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Intramolecular Addition of γ-Chloro Carbanions to Electrophilic Groups: Synthesis of Tricyclic Tetrahydrofurans, Pyrrolidines, and Cyclopentanes

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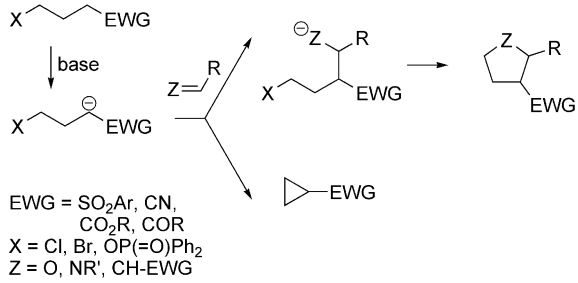
Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

Keywords: Carbanions / Aldol reactions / Cyclization / Nucleophilic substitution / Polycycles

Carbanions of 3-chloropropyl phenyl sulfones containing electrophilic groups such as carbonyl and imino groups in the *ortho* position of the phenyl ring add intramolecularly to these groups to give aldol-type anions. These anions undergo intramolecular 1,5-substitution of chlorine to give tricyclic derivatives of tetrahydrofuran, pyrrolidine, and cyclopentane.

Introduction

γ-Halo carbanions are short-lived intermediates that undergo rapid intramolecular substitution to afford cyclopropanes.[1–3] Due to the high rate of this reaction, often termed γ-elimination, intermolecular reactions of γ-halo carbanions are not highly recognized. We have found[4–11] that γ-chloro carbanions can be intermolecularly trapped when they are generated by deprotonation of appropriate precursors in the presence of active electrophilic partners.[12] For instance, treatment of a mixture of 3-chloropropyl phenyl sulfone and benzaldehyde with *t*BuOK in THF at low temperature results in the formation of 2-phenyl-3-(phenylsulfonyl)tetrahydrofuran in excellent yield.[4] The reaction proceeds through the fast and reversible addition of the γ-chloro carbanion to the aldehyde followed by intramolecular 1,5-substitution of the intermediate aldol-type adduct (Scheme 1).



Scheme 1. Intra- and intermolecular reactions of γ-halo carbanions.

In general, addition of γ-chloro carbanions that contain nucleophilic and electrophilic centers in one molecule in a 1,3 relation to the electron-deficient double bonds C=O, C=N, and C=C of aldehydes, imines, and Michael acceptors, respectively, generates intermediates with nucleophilic and electrophilic centers in a 1,5 relation. Further intramolecular substitution in these intermediates should give substituted tetrahydrofurans,[4,5] pyrrolidines,[5,7] and cyclopentanes.[5,6] Indeed, we have shown that proper selection of the γ-chloro carbanion precursors and electrophilic partners opens interesting possibilities for the synthesis of these five-membered heterocyclic and carbocyclic compounds. The main problem that limits the scope and versatility of this synthetic tool is the high rate of intramolecular 1,3-substitution; thus, the synthesis of the above-mentioned five-membered ring systems depends upon the competition between 1,3-intramolecular substitution and intermolecular addition to electrophilic partners. Taking into account the reversibility of the addition, the overall success of the synthesis of these compounds depends not only on the aforementioned competition, but also on the position of the equilibrium and the rates of intramolecular 1,5-substitution in the intermediate anionic adducts. The reversibility of the addition and the rate of 1,5-substitution acting as important factors in the synthesis of tetrahydrofurans by the reaction of γ-chloro carbanions with aldehydes were clearly demonstrated.[8] We have observed that the crucial competition can be controlled in a few ways: by changing the leaving group[4,8,9] and nucleophilicity of the carboanionic center,[4,6,7,10] by introducing substituents in the carbanion chain,[11] by separating the leaving group and the carboanionic centers in the γ-chloro carbanions by introducing C=C bonds, and by varying the solvents and counterions, etc.

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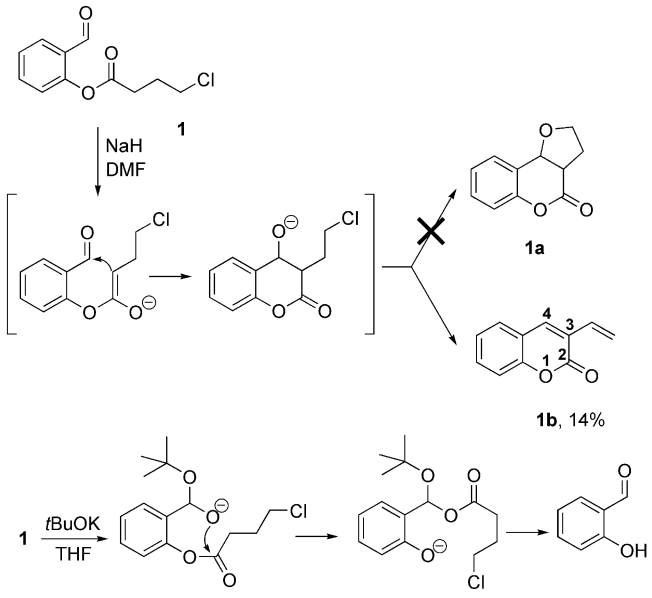
Results and Discussion

Taking into account that intramolecular reactions are usually faster than their intermolecular counterparts, provided there are no steric difficulties, we studied the reactions of γ-chloro carbanions containing an additional carbonyl group or similar electrophilic fragments in a proper position of the γ-chloro carbanion molecule. We expected that in such systems 1,5- or 1,6-intramolecular additions of the carbanion would be preferred over 1,3-intramolecular substitution. As model precursors of such γ-chloro carbanions we chose benzene derivatives that contain electrophilic groups in an *ortho* relation to the γ-chloro carbanion moiety. The main goal of the study was to verify the presented hypothesis by synthesizing new heterocycles, whereas mechanistic investigations were secondary and limited to systems where clear conclusions could be outlined.

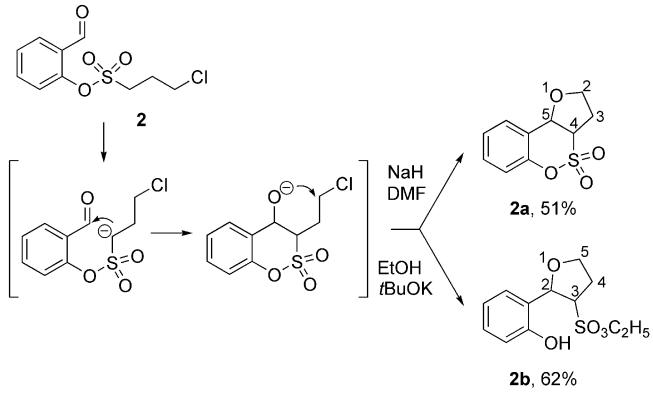
The first, readily accessible compound of this type that was tested was the 4-chlorobutyrate of salicylaldehyde **1**. We expected that the γ-chloro enolate generated by treatment of this ester with a strong base would add to the aldehyde carbonyl group to produce an aldol-type anion that should give, by intramolecular 1,5-substitution, a tricyclic tetrahydrofuran derivative **1a** (Scheme 2).



Scheme 2. Instead of expected tricyclic lactone **1a**, reaction of **1** with NaH in DMF yields coumarin derivative **1b** in low yield. However, reaction with *t*BuOK in THF leads to neighboring group accelerated cleavage of the ester function and release of salicylaldehyde exclusively.

Unfortunately, when **1** was treated with our standard base *t*BuOK in THF the only products were salicylaldehyde and 4-chlorobutyric acid, even without aqueous treatment of the reaction mixture. Apparently, the initial process was addition of the *t*BuO$^-$ anion to the aldehyde followed by intramolecular addition of the produced hemiacetal anion to the ester functionality and subsequent departure of the phenolic anion of salicylaldehyde.[13] On the other hand, when **1** was treated with NaH in DMF, apart from products of decomposition, vinylcoumarin **1b** was obtained in 14% yield (Scheme 2).

Next, we studied reactions of (3-chloropropane)sulfonate derivative **2**. Because esters of sulfonic acids are less susceptible to nucleophilic attack on sulfur, we expected that the desired 1,6-intramolecular addition of the γ-halo carbanion should proceed to give tricyclic tetrahydrofuran derivative **2a**. Indeed, when **2** was treated with *t*BuOK in THF at –40 °C to room temperature expected compound **2a** was obtained in a moderate yield of 30%. A substantially better yield (51%) of **2a** was obtained when **2** was treated with NaH in DMF. On the other hand, when the reaction was carried out in ethanol, the main product was ethyl sulfonate **2b** (62% yield). It seems that this product was formed by base-inducted ethanolysis of **2a** (Scheme 3).

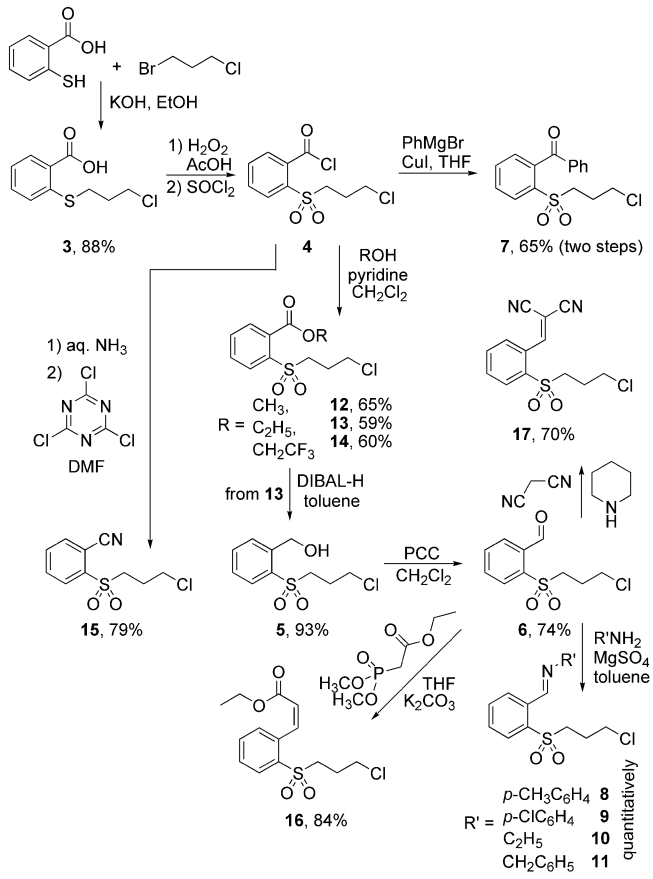


Scheme 3. Reaction of sulfonate precursor **2** gave tricyclic compound **2a**; in ethanol, transesterified product **2b** was obtained.

