

AN EFFICIENT SYNTHESIS OF 6-(4-CHLOROPHENYL)-2,2-DIMETHYL-7-PHENYL-2,3-DIHYDRO-1H-PYRROLIZINE, A KEY INTERMEDIATE IN THE LICOFELONE SYNTHESIS

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Received March 3, 2009

Accepted April 21, 2009

Published online June 23, 2009

Dedicated to Dr. Alfred Bader, a friend and an exceptional human being, on the occasion of his 85th birthday in recognition of his outstanding contributions to the science of chemistry.

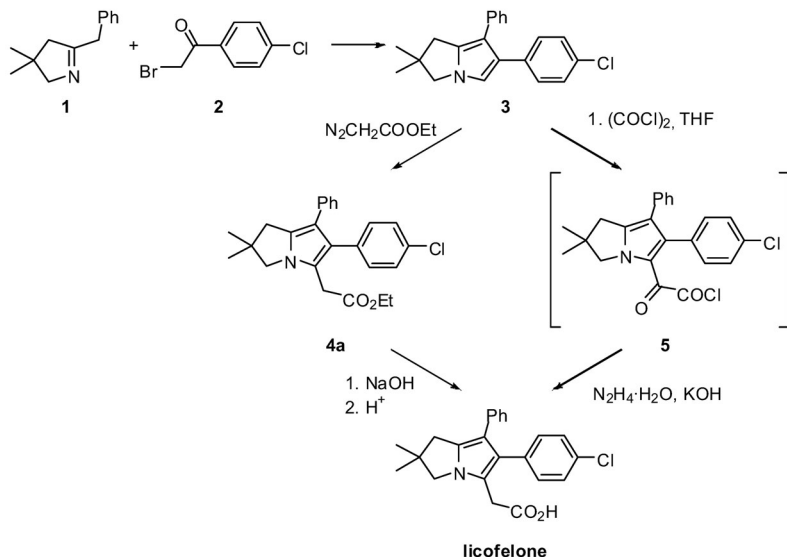
An efficient synthesis of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine, a key intermediate for the synthesis of licofelone, an anti-inflammatory drug currently undergoing evaluation of the phase-III clinical studies, is described. The method is based on a novel synthesis of unstable 5-benzyl-3,3-dimethyl-3,4-dihydro-2H-pyrrole, which is then treated with 2-bromo-1-(4-chlorophenyl)ethan-1-one. 2,2-Dimethyl-5-phenylpent-4-ynal with benzylamines provides the corresponding Schiff bases. Migration of the C=N double bond in these *N*-(2,2-dimethyl-5-phenylpent-4-yn-1-ylidene)benzylamines into conjugation with the aromatic ring using various base/solvent systems was studied. Acid hydrolysis of the formed Schiff bases then provided 2,2-dimethyl-5-phenylpent-4-yn-1-amine and 2,2-dimethyl-5-phenylpenta-3,4-dien-1-amine; their ratio was influenced mainly by the reaction conditions. Cyclization of these amines using Ag or Au catalysts then led to 5-benzyl-3,3-dimethyl-3,4-dihydro-2H-pyrrole.

Keywords: Licofelone; Schiff bases; Cyclization; Double bond migration; Isomerization; Pyrroles; Pyrrolizines; Au catalysis; Amines; Alkynes; Allenes.

Licofelone (ML3000)¹, a dual cyclooxygenase/5-lipoxygenase inhibitor developed by Merckle, is the first member of this new class of analgesic and anti-inflammatory drugs currently undergoing evaluation of the phase-III clinical studies for treatment of osteoarthritis².

There are several methods for construction of the parent moiety of the drug; it is usually formed by condensation of rather unstable 5-benzyl-3,3-dimethyl-3,4-dihydro-2H-pyrrole (**1**) with 2-bromo-1-(4-chlorophenyl)ethan-1-one (**2**) providing 2,3-dihydro-1H-pyrrolizine **3** (refs³⁻⁵). Though,

