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1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride in combination with triethylamine: an improved catalytic system for hydroacylation/reduction of activated ketones

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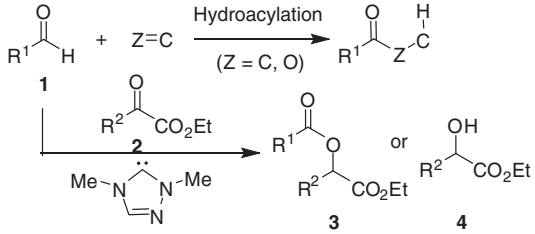
ABSTRACT

A rapid, economic, and high yielding methodology has been developed for hydroacylation/reduction of activated ketones by using 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride as a catalyst in combination with triethylamine. The reaction proceeded at an ambient temperature via generating N-heterocyclic carbene in situ that interacted with the (hetero)aryl aldehyde employed. While the reduction of ketones takes place in MeOH, the hydroacylation process was found to be effective in THF for both electron rich and deficient aldehydes.

The intramolecular hydroacylations of alkene in the presence of transition metal catalysts especially the rhodium(I)-salts have become a powerful strategy to prepare various carbocyclic structures.[1] The methodology essentially involves the use of an aldehyde as a source of hydroacylating agent and proceeds via selective oxidation of aldehydic C–H. While a number of reports are available on hydroacylations (Scheme 1) of alkene (Z = C), an analogous process involving aldehydes and carbonyl group (Z = O), however, was not explored until recently. For example, the hydroacylation of α-keto esters (**2**) with aldehydes (**1**) catalyzed by N-heterocyclic carbenes (Scheme 1) was reported only in 2006.[2] In this process, the carbene generated from a triazolium salt and DBU facilitated selective catalytic oxidation of a C–H bond with concomitant reduction of a ketone. Very recently, intramolecular hydroacylation of ketone in the presence of an Rh catalyst leading to lactone has been reported.[3] Nevertheless, the N-heterocyclic carbene (NHC) mediated hydroacylation can be carried out in an aprotic or protic solvent such as CH_2Cl_2 or MeOH (or EtOH) affording a hydroacylation product **3** or the carbonyl reduction product **4** depending on the nature of solvent used (Scheme 1). The reaction was carried out using 10–15 mol % of triazolium salt for 9–24 h and yields of products generally varied from 0% to 83% in the case of **3** and 71% to 96% in the case of **4**. In our effort to develop a rapid and more economic process for the reduction/hydroacylation of α-keto esters (**2**) with aldehydes (**1**) we now report our preliminary results on the use of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl) in combination with triethylamine as an alternative source of N-heterocyclic carbene (NHC).

Based on earlier reports on the interaction of NHC with aldehydes,[4] 1,4-dimethyl-1*H*-1,2,4-triazol-4-ium iodide was used to generate the active carbene species for hydroacylation reactions. We hypothesized that N-heterocyclic salts based on similar five-membered ring containing two hetero atoms (e.g. **A–D**, Figure 1) might be equally effective for the generation of NHC. Indeed,



Scheme 1. Hydroacylation of alkene and carbonyl compound.

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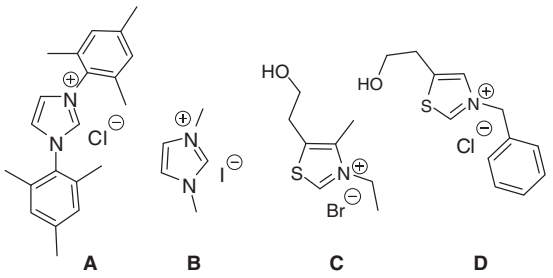


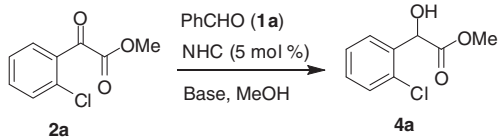
Figure 1. Salts as potential source of NHC.

imidazolylidene carbenes have been investigated as ligands in coordination chemistry, as powerful steering/controlling elements in transition-metal catalysis,[5] as well as in metal-free catalysts for organic reactions.[4b,c,6,7] Thus, we assessed the reaction of benzaldehyde (**1a**) with methyl 2-(2-chlorophenyl)-2-oxoacetate (**2a**) in the presence of salts **A**–**D** using various bases in methanol. As expected, the carbonyl reduction product **4a** was isolated in these cases and results are summarized in Table 1.

