

First Friedel–Crafts Reaction of the Baylis–Hillman Adducts Derived from Nitroolefins: Application towards Synthesis of Pyrrolidines and Spiropyrrrolidines

Manickam Bakthadoss,* Nagappan Sivakumar

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India

Fax +91(44)22352494; E-mail: bhakthadoss@yahoo.com

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Abstract: A general and simple protocol for the arylation of Baylis–Hillman adducts derived from nitroolefins leading to novel classes of (*E*)-2-nitro-1,3-diarylprop-1-enes and 1-[(*E*)-2-nitro-3-arylallyl]naphthalenes via an intermolecular Friedel–Crafts reaction have been achieved. Further application of these compounds has been demonstrated for the synthesis of pyrrolidines and 3-spiropyrrrolidines which are integral components of many natural products and bioactive molecules.

Key words: Baylis–Hillman reaction, Friedel–Crafts reaction, intermolecular [3+2] cycloaddition, arylation, spiro compounds

The Baylis–Hillman reaction is a well-known coupling reaction of aldehydes and activated alkenes catalyzed by tertiary amines or tertiary phosphines¹ and has emerged as a carbon–carbon bond-forming reaction producing densely functionalized molecules that have been utilized for various organic transformations.^{2–7} The Friedel–Crafts reaction is a widely used reaction in academic as well as industrial fields.^{8–13} The Friedel–Crafts reaction with Baylis–Hillman adducts was initially reported by Basavaiah et al. and, following this pioneering work, various reports have appeared in connection with Friedel–Crafts chemistry on Baylis–Hillman adducts. For example, Basavaiah et al. have described the synthesis of functionalized indene and indane derivatives via intramolecular Friedel–Crafts reaction of Baylis–Hillman adducts in the presence of P₂O₅.¹⁴ They have also synthesized the antifungal natural product, bonducellin methyl ether, involving an intramolecular Friedel–Crafts reaction as the key step.¹⁵ There are also reports describing the Friedel–Crafts reaction of Baylis–Hillman adducts in the synthesis of 2-benzoxepines, 2-benzazepines, 7*H*-benzocycloheptane, indeno[1,2-*b*]quinolin-10-ones, 1-hydroxynaphthalenes, and methylenediphenyl-bis-chromanones.^{16–20}

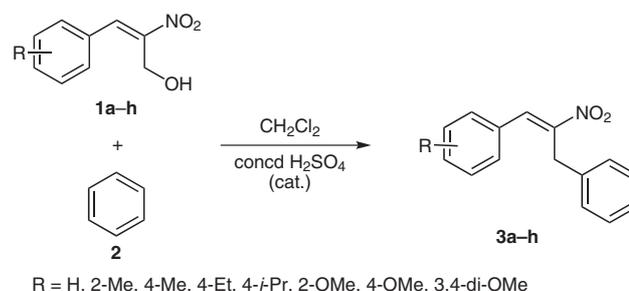
However, there is no report available in the literature for the Friedel–Crafts reaction of the Baylis–Hillman adducts derived from nitroolefins. We envisaged that such adducts would undergo Friedel–Crafts reaction to produce a new class of diaryl compounds.

The synthesis of nitrogen- and oxygen-containing heterocycles continues to be an important and challenging area

in the field of organic chemistry.²¹ The 1,3-dipolar cycloaddition reaction is an important method for the preparation of five-membered heterocycles. The reaction of an azomethine ylide with an alkene provides the pyrrolidine moiety which is present in numerous natural products and biologically active molecules.²² It is well documented in the literature that the Baylis–Hillman adducts have been utilized for the synthesis of various heterocycles.²³ However, the synthesis of heterocyclic spiro compounds via azomethine ylide based [3+2] cycloaddition using Friedel–Crafts products of Baylis–Hillman adducts derived from nitroolefins has not been reported to date.

In continuation of our interest in the Baylis–Hillman chemistry,^{14,15,24} herein we report the first protocol for the syntheses of (*E*)-2-nitro-1,3-diarylprop-1-enes and 1-[(*E*)-2-nitro-3-arylallyl]naphthalenes via an intermolecular Friedel–Crafts reaction. Furthermore we also disclose a simple and convenient route for the synthesis of pyrrolidine and 3-spiropyrrrolidine frameworks using the Friedel–Crafts products of Baylis–Hillman adducts derived from nitroolefins with sarcosine-based dipoles (generated via in situ imine formation and decarboxylation) by an intermolecular [3+2] cycloaddition reaction sequence.

