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First Long-Distance $S_{RN}1$ on a propargylic chloride

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ABSTRACT

We report here the first example of a Long-Distance $S_{RN}1$ (LD-$S_{RN}1$) reaction on a propargylic chloride. The reaction of 1-(3-chloroprop-1-ynyl)-4-nitrobenzene (**1**) with nitronate anions led to both the formation of the C-alkylation product through an LD-$S_{RN}1$ mechanism and the ethylenic compound resulting from nitrous acid elimination on the C-alkylation product **2**. In contrast with previous work on LD-$S_{RN}1$ reactivity, no O-alkylation product was observed. Only one original product **4** was isolated under phase transfer conditions, resulting from a nucleophilic attack by 2-nitropropane anion on the electrophilic alkyne. This LD-$S_{RN}1$ reactivity did not extend to sulfinate anions; the reaction of **1** with sulfinate anions yielded original ethylenic disulfone compounds which were formed via an ionic process.

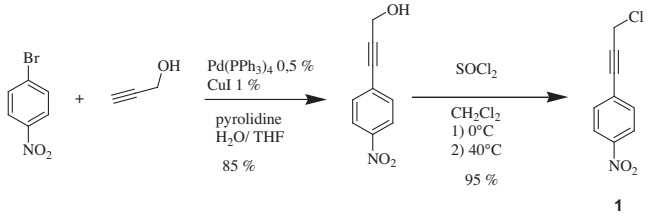
The concept of Long-Distance Radical Nucleophilic Substitution (LD-$S_{RN}1$) involves a long distance between the electron withdrawing and the leaving group.[1] LD-$S_{RN}1$ reactions were explored by Barker and Norris with a reaction between α-alkyl-γ(*p*-nitrophenyl) alkyl chloride[2] and various nucleophiles. This concept was further explored in heterocyclic[3] and in quinonic series.[4] All this previous research concluded that LD-$S_{RN}1$ reactivity is often in competition with another reactivity, usually S_N2. For example, the Barker and Norris substrate reacted with 2-nitropropane anion via an S_N2 pathway.[2] Moreover, in heterocyclic series, (*E*)-2-[4-(chloromethyl)styryl]-1-methyl-5-nitro-1*H*-imidazole under LD-$S_{RN}1$ conditions gave a majority of O-alkylation products.[3a]

Under our program directed toward the single electron transfer (SET) reaction,[1,5] we considered the possibility that a propargylic chloride might be reactive under LD-$S_{RN}1$ conditions with various nucleophiles. Never previously reported, LD-$S_{RN}1$ on alkynes would be invaluable in the preparation of original substrates. Alkyne moieties have elicited great interest in connection with many reactions, such as 'click' chemistry reactions, metal-catalysis, or polymerization reactions.[6]

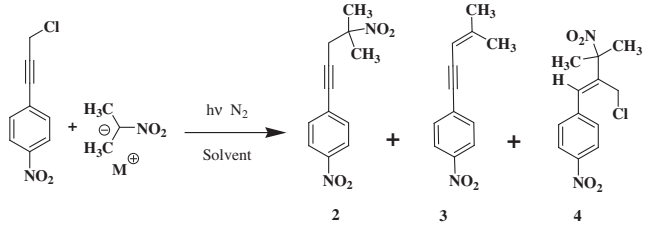
Continuing in the vein of this study on $S_{RN}1$ (LD-$S_{RN}1$) reactivity, we explored this concept in alkyne series, reporting here the reaction between nitronate and sulfinate anions under $S_{RN}1$ experimental conditions (LD-$S_{RN}1$). We synthesized the 1-(3-chloroprop-1-ynyl)-4-nitrobenzene **1,** using a Sonogashira cross-coupling reaction (Scheme 1).