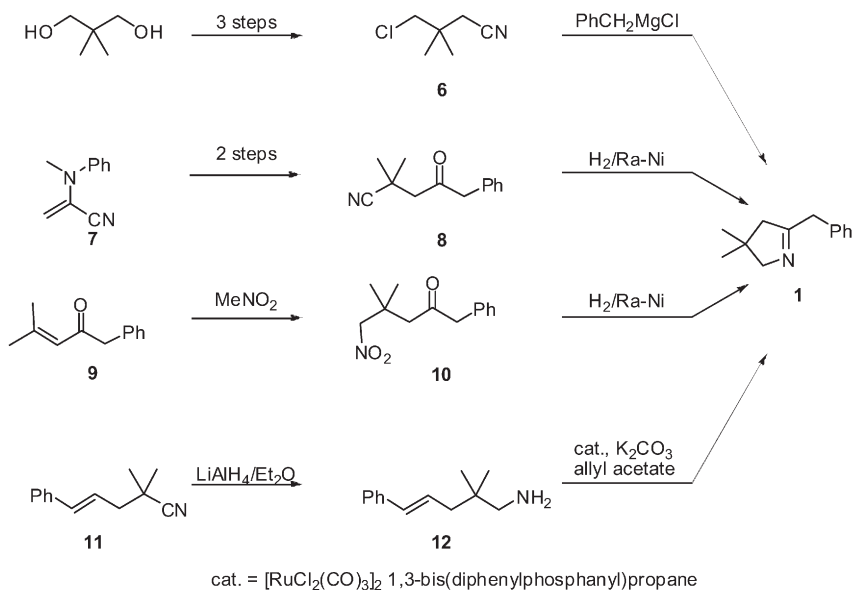
a different synthesis of **3** based on the Suzuki cross-coupling reaction has been published^{6–8}, the original method using the intermediacy of **1** seems to be more efficient. Compound **3** when treated with ethyl diazoacetate gives ester **4a** and its hydrolysis gives licofelone. Alternatively, compound **3** treated with oxalyl chloride gives acyl chloride **5**, which under the conditions of Wolff–Kishner reduction then provides licofelone (Scheme 1)^{3–5}. Recently we have reported a new efficient synthesis of **4a** and its analogs based on Fenton-type radical alkylation of compound **3** with iodoacetates⁹.



SCHEME 1
Synthesis of licofelone

Several methods of synthesis of **1** have been described (Scheme 2), but none of them seems to be efficient enough for industrial production. The first described synthesis³ leading to low yields of **1** is based on treatment of 4-chloro-3,3-dimethylbutanenitrile (**6**), obtained in three steps from commercially available 2,2-dimethylpropane-1,3-diol, with benzylmagnesium chloride. Better yields can be obtained by synthesis⁴ based on cyanohydrin reaction of chloroacetaldehyde and *N*-methylaniline followed by elimination of hydrogen chloride under PTC conditions. The formed 2-(*N*-methylanilino)acrylonitrile (**7**) is transformed into nitrile **8** and its reduction on Raney nickel leads directly to required compound **1**. Recently, a synthesis based on the Michael addition of nitromethane to **9** and subsequent

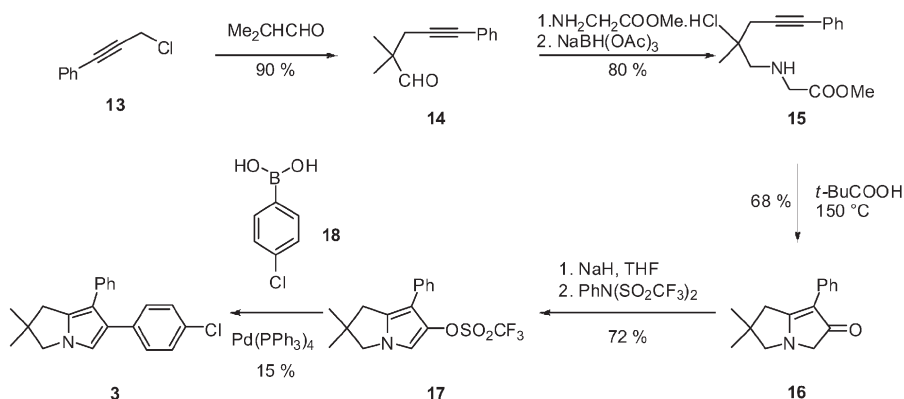
reductive cyclization of the primarily formed nitro derivative **10** has been described¹⁰; however, no yields are given throughout the patent. The last described synthetic route to **1** is based on the alkylation of isobutyronitrile with cinnamyl bromide providing nitrile **11** (ref.¹¹), which is then reduced with LiAlH_4 to unsaturated amine **12** (ref.¹²). The final cyclization¹³ of **12** into **1** is catalyzed with $[\text{RuCl}_2(\text{CO})_3]_2$ -1,3-bis(diphenylphosphanyl)propane.



