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Zinc Chloride Catalyzed Amino Claisen Rearrangement of 1-*N*-Allylindolines: An Expedient Protocol for the Synthesis of Functionalized 7-Allylindolines

Abstract: 7-Allylindolines are valuable synthons for designing biologically active molecular libraries. Lewis acid catalyzed amino-Claisen rearrangement provides a one pot synthetic entry to these heteroarenes. In this context, Zinc chloride ($ZnCl_2$)–N,N-dimethylformamide system efficiently catalyzed amino-Claisen rearrangements of 1-*N*-allylindolines to 7-allylindolines. The rearrangement is influenced by stereoelectronic effects of substituents present in 1-*N*-allylindolines. The substrates containing electron donating functionalities underwent rearrangement at lower temperature than substrates with electron withdrawing functional groups. The regioselectivity of the process is governed by the substitution pattern on allyl moiety in 1-*N*-allylindoline as well as $ZnCl_2$ catalyst loading in the reaction system.

Keywords: Amino-Claisen rearrangement, 1-*N*-allylindoline, 7-allylindolines, Lewis acid catalysis.

Introduction

The 7-allylindoline nucleus is prevalent as structural motif for designing indole scaffolds of pharmaceutical importance [1-8]. The Carbon- Carbon bond forming reactions have proven to be the most powerful tool in designing such types of molecular libraries for organic, combinatorial and medicinal chemistry [9-10]. The Claisen rearrangements of vinyl and aryl allyl ether are exploited as an expeditious approach to Carbon-Carbon bond formation in organic syntheses [11-13]. In contrast, the amino-Claisen rearrangement, the nitrogen analogue of Claisen rearrangement has attracted little attention due to several limitations including slow rates, the need of higher temperature and low yields due to simultaneous allylic cleavage or cyclization leading to C-N bond formation. Therefore, there is the great dearth of examples exists in the literature for amino- Claisen rearrangements in aromatic and heteroaromatic series.

The well documented and classical approach of thermal and uncatalyzed amino Claisen rearrangement of *N*-allylindolines is suffered from severe drawbacks including thermal decomposition of the substrate and side reactions owing to the requirement of high temperature of 250-280ºC, led to poor yields of 7-allylindolines [14-15]. The limitation associated with the thermal amino-Claisen rearrangement stimulated further interest of synthetic organic chemist for developing milder methods. The strategy of Lewis acid catalysis facilitates the amino Claisen rearrangement of indolines *via* a charge accelerated process. In this series, the amino- Claisen rearrangement of *N*-allylindolines has already been reported in different catalytic systems *viz* in $ZnCl_2$-xylene [16], $BF_3.OEt_2$- sulfolane [17], $BF_3.OEt_2$- sulfolane for the synthesis of novel indole analogue of mycophenolic acid as potential antineoplastic agents [18] and in TFA – CH_2Cl_2 for the total synthesis of (+)- Okaramine J [19]. Although, these methods are advantageous over uncatalyzed rearrangements for accessing 7-allylindolines, still, some of these methods could not overcome the requirement of higher temperature, longer reaction times, costly catalyst loading in reaction systems and poor yields of targeted molecules. These limitations led us to explore the generality of this important strategic tool for C-C bond formation for targeted molecules from 1-H-*N*-allylindolines to 7-allylindolines. As a part of our ongoing interest, in Lewis acid catalyzed amino Claisen rearrangement [20-22], we found that $ZnCl_2$ is an efficient catalyst for influencing the reaction. Therefore, $ZnCl_2$–*N,N*-dimethylformamide catalytic system was employed for effecting amino-Claisen rearrangement of

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N-allylindolines in a view to explore the versatility of the substrates containing electron withdrawing or electron donating functionalities in aryl ring with different patterns of allylic functionality to furnish 7-allylindoline derivatives. The development of reaction presented herein, takes the advantage of an efficient, one pot and regioselective synthetic entry to functionalized 7-allylindolines under very mild reaction conditions. The results emanated from the present study are described herein.

