

Synthesis of benzofuran derivatives using one-pot multicomponent reaction of isocyanides via ZnO-NRs

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Abstract: In this work ZnO-NR as reusable catalyst promoted Strecker-type reaction of 2,4-dihydroxyacetophenone, isopropenylacetylene, trimethylsilyl cyanide, primary amines and isocyanides carried out at ambient temperature under solvent-free conditions and produced amino nitriles benzofuran derivatives in high yields. Short time of reaction, high yields of product, easy separation of catalyst and products are some benefits of this procedure.

Keywords: Strecker reaction, Antioxidant ability, α -amino nitrile benzofurans, Five component reaction, DPPH radical scavenging, ZnO nanorod.

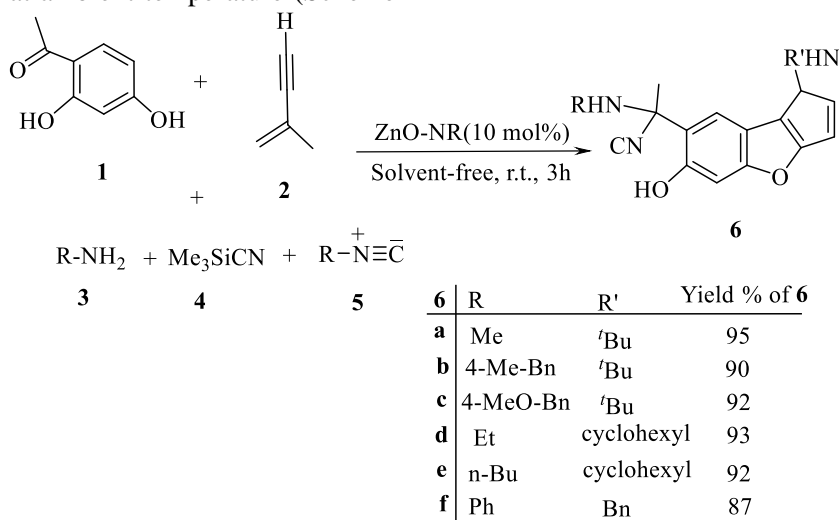
Introduction

Procedures of green chemistry are imperative for taking care of resources and reducing prices [1-3]. Over the last decade, multicomponent reactions (MCRs) are very important kind of reaction because in these reactions more than two reactants mixed and generate one product in one-pot procedure [4-10] that in comparison to multi-step methods, MCRs are economically useful and environmentally safe [11-14]. Multicomponent reactions are very interesting for combinatorial approaches to search for leads of drugs and agrochemicals [15-26]. The one-pot preparation of different and intricate compounds with small heterocycles represents an important tool in synthetic chemistry [27]. From the life science position, Strecker reaction is very considerable, simple and easy procedure's multicomponent reaction [28] for the synthesis of amino nitriles that was discovered in 1850. Also α -amino nitriles as one of the very useful precursors for the synthesis of heterocyclic compounds, α -amino acids [29] and other biologically active molecules [30-31].

α -Amino acids have the greatest biological and inexpensive worth as a result of their extensive use in chemistry and biology. For example, they are the starting materials for the synthesis of proteins and have many applications as the chiral basic compounds in the pharmaceutical industry [32, 33]. Therefore, Strecker reaction is a significant reaction in organic synthesis that include the multi-component condensation of carbonyl compounds such as aldehydes or ketones, amines, and trimethylsilyl cyanide in the presence of acidic catalysts [34-40]. Using of nanocatalysts is very important in organic reaction [41] and these reactions have high yields and good selectivity in the presence of nanocatalysts than to their bulk-sized forms [42, 43]. Among them, the ZnO nanocatalyst was used in the organic synthesis due to be cheap and safe catalyst [44-47]. In recent times, biologists, medicinal and food chemist test and discover new and efficient synthetic antioxidant compounds for protective of humans against these diseases. Herein, in continuation of our attempts to expand new synthetic procedure for chief organic compounds [48-60] a procedure for synthesis of some amino nitriles benzofuran derivatives *via* an efficient five-component reaction between 2,4-

