Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2007–2011

Expeditious synthesis of 3-arylidenelactams and 3-arylidenelactones from *N*-tosylaziridine derivatives

Ka Young Lee, Hyun Seung Lee and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea

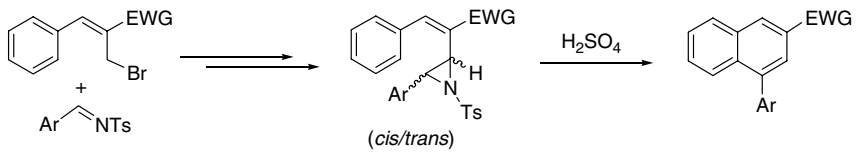
Received 11 December 2006; revised 28 December 2006; accepted 12 January 2007
Available online 18 January 2007

Abstract—An expeditious synthetic method of 3-arylidenelactams was developed starting from *N*-tosylaziridines, which were made from the reaction of *N*-tosylimines and cinnamyl bromides by using the sulfur ylide chemistry. The regioselective ring-opening reaction of *N*-tosylaziridines with anilines, as external nucleophiles, and the following lactamization afforded 3-arylidenelactams. In the absence of external nucleophiles, intramolecular lactonization occurred to afford 3-arylidenelactones.

A variety of lactams are found in biologically important compounds and numerous synthetic methods for these compounds have been studied and reported.[1] One of the important methods for lactam skeleton involved the chemical transformation of aziridine derivatives.[1b] The ring-opening reaction of *N*-tosylaziridines with a variety of nucleophiles has been used in organic synthesis.[2] Recently, we reported the successful synthesis of 1-arylnaphthalene derivatives via the intramolecular Friedel–Crafts reaction of *N*-tosylaziridines, which were made from Baylis–Hillman adducts (Scheme 1).[3]

As a continuous study on this useful intermediate, *N*-tosylaziridines,[3,4] we presumed that we could prepare 3-arylidenelactam derivatives as shown in Scheme 2. Actually, the reaction of *N*-tosylaziridine **1a** and aniline (**2a**), as the representative external nucleophile, in CH_3CN in the presence of $LiClO_4$ (1.2 equiv) afforded the expected lactam **4a** in a 75% yield as a single stereoisomer (trans-form, vide infra) under refluxing conditions for 24 h.[5] When we carried out the same reaction at room temperature we did not observe the formation of lactam **4a**, instead we isolated the vicinal diamine derivative **3a** in an 85% yield as a single regio- and stereoisomer (anti-form).[5] Vicinal diamine **3a** was converted to **4a** in a 78% yield in the presence of $LiClO_4$. The results suggested that the reaction might occur via the S_N1 type mechanism as depicted in Scheme 2: (i) regioselective ring-opening of *N*-tosylaziridine by the assistance of $LiClO_4$ to the more stable benzylic carbocation intermediate (**I**), (ii) reaction with aniline (**2a**) to form *anti*-diamine **3a** stereoselectively, and (iii) lactamization to *trans*-lactam **4a**. From the literature survey the regioselective ring-opening of *N*-tosylaziridine at the benzylic position might be the preferred pathway under acidic conditions (like S_N1 type conditions).[2e–k] Although we could not rule out completely the possibility for the formation of the other regio- and/or stereoisomers, we could isolate **3a** only.

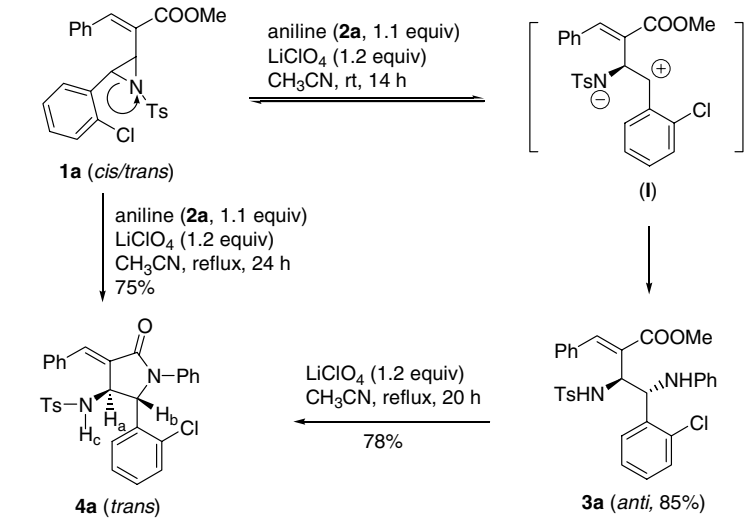
The stereochemistry of lactam compound **4a** was thought to be as trans-form based on the coupling



Scheme 1.

