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SYNTHESIS OF α-HALOBUTENOLIDES USING THE NUCLEOPHILICITY OF MAGNESIUM ALKYLIDENE CARBENOIDS†

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Abstract – α-Halobutenolides were synthesized from halomethyl *p*-tolyl sulfoxides, α-bromoketones, and phenyl chloroformate in three steps using the nucleophilicity of magnesium alkylidene carbenoids. The reaction of α-bromoketones with [halo(*p*-tolylsulfinyl)methyl]lithiums and the subsequent basification of the reaction mixture using an aqueous NaOH solution afforded 1-chloro-3-hydroxyprop-1-enyl *p*-tolyl sulfoxides in 83–99% yield. A phenoxycarbonyl group was then introduced to the hydroxyl group of the sulfoxides by reacting with phenyl chloroformate in the presence of pyridine. The sulfoxide/magnesium exchange reaction of the cyclization precursors with *i*-PrMgCl•LiCl led to the formation of α-halobutenolides in moderate to good yields.

α,β-Unsaturated γ-lactones, also referred to as butenolides and furan-2(5*H*)-ones, are a fundamental class of heterocyclic compounds. The butenolide motif is present in many natural products, and the synthesis and synthetic utility of butenolides have been studied in great depth.[1] Among the butenolides, α-halobutenolides play an important role in organic synthesis (Figure 1). α-Bromobutenolides are used for the synthesis of α-arylbutenolides, including the naturally occurring eutypoid A, microperfuranone, gymnoascolide A,[2] and anti-inflammatory drug rofecoxib[3] via the cross-coupling reaction. α-(1-Hydroxyalkyl)butenolides isolated from the fermentation of TÜ99[4] and seed germination stimulants[5] are synthesized from α-halobutenolides via the halogen/lithium exchange reaction and the subsequent reaction of the resulting α-lithiated butenolides with electrophiles. Furthermore, an α-halobutenolide

†This paper is dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday.

skeleton is found in rubrolides[6] and mutagen X,[7] which is a contaminant in chlorinated water.[8] The typical synthetic method of α-halobutenolides consists of constructing a multi-substituted α,β-unsaturated lactone ring in several steps and a halogenation-dehydrohalogenation process. The development of a novel method for the synthesis of α-halobutenolides from readily available materials in short steps with a *de novo* lactone ring formation is expected to contribute to the further advancement of the above chemistry.

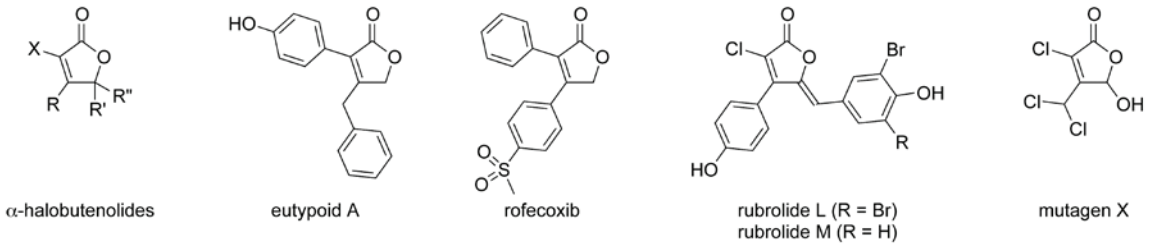
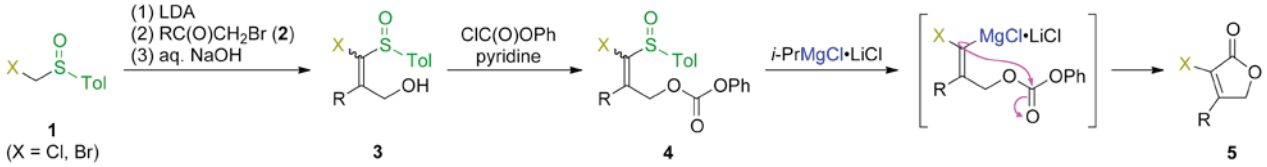