Among all the salts screened, the use of sterically encumbered 1,3-*bis*(2,4,6-trimethylphenyl)imidazolium chloride (**A**) was found to be the most effective in terms of product yield (Table 1, entries 2–4). The maximum yield was achieved by using 5 mol % of **A** and Et_3N as a base (Table 1, entry 4) and the reaction was completed within 5 h. The use of other inorganic/organic bases such as NaOH and DBU was examined (Table 1, entries 1 and 2) and was found to be less effective. Among the other salts examined, 1,3-dimethyl-1*H*-imidazol-3-ium iodide (**B**) afforded **4a** in moderate yields (Table 1, entries 5 and 6) whereas thiazolium salts **C** and **D** provided **4a** in low yields even after 20 h (Table 1, entries 7 and 8). The effectiveness of **A** perhaps can be accounted by the steric and electronic properties that tuned its desired reactivity toward aldehydes after the generation of NHC.[8,9]

Having established the optimum reaction conditions[10] for the present NHC-mediated process, we then examined the further application of salt **A** in this reduction process. Thus a range of substituted aromatic α-keto esters **2** were employed which provided the desired alcohols (**4**) in good to excellent yields (Table 2). As evident from Table 2, various esters, such as methyl, ethyl, *i*-propyl, or *i*-butyl were employed and the presence of substituents, such as fluoro, chloro, bromo, or methoxy at the phenyl ring was well tolerated. Notably, the presence of a phenolic group did not affect the reduction process and the corresponding alcohol was isolated in good yield. All the alcohols isolated were well char-

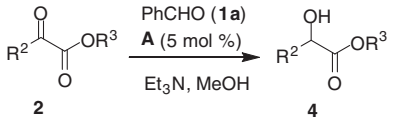
Table 1
The NHC-mediated reaction of **1a** with **2a** in a protic solvent[a]

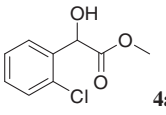
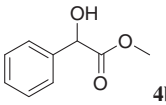
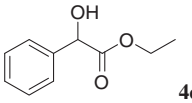
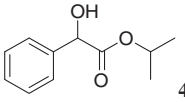
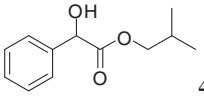
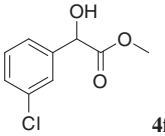
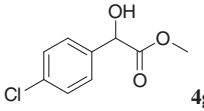
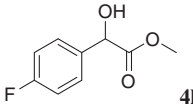
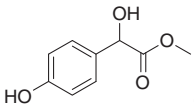
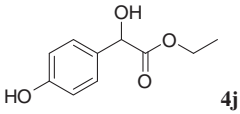
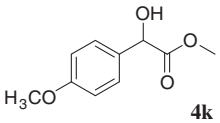
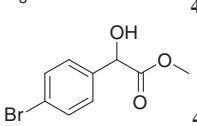


Entry	NHC ligands (mol %)	Base	Time (h)	Yield (%)
1	**A** (10)	NaOH	5	40
2	**A** (10)	DBU	10	80
3	**A** (10)	Et_3N	5	90
4	**A** (5.0)	Et_3N[b]	5	95
5	**B** (10)	DBU	10	50
6	**B** (10)	Et_3N	7	70
7	**C** (10)	Et_3N	20	40
8	**D** (10)	Et_3N	20	35

[a] The reaction was carried out using **1a** (2.83 mmol), **2a** (4.24 mmol), NHC ligand (**A**–**D**) and a base (0.42 mmol) in MeOH at 25 °C under nitrogen.
[b] 0.21 mmol of Et_3N was used.