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dihydroxyacetophenone **1**, isopropenylacetylene **2** [64, 65] primary amines **3**, trimethylsilyl cyanide **4** and isocyanides along with ZnO-nanorod as catalyst under solvent-free conditions at ambient temperature (Scheme



Scheme 1: Generation of amino nitriles benzofuran derivatives

Results and discussion

Chemistry

Sodium dodecyl sulfate (SDS) was used for the preparation of ZnO nanorods. This compound was used for the controlling the morphologies of ZnO nanorod as a directing agent. The shape of ZnO-nanorods confirmed by scanning electron microscope (SEM) (Figure 1). In addition, X-ray Powder Diffraction (XRD) image of ZnO-NR is displayed in Figure 2. The diameter and length of the nanorods were 50-70 nm and 300-600 nm respectively. Debye-Scherrer's equation ($D = K\lambda / \beta \cos \theta$) was used for the calculating the crystallite size (D) of ZnO-NR based on the strongest intensity peak. In this equation, D is the particle size, λ is full-width at half-maximum or half-width (FWHM) in radians and h is the position of the maximum of diffraction peak, K is the so-called shape factor (0.89), λ is Bragg's diffraction angle and λ is the X-ray wavelength used (1.5406 Å for CuK α). By using this equation, the average crystal size is about 30 nm for ZnO-NR. All the significant peaks were consonant with the reference model, which confirmed on the basis of JCPDS file No. 36-1451.

The ZnO-NRs as effective catalyst in the synthesis of α -amino nitrile benzofurans

In the first step of this research, the reaction of 2,4-dihydroxyacetophenone **1**, isopropenylacetylene **2**, methyl amine **3a**, trimethylsilyl cyanide **4** and *tert*-butyl isocyanides **5a** was used as a sample reaction to attain the best reaction conditions. The results showed this reaction performed with catalyst and haven't any product without catalyst after 12 h (entry 1, Table 1).

1). In addition, the antioxidant activity of some new synthesized derivatives was examined.

For improving the reaction conditions, the model reaction was tested with adding 10 mol% commercial zinc oxide CM-ZnO to the mixture of reaction. In this condition, the yield of **6a** achieved 28% after 10 h (entry 3, Table 1). In continuous, the model reaction was carried out in the presence of 10 mol% of ZnO-NRs and the compound **6a** produced in 95% yield after 3 h (Table 1). Then, different amounts (10-25 mol%) of ZnO-NRs was tested for achieving the optimum amounts. The result displayed that 10 mol% of catalyst are sufficient to obtaining an excellent yield (Table 1). As a result, these outcomes displayed the significant role of ZnO-NRs as a catalyst in this reaction. By increasing of temperature wasn't seen any significant change on yield of **6a**.

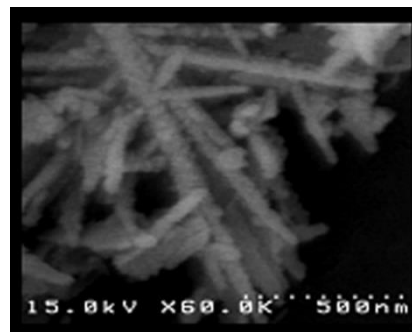


Figure 1. Scanning electron microscope image of ZnO-NR

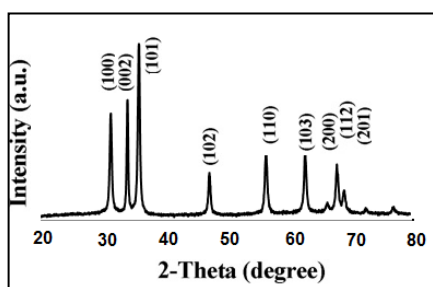


Figure 2. X-ray Powder Diffraction spectrum of ZnO-NR

Table 1. Achieving optimization conditions for the synthesis of **6a**

Entry	Catalyst	Catalst	Yield% ^a
1	none	-	-
2	none	-	-
3	CM-ZnO	10	28
4	CM-ZnO	10	28
5	ZnO-NR	10	95
6	ZnO-NR	15	96
7	ZnO-NR	15	96
8	Fe ₃ O ₄ -MNPs	10	80
9	Fe ₃ O ₄ -MNPs	10	80
10	Fe ₃ O ₄ -MNPs	15	82
11	CuO-NPs	10	75
12	CuO-NPs	15	76

For the obtaining the optimization conditions, the effects of solvents were tested for the generation of **6a** in high yields in the presence of 10 mol% of ZnO-NRs. The outcomes show that solvent-free conditions is the best media for performing the reaction and product **6a** have higher yields than to other solvents (Table 2). As shown in the Table 1 and Table 2, ZnO-NRs (10 mol%), room temperature and solvent-free conditions were used as optimum reaction condition.

