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CuI/La(OTf)$_3$ catalyzed, one-pot synthesis of isomeric ellipticine derivatives in ionic liquid

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ABSTRACT

An efficient method for one-pot synthesis of isomeric ellipticine derivatives through CuI/La(OTf)$_3$ catalyzed sequential inter/intramolecular cyclization of substituted alkynes with imines followed by aromatization is reported in good to excellent yields.

1. Introduction

Ellipticine and its analogues have received a vast amount of attention because of their anticancer properties due to interaction with DNA. Its derivatives exhibit promising results in the treatment of osteolytic breast cancer metastases, kidney sarcoma, brain tumours and myeloblastic leukemia.[1] The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects and complete lack of haematological toxicity.[2] Recently, it was demonstrated that ellipticine covalently binds to DNA in vitro and in vivo after being enzymatically activated with cytochrome P450 or peroxidases.[3] Thus, the development of efficient and general methods for the synthesis of this class of compounds has received much attention.[4] Similarly, the structurally related aryl- and heteroaryl annulated carbazoles have also received considerable synthetic attention.[4,5]

Despite the great interest that has given rise to much synthetic work on ellipticine and its derivatives, very little attention has been focused on the synthesis of its isomers and fused with other biologically important molecules.[6] Although variety of reports available for synthesis, most of these methods required harsh reaction conditions and large number of steps involved for preparation of requisite starting materials. The synthesis of these compounds with different substituents at specific locations starting from easily available materials is far from being well established. Still, general and facile synthetic approaches are required to obtain analogues for pharmacological evaluation.

The numerous advantages of transition metals[7] and copper catalysts make them highly attractive for chemical synthesis from environmental and economic points of view. Copper(I) iodide is an inexpensive, nontoxic, insensitive catalyst to air in comparison to other transition metals, such as Pd, Pt, Ru and Au. Therefore, Cu catalyzed cyclization has been well accepted as a convenient tool for the synthesis of heterocycles.[8]

Herein, we report a straightforward CuI/La(OTf)$_3$ catalyzed tandem reaction for the efficient synthesis of isoellipticine derivatives in ionic liquid [Bmim][BF$_4$]. Ionic liquids are increasingly used as reaction media in organic synthesis as they offer a wide range of advantages over classical organic solvents. [Bmim][BF$_4$] has been exploited as an efficient Lewis acid promoter in various organic transformations.[9] To the best of our knowledge there is no report available for the preparation of isomeric ellipticine derivatives under copper catalysis.

2. Results and discussion

The reaction of imine derived from **1c** (2.0 mmol) and **2a** (2.0 mmol) with phenylacetylene (1.0 mmol) in the presence of CuI/La(OTf)$_3$ in [Bmim][BF$_4$] afforded **4c** along with the side product **4ca**. One equivalent of imine underwent the cyclization with phenylacetylene to dihydropyridocarbazole, which further aromatized to the product **4c** (another equivalent of imine acted as a hydrogen acceptor and underwent reductive amination, i.e., **4ca**).

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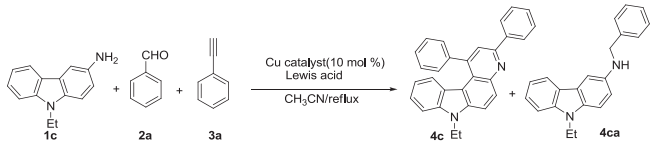
The experimental results are summarized in Table 1. Initially the reaction was performed in CH_3CN with BF_3–OEt_2 as a catalyst at reflux temperature (Table 1, entry 1). In the absence of CuI (10 mol %), only imine formation was observed. In the presence of 10 mol % of CuI the desired product **4c** was obtained with 40% yield after 24 h reflux in CH_3CN (entry 2).

