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Synthesis of highly functionalized piperidines by one-pot multicomponent reaction using tetrabutylammonium tribromide (TBATB)

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ABSTRACT

Tetrabutylammonium tribromide (TBATB) has been found to be an efficient catalyst for the one-pot synthesis of highly substituted piperidines through a combination of 1,3-dicarbonyl compounds, aromatic aldehydes, and various amines in ethanol at room temperature. Atom economy, good yields, environmentally benign, and mild reaction conditions are some of the important features of this protocol.

Recently, multicomponent reactions (MCRs)[1] have been paid much attention by synthetic organic chemists from all over the world because the building of architecturally complex molecules with diverse range of complexity can easily be achieved from readily available starting materials. In most of the cases a single product was obtained from three or more different substrates by reacting in a well-defined manner through MCRs.[2] These time-efficient reactions are environmentally benign and atom economic. MCRs are cost-effective since the expensive purification processes as well as the protection–deprotection steps are non-existent.[3] The synthesis of heterocycles using MCRs is a domain of classical carbonyl condensation chemistry. Among various carbonyl compounds, 1,3-dicarbonyl derivatives represent important synthetic building blocks, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a large variety of synthetic transformations.[4] Thus, the high synthetic potential of these easily accessible reagents have found numerous applications, especially for the synthesis of complex heterocyclic molecules.[5]

The piperidines and their analogues are important heterocycles that are present in many naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals.[6] Some of them also act as pharmaceutical agents.[7] Compounds containing piperidine structural motif exhibit anti-hypertensive,[8] antibacterial,[9] antimalarial,[10] anticonvulsant, and anti-inflammatory activities.[11] Thus, the synthesis of highly substituted piperidines has gained considerable attention,[12] and a number of procedures have been developed using several approaches such as tandem cyclopropane ring-opening/Conia-ene cyclization,[13] imino Diels–Alder reactions,[14] aza-Prins-cyclizations,[15] intramolecular Michael reactions,[16] and intramolecular Mannich reaction onto iminium ions.[17] The functionalized piperidines have been reported using MCRs strategy by employing bromodimethylsulfonium bromide (BDMS),[18] $InCl_3$,[19] and L-proline/TFA.[10] However, the use of expensive and excess amount of catalysts are some of the disadvantages of the above-mentioned methods. Therefore, there is a need for highly efficient, versatile, and eco-friendly synthetic protocol to obtain these valuable compounds in good yields.

Chaudhuri et al. reported environmentally benign synthesis of tetrabutylammonium tribromide (TBATB) as a useful brominating reagent.[20] The efficacy of these organic ammonium tribromides was demonstrated for several organic transformations such as deprotection of dithioacetals,[21a] conversion of carbonyl compounds into 1,3-oxathiolanes and vice-versa,[21b] and synthesis of α-bromo enones[21c] with various naturally occurring flavone derivatives.[21d] A wide variety of organic transformations were developed involving tetrabutylammonium tribromide (TBATB) by other authors.[22] Because of the unique properties of the reagent tetrabutylammonium tribromide (TBATB), it would be an efficient catalyst for the one-pot synthesis of the highly functionalized piperidines from the reaction of 1,3-dicarbonyl compounds, aromatic aldehydes, and amines. In this Letter, a one-pot MCR leading to highly functionalized piperidine derivatives along with their mechanistic aspects is reported (Scheme 1).

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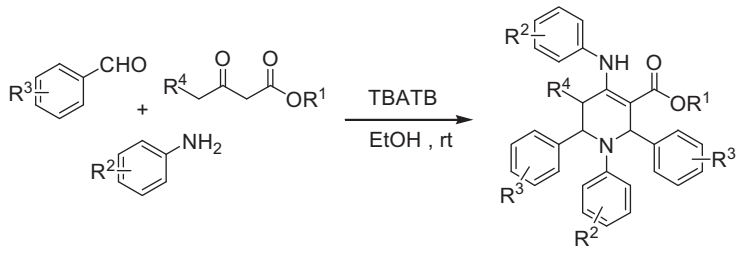


Scheme 1. Synthesis of functionalized piperidines.