To execute our idea, first we chose the Baylis–Hillman adduct (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**1a**)²⁵ derived from nitrostyrene and formaldehyde as starting material for the Friedel–Crafts reaction. The best results were obtained with addition of a catalytic amount of concentrated H₂SO₄ to the solution of a compound **1a** in benzene (**2**) at room temperature, successfully leading to the desired (*E*)-(2-nitroprop-1-ene-1,3-diyl)dibenzene (**3a**) in 75% yield after column chromatography (Scheme 1). The ¹H NMR spectrum of compound **3a** showed a singlet for CH₂ protons at δ = 4.25 ppm. The aromatic protons appeared as



Scheme 1

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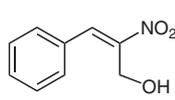
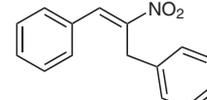
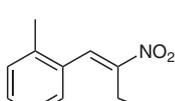
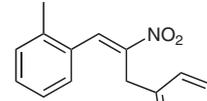
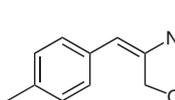
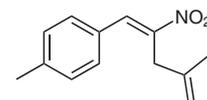
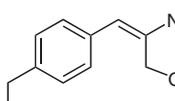
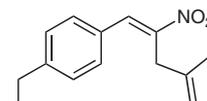
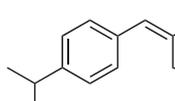
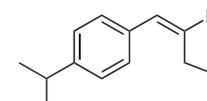
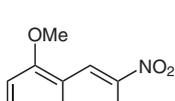
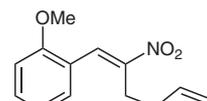
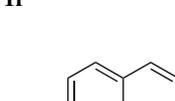
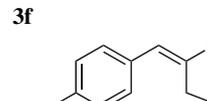
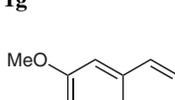
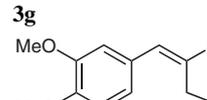
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multiplet in the region of $\delta = 7.19$ – 7.43 ppm, and the olefinic proton appeared as singlet at $\delta = 8.29$ ppm.

Encouraged by this result, we prepared a variety of (*E*)-2-nitro-3-arylprop-2-en-1-ols **1b–h** as starting materials for the syntheses of (*E*)-2-nitro-1,3-diarylprop-1-enes. Treatment of the compounds **1b–h** with catalytic amount of concentrated H_2SO_4 successfully led to the desired compounds **3b–h** in 65–70% yields (Scheme 1). The results are summarized in Table 1.

To explore the generality of the reaction we treated Baylis–Hillman adduct **1a** with *p*-xylene (**4**) in the presence of a catalytic amount of concentrated H_2SO_4 which resulted in the desired Friedel–Crafts product, that is, 1,4-dimethyl-2-[(*E*)-2-nitro-3-phenylallyl]benzene (**5a**) in 77% yield after column chromatography purification (Scheme 2). The ^1H NMR spectrum of compound **5a** showed two singlets for two methyl protons at $\delta = 2.25$ and 2.30 ppm. The benzylic protons showed a singlet at $\delta = 4.13$ ppm, and the

Table 1 Friedel–Crafts Reaction on Baylis–Hillman Adducts Derived from Nitroolefins with Benzene

Entry	Substrate	Product ^a	Yield (%) ^{b,c}
1	 1a	 3a	75
2	 1b	 3b	65
3	 1c	 3c	70
4	 1d	 3d	67
5	 1e	 3e	70
6	 1f	 3f	68
7	 1g	 3g	65
8	 1h	 3h	70

^a All reactions were carried out using 2 mmol of Baylis–Hillman alcohol **1a–h** with benzene (0.5 mL) in 5 mL of CH_2Cl_2 and a catalytic amount of concd H_2SO_4 at r.t. for 0.5 h.

^b All products gave satisfactory IR, ^1H NMR, ^{13}C NMR, MS spectral data and elemental analyses.