Table 1
Synthesis of isomeric ellipticine derivatives



Entry	Catalyst	Time (h)	Yield[a] (%)
1	BF_3–OEt_2 (20 mol %)	24	—
2	CuI/BF_3–OEt_2 (20 mol %)	24	40
3	CuI/CF_3–COOH (20 mol %)	24	42
4	CuI/$InCl_3$ (20 mol %)	12	70
5	CuI/In(OTf)$_3$ (10 mol %)	12	75
6	CuI/Ag(OTf) (10 mol %)	12	52
7	CuI/Cu(OTf)$_2$ (10 mol %)	12	72
8	CuI/Sc(OTf)$_3$ (10 mol %)	8	83
9	CuI/Yb(OTf)$_3$ (10 mol %)	8	82
10	CuI/La(OTf)$_3$ (10 mol %)	8	85
11	CuBr/La(OTf)$_3$ (10 mol %)	10	62
12	CuCl/La(OTf)$_3$ (10 mol %)	12	51
13	CuI/La(OTf)$_3$ (10 mol %)/THF	8	72
14	CuI/La(OTf)$_3$ (10 mol %)/Toluene	8	75
15	CuI/La(OTf)$_3$ (10 mol %)/DMSO[b]	8	73
16	CuI/La(OTf)$_3$ (10 mol %)/[Bmim][Cl]	6	88
17	*CuI/La(OTf)$_3$ (10 mol %)/[Bmim][BF$_4$]*	*4*	*93*
18	CuI/La(OTf)$_3$ (10 mol %)/[Bmim][PF_6]	4	90
19	CuI(10 mol %)/[Bmim][BF_4]	6	60
20	CuI(30 mol %)/[Bmim][BF_4]	6	62

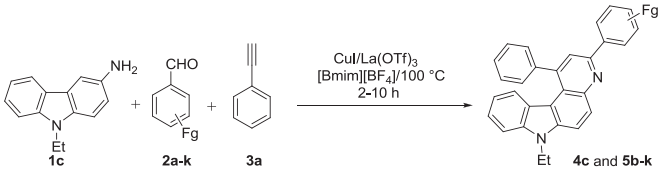
[a] Yield refers to column purified product. For the entries 1–12, acetonitrile was used as a solvent. For the entries 13 and 14 reflux temperature of the corresponding solvent was maintained.
[b] Temperature was maintained at 100 °C and above the temperature, yield was low. For the entries 16–20, 1.0 mL of ionic liquid was used. In all entries, catalyst mol % was calculated relative to phenylacetylene.

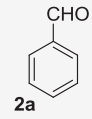
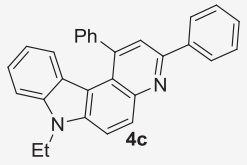
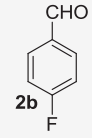
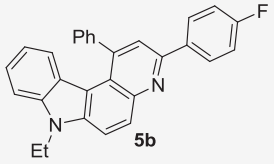
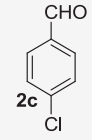
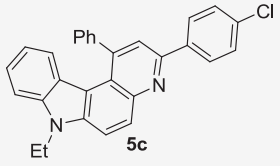
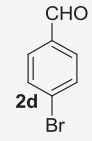
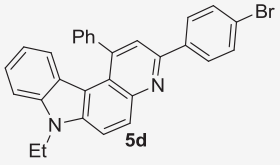
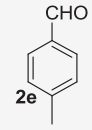
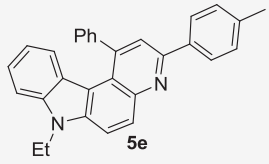
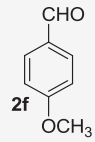
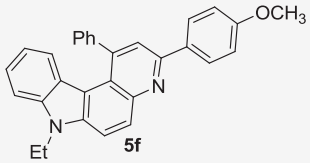
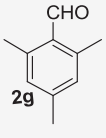
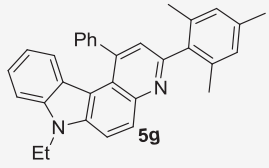
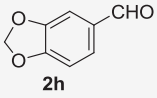
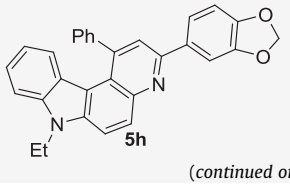
Therefore CuI is necessary to activate the triple bond. A series of different Lewis and Brønsted acids were investigated to improve the reaction yield. Interestingly, when $InCl_3$ was used as a Lewis acid, yield was randomly increased to 70% in 12 h (entry 4). The use of Cu(OTf)$_2$ and In(OTf)$_3$ increased the reaction yield further (entry 5 and 7) and transition metal triflates, such as Scandium triflate, Ytterbium triflate and Lanthanum triflate also furnished the reaction in good yield (entry 8–10). All the three triflates were similar in reactivity in terms of reaction yield.

