New catalytic system for aminohalogenation of β-methyl-β-nitrostyrenes to give opposite regiochemistry†

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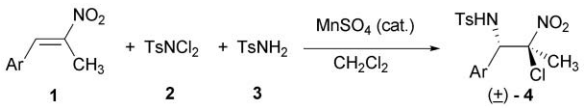
A new combination of catalyst and co-additive has been found for aminohalogenation reaction of β-methyl-β-nitrostyrenes with *N*,*N*-dichloro-*p*-tolunesulfonamide (4-$TsNCl_2$). The reaction was achieved by using $MnSO_4$ as the catalyst together with tolunesulfonamide to give vicinal haloamino nitroalkanes with opposite regiochemistry to that generated from other electron-deficient olefins observed previously. The reaction proceeded smoothly at room temperature under nitrogen atmosphere to give useful to good yields and excellent regio and stereoselectivity. A mechanism involving the formation of chloronium intermediate was proposed to explain the resulting regio and stereochemistry.

Introduction

Aminohalogenation of olefins has become an useful tool to create carbon–nitrogen and carbon–halogen bonds in tandem fashions.[1–4] The resulting 1,2-haloamines from this reaction are important building blocks in organic and medicinal chemistry[5] because they can be easily converted into a variety of derivatives by replacing their halogen atoms *via* intramolecular or inter-molecular substitution processes.[6] In the past ten years, several new aminohalogenation systems have been developed by using various nitrogen/halogen sources, such as *N*,*N*-dichloro-2-nitrobenzenesulfonamide,[6c,7] *N*,*N*-dichloro-*p*-toluene sulfonamide ($TsNCl_2$),[8] *N*,*N*-dichlorobenzenesulfonamide,[3c,9] *N*,*N*-dibromo-*p*-toluenesulfonamide,[10] *N*,*N*-dibromobenzene sulfonamide,[11a–c] chloramine-T[11d,e] and *p*-tolunesulfonamide/*N*-bromosuccinimine.[12] A series of electron-deficient alkenes including α,β-unsaturated carboxylic esters,[8c–e] α,β-unsaturated ketones,[13] methylenecyclo-propanes,[14] vinylidenecyclopropanes[14] and α,β-unsaturated nitriles[15] have been employed as the substrates for this reaction by using metal catalysts.[16–19] Recently, we reported that the aminohalogenation reaction of β-nitrostyrenes with $TsNCl_2$ occurred smoothly in the presence of 4-dimethylaminopyridine and copper(I) chloride as catalysts to afford vicinal dichloroamino products[20] in which the nitro group can be readily converted into amine functionality to give diamines of chemically and biologically importance.[21] Later on, we attempted to utilize β-methyl-β-nitrostyrenes as the substrates for the same reaction, but the success has been limited. In this paper we would like to report the aminohalogenation reaction of β-methyl-β-nitrostyrenes with $TsNCl_2$ can be achieved by using $MnSO_4$ as the catalyst and $TsNH_2$ as a co-additive. This new catalytic system resulted in vicinal monochloroamino products with opposite regiochemistry to that of other common electron-deficient olefin-based aminohalogenation processes (Scheme 1).[16–19]



Scheme 1 Reaction of 1-aryl-2-nitropropene with $TsNCl_2$/$TsNH_2$.

Results and discussion

Initially, the reaction of β-methyl-β-nitrostyrenes with $TsNCl_2$ was conducted under the same catalytic condition which has been successfully utilized for previous β-nitrostyrene-based aminohalogenation.[20] Under this condition the reaction occurred very slowly with most starting materials remained even after the reaction was performed for a long period of time (>10 h). We next studied this reaction by using metal catalysts in dichloromethane together with $TsNH_2$ as a co-additive. Pleasingly, we found that β-methyl-β-nitrostyrene can react with $TsNCl_2$ smoothly in the presence of $MnSO_4$ as the catalyst to give 1,2-chloroamino products in a good yield of 76% (Table 1, entry 1). Careful ^{1}H-NMR analysis of the product revealed that a chlorine moiety was attached to the α-carbon position of nitroalkane instead of on the β-carbon position as encountered in nearly all of the previous cases where electron-withdrawing olefins were employed.[17] Besides using $MnSO_4$ as the catalyst, $Ni(OAc)_2$ can also catalyze the reaction to give a chemical yield of 50% (Table 1, entry 2). As shown in Table 1, other metal catalysts, such as AgOAc, $Cu(OAc)_2$, AgOTs, $CuCl_2$, CuCl, CuI, $PdCl_2$ and CuOTf either resulted in no products or gave poor yields with most β-methyl-β-nitrostyrene unconsumed (Table 1, entries 3–10). While DMAP can catalyze the reaction to give a chemical yield of 10% (Table 1, entry 11).