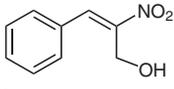
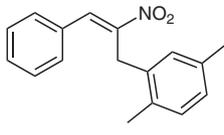
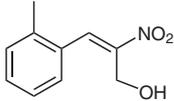
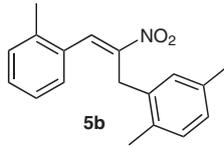
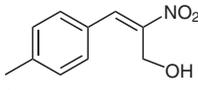
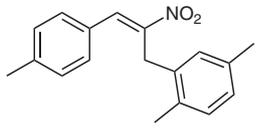
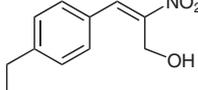
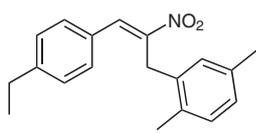
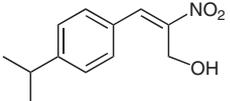
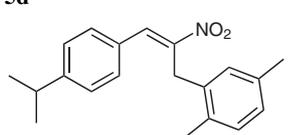
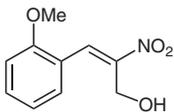
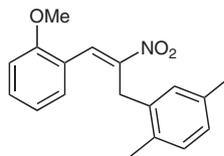
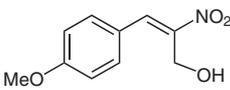
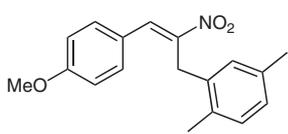
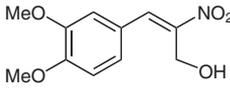
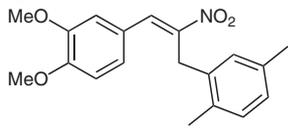
^c Yields of the pure products **3a–h** obtained after column chromatography (silica gel, 2% EtOAc in hexanes).

aromatic protons appeared in the region of $\delta = 6.83\text{--}7.41$ ppm. The olefinic proton appeared as a singlet at $\delta = 8.37$ ppm.

A variety of Baylis–Hillman adducts **1b–h** with *p*-xylene smoothly led to the desired Friedel–Crafts products **5b–h** in 65–72% yields (Scheme 2, Table 2).

To extend the generality of the procedure further we employed naphthalene (**6**) as the arene. Treatment of Baylis–

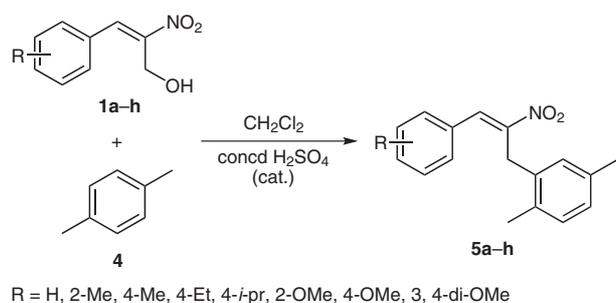
Table 2 Friedel–Crafts Reaction on Baylis–Hillman Adducts Derived from Nitroolefins with *p*-Xylene

Entry	Substrate	Product ^a	Yield (%) ^{b,c}
1	 1a	 5a	77
2	 1b	 5b	72
3	 1c	 5c	70
4	 1d	 5d	67
5	 1e	 5e	68
6	 1f	 5f	65
7	 1g	 5g	65
8	 1h	 5h	67

^a All reactions were carried out using 2 mmol of Baylis–Hillman alcohol **1a–h** with *p*-xylene (0.5 mL) in 5 mL of CH_2Cl_2 and catalytic amount of concd H_2SO_4 at r.t. for 0.5 h.

^b All products gave satisfactory IR, ^1H NMR, ^{13}C NMR, MS spectral data and elemental analyses.

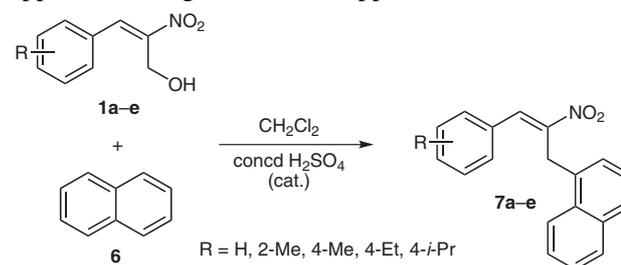
^c Yields of the pure products **5a–h** obtained after column chromatography (silica gel, 2% EtOAc in hexanes).



Scheme 2

Hillman adducts **1a–e** with naphthalene in the presence of catalytic amount of concentrated H₂SO₄ led to the anticipated 1-[(*E*)-2-nitro-3-aryallyl]naphthalenes **7a–e** in 67–

77% yields (Scheme 3, Table 3). The ¹H NMR spectrum of compound **7a** showed a singlet for CH₂ protons at δ = 4.68 ppm. The aromatic protons appeared as multiplet in the region of δ = 7.23–7.99 ppm, and the olefinic proton appeared as singlet at δ = 8.00 ppm.