Figure 1. Chemical structures of α-halobutenolides and α-arylbutenolides

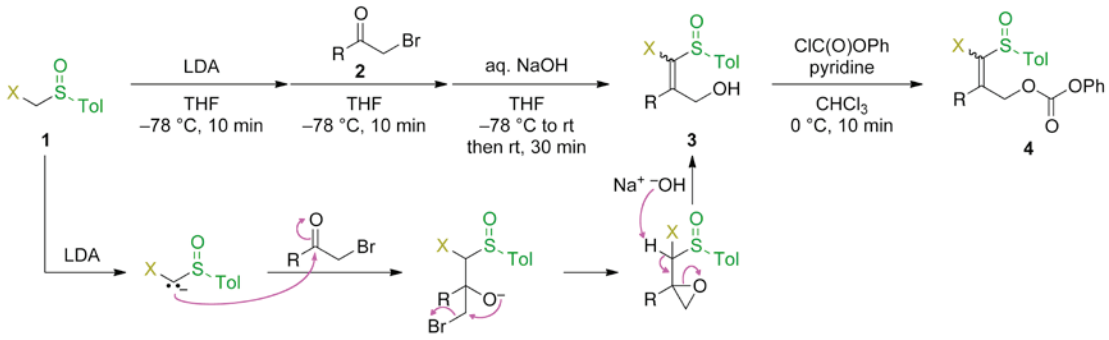
Magnesium alkylidene carbenoids are a class of organomagnesium compounds in which magnesium and halogen atoms are attached to a vinylic carbon atom.[9] Intriguingly, magnesium alkylidene carbenoids act as electrophiles toward the carbon and heteroatom nucleophiles.[10] We have reported the synthesis of multi-substituted alkenes using the electrophilicity of magnesium alkylidene carbenoids.[11] However, the synthetic applications of the nucleophilicity of magnesium alkylidene carbenoids have not been fully explored.[12,13] We recently found that magnesium carbenoids with an electrophilic functional group, such as cyano and (phenoxycarbonyl)oxy groups, can be generated from the corresponding 1-chloroalkyl *p*-tolyl sulfoxides via the sulfoxide/magnesium exchange reaction.[14] The resulting magnesium carbenoids act as nucleophiles toward the intramolecular electrophilic functional group to yield cyclized products. If magnesium alkylidene carbenoids with the [(phenoxycarbonyl)oxy]methyl group can be generated, the resulting carbenoids would cyclize to give α-halobutenolides (Scheme 1). Herein, we report a novel synthetic method of α-halobutenolides using the nucleophilicity of magnesium alkylidene carbenoids.



Scheme 1. Synthesis of α-halobutenolides **5** via the nucleophilic cyclization of magnesium alkylidene carbenoids generated from sulfoxides **4** and *i*-PrMgCl•LiCl

We designed cyclization precursors **4** consisting of a 1-chlorovinyl *p*-tolyl sulfoxide unit and a phenyl carbonate unit (Scheme 1). Therefore, the 1-chloro-3-hydroxyprop-1-enyl *p*-tolyl sulfoxides **3** are key synthetic intermediates. Inspired by the Darzens reaction,[15] we developed a useful method for the synthesis of sulfoxides **3** from halomethyl *p*-tolyl sulfoxides **1** and α-bromoketones **2** (Table 1).[16] For instance, chloromethyl *p*-tolyl sulfoxide (**1a**) was treated with LDA in THF at –78 °C, and 1-bromo-4-phenylbutan-2-one (**2a**) was added to the reaction mixture (entry 1). The reaction mixture was then basified using an aqueous NaOH solution. As a result, sulfoxide **3a** was formed as a 1:1 mixture of geometric isomers in 99% yield. The reaction seems to proceed as follows. Nucleophilic addition of [chloro(*p*-tolylsulfinyl)methyl]lithium to α-bromoketone **2a** gives the adduct, and the subsequent nucleophilic substitution of the resulting lithium alkoxide with an intramolecular bromomethyl unit gives β,γ-epoxy sulfoxide. The addition of an aqueous NaOH solution to the reaction mixture containing β,γ-epoxy sulfoxide results in β-elimination, to give sulfoxide **3a**.[17] A diverse range of sulfoxides **3b–g** with an alkyl or aryl substituent at the 2-position could be prepared from sulfoxide **1a** and the corresponding α-bromoketones **2b–g** in 83–98% yield (entries 2–7). The synthetic method was applicable to the synthesis of bromo analog **4h** (entry 8). The reaction of sulfoxides **3** with phenyl chloroformate in the presence of pyridine yielded cyclization precursors **4** with high efficiency.[18]