Keywords: *N*-Tosylaziridines; γ-Lactams; γ-Lactones; Baylis–Hillman adducts.
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; e-mail: kimjn@chonnam.ac.kr

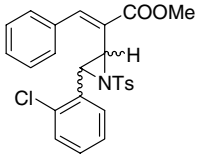
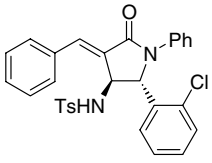
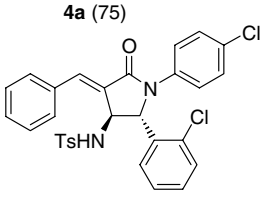
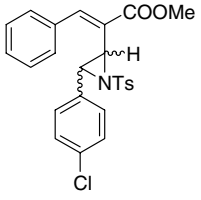
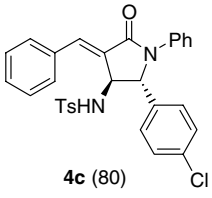
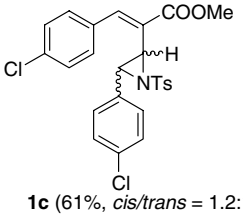
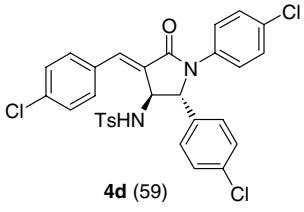
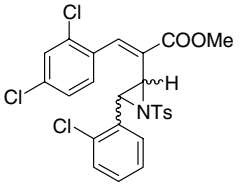
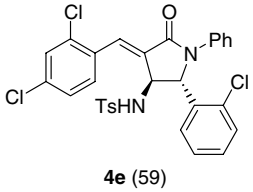
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.062

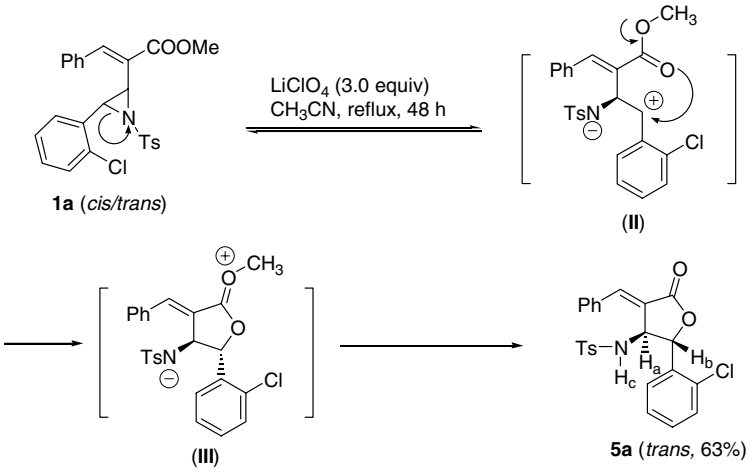


H_a (δ = 4.69 ppm, d, J_{ac} = 8.1 Hz)
H_b (δ = 5.76 ppm, s, J_{ab} = 0 Hz)
H_c (δ = 4.23 ppm, d, J_{ac} = 8.1 Hz, D_2O exchangeable)
D_2O treatment: H_c disappeared and H_a was converted to singlet

Scheme 2.

Table 1. Synthesis of 3-arylidene-4,5-disubstituted-γ-butyrolactam derivatives

Entry	Aziridines	Conditions	Lactams (%)
1	 **1a** (70%, *cis/trans* = 1:3)	Aniline (**2a**, 1.1 equiv), $LiClO_4$ (1.2 equiv), CH_3CN, reflux, 24 h	 **4a** (75)
2	**1a**	4-Chloroaniline (**2b**, 1.1 equiv), $LiClO_4$ (1.2 equiv), CH_3CN, reflux, 24 h	 **4b** (90)
3	 **1b** (64%, *cis/trans* = 1.4:1)	Aniline (**2a**, 1.1 equiv), $LiClO_4$ (1.5 equiv), CH_3CN, reflux, 24 h	 **4c** (80)
4	 **1c** (61%, *cis/trans* = 1.2:1)	**2b** (1.1 equiv), $LiClO_4$ (1.2 equiv), CH_3CN, reflux, 14 h	 **4d** (59)
5	 **1d** (61%, *cis/trans* = 3:2)	**2a** (1.1 equiv), $LiClO_4$ (1.5 equiv), CH_3CN, reflux, 48 h	 **4e** (59)



Scheme 3.