Scheme 3

Table 3 Friedel–Crafts Reaction on Baylis–Hillman Adducts Derived from Nitroolefins with Naphthalene

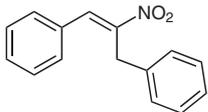
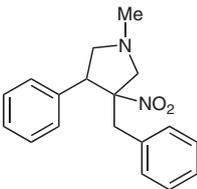
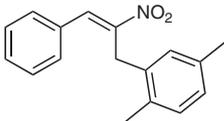
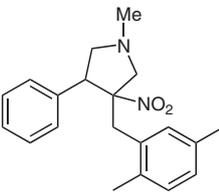
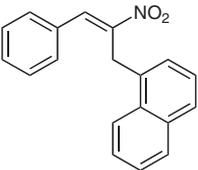
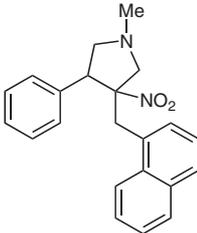
Entry	Substrate	Product ^a	Yield (%) ^{b,c}
1			77
2			72
3			70
4			67
5			68

^a All reactions were carried out using 2 mmol of Baylis–Hillman alcohol **1a–e** with naphthalene (2 mmol) in 5 mL of CH₂Cl₂ and catalytic amount of concd H₂SO₄, at r.t. for 0.5 h.

^b All products gave satisfactory IR, ¹H NMR, ¹³C NMR, MS spectral data and elemental analyses.

^c Yields of the pure products **7a–e** obtained after column chromatography (silica gel, 2% EtOAc in hexanes).

Table 4 Synthesis of Pyrrolidine Compounds from Friedel–Crafts Products

Entry	Substrate	Product ^a	Yield (%) ^{b,c}
1	 3a	 8	77
2	 5a	 9	72
3	 7a	 10	70

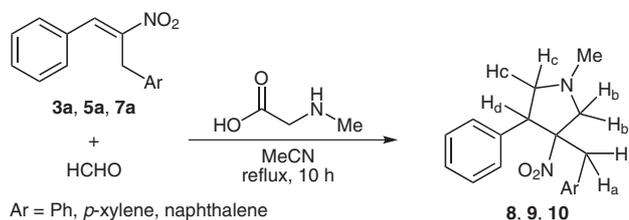
^a All reactions were carried out using 1 mmol of Friedel–Crafts products **3a**, **5a**, and **7a** with *N*-methyl glycine (3 mmol), and formaldehyde (6 mmol) in 8 mL MeCN under reflux conditions for 10 h.

^b All products gave satisfactory IR, ¹H NMR, ¹³C NMR, MS spectral data and elemental analyses.

^c Yields of the pure products **8–10** obtained after column chromatography (silica gel, 10% EtOAc in hexanes).

To demonstrate the application of the 1,3-diaryl compounds thus obtained, we have utilized them for [3+2]-cycloaddition reaction for the construction of pyrrolidines and spiro pyrrolidines. We first selected (*E*)-2-nitroprop-1-ene-1,3-diyl)dibenzene (**3a**) derived from Baylis–Hillman adduct **1a** as a starting material for cycloaddition with the dipole generated from *N*-methyl glycine and HCHO. Best results were obtained when **3a** was treated with HCHO and *N*-methyl glycine without catalyst in acetonitrile for 10 hours at reflux, successfully providing 3-benzyl-1-methyl-3-nitro-4-phenylpyrrolidine (**8**) in good yield (77%) after column chromatography purification (Scheme 4). The ¹H NMR spectrum of compound **8** showed a singlet for NCH₃ protons at $\delta = 2.44$ ppm. The benzylic two H_a protons appeared as two doublets at $\delta = 2.53$ and 2.62 ppm. One of the H_b proton and one of the H_c proton appeared as multiplet in the region of $\delta = 2.75$ –2.86 ppm. One of the H_b proton appeared as doublet at $\delta = 3.60$ ppm, and one of the H_c proton showed a triplet at $\delta = 3.26$ ppm. The H_d proton appeared as a triplet at $\delta = 4.07$ ppm. The aromatic protons appeared as a multiplet in the region of $\delta = 6.91$ –7.52 ppm.