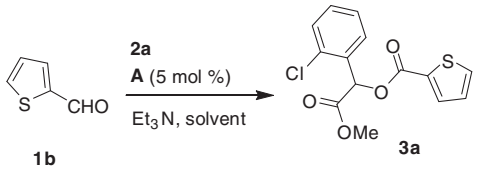
Table 2
NHC(**A**)-mediated reduction of α-keto ester **2**[a]



Entry	R^2	R^3	Alcohol (**4**)	Yield[b] (%)
1	*o*-ClC_6H_4	Me	 **4a**	95
2	Ph	Me	 **4b**	86
3	Ph	Et	 **4c**	91
4	Ph	*i*-Pr	 **4d**	90
5	Ph	*i*-Bu	 **4e**	85
6	*m*-ClC_6H_4	Me	 **4f**	95
7	*p*-ClC_6H_4	Me	 **4g**	94
8	*p*-FC_6H_4	Me	 **4h**	90
9	*p*-HOC_6H_4	Me	 **4i**	95
10	*p*-HOC_6H_4	Et	 **4j**	93
11	*p*-$MeOC_6H_4$	Me	 **4k**	95
12	*p*-BrC_6H_4	Me	 **4l**	88

[a] The reaction was carried out using **1a** (2.83 mmol), **2** (4.24 mmol), NHC ligand **A** (0.14 mmol) and Et_3N (0.21 mmol) in MeOH (9.0 mL) at 25 °C for 5 h under nitrogen.
[b] Isolated yield.

Table 3
The reaction of **1b** with **2a** in the presence of **A** and Et_3N in aprotic solvents[a]



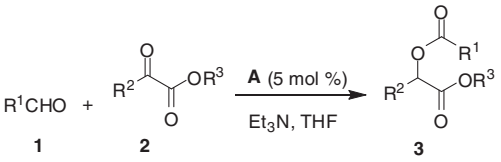
Entry	Solvent	Time (h)	Yield (%)
1	CH_2Cl_2	12	75
2	$ClCH_2CH_2Cl$	12	60
3	THF	6	85
4	Acetone	20	10
5	CH_3CN	24	20
6	EtOAc	24	10
7	DMF	24	No product

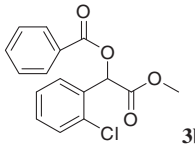
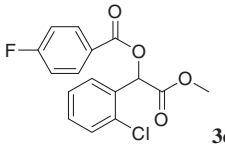
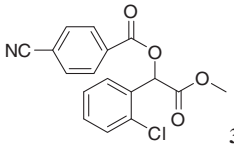
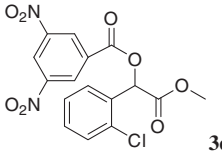
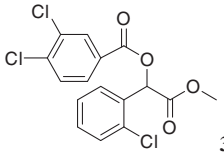
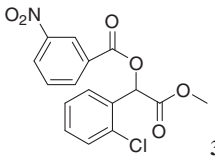
[a] The reaction was carried out using **1b** (2.83 mmol), **2a** (4.24 mmol), NHC ligand **A** (0.14 mmol) and Et_3N (0.21 mmol) in a solvent at 25 °C under nitrogen.

acterized by spectral data and each of them was found to be a racemic mixture (1:1) of two antipodes as indicated by HPLC study.

Since the use of aprotic solvent such as CH_2Cl_2 is known to afford hydroacylated product **3**, we examined the reaction of **2a** with thiophene-2-carbaldehyde (**1b**) in the presence of **A** (5 mol %) and Et_3N in various aprotic solvents including CH_2Cl_2 (Table 3). Among all the solvents tested THF was found to be the most effective in terms of product yield and the reaction was completed within 6 h (entry 3, Table 1). While the use of CH_2Cl_2 provided satisfactory yield of the product, the duration of the reaction was 12 h (entry 1, Table 3). To evaluate the scope of this hydroacylation reaction[11] carried out in a non-chlorinated solvent we employed a range of aldehydes and the corresponding hydroacylated products were obtained in good yields (Table 4). Aldehydes containing either electron donating or withdrawing groups were found to be equally effective. Notably, previously reported hydroacylation reaction mediated by triazolium salt was found to afford lower yields of products when electron deficient aldehydes were employed.[2]