It was found that 2 equiv. of $TsNCl_2$ and $TsNH_2$ were necessary for the complete conversion while larger loading of these two

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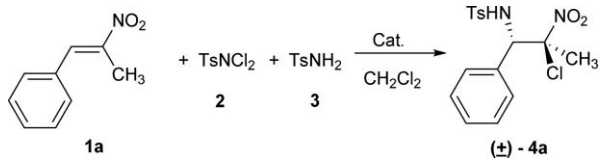
† Electronic supplementary information (ESI) available: General experimental procedures, ^{1}H and ^{13}C NMR spectra for compounds **4a–4h**. CCDC reference number 677516. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b914944a

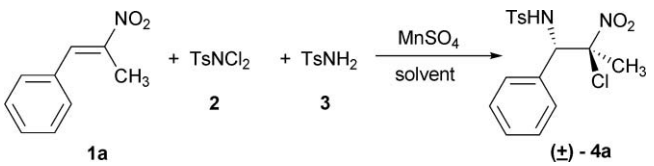
Table 1 Results of aminohalogenation of β-methyl-β-nitrostyrene with $TsNCl_2/TsNH_2$ using various metal catalysts[a]



Entry	Catalysts	Time/h	Yield (%)[b]	Selectivity [d](*anti*/*syn*)
1	$Ni(OAc)_2$	48	50	10 : 1
2	$MnSO_4$	48	76	12 : 1
3	AgOAc	48	30	9 : 1
4	$CuCl_2$	48	N.R.[c]	—
5	CuI	48	N.R.[c]	—
6	CuCl	48	N.R.[c]	—
7	$PdCl_2$	48	N.R.[c]	—
8	CuOTf	48	N.R.[c]	—
9	AgOTs	48	30	8 : 1
10	$Cu(OAc)_2$	48	40	8 : 1
11	DMAP	48	10	8 : 1

[a] Conditions: **1a** (1.0 mmol), $TsNCl_2$ (2.0 mmol) and $TsNH_2$ (2.0 mmol) in CH_2Cl_2 (5 mL) in the presence of catalysts (20 mol%) and 4 Å molecular sieves (500 mg) at r.t. under nitrogen protection. [b] Isolated yield after chromatographic purification. [c] No reaction was observed. [d] As shown by ^{1}H-NMR spectroscopic analysis of the crude product; there is no regioisomer observed for each case.

Table 2 Solvent effect on aminohalogenation of β-methyl-β-nitrostyrenes with $TsNCl_2/TsNH_2$[a]



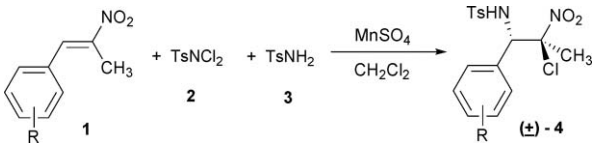
Entry	$MnSO_4$ (mmol%)	Solvent	Time/h	Yield [b](%)	Selectivity [c](*anti*/*syn*)
1	20	CH_2Cl_2	24	50	12 : 1
2	20	CH_2Cl_2	48	76	12 : 1
3	20	CH_3CN	48	55	10 : 1
4	20	$CHCl_3$	48	40	9 : 1
5	20	THF	48	N.R.[c]	—
6	20	Toluene	48	N.R.[c]	—
7	20	DMF	48	N.R.[c]	—
8	10	CH_2Cl_2	48	60	12 : 1
9	30	CH_2Cl_2	48	75	12 : 1