Result and discussion

A mixture of 1-H-*N*-allylindoline **1a-g** and ZnCl₂ (3.0 equiv.) in *N,N*-dimethylformamide as a solvent was heated at a temperature range of 120-150⁰ C under argon for two hours to furnish **2 a-g** (Scheme 1) in moderate to good yields. The use of this catalytic system reduced the formation of by products and other tarry products arising due to side reactions as compared to an uncatalyzed thermal process. The result is attributed to the use of polar and aprotic solvent DMF in which ZnCl₂ catalyst showed enhanced solubility than any other nonpolar solvent. All reactions produced only a [3,3]-sigmatropic product but under similar conditions the amino Claisen rearrangement of 5-methyl-1-*N*-(3-methyl-2-butenyl)indoline (**1h**) proceeded slowly to form a mixture of 5-methyl-7-(3-methyl-2-butenyl) indoline (**2h**) and 1,2,5,6-tetrahydro-4,4,8-trimethyl-4H-pyrrolo[3,2,1-ij] quinoline (**3**). The formation of **2h** is presumed to be formed from **1h,** apparently by the cleavage followed by electrophilic attack of the allylic moiety on the adjacent position of heteroaryl ring without inversion of the allyl group. The failure of **1h** to undergo 3,3-sigmatropic process could be assigned to the steric hindrance on the allyl moiety while passing through the concerted reaction to furnish **2h**. The regioisomer **3** probably arose due to the acid catalyzed cyclization of **2h** *via* ionic C-C bond formation (Scheme 1) [16].

However, the formation of **3** was effectively inhibited by increasing the amount of ZnCl₂ (4.0 equiv.) and shortening the reaction time (1.0 h) thereby providing the regioselectivity by altering the reaction centre on the substrate to give **2h** in 77% yield as the sole product. In contrast, **1f,** cleanly underwent the rearrangement at lowest temperature to furnish **2f** in good yield (86 %). This result can be attributed to the higher reactivity of the allyl group owing to the steric hindrance in the Lewis acid mediated "charge induced" 3,3-sigmatropic rearrangement process. With ongoing similar problems, **1e** reacted faster than **1g** in a *3,3*-sigmatropic process to give **2e** (83%) and **2g** (77%) respectively, again giving the evidence for inherited

regioselectivity within the reaction process. All products are well characterized by elemental analysis, IR, ¹H NMR, ¹³C NMR and Mass spectral data.

Conclusion

This rearrangement tolerated electron rich as well as electron deficient substituents on the arene ring of heteroaromatic system without involving the formation of any cyclized product thereby providing excellent regioselectivity to the process. 1-H-*N*-allylindoline having electron donating groups underwent rearrangement at lower temperature as compared to electron deficient ones in moderate to good yields. The reaction also tolerated acid and base sensitive functionalities on the aryl ring of indoline system under mild reaction conditions. These results are consistent to the proposed mechanism of Lewis acid catalyzed amino Claisen rearrangement via charge accelerated process [20]. Hence, this C-N activation protocol for effecting amino-Claisen rearrangement of 1-H-*N*-allylindolines provided a one pot, regioselective and an efficient synthetic entry to difficultly accessible 7-allylindolines and should find applicability for creating more sophisticated chemical transformations.

Experimental Details

1-H-*N*-allylindolines **1a-h** were prepared by using the typical procedure for N-allylation of corresponding 1-H-indolines [23]. 1-H-*N*-allylindolines **1a-h** furnished corresponding 7-allylindolines **2a-h** which were characterized on the basis of elemental analysis, IR, ¹H, ¹³CNMR and MS data as given below. IR spetra were recorded on Pye Unicam Model SP3-300 infracord in neat. ¹H and ¹³C NMR spectra were recorded on a FT NMR Brucker AM 300L Spectrometer using CDCl₃ as solvent and TMS as an internal reference at 300 MHz. and 100 MHz respectively. Mass spectra were recorded on a Jeol D-300 (EI) Spectrometer using CDCl₃ as solvent.