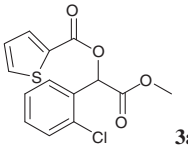
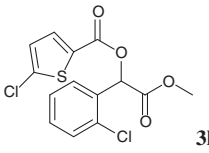
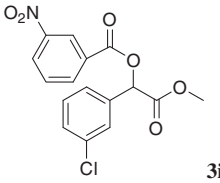
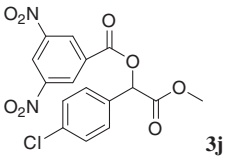
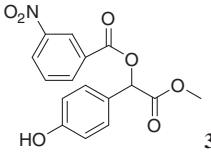
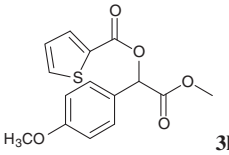
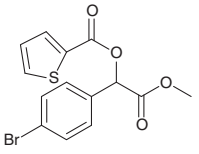
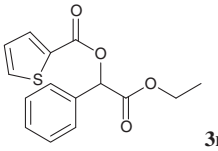
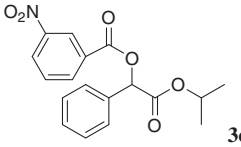
Table 4
Scope of NHC(**A**)-mediated hydroacylation process[a]



Entry	R^1	R^2 =	R^3 =	Ester (**3**)	Yield[b] (%)
1	Ph	*o*-ClC_6H_4	Me	 **3b**	76
2	4-F-Ph	*o*-ClC_6H_4	Me	 **3c**	78
3	4-CN-Ph	*o*-ClC_6H_4	Me	 **3d**	79
4	3,5 NO_2-Ph	*o*-ClC_6H_4	Me	 **3e**	81
5	3,4 Cl-Ph	*o*-ClC_6H_4	Me	 **3f**	83
6	3-NO_2-Ph	*o*-ClC_6H_4	Me	 **3g**	80

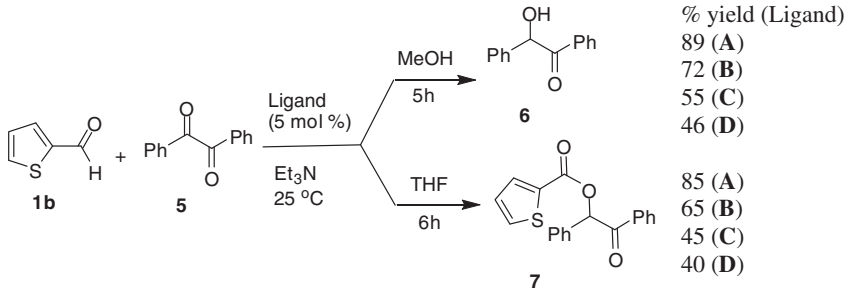
(*continued on next page*)

Table 4 (*continued*)

Entry	R^1	R^2 =	R^3 =	Ester (**3**)	Yield[b] (%)
7	2-Thiophene	*o*-ClC_6H_4	Me	 **3a**	85
8	5-Chloro-2-thiophene	*o*-ClC_6H_4	Me	 **3h**	84
9	3-NO_2-Ph	*m*-ClC_6H_4	Me	 **3i**	80
10	3,5-NO_2-Ph	*p*-ClC_6H_4	Me	 **3j**	78
11	3-NO_2-Ph	*p*-HOC_6H_4	Me	 **3k**	84
12	2-Thiophene	*p*-$MeOC_6H_4$	Me	 **3l**	80
13	2-Thiophene	*p*-BrC_6H_4	Me	 **3m**	76
14	2-Thiophene	Ph	Et	 **3n**	81
15	3-NO_2-Ph	Ph	*i*-Pr	 **3o**	83

[a] The reaction was carried out using **1** (2.83 mmol), **2** (4.24 mmol), NHC ligand **A** (0.14 mmol) and Et_3N (0.21 mmol) in THF (9.0 mL) at 25 °C for 6 h under nitrogen.
[b] Isolated yield.