Table 2. Optimization of solvent and temperature for the synthesis of **6a**

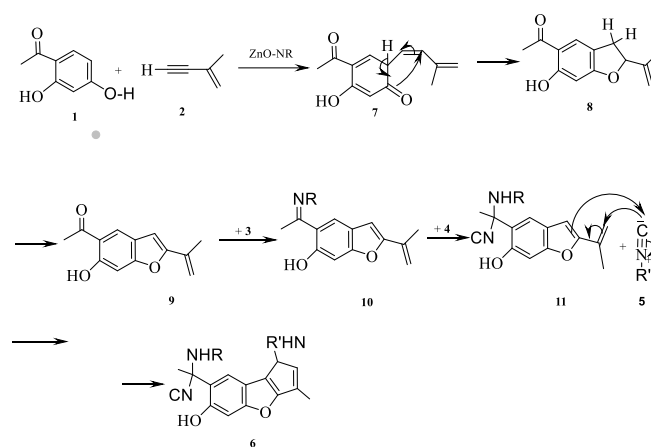
Entry	Solvent	Temp. °C	Time (h)	Yield% ^a
1	Toluene	90	10	55
2	Toluene	120	10	55
3	CH ₂ Cl ₂	-	10	80
4	CH ₂ Cl ₂	50	10	80
5	H ₂ O	-	10	---
6	H ₂ O	80	10	---
7	Solvent-free	---	3	95
8	Solvent-free	50	5	95
9	CH ₃ Cl	---	8	78
10	EtOH	---	15	---
11	CH ₃ CN	----	12	87
12	DMF	50	12	35

The reusing ability of ZnO-NRs as catalyst was tested in the model reaction (synthesis of **6a**). The results showed ZnO-NRs could be reused five times without considerable loss of activity (Table 3). After each reaction, the catalyst was separated by filtration, cleaned with ethyl acetate, dried at room temperature for 24 h, and utilized for the next catalytic cycle.

Table 3. The reusing ability of catalyst for the synthesis of **6a**

Run	Yield % ^a
1 st	95
2 nd	93
3 nd	90
4 nd	87
5 nd	85

For confirming the structure of synthesized compounds **6a**, IR, ¹H NMR, ¹³C NMR and mass spectral data was used. For instance, the ¹H NMR spectrum of **6a** displayed one singlet at 1.25 for *tert*-butyl group, two singlets at δ = 1.94 and 2.16 ppm for methyl protons, one singlet at δ = 2.47 ppm for NMe protons, one singlet at 3.39 ppm for -CH proton, three singlets for methin proton at δ = 5.36, 7.03 and 7.83, two singlet at δ = 6.04 and 6.18 ppm for NH proton and one singlet for OH proton at δ = 8.12 ppm. The ¹³C NMR spectrum of **6a** displayed resonances confirming the proposed structure. The mass spectrum of **6a** displayed the molecular ion peak at m/z = 339. Although there aren't details about the mechanism of these reactions, we have proposed the mechanism of reaction in Scheme 2.



Scheme 2. Suggested mechanism for the formation of **6**.

According to proposed mechanism, the first 2,4-dihydroxyacetophenone **1** and isopropenylacetylene **2** is reacted in the presence of ZnO-NR to generated 5-acetyl-6-hydroxy-2-isopropenylbenzofuran

9. Then primary amine **3** reacts with intermediate **7** and produced imine **10**. In the presence of ZnO-NRs TMSCN **4** reacts with intermediate **11** and produce intermediate **13** that react with isocyanide **5** and produce product **6** in excellent yields.