For the first step, our synthesis was inspired by the work of Chinchilla[7] on Sonogashira reactions. To optimize the rate of coupling reaction, a mixture of tetrahydrofuran and water (90/10) was used as the solvent. The second step was a classic chlorination of the alcohol with $SOCl_2$ in dichloromethane to obtain **1** in 95% yield.[8]

Treated under various electron transfer conditions[9,10] with 2-nitropropane anion, the 1-(3-chloroprop-1-ynyl)-4-nitrobenzene (**1**) led to the formation of three compounds: the expected C-alkylation product **2**, the ethylenic compound **3** resulting from nitrous



Scheme 1. Synthesis of propargylic chloride **1**.



Scheme 2. Reactivity of propargylic chloride **1** with the 2-nitropropane anion under $S_{RN}1$ conditions.

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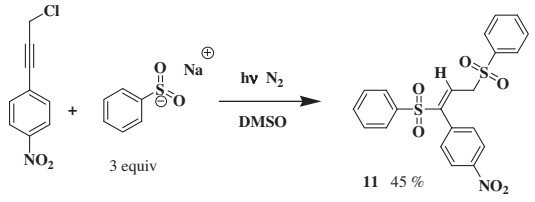
Table 1
Reactivity of **1** with 2-nitropropane anion

Entry[a]	M	Equiv of anion	Solvent	Time	Yield **2**[11] (%)	Yield **3**[11] (%)	Yield **4**[11] (%)	Yield C-alkylation (%)
1	Li	3	DMSO	1 min	75	10	—	85
2	Li	3	DMSO	5 min	40	50	—	90
3	Li	3	DMSO	25 min	32	68	—	100
4	Li	3	DMSO	1 h	15	77	—	92
5	Li	3	DMF	36 h	25	25	25	50
6[b]	Na	3	DMSO	25 min	65	30	—	95
7[c]	NBu_4	3	CH_2Cl_2/H_2O	48 h	20	—	30	20
8[d]	NBu_4	3	CH_2Cl_2/H_2O	48 h	20	—	30	20
9	Li	2	DMSO	25 min	42	55	—	97
10	Li	4	DMSO	25 min	40	58	—	98
11	Li	6	DMSO	25 min	35	60	—	95

[a] All reactions were performed under nitrogen and irradiation with a 300 W fluorescent lamp using 1 equiv of **1**. All yields refer to chromatographically isolated pure products and are relative to the electrophile.
[b] 2-Nitropropane salt was formed in situ using NaH in DMSO and 2-nitropropane.
[c] Phase transfer conditions with NBu_4Br in water.
[d] Phase transfer conditions with NBu_4OH 40% in water.

acid elimination on the C-alkylation product **2**, and an original allyl chloride **4** (Scheme 2, Table 1).[11] The best overall yield (100%) of C-alkylation products **2** + **3** was obtained under Kornblum conditions[9] with DMSO as the solvent with 3 equiv of 2-nitropropane anion for 25 min under inert atmosphere and light catalysis (Entry 3). We note that the ethylenic compound **3** was predominant (68% vs 32%). When we used NaH in DMSO and 2-nitropropane to form the 2-nitropropane salt in situ (Entry 6), we obtained the C-alkylation products in 95% overall yield after 25 min. Under these conditions, the ratio between compounds **2** and **3** is in favor of C-alkylation product **2** (65% vs 30%).

Under Norris conditions,[10] phase transfer reaction conditions (Entries 7 and 8), we observed the starting chloride **1** with or without degradation products and only 20% of C-alkylation product **2**. Moreover, an original product **4** was isolated. High resolution Mass Spectrometry ESI-MS and RMN NOESY permitted us to determine

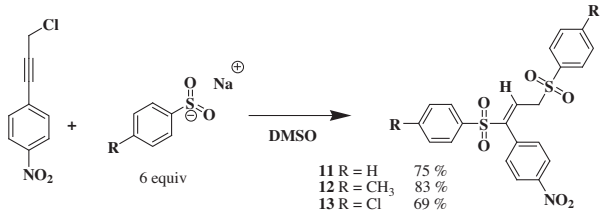


Scheme 4. Reaction of **1** with benzenesulfinic acid sodium salt under $S_{RN}1$ conditions.