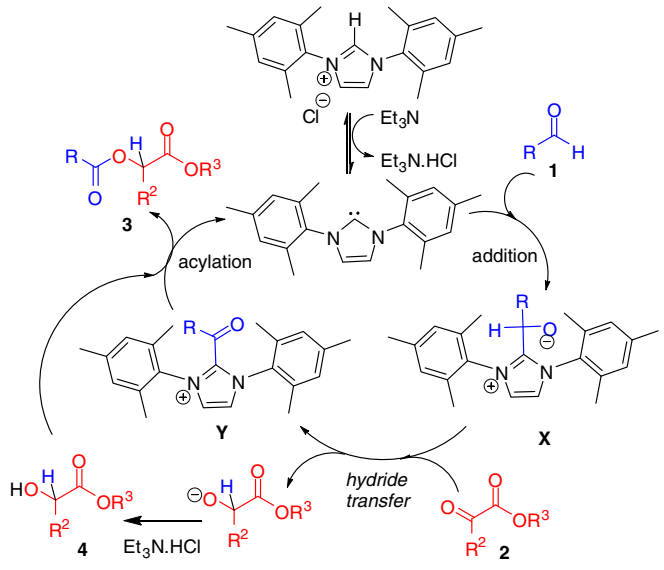
We were able to carry out the present hydroacylation/reduction process within a shorter period of time, e.g. 5–6 h (vs 9–24 h by triazolium salt-DBU method)[2] without increasing the reaction temperature. While many organic reactions are performed by providing an external energy, usually heating, a synthetic process that does not require external heating is expected to be more practical and economic. Moreover, such a process is particularly handy for substrates that are sensitive to heat or occasions where prolonged heating of the reaction mixture needs to be avoided. A comparison between the present hydroacylation process and that reported in the literature (see Supplementary data) revealed that the present process involves the use of a cheaper and lower quantity of catalyst, a commonly used base and non-chlorinated solvent. The use of chlorinated solvent is associated with the health hazard and environmental problem especially when used in large volume in scale-up synthesis.



Scheme 2. Keto-reduction and hydroacylation of benzil (**5**).

In order to explore the potential of NHC ligand **A** further we examined the effect of ligands **A**–**D** in the reactions with enolizable aldehydes or other activated ketones. Thus both the keto-reduction and hydroacylation processes were examined using benzil and several aldehydes such as thiophene-2-carbaldehyde (Scheme 2), 3-phenylpropanal and propionaldehyde (see Supplementary data). While the keto-reduction of benzil (**5**) proceeded well using thiophene-2-carbaldehyde (**1b**) in the presence of all the ligands (Scheme 2), the reaction provided a mixture of unidentified products when enolizable aldehydes were used. A similar observation was also noted during the hydroacylation process indicating that the present method is not effective for enolizable aldehydes. Nevertheless, once again **A** was found to be the best among the four NHC ligands tested in terms of product yield.

Mechanistically, the hydroacylation/reduction process proceeds via a generation of a tetrahedral intermediate **X** due to the interaction of NHC with an aldehyde **1** (Scheme 3). The presence of bulky and electron rich 2,4,6-trimethylphenyl moiety facilitated the generation of NHC in the presence of a milder base such as Et_3N. A hydride transfer from **X** to the α-keto ester **2** (Cannizzaro-type reaction) provides an acyl heteroazolium species **Y** and the alcohol **4** via regioselective reduction of the keto group of **2**. The alcohol **4** is then O-acylated by **Y** possessing an acyl iminium moiety responsible for the transfer of acyl group to the hydroxyl moiety. As a result the NHC is regenerated to complete the catalytic cycle yielding the hydroacylation product **3**. While the formation of alcohol **4** instead of **3** in a protic solvent is not clearly understood at this stage the transfer of acyl group from **Y** to the solvent molecules (e.g. MeOH that are present in excess) rather than alcohol **4** is more likely in this case. The reason for THF to serve as a better solvent than CH_2Cl_2 is perhaps due to its ability to facilitate the acyl group transfer from **Y** to alcohol **4** via transient formation of a THF–acylium complex (the oxygen of THF is very exposed and thus the lone pairs can easily coordinate to the electron deficient centers).



Scheme 3. Proposed mechanism of NHC-mediated reduction/hydroacylation.[2]

In conclusion, we have demonstrated that the combination of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**A**) and triethylamine facilitates hydroacylation/reduction of activated ketones at ambient temperature via generating N-heterocyclic carbene in situ. The advantages of the present process include the use of (i) readily available, cheaper and lower quantity of catalyst/base and (ii) shorter reaction time. Moreover, the hydroacylation reaction can be carried out efficiently in a non-chlorinated solvent and was found to be effective for both electron rich and deficient aldehydes. The methodology, therefore, has potential to become a practical alternative to the previously reported method and would find wide applications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.022.