General procedure for the preparation of 7-allylindolines

A mixture of 1-H-*N*-allylindolines (**1a-h**) (2.57 g, 14.9 mmol), ZnCl₂ (6.10 g 44.7 mmol, 3.0 equiv.) and DMF (25 mL) were heated under argon at the temperature 120-150⁰C for 2hr. The mixture was cooled and poured into ice water (50 mL) and 10% HCl solution was added dropwise to make the solution acidic (pH 1). The solution was washed with CHCl₃ (2 x 40 mL), the aqueous layer was
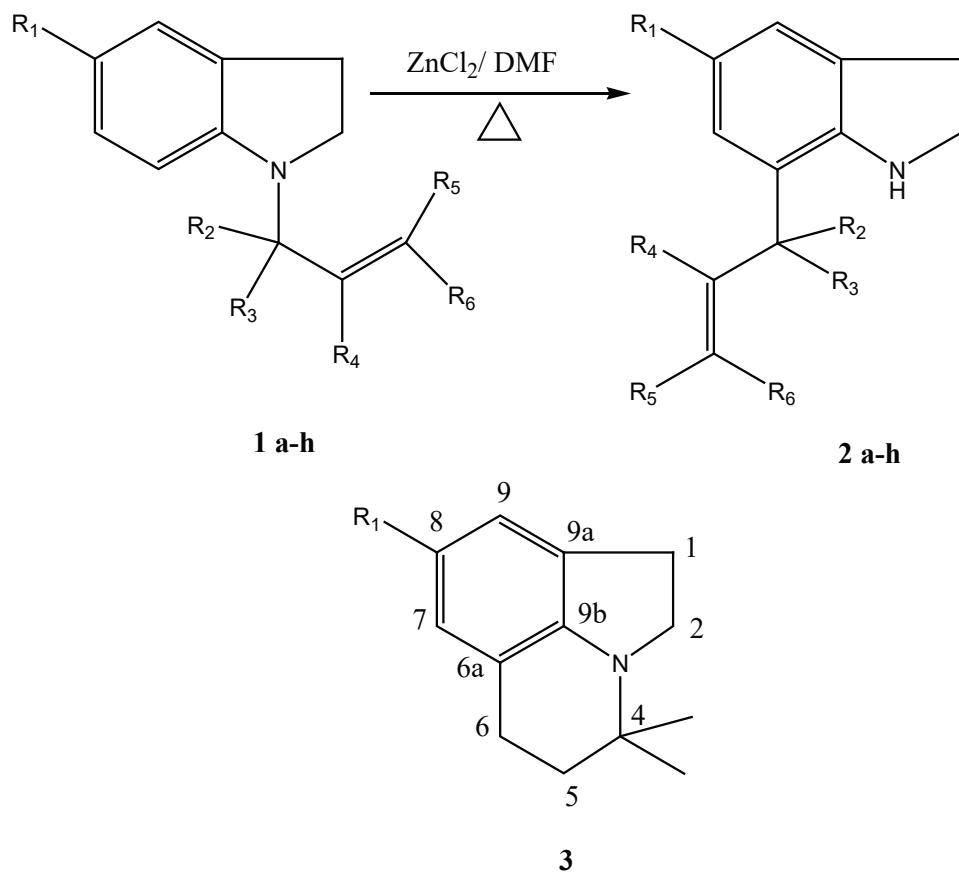
Scheme 1 Substrate Scope in Amino Claisen rearrangement.

1-*N*-allylindolines (1 a-h)

1a	R1= CH₃, R2, R3, R4, R5, R6 =H
1b	R1= OCH₃, R2, R3, R4, R5, R6= H
1c	R1= NO₂, R2, R3, R4, R5, R6 =H
1d	R1=COOEt, R2, R3, R4,R5, R6 = H
1e	R1=CH₃, R2, R3, R5, R6=H, R4=CH₃
1f	R1=CH₃,R2 =CH₃, R3, R4, R5, R6= H
1g	R1=CH₃, R2,R3,R4, R5= H,R6 = CH₃
1h	R1=CH₃,R2 , R3,R4= H, R5,R6 = CH₃

7-Allylindolines (2 a-h)

2a	R1= CH₃, R2, R3, R4, R5, R6 = H
2b	R1=OCH₃, R2, R3, R4, R5, R6 = H
2c	R1= NO₂, R2, R3, R4, R5, R6 = H
2d	R1=COOEt, R2, R3, R4, R5,R6 =H
2e	R1=CH₃, R2, R3, R5, R6=H, R4=CH₃
2f	R₁=CH₃,R2 ,R3, R4, R6= H, R5 = CH₃
2g	R1=CH₃, R2 = CH₃,R3, R4, R5,R6 = H
2h	R1=CH₃, R2 , R3, R4= H, R5, R6 = CH₃

made alkaline with addition of 10 % NaOH solution and extracted with ether (3 x 50 mL). The combined ether extracts were washed with water (60 mL), dried over $MgSO_4$ and concentrated. The residues were purified by column chromatography on silica gel (hexane : ethyl acetate; 10:1) to afford 7-allylindolines (**2a-h**).