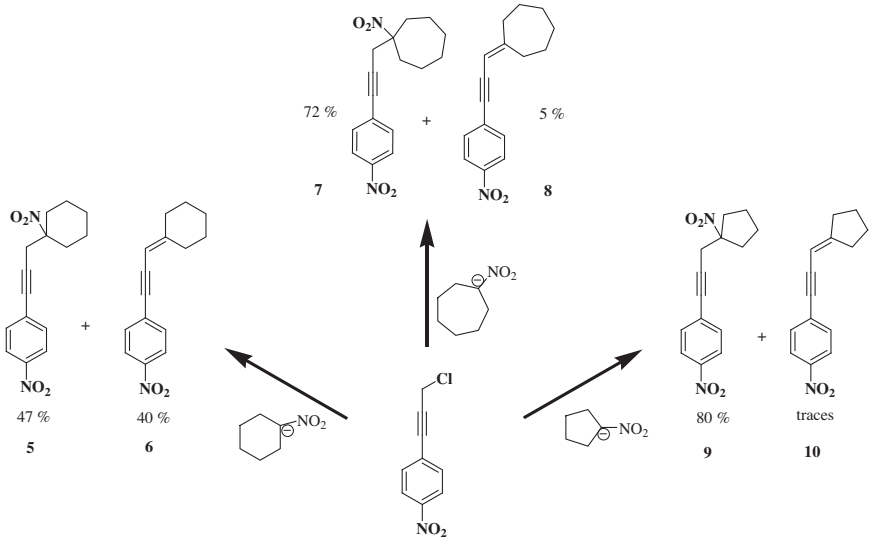
Table 2
Inhibition of reaction of **1** with the 2-nitropropane anion

Entry[a]	Scavenger	Yield (**2**) (%)	Yield (**3**) (%)	Yield (**4**) (%)
3	—	32	68	0
12	TEMPO 1 Equiv	0	0	62
13	TEMPO 0,1 Equiv	0	0	41
14	$CuCl_2$ 1 Equiv	10	15	28
15	$CuCl_2$ 0,1 Equiv	5	10	15

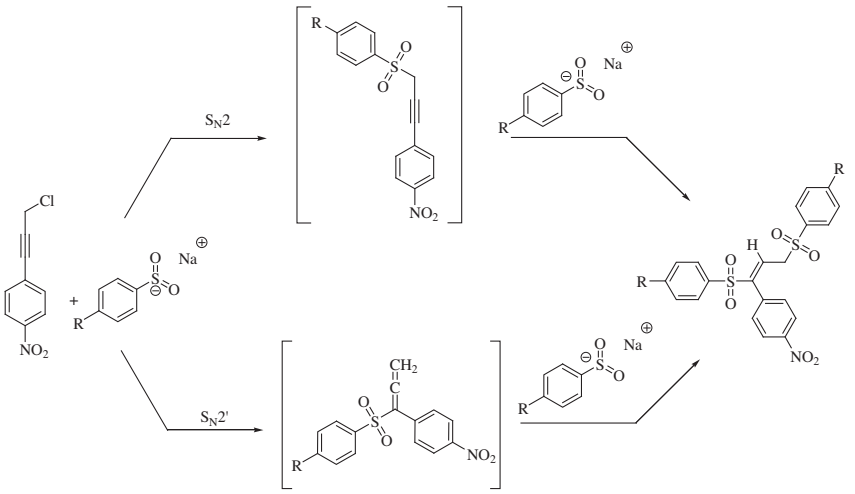
[a] All reactions were performed under Entry 3 conditions.



Scheme 5. Reaction of **1** with other benzenesulfinic acid sodium salts.



Scheme 3. Reaction of **1** with nitrocycloalkanes.



Scheme 6. Mechanism for the formation of **11**–**13**.

the structure of **4** as (*Z*)-1-(2-(chloromethyl)-3-methyl-3-nitrobut-1-enyl)-4-nitrobenzene.