Table 1
Optimization of reaction conditions for the synthesis of functionalized piperidine **1a**

Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[a] (%)
1	CH_3CN	No catalyst	12	0
2	CH_3CN	10	12	66
3	EtOH	05	10	56
4	EtOH	10	10	78
5	EtOH	20	10	69
6	CH_2Cl_2	10	10	54
7	CH_3OH	10	12	68
8	Neat	10	5	51

[a] Isolated yield.

In the beginning of the study, a mixture of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) in acetonitrile (5 mL) was treated with 10 mol % of TBATB at room temperature. The solid product was filtered and washed with ethanol to give functionalized piperidine **1a** in 66% yield. The product was characterized by its melting point, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. A series of trial reactions were performed with a combination of 4-methylbenzaldehyde, aniline, and methyl acetoacetate to obtain the best result in terms of yield and reaction time for the formation of **1a** (Table 1). Several solvents were screened prior to concluding ethanol as the best solvent. In the neat reaction, the product was obtained in moderate yields (51%), and it is probably due to the lack of effective interaction of reactants with the catalyst.

Using the optimal reaction conditions, the reaction of benzaldehyde with aniline and methyl acetoacetate was studied and the product **1b** was obtained in good yields. The reactions of various aromatic aldehydes containing substituents in the aromatic ring such as OMe, Cl, Br, and NO_2 with aniline and methyl acetoacetate were performed under the same reaction conditions. The reaction time and the percentage yield of the products **1c–h** are shown in Table 2. However, in case of 3- and 4-nitrobenzaldehydes the products were obtained in low yield (Table 2, entries 7 and 8). This may be attributed to the formation of more stable imine having an extra conjugation in the presence of nitro group. This stable imine is less reactive and has less solubility in ethanol. Some of the aldehydes such as β-naphthaldehyde and *n*-butanal did not give their corresponding functionalized piperidines.

Several aliphatic and aromatic amines were examined to study the generality and scope of the present protocol. Various anilines with substituents such as Me, OMe, Br, and NO_2 were treated with 4-methylbenzaldehyde and methyl acetoacetate under identical reaction conditions. All these reactions underwent smoothly to provide the corresponding piperidine derivatives **1i–l**, in moderate to good yields (Table 2, entries 9–12). Similarly, aliphatic amines such as *n*-butylamine and benzylamine also yielded the corresponding piperidines **1m** and **1n**, respectively, in moderate yields. The present method failed to furnish the expected piperidine derivative with α-naphthylamine, which may be due to steric hindrance of the bulky naphthyl group.

Table 2
Synthesis of functionalized piperidines using TBATB in ethanol[23]

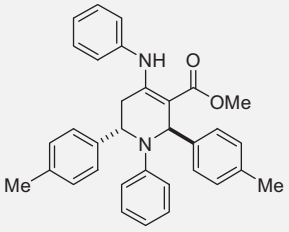
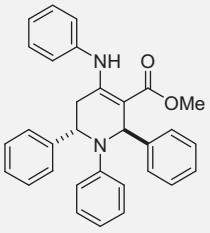
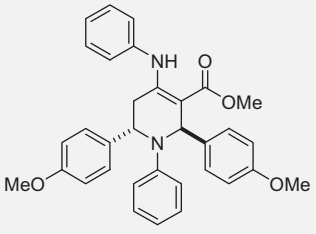
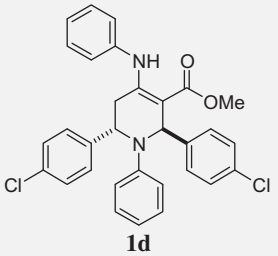
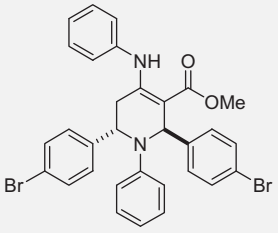
Entry	Product[a]	Time	Yield[b] (%)
1	 **1a**	8	78
2	 **1b**	24	74
3	 **1c**	8	80
4	 **1d**	10	82
5	 **1e**	8	80

Table 2 (*continued*)

