. Chem.* **2009**, *7*, 3280–3284; (d) Wang, Z.; Zhang, Y. M.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Synlett* **2008**, 2667–2670; (e) Wu, X. L.; Wang, G. W. *Tetrahedron* **2009**, *65*, 8802–8807; (f) Wei, J. F.; Chen, Z. G.; Lei, W.; Zhang, L. H.; Wang, M. Z.; Shi, X. Y.; Li, R. T. *Org. Lett.* **2009**, *11*, 4216–4219.
13. (a) Li, G.; Wei, H. X.; Kim, S. H. *Tetrahedron* **2001**, *57*, 8407; (b) Li, G.; Kim, S. H.; Wei, H. X. *Tetrahedron Lett.* **2000**, *41*, 8699.
14. Li, Q.; Shi, M.; Timmons, C.; Li, G. *Org. Lett.* **2006**, *8*, 625.
15. Han, J.; Zhi, S.; Wang, L.; Pan, Y.; Li, G. *Eur. J. Org. Chem.* **2007**, 1332.
16. (a) Qi, X.; Lee, S. H.; Kwon, J. Y.; Kim, Y.; Kim, S. J.; Lee, Y. S.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 9140; (b) Nadir, U. K.; Singh, A. *Synth. Commun.* **2004**, *37*, 1337; (c) Ye, C.; Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 856.
17. (a) Wang, G. W.; Wu, X. L. *Eur. J. Org. Chem.* **2008**, 6239; (b) Wu, X. L.; Wang, G. W. *J. Org. Chem.* **2007**, *72*, 9398.
18. Chen, Z. G.; Wei, J. F.; Li, R. T.; Shi, X. Y.; Zhao, P. F. *J. Org. Chem.* **2009**, *74*, 1371.
19. (a) Li, G.; Wei, H. X.; Kim, S. H. *Org. Lett.* **2000**, *2*, 2249; (b) Raghavan, S.; Reddy, S. R.; Tony, K. A.; Kumar, C. N.; Nanda, S. *Synlett* **2001**, 851; (c) Volonterio, A.; Bravo, P.; Panzeri, W.; Pesenti, C.; Zanda, M. *Eur. J. Org. Chem.* **2002**, 3336.
20. (a) Zhi, S.; Han, J.; Lin, C.; An, G.; Pan, Y.; Li, G. *Synthesis* **2008**, 1570; (b) Zhi, S.; Li, T.; An, G.; Pan, Y. *Acta Crystallogr., Sect. E* **2008**, *64*, o357.
21. (a) Kotti, S. S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101; (b) Li, G.; Wei, H. X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277; (c) Wang, B.; Du, H. F.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224; (d) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147; (e) Muniz, K.; Streuff, J.; Chavez, P.; Hovelmann, C. H. *Chem. An Asian J.* **2008**, *3*, 1255; (f) Du, H. F.; Zhao, B. G.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590.
22. General procedure for aminohalogenation (Table 3). Into a dry vial were added β-methyl-β-nitrostyrenes (1 mmol), $TsNH_2$ (2.0 mmol), $Mn(OAc)_2$ (0.20 mmol), 4 Å molecular sieves (500 mg), then was added dichloromethane (5.0 mL) under nitrogen atmosphere. The mixture was stirred for 10 min before $TsNBr_2$ (2.0 mmol) was added. The resulting mixture was stirred at room temperature for 48 h. The reaction was then quenched with saturated aqueous Na_2SO_3 (5.0 mL). All the solid precipitates were filtered off and washed with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine and dried with anhydrous sodium sulfate. Purification by TLC (EtOAc/petroleum ether, 1:4 v/v) provided the pure product. Characterized data for **2a**: White solid. Mp 175–176 °C. IR (KBr): υ = 3270, 1598, 1564, 1334, 1161, 895, 816 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.51 (m, 2H), 7.02–7.20 (m, 7H), 6.43 (d, *J* = 10.8 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H), 2.30 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.4, 137.9, 133.9, 129.6, 129.4, 128.8, 128.3, 127.2, 97.9, 65.7, 26.4, 20.7 ppm. MS (EI) *m*/*z*: 434.8 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{17}BrN_2O_4S$: C, 46.50; H, 4.15; N, 6.78. Found: C, 46.48; H, 4.11; N, 6.75; CCDC number: 686202.