The reaction of **1** with the 2-nitropropane anion, under the optimal conditions, in the presence of classic inhibitors (2,2,6,6-tetramethyl-1-piperidinyloxy or TEMPO as the radical trap and $CuCl_2$) gave effective inhibition, indicating an LD-$S_{RN}1$ mechanism for the formation of **2** (Table 2).

The formation of compounds **2** and **3** is explained by the LD-$S_{RN}1$ process leading to C-alkylation product **2**. From product **2**, in the presence of an excess of the anion, nitrous acid elimination gives ethylenic compound **3**. However, inhibitions were accompanied by the formation of compound **4**. The formation of this product seems to be due to an ionic process and was the result of a nucleophilic addition of the 2-nitropropane anion on the electrophilic alkyne conjugated with *p*-nitrobenzene moiety.

In order to generalize this concept, we extended this reaction to other nucleophiles such as nitrocycloalkanes and synthesized the corresponding C-alkylation products **5**, **7**, **9** and the ethylenic products **6**, **8**, **10**[12] as shown in Scheme 3. All nitroalkanes were commercially available and their conversion to anions was realized in situ with NaH in DMSO. All the reactions were performed using 3 equiv of nitrocycloalkane, in DMSO at rt, for 25 min (Table 1, Entry 6 conditions).

The possible extension of this LD-$S_{RN}1$ reactivity to S-centered anions[3b] was investigated using the benzenesulfinic acid anion. However, this reaction did not yield the expected S-alkylation product; instead, an original ethylenic disulfone compound **11** was observed, accompanied by intractable tarry matter. High resolution Mass Spectrometry ESI-MS and NOESY studies permitted us to determine the structure of **11** as (*E*)-1-(1,3-bis(phenylsulfonyl)prop-1-enyl)-4-nitrobenzene.

After optimization under $S_{RN}1$ reaction conditions, the best yield of **11** (45%) was obtained with 3 equiv of sulfinate anion in DMSO, stirred at rt for 5 h (Scheme 4). An inhibition reaction with 1 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under the optimal conditions led to the same product with an equivalent yield (45%). The inhibition experiments showed that the formation of product **11** was not sensitive to the presence of classic inhibitors of $S_{RN}1$ reactions. The formation of this compound was not a radical process. Thus, the LD-$S_{RN}1$ conditions (inert atmosphere and hν irradiation) were not required to form **11**. We therefore investigated a possible reaction of nitrobenzyl propargylic chloride **1** with 6 equiv of benzenesulfinic acid sodium salt under non-radical conditions (air and no light irradiation). Under these conditions, product **11** was obtained in 75% yield.

In order to extend this propargyl chloride reactivity to sulfinate anions, we used other sulfinate anions such as *p*-toluenesulfinic and *p*-chlorobenzene sulfinic acid sodium salt (Scheme 5) in the reaction with **1** under optimized conditions (non radical). We observed the formation of new compounds **12** and **13** in respectively 83% and 69% yields.[13]

The formation of these ethylenic disulfone derivatives **11–13** may be explained by two pathways (Scheme 6). The first step could be an S_N2 or an S_N2' reaction forming respectively an alkyne sulfone or an allene sulfone intermediate. This step could be followed by a nucleophilic addition of sulfinate anion on the intermediate to form **11–13**. However, the absence of isolated intermediates or by-products in this reaction makes it impossible to describe this mechanism clearly.