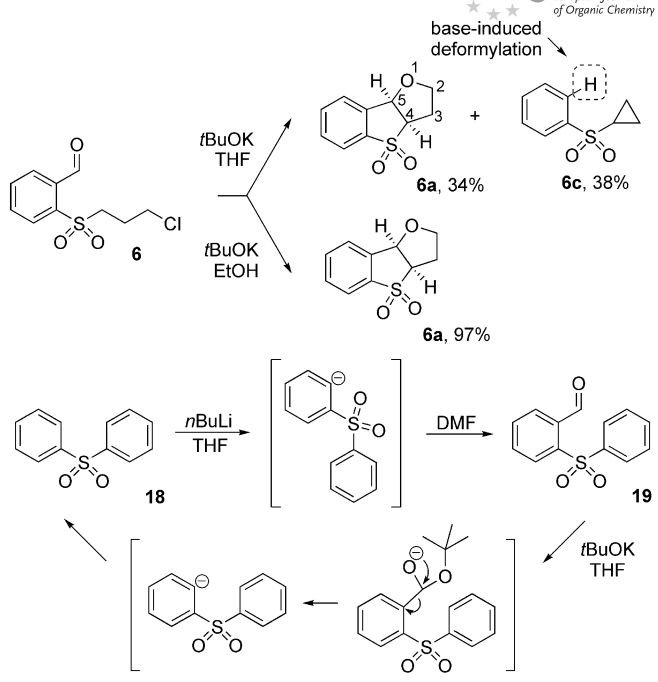
Interesting model compounds for verification of our concept appeared to be (3-chloropropyl)phenyl sulfones **6**–**17** containing carbonyl or other groups acting as an electrophilic partner in the *ortho* position of the phenyl ring. Synthesis of these compounds is presented in Scheme 4.

Treatment of sulfonyl aldehyde **6** with *t*BuOK in THF gave expected tricyclic tetrahydrofuran derivative **6a**, but in moderate yield only, together with a cyclopropyl phenyl sulfone (Scheme 5). The initially generated carbanion of **6** adds to the carbonyl group to give an aldol-type intermediate as two diastereoisomers (*cis* and *trans*). We assume that under these conditions only the *cis* isomer can enter the 1,5-intramolecular substitution to give **6a**.

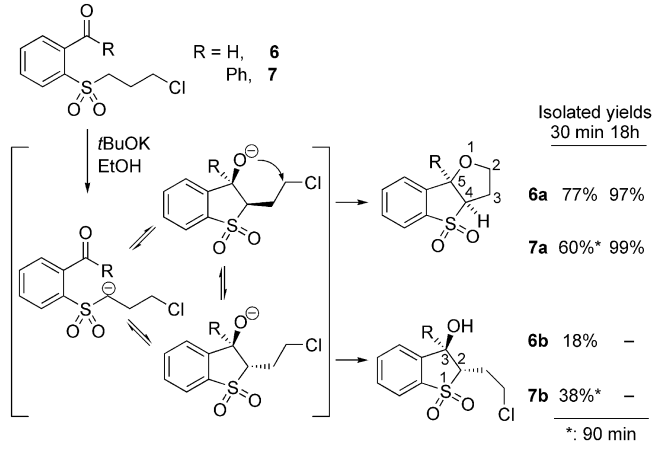
It appears that under these conditions, intramolecular 1,5-addition and 1,3-substitution proceed with comparable rates. The *cis* isomer of the anionic adduct cyclizes to **6a**, whereas the *trans* isomer can epimerize. The cyclopropyl sulfone produced by 1,3-substitution is subsequently deformylated through the addition of *t*BuOK to the carbonyl group followed by splitting of the C–C bond in the hemiacetal anion to produce cyclopropyl phenyl sulfone (**6c**) and *tert*-butyl formate. To confirm the last step, we prepared 2-formyldiphenyl sulfone (**19**) by lithiation of diphenyl sulfone (**18**) followed by reaction with dimethyl formamide.[14] This sulfone treated with potassium *tert*-butoxide in THF



Scheme 4. Synthesis of compounds **3**–**16**.



Scheme 5. Product distribution in the reaction of **6** with *t*BuOK depends on the solvent: reaction in THF gives a mixture of tetrahydrofuran (i.e., **6a**) and cyclopropane (i.e., **6c**) derivatives, whereas in EtOH **6a** is formed exclusively. The mechanism of the base-induced deformylation to cyclopropane derivative **6c** in THF was established on the basis of the reactivity of model substrate **19** (see text).

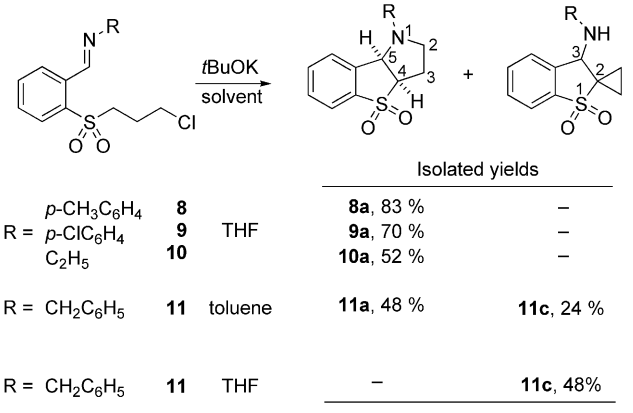


Scheme 6. Reaction of **6** and **7** with *t*BuOK in EtOH gives tricyclic *cis* isomers **6a** and **7a** in excellent yields. When the reaction is stopped after a short time only uncyclized *trans* adducts **6b** and **7b** are observed (see the text).

underwent complete deformylation to give quantitatively diphenyl sulfone (**18**). To improve the yield of **6a** the reaction of **6** with *t*BuOK was carried out in ethanol. It was observed earlier that this solvent favors aldol-type addition in intermolecular reactions of γ-chloro enolates to aldehydes and ketones, perhaps due to solvation of the aldol-type anion, which thus improves the overall yields of the tetrahydrofurans.[10]

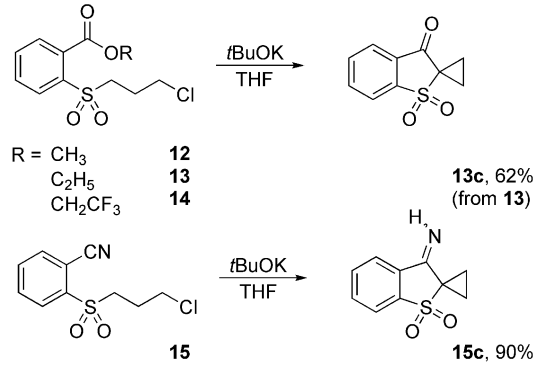
Indeed, the reaction of **6** and **7** with *t*BuOK in ethanol (the acting base was actually potassium ethoxide) carried out for a long time (18–22 h) gave **6a** and **7a** in 97 and 99% yield, respectively. On the other hand, when the reactions were stopped after a short time, besides **6a** and **7a**, the *trans* isomers of aldol-type adducts **6b** and **7b** were isolated (Scheme 6). Obviously the initially formed *trans* adducts **6b** and **7b** in protic media were epimerized to *cis* isomers of **6b** and **7b**, which underwent intramolecular 1,5-substitution to **6a** and **7a**.

Imines are weaker electrophiles than aldehydes; however, they still react with γ-chloro carbanions to give substituted pyrrolidines. Treatment of imines **8**, **9**, and **10** with *t*BuOK in THF gave expected tricyclic pyrrolidine derivatives **8a**, **9a**, and **10a** in good yields. On the other hand, when the reaction of **11** was carried out under the same conditions, spirocyclopropane derivative **11c** was formed. Thus, in this case, 1,3-intramolecular substitution leading to cyclopropane was faster than 1,5-addition. Subsequent deprotonation of the sulfonyl cyclopropane followed by addition of its carbanion to the imino group gives **11c**. On the other hand, when **11** was treated with *t*BuOK in toluene, 48% of derivative of pyrrolidine **11a** was obtained together with cyclopropane **11c** (24%, Scheme 7).



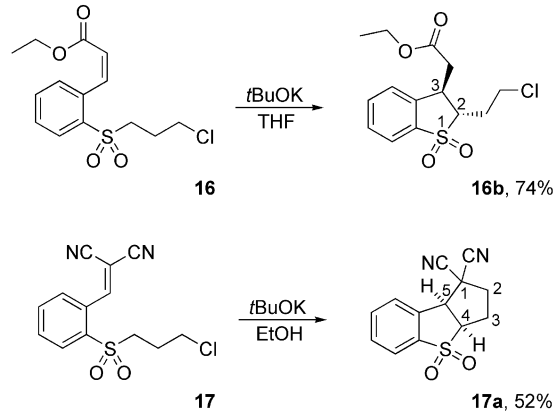
Scheme 7. Reactions of imines **8**–**11** with *t*BuOK in THF and toluene.

We then have found that esters **12**–**14** and nitrile **15**, when treated with *t*BuOK, gave exclusively spirocyclopropane derivatives **13c** and **15c**. Due to the rather low electrophilic activity of the alkoxycarbonyl and cyano groups, 1,3-intramolecular substitution producing sulfonyl cyclopropane proceeds faster than 1,5-addition. Further deprotonation of the produced cyclopropane and addition of the cyclopropyl carbanion gives **13c** and **15c**; variation of the reaction conditions – solvents, counterions – does not change the reaction course (Scheme 8). However, **13c** and **15c** may be alternatively formed by addition of the γ-halo carbanion to the multiple bond, followed by proton transfer from the acidic α position, and subsequent cyclization to cyclopropane derivative, but the latter possibility seems to be less feasible.