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10. *Typical procedure for NHC(**A**)-mediated reduction of α-keto ester* **2**: To a mixture of imidazolium salt **A** (48 mg, 0.14 mmol) and distilled benzaldehyde (300 mg, 2.83 mmol) in MeOH (9.0 mL) was added triethylamine (21.5 mg, 0.21 mmol) followed by methyl 2-(2-chlorophenyl)-2-oxoacetate (842 mg, 4.24 mmol) under nitrogen atmosphere. The mixture was then stirred at 25 °C for 5 h until benzaldehyde was consumed (monitored by TLC). After completion of the reaction the mixture was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (230–400 mesh) using 10–15% EtOAc–hexane; spectral data of **4a**: IR (film) 3467, 2954, 1741, 1222, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.43–7.53 (2H, m, CH_{arom}), 7.32–7.39 (2H, m, CH_{arom}), 6.36 (1H, d, J = 5.6 Hz, OH), 5.44 (1H, d, J = 6.0 Hz, C_6H_4CHOH); 3.62 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.8, 70.1, 126.9, 128.6, 129.5, 129.6, 133.2, 135.9, 173.3; mass (ES) m/z 223 $(M+Na)^+$; HRMS calculated for $C_9H_{10}O_3Cl$ $[M+H]^+$ 201.0318. Found 201.0323. Compound **4f**: IR (film) 3460, 2954, 1741, 1215, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.43 (4H, m, CH_{arom}), 5.15 (1H, d, J = 5.6 Hz, C_6H_4CHOH), 3.77 (3H, s, OCH_3), 3.55 (1H, d, J = 5.6 Hz, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 53.1, 72.2, 124.7, 126.6, 128.5, 129.7, 134.4, 140.0, 173.4; mass (ES) m/z 223 $(M+Na)^+$; HRMS calculated for $C_9H_{10}O_3Cl$ $[M+H]^+$ 201.0318. Found 201.0327.

11. *A typical procedure for hydroacylation reaction*: To a mixture of imidazolium salt **A** (48 mg, 0.14 mmol) and 2-thiophene-2-carbaldehyde (317 mg, 2.83 mmol) in THF (9.0 mL) was added triethylamine (21.5 mg, 0.21 mmol) followed by methyl 2-(2-chlorophenyl)-2-oxoacetate (842 mg, 4.24 mmol) under nitrogen atmosphere. The mixture was then stirred at 25 °C for 6 h until the aldehyde was consumed (monitored by TLC). After completion of the reaction the mixture was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (230–400 mesh) using 5–10% EtOAc–hexane; spectral data of **3a**: IR (film): 2949, 1750, 1719, 1253, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.04 (1H, m, $CH_{thiophene}$), 7.91 (1H, m, $CH_{thiophene}$), 7.44–7.62 (4H, m, C_6H_4), 7.25 (1H, m, $CH_{thiophene}$), 6.57 (1H, s, CH), 3.73 (3H, s, OCH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 52.9, 71.3, 127.9, 128.6, 129.9, 130.0, 131.2, 131.3, 131.5, 133.1, 134.9, 135.1, 160.3, 167.8; mass (ES) m/z 328.4 $(M+NH_4)^+$; HRMS: calculated for $C_{14}H_{12}O_4SCl$ $[M+H]^+$ 311.0145. Found 311.0153. Compound **3h**: IR (film): 2952, 1751, 1708, 1289, 763 cm^{-1}; ^1HNMR (400 MHz, DMSO-d_6); δ 7.82 (1H, d, J = 4.0 Hz, $CH_{thiophene}$), 7.44–7.60 (4H, m, o-ClC_6H_4), 7.32 (1H, d, J = 4.0 Hz, $CH_{thiophene}$), 6.67 (1H, s, CH), 3.73 (3H, s, OCH_3); ^{13}C NMR (50 MHz, DMSO-d_6): δ 52.9, 71.5, 127.9, 128.9, 129.7, 129.9, 130.2, 131.2, 131.4, 133.2, 135.0, 159.2, 167.6; mass (ES) m/z 362 $(M+NH_4)^+$; HRMS calculated for $C_{14}H_{11}O_4SCl_2$ $[M+H]^+$ 344.9755. Found 344.9753.