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Aza-Michael addition of amines to activated alkenes catalyzed by Silica supported perchloric acid under a solvent-free condition ¶

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Abstract: An efficient aza-Michael addition of amines to a series of α,β-unsaturated ketones, carboxylic esters, nitriles and chalcones has been carried out using perchloric acid supported over silica gel ($HClO_4$-SiO_2) at room temperature in high yields under solvent-free reaction conditions.

***Key words*:** Aza-Michael addition, amines, synthetic methods, electron-deficient alkenes, $HClO_4$-SiO_2, solvent-free.

1. Introduction

The Michael reaction and its modified form such as aza-Michael, thio-Michael and carba-michael reaction is one of the most exploited reactions in organic chemistry. [1] The β-amino esters/ketones/nitriles are useful synthons for the preparation of several nitrogen containing bioactive natural products, [2] antibiotics [3] and chiral auxiliaries. [4] Besides this, a large number of biologically active compounds contain β-amino-ketone or ester moiety. [5] The development of novel synthetic methodologies for the preparation of these compounds is an attractive area of research in synthetic organic chemistry. Although β-amino ketones can be prepared by classical Mannich reaction, [6] it has several drawbacks, such as, harsh reaction conditions, longer reaction time etc. Therefore, a variety of methods appeared in the literature for the synthesis of β-amino ketones, esters or nitriles. [7] Among the different synthetic methodologies, one of the most frequently used is the conjugate addition of amines to α,β-unsaturated ketones or esters or nitriles, which is termed as aza-Michael reaction. [1] In general, the aza-Michael reaction requires a basic condition [8] or some special reaction condition. [9] However, in some cases, use of stoichiometric amount catalysts with reactive substrates resulted several side reactions. [10] As a result, a wide variety of catalysts have been cited in the literature and in particular various Lewis acid catalyzed reaction have been carried out to minimize shortcomings.[11] Despite their usefulness, many of these procedures often require large amount of reagents, prolonged reaction time, drastic reaction condition and stoichiometric amount of Lewis acid catalyst such as $AlCl_3$, $TiCl_4$ and $SnCl_4$. Therefore, development for an alternative method which can overcome these limitations is always welcome.

Use of heterogeneous catalysts for the organic transformation is rapidly growing over the homogeneous catalyst systems because of several advantages of the heterogeneous catalysts such as, high stability, ease of handling, recovery and reuse, non-corrosive nature, long time persisting

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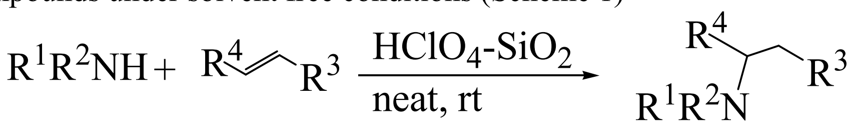
catalytic activity and environmentally friendliness.[12] Recently, we reported [13] several organic transformations catalyzed by the perchloric acid supported over silica gel ($HClO_4$-SiO_2), a solid supported acid catalyst. It is very cheap, readily prepared in the laboratory [14] and can be stored for a long time without any significant loss of catalytic activity. As a part of our continuing effort to explore the catalytic potential of $HClO_4$-SiO_2, we revealed that $HClO_4$-SiO_2 may efficiently activate Michael acceptors resulting clean formation of aza-Michael addition products without formation of side products in a short reaction time under a solvent free reaction condition. In this letter, we are disclosing our finding on $HClO_4$-SiO_2 catalyzed Michael addition of amines to α,β-unsaturated compounds under solvent free conditions (Scheme 1)