Analytical data of the compounds:

7-Allyl-5-methylindoline (2a): The compound was obtained from **1a** at the temperature 120 -130⁰C in 78 % yield as pale yellow oil; IR (neat) : 3380, 2836, 1615, 1485, 1450,

1250, 995, 910 cm⁻¹; ¹H NMR: δ 3.15 (t, J = 8.2 Hz, 2H, C₃-H), 3.41 (dd, J = 6.1 Hz, J = 1.2 Hz, 2H, -CH₂-C=C), 3.66- 3.91(m 3H, NH and C₂ H), 5.26-5.30 (m, 2H, -C=CH₂), 6.04- 6.17 (m, 1H, -C-CH=C), 6.60-7.20 (m, 2H, Ar-H), 2.60 (s, 3H, Ar-CH₃); ¹³C NMR: δ 146.6 (C8), 135.6 (-CH=CH₂), 127.3 (C6), 126.3 (C9), 126.5 (C4), 125.6 (C5), 121.9 (C7), 116.1 (-C=CH₂), 46.5 (C2), 38.3 (Ar-CH₂), 30.4 (C3), 23.6 (Ar-CH₃); MS: m/z 173 (M⁺); Anal. Calcd for C₁₂H₁₅N: C, 83.23; H, 8.67; N, 8.09. Found: C, 83.26; H, 8.98; N, 8.06.

7-Allyl-5-methoxyindoline (2b): The compound was obtained from **1b** at 130 -135⁰C in 62 % yield as brown oil; IR (neat) : 3382, 2936, 2832, 1615, 1485, 1460, 1246, 990,

900 cm^{-1}; ^{1}H NMR : δ 2.99 (t, *J* = 8.4 Hz, 2H, C$_3$-H), 3.33 (dd, *J* = 6.3 Hz, *J* = 1.2 Hz, 2H, -CH$_2$-C=C), 3.57- 3.78 (m 3H, NH and C$_2$ H), 5.01-5.09 (m, 2H, -C=CH$_2$), 5.97- 6.27 (m, 1H, -C-CH=C), 6.70-7.19 (m, 2H, Ar-H), 3.78 (s, 3H, Ar-OCH$_3$); ^{13}C NMR : δ 147.8 (C5), 141.6 (C8), 135.6 (CH=CH$_2$), 127.7 (C9), 122.1 (C7), 116.3 (C=CH$_2$), 115.4 (C6), 108.9 (C4), 47.2 (C2), 38.8 (Ar-CH$_2$), 31.2 (C3), 29.6 (Ar-CH$_3$); MS : *m/z* 189 (M[+]); Anal. Calcd for C$_{12}$H$_{15}$NO: C, 76.19; H, 7.94; N, 7.40. Found: C, 76.08; H, 7.98; N, 7.36.

7-Allyl-5-nitroindoline (2c): The compound was obtained from **1c** at 140 -150⁰C in 80 % yield as yellow oil; IR (neat) : 3432, 3386, 2960, 2860, 1632, 1594, 1520, 1260, 1456, 1441, 1350, 1309, 1275, 995 910 cm^{-1}; ^{1}H NMR : δ 3.11 (t, *J* = 8.2-8.4 Hz, 2H, C$_3$-H), 3.42 (dd, *J* = 6.0 Hz, *J* =1.2 Hz, 2H, -CH$_2$-C=C), 3.66- 4.01 (m 3H, NH and C$_2$ H), 5.07-5.15 (m, 2H, -C=CH$_2$), 5.91- 6.02 (m, 1H, -C-CH=C), 7.05-7.28 (m, 2H, Ar-H); ^{13}C NMR : δ 155.3 (C8), 135.6 (C5), 135.4 (-CH=CH$_2$), 128.6 (C9), 122.6 (C7), 121.2 (C6), 119.6 (C4), 116.9 (-C=CH$_2$), 46.1 (C2), 37.8 (Ar-CH$_2$), 29.3 (C3); MS : *m/z* 204 (M[+]); Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_2$: C, 64.71; H, 5.88; N, 13.73. Found: C, 64.74; H, 5.80; N, 13.76.