Table 2. Synthesis of 3-arylidene-4,5-disubstituted-γ-butyrolactam derivatives

Entry	Aziridines	Conditions	Lactams (%)
1	**1a**	$LiClO_4$ (3.0 equiv), CH_3CN, reflux, 48 h	**5a** (63)
2	**1e** (84%, *cis/trans* = 1:1.7)	$LiClO_4$ (2.0 equiv), CH_3CN, reflux, 52 h	**5b** (56)
3	**1f** (63%, *cis/trans* = 5:1)	$LiClO_4$ (2.0 equiv), CH_3CN, reflux, 50 h	**5c** (31)
4	**1g** (62%, *cis/trans* = 1:1.4)	$LiClO_4$ (2.0 equiv), CH_3CN, reflux, 20 h	**5d** (58)
5	**1h** (60%, *cis/trans* = 1:2)	$LiClO_4$ (3.0 equiv), CH_3CN, reflux, 48 h	**5d** (39)

constant between the protons H_a and H_b. Actually, H_a and H_b did not couple with each other. Based on D_2O treatment experiment we assigned the doublet at $\delta = 4.23$ ppm as the proton H_c. The two protons H_a and H_c coupled each other with coupling constant of $J = 8.1$ Hz. The absence of coupling between H_a and H_b stated that the dihedral angle between them must be nearly orthogonal. The results could be anticipated easily when we think about the steric bulkiness of 2-chlorophenyl group and the tosylamino moiety.

By using similar conditions we carried out the synthesis of various 3-arylidenelactam derivatives **4b–e** and the results are summarized in Table 1. As shown the stereochemistry of *N*-tosylaziridines[3,4a,b] did not affect the stereochemistry of products **4a–e**. The synthesis of requisite aziridine derivatives **1a–h** was carried out by using the well-known ylide chemistry from the reaction of corresponding *N*-tosylimines and cinnamyl bromides, which could be synthesized from the Baylis–Hillman adduct as in our previous paper.[3]

As a next trial we carried out the reaction of **1a** in the absence of an external nucleophile. A variety of lactone derivatives are also found in biologically important compounds and numerous synthetic methods for these compounds have been studied.[6] Literature survey revealed that ester group can be used as an internal nucleophile toward some reactive electrophilic partner.[7] Thus we examined the reaction of **1a** and expected the formation of 3-arylidenelactone derivative **5a** as in Scheme 3.

As expected the reaction of **1a** under the influence of $LiClO_4$ in CH_3CN furnished **5a** in a 63% yield.[8] In order to optimize the reaction conditions we examined a variety of conditions, which afforded the following results: (a) 44% yield of **5a** by using $Mg(ClO_4)_2$ (2 equiv)/CH_3CN/reflux/36 h; (b) 47% yield of **5a** by using TfOH (1 equiv)/CH_2Cl_2/0 °C–rt, 48 h; (c) 46% yield of **5a** by using BF_3 etherate/CH_2Cl_2/0 °C–rt/36 h; (d) 50% yield of **5a** by using $Sc(OTf)_3$ (0.4 equiv)/CH_3CN/rt, 48 h; (e) trace amount of **5a** by using $LiClO_4$ (3 equiv)/benzene/reflux, 48 h. In all cases we could obtain **5a** but the yield was not better than the original conditions ($LiClO_4$/CH_3CN). The coupling constant between H_a and H_b was zero again as for the cases of 3-arylidenelactams thus we assigned the stereochemistry of **5a** as trans-form. The plausible mechanism for the formation of **5a** is also depicted in Scheme 3. However, we could not rule out the possibility for the reaction mechanism completely at this stage involving moisture in the reaction medium: ring-opening of *N*-tosylaziridine by water and subsequent lactonization to lactone **5a**. As shown in Table 2, we prepared 3-arylidenelactones **5b–d** similarly with somewhat low yield than the corresponding lactam cases.

In summary, we have developed an efficient synthetic method of 3-arylidenelactams from *N*-tosylaziridines via the regioselective ring-opening reaction with anilines and the following lactamization. In the absence of aniline, intramolecular lactonization occurred to afford 3-arylidenelactones in moderate yields.