[a] Conditions: **1a** (1.0 mmol), $TsNCl_2$ (2.0 mmol) and $TsNH_2$ (2.0 mmol) in CH_2Cl_2 (5 mL) in the presence of $MnSO_4$ and 4 Å molecular sieves (500 mg) at r.t. with N_2. [b] Isolated yield after chromatographic purification. [c] No reaction was observed. [d] As shown by ^{1}H-NMR spectroscopic analysis of the crude product; there is no regioisomer observed for each case.

reactants did not show any improvement. Meanwhile, $MnSO_4$ catalyst loading of 20 mol% and the use of 4 Å molecular sieves are also required to achieve optimal yields.

We next studied the solvent effects on this reaction attempting to improve its outcomes. Interestingly, as revealed in Table 2, CH_2Cl_2 which was used first was proven to be the best while other solvents, such as CH_3CN, $CHCl_3$, THF, $C_6H_5CH_3$ and DMF, resulted in either no products or lower yields under the same conditions. And the reaction was almost completed within 48 h.

Table 3 Scope of aminohalogenation of β-methyl-β-nitrostyrenes with $TsNCl_2/TsNH_2$[a]



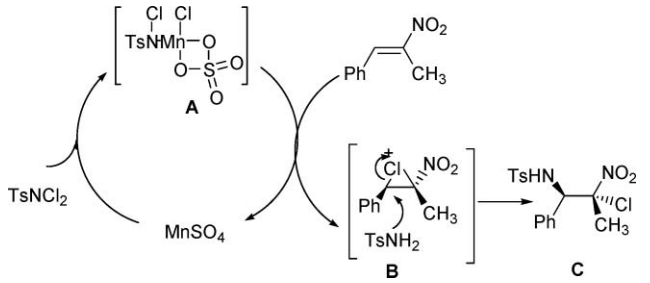
Entry	*R*	Time/h	Product	Selectivity [b](*anti*/*syn*)	Yield [c](%)
1	H	48	**4a**	12 : 1	76
2	4-CH_3	48	**4b**	10 : 1	76
3	4-CH_3O	48	**4c**	10 : 1	71
4	4-Cl	48	**4d**	12 : 1	71
5	4-F	48	**4e**	9 : 1	42
6	2-Cl	48	**4f**	30 : 1	50
7	4-NO_2	72	**4g**	18 : 1	36
8	2-F	48	**4h**	8 : 1	52

[a] Conditions: **1** (1.0 mmol), $TsNCl_2$ (2.0 mmol), and $TsNH_2$ (2.0 mmol) in CH_2Cl_2 (5 mL) in the presence of $MnSO_4$ (20 mol%) and 4 Å molecular sieves (500 mg) at r.t. under nitrogen protection. [b] As shown by ^{1}H-NMR spectroscopic analysis of the crude product; there is no regioisomer observed for each case. [c] Isolated yield after chromatographic purification.

A series of β-methyl-β-nitrostyrene derivatives that were available in our labs at the time of conducting this project were employed for this reaction to find the scope of substrates. As shown in Table 3, eight β-methyl-β-nitrostyrenes are suitable for this reaction to give useful to good chemical yields (36–76%). These substrates showed good to excellent stereoselectivity with ratios ranging from 8 : 1 to 30 : 1. There was no regioisomer observed for each of these cases. In the case of *p*-nitro-β-methyl-β-nitrostyrene containing a strong electron-withdrawing group (Table 3, entry 7), a poor yield was obtained even after the reaction time was extended to 72 h. Unlike our previous DMAP-catalyzed-aminohalogenation in which a strong electron-donating group attached substrate, 4-methoxy-β-nitrostyrene, gave a chemical yield of 65%,[20] the present catalytic system of using 4-methoxy-β-methyl-β-nitrostyrene as the substrate resulted in an improved yield of 71% (Table 3, entry 3). The structure of product **4b** has been unambiguously confirmed by X-ray diffraction.[22]

Unlike our previous aminohalogenation in which the mechanism involves the formation of aziridinium intermediates which can explain the resulting regio- and stereochemistry.[6–8,13–15] During those processes, the resulting aziridinium intermediates were attached by chlorine anion on β-positions of electron-deficient olefins. This mechanism has been unambiguously proven by the related electrophilic diamination.[21a,b] However, based on the resulting regio- and stereochemistry of the present aminohalogenation, we would like to propose an alternative mechanism which involves predominant formation of chloronium intermediates (Scheme 2).