Table 1. Synthesis of cyclization precursors **4**



Entry	1	X	2	R	3	Yield of **3** (%)	Geometric ratio	4	Yield of **4** (%)
1	**1a**	Cl	**2a**	$PhCH_2CH_2$	**3a**	99	1:1	**4a**	99
2	**1a**	Cl	**2b**	Me	**3b**	92	1:1.6	**4b**	99
3	**1a**	Cl	**2c**	Ph	**3c**	93	1:3.5	**4c**	94
4	**1a**	Cl	**2d**	$4\text{-}MeOC_6H_4$	**3d**	98	1:2.9	**4d**	99
5	**1a**	Cl	**2e**	$4\text{-}BrC_6H_4$	**3e**	83	1:2.1	**4e**	92
6	**1a**	Cl	**2f**	2-thienyl	**3f**	95	1:2.3	**4f**	95
7	**1a**	Cl	**2g**	(*E*)-pent-1-enyl	**3g**	90	1:2.7	**4g**	94
8	**1b**	Br	**2a**	$PhCH_2CH_2$	**3h**	91	1:0.7	**4h**	83

Table 2. Synthesis of α-halobutenolides **5**

Entry	**4**	R	X	**5**	Yield (%)
1	**4a**	$PhCH_2CH_2$	Cl	**5a**	76
2	(*E*)-**4a**	$PhCH_2CH_2$	Cl	**5a**	78
3	(*Z*)-**4a**	$PhCH_2CH_2$	Cl	**5a**	74
4 [a]	**4b**	Me	Cl	**5b**	60
5	**4c**	Ph	Cl	**5c**	60
6	**4d**	4-$MeOC_6H_4$	Cl	**5d**	65
7	**4e**	4-BrC_6H_4	Cl	**5e**	54
8	**4f**	2-thienyl	Cl	**5f**	41
9	**4g**	(*E*)-pent-1-enyl	Cl	**5g**	58
10 [b]	**4h**	$PhCH_2CH_2$	Br	**5h**	46

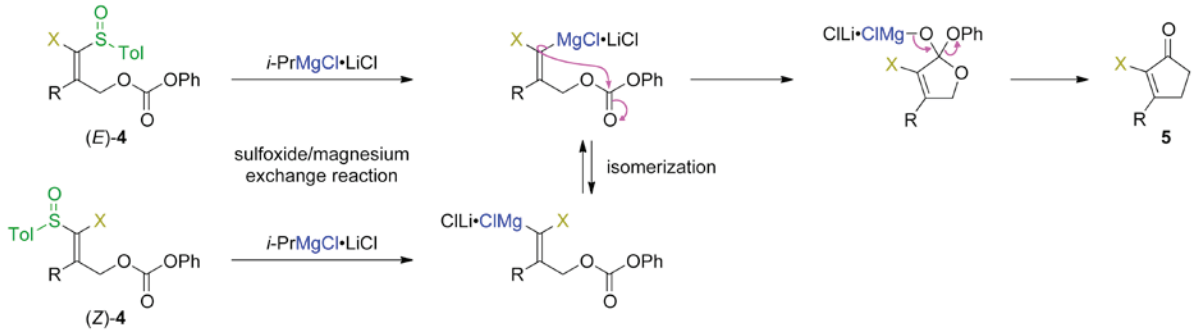
[a] *i*-PrMgCl was used instead of *i*-PrMgCl•LiCl.

[b] *i*-PrMgBr was used instead of *i*-PrMgCl•LiCl.