Scheme 8. Cyclization of sulfones **12**–**15** under basic conditions to give cyclopropane derivatives **13c** and **15c**.[15]

Finally, we verified the possibility to synthesize tricyclic cyclopentane derivatives through the reaction of chloropropyl aryl sulfones containing Michael acceptor fragments **16** and **17** in the *ortho* position of the phenyl ring (Scheme 9). Treatment of **16** with *t*BuOK in THF gave the Michael-type adduct, which under the applied reaction conditions does not cyclize. On the other hand, when **17** was treated with *t*BuOK in EtOH the expected tricyclic cyclopentane derivative was obtained in good yield. In this case, the intramolecular 1,5-Michael addition was followed by intramolecular 1,5-nucleophilic substitution in the produced anionic adduct.



Scheme 9. Under basic conditions in THF, cinnamate **16** gives uncyclized adduct **16b**,[16] whereas malonodinitrile derivative **17** cyclizes in ethanol to desired tricyclic compound **17a**.

Conclusions

The results presented in this paper confirm our expectation that when γ-chloro carbanions contain additional electrophilic fragments in a proper spatial position intramolecular 1,5- or 1,6-addition of the carbanions to such fragments proceeds faster than intramolecular 1,3-substitution, which leads to the formation of cyclopropanes. Further 1,5-substitution in the produced anionic adducts gives polycyclic tetrahydrofuran, pyrrolidine, and cyclopentane derivatives. The investigated substrates required individual optimization of the reaction conditions, but the methodology has proved to be suitable and useful for the construction of five- and six-membered rings.

Experimental Section

General: Reactions of carbanions were conducted in flame-dried glassware under an atmosphere of argon. Column chromatography was performed with Fisher Scientific Matrex Silica 60 (35–70 micron). Melting points were measured with a Griffin electrothermal apparatus. IR spectra were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker DPX300 or DRX500 Fourier Transform spectrometers by using an internal deuterium lock. Electrospray ionization (ESI) was performed with either a Micromass LCT TOF spectrometer or a Waters-Micromass ZMD spectrometer. High-resolution mass spectrometry (HRMS) was obtained by peak matching with the use of polyethylene glycol as a standard.

1: Triethylamine (10.30 g, 102 mmol) in Et_2O (20 mL) was added dropwise to a solution of salicylaldehyde (12.21 g, 100 mmol) and 4-chlorobutyryl chloride (14.10 g, 100 mmol) in Et_2O (130 mL) at –10 °C. After 5 min, the mixture was warmed to room temperature and after 18 h water (300 mL) was added. The mixture was then extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with aqueous K_2CO_3 (2 × 150 mL), water (2 × 150 mL), and brine (100 mL) and then dried with $MgSO_4$. The

solvent was evaporated, and the mixture was distilled to yield **1** (16.6 g, 73%). Oil, b.p. 120–125 °C/4 × 10^{-2} Torr. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.18–2.34 (m, 2 H, CH_2CH$_2$Cl), 2.89 (t, $J_{H,H}$ = 7.1 Hz, 2 H, CH$_2$CH_2CH$_2$Cl), 3.71 (t, $J_{H,H}$ = 6.3 Hz, 2 H, CH_2Cl), 7.18 (dd, $J_{H,H}$ = 8.0, 1.1 Hz, 1 H, H_{arom}), 7.42 (ddd, $J_{H,H}$ = 7.6, 7.6, 1.1 Hz, 1 H, H_{arom}), 7.64 (ddd, $J_{H,H}$ = 8.0, 7.4, 1.8 Hz, 1 H, H_{arom}), 7.87 (dd, $J_{H,H}$ = 7.7, 1.8 Hz, 1 H, H_{arom}), 10.07 (s, 1 H, CHO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 27.3, 31.0, 43.9, 123.4, 126.5, 128.0, 131.9, 135.3, 151.0, 171.0, 188.8 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 2965, 2862, 2754, 1764, 1699, 1605, 1581, 1482, 1456, 1412, 1369, 1308, 1276, 1198, 1124, 929, 757, 649, 425 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 226 (2) [M$^+$], 173 (2), 122 (59), 107 (31), 105 (100). $C_{11}H_{11}ClO_3$ (226.66): calcd. C 58.29, H 4.89, Cl 15.64; found C 58.62, H 4.89, Cl 15.16.

Reaction of 1 with *t*BuOK in THF: *t*BuOK (224 g, 2 mmol) in THF (2 mL) was added dropwise to a solution of **1** (226 mg, 1 mmol) in THF (5 mL) at –70 °C under an atmosphere of argon. After 30 min, the mixture was warmed to room temperature and after 15 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. ^{1}H NMR analysis showed the presence of salicylaldehyde only (as compared with original sample).

Reaction of 1 with NaH in DMF: Solid NaH (0.027 g, 1.1 mmol) was added to a solution of **1** (0.226 g, 1 mmol) in DMF (5 mL) at –40 °C under an atmosphere of argon. After 30 min the mixture was warmed to room temperature and after 20 h an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **1b** (0.024 g, 14%) and unreacted **1** (0.011 g, 5%). Data for **1b**: Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 5.41 (dd, $J_{H,H}$ = 11.3, 1.1 Hz, 1 H, =CH$_E$H$_Z$), 6.11 (dd, $J_{H,H}$ = 17.6, 1.1 Hz, 1 H, =CH$_E$H$_Z$), 6.66 (ddd, $J_{H,H}$ = 17.6, 11.3, 0.7 Hz, 1 H, C*H*=), 7.18–7.21 (m, 1 H, H_{arom}), 7.22–7.26 (m, 1 H, H_{arom}), 7.40–7.44 (m, 2 H, H_{arom}), 7.63 (s, 1 H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 116.4, 119.4, 119.5, 124.5, 125.1, 127.8, 130.5, 131.3, 137.6, 153.1, 160.2 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 3040, 1760, 1717, 1626, 1604, 1456, 1369, 1001, 950, 921, 751, 733, 643, 631, 454 cm^{-1}. HRMS (FD): calcd. for $C_{11}H_8O_2$ 172.0524; found 172.0522.

2: To a solution of salicylaldehyde (1.83 g, 15 mmol) and (3-chloropropane)sulfonyl chloride (2.66 g, 15 mmol) in Et_2O (20 mL) at –10 °C Et_3N was added dropwise (1.55 g, 15.3 mmol) in Et_2O (3 mL). After 5 min the mixture was warmed to room temperature and after 20 h water (45 mL) was added. The mixture was then extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with aqueous K_2CO_3 (2 × 30 mL), water (2 × 30 mL), and brine (30 mL) and then dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **2** (2.00 g, 65%). Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.47–2.55 (m, 2 H, CH_2CH$_2$Cl), 3.60–3.65 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.73–3.78 (m, 2 H, CH_2Cl), 7.40–7.50 (m, 2 H, H_{arom}), 7.62–7.70 (m, 1 H, H_{arom}), 7.96–8.22 (m, 1 H, H_{arom}), 10.29 (s, 1 H, CHO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 26.70, 42.17, 48.90, 123.55, 127.78, 130.42, 132.90, 135.56, 149.35, 187.91 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 2969, 1699, 1603, 1481, 1455, 1370, 1351, 1311, 1274, 1187, 1159, 1090, 878, 813, 779 cm^{-1}. HRMS (FD): calcd. for $C_{10}H_{11}ClNaO_4S$ 284.9959; found 284.9951.

Reaction of 2 with NaH in DMF: Solid NaH (0.027 g, 1.1 mmol) was added to a solution of **2** (0.264 g, 1 mmol) in DMF (5 mL) at –40 °C under an atmosphere of argon. After 30 min the mixture was warmed to room temperature and after 30 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **2a** (0.113 g, 51%). M.p. 153–154 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.54–2.68 (m, 2 H, 3-H), 3.91–3.97 (m, 1 H, 2-H), 4.02–4.07 (m, 1 H, 2-H), 4.17 (ddd, $J_{H,H}$ = 9.3, 7.7, 6.2 Hz, 1 H, 4-H), 5.36 (d, $J_{H,H}$ = 7.7 Hz, 1 H, 5-H), 7.13 (dd, $J_{H,H}$ = 8.1, 1.0 Hz, 1 H, H_{arom}), 7.30 (dt, $J_{H,H}$ = 8.1, 1.0 Hz, 1 H, H_{arom}), 7.39 (dt, $J_{H,H}$ = 8.1, 1.6 Hz, 1 H, H_{arom}), 7.52 (dd, $J_{H,H}$ = 8.1, 1.6 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 28.4, 58.9, 66.8, 77.7, 119.2, 122.8, 126.6, 130.3, 130.7, 150.1 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 2963, 2924, 2879, 1489, 1457, 1372, 1186, 1162, 1152, 1109, 1093, 1050, 896, 786, 758, 546 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{10}O_4SNa$ 249.0192; found 249.0197. $C_{10}H_{10}O_4S$ (226.25): calcd. C 53.09, H 4.46, S 14.17; found C 53.15, H 4.56, S 14.20.

Reaction of 2 with *t*BuOK in EtOH: Solid *t*BuOK (0.224 g, 2 mmol) was added to a solution of **2** (0.264 g, 1 mmol) in EtOH (5 mL) at room temperature under an atmosphere of argon. After 1 h an aqueous solution of NH_4Cl was added, and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **2b** (0.168 g, 62%). Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.13 (t, $J_{H,H}$ = 7.1 Hz, 3 H, CH$_2$CH_3), 2.55–2.62 (m, 1 H, 4-H), 2.72–2.79 (m, 1 H, 4-H), 3.81 (dt, $J_{H,H}$ = 9.9, 7.1 Hz, 1 H, 3-H), 3.93–4.00 (m, 2 H, CH_2CH$_3$), 4.09 (ddd, $J_{H,H}$ = 9.2, 6.0, 3.5 Hz, 1 H, 5-H), 4.42 (dt, $J_{H,H}$ = 8.5, 5.7 Hz, 1 H, 5-H), 5.26 (d, $J_{H,H}$ = 6.0 Hz, 1 H, 2-H), 6.82 (dd, $J_{H,H}$ = 8.1, 1.0 Hz, 1 H, H_{arom}), 6.89 (dt, $J_{H,H}$ = 7.5, 1.0 Hz, 1 H, H_{arom}), 7.08 (br. s, 1 H, OH), 7.16–7.20 (m, 1 H, H_{arom}), 7.22–7.24 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 14.9, 28.3, 63.2, 65.6, 66.6, 81.1, 116.6, 119.7, 119.8, 128.2, 129.3, 154.8 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 3431, 2985, 2884, 1599, 1504, 1495, 1459, 1344, 1166, 1062, 1000, 917, 757, 494 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}O_5SNa$ 295.0611; found 295.0599.