At the first step of the present reaction, the catalyst, $MnSO_4$, activates the N–Cl bond of $TsNCl_2$ to generate a new intermediate **A**. At the second step, 'Cl^+' is delivered from intermediate **A** to C=C double bond of the substrate to give the chloronium intermediate **B**. The positively charged chloronium intermediate **B** is opened by *p*-toluenesulfonamide on its α-position which is loaded by more positive charge than its β-position. In our previous DMAP-catalyzed-aminohalogenation without the use of $TsNH_2$ as the co-additive,[20] *N*-chlorohaloamine products were generated and needed one more step of reductive hydrolysis, and the present



Scheme 2 Mechanism hypothesis for aminohalogenation of β-methyl-β-nitrostyrenes with $TsNCl_2/TsNH_2$.

reaction afforded the final haloamino product **C** by opening directly. To confirm the mechanism, α-methyl-β-nitrostyrene and cinnamate were employed as substrates under the same catalytic condition, but no reaction was observed.

Conclusions

In conclusion, a new regio- and stereoselective amino-chlorination of β-methyl-β-nitrostyrenes using $MnSO_4$ as the catalyst and $TsNH_2/TsNCl_2$ as the halogen/nitrogen source has been established. The reaction is convenient to carry out at room temperature, and provides an easy approach to vicinal haloamino nitroalkanes with opposite regiochemistry to that of other electron-deficient olefins previously observed. Useful to good chemical yields and excellent regio- selectivities have been achieved.

Experimental

General methods

All moisture-sensitive reactions were performed under nitrogen in glassware that had been flame-dried. Solvents were dried and distilled prior to use. Flash chromatography was performed on silica gel 60 (F-254) TCL plates (20 cm × 20 cm). Melting points are uncorrected. IR spectra were collected with a Bruker Vector 22 instrument (KBr pellets). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were acquired in deuterated dimethylsulfoxide (CD_3SOCD_3), deuterated acetone (CD_3COCD_3) and deuterated chloroform ($CDCl_3$). Elemental analyses were performed with a Perkin-Elmer 240 elemental analysis instrument. Mass spectra of new compounds were measured with a Finnigan LCQ electrospray mass spectrometer.

Starting materials

Starting materials β-methyl-β-nitrostyrenes (**1a–1h**) were prepared according to the reported methods.[23]

General procedure for aminochlorination

Into a dry vial was added **1** (1.0 mmol), $TsNH_2$ (340 mg, 2.0 mmol), catalyst (0.20 mmol, 0.20 equiv), 4 Å molecular sieves (500 mg, pre-dried in the oven at 200 °C overnight), and freshly distilled dichloromethane (5.0 mL) with nitrogen atmosphere. The mixture was stirred at room temperature for 10 min before $TsNCl_2$ (480 mg, 2 mmol) was added. The resulting mixture was stirred at room temperature for 48 h in the capped vial nitrogen atmosphere protection and the reaction was then quenched with saturated aqueous Na_2SO_3 (5.0 mL) solution. The 4 Å molecular sieves and other solid precipitates were filtered off and washed with EtOAc (3 × 10 mL). The combined organic phases were washed with brine and dried with anhydrous sodium sulfate. The organic solution was concentrated and purified *via* flash chromatography with EtOAc and petroleum ether (v/v = 1 : 4) as the eluent to give the pure products.