However we preferred La(OTf)$_3$ for further optimization since it is cheaper and also stable to moisture. We have examined the catalytic activity of CuI, CuBr and CuCl (entry 11 and 12) and among them CuI was found to be efficient. Several solvents like, THF, DMSO, toluene and CH_3CN were screened, of which CH_3CN found to be better (entry 13–15). Interestingly, when acetonitrile was replaced by [Bmim][Cl], the yield increased to 88% (entry 16). The yield further improved by replacing the counter ion [Cl^-] with [BF_4^-] (entry 17). We also tried the reaction without using La(OTf)$_3$ and it gave only 60% yield (entry 19). This indicates that the reaction can proceed without using La(OTf)$_3$, however CuI is essential. Finally the optimal reaction conditions for this reaction is as follows: a mixture of CuI (10 mol %) and La(OTf)$_3$ (10 mol %) as catalysts in [Bmim][BF_4] at 100 °C for 4 h (entry 17). The crystal structures of both **4c** and **4ca** were confirmed by single crystal X-ray analysis.[10]

Having optimized the reaction conditions, the generality of the reaction with CuI/La(OTf)$_3$ in [Bmim][BF_4] with different substituted aldehydes was examined (Table 2). Substituents having

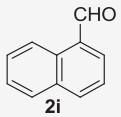
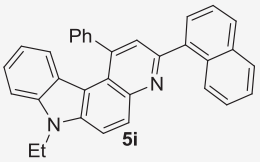
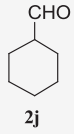
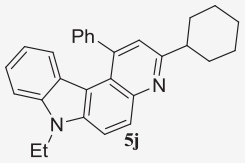
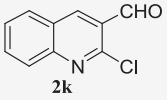
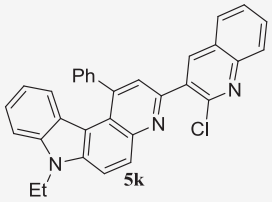
Table 2
Synthesis of isomeric ellipticine derivatives with different substituted aldehydes (**2a**–**k**)



Entry	Aldehydes	Products	Yield (%)
1			93
2			86
3			85
4			82
5			95
6			91
7			96
8			82

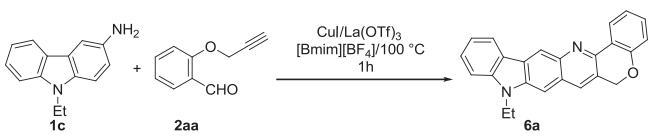
(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehydes	Products	Yield (%)
9	 2i	 5i	80
10	 2j	 5j	92
11	 2k	 5k	65

an electron poor (**5b**–**d**) or electron rich (**5e**–**g**) or heteroaromatic group (**5k**) gave the desired products in good to excellent yields. Even in the case of strong electron deficient 4-fluorobenzaldehyde (**2b**) also gave **5b** with 86% yield (Table 2, entry 2). Electron rich aldehyde, such as 2,4,6-trimethyl benzaldehyde (**2g**) produced highest yield (96%) in this intermolecular cyclization (entry 7). Piperonal (**2h**), which has the powerful aroma therapeutic quality, was also participated in this reaction, gave 82% yield (entry 8). When we used 1-napthaldehyde (**2i**) in this reaction furnished 80% yield (entry 9). Saturated aldehyde, cyclohexanal (**2j**) produced 92% yield within 3 h (entry 10). But in the case of heteroaromatic aldehyde, such as 2-chloro-quinoline-3-carboxyaldehyde (**2k**) furnished only 65% yield (entry 11). Substrates bearing functional groups, such as F, Cl, Br and OCH_3 were tolerated. This made possible the further derivatization of the products. Product **5g** was also confirmed by single crystal X-ray analysis.[10]