Conclusion

In conclusion, we investigate multicomponent reaction of 2,4-dihydroxyacetophenone **1**, isopropenylacetylene **2**, primary amines **3**, trimethylsilyl cyanide **4** and isocyanides along with ZnO-NRs as reusable catalyst at room temperature under solvent-free conditions which generates α -amino nitrile benzofuran derivatives in high yields. The chief benefits of our method are high atom economy, green reaction conditions, higher yield, shorter reaction times, and easy work-up, which are in good agreement with some principles of green chemistry.

Experimental

General

General procedure for preparation of ZnO nanorods

ZnO-NRs in these reactions were prepared according to reported article.⁶⁶

General procedure for preparation of compounds **6**

2,4-dihydroxyacetophenone **1** (2 mmol) and isopropenylacetylene **2** (2 mmol) was mixed and stirred for 30 min in the presence of ZnO-NR (10 mol%) under solvent-free conditions at room temperature. After 30 min primary amine **3** (2 mmol) was added to the mixture gently and the mixture was stirred for 15 min. After this time TMSCN **4** (2 mmol) was added to mixture and stirred for 15 min. After completion of the reaction, as indicated by TLC, isocyanides **5** add to mixture in the presence of catalyst. After completion of the reaction, Ethyl acetate (5 mL) was added to mixture and catalyst separated by filtration and after the removing solvent in vacuum; the residue was purified by column chromatography (SiO₂; AcOEt/hexane 1/5) to afford the corresponding α -amino nitrile benzofurans **6**.

1-[1-(tert-butyl amino)-1H-cyclopenta[b][1]benzofuran-7-yl]-1-(methylanino)ethyl cyanide (6a).

Yellow powder, mp 135-137°C, Yield: 0.64 g (95%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3400, 3379, 2880, 2235, 1609, 1507, 1463, 1295, 1135, 1015, 782 cm^{-1} . ¹H NMR (500 MHz, CDCl₃): 1.25 (9 H, s, Me₃C), 1.94 (3 H, s, Me), 2.16 (3 H, s, Me), 2.47 (3 H, s, NMe), 3.35 (1 H, m, CH), 6.03 (1 H, d, ³J = 6.5 Hz, CH), 6.04 (1 H, s, NH), 6.12 (1 H, s, NH), 7.03 (1 H, s, CH), 7.83 (1 H, s, CH), 8.12 (1 H, s, OH)

ppm. ¹³C NMR (125.7 MHz, CDCl₃): 18.6 (Me), 26.3 (Me), 28.5 (Me₃C), 31.3 (Me), 46.3 (CH), 59.6 (Me₃C), 60.3 (C), 101.7 (CH), 113.4 (C), 115.3 (C), 116.4 (C), 119.2 (CN), 120.6 (CH), 121.8 (CH), 123.4 (C), 140.3 (C), 151.2 (C), 152.4 (C) ppm. EI-MS: 339 (M⁺, 15), 282 (86), 57 (100). Anal. Calcd for C₂₀H₂₅N₃O₃ (339.43): C 70.77, H 7.42, N 12.38; Found: C 70.92, H 7.63, N 12.54.

1-[1-(tert-butyl amino)-1H-cyclopenta[b][1]benzofuran-7-yl]-1-(4-methylbenzylamino)ethyl cyanide (6b).

Yellow powder, mp 152-154°C, Yield: 0.79 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3445, 3375, 2883, 2242, 1614, 1524, 1474, 1287, 1137, 1020, 795 cm^{-1} . ¹H NMR (500 MHz, CDCl₃): 1.36 (9 H, s, Me₃C), 2.03 (3 H, s, Me), 2.17 (3 H, s, Me), 2.34 (3 H, s, Me), 3.37 (1 H, m, CH), 4.12 (1 H, d, ²J = 4.6 Hz, CH), 4.38 (1 H, d, ²J = 3.8 Hz, CH), 6.12 (1 H, d, ³J = 6.8 Hz, CH), 6.12 (1 H, s, NH), 6.23 (1 H, s, NH), 7.08 (1 H, s, CH), 7.24 (2 H, d, ³J = 7.6 Hz, 2 CH), 7.36 (2 H, d, ³J = 7.6 Hz, 2 CH), 7.76 (1 H, s, CH), 8.14 (1 H, s, OH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): 18.7 (Me), 21.2 (Me), 26.5 (Me₃C), 28.3 (Me), 45.8 (CH), 49.2 (CH₂N), 56.3 (Me₃C), 60.2 (C), 101.2 (CH), 114.2 (C), 115.6 (C), 116.3 (C), 119.4 (CN), 121.3 (CH), 122.5 (CH), 123.7 (C), 127.3 (2 CH), 129.6 (2 CH), 131.2 (C), 138.2 (C), 141.3 (C), 151.2 (C), 153.4 (C) ppm. EI-MS: 429 (M⁺, 15), 105 (96), 57 (100). Anal. Calcd for C₂₇H₃₁N₃O₂ (429.55): C 75.49, H 7.27, N 9.78; Found: C 75.63, H 7.42, N 9.93.