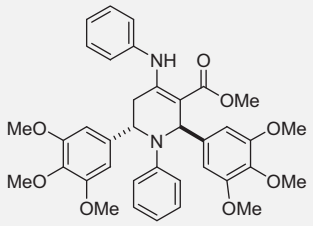
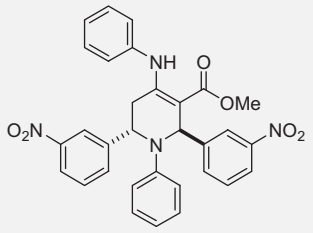
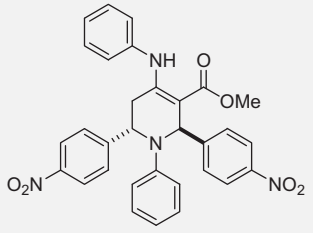
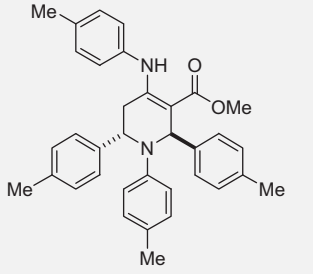
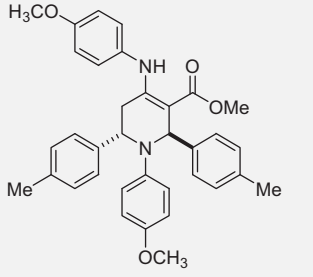
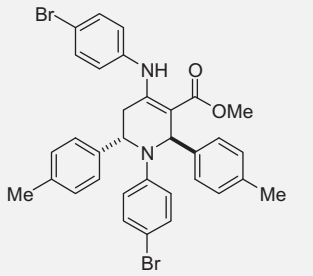
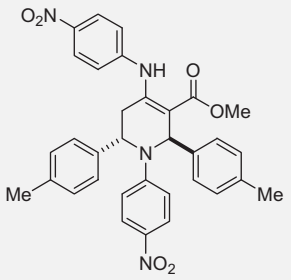
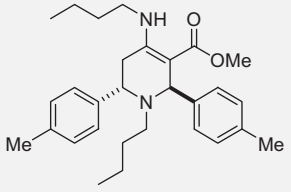
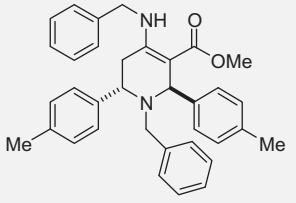
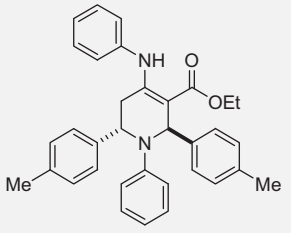
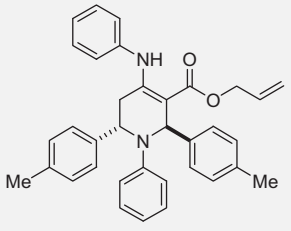
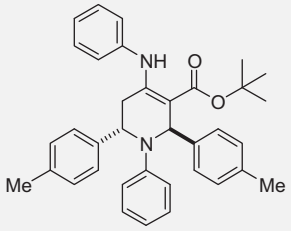
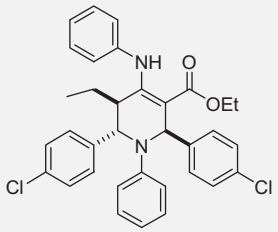
Entry	Product[a]	Time	Yield[b] (%)
6	 **1f**	30	60
7	 **1g**	36	30
8	 **1h**	26	28
9	 **1i**	12	75
10	 **1j**	9	72
11	 **1k**	8	63

Table 2 (*continued*)

Entry	Product[a]	Time	Yield[b] (%)
12	 **1l**	24	54
13	 **1m**	47	51
14	 **1n**	45	51
15	 **1o**	9	70
16	 **1p**	29	62
17	 **1q**	15	64

(*continued on next page*)

Table 2 (*continued*)

Entry	Product[a]	Time	Yield[b] (%)
18	 **1r**	30	31

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectrometry, and elemental analysis.
[b] Isolated yield.

The reaction was further examined for various 1,3-dicarbonyl compounds such as ethyl acetoacetate, allyl acetocetate, and *t*-butyl acetoacetate with 4-methylbenzaldehyde and aniline (Table 2, entries 15–18) in ethanol was catalyzed by 10 mol % TBATB. The desired piperidine derivative **1o–q** was obtained in good yields as shown in Table 2. This confirms that the alkoxy (–OR) moiety present in the ester functionality does not have any major role in determining the course of the reaction.