In conclusion, what we have described here is the first example of an LD-$S_{RN}1$ reaction on a propargylic chloride. The reaction of 1-(3-chloroprop-1-ynyl)-4-nitrobenzene (**1**) with nitronate anions led to both the formation of the C-alkylation product through an LD-$S_{RN}1$ mechanism and the ethylenic compound resulting from nitrous acid elimination on the C-alkylation product **2**. In contrast with previous work on LD-$S_{RN}1$ reactivity, no O-alkylation product was observed. Only original product **4** was isolated under phase transfer conditions, resulting from a nucleophilic attack of 2-nitropropane anion on the electrophilic alkyne. This LD-$S_{RN}1$ reactivity did not extend to sulfinate anions, the reaction of **1** with sulfinate anions yielded original ethylenic disulfone compounds which were formed via an ionic process. Pharmacological evaluation of all these synthesized compounds is in progress, particularly regarding the original ethylenic disulfone compounds, which are known to have anticancer potential.[14]

Acknowledgments

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8. Compound **1**: Brown solid, mp 58.3 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.37 (s, 2H); 7.56 (d, J = 8.9 Hz, 2H); 8.16 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.4 (CH_2); 84.1 (C); 88.9 (C); 123.6 (2xCH); 128.9 (C); 132.7 (2xCH); 147.5 (C). Anal Calcd for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.37; H, 3.18; N, 7.19.
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11. *Purified by silica gel chromatography with CH_2Cl_2/petroleum ether (5/5). New products:* Compound **2**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.75 (s, 6H); 3.10 (s, 2H); 7.53 (d, J = 8.9 Hz, 2H); 8.17 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.6 (2xCH$_3$); 31.7 (CH_2); 86.7 (C); 88.9 (C); 123.5 (2xCH); 129.5 (C); 132.5 (2xCH); 147.1 (C). Anal Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.19; H, 5.01; N, 11. Compound **3**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1,90 (s, 3H); 2,00 (s, 3H); 5.50 (s, 1H); 7.53 (d, J = 8.9 Hz, 2H); 8.17 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3); 25.1 (CH_3); 89.9 (C); 93.5 (C); 104.7 (CH); 123.6 (2xCH); 131.1 (C); 131.8 (2xCH); 146.5 (C); 151.9 (C). Anal Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.57; H, 5.66; N, 6.86. Compound **4**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71 (s, 6H); 3.76 (s, 2H); 6.76 (s, 1H); 7.32 (d, J = 8.5 Hz, 2H); 8.15 (d, J = 8.5 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.9 (2xCH$_3$); 34.2 (CH_2); 90.5 (C); 123.8 (2xCH); 128.6 (2xCH); 138.4 (CH); 144.4 (C). HRMS Calcd for $C_{12}H_{13}ClN_2O_4$ [M+NH_4^+]: 302.0902, Found: 302.0906.
12. *Purified by silica gel chromatography with CH_2Cl_2/petroleum ether (5/5).* Compound **5**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.64 (m, 8H); 2.48 (m, 2H); 3.01 (s, 2H); 7.51 (d, J = 8.9 Hz, 2H); 8.15 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.1 (2xCH$_2$); 24.7 (CH_2); 30.9 (2xCH$_2$); 36.2 (CH_2); 89.8 (C); 93.2 (C); 96.2 (C); 123.5 (2xCH); 131.1 (C); 131.8 (2xCH); 146.4 (C). Anal Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.34; H, 5.77; N, 9.65. Compound **6**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (m, 8H); 3.70 (m, 2H); 5.45 (s, 1H); 7.53 (d, J = 8.9 Hz, 