1-[1-(tert-butylamino)-1H-cyclopenta[b][1]benzofuran-7-yl]-1-(4-methoxybenzylamino) ethyl cyanide (6c).

Yellow powder, mp 167-169°C, Yield: 0.81 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3475, 3378, 2892, 2254, 1623, 1537, 1478, 1285, 1142, 1025, 803 cm^{-1} . ¹H NMR (500 MHz, CDCl₃): 1.32 (9 H, s, Me₃C), 2.05 (3 H, s, Me), 2.14 (3 H, s, Me), 3.42 (1 H, s, CH), 3.87 (3 H, s, MeO), 4.02 (1 H, d, ²J = 4.5 Hz, CH), 4.15 (1 H, d, ²J = 4.5 Hz, CH), 5.83 (1 H, d, ³J = 6.5 Hz, CH), 6.15 (1 H, s, NH), 6.22 (1 H, s, NH), 7.13 (1 H, s, CH), 7.22 (2 H, d, ³J = 7.6 Hz, 2 CH), 7.33 (2 H, d, ³J = 7.6 Hz, 2 CH), 7.75 (1 H, s, CH), 8.15 (1 H, s, OH) ppm. ¹³C NMR (125.7 MHz, CDCl₃): 18.8 (Me), 25.8 (Me₃C), 28.6 (Me), 46.2 (CH), 49.5 (CH₂N), 54.2 (Me₃C), 55.6 (MeO), 60.3 (C), 101.4 (CH), 114.2 (C), 115.3 (2 CH), 116.3 (C), 116.8 (C), 119.6 (CN), 120.5 (CH), 121.6 (CH), 123.4 (C), 129.6 (2 CH), 135.2 (C), 141.2 (C), 150.7 (C), 152.3 (C), 158.3 (C) ppm. EI-MS: 445 (M⁺, 10), 388 (68), 57 (100). Anal. Calcd for C₂₇H₃₁N₃O₃ (445.55): C 72.78, H 7.01, N 9.43; Found: C 72.93, H 7.18, N 9.64.

1-[1-(cyclohexylamino)-1H-cyclopenta[b][1]benzofuran-7-yl]-1-(ethylamino)ethylcyanide (6d).

Pale yellow powder, mp 125-127°C, Yield: 0.70 g (93%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3487, 3382, 2893, 2237, 1617, 1525, 1474, 1286, 1138, 1027, 789 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): 1.13 (2 H, m, CH_2), 1.35 (3 H, t, $^3J = 7.4$ Hz, Me), 1.53 (4 H, m, 2 CH_2), 1.68 (4 H, m, 2 CH_2), 1.97 (3 H, s, Me), 2.03-2.14 (1 H, m, CH), 2.16 (3 H, s, Me), 2.56 (1 H, m, CHN), 2.76-2.93 (1 H, m, CH), 3.34 (1 H, m, CH), 5.86 (1 H, d, $^3J = 3.9$ Hz, CH), 6.08 (1 H, s, NH), 6.12 (1 H, s, NH), 7.06 (1 H, s, CH), 7.85 (1 H, s, CH), 8.14 (1 H, s, OH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): 14.8 (Me), 19.2 (Me), 24.8 (CH_2), 26.8 (2 CH_2), 28.4 (Me), 34.2 (2 CH_2), 40.2 (CH_2N), 49.2 (CH), 55.6 (CH), 59.2 (C), 101.5 (CH), 114.2 (C), 116.4 (C), 117.3 (C), 118.2 (C), 119.5 (CN), 120.6 (CH), 123.4 (CH), 136.4 (C), 151.7 (C), 152.6 (C) ppm. EI-MS: 379 (M^+ , 10), 77 (62), 97 (100). Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2$ (379.49): C 72.79, H 7.70, N 11.07; Found: C 72.93, H 7.86, N 11.23.