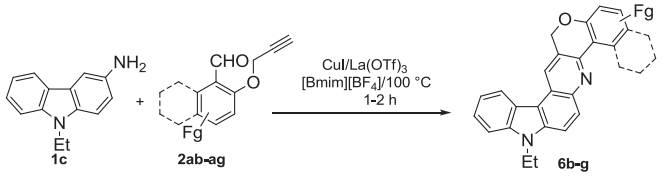
An intramolecular version of this reaction could provide a valuable route to isoellipticine fused with dihydro chromene derivatives. We have carried out the reaction of *O*-propargylated salicylaldehyde (**2aa**) with **1c** in the presence of CuI/La(OTf)$_3$ in ionic liquid (Scheme 1). Surprisingly the reaction was completed within one hour in 95% yield. In ^{1}H NMR spectrum of **6a**, unexpected two singlets at δ 7.93 and 8.87 was observed and after careful analysis, we identified the cyclization occurred through second position of the carbazole ring unlike in the intermolecular case, where it happened through fourth position of the carbazole ring. The structure was also further proved by single crystal X-ray analysis.[10]

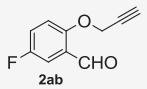
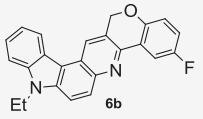
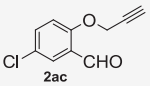
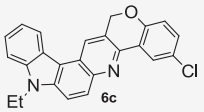
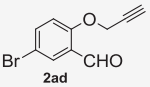
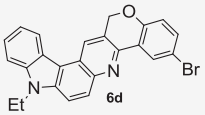
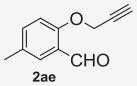
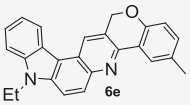
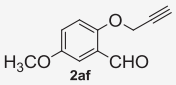
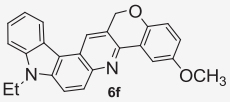
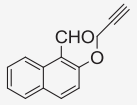
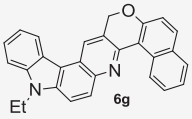


Scheme 1. Synthesis of isoellipticine derivative fused with chromene.

With substituted *O*-propargyl aldehydes (**2ab**–**ag**), reaction proceeded smoothly under the optimized reaction conditions and the results are summarized in Table 3. In all the cases, the corresponding intramolecular cyclization products (**6b**–**g**) were obtained in excellent yields (80–96%) and the cyclization occurs through the fourth position of the carbazole ring. Bromo

Table 3
Reactions of substituted aldehydes (**2ab**–**ag**) in intramolecular cyclization



Entry	Aldehydes	Products	Yield (%)
1	 2ab	 6b	85
2	 2ac	 6c	84
3	 2ad	 6d	80
4	 2ae	 6e	96
5	 2af	 6f	93
6	 2ag	 6g	84

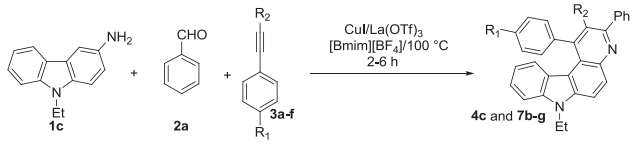
substituted aldehyde (**2ad**) gave 80% yield (Table 3, entry 3), whereas methyl substituted aldehyde (**2ae**) produced 96% yield (entry 4). The reaction of *O*-propargylated naphthaldehyde (**2ag**) with 9-ethyl-3-aminocarbazole in the presence of Cu/La(OTf)$_3$ in ionic liquid afforded **6g** with 84% yield (entry 6). The products **6b** and **6g** were also confirmed by single crystal X-ray analysis.[10]

Having established the suitable reaction conditions, we explored the scope and generality of the methodology with substituted alkynes and the results are summarized in Table 4. Yield of 75% was obtained with diphenylacetylene (**7b**). Substitution on the other side of the alkyne carbon with electron donating groups (**7c**–**e**) proceeds with excellent yields. Even with trimethylsilyl acetylene (2.0 equiv), the reaction proceeded smoothly with 72% yield (**7g**). As silyl end groups on the alkynes are lost upon the work-up, access to the unfunctionalized products were obtained easily.[11] Crystal structures of **7b**, **7d**, **7e** and **7f** were achieved in order to confirm their structures.[10]

The copper catalyzed cyclization of substituted aminocarbazoles (**1a**–**i**) under the optimized conditions were carried out and the results are summarized in Table 5. In most cases, the corresponding products **4a**–**i** were obtained in excellent yields. However **1i** has the slower rate of the reaction and the corresponding product **4i** was obtained in only 72% yield. This may be due to the steric hindrance caused by two methyl substituents (Table 5, **4i**).