In addition, the reaction of ethyl butyrylacetate with 4-chlorobenzaldehyde and aniline was performed under identical reaction conditions to study the effect of an alkyl group at the β position of 1,3-dicarbonyl compound. The product of the reaction was a fully substituted piperidine **1r** in 31% yield. The low yield of product **1r** was due to the steric hindrance of alkyl group. We suggest that any enolizable alkyl group in the β position of 1,3-dicarbonyl compounds is sufficient for the formation of highly functionalized piperidines using MCRs (Scheme 2). The methods to prepare a large number of fully functionalized piperidine derivatives are under investigation.

All the products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra and by elemental analysis and well matched with the literature-reported compounds.[10,18,19] The structure as well as the relative stereochemistry of piperidine **1l** were confirmed by X-ray crystallographic analysis[24] (Figure 1).

The formation of piperidines through a Knoevenagel-type intermediate followed by [4+2] aza-Diels–Alder reaction has been proposed by various groups.[11,18,19] It was projected that β-keto ester reacts with amine to give enamine **5**, which reacts further with aldehyde to give a Knoevenagel-type product. This acts as a reactive diene and it undergoes aza-Diels–Alder reaction with imine **6** to give substituted piperidines. In support of this mechanism, the intermediate diene isolation was attempted with other reactive dienophiles such as dimethyl acetylenedicarboxylate and maleic anhydride, but in vain. Since no cycloaddition products were obtained, an alternate plausible mechanism for the product formation is proposed (see Scheme 3). TBATB reacts with ethanol which yields dry HBr[22e] and subsequently results in the formation of enamine **5** and imine **6** (Scheme 3). It is well known that enamine **5** would be a better nucleophile and the nucleophilic attack will take place preferentially on the activated imine **6** to give intermediate **7** through intermolecular Mannich-type reaction. The intermediate **7** reacts with aldehyde to give intermediate **8** by the elimination of a water molecule. There is a spontaneous tendency in the presence of HBr for tautomerization to give the intramolecular hydrogen bonded species either **9** or **10**. The tautomer **10** immediately undergoes intramolecular Mannich-type reaction to form intermediate **11**. The tautomer **9** would give a four-membered ring product **12**, which is unfavorable. The intermediate **11** tautomerizes to give the final piperidine derivative **1** due to conjugation with the ester group. In conclusion, the product formation is going through inter- and intramolecular Mannich-type reactions.