1-[1-(cyclohexylamino)-1H-cyclopenta[b][1]benzofuran-7-yl]-1-(butylamino)ethylcyanide (6e).

Yellow powder, mp 158-160°C, Yield: 0.55 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3468, 3387, 2895, 2246, 1622, 1534, 1478, 1292, 1143, 1032, 794 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): 1.12 (3 H, t, $^3J = 7.4$ Hz, Me), 1.15 (2 H, m, CH_2), 1.37-1.45 (2 H, m, CH_2), 1.54-1.62 (6 H, m, 3 CH_2), 1.73 (4 H, m, 2 CH_2), 1.98 (3 H, s, Me), 2.15 (3 H, s, Me), 2.63 (1 H, m, CHN), 2.82-2.96 (2 H, m, CH_2N), 3.68 (1 H, m, CH), 6.04 (1 H, d, $^3J = 6.8$ Hz, CH), 6.10 (1 H, s, NH), 6.23 (1 H, s, NH), 7.14 (1 H, s, CH), 7.87 (1 H, s, CH), 8.06 (1 H, s, OH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): 14.3 (Me), 18.7 (Me), 21.3 (CH_2), 25.6 (CH_2), 26.3 (2 CH_2), 28.2 (Me), 32.2 (CH_2), 34.2 (2 CH_2), 44.3 (CH_2N), 48.6 (CH), 56.7 (CH), 60.2 (C), 101.7 (CH), 114.2 (C), 116.4 (C), 117.2 (C), 118.3 (C), 119.2 (CN), 121.6 (CH), 122.5 (CH), 136.3 (C), 151.2 (C), 152.4 (C) ppm. EI-MS: 407 (M^+ , 15), 309 (62), 98 (100). Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_2$ (407.55): C 73.68, H 8.16, N 10.31; Found: C 73.83, H 8.32, N 10.48.

1-[1-(benzylamino)-1H-cyclopenta[b][1]benzofuran-7-yl]-1-(phenylamino)ethylcyanide (6f).

Yellow powder, mp 185-187°C, Yield: 0.76 g (87%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3460, 3392, 2897, 2253, 1645, 1557, 1483, 1297, 1152, 1048, 825 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): 2.14 (3 H, s, Me), 2.25 (3 H, s, Me), 3.56 (1 H, m, CH), 3.82-3.87 (2 H, m, NCH_2), 6.14 (1 H, d, $^3J = 6.8$ Hz, CH), 6.12 (1 H, s, NH), 6.23 (1 H, s, NH), 6.94 (1 H, t, $^3J = 7.6$ Hz, CH), 7.15 (1 H, t, $^3J = 7.6$ Hz, CH), 7.23 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.28 (2 H, t, $^3J = 7.6$ Hz, 2 CH), 7.34 (2 H, t, $^3J = 7.6$ Hz, 2 CH), 7.42 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.48 (1 H, s, CH), 7.63 (1 H, s, CH), 8.13 (1 H, s,

OH) ppm. ^{13}C NMR (125.7 MHz, CDCl_3): 18.9 (Me), 29.2 (Me), 50.3 (CH), 52.7 (CH_2N), 63.4 (C), 101.6 (CH), 107.2 (C), 115.2 (C), 117.4 (C), 118.6 (2 CH), 120.2 (CH), 121.3 (CH), 121.4 (C), 122.7 (CH), 127.2 (2 CH), 128.3 (CH), 129.4 (2 CH), 131.2 (CN), 131.8 (2 CH), 139.2 (C), 140.4 (C), 141.8 (C), 151.4 (C), 154.2 (C) ppm. EI-MS: 435 (M^+ , 15), 344 (68), 91 (100). Anal. Calcd for $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_2$ (435.52): C 77.22, H 5.79, N 9.65; Found: C 77.42, H 5.93, N 9.83.

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