3: Solid KOH (31.5 g, 0.56 mol) was slowly added to an intensively stirred suspension of 2-mercaptobenzoic acid (30.83 g, 0.2 mol) and 1-bromo-3-chloropropane (47.66 g, 0.3 mol) in EtOH (300 mL). The mixture was heated at reflux for 3.5 h, cooled to room temperature, and poured to a mixture of water (1500 mL) and concentrated aqueous HCl (80 mL). After 18 h the solid was filtered, washed with 30% solution of EtOH in water, and dried to give **3** (46 g, 88%). The crude product was used to the next reaction without further purification. M.p. 126–128 °C (EtOH). ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 1.96–2.12 (m, 2 H, CH_2CH$_2$Cl), 3.04 (t, $J_{H,H}$ = 7.2 Hz, 2 H, CH_2CH$_2$CH$_2$Cl), 3.76 (t, $J_{H,H}$ = 6.4 Hz, 2 H, CH_2Cl), 7.15–7.27 (m, 1 H, H_{arom}), 7.37–7.58 (m, 2 H, H_{arom}), 7.86 (dd, $J_{H,H}$ = 7.8, 1.6 Hz, 1 H, H_{arom}), 13.00 (br. s, 1 H, COOH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 28.0, 30.8, 44.1, 124.1, 125.6, 128.6, 131.0, 132.4, 140.0, 167.5 ppm. IR (KBr): $\tilde{\nu}$ = 2970, 2644, 1677, 1561, 1463, 1411, 1319, 1277, 1251, 1150, 1060, 1047, 923, 741, 704, 554 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 232 (30) [M$^+$], 230 (82), 194 (8), 184 (6), 176 (8), 167 (34), 153 (41), 150 (49), 136 (100). $C_{10}H_{11}ClO_2S$ (230.72): calcd. C 52.06, H 4.81, Cl 15.37, S 13.87; found C 52.33, H 4.91, Cl 14.09, S 13.94.

General Procedure of the Synthesis 12–14: Crude **3** (23.05 g, 100 mmol) was dissolved in acetic acid (200 mL). The mixture was warmed to 90 °*C* and hydrogen peroxide (30%, 23.02 g, 203 mmol) was added dropwise. The mixture was gently heated at reflux for 3 h, acetic acid was evaporated under vacuum, the residue was treated with thionyl chloride (30.8 g, 259 mmol) and then warmed

at 50 °C for 20 h. The mixture was evaporated, and the residue was dissolved in a mixture of CH_2Cl_2 (100 mL) and alcohol (250 mmol) at 0 °C. To this solution was slowly added pyridine (17.5 g, 221 mmol) in CH_2Cl_2 (100 mL) over 20 min. The mixture was left at room temperature for 20 h, washed with dilute aqueous HCl (2 × 100 mL), $NaHCO_3$ (2 × 100 mL), and brine (2 × 100 mL), and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **12**–**14**.

12: Yield 65% (18.1 g), oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.23–2.37 (m, 2 H, CH_2CH$_2$Cl), 3.64–3.72 (m, 4 H, CH_2CH$_2$CH_2Cl), 3.98 (s, 3 H, OCH_3), 7.62–7.74 (m, 3 H, H_{arom}), 8.04–8.11 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 25.7, 42.8, 53.3, 53.8, 129.8, 130.6, 131.1, 133.4, 133.7, 137.7, 167.4 ppm. IR (film): $\tilde{\nu}$ = 3003, 2955, 1735, 1434, 1295, 1262, 1153, 1125, 1058, 957, 830, 787, 765, 739, 598, 569, 538 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 276 (<1) [M$^+$], 245 (29), 199 (58), 181 (62), 169 (58), 148 (73), 135 (83), 105 (100), 92 (50), 77 (57). HRMS (EI): calcd. for $C_{11}H_{13}ClO_4S$ 276.0223; found 276.0230. $C_{11}H_{13}ClO_4S$ (276.74): calcd. C 47.74, H 4.73, Cl 12.81, S 11.59; found C 47.80, H 4.91, Cl 12.83, S 11.76.

13: Yield 59% (17.2 g), oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.41 (t, $J_{H,H}$ = 7.2 Hz, 3 H, OCH$_2$CH_3), 2.21–2.36 (m, 2 H, CH_2CH$_2$Cl), 3.62–3.73 (m, 4 H, CH_2CH$_2$CH_2Cl), 4.44 (q, $J_{H,H}$ = 7.2 Hz, 2 H, OCH_2CH$_3$), 7.60–7.74 (m, 3 H, H_{arom}), 8.01–8.12 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 14.0, 25.7, 42.8, 53.9, 62.5, 129.8, 130.6, 131.0, 133.7, 133.8, 137.5, 167.0 ppm. IR (film): $\tilde{\nu}$ = 2983, 1732, 1441, 1368, 1293, 1261, 1153, 1123, 1058, 740, 599, 538 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 290 (1) [M$^+$], 247 (14), 245 (38), 213 (11), 195 (8), 185 (37), 182 (16), 169 (60), 162 (16), 149 (16), 145 (31), 121 (22), 105 (100). $C_{12}H_{15}ClO_4S$ (290.77): calcd. C 49.57, H 5.20, Cl 12.19, S 11.03; found C 49.62, H 5.35, Cl 12.08, S 10.91.

14: Yield 60% (20.6 g), oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.27–2.34 (m, 2 H, CH_2CH$_2$Cl), 3.61–3.69 (m, 4 H, CH_2CH$_2$CH_2Cl), 4.74 (q, $J_{H,H}$ = 8.4 Hz, 2 H, CH_2CF$_3$), 7.72–7.78 (m, 3 H, H_{arom}), 8.09–8.13 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 25.6, 42.7, 53.9, 61.9 (q, $J_{C,F}$ = 36.7 Hz), 121.7, 123.9, 130.1, 130.9, 131.5, 132.0, 133.9, 138.2, 165.3 ppm. IR (film): $\tilde{\nu}$ = 2972, 1755, 1574, 1441, 1415, 1303, 1250, 1155, 1115, 1063, 964, 784, 764, 739, 663, 599, 569, 535 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 267 (28), 203 (50), 181 (55), 145 (88), 120 (26), 105 (100), 91 (60), 41 (58). HRMS (ESI): calcd. for $C_{12}H_{12}ClF_3O_4NaS$ 366.9989; found 366.9987.

5: DIBAL-H (13 mL, 13 mmol, 1 M in toluene) was added dropwise to a solution of **13** (1.79 g, 6.2 mmol) in toluene (35 mL) at 0 °C under an atmosphere of argon. After 80 min, MeOH (10 mL), an aqueous solution of NH_4Cl (30 mL), and hydrochloric acid (10 mL) were added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with aqueous $NaHCO_3$ (30 mL) and brine (30 mL) and then dried with $MgSO_4$. The solvent was evaporated, and crude product **5** was obtained (1.43 g, 93% yield) and used in the next reaction without further purification. Oil. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.12–2.35 (m, 2 H, CH_2CH$_2$Cl), 3.10 (t, $J_{H,H}$ = 6.7 Hz, 1 H, OH), 3.35–3.46 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.64 (dd, $J_{H,H}$ = 6.2, 6.2 Hz, 2 H, CH_2Cl), 4.93 (d, $J_{H,H}$ = 6.7 Hz, 2 H, CH_2OH), 7.47–7.72 (m, 3 H, H_{arom}), 8.00 (dd, $J_{H,H}$ = 7.6, 1.0 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 25.5, 42.7, 53.9, 63.0, 128.8, 130.7, 131.7, 134.6, 136.9, 140.5 ppm. IR (film): $\tilde{\nu}$ = 3503, 2965, 1442, 1299, 1192, 1150, 1120, 1023, 765, 605, 572, 537 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 250 (1), 248 (3) [M$^+$], 233 (7), 231 (19), 171 (11), 153 (100), 145 (12), 143 (34), 137 (22), 125 (29), 109 (43), 107 (79), 105 (59). $C_{10}H_{13}ClO_3S$ (248.73): calcd. C 48.29, H 5.27, Cl 14.25, S 12.89; found C 48.36, H 5.40, Cl 14.27, S 12.93.

6: To an intensively stirred solution of **5** (4.60 g, 18.5 mmol) in CH_2Cl_2 (100 mL) was added pyridinium chlorochromate (PCC, 4.01 g, 18.6 mmol) over 10 min. After 1 h, a second portion of PCC (0.41 g, 1.9 mmol) was added, and the mixture was stirred for 5 h. Then, the mixture was filtered through Celite, and the solvent was evaporated. Column chromatography (hexane/EtOAc) gave **6** (3.38 g, 74%). M.p. 47–50 °C (EtOH). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.20–2.36 (m, 2 H, CH_2CH$_2$Cl), 3.42–3.53 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.65 (t, $J_{H,H}$ = 6.1 Hz, 2 H, CH_2Cl), 7.75–7.89 (m, 2 H, H_{arom}), 8.04–8.16 (m, 2 H, H_{arom}), 10.75 (s, 1 H, CHO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 25.5, 42.5, 55.1, 130.5, 130.6, 133.8, 134.3, 134.9, 139.6, 189.5 ppm. IR (KBr): $\tilde{\nu}$ = 2931, 1685, 1588, 1413, 1295, 1262, 1193, 1146, 1111, 958, 825, 750, 727, 606, 532 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 247 (1) [M$^+$], 231 (11), 229 (31), 169 (100), 153 (12), 142 (26). $C_{10}H_{11}ClO_3S$ (246.71): calcd. C 48.68, H 4.49, Cl 14.37, S 13.00; found C 48.50, H 4.64, Cl 14.24, S 13.09.