2-Chloro-2-nitro-1-(4-toluenesulfonamido)-1-phenylpropane (4a). A white solid (mp 150–151 °C); IR (KBr): ν = 3272, 1598, 1565, 1333, 1167, 1048, 704, 678 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.47 (d, J = 8.4 Hz, 2 H), 7.20–7.10 (m, 3 H), 7.05–6.98 (m, 4 H), 5.78 (d, J = 10.8 Hz, 1 H), 5.18 (d, J = 10.8 Hz, 1H), 2.30 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.2, 137.6, 133.1, 129.1, 128.9, 128.5, 127.9, 12.6.8, 106.7, 64.8, 26.2, 20.4 ppm. EIMS m/z: 391 (M + Na$^+$,100), 313 (24), 282 (74), 260 (5); Anal. Calcd. for $C_{16}H_{17}ClN_2O_4S$: C, 52.10; H, 4.65; N, 7.60; Found: C, 52.05; H, 4.59; N, 7.49.

2-Chloro-2-nitro-1-(4-toluenesulfonamido)-1-(4-methylphenyl) propane (4b). A white solid (mp 166–167 °C); IR (KBr): ν = 3262, 1595, 1562, 1342, 1160, 1051, 893, 814 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.47 (d, J = 8.4 Hz, 2 H), 7.06–7.03 (d, J = 8.4 Hz, 2 H), 6.93–6.86 (m, 4 H), 5.88 (d, J = 10.5 Hz, 1 H), 5.14 (d, J = 10.5 Hz, 1H), 2.31 (s, 3 H), 2.25 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.1, 138.4, 137.6, 130.1, 129.0, 128.9, 128.6, 128.5, 126.8, 106.8, 64.7, 26.1, 20.4, 20.1 ppm. EIMS m/z: 405 (M + Na$^+$,100), 327 (24), 296 (74), 274 (5); Anal. Calcd. for $C_{17}H_{19}ClN_2O_4S$: C, 53.33; H, 5.00; N, 7.32; Found: C, 53.28; H, 4.96; N, 7.28.

2-Chloro-2-nitro-1-(4-toluenesulfonamido)-1-(4-methoxyphenyl) propane (4c). A white solid (mp 142–143 °C); IR (KBr): ν = 3248, 1615, 1563, 1341, 1256, 1159, 863, 816 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.48 (d, J = 8.4 Hz, 2 H), 7.07–7.05 (d, J = 8.4 Hz, 2 H), 6.94–6.91 (d, J = 8.7 Hz, 2H), 6.64–6.61 (d, J = 8.7 Hz, 2H), 5.82 (d, J = 10.5 Hz, 1 H), 5.14 (d, J = 10.5 Hz, 1H), 3.73 (s, 3 H), 2.32 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3SOCD_3): δ = 159.7, 143.0, 137.6, 130.7, 129.5, 126.8, 125.1, 113.6, 106.4, 64.6, 55.5, 25.2, 21.2 ppm. EIMS m/z: 421 (M + Na$^+$,70), 312 (100), 290 (4), 228 (4), 118 (2); Anal. Calcd. for $C_{17}H_{19}ClN_2O_5S$: C, 51.19; H, 4.80; N, 7.02; Found: C, 51.14; H, 4.76; N, 6.96.

2-Chloro-2-nitro-1-(4-toluenesulfonamido)-1-(4-chlorophenyl) propane (4d). A white solid (mp 168–169 °C); IR (KBr): ν = 3260, 1596, 1566, 1341, 1159, 893, 818 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.47 (d, J = 8.7 Hz, 2 H), 7.10–7.07 (m, 4 H), 6.96–6.93 (m, 2 H), 5.95 (d, J = 10.8 Hz, 1 H), 5.18 (d, J = 10.8 Hz, 1 H), 2.35 (s, 3 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 143.4, 137.4, 134.2, 131.9, 130.7, 129.2, 128.0, 126.9, 106.5, 64.2, 26.4, 20.4 ppm. EIMS m/z: 425 (M + Na$^+$,100), 347 (14), 316 (60), 282 (18), 186 (5), 154 (7), 118 (4); Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O_4S$: C, 47.65; H, 4.00; N, 6.95; Found: C, 47.59; H, 3.98; N, 6.91.