We have also examined the reaction of 3,6-diaminocarbazole with benzaldehyde, phenylacetylene and **2aa** under the same reaction conditions (Scheme 2). The intermolecular reaction

Table 4
Synthesis of isomeric ellipticine derivatives from different substituted alkynes (**3a–g**)



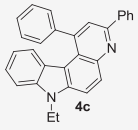
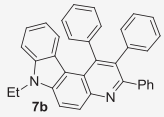
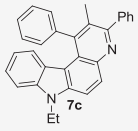
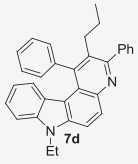
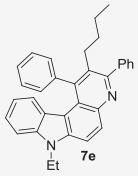
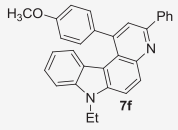
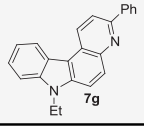
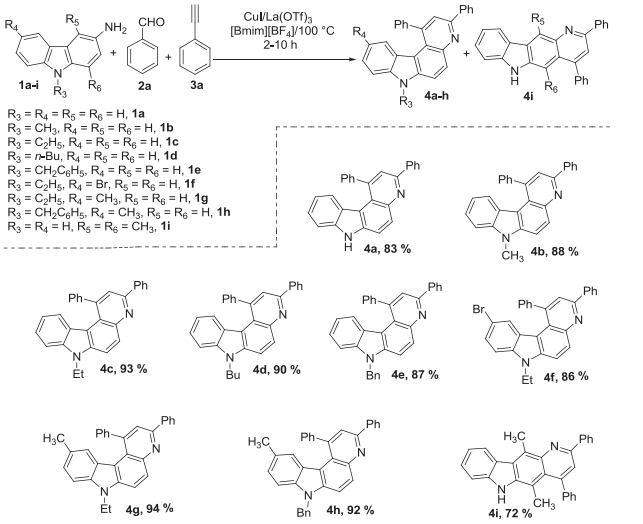
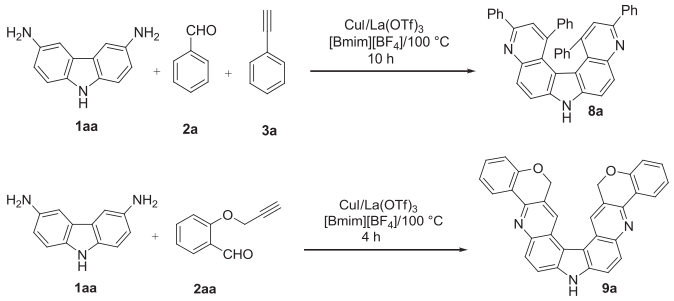
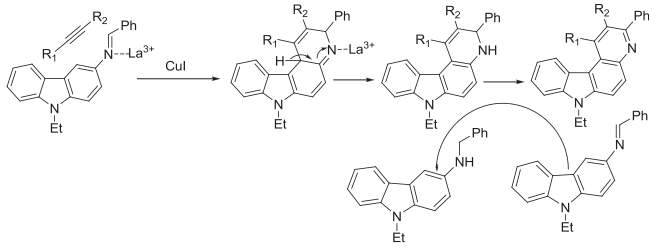
Entry	R_1	R_2	Products	Yield (%)
1	H	H		93
2	H	Ph		75
3	H	CH_3		90
4	H	n-C_3H_7		91
5	H	n-C_4H_9		94
6	OCH_3			95
7				72

Table 5
Synthesis of isomeric ellipticine derivatives with substituted aminocarbazoles (**1a–i**)





Scheme 2. Synthesis of bis products.