Reaction of 6 with *t*BuOK in THF: *t*BuOK (0.112 g, 1 mmol) in THF (2 mL) was added dropwise to a solution of **6** (123 mg, 0.5 mmol) in THF (5 mL) at –70 °C under an atmosphere of argon. After 30 min the mixture was warmed to room temperature and after 15 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **6a** (0.037 g, 34%) and **6c**[4] (0.035 g, 38%). Data for **6a**: Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.34–2.43 (m, 1 H, 3-H), 2.65–2.72 (m, 1 H, 3-H), 3.57–3.63 (m, 1 H, 2-H), 3.98 (ddd, $J_{H,H}$ = 9.0, 7.6, 3.3 Hz, 1 H, 2-H), 4.04 (ddd, $J_{H,H}$ = 9.9, 7.1, 2.9 Hz, 1 H, 4-H), 5.74 (d, $J_{H,H}$ = 7.1 Hz, 1 H, 5-H), 7.59 (ddd, $J_{H,H}$ = 8.1, 7.2, 1.2 Hz, 1 H, H_{arom}), 7.63 (d, $J_{H,H}$ = 7.0 Hz, 1 H, H_{arom}), 7.67 (ddd, $J_{H,H}$ = 8.1, 7.2, 1.2 Hz, 1 H, H_{arom}), 7.73 (d, $J_{H,H}$ = 7.8 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 29.1, 63.2, 67.9, 79.8, 121.1, 127.6, 131.0, 134.1, 136.1, 139.8 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 3626, 3061, 2985, 2872, 1956, 1584, 1470, 1452, 1299, 1260, 1205, 1173, 1146, 1120, 1049, 925, 888, 841, 757, 634, 592, 558, 536, 488, 427 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 210 (14) [M$^+$], 167 (95), 163 (30), 147 (14), 137 (100), 115 (88). $C_{10}H_{10}O_3S$ (210.25): calcd. C 57.13, H 4.79, S 15.25; found C 57.03, H 4.72, S 15.21.

Synthesis of **19** was performed according to a procedure described in the literature.[14]

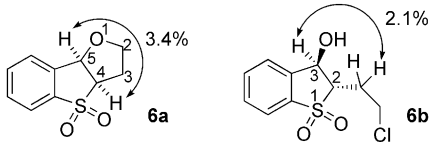
Deformylation of 19: *t*BuOK (0.112 g, 1 mmol) in THF (2 mL) was added dropwise to a solution of **19** (0.123 g, 0.5 mmol) in THF (5 mL) at –70 °C under an atmosphere of argon. After 30 min the mixture was warmed to room temperature and after 15 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. The residue was recrystallized from EtOH to give **19** (0.103 g, 95%). M.p. 93–94 °C (CCl_4); ref.[14] 93 °C. ^{1}H NMR spectroscopic data consistent with the literature.[14]

Reaction of 6 with *t*BuOK in EtOH: *t*BuOK (0.241 g, 2.15 mmol) in EtOH (1 mL) was added dropwise to a solution of **6** (0.247 g, 1 mmol) in EtOH (5 mL) at room temperature under an atmosphere of argon. After 30 min an aqueous solution of NH_4Cl was added, and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **6a** (0.162 g, 77%) and **6b** (0.045 g, 18%). Data for **6b**: Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.34–2.44 (m, 1 H, CH*H*CH$_2$Cl),

2.57–2.65 (m, 1 H, C*H*HCH$_2$Cl), 3.20 (d, $J_{H,H}$ = 8.3 Hz, 1 H, OH), 3.55–3.61 (m, 1 H, 2-H), 3.79–3.91 (m, 2 H, CH_2Cl), 5.04 (dd, $J_{H,H}$ = 8.3, 7.4 Hz, 1 H, 3-H), 7.53–7.58 (m, 1 H, H$_{arom}$), 7.64–7.74 (m, 3 H, H$_{arom}$) ppm. ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C): δ = 29.3, 41.5, 66.7, 72.6, 121.3, 125.5, 130.3, 134.1, 137.9, 139.6 ppm. IR (CH$_2$Cl$_2$ film): $\tilde{\nu}$ = 3469, 2928, 1632, 1698, 1467, 1453, 1292, 1182, 1151, 1122, 1085, 1048, 944, 915, 759, 705, 660, 593, 560, 511 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 248 (16), 246 (44) [M$^+$], 231 (15), 229 (39), 197 (31), 169 (100), 154 (19), 153 (19), 142 (30), 137 (41). $C_{10}H_{11}ClO_3S$ (246.71): calcd. C 48.68, H 4.49, Cl 14.37, S 13.00; found C 48.71, H 4.70, Cl 14.87, S 13.22.

The same reaction carried out for 18 h gave **6a** (0.203 g, 97%) as the only product.

The stereochemistry of **6a** and **6b** was established on the basis of NOE experiments.



7: Phenylmagnesium bromide (3.34 mL, 10 mmol, 3 M in THF) was added dropwise to a suspension of **4** (2.81 g, 10 mmol) and CuI (1.91 g, 10 mmol) in THF (60 mL) at –5 °C. The mixture was warmed to room temperature and after 2 h a 5% aqueous solution of HCl (60 mL) and ammonia (60 mL) were added, and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **7** (2.09 g, 65%). M.p. 99–100 °C (EtOH). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ = 2.20–2.34 (m, 2 H, CH_2CH$_2$Cl), 3.54–3.69 (m, 4 H, CH_2CH$_2$CH_2Cl), 7.39–7.51 (m, 3 H, H$_{arom}$), 7.57–7.66 (m, 1 H, H$_{arom}$), 7.68–7.74 (m, 2 H, H$_{arom}$), 7.76–7.84 (m, 2 H, H$_{arom}$), 8.08–8.16 (m, 1 H, H$_{arom}$) ppm. ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C): δ = 25.7, 42.7, 55.2, 128.5, 130.0, 130.4, 130.6, 133.1, 133.9, 136.3, 137.9, 140.5, 144.4, 161.1 ppm. IR (KBr): $\tilde{\nu}$ = 3319, 3094, 2962, 1668, 1595, 1581, 1450, 1312, 1293, 1271, 1196, 1152, 1115, 936, 780, 771, 709, 634, 569, 537 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 245 (25), 240 (28), 213 (36), 182 (74), 169 (37), 152 (55), 105 (100), 77 (72). HRMS (ESI): calcd. for $C_{16}H_{15}ClNaO_3S$ 345.0323; found 345.0327. $C_{16}H_{15}ClO_3S$ (322.81): calcd. C 59.53, H 4.68, Cl 10.98, S 9.93; found C 59.37, H 4.79, Cl 10.96, S 10.04.

Reaction of 7 with *t*BuOK in EtOH: *t*BuOK (0.112 g, 1 mmol) in EtOH (2 mL) was added dropwise to a solution of **7** (0.161 g, 0.5 mmol) in EtOH (5 mL) at room temperature under an atmosphere of argon. After 90 min an aqueous solution of NH_4Cl was added, and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **7a** (0.085 mg, 60%) and **7b** (0.061 g, 38%). Data for **7a**: M.p. 118–119 °C (EtOH). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ = 2.37–2.57 (m, 1 H, 3-H), 2.71–2.84 (m, 1 H, 3-H), 3.66–3.78 (m, 1 H, 2-H), 3.95 (dd, $J_{H,H}$ = 9.4, 2.4 Hz, 1 H, 4-H), 4.16–4.25 (m, 1 H, 2-H), 7.23–7.48 (m, 6 H, H$_{arom}$), 7.53–7.65 (m, 2 H, H$_{arom}$), 7.72–7.82 (m, 1 H, H$_{arom}$) ppm. ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C): δ = 29.7, 68.1, 71.1, 90.9, 120.5, 125.4, 127.1, 128.1, 128.6, 130.7, 134.5, 139.5, 140.4, 141.9 ppm. IR (CH$_2$Cl$_2$ film): $\tilde{\nu}$ = 3082, 2970, 2862, 1449, 1297, 1175, 1144, 1121, 1055, 986, 767, 759, 748, 705, 560, 509, 495 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 286 (20) [M$^+$], 239 (41), 213 (100), 178 (26), 165 (61), 136 (24), 115 (26), 105 (18), 77 (21). HRMS (ESI): calcd. for $C_{16}H_{14}NaO_3S$ 309.0556; found 309.0560. $C_{16}H_{14}O_3S$ (286.35): calcd. C 67.11, H 4.93, S 11.20; found C 67.19, H 4.94, S 11.35. Data for **7b**: M.p. 124–125 °C (EtOH). ^{1}H NMR (200 MHz, CDCl$_3$, 25 °C): δ = 1.81–2.09 (m, 2 H, CH_2CH$_2$Cl), 2.95 (br. s, 1 H, OH), 3.67 (dd, $J_{H,H}$ = 7.1, 5.8 Hz, 1 H, CH_2Cl), 4.02 (dd, $J_{H,H}$ = 8.7, 5.8 Hz, 1 H, 2-H), 7.22–7.36 (m, 5 H, H$_{arom}$), 7.41–7.47 (m, 1 H, H$_{arom}$), 7.57–7.71 (m 2 H, H$_{arom}$), 7.80–7.87 (m, 1 H, H$_{arom}$) ppm. ^{13}C NMR (50 MHz, CDCl$_3$, 25 °C): δ = 28.4, 41.3, 69.3, 80.2, 121.1, 125.8, 126.4, 128.4, 128.5, 130.7, 134.7, 138.4, 139.5, 143.7 ppm. IR (CH$_2$Cl$_2$ film): $\tilde{\nu}$ = 3460, 3061, 2923, 1496, 1449, 1298, 1152, 1123, 1042, 763, 749, 702, 589, 562, 544, 506 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 322 (<1) [M$^+$], 304 (19), 273 (10), 213 (100), 195 (56), 181 (14), 165 (9), 152 (14), 105 (20), 77 (22). HRMS (ESI): calcd. for $C_{16}H_{15}ClNaO_3S$ 345.0323; found 345.0307. $C_{16}H_{15}ClO_3S$ (322.81): calcd. C 59.53, H 4.68, Cl 10.98, S 9.93; found C 59.51, H 4.85, Cl 10.82, S 9.88.