R^3 = CN, COOEt, COEt, COMe; R^4 = H, Ar

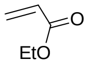
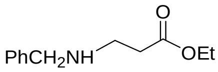
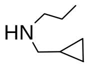
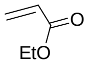
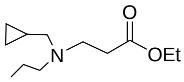
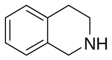
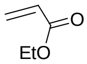
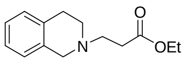
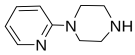
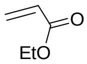
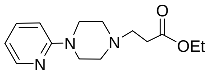
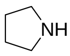
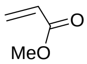
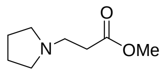
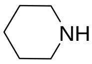
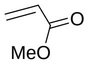
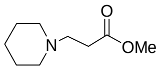
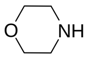
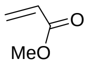
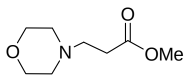
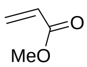
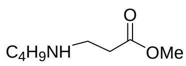
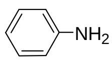
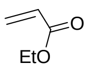
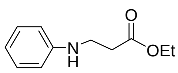
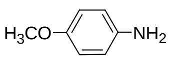
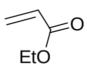
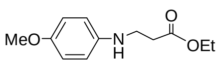
Scheme 1

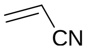
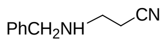
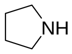
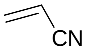
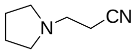
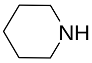
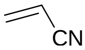
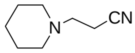
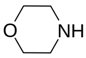
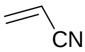
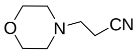
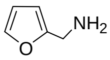
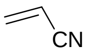
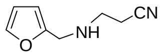
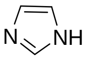
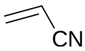
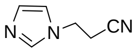
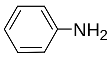
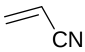
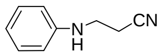
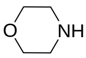
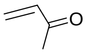
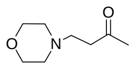
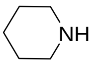
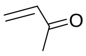
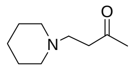
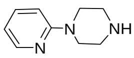
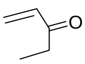
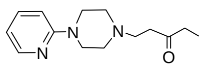
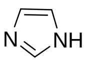
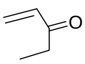
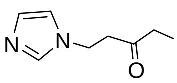
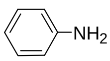
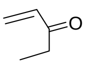
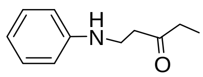
2. Results and Discussion

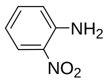
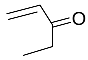
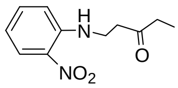
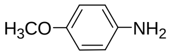
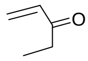
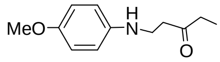
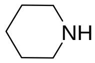
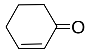
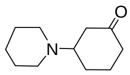
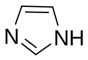
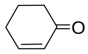
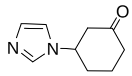
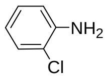
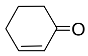
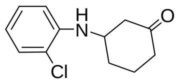
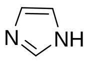
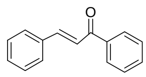
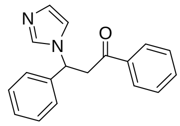
In a set of initial experiments, methyl vinyl ketone was allowed to react with morpholine in an equimolar ratio in the presence of a varied quantity of $HClO_4$-SiO_2. After a series of experimentations, it was observed that excellent yield of the Michael adduct can be achieved by reacting a mixture of morpholine (1.2 equiv.) and methyl vinyl ketone (1.0 equiv) in the presence of $HClO_4$-SiO_2 (100 mg) at room temperature. Following similar reaction condition a series of aza-Michael adducts have been prepared using a diverse range of amines and conjugated alkenes, such as, α,β-unsaturated nitriles, α,β-unsaturated carboxylic acid esters, chalcones etc. which is summarized in Table 1. Addition of primary amines such as benzyl amine, butyl amine resulted only monoalkylated products. Aromatic amines showed poor reactivity towards the Michael addition compared to aliphatic amines. No side products were observed by using excess amines. Pure product could be obtained by removal of the catalyst by filtration followed by column chromatography. The catalyst system was found to be recyclable and the reaction condition can be scaled up. In order to test the reusability of the catalyst, a reaction of methyl vinyl ketone (10 mmol) and morpholine (11 mmol) was carried out in the presence of $HClO_4/SiO_2$ (1 g) and the catalyst was recovered after completion and activated by heating at 100 °C under vacuum for 1 h. The recovered catalyst was reused for the aza-Michael reaction of a another batch of methyl vinyl ketone (10 mmol) and morpholine (11 mmol) giving 90% yield of the desired product after 1 h. Again, the catalyst was recovered, reactivated and reused repeatedly for three more consecutive times for aza-Michael reactions affording 85%, 70% and 70% yields respectively. From this observation, it is clear that the reaction can be scaled up and the catalyst is reusable with a little decrease of catalytic activity. Products were characterized by ^{1}H NMR and mass spectroscopy and for known compounds compared with the literature data [15, 16].