7-Allyl-5-carbethoxyindoline (2d): The compound was obtained from **1d** at 135 -145⁰C in 79 % yield as pale yellow oil; IR (neat) : 3486, 3372, 2958, 1690, 1620, 1586, 1570, 1456, 1432, 1310, 1280, 1248, 1200, 1085, 1070, 985, 900 cm^{-1}; ^{1}H NMR : δ 3.18 (t, *J* = 8.1 Hz, 2H, C$_3$-H), 3.42 (d, *J* = 1.0 Hz, 2H, -CH$_2$-C=C), 3.65- 3.86 (m 3H, NH and C$_2$ H), 5.08-5.10 (m, 2H, -C=CH$_2$), 6.05- 6.75 (m, 1H, -C-CH=C), 6.20-6.89 (m, 2H, Ar-H), 2.56 (q, *J* = 8.1 Hz, 2H, COOCH$_2$-C), 1.14 (t, *J* =7.8 Hz, 3H, COO.C-CH$_3$); ^{13}C NMR : δ 260 (Ar-COOCH$_2$-C), 166 (Ar-COOC-C), 154.3(C8), 135.8 (-CH=CH$_2$), 127.3 (C6), 126.6 (C9), 125.7 (C4), 121.4 (C7), 117.5 (C5), 116.3 (-C=CH$_2$), 46.8 (C2), 38.9 (Ar-CH$_2$), 29.9 (C3); MS : *m/z* 204 (M[+]); Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_2$: C, 64.71; H, 5.88; N, 13.73. Found: C, 64.74; H, 5.80; N, 13.76.

5-Methyl-7-(2-methylallyl)indoline (2e): The compound was obtained from **1e** at 130 -140⁰C in 83 % yield as pale yellow oil; IR (neat) : 3375, 2840, 1640, 1485, 1450, 1250, 910 cm^{-1}; ^{1}H NMR : δ 3.17 (t, *J* = 8.1Hz, 2H, C$_3$-H), 3.46 (dd, *J*=6.8 Hz, *J*=1.4 Hz, 2H, -CH$_2$-C=C), 3.60- 3.80 (m, 3H, NH and C$_2$ H), 5.26-5.30 (dd, *J* = 18 Hz, *J* = 2 Hz, 2H, -C=CH$_2$), 1.86 (s, 3H, -C-C(CH$_3$)=C), 6.60-7.20 (m, 2H, Ar-H), 2.58 (s, 3H, Ar-CH$_3$); ^{13}C NMR : 146.8 (C8), 142.8 (CH=CH$_2$), 127.7 (C6), 126.6 (C9), 126.4 (C4), 125.3 (C5), 121.9 (C7), 111.3 (-C=CH$_2$), 46.8 (C2), 38.9 (Ar-CH$_2$), 30.8 (C3), 24.9 (Ar-CH$_3$), 22.1(CH$_3$-CH=C); MS : *m/z* 187 (M[+]); Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_2$: C, 83.32; H, 90.91; N, 7.49. Found: C, 83.39; H, 90.87; N, 7.51.

5-Methyl-7-(*trans*-2-butenyl)indoline (2f): The compound was obtained from **1f** at 120 -130⁰C in 86 % yield

as pale yellow oil; IR (neat) : 3386, 3050, 2945, 2847, 1600, 1460, 1255, 970 cm^{-1}; ^{1}H NMR : δ : 3.18 (t, *J* = 8.2-8.4 Hz, 2H, C$_3$-H), 3.48 (dd, *J* = 6.6 Hz, *J* =1.2 Hz, 2H, -CH$_2$-C=C), 3.66-3.80 (m, 3H, NH and C$_2$ H), 6.02- 6.19 (m, 1H, -C-CH=C), 5.10-5.30 (m, 1H, -C=CH-C), 1.64 (d, *J* =18 Hz, 3H, -C=C-CH$_3$), 6.80-7.19 (m, 2H, Ar-H), 2.50 (s, 3H, Ar-CH$_3$); ^{13}C NMR : δ 146.6 (C8), 127.6 (C6), 126.5 (CH=CH$_2$), 126.4 (C9), 126.1 (C4), 125.3 (-C=CH$_2$), 125.2 (C5), 121.9 (C7), 46.9(C2), 38.8 (Ar-CH$_2$), 30.9 (C3), 24.2(Ar-CH$_3$), 18.3 (=CH.CH$_3$); MS : *m/z* 187 (M[+]); Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_2$: C, 83.42; H, 9.09; N, 7.49. Found: C, 83.40; H, 9.12; N, 7.51.