SCHEME 2
 The known methods of synthesis of **1**

Synthesis of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (**3**) via 2,3-dihydro-1H-pyrrolizine **16** described by Cossy et al.^{7,8} is shown in Scheme 3. Starting 1-chloro-3-phenylprop-2-yne (**13**) treated with isobutyraldehyde provides aldehyde **14**. Reductive amination of **14** with methyl glycinate gives a good yield of **15** and its thermal cyclization yields 2,3-dihydro-1H-pyrrolizin-6(5H)-one **16**. Suzuki cross-coupling of the corresponding triflate provides only low yields of **3**.

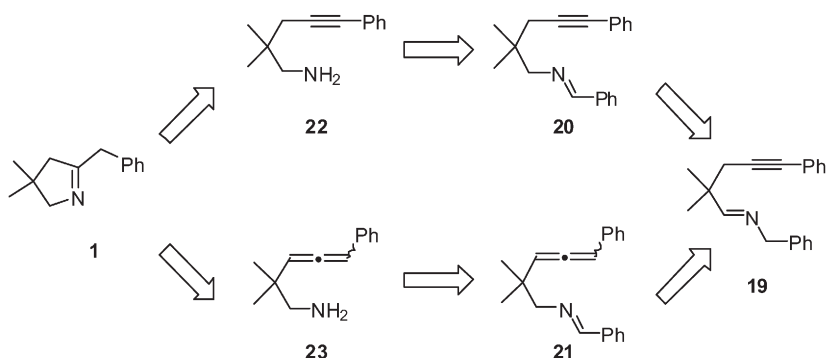
There are several reports^{14–16} describing base-catalyzed carbon-nitrogen double bond migration in Schiff bases derived from aliphatic aldehydes and benzylamine. Acid hydrolysis of the resulting rearranged Schiff bases provided an entry to make amines from aldehydes. We decided to utilize this



SCHEME 3

Synthesis of **3** by Suzuki cross-coupling

approach in the synthesis of **1** (see retrosynthetic analysis in Scheme 4). We assumed that under the conditions used for the isomerization, the triple bond in **19** could remain untouched to give **20** or could undergo isomerization to the corresponding allene **21**. In both cases amines **22** and **23** formed in the following step were considered to be potential intermediates in the synthesis of **1**.



SCHEME 4

Retrosynthesis of **1**

RESULTS AND DISCUSSION

Aldehyde **14**, which was prepared in good yields by a known procedure^{7,8}, treated with benzylamine under standard conditions¹⁵, provided Schiff base **19a**. Its base-catalyzed isomerization provided mixtures of both pos-

sible products **20a** and **21a**. Similarly, using the respective benzylamines, Schiff bases **19b**, **19c** were obtained and their isomerization was also studied. The ratio **20/21** was influenced mainly by the used base/solvent systems, the influence of the R was negligible and therefore compound **19a** was mostly used (Table I). Mixtures of **20** and **21** were then hydrolyzed with aqueous oxalic acid to get the corresponding mixtures of oxalates of amines **22** and **23**.

TABLE I
Base-catalyzed isomerization of compounds **19**

Starting compound	Conditions	Ratio of 22/23	Notes
19a	<i>t</i> -BuOK, DMSO, 20 °C, 1 h	2:1	Impurities formed
19a	<i>t</i> -BuOK, THF, 20 °C, 1 h	7:1	
19a	<i>t</i> -BuOK, THF, reflux, 1 h	4:1	
19a	<i>t</i> -BuOK, toluene, reflux, 1 h	5:1	
19a	<i>t</i> -BuOK, MeCN, reflux, 1 h	6:1	Impurities formed
19a	KDMO, THF, reflux, 1 h	6:1	
19a	KDMO, THF, 0 °C, 1 h	8:1	
19a	KDMO, THF, -30 °C, 2 h	25:1	
19a	KDMO, THF, -50 °C, 20 h	>99:1	
19b	<i>t</i> -BuOK, THF, reflux, 1 h	3.5:1	
19c	<i>t</i> -BuOK, THF, reflux, 1 h	3:1	

When the isomerization with potassium 3,7-dimethyl-3-octan-3-olate (KDMO) was performed at -50 °C, acetylenic compound **20a** strongly prevailed so that after hydrolysis only amine **22** was obtained as oxalate salt. On the other hand, we failed to get only allenic compound **21a**.