Scheme 3. Expected mechanism of the reaction.

proceeded well and furnished the corresponding product in 62% yield. Product **8a** was confirmed by single crystal analysis.[10] The intramolecular pathway of diaminocarbazole gave 76% yield and there is no monocyclized product was observed.

Though the mechanism of copper catalyzed cyclization is well known,[12] scanty reports are available for the use of alkyne as a dienophile.[13] When a terminal alkyne was used, the copper catalyzed reaction can be proceeded through a reported mechanism[14] but in case of disubstituted alkynes, the reported mechanism may not be suitable since there is no terminal hydrogen. According to HSAB theory hard Lewis acid, La^{3+} coordinates the hard Lewis base site of nitrogen lone pair and increases the electron deficiency of the imine, cyclization followed by aromatization (Scheme 3).

In summary, we described for the first time the synthesis of isomeric ellipticine derivatives with inter and intramolecular cyclization catalyzed by CuI/La(OTf)$_3$. Further studies in this area including the mechanistic study are being conducted in our laboratory.

3. Experimental section

3.1. General procedure

In a round bottom flask equipped with a magnetic stirring bar, 2.0 mmol of aminocarbazole, 2.0 mmol of aldehyde, 1.0 mmol of alkyne in 1.0 mL of [Bmim][BF$_4$] ionic liquid, was added 10 mol % of La(OTf)$_3$ and 10 mol % of CuI. Reaction mixture was stirred at 100 °C for appropriate time. After completion of the reaction, as indicated by the TLC, water (20 mL) was added to the crude reaction mass. Then aqueous layer was extracted with dichloromethane (3×20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under the reduced pressure.

Product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate) afforded the corresponding products.

*3.1.1. 1,3-Diphenyl-7H-pyrido[2,3-c]carbazole (**4a**).* Mp 222 °C; R_f (30% EtOAc/hexane): 0.40; IR (KBr): 3395, 3057, 1556, 1412, 796, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.68 (1H, s); 8.28 (3H, d, J=7.8 Hz); 7.95 (1H, s); 7.81 (1H, d, J=8.0 Hz); 7.45–7.61 (8H, m); 7.38 (1H, d, J=7.2 Hz); 7.22 (1H, t, J=7.8 Hz); 6.70 (1H, t, J=7.6 Hz); 6.02 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 153.3, 147.0, 146.8, 142.8, 139.7, 138.7, 138.4, 129.7, 129.2, 129.0, 128.9, 128.3, 127.4, 124.9, 124.2, 123.9, 122.5, 121.3, 121.0, 119.2, 116.5, 115.0, 110.3 (aromatic C); m/z=371 ($M+H^+$), positive mode. Anal. Calcd for $C_{27}H_{18}N_2$: C, 87.54; H, 4.90; N, 7.56%. Found: C, 87.45; H, 4.88; N, 7.61%.

*3.1.2. 9-Ethyl-6,9-dihydrochromeno[3′,4′:5,6]pyrido[3,2-b]carbazole (**6a**).* Mp 202 °C; R_f (10% EtOAc/hexane)=0.59; IR (KBr): 3045, 1602, 1224, 819, 738, 480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ: 8.87 (1H, s); 8.58 (1H, d, J=8.0 Hz); 8.29 (1H, d, J=7.2 Hz); 7.93 (1H, s); 7.53–7.61 (2H, m); 7.33–7.40 (2H, m); 7.30 (1H, t, J=7.8 Hz); 7.23 (1H, t, J=7.6 Hz); 7.07 (1H, d, J=7.8 Hz); 5.40 (2H, s, OCH2); 4.37 (2H, q, J=8.0 Hz, N–CH_2CH_3); 1.49 (3H, t, J=7.8 Hz, N–CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 157.2, 146.1, 142.8, 142.7, 139.7, 131.2, 129.9, 128.2, 127.8, 126.5, 125.2, 124.4, 123.8, 122.7, 122.5, 121.6, 120.0, 119.2, 117.3, 108.3, 102.3 (aromatic C), 68.8, 37.7, 13.3 (aliphatic C); m/z=351 ($M+H^+$), positive mode. Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99%. Found: C, 82.35; H, 5.13; N, 8.11%.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.095.

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