The same reaction carried out for 22 h gave **4a** (0.140 g, 99%) as the only product.

General Procedure for the Synthesis of 8–11: A mixture of **6** (0.494 g, 2 mmol), amine (2 mmol), and anhydrous $MgSO_4$ (0.962 g, 8 mmol) in toluene (10 mL) was stirred at room temperature for 24 h. The mixture was then was filtered, and the solvent was evaporated. Crystalline products were recrystallized from EtOH.

8: Yield quant., m.p. 88–90 °C (EtOH). ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ = 2.19–2.26 (m, 2 H, CH_2CH$_2$Cl), 2.39 (s, 3 H, CH$_3$), 3.32–3.36 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.61 (t, $J_{H,H}$ = 6.2 Hz, 2 H, CH_2Cl), 7.23 (m, 4 H, H$_{arom}$), 7.65 (dt, $J_{H,H}$ = 7.8, 1.3 Hz, 1 H, H$_{arom}$), 7.74–7.78 (m, 1 H, H$_{arom}$), 8.08 (dd, $J_{H,H}$ = 7.9, 1.1 Hz, 1 H, H$_{arom}$), 8.39 (dd, $J_{H,H}$ = 7.8, 1.1 Hz, 1 H, H$_{arom}$), 9.40 (s, 1 H, N=C*H*) ppm. ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C): δ = 21.1, 25.6, 42.5, 54.7, 121.3, 129.5, 129.9, 130.1, 130.8, 134.1, 135.8, 137.2, 137.9, 148.5, 155.3 ppm. IR (KBr): $\tilde{\nu}$ = 3064, 3023, 2970, 2921, 1618, 1562, 1506, 1463, 1438, 1311, 1290, 1147, 1114, 1059, 1019, 962, 840, 819, 776, 750, 708, 635, 600, 541, 523, 496 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 335 (65) [M$^+$], 286 (21), 229 (61), 195 (72), 153 (97), 106 (100), 91 (57), 65 (56), 41 (43). HRMS (EI): calcd. for $C_{17}H_{18}ClNO_2S$ 335.0747; found 335.0734. $C_{17}H_{18}ClNO_2S$ (335.86): calcd. C 60.80, H 5.40, Cl 10.56, N 4.17, S 9.55; found C 60.76, H 5.46, Cl 10.51, N 4.01, S 9.62.

9: Yield quant., m.p. 80–82 °C (EtOH). ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ = 2.21–2.27 (m, 2 H, CH_2CH$_2$Cl), 3.32–3.36 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.63 (t, $J_{H,H}$ = 6.1 Hz, 2 H, CH_2Cl), 7.22–7.26 (m, 2 H, H$_{arom}$), 7.36–7.40 (m, 2 H, H$_{arom}$), 7.68 (dt, $J_{H,H}$ = 7.6, 1.2 Hz, 1 H, H$_{arom}$), 7.77 (t, $J_{H,H}$ = 7.6 Hz, 1 H, H$_{arom}$), 8.09 (dd, $J_{H,H}$ = 7.8, 1.2 Hz, 1 H, H$_{arom}$), 8.39 (dd, $J_{H,H}$ = 7.8, 1.2 Hz, 1 H, H$_{arom}$), 9.37 (s, 1 H, N=C*H*) ppm. ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C): δ = 25.6, 42.5, 54.8, 122.6, 129.4, 129.6, 130.2, 131.2, 132.7, 134.2, 135.3, 138.2, 149.5, 156.7 ppm. IR (KBr): $\tilde{\nu}$ = 3065, 2965, 1616, 1561, 1486, 1312, 1290, 1262, 1188, 1147, 1113, 1091, 1059, 878, 832, 757, 722, 591, 570, 540, 520 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 355 (5) [M$^+$], 229 (52), 213 (50), 178 (45), 153 (72), 126 (51), 111 (41), 75 (53), 41 (100). HRMS (ESI): calcd. for $C_{16}H_{15}Cl_2NNaO_2S$ 378.0093; found 378.0100. $C_{16}H_{15}Cl_2NO_2S$ (356.27): calcd. C 53.94, H 4.24, Cl 19.90, N 3.93, S 9.00; found C 53.83, H 4.10, Cl 19.72, N 3.80, S 9.16.

10: Yield quant., oil. ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ = 1.33 (t, $J_{H,H}$ = 7.3 Hz, 3 H, CH$_3$), 2.18–2.24 (m, 2 H, CH_2CH$_2$Cl), 3.29–3.33 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.63 (t, $J_{H,H}$ = 6.2 Hz, 2 H, CH_2Cl), 3.75 (dq, $J_{H,H}$ = 7.3, 1.5 Hz, 2 H, CH_2CH$_3$), 7.59 (dt, $J_{H,H}$ = 7.9, 1.4 Hz, 1 H, H$_{arom}$), 7.69 (dt, $J_{H,H}$ = 7.7, 1.0 Hz, 1 H, H$_{arom}$), 8.03 (dd, $J_{H,H}$ = 7.9, 1.3 Hz, 1 H, H$_{arom}$), 8.11 (dd, $J_{H,H}$ = 7.7, 1.3 Hz, 1 H, H$_{arom}$), 9.14 (s, 1 H, N=C*H*) ppm. ^{13}C NMR (125 MHz, CDCl$_3$,

25 °C): δ = 16.0, 25.6, 42.6, 54.5, 56.2, 129.5, 129.8, 130.3, 134.1, 136.1, 137.3, 157.3 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 2971, 2933, 1636, 1442, 1309, 1150, 1119, 767, 598, 570, 540 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 273 (<1) [M^+], 196 (100), 152 (55), 131 (23), 103 (74), 77 (13), 44 (54). HRMS (ESI): calcd. for $C_{12}H_{16}ClNNaO_2S$ 296.0483; found 296.0496. $C_{12}H_{16}ClNO_2S$ (273.78): calcd. C 52.65, H 5.89, Cl 12.95, N 5.12, S 11.71; found C 52.53, H 5.81, Cl 12.71, N 4.87, S 11.78.

11: Yield quant., oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.13–2.19 (m, 2 H, C*H*$_2$CH$_2$Cl), 3.22–3.27 (m, 2 H, C*H*$_2$CH$_2$CH$_2$Cl), 3.56 (t, $J_{H,H}$ = 6.2 Hz, 2 H, C*H*$_2$Cl), 4.90 (d, $J_{H,H}$ = 1.2 Hz, 2 H, C*H*$_2$N=), 7.26–7.31 (m, 1 H, H_{arom}), 7.36 (d, $J_{H,H}$ = 4.4 Hz, 4 H, H_{arom}), 7.60 (dt, $J_{H,H}$ = 7.6, 1.2 Hz, 1 H, H_{arom}), 7.69 (dt, $J_{H,H}$ = 7.6, 1.0 Hz, 1 H, H_{arom}), 8.03 (dd, $J_{H,H}$ = 7.8, 1.0 Hz, 1 H, H_{arom}), 8.16 (dd, $J_{H,H}$ = 7.7, 1.2 Hz, 1 H, H_{arom}), 9.24 (s, 1 H, N=C*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 25.5, 42.5, 54.5, 65.5, 127.3, 128.2, 128.6, 129.6, 129.8, 130.5, 134.1, 135.8, 137.5, 138.5, 158.7 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 3064, 3029, 2923, 1634, 1495, 1453, 1309, 1149, 1119, 1062, 1027, 754, 700, 597, 569, 539, 510 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 335 (3) [M^+], 258 (7), 194 (14), 150 (9), 118 (8), 106 (8), 91 (100), 65 (16), 41 (13). HRMS (EI): calcd. for $C_{17}H_{18}ClNO_2S$ 335.0747; found 335.0758. $C_{17}H_{18}ClNO_2S$ (335.86): calcd. C 60.80, H 5.40, Cl 10.56, N 4.17, S 9.55; found C 60.66, H 5.35, Cl 10.37, N 4.02, S 9.61.

General Procedure for Reactions of 8–11 with *t*BuOK in THF: *t*BuOK (0.112 g, 1 mmol) in THF (2 mL) was added dropwise to a solution of imine (0.5 mmol) in THF (5 mL) at –70 °C under an atmosphere of argon. After 30 min the mixture was warmed to room temperature and after 15 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. The products were isolated and purified by column chromatography (hexane/EtOAc).

8a: Yield 83%, m.p. 234–236 °C (EtOH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 3 H, CH_3), 2.40 (dq, $J_{H,H}$ = 13.6, 8.8 Hz, 1 H, 3-H), 2.51–2.59 (m, 1 H, 3-H), 3.41 (dt, $J_{H,H}$ = 8.8, 7.0 Hz, 1 H, 2-H), 3.52 (ddd, $J_{H,H}$ = 9.3, 8.8, 3.7 Hz, 1 H, 2-H), 4.09 (dt, $J_{H,H}$ = 8.8, 7.1 Hz, 1 H, 4-H), 5.63 (d, $J_{H,H}$ = 7.1 Hz, 1 H, 5-H), 6.76–6.80 (m, 2 H, H_{arom}), 7.12–7.16 (m, 2 H, H_{arom}), 7.50–7.54 (m, 3 H, H_{arom}), 7.72–7.76 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 20.3, 26.7, 48.7, 61.9, 63.0, 113.0, 121.8, 127.0, 127.7, 130.0, 130.1, 133.9, 137.5, 140.1, 145.2 ppm. IR (KBr): $\tilde{\nu}$ = 3031, 2921, 2842, 1618, 1516, 1478, 1358, 1327, 1292, 1256, 1184, 1143, 1114, 835, 801, 763, 594, 570, 533, 506 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 299 (100) [M^+], 234 (50), 208 (33), 133 (42), 118 (72), 91 (46), 65 (20). HRMS (EI): calcd. for $C_{17}H_{17}NO_2S$ 299.0980; found 299.0986. $C_{17}H_{17}NO_2S$ (299.39): calcd. C 68.20, H 5.72, N 4.68, S 10.71; found C 68.21, H 5.73, N 4.60, S 10.72.