With the key cyclization precursors **4** in hand, we attempted the sulfoxide/metal exchange reaction leading to the formation of α-halobutenolides **5**. The choice of organometallic reagent for the reaction is a key issue because the sulfoxide/metal exchange reaction of the organometallic reagent with the sulfoxide unit should take precedence over the reaction of the organometallic reagent with the phenyl carbonate unit for the generation of bifunctional (nucleophilic/electrophilic) chemical species.[19] In addition, the organometallic reagent must be unreactive to the α-halobutenolides **5** as products. We examined the reaction of sulfoxide **4a** with organometallic reagents, including BuLi, *i*-PrMgCl, *i*-PrMgBr, *i*-PrMgCl•LiCl, and *c*-C_5H_9MgCl, under various reaction conditions and found that *i*-PrMgCl•LiCl (turbo Grignard reagent) was the reagent of choice for our purpose.[20] Sulfoxide **4a** was treated with *i*-PrMgCl•LiCl in THF at 0 °C, and the reaction mixture was stirred at room temperature for 30 min (Table 2, entry 1).[21] The desired α-chlorobutenolide **5a** was obtained in 76% yield. When the reaction was conducted with each of the geometric isomers (*E*)-**4a** and (*Z*)-**4a**, α-chlorobutenolide **5a** was obtained in 78% and 74% yield, respectively (entries 2 and 3). Because the reaction with both (*E*)- and (*Z*)-isomers gave α-chlorobutenolide **5a** in good yields, the substrate scope was explored using a mixture of geometric isomers. A variety of β-alkyl- and β-aryl-substituted α-chlorobutenolides **5b–g** were obtained in 41–65% yield (entries 4–9). In all cases, vinyl chlorides, which originated from the protonation of unreacted

magnesium alkylidene carbenoids, were formed as side products in 10–46% yield. The reaction of 2-methyl-substituted sulfoxide **4b** with *i*-PrMgCl•LiCl afforded α-chloro-β-methylbutenolide **5b** in 33% yield, and the use of *i*-PrMgCl instead of *i*-PrMgCl•LiCl improved the reaction efficiency (entry 4). It is substantially important to use *i*-PrMgBr for the reaction with bromo analog **4h** (entry 10). Otherwise, both α-bromobutenolide **5h** and α-chlorobutenolide **5a** were formed in 30% and 21% yield, respectively.[12] Total synthesis of rubrolides L and M has been achieved using α-chlorobutenolide **4d** with a 4-methoxyphenyl group at the β-position as a key synthetic intermediate via vinylogous aldol condensation (Figure 1).[6]

A plausible reaction mechanism for the formation of α-halobutenolides **5** is depicted in Scheme 2. Sulfoxide/magnesium exchange reaction of sulfoxides **4** with *i*-PrMgCl•LiCl generates magnesium alkylidene carbenoids. Magnesium alkylidene carbenoids generated from (*E*)-isomers (*E*)-**4** can react with an intramolecular carbonyl group to give α-halobutenolides **5**. However, magnesium alkylidene carbenoids generated from (*Z*)-isomers (*Z*)-**4** are not expected to cyclize because the magnesium atom and the [(phenoxycarbonyl)oxy]methyl group are located *trans* to each other. Nevertheless, the reaction with (*Z*)-isomer gave α-chlorobutenolide (Table 2, entry 3). This result suggests that the geometry of the magnesium alkylidene carbenoids isomerizes gradually. In fact, geometric isomerization of magnesium alkylidene carbenoids is known to occur even at –78 °C.[12]



Scheme 2. A plausible mechanism for the nucleophilic cyclization of magnesium alkylidene carbenoids generated from geometric isomers (*E*)-**4** and (*Z*)-**4**

In summary, we developed a novel method for the synthesis of α-halobutenolides from readily available materials in three steps. Cyclization precursors were prepared from α-bromoketones, halomethyl *p*-tolyl sulfoxides, and phenyl chloroformate with high efficiency, and the chemoselective sulfoxide/magnesium exchange reaction of the cyclization precursors with *i*-PrMgCl•LiCl led to the formation of α-halobutenolides. Further investigation of the synthetic applications of magnesium alkylidene carbenoids using their nucleophilicity is currently ongoing and will be reported in due course.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

General methods and characterization data for cyclization precursors **4** and α-halobutenolides **5** are available.