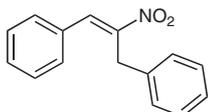
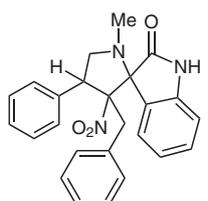
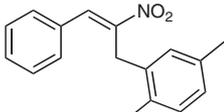
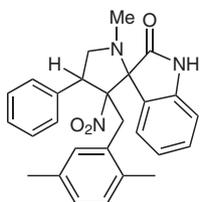
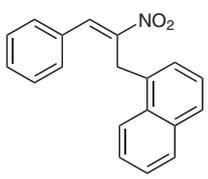
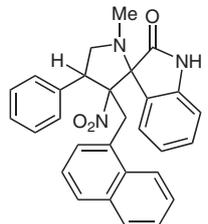
Encouraged by this result, we successfully converted 1,4-dimethyl-2-[(*E*)-2-nitro-3-phenylallyl]benzene (**5a**) and 1-[(*E*)-2-nitro-3-phenylallyl]naphthalene (**7a**) into pyrrolidines **9** and **10** using HCHO and *N*-methyl glycine in

**Scheme 4**

72% and 70% yields, respectively (Scheme 4). The results are summarized in Table 4.

To probe further the application of the Friedel–Crafts products, we subjected **3a**, **5a**, and **7a** with the dipole generated from isatin and *N*-methylglycine to construct spiro pyrrolidines. Best results were obtained when **3a**, **5a**, and **7a** were treated with isatin and *N*-methylglycine without catalyst in acetonitrile solvent for 10 hours at reflux, successfully providing the desired spiro pyrrolidine oxindole compounds **11**, **12**, and **13**, respectively, in 76–84% yields (Scheme 5, Table 5). The ¹H NMR spectrum of compound **11** showed a singlet for NCH₃ protons at $\delta = 2.19$ ppm. The benzylic two H_a protons appeared as two doublets at $\delta = 3.47$ and 3.61 ppm. Two triplets were observed at $\delta = 3.69$ and 3.93 ppm for two H_b protons. The H_c proton showed a triplet at $\delta = 5.05$ ppm. The aromatic protons

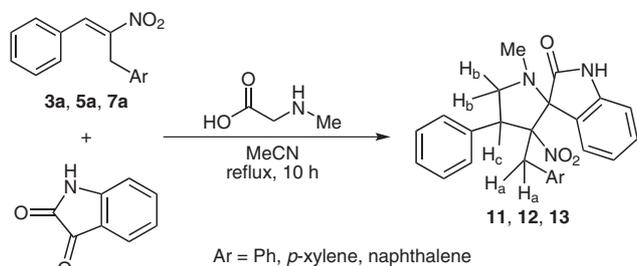
Table 5 Synthesis of 3-Spiropyrrolidine Compounds from Baylis–Hillman Adducts

Entry	Substrate	Product ^a	Yield (%) ^{b,c}
1			80
2			84
3			76

^a All reactions were carried out using 1 mmol of Friedel–Crafts products **3a**, **5a**, and **7a** with *N*-methylglycine (1 mmol) and isatin (1 mmol) in 8 mL MeCN under reflux conditions for 10 h.

^b All products gave satisfactory IR, ¹H NMR, ¹³C NMR, and MS spectral data.

^c Yields of the pure products **11–13** obtained after column chromatography (silica gel, 20% EtOAc in hexanes).

**Scheme 5**

appeared as a multiplet in the region of $\delta = 6.37\text{--}7.56$ ppm.

In conclusion this methodology represents the first Friedel–Crafts reaction of the Baylis–Hillman adducts derived from nitroolefins with a variety of arenes, mediated by concentrated H₂SO₄, providing a simple route for the synthesis of (*E*)-2-nitro-1,3-diarylprop-1-enes and 1-[(*E*)-2-nitro-3-arylallyl]naphthalenes. Further application of these compounds has been demonstrated for the synthesis of pyrrolidines and 3-spiropyrrolidines.

General Procedure for the Synthesis of (*E*)-(2-Nitroprop-1-ene-1,3-diyl)dibenzene (**3a**)

To a stirred solution of (*E*)-2-nitro-3-phenylprop-2-en-1-ol (**1a**, 0.36 g, 2 mmol) in CH₂Cl₂ (5 mL), benzene (0.5 mL) was added at r.t. The reaction mixture was cooled to 0 °C and then a catalytic amount of concd H₂SO₄ was added dropwise and the mixture stirred at r.t. (ca. 0.5 h). After completion of reaction (TLC), the mixture was poured into H₂O, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated. The crude product thus obtained was purified by column chromatography on silica gel (Acme 100–200 mesh), using (2%, EtOAc–hexanes) to provide the pure compound **3a** in 75% (0.36 gm) yield as a yellow oil.