9a: Yield 70%, m.p. 243–245 °C (EtOH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.41 (dq, $J_{H,H}$ = 13.7, 8.8 Hz, 1 H, 3-H), 2.54–2.61 (m, 1 H, 3-H), 3.42 (dt, $J_{H,H}$ = 8.8, 7.1 Hz, 1 H, 2-H), 3.52 (ddd, $J_{H,H}$ = 8.8, 8.4, 3.7 Hz, 1 H, 2-H), 4.11 (dt, $J_{H,H}$ = 8.8, 7.1 Hz, 1 H, 4-H), 5.63 (d, $J_{H,H}$ = 7.1 Hz, 1 H, 5-H), 6.76–6.80 (m, 2 H, H_{arom}), 7.25–7.29 (m, 2 H, H_{arom}), 7.47–7.51 (m, 1 H, H_{arom}), 7.52–7.56 (m, 2 H, H_{arom}), 7.73–7.77 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 26.6, 48.6, 61.7, 63.0, 114.0, 122.0, 123.3, 126.8, 129.5, 130.3, 134.1, 137.6, 139.5, 145.7 ppm. IR (KBr): $\tilde{\nu}$ = 2858, 1597, 1494, 1476, 1360, 1296, 1258, 1188, 1144, 1115, 1096, 835, 807, 769, 705, 584, 533 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 319 (100) [M^+], 254 (54), 228 (26), 153 (50), 138 (79), 129 (33), 115 (54), 103 (18), 75 (25). HRMS (EI): calcd. for $C_{16}H_{14}ClNO_2S$ 319.0434; found 319.0432.

10a: Yield 52%, m.p. 70–71 °C (EtOH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.07 (t, $J_{H,H}$ = 7.1 Hz, 3 H, CH_2CH_3), 1.16 (ddd, $J_{H,H}$ = 9.7, 7.5, 5.3 Hz, 1 H, 3-H), 1.37–1.43 (m, 1 H, 3-H), 1.56 (ddd, $J_{H,H}$ = 10.7, 7.5, 5.7 Hz, 2 H, 2-H and 4-H), 1.68 (ddd, $J_{H,H}$ = 10.7, 7.5, 5.3 Hz, 1 H, 2-H), 2.52 (dq, $J_{H,H}$ = 11.3, 7.1 Hz, 1 H, CH_2CH$_3$), 2.73 (dq, $J_{H,H}$ = 11.3, 7.1 Hz, 1 H, CH_2CH$_3$), 4.26 (s, 1 H, 5-H), 7.51–7.58 (m, 2 H, H_{arom}), 7.60–7.64 (m, 1 H, H_{arom}), 7.80 (d, $J_{H,H}$ = 7.7 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 9.1, 13.8, 15.5, 40.4, 45.4, 60.3, 121.3, 126.6, 129.6, 133.0, 139.3, 140.1 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 3341, 2968, 2869, 1466, 1453, 1289, 1152, 1115, 1062, 1034, 969, 760, 724, 574 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 237 (8) [M^+], 222 (21), 193 (100), 151 (59), 144 (28), 132 (88), 118 (24), 91 (21), 44 (75). HRMS (EI): calcd. for $C_{12}H_{15}NO_2S$ 237.0824; found 237.0814. $C_{12}H_{15}NO_2S$ (237.32): calcd. C 60.73, H 6.37, N 5.90, S 13.51; found C 60.65, H 6.28, N 5.82, S 13.68.

11c: Yield 48%, oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.11–1.17 (m, 1 H, C*H*HCH$_2$), 1.45–1.51 (m, 1 H, CH*H*CH$_2$), 1.59–1.64 (m, 1 H, CH$_2$C*H*H), 1.66–1.72 (m, 1 H, CH$_2$CH*H*), 1.83 (s, 1 H, NH), 3.68 (d, $J_{H,H}$ = 13.2 Hz, 1 H, C*H*HNH), 3.89 (d, $J_{H,H}$ = 13.2 Hz, 1 H, CH*H*NH), 4.30 (s, 1 H, 3-H), 7.23–7.28 (m, 1 H, H_{arom}), 7.30–7.33 (m, 4 H, H_{arom}), 7.53–7.60 (m, 2 H, H_{arom}), 7.62–7.66 (m, 1 H, H_{arom}), 7.79–7.82 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 9.2, 13.9, 45.5, 49.9, 59.6, 121.4, 126.6, 127.3, 128.0, 128.5, 129.7, 133.1, 139.4, 139.5, 139.9 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 3342, 3063, 3029, 1495, 1453, 1290, 1152, 1115, 1062, 1031, 966, 760, 700, 573 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}NNaO_2S$ 322.0872; found 322.0885.

Reaction of 11 with *t*BuOK in Toluene: Solid *t*BuOK (0.112 g, 1 mmol) was added to a solution of **11** (0.168 g, 0.5 mmol) in toluene (5 mL) at –70 °C under an atmosphere of argon. After 30 min the mixture was warmed to room temperature and after 15 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **11a** (48%, 0.068 g) and **11c** (24%, 0.034 g). Data for **11a**: M.p. 105–107 °C (EtOH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.34–2.43 (m, 1 H, 3-H), 2.50–2.57 (m, 1 H, 3-H), 2.73–2.79 (m, 1 H, 2-H), 2.83–2.90 (m, 1 H, 2-H), 3.70 (d, $J_{H,H}$ = 13.0 Hz, 1 H, C*H*HN), 3.96 (d, $J_{H,H}$ = 13.0 Hz, 1 H, CH*H*N), 4.00–4.05 (m, 1 H, 4-H), 4.63 (d, $J_{H,H}$ = 7.1 Hz, 1 H, 5-H), 7.26–7.30 (m, 1 H, H_{arom}), 7.31–7.39 (m, 4 H, H_{arom}), 7.44 (d, $J_{H,H}$ = 7.6 Hz, 1 H, H_{arom}), 7.51 (t, $J_{H,H}$ = 7.3 Hz, 1 H, H_{arom}), 7.57 (t, $J_{H,H}$ = 7.3 Hz, 1 H, H_{arom}), 7.72 (d, $J_{H,H}$ = 7.6 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 25.7, 53.1, 58.7, 63.3, 67.9, 121.5, 127.3, 127.5, 128.5, 128.8, 130.1, 133.5, 138.1, 138.4, 139.4 ppm. IR (KBr): $\tilde{\nu}$ = 3024, 2965, 2932, 2808, 1451, 1304, 1210, 1153, 1124, 1057, 859, 760, 734, 703, 558, 537, 496 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{17}NNaO_2S$ 322.0872; found 322.0866. $C_{17}H_{17}NO_2S$ (299.39): calcd. C 68.20, H 5.72, N 4.68, S 10.71; found C 68.23, H 5.71, N 4.62, S 10.78.

Reaction of 13 with *t*BuOK in THF: *t*BuOK (0.112 g, 1 mmol) in THF (2 mL) was added dropwise to a solution of **13** (0.145 g, 0.5 mmol) in THF (5 mL) at –70 °C under an atmosphere of argon. After 30 min the mixture was warmed to room temperature and after 15 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Recrystallization from EtOH gave **13c** (0.064 g, 62%). M.p. 88–90 °C (EtOH). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.88–1.92

(m, 2 H, C*H*HC*H*H), 2.01–2.04 (m, 2 H, CH*H*CH*H*), 7.82 (dt, $J_{H,H}$ = 7.6, 1.0 Hz, 1 H, H_{arom}), 7.94 (dt, $J_{H,H}$ = 7.6, 1.2 Hz, 1 H, H_{arom}), 8.02–8.07 (m, 2 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 19.5, 47.1, 121.7, 124.0, 132.5, 133.8, 136.3, 146.4, 189.3 ppm. IR (KBr): $\tilde{\nu}$ = 3089, 1720, 1587, 1455, 1310, 1294, 1207, 1149, 988, 786, 751, 684, 602, 568 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 208 (92) [M$^+$], 178 (23), 169 (20), 152 (40), 115 (22), 104 (100), 76 (43), 50 (18). HRMS (EI): calcd. for $C_{10}H_8O_3S$ 208.0194; found 208.0193. $C_{10}H_8O_3S$ (208.24): calcd. C 57.68, H 3.87, S 15.40; found C 57.53, H 4.03, S 15.18.

Under the same conditions, **12** and **14** gave **13c** as the only product (crude reaction mixtures were analyzed by NMR spectroscopy; products were not isolated).

15: Crude **3** (6.65 g, 24 mmol) in CH_2Cl_2 (30 mL) was added dropwise to an aqueous solution of ammonia (30 mL, 25%) at 0 °C. After 10 min the mixture was warmed to room temperature and after 24 h the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. The mixture was filtered, evaporated, dissolved in DMF (15 mL) and 2,4,6-trichloro-[1,3,5]triazine (1.29 g, 7 mmol) in *tert*-butyl methyl ether (38 mL) was added dropwise. After 24 h at room temperature, water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **15** (4.56 g, 79%). M.p. 70–71 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.26–2.32 (m, 2 H, CH_2CH$_2$Cl), 3.52–3.56 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.67 (t, $J_{H,H}$ = 6.2 Hz, 2 H, CH_2Cl), 7.81 (dt, $J_{H,H}$ = 7.4, 1.5 Hz, 1 H, H_{arom}), 7.86 (dt, $J_{H,H}$ = 7.7, 1.5 Hz, 1 H, H_{arom}), 7.95 (dd, $J_{H,H}$ = 7.4, 1.5 Hz, 1 H, H_{arom}), 8.19 (dd, $J_{H,H}$ = 7.7, 1.5 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 25.5, 42.4, 52.6, 111.5, 115.4, 130.5, 133.4, 134.0, 135.6, 141.3 ppm. IR (KBr): $\tilde{\nu}$ = 3089, 2918, 2230, 1315, 1261, 1197, 1155, 1125, 1066, 774, 761, 568, 548 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 151 (11), 144 (53), 117 (15), 103 (100), 76 (25), 51 (13), 41 (73), 39 (30). HRMS (ESI): calcd. for $C_{10}H_{10}ClNNaO_2S$ 266.0013; found 266.0004. $C_{10}H_{10}ClNO_2S$ (243.71): calcd. C 49.28, H 4.14, Cl 14.55, N 5.75, S 13.16; found C 49.17, H 4.20, Cl 14.56, N 5.76, S 12.94.