2H); 8.15 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.1 (CH_2); 27.6 (CH_2); 28.2 (CH_2); 29.8 (CH_2); 32.0 (CH_2); 89.8 (C); 93.2 (C); 101.1 (CH); 123.5 (2xCH); 128.6 (C); 131.8 (2xCH); 146.4 (C); 159.4 (C). HRMS Calcd for $C_{15}H_{15}NO_2$ [M+Na^+]: 264.0995, Found: 264.0992. Compound **7**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.63 (m, 8H); 2.02 (m, 2H), 2.54 (m, 2H); 3.06 (s, 2H); 7.51 (d, J = 8.9 Hz, 2H); 8.16 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.2 (2xCH$_2$); 29.8 (2xCH$_2$); 32.2 (CH_2); 37.2 (2xCH$_2$); 89.2 (C); 94.4 (C); 100.8 (C); 123.5 (2xCH); 129.7 (C); 132.5 (2xCH); 147.1 (C). Anal Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 64.05; H, 6.30; N, 9.18. Compound **8**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (m, 8H); 2.61 (m, 4H); 5.52 (s, 1H); 7.52 (d, J = 8.9 Hz, 2H); 8.17 (d, J = 8.9 Hz, 2H). Compound **9**: yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70 (s, 8H); 3.15 (s, 2H); 7.47 (d, J = 8.9 Hz, 2H); 8.17 (d, J = 8.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.0 (2xCH$_2$), 30.1 (CH_2), 37.4 (2xCH$_2$), 81.8 (C), 89.4 (C), 97.2 (C), 123.6 (2xCH), 129,7 (C), 132,5 (2xCH), 147,1 (C). HRMS Calcd for $C_{14}H_{14}N_2O_4$ [M+Na^+]: 297.0845, Found: 297.0846.
13. *Purified by alumina gel chromatography with CH_2Cl_2/petroleum ether (5/5).* Compound **11**: orange solid, mp 162.4 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.43 (s, 2H); 7.52–7.69 (m, 8H); 7.72–7.77 (m, 2H); 7.92 (d, J = 8.5 Hz, 2H); 8.20 (s, 1H); 8.27 (d, J = 8.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.7 (CH_2); 124.1 (2xCH); 128.1 (2xCH); 128.7 (2xCH); 129.4 (4xCH); 130.0 (2xCH); 134.1 (CH); 134.4 (CH); 135.5 (C); 138.6 (C); 138.7 (C); 139.5 (C); 144.4 (CH); 148.6 (C). HRMS Calcd for $C_{21}H_{17}NO_6S_2$ [M+NH_4^+]: 461.0836, Found: 461.0836. Compound **12**: yellow solid, mp 200.4 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H); 2.46 (s, 3H); 4,41 (s, 2H); 7,31–7.39 (m, 4H); 7.60–7.83 (m, 5H); 8.15 (s, 2H); 8.26 (d, J = 8.8 Hz, 2H). ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 20.7 (2xCH$_3$); 53.7 (CH_2); 123.6 (2xCH); 128.2 (2xCH); 128.8 (2xCH); 129.7 (2xCH); 129.8 (2xCH); 130.2 (2xCH); 136.5 (C); 136.8 (C); 137.0 (C); 139.6 (C); 143.4 (CH); 144.9 (C); 145.1 (C); 148.2 (C). HRMS Calcd for $C_{23}H_{21}NO_6S_2$ [M+NH_4^+]: 489.1149, Found: 489.1144. Compound **13**: yellow solid, mp 166.3 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 4,43 (s, 2H); 7.47–7.57 (m, 4H); 7.68–7.74 (m, 4H); 7.86 (d, J = 8.6 Hz, 2H); 8.19 (s, 1H); 8.30 (d, J = 8.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.7 (CH_2); 124.2 (2xCH); 129.6 (2xCH); 129.7 (2xCH); 129.8 (2xCH); 130.0 (2xCH); 130.1 (2xCH); 135.1 (C); 137.1 (C); 137.6 (C); 138.4 (C); 141.1 (C); 141.5 (C); 145.1 (CH); 148.7 (C). HRMS Calcd for $C_{21}H_{15}Cl_2NO_6S_2$ [M+NH_4^+]: 529.0056, Found: 529.0052.
14. (a) Chahrour, O.; Ashraf, A.; Lam, F.; Midgley, C.; Wang, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3066–3069; (b) Vedula, M. S.; Pulipaka, A. B.; Venna, C.; Chintakunta, V. K.; Jinnapally, S.; Kattuboina, V. A.; Vallakati, R. K.; Basetti, V.; Akella, V.; Rajgopal, S.; Reka, A. K.; Teepireddy, S. K.; Mamnoor, P. K.; Rajagopalan, R.; Bulusu, G.; Khandelwal, A.; Upreti, V. V.; Mamidi, S. R. *Eur. J. Med. Chem.* **2003**, *38*, 811–824.