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16. *Typical procedure*: A 1.65 M solution of BuLi in hexane (2.18 mL, 3.60 mmol) was added to a solution of *i*-Pr_2NH (364 mg, 3.60 mmol) in THF (40 mL) at 0 °C, and the mixture was stirred at 0 °C for 10 min. A solution of **1a** (683 mg, 3.60 mmol) in THF (4.0 mL) was added to the solution of LDA in THF at –78 °C, and the mixture was stirred at –78 °C for 10 min. A solution of **2a** (543 mg, 2.40 mmol) in THF (4.0 mL) was added to the mixture at –78 °C, and the mixture was stirred at –78 °C for 10 min. An aqueous NaOH solution (approximately 10%, 5.0 mL) was added to the mixture at –78 °C, and the mixture was stirred at room temperature for 30 min. The reaction was quenched with sat. aq NH_4Cl (5.0 mL), and the mixture was extracted with $CHCl_3$ (50 mL × 3) The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane-EtOAc, 3:1) to afford (*E*)-**3a** (R_f = 0.15, 387 mg, 1.16 mmol, 48.3%) and (*Z*)-**3a** (R_f = 0.10, 403 mg, 1.20 mmol, 50.4%). (*E*)-**3a**: Colorless crystals; mp 83.5–84.5 °C (hexane/EtOAc); IR (KBr): 3382 (OH), 3021, 2956, 2934, 2867, 1604, 1495, 1454, 1088, 1045, 1014, 958, 808, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 2.48–2.53 (br m, 1H), 2.74–2.89 (m, 4H), 4.43 (dd, *J* = 7.6, 12.8 Hz, 1H), 4.68 (dd, *J* = 4.7, 12.8 Hz, 1H), 7.14–7.32 (m, 7H), 7.48 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.4 (CH_3), 32.8 (CH_2), 34.5 (CH_2), 61.2 (CH_2), 124.9 (CH), 126.3 (CH), 128.4 (CH), 128.5 (CH), 129.8 (CH), 137.0 (C), 137.7 (C), 140.4 (C), 141.8 (C), 149.2 (C); MS (FAB^+): *m*/*z* (%) = 335 ($[M+H]^+$, 100), 317 (58), 91 (26); HRMS (FAB^+): *m*/*z* [$(M+H)^+$] calcd for $C_{18}H_{20}ClO_2S$: 335.0873; found: 335.0873. (*Z*)-**3a**: Colorless crystals; mp 91.5–93.0 °C (hexane/EtOAc); IR (KBr): 3382 (OH), 3021, 2928, 1493, 1429, 1359, 1083, 1047, 1011, 811, 746, 700 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$): δ = 1.88–1.98 (br m, 1H), 2.41 (s, 3H), 2.90–3.07 (m, 2H), 3.12–3.28 (m, 2H), 4.42 (dd, *J* = 6.5, 14.6 Hz, 1H), 4.48 (dd, *J* = 6.2, 14.6 Hz, 1H), 7.25–7.38 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.4 (CH_3), 32.7 (CH_2), 35.0 (CH_2), 62.4 (CH_2), 124.7 (CH), 126.5 (CH), 128.6 (CH), 128.7 (CH), 129.8 (CH), 133.8 (C), 137.5 (C), 140.3 (C), 141.8 (C), 150.1 (C); MS (FAB$^+$): *m*/*z* (%) = 335 ([M+H]$^+$, 100), 91 (18); HRMS (FAB$^+$): *m*/*z* [(M+H)$^+$] calcd for $C_{18}H_{20}ClO_2S$: 335.0873; found: 335.0871.