To compare the catalytic activity of $HClO_4$-SiO_2 over ordinary Silica, an identical experiment was performed by stirring an intimate mixture of methyl vinyl ketone (1.0 mmol), morpholine (1.2 mmol) and silica (240-400 mesh, 100 mg) at room temperature. No aza-Michael addition product was formed even after 24 h, indicating the requirement of $HClO_4$-SiO_2 for the successful outcome of the reaction. Furthermore, use of $HClO_4$-SiO_2 in the aza-Michael addition of amines to conjugated alkenes, reduces the cost of the catalysts, which have been used earlier for same transformation and in some cases the reaction completed in much less time. It is not very clear whether $HClO_4$-SiO_2 act as a solid acid catalyst or as a reservoir providing a small concentration of perchloric acid in solution. However, from the experiments carried out using recovered $HClO_4$-SiO_2 may explain that it acts as a solid acid in the aza-Michael reaction.

Table 1: $HClO_4$-SiO_2 catalyzed aza-Michael addition of amines to activated alkenes under solvent-free condition.[a]

Entry	**Amines (a)**	**Alkenes**	**Product (b)**[b]	**Time (h)**	**Yield (%)**	**Ref**
1	$PhCH_2NH_2$		 **1**	0.5	90	–
2			 **2**	0.75	92	–
3			 **3**	1	90	–
4			 **4**	1	92	–
5			 **5**	0.75	96	11i
6			 **6**	0.75	95	11i
7			 **7**	0.75	92	11f
8	$C_4H_9NH_2$		 **8**	0.75	92	11i
9			 **9**	5	65	–
10				6	70	–

			10			
11	$PhCH_2NH_2$		 **11**	0.75	92	11i
12			 **12**	0.75	90	11i
13			 **13**	0.75	92	11i
14			 **14**	0.75	90	11f
15			 **15**	1	88	–
16			 **16**	7	70	–
17			 **17**	7	50	2b
18			 **18**	0.75	95	11f
19			 **19**	0.75	95	11g
20			 **20**	1	90	–
21			 **21**	1	85	–
22			 **22**	1	80	–

23			 **23**	1	82	–
24			 **24**	1	85	–
25			 **25**	0.75	90	11h
26			 **26**	1	85	11h
27			 **27**	1.5	80	–
28			 **28**	2	72	–

[a] Reaction condition: A mixture of amine (1.2 mmol), conjugated alkene (1.0 mmol) and $HClO_4$-SiO_2 (100 mg) was stirred at room temperature for appropriate time.
[b] Isolated yield.

3. Conclusion

In summary, a convenient method has been developed for the aza-Michael addition of aliphatic or aromatic amines to the activated alkenes catalyzed by $HClO_4$-SiO_2. Following this generalized methodology aza-Michael addition can be carried out on α,β-unsaturated esters, ketones and nitriles. Use of inexpensive and reusable catalyst, solvent-free reaction condition, short reaction time, excellent chemoselectivity, high yield and ease of purification of the products are the key features of this elegant protocol for which it may be considered as an effective alternative to the existing methodologies.