2-Chloro-2-nitro-1-(4-toluenesulfonamido)-1-(4-fluorophenyl) propane (4e). A white solid (mp 181–183 °C, yield); IR (KBr): ν = 3261, 1606, 1571, 1342, 1157, 896, 814 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.47 (d, J = 8.1 Hz, 2 H), 7.09–7.07 (m, 3 H), 7.02–6.79 (m, 4 H), 5.70 (d, J = 10.5 Hz, 1 H), 5.19 (d, J = 10.5 Hz, 1 H), 2.32 (s, 3 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 164.3, 161.1, 143.2, 137.6, 131.2,

131.0, 129.3, 129.1, 126.9, 114.8, 114.6, 106.8, 64.1, 26.2, 20.3 ppm. EIMS *m/z*: 409 (M + Na^+, 61), 331 (26), 300 (100), 278 (5), 154 (5); Anal. Calcd. for $C_{16}H_{16}ClFMnN_2O_4S$: C, 43.50; H, 3.65; N, 6.34; Found: C, 43.47; H, 3.61; N, 6.30.

2-Chloro-2-nitro-1-(4-toluenesulfonamido)-1-(2-chlorobenzyl) propane (4f). A white solid (mp 170–172 °C); IR (KBr): $\nu = 3251$, 1595, 1565, 1339, 1164, 913, 863, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.58–7.56$ (d, $J = 7.8$ Hz, 2 H), 7.22–7.06 (m, 6 H), 6.46 (d, $J = 10.8$ Hz, 1 H), 5.81 (d, $J = 10.8$ Hz, 1 H), 2.31 (s, 3 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3SOCD_3): $\delta =$ 161.6, 158.3, 143.4, 136.9, 131.3, 129.6, 126.6, 124.7, 121.0, 115.1, 104.7, 57.0, 24.3, 20.9 ppm. EIMS *m/z*: 425 (M + Na^+,100), 347 (10), 316 (50), 285 (5), 119 (5); Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O_4S$: C, 47.65; H, 4.00; N, 6.95; Found: C, 47.61; H, 3.95; N, 6.90.

2-chloro-2-nitro-1-(4-toluenesulfonamido)-1-(4-nitrophenyl) propane (4g). A white solid (mp 218–220 °C); IR (KBr): $\nu =$ 3253, 1609, 1595, 1351, 1163, 1071, 877, 844 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.01–7.98$ (d, $J = 9.0$ Hz, 2 H), 7.52–7.49 (d, $J = 8.4$ Hz, 2 H), 7.24–7.22 (d, $J = 9.0$ Hz, 2 H), 7.10–7.07 (d, $J = 8.4$ Hz, 2 H), 5.71 (d, $J = 10.8$ Hz, 1 H), 5.34 (d, $J =$ 10.8 Hz, 1H), 2.32 (s, 3 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3SOCD_3): $\delta = 147.7$, 143.5, 140.4, 137.1, 131.1, 129.6, 127.0, 123.2, 105.2, 64.2, 25.1, 21.1 ppm. EIMS *m/z*: 437 (M + Na^+, 70), 314 (22), 300 (100), 226 (12), 186 (20), 154 (23), 118 (70); Anal. Calcd. for $C_{16}H_{16}ClN_3O_6S$: C, 46.44; H, 3.90; N, 10.15; Found: C, 46.39; H, 3.88; N, 10.13.

2-Chloro-2-nitro-1-(4-toluenesulfonamido)-1-(2-fluorophenyl) propane (4h). A white solid (mp 168–169 °C); IR (KBr): $\nu =$ 3260, 1615, 1565, 1346, 1164, 814, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.55–7.52$ (d, $J = 8.1$ Hz, 2 H), 7.24–6.80 (m, 6 H), 6.01 (d, $J = 10.8$ Hz, 1 H), 5.45 (d, $J = 10.8$ Hz, 1H), 2.30 (s, 3 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3SOCD_3): $\delta = 143.3$, 137.0, 136.9, 134.6, 131.6, 131.5, 130.6, 130.1, 129.7, 129.5, 127.5, 126.6, 104.6, 59.7, 23.9, 21.2 ppm. EIMS *m/z*: 409 (M + Na^+,100), 331(18), 300 (74), 278 (9); Anal. Calcd. for: $C_{16}H_{16}ClFN_2O_4S$: C, 49.68; H, 4.17; N, 7.24; Found: C, 49.65; H, 4.13; N, 7.21.

Acknowledgements

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