5-Methyl-7-(1-methylallyl)indoline (2g): The compound was obtained from **1g** at 130 -140⁰C in 77 % yield as pale yellow oil; IR (neat) : 3380, 2840, 1640, 1480, 1440, 1250, 990, 910 cm^{-1}; ^{1}H NMR : δ 3.16 (t, *J* = 8.2 Hz, C$_3$-H), 2.98 (m, 1H, -CH-C=C), 1.67 (dd, *J* = 6.5 Hz, *J* =1.4 Hz 3H, -C(CH$_3$)-C=C), 3.65- 3.86 (m 3H, NH and C$_2$ H), 5.12-5.30 (m, 2H, -C=CH$_2$), 6.05- 6.15 (m, 1H, -C-CH=C), 6.60-7.00 (m, 2H, Ar-H), 2.60 (s, 3H, Ar-CH$_3$); ^{13}C NMR : δ 144.6 (C8), 138.2 (CH=CH$_2$), 127.9 (C7), 127.3 (C6), 126.8 (C4), 126.3 (C9), 125.4 (C5), 115.3 (-C=CH$_2$), 46.8 (C2), 38.4 (Ar-CH$_2$), 31.2 (C3), 24.4 (Ar-CH$_3$), 20.9 (Ar-CH.CH$_3$); MS : *m/z* 186 (M[+]); Anal. Calcd. for C$_{11}$H$_{12}$N$_2$O$_2$: C, 83.87; H, 8.60; N, 7.53. Found: C, 83.91; H, 8.58; N, 7.50.

5-Methyl-7-(3-methyl-2-butenyl)indoline (2h): The compound was obtained from **1h** at 140 -150⁰C in 78 % yield as yellow oil; IR (neat) : 3380, 3045, 2970, 2850, 1670, 1625, 1455, 1260, 835 cm^{-1}; ^{1}H NMR : δ : 3.10 (t, *J*=8.2-8.4 Hz 2H, C$_3$-H), 3.43 (dd, *J* = 6.1 Hz, *J* =1.2 Hz 2H, -CH$_2$-C=C), 3.50- 3.60 (m, 3H, NH and C$_2$ H), 5.24 (t, *J* = 2.1 Hz 1H, -C-CH=C), 1.91 [s, 6H, -C-C=C(CH$_3$)$_2$], 6.61-7.16 (m, 2H, Ar-H), 2.50 (s, 3H, Ar-CH$_3$); ^{13}C NMR : δ 146.6 (C8), 131.8 [=**C**(CH$_3$)$_2$], 127.6 (C6), 127.4 (C9), 126.8 (C4), 125.4 (C5), 122.6 [-**C**H=C.(CH$_3$)$_2$], 121.8 (C7), 47.1 (C2), 32.6 (Ar-CH$_2$), 30.8 (C3), 24.6 [-C-C=C(**C**H$_3$)$_2$], 23.8 (Ar-CH$_3$), 18.8 [-C-C=C(**C**H$_3$)$_2$]; MS : *m/z* 201 (M[+]); Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_2$: C, 83.58; H, 9.45; N, 6.97. Found: C, 83.60; H, 9.44; N, 6.99.

1,2,5,6-Tetrahydro-4,4,8-trimethyl-4H-pyrrolo[3,2,1-ij]quinoline (3): The compound was obtained from **1h** at 140 -150⁰C in 15 % yield as pale yellow oil; IR (neat) : 3380, 3050, 2875, 2860, 1670, 1630, 1460, 1250 cm^{-1}; ^{1}H NMR : δ 2.93 (t, *J* = 8.3 Hz, 2H, C$_3$-H), 2.82-2.89 (m 2H, -CH$_2$-C-C), 3.58 (t, *J* = 8.1 Hz 2H, C$_2$- H), 2.62 (t, *J* = 8 Hz 2H, -C-CH$_2$-C), 1.07 [s, 6H, -C-C-C(CH$_3$)$_2$], 6.49-6.86 (m, 2H, Ar-H), 2.58 (s, 3H, Ar-CH$_3$); ^{13}C NMR : δ 145.7 (9b), 127.6 (9a), 127.7 (C7), 126.3 (C9), 126.8 (C5), 121.9 (6a), 47.9 (C2), 29.3 (C3), 28.9 (C6), 24.9 [-C-C=C(**C**H$_3$)$_2$], 24.9 [-C-C=C(**C**H$_3$)$_2$], 24.1 (Ar-CH$_3$), 22.0 (C5); MS : *m/z* 201 (M[+]); Anal. Calcd for C$_{11}$H$_{12}$N$_2$O$_2$: C, 83.58; H, 9.45; N, 6.97. Found: C, 83.56; H, 9.41; N, 6.96.

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