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Chem. **2006**, *71*, 2911-2913; (f) Tiwari, P.; Misra, A. K. *Tetrahedron Lett.* **2006**, *47*, 3573-3576; (g) Agnihotri, G.; Misra, A. K. *Tetrahedron Lett.* **2006**, 3653-3658.

[14] **Preparation of $HClO_4$-SiO_2:** $HClO_4$ (1.8 g, 12.5 mmol, as a 70% aq solution) was added to a suspension of SiO_2 (230-400 mesh, 23.7 g) in Et_2O (70.0 mL). The mixture was concentrated and the residue was heated at 100°C for 72 h under vacuum to furnish $HClO_4$-SiO_2 (0.5 mmol/g) as a free flowing powder.

[15] **Typical experimental procedure**: To magnetically well stirred mixture of amine (1.2 mmol) and α,β-unsaturated ketone or ester or nitrile (1.0 mmol) was added $HClO_4$-SiO_2 (100 mg) at room temperature and the reaction mixture was allowed to stir at room temperature for appropriate time as mentioned in Table 1. After completion of the reaction, the reaction mixture was filtered, washed with CH_2Cl_2 and concentrated under reduced pressure. Column chromatography of the crude product over SiO_2 afforded pure aza-Michael adducts.

[16] Spectral data for compounds which are not reported earlier: **Compound 1**: Rf: 0.77 (Hexane-EtOAc; 2:1); IR (Neat): 1730, 1581, 1457, 1398, 1189, 1029, 752, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32-7.21 (m, 5 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.8 (s, 2 H), 2.89 (t, *J* = 6.4 Hz, 2 H), 2.52 (t, *J* = 6.4 Hz, 2 H), 1.84 (s, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ESI-MS: *m/z* 208.1 $[M+1]^+$; Anal. Calcd. for $C_{12}H_{17}NO_2$ (207): C, 69.54; H, 8.27; found: C, 69.32; H, 8.50. **Compound 2**: Rf: 0.25 (Hexane-EtOAc; 1:1); IR (Neat); 1737, 1597, 1460, 1351, 1194, 1049, 761, 670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.12 (q, *J* = 7.1 Hz, 2 H), 2.86 (t, *J* = 7.1 Hz, 2 H), 2.48-2.40 (m, 4 H), 2.33 (d, *J* = 6.4 Hz, 2 H), 1.46 (q, *J* = 7.4 Hz, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.88 (2 t, *J* = 7.3 Hz, 4 H), 0.51-0.45 (m, 2 H), 0.11-0.06 (m, 2 H); ESI-MS: *m/z* 214.1 $[M+1]^+$; Anal. Calcd. for $C_{12}H_{23}NO_2$ (213): C, 67.57; H, 10.87; found: C, 67.30; H, 11.1. **Compound 3**: Rf: 0.25 (Hexane-EtOAc; 1:1); IR (Neat); 2368, 2145, 1733, 1597, 1351, 1184, 745 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.12-7.07 (m, 3 H), 7.00-6.98 (m, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.66 (s, 2 H), 2.92-2.85 (m, 4 H), 2.80-2.76 (m, 2 H), 2.60 (t, *J* = 7.3 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ESI-MS: *m/z* 234.1 $[M+1]^+$; Anal. Calcd. for $C_{14}H_{19}NO_2$ (233): C, 72.07; H, 8.21; found: C, 71.82; H, 8.45. **Compound 4**: Rf: 0.81 (Hexane-EtOAc; 2:1); IR (Neat); 2370, 2124, 1732, 1594, 1482, 1438, 1246, 1178, 774, 734 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.16-8.14 (m, 1 H), 7.46-7.41 (m,1 H), 6.61-6.56 (m, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.53 (2t, *J* = 5.1 Hz, 4 H), 2.73 (t, *J* = 7.2 Hz, 2 H), 2.59-2.49 (m, 6 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ESI-MS: *m/z* 264.1 $[M+1]^+$; Anal. Calcd. for $C_{14}H_{21}N_3O_2$ (263): C, 63.85; H, 8.04; found: C, 63.62; H, 8.30. **Compound 9**: Rf: 0.44 (Hexane-EtOAc; 7:1); IR (Neat); 2373, 1728, 1603, 1508, 1253, 1183, 1028, 751, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19-7.14 (m, 2 H), 6.70 (t, *J* = 7.3 Hz, 1 H), 6.62-6.59 (m, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.46 (t, *J* = 6.3 Hz, 2 H), 2.61 (t, *J* = 6.3 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H); ESI-MS: *m/z* 194.1 $[M+1]^+$; Anal. Calcd. for $C_{11}H_{15}NO_2$ (193): C, 68.37; H, 7.82; found: C, 68.10; H, 8.0. **Compound 10**: Rf: 0.74 (Hexane-EtOAc; 5:1); IR (Neat); 2372, 1730, 1596, 1516, 1350, 1241, 1181, 1036, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.75 (d, *J* = 8.9 Hz, 2 H), 6.58 (d, *J* = 8.9 Hz, 2 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.76 (bs, 3 H), 3.40 (t, *J* = 6.3 Hz, 2 H), 2.59 (t, *J* = 6.3 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ESI-MS: *m/z* 224.1 $[M+1]^+$; Anal. Calcd. for $C_{12}H_{17}NO_3$ (223): C, 64.55; H, 7.67; found: C, 64.37; H, 7.95. **Compound 15**: Rf: 0.66 (Hexane-EtOAc; 1:1); IR (Neat); 2373, 2249, 1630, 1463, 1147, 1011, 918, 745, 600 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.33 (m, 1 H), 6.32-6.30 (m, 1 H), 6.19-6.18 (m, 1 H), 3.83 (bs, 2 H), 2.92 (t, *J* = 6.6 Hz, 2 H), 2.49 (t, *J* = 6.6 Hz, 2 H); ESI-MS: *m/z* 151 $[M+1]^+$; Anal. Calcd. for $C_8H_{10}N_2O$ (150): C, 63.98; H, 6.71; found: 63.80; H, 6.95. **Compound 16**: Rf: 0.64 (CH_2Cl_2-MeOH; 19:1); IR (Neat); 2373, 1595, 1351, 765, 604 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.52 (bs, 1 H), 7.12-7.09 (m, 1 H), 7.01-6.99 (m, 1 H), 4.28