Acknowledgements

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2006-311-C00384). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

1. For the synthesis and biological activities of α-methylene-γ-butyrolactams and α-alkylidene-γ-butyrolactams, see: (a) Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376–3378; (b) Iwamoto, K.; Kojima, M.; Chatani, N.; Murai, S. *J. Org. Chem.* **2001**, *66*, 169–174; (c) Iyer, S.; Ramesh, C.; Kulkarni, G. M. *Synlett* **2001**, 1241–1244; (d) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem.* **2005**, *48*, 3516–3521; (e) Qiao, L.; Wang, S.; George, C.; Lewin, N. E.; Blumberg, P. M.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 6629–6630; (f) Nyzam, V.; Belaud, C.; Zammattio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835–1843; (g) Lee, E.; Kang, T. S. *Bull. Korean Chem. Soc.* **1993**, *14*, 431–432; (h) Dembele, Y. A.; Belaud, C.; Villieras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511–514; (i) Blaszczyk, E.; Krawczyk, H.; Janecki, T. *Synlett* **2004**, 2685–2688; (j) Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621–1625; (k) Beji, F.; Lebreton, J.; Villieras, J.; Amri, H. *Tetrahedron* **2001**, *57*, 9959–9962.
2. For the ring-opening reactions of aziridine derivatives, see: (a) Sabitha, G.; Babu, S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343–345; (b) Ungureanu, I.; Klotz, P.; Mann, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4615–4617; (c) Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *J. Chem. Soc., Chem. Commun.* **1987**, 153–155; (d) Fan, R.-H.; Hou, X.-L. *Tetrahedron Lett.* **2003**, *44*, 4411–4413; (e) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 2537–2539; (f) Yadav, J. S.; Reddy, B. V. S.; Jyothirmai, B.; Murty, M. S. R. *Synlett* **2002**, 53–56; (g) Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* **1999**, *40*, 9325–9327; (h) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M. *Synlett* **2001**, 1417–1418; (i) Prasad, B. A. B.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4677–4679; (j) Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S. *Tetrahedron Lett.* **2002**, *43*, 7361–7363; (k) Yadav, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* **2002**, *43*, 1565–1567.
3. Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 977–980.
4. For the synthesis and stereochemistry of aziridines involving sulfur ylide chemistry, see: (a) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Chen, M.-B. *J. Org. Chem.* **1996**, *61*, 4641–4648; (b) Li, A.-H.; Dai, L.-X.; Hou, X.-L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2725–2729; (c) Zhou, Y.-G.; Li, A.-H.; Hou, X.-L.; Dai, L.-X. *Tetrahedron Lett.* **1997**, *38*, 7225–7228; (d) Li, A.-H.; Dai, L.-X.; Hou, X.-L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 867–869; (e) Matano, Y.; Yoshimune, M.; Suzuki, H. *J. Org. Chem.* **1995**, *60*, 4663–4665.
5. Typical procedure for the synthesis of **4a** and the selected spectroscopic data of **3a** and **4a** are as follows. Typical procedure of **4a**: To a stirred solution of **1a** (234 mg, 0.5 mmol) and aniline (52 mg, 0.56 mmol) in CH_3CN (3 mL) was added $LiClO_4$ (64 mg, 0.6 mmol) and heated to reflux for 24 h. After the usual aqueous extractive workup and flash column chromatography (hexanes/EtOAc, 5:1), we obtained **4a** as a solid, 199 mg (75%). Compound **3a**: white solid, mp 156–157 °C; IR (KBr) 3390,

3273, 1699, 1601, 1506, 1161 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.22 (s, 3H), 3.79 (s, 3H), 4.82 (t, $J = 10.0$ Hz, 1H), 4.90 (br s, 1H), 5.57 (t, $J = 10.0$ Hz, 1H), 5.86 (d, $J = 8.0$ Hz, 2H), 6.35 (t, $J = 7.5$ Hz, 1H), 6.67 (t, $J = 7.5$ Hz, 2H), 6.95–7.10 (m, 5H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.46–7.50 (m, 5H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.78 (s, 1H), 8.44 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.83, 51.97, 54.60, 56.53, 112.89, 116.92, 126.27, 127.00, 127.91, 128.29, 128.40, 128.52, 128.83, 128.97, 129.08, 129.19, 130.96, 133.30, 134.62, 137.65, 137.78, 141.67, 142.12, 145.66, 167.03; ESIMS m/z 561 (M^++H). Anal. Calcd for $C_{31}H_{29}ClN_2O_4S$: C, 66.36; H, 5.21; N, 4.99. Found: C, 66.03; H, 5.44; N, 4.81.

Compound **4a**: yellow solid, mp 138–139 °C (dec.); IR (KBr) 3383, 1720, 1645, 1601, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 4.23 (d, $J = 8.1$ Hz, 1H, D_2O exchangeable), 4.69 (d, $J = 8.1$ Hz, 1H), 5.76 (s, 1H), 6.62 (d, $J = 7.8$ Hz, 2H), 6.87 (t, $J = 7.5$ Hz, 2H), 6.98–7.57 (m, 14H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.62, 57.04, 64.67, 114.39, 119.36, 127.28, 128.39, 128.96, 129.10, 129.14, 129.21, 129.61, 129.67, 130.53, 130.83, 131.11, 133.10, 133.43, 135.11, 135.36, 140.84, 144.42, 144.91, 166.57; ESIMS m/z 529 (M^++H). Anal. Calcd for $C_{30}H_{25}ClN_2O_3S$: C, 68.11; H, 4.76; N, 5.30. Found: C, 68.23; H, 4.92; N, 5.19.