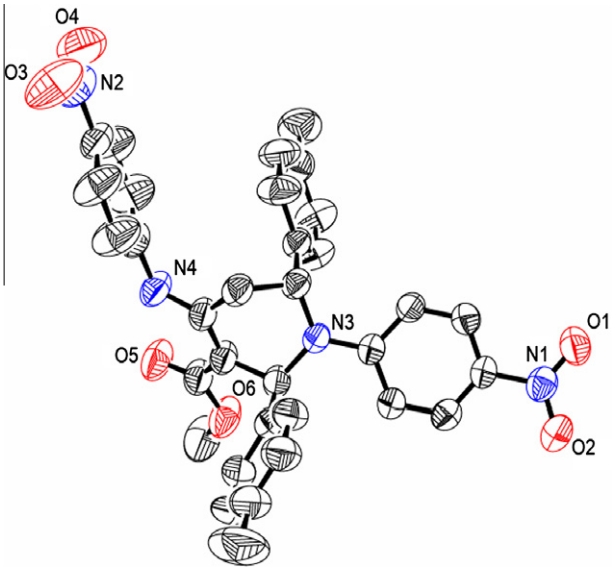
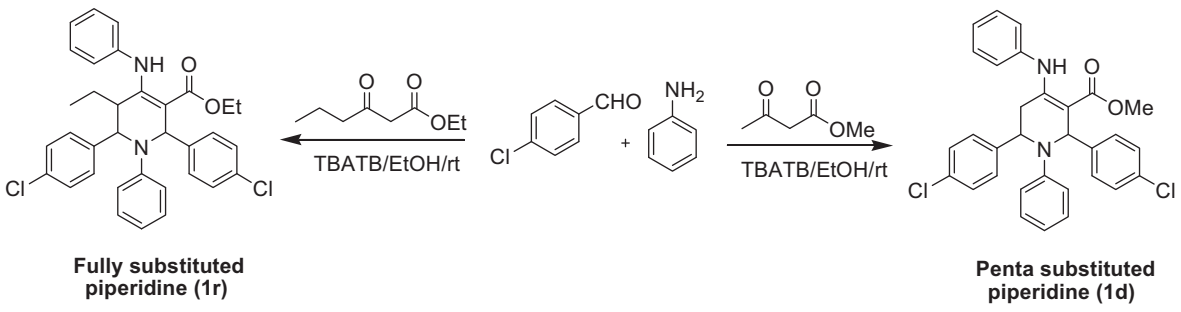
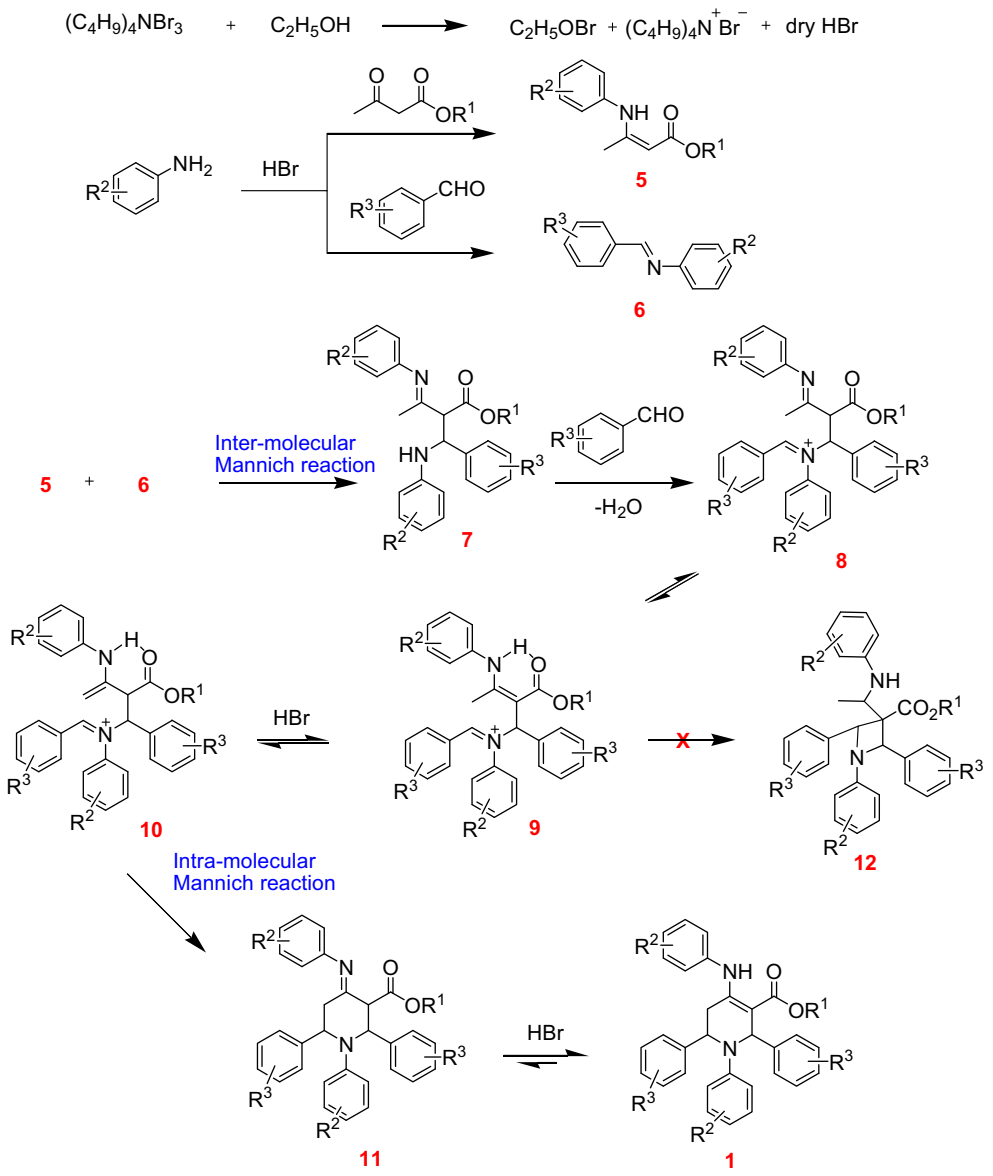


Figure 1. ORTEP diagram of **1l** (CCDC 775694).