(t, *J* = 6.7 Hz, 2 H), 2.81 (t, *J* = 6.6 Hz, 2 H); ESI-MS: *m/z* 122.2 $[M+1]^+$; Anal. Calcd. for $C_6H_7N_3$ (121): C, 59.49; H, 5.82; found: C, 59.30; H, 6.0. **Compound 20**: Rf: 0.78 (Hexane-EtOAc; 1:1); m.p. 62 ^oC; IR (KBr); 2374, 1697, 1597, 1482, 1437, 1262, 1165, 982, 775, 734 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.15-8.12 (m, 1 H), 7.46-7.38 (m, 1 H), 6.61-6.55 (m, 2 H), 3.53-3.48 (m, 4 H), 2.74-2.40 (m, 10 H), 1.06 (t, *J* = 7.3 Hz, 3 H); ESI-MS: *m/z* 248 $[M+1]^+$; Anal. Calcd. for $C_{14}H_{21}N_3O$ (247): C, 67.98; H, 8.56; found: C, 67.75; H, 8.78. **Compound 21**: Rf: 0.46 (CH_2Cl_2-MeOH; 9:1); IR (Neat); 2374, 1714, 1510, 1220, 767, 665 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41 (bs, 1 H), 6.96 (bs, 1 H), 6.84 (bs, 1 H), 4.22 (t, *J* = 6.4 Hz, 2 H), 2.84 (t, *J* = 6.4 Hz, 2 H), 2.37 (q, *J* = 7.3 Hz, 2 H), 1.03 (t, *J* = 7.3 Hz, 3 H); ESI-MS: *m/z* 153.1 $[M+1]^+$; Anal. Calcd. for $C_8H_{12}N_2O$ (152): C, 63.13; H, 7.95; found: C, 62.90; H, 8.15. **Compound 22**: Rf: 0.55 (Hexane-EtOAc; 6:1); m.p. 56 ^oC; IR (KBr): 2131, 1704, 1606, 1433, 1103, 746, 692 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.18-7.13 (m, 2 H), 6.72-6.67 (m, 1 H), 6.60-6.57 (m, 2 H), 3.44 (t, *J* = 6.1 Hz, 2 H), 2.72 (t, *J* = 6.1 Hz, 2 H), 2.41 (q, *J* = 7.3 Hz, 2 H), 1.08 (t, *J* = 7.3 Hz, 3 H); ESI-MS: *m/z* 278.1 $[M+1]^+$; Anal. Calcd. for $C_{11}H_{15}NO$ (177): C, 74.54; H, 8.53; found; C, 74.35; H, 8.75. **Compound 23**: Rf: 0.71 (Hexane-EtOAc; 7:1); m.p. 64 ^oC; IR (KBr); 2373, 1711, 1597, 1352, 743 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.15-8.05 (m, 2 H), 7.45-7.41 (m, 1 H), 6.85 (d, *J* = 8.3 Hz, 1 H), 6.67-6.58 (m, 1 H), 3.60 (dd, *J* = 12.5 and 6.6 Hz, 2 H), 2.83 (t, *J* = 6.7 Hz, 2 H), 2.49 (q, *J* = 7.3 Hz, 2 H), 1.08 (t, *J* = 7.3 Hz, 3 H); ESI-MS: *m/z* 223 $[M+1]^+$; Anal. Calcd. for $C_{11}H_{14}N_2O_3$ (222): C, 59.45; H, 6.35; found: C, 59.22; H, 6.56. **Compound 24**: Rf: 0.65 (Hexane-EtOAc; 2:1); IR (Neat); 2372, 1708, 1612, 1512, 1244, 1034, 827, 757 cm^{-1}.^1H NMR ($CDCl_3$, 300 MHz): δ 6.16 (d, *J* = 8.9 Hz, 2 H), 5.94 (d, *J* = 8.9 hz, 2 H), 3.12 (s, 3 H), 2.74 (t, *J* = 6.0 Hz, 2 H), 2.07 (t, *J* = 6.1 Hz, 2 H), 1.82-1.76 (m, 2 H), 0.42 (t, *J* = 8.0 Hz, 3 H); ESI-MS: *m/z* 208.1 $[M+1]^+$; Anal. Calcd. for $C_{12}H_{17}NO_2$ (207): C, 69.54; H, 8.27; found: C, 69.35; H, 8.52. **Compound 27**: Rf: 0.77 (Hexane-EtOAc; 3:1); IR (Neat); 2375, 1709, 1593, 1507, 1460, 1040, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27-7.24 (m, 1 H), 7.15-7.09 (m, 1 H), 6.67-6.61 (m, 2 H), 2.90-2.83 (m, 1 H), 2.47-2.23 (m, 4 H), 2.16-2.05 (m, 2 H), 1.82-1.68 (m, 2 H); ESI-MS: *m/z* 224.1 $[M+1]^+$; Anal. Calcd. for $C_{12}H_{14}ClNO$ (223): C, 64.43; H, 6.31; found: C, 64.2; H, 6.55. **Compound 28**: Rf: 0.53 (EtOAc); IR (Neat); 2372, 1710, 1596, 1350, 1021, 751, 692 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01-7.92 (m, 4 H), 7.65-7.21 (m, 6 H), 7.07-6.95 (m, 3 H), 6.09-6.04 (m, 1 H), 3.98-3.71 (m, 2 H); ESI-MS: *m/z* 277.1 $[M+1]^+$; Anal. Calcd. for $C_{18}H_{16}N_2O$ (276): C, 78.24; H, 5.84; found: C, 78.0; H, 6.0.