6. For the synthesis and biological activities of α-methylene-γ-butyrolactones and α-alkylidene-γ-butyrolactones, see: (a) Bauchat, P.; Le Rouille, E.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1991**, *128*, 267–271; (b) Paquette, L. A.; Mendez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301–4304; (c) Nokami, J.; Tamaoka, T.; Ogawa, H.; Wakabayashi, S. *Chem. Lett.* **1986**, 541–544; (d) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147–1152; (e) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114–4125; (f) Gasperi, T.; Loreto, M. A.; Tardella, P. A.; Veri, E. *Tetrahedron Lett.* **2003**, *44*, 4953–4956; (g) Pohmakotr, M.; Sampaongoen, L.; Issaree, A.; Tuchinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2003**, *44*, 6717–6720; (h) Seki, M.; Shimizu, T.; Matsumoto, K. *J. Org. Chem.* **2000**, *65*, 1298–1304; (i) Castulik, J.; Mazal, C. *Tetrahedron Lett.* **2000**, *41*, 2741–2744; (j) Mincheva, Z. P.; Gao, Y.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7947–7950; (k) Lee, J.; Sharma, R.; Wang, S.; Milne, G. W. A.; Lewin, N. E.; Szallasi, Z.; Blumberg, P. M.; George, C.; Marquez, V. E. *J. Med. Chem.* **1996**, *39*, 36–45; (l) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 2381–2382.

7. For the examples of cyclization involving the ester moiety, see: (a) Alvernhe, G.; Lacombe, S.; Laurent, A.; Marquet, B. *J. Chem. Res.* **1980**, 54–55; (b) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936–5942; (c) Wawrzenczyk, C.; Grabarczyk, M.; Bialonska, A.; Ciunik, Z. *Tetrahedron* **2003**, *59*, 6595–6601; (d) Mead, K. T.; Yang, H.-L. *J. Org. Chem.* **1990**, *55*, 2991–2992.

8. Typical procedure for the synthesis of **5a** and the selected spectroscopic data of **5a** and **5b** are as follows. Typical procedure of **5a**: To a stirred solution of **1a** (234 mg, 0.5 mmol) in CH_3CN (3 mL) was added $LiClO_4$ (160 mg, 1.5 mmol) and heated to reflux for 48 h. After the usual aqueous extractive workup and flash column chromatography (hexanes/ether, 1:1) we obtained **5a** as a solid, 144 mg (63%).

Compound **5a**: white solid, mp 144–145 °C; IR (KBr) 3259, 1755, 1645, 1338, 1159 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.34 (s, 3H), 5.06 (s, 1H), 5.56 (s, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.25–7.51 (m, 8H), 7.61–7.74 (m, 3H), 8.86 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.00, 55.53, 82.04, 122.32, 126.25, 127.89, 128.19, 128.68, 129.68, 130.08, 130.90, 131.11, 131.42, 132.30, 132.44, 134.51, 138.20, 141.73, 143.14, 169.81; ESIMS m/z 454 (M^++H). Anal. Calcd for $C_{24}H_{20}ClNO_4S$: C, 63.50; H, 4.44; N, 3.09. Found: C, 63.48; H, 4.65; N, 2.97.

Compound **5b**: white solid, mp 179–180 °C; IR (KBr) 3253, 1757, 1647, 1591 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 4.99 (d, $J = 6.9$ Hz, 1H), 5.80 (s, 1H), 6.02 (d, $J = 6.9$ Hz, 1H, D_2O exchangeable), 7.08 (dd, $J = 7.5$ and 1.8 Hz, 1H), 7.14–7.30 (m, 6H), 7.33–7.38 (m, 3H), 7.60–7.63 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.48, 56.70, 83.28, 121.84, 127.07, 127.28, 127.87, 129.16, 129.69, 130.21, 130.32, 130.59, 132.27, 132.63, 134.74, 137.44, 137.48, 141.97, 143.97, 170.80; ESIMS m/z 488 (M^++H). Anal. Calcd for $C_{24}H_{19}Cl_2NO_4S$: C, 59.02; H, 3.92; N, 2.87. Found: C, 58.91; H, 3.89; N, 2.94.