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18. *Typical procedure*: Phenyl chloroformate (1.96 g, 12.5 mmol) was added to a solution of pyridine (989 mg, 12.5 mmol) and **3a** (837 mg, 2.50 mmol) in $CHCl_3$ (25 mL) at 0 °C, and the mixture was stirred at 0 °C for 10 min. The reaction was quenched with sat. aq NH_4Cl (4.0 mL), and the mixture was extracted with $CHCl_3$ (20 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [R_f = 0.47 (hexane-EtOAc, 3:1)] to afford **4a** (1.13 g, 2.48 mmol, 99%). (*E*)-**4a**: Colorless oil; IR (neat): 3062, 3028, 2926, 2867, 1770 (C=O), 1593, 1495, 1456, 1374, 1242, 1163, 1089, 1062, 1022, 811, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 2.73–2.91 (m, 4H), 5.18 (d, *J* = 12.6 Hz, 1H), 5.26 (d, *J* = 12.6 Hz, 1H), 7.16–7.23 (m, 5H), 7.25–7.33 (m, 5H), 7.39–7.44 (m, 2H), 7.51–7.54 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.4 (CH_3), 32.7 (CH_2), 34.5 (CH_2), 65.6 (CH_2), 120.8 (CH), 124.8 (CH), 126.3 (CH), 126.5 (CH), 128.3 (CH), 128.6 (CH), 129.6 (CH), 129.9 (CH), 137.5 (C), 139.9 (C), 142.0 (C), 142.2 (C), 142.3 (C), 150.9 (C), 153.2 (C); MS (FAB$^+$): *m*/*z* (%) = 455 ([M+H]$^+$, 29), 317 (100), 177 (18), 141 (19), 91 (32); HRMS (FAB$^+$): *m*/*z* [(M+H)$^+$] calcd for $C_{25}H_{24}ClO_4S$: 455.1084; found: 455.1088. (*Z*)-**4a**: Colorless crystals; mp 99.0–100.0 °C (hexane/EtOAc); IR (KBr): 3061, 3030, 2962, 2934, 1762 (C=O), 1592, 1495, 1457, 1425, 1369, 1286, 1251, 1210, 1086, 1054, 1018, 947, 802, 748, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 2.90–3.04 (m, 2H), 3.11–3.23 (m, 2H), 5.02 (d, *J* = 14.0 Hz, 1H), 5.08 (d, *J* = 14.0 Hz, 1H), 7.16–7.19 (m, 2H), 7.25–7.29 (m, 6H), 7.33–7.42 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.4 (CH_3), 32.9 (CH_2), 35.0 (CH_2), 66.9 (CH_2), 120.8 (CH), 124.7 (CH), 126.3 (CH), 126.7 (CH), 128.5 (CH), 128.8 (CH), 129.6 (CH), 129.9 (CH), 137.5 (C), 138.2 (C), 139.7 (C), 142.0 (C), 142.6 (C), 150.9 (C), 153.2 (C); MS (FAB$^+$): *m*/*z* (%) = 455 ([M+H]$^+$, 100), 317 (48), 154 (46), 136 (43), 93 (55); HRMS (FAB$^+$): *m*/*z* [(M+H)$^+$] calcd for $C_{25}H_{24}ClO_4S$: 455.1084; found: 455.1087.
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21. *Typical procedure*: A solution of **4a** (45.5 mg; 0.100 mmol) in THF (0.6 mL) was added to a solution of *i*-PrMgCl•LiCl (0.40 mmol) in THF (4.4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 30 min. The reaction was quenched with sat. aq NH_4Cl (2.0 mL), and the mixture was extracted with $CHCl_3$ (15 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [R_f = 0.19 (hexane-EtOAc, 3:1)] to afford **5a** (22.2 mg, 0.076 mmol, 76%) as colorless crystals. Mp 71.0–72.0 °C (hexane/EtOAc); IR (KBr): 2932, 1756 (C=O), 1651, 1602, 1496, 1455, 1353, 1136, 1037, 996, 758, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.81–2.95 (m, 4H), 4.55 (s, 2H), 7.16–7.19 (m, 2H), 7.22–7.35 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 28.7, 32.6, 71.3, 119.8, 126.9, 128.1, 128.9, 139.2, 159.0, 168.5; MS (EI): *m*/*z* (%) = 222 (M^+, 6), 187 (7), 91 (100); HRMS (EI): *m*/*z* [M^+] calcd for $C_{12}H_{11}ClO_2$: 222.0448; found: 222.0446.