In conclusion, we have found that the formation of highly functionalized piperidines is possible in the presence of TBATB as catalyst via one-pot five-component reaction at room temperature from readily available starting materials. Some advantages of this MCRs protocol are good yields, mild reaction conditions, environmentally benign catalyst, absence of tedious separation procedures, superior atom-economy, and low cost. In addition, mechanistic studies revealed another possibility for the formation of piperidines through double Mannich-type reactions.



Scheme 2. Criteria for the formation of piperidine derivatives.



Scheme 3. A plausible mechanism for the formation of highly substituted piperidine.

Acknowledgments

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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.2010.06.069.

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23. *General procedure for the synthesis of highly functionalized piperidines* **1**: To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of ethanol was added TBATB (0.1 mmol) and stirred at room temperature. After 20 min, aromatic aldehyde (2 mmol) was added to the reaction mixture and stirring was continued. After completion of the reaction, a thick precipitate was obtained. The solid product was filtered off and washed with ethanol. The pure product was characterized by conventional spectroscopic methods. *Spectral data for compound* (**1l**): yield 0.312 g, 54%. Yellow solid, mp 253–254 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.55 (s, 1H), 8.00 (d, 2H, J = 9.2 Hz), 7.97 (d, 2H, J = 9.6 Hz), 7.13 (s, 6H), 7.02 (d, 2H, J = 8.0 Hz), 6.54 (d, 2H, J = 9.6 Hz), 6.48 (s, 1H), 6.43 (d, 2H, J = 9.2 Hz), 5.27 (d, 1H, J = 3.2 Hz), 3.99 (s, 3H), 3.06 (dd, 1H, J = 15.2, 5.6 Hz), 2.94 (dd, 1H, J = 15.2, 2.4 Hz), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 153.3, 151.9, 144.1, 138.3, 138.1, 137.9, 137.5, 137.2, 130.0, 129.7, 126.2, 126.1, 125.9, 125.1, 123.1, 112.3, 102.0, 58.5, 55.8, 52.0, 33.8, 21.3, 21.2; IR ν_{max} (KBr): 1658, 1587 cm^{-1}. Anal. Calcd for $C_{33}H_{30}N_4O_6$ (578.62): C, 68.50; H, 5.23; N, 9.68. Found: C, 68.39; H, 5.14; N, 9.88; HRMS (ESI): calcd for $C_{33}H_{30}N_4O_6$ $[M+H]^+$: m/z = 579.2244; found: 579.2244. *Spectral data for compound* (**1r**): yield 0.177 g, 31%. White solid, mp 239–241 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.78 (s, 1H), 7.38–7.43 (m, 4H), 7.34 (d, 2H, J = 8.4 Hz, 2H), 7.12–7.25 (m, 10H), 6.78 (d, 2H, J = 8.0 Hz), 5.99 (s, 1H), 4.86 (d, 1H, J = 4.0 Hz), 4.33–4.25 (m, 1H), 4.15–4.07 (m, 1H), 3.04 (m, 1H), 1.22 (t, 3H, J = 7.2 Hz), 0.77–0.85 (m, 1H), 0.67–0.76 (m, 1H), 0.18 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2, 161.8, 151.2, 154.8, 139.9, 139.1, 132.7, 132.4, 129.6, 129.0, 128.9, 128.5, 128.4, 126.6, 126.3, 119.2, 116.2, 95.6, 63.8, 61.7, 60.0, 43.1, 22.2, 14.6, 12.1; IR ν_{max} (KBr): 1655, 1594 cm^{-1}. Anal Calcd for $C_{34}H_{32}N_2O_2Cl_2$ (571.54): C, 71.45; H, 5.64; N, 4.90. Found: C, 71.34; H, 5.53; N, 5.02.
24. Complete crystallographic data of **1l** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 775694. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).