Experimental Procedure for the Synthesis of 3-Benzyl-1-methyl-3-nitro-4-phenylpyrrolidine (**8**)

A mixture of (*E*)-(2-nitroprop-1-ene-1,3-diyl)dibenzene (**3a**, 1 mmol, 0.26 g), HCHO (6 mmol, 0.20 g), and *N*-methyl glycine (3 mmol, 0.2 g) in MeCN (8 mL) was heated to reflux for 10 h. After the completion of the reaction (TLC), the reaction mixture was concentrated, and the resulting crude material was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na₂SO₄), filtered, and the organic layer was concentrated and the residue purified by column chromatography on silica gel (Acme 100–200 mesh), using EtOAc–hexanes (1:9) to afford the title compound **8** as a colorless solid in 77% (0.23 g) yield.

Experimental Procedure for the Synthesis of 3'-Benzyl-1'-methyl-3'-nitro-4'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (11)

A mixture of (*E*)-(2-nitroprop-1-ene-1,3-diyl)dibenzene (**3a**, 1 mmol, 0.26 g), isatin (1 mmol, 0.2 g), and *N*-methyl glycine (1 mmol, 0.13 g) in MeCN (8 mL) was heated to reflux for 10 h. After completion of reaction (TLC), the reaction mixture was concentrated, and the resulting crude material was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (Na₂SO₄), filtered, concentrated and purified by column chromatography on silica gel (Acme 100–200 mesh), using EtOAc–hexanes (2:8) to provide **11** as a colorless solid in 80% (0.33 g) yield.

(*E*)-(2-Nitroprop-1-ene-1,3-diyl)dibenzene (3a)

Yield 75%. IR (KBr): 1645, 1575, 1505, 1318 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 4.25 (s, 2 H), 7.19–7.43 (m, 10 H), 8.29 (s, 1 H). ¹³C NMR (75 MHz, CDCl₃): δ = 32.99, 127.03, 127.69, 128.98, 129.17, 129.72, 130.47, 132.05, 135.51, 136.28, 149.70. MS: *m/z* = 239 [M⁺]. Anal. Calcd for C₁₅H₁₃NO₂: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.25; H, 5.41; N, 5.91.

3-Benzyl-1-methyl-3-nitro-4-phenylpyrrolidine (8)

Mp 82–84 °C. Yield 77%. IR (KBr): 1623, 1537, 1312 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 2.44 (s, 3 H), 2.53 (d, *J* = 14.4 Hz, 1 H), 2.62 (d, *J* = 11 Hz, 1 H), 2.75–2.86 (m, 2 H), 3.26 (t, *J* = 9.7 Hz, 1 H), 3.60 (d, *J* = 11.7 Hz, 1 H), 4.07 (t, *J* = 8.1 Hz, 1 H), 6.91–7.52 (m, 10 H). ¹³C NMR (75 MHz, CDCl₃): δ = 41.98, 42.73, 54.60, 61.35, 62.99, 100.49, 127.49, 127.93, 128.56, 128.66, 129.14, 129.71, 134.73, 136.93. MS: *m/z* = 296 [M⁺]. Anal. Calcd for C₁₈H₂₀N₂O₂: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.97; H, 6.85; N, 9.49.

3-Benzyl-1'-methyl-3'-nitro-4'-phenylspiro(indoline-3,2'-pyrrolidin)-2-one (11)

Mp 180–182 °C. Yield 80%. IR (KBr): 3268, 1648, 1525, 1342 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 2.19 (s, 3 H), 3.47 (d, *J* = 15.9 Hz, 1 H), 3.61 (d, *J* = 15.9 Hz, 1 H), 3.69 (t, *J* = 9.0 Hz, 1 H), 3.93 (t, *J* = 9.0 Hz, 1 H), 5.05 (t, *J* = 8.7 Hz, 1 H), 6.37–7.56 (m, 15 H). ¹³C NMR (75 MHz, CDCl₃): δ = 35.23, 37.43, 50.27, 59.52, 79.59, 107.11, 109.70, 123.50, 125.22, 125.63, 125.91, 127.46, 127.52, 128.30, 129.49, 130.41, 131.01, 134.23, 137.47, 140.94, 175.77. MS: *m/z* = 413 [M⁺]. Anal. Calcd for C₂₅H₂₃N₃O₃: C, 72.62; H, 5.61; N, 10.16. Found: C, 72.58; H, 5.67; N, 10.10.

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