Reaction of **15** with *t*BuOK in THF was performed according to the same procedure as that used for **12**–**14**, yield 90% (as a mixture of geometric isomers observed by NMR spectroscopy).

Data for 15c: M.p. 148–149 °C (EtOH). Mixture of isomers (ca. 1:1). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25 °C): δ = 1.73–1.76 (m, 4 H, C*H*HC*H*H), 1.80–1.90 (m, 4 H, CH*H*CH*H*), 7.88–7.96 (m, 4 H, H_{arom}), 8.11–8.16 (m, 2 H, H_{arom}), 8.17–8.20 (m, 1 H, H_{arom}), 8.36–8.41 (m, 1 H, H_{arom}), 10.65 (s, 1 H, NH=), 11.29 (s, 1 H, NH=) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 25 °C): δ = 16.6, 17.2, 44.5, 44.5, 121.0, 121.4, 122.7, 123.5, 130.5, 133.9, 133.9, 134.0, 134.1, 141.1, 141.6, 165.3, 165.7 ppm. IR (KBr): $\tilde{\nu}$ = 3210, 3087, 1638, 1355, 1305, 1152, 1120, 1051, 964, 770, 655, 595, 565, 532, 503 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 207 (90) [M$^+$], 151 (37), 142 (36), 115 (46), 103 (100), 76 (48), 39 (30). HRMS (EI): calcd. for $C_{10}H_9NO_2S$ 207.0354; found 207.0348. $C_{10}H_9NO_2S$ (207.25): calcd. C 57.95, H 4.38, N 6.76, S 15.47; found C 58.00, H 4.28, N 6.85, S 15.45.

The same experiment was repeated, and the crude reaction mixture was quenched with 10% aqueous HCl (10 mL), heated at reflux for 30 min, evaporated, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was recrystallized from EtOH to give **13c** (yield 90%).

16: A suspension of ethyl (dimethoxyphosphoryl)acetate (0.392 g, 2 mmol), **6** (0.494 g, 2 mmol), and solid K_2CO_3 (0.828 g, 8 mmol) in THF (10 mL) was stirred for 24 h at room temperature. The solid was filtered off, water (30 mL) was added, and the residue was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. The product was purified by column chromatography (hexane/EtOAc) to give **16** (0.53 g, 84%). A minor amount of the *E* isomer (yield 4%) was also isolated. Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.14 (t, $J_{H,H}$ = 7.1 Hz, 3 H, CH_2CH_3), 2.09–2.15 (m, 2 H, CH_2CH$_2$Cl), 3.24–3.29 (m, 2 H, CH_2CH$_2$ CH$_2$Cl), 3.57 (t, $J_{H,H}$ = 6.3 Hz, 2 H, CH_2Cl), 4.06 (q, $J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH$_3$), 6.20 (d, $J_{H,H}$ = 11.9 Hz, 1 H, CH=C*H*CO$_2$), 7.35 (d, $J_{H,H}$ = 7.5 Hz, 1 H, H_{arom}), 7.54 (t, $J_{H,H}$ = 7.8 Hz, 1 H, H_{arom}), 7.61 (dt, $J_{H,H}$ = 7.5, 1.1 Hz, 1 H, H_{arom}), 7.68 (d, $J_{H,H}$ = 11.9 Hz, 1 H, C*H*=CHCO$_2$), 8.02 (dd, $J_{H,H}$ = 7.8, 1.1 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 14.0, 25.7, 42.8, 52.8, 60.6, 123.2, 128.7, 129.5, 130.7, 133.5, 135.7, 136.9, 142.0, 165.5 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 2982, 1716, 1469, 1404, 1384, 1306, 1203, 1152, 1120, 1027, 803, 768, 601, 570, 524 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 175 (53), 147 (100), 131 (14), 103 (16), 91 (8), 77 (8), 41 (10). HRMS (ESI): calcd. for $C_{14}H_{17}ClNaO_4S$ 339.0428; found 339.0422. $C_{14}H_{17}ClO_4S$ (316.81): calcd. C 53.08, H 5.41, Cl 11.19, S 10.12; found C 53.06, H 5.30, Cl 11.13, S 10.25.

Reaction of 16 with *t*BuOK in THF: *t*BuOK (0.095 g, 0.85 mmol) dissolved in THF (1 mL) was added dropwise to a solution of **16** (0.135 g, 0.43 mmol) in THF (5 mL) at –70 °C under an atmosphere of argon. After 1 h the mixture was warmed to room temperature and after 15 min an aqueous solution of NH_4Cl was added. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **16b** (yield 74%). Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.27 (t, $J_{H,H}$ = 7.2 Hz, 3 H, CH_2CH_3), 2.07–2.15 (m, 1 H, C*H*HCH$_2$Cl), 2.56–2.64 (m, 1 H, CH*H*CH$_2$Cl), 2.82 (dd, $J_{H,H}$ = 16.9, 5.5 Hz, 1 H, C*H*HCO$_2$), 2.95 (dd, $J_{H,H}$ = 16.9, 7.7 Hz, 1 H, CH*H*CO$_2$), 3.56–3.66 (m, 2 H, 2-H and 3-H), 3.79–3.88 (m, 2 H, CH_2Cl), 4.20 (q, $J_{H,H}$ = 7.2 Hz, 2 H, CH_2CH$_3$), 7.40 (dq, $J_{H,H}$ = 7.7, 0.8 Hz, 1 H, H_{arom}), 7.51 (tt, $J_{H,H}$ = 7.6, 0.8 Hz, 1 H, H_{arom}), 7.61 (dt, $J_{H,H}$ = 7.6, 1.2 Hz, 1 H, H_{arom}), 7.75 (dt, $J_{H,H}$ = 7.7, 0.6 Hz, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 14.1, 32.3, 38.7, 40.8, 41.5, 61.3, 62.9, 122.0, 126.2, 129.5, 133.9, 138.0, 138.9, 170.9 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 2982, 1731, 1296, 1190, 1155, 1127, 761, 576, 542 cm^{-1}. MS (ESI, 70 eV): *m*/*z* (%) = 316 (3) [M$^+$], 271 (19), 229 (16), 142 (89), 128 (100), 115 (45), 103 (22), 88 (27), 77 (19). HRMS (EI): calcd. for $C_{14}H_{17}ClO_4S$ 316.0536; found 316.0545. $C_{14}H_{17}ClO_4S$ (316.81): calcd. C 53.08, H 5.41, Cl 11.19, S 10.12; found C 52.88, H 5.51, Cl 11.10, S 10.14.

17: To a solution of **6** (0.988 g, 4 mmol) and malonodinitrile (0.276 g, 4.16 mmol) in EtOH (8 mL) was added a few drops of piperidine. The reaction mixture was heated at reflux for 20 h, then the solvent was evaporated, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. Column chromatography (hexane/EtOAc) gave **17** (0.823 g, 70%). Oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.20–2.27 (m, 2 H, CH_2CH$_2$Cl), 3.24–3.28 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 3.65 (t, $J_{H,H}$ = 6.1 Hz, 2 H, CH_2Cl), 7.80–7.88 (m, 2 H, H_{arom}), 7.97–7.99 (m, 1 H, H_{arom}), 8.15–8.18 (m, 1 H, H_{arom}), 8.87 [s, 1 H, C*H*=C(CN)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 25.4, 42.3, 54.2, 89.2, 111.2, 112.2, 130.2, 130.5, 131.1, 133.4, 134.7, 137.9, 157.8 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 3065, 2926, 2235, 1699, 1598,

1563, 1466, 1441, 1308, 1211, 1151, 1119, 1064, 960, 851, 792, 764, 619, 595, 568, 540, 517 cm^{-1}.

Reaction of 17 with *t*BuOK in EtOH: To a solution of **17** (0.147 g, 0.5 mmol) in EtOH (5 mL) was dropwise added *t*BuOK (0.112 g, 1 mmol) in EtOH (2 mL) at room temperature. After 48 h an aqueous solution of NH_4Cl (10 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 20 mL), The combined organic phases were washed with brine (20 mL) and dried with $MgSO_4$. Column chromatography (hexanes/EtOAc) gave **17a** (0.067 g, 52%). Oil. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.35–2.44 (m, 1 H, 3-H), 2.68–2.73 (m, 1 H, 3-H), 3.62 (dt, $J_{H,H}$ = 9.1, 6.1 Hz, 1 H, 2-H), 4.00 (ddd, $J_{H,H}$ = 9.1, 7.6, 3.3 Hz, 1 H, 2-H), 4.04 (ddd, $J_{H,H}$ = 9.9, 7.1, 2.8 Hz, 1 H, 4-H), 5.76 (d, $J_{H,H}$ = 7.1 Hz, 1 H, 5-H), 7.57–7.65 (m, 2 H, H_{arom}), 6.67–7.71 (m, 1 H, H_{arom}), 7.72–7.76 (m, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 29.1, 63.3, 67.9, 79.8, 121.1, 127.6, 131.1, 134.2, 136.1, 139.8 ppm. IR (CH_2Cl_2 film): $\tilde{\nu}$ = 2984, 2873, 1721, 1452, 1304, 1175, 1149, 1123, 1052, 761, 559, 537, 489 cm^{-1}.

The stereochemistry of **17a** was established by comparison of the corresponding ^1H NMR signals (coupling constants) to **6a**. **17a** δ = 5.76 (d, $J_{H,H}$ = 7.1 Hz, 1 H, 5-H); **6a** δ = 5.74 (d, $J_{H,H}$ = 7.1 Hz, 1 H, 5-H) ppm.

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[15] When the reaction of **15** was quenched with 10% aqueous HCl and heated at reflux for 30 min, **13c** (90%) was isolated.
[16] The reaction of **16** conducted in EtOH was very unselective; thus, only limited mechanistic conclusions are available in this case.

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