Successful cyclization of amino derivative **22** or its mixtures with **23** can be achieved by catalysis of various silver salts (Table II). The best results were achieved with AgBF₄. Similar results were obtained also with AgClO₄ or PhCOOAg. A rather slower reaction was observed using Ag₂CO₃. The cyclizations were usually performed in refluxing dichloromethane, but similar results were also observed in THF or toluene. The reaction mixture after complete conversion (GC) was simply worked-up by pouring into a brine solution, filtering off the insoluble portion and evaporating the filtrate. Due to the known instability of 5-benzyl-3,3-dimethyl-3,4-dihydro-2*H*-pyrrole (**1**), the formed residue was directly used in the preparation of **3**. In

this compound, the Ag content was found below the measurement limits using inductively coupled plasma atomic emission spectroscopy (ICP AES) analysis.

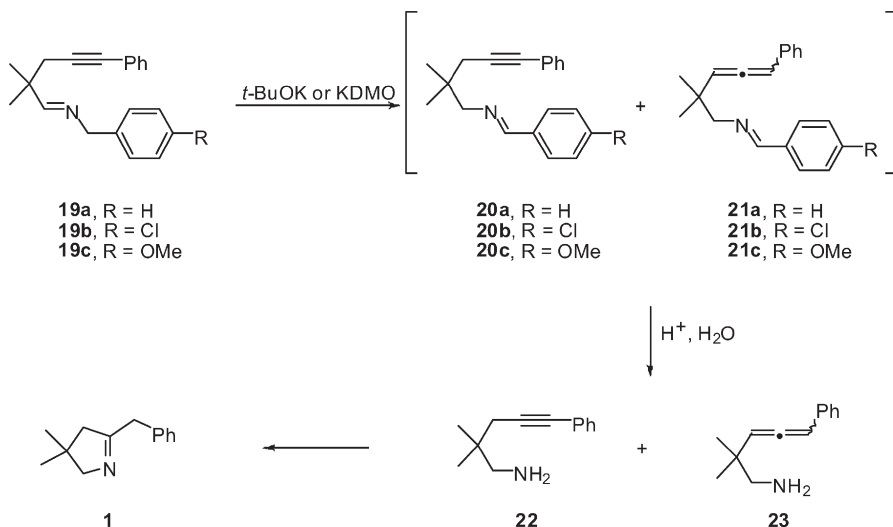
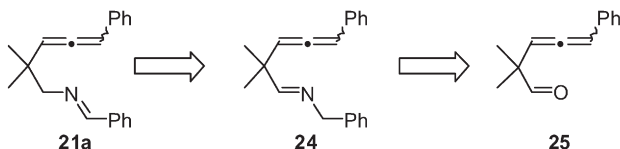
TABLE II
Catalytic cyclization of compounds **22** and **23** to 5-benzyl-3,3-dimethyl-3,4-dihydro-2H-pyrrole (**1**)

Molar ratio 22/23	Conditions	Conversion, (yield)	Notes
4:1	AgBF ₄ , CH ₂ Cl ₂ , 40 °C, 6 h	100% (quant.)	
>99:1	AgBF ₄ , CH ₂ Cl ₂ , 40 °C, 4 h	100% (quant.)	
4:1	AgClO ₄ , CH ₂ Cl ₂ , 40 °C, 6 h	100% (quant.)	
4:1	PhCO ₂ Ag, CH ₂ Cl ₂ , 40 °C, 24 h	100%	96% after 6 h
4:1	Ag ₂ CO ₃ , CH ₂ Cl ₂ , 40 °C, 24 h	98%	55% after 6 h
4:1	AuCl ₃ , CH ₂ Cl ₂ , 40 °C, 4 h	100%	
9:1	PdCl ₂ , CH ₂ Cl ₂ , 40 °C, 24 h	70%	
4:1	Pd/C, CH ₂ Cl ₂ , 40 °C, 24 h	18%	all allene disappeared
4:1	CHCl ₃ , reflux, 24 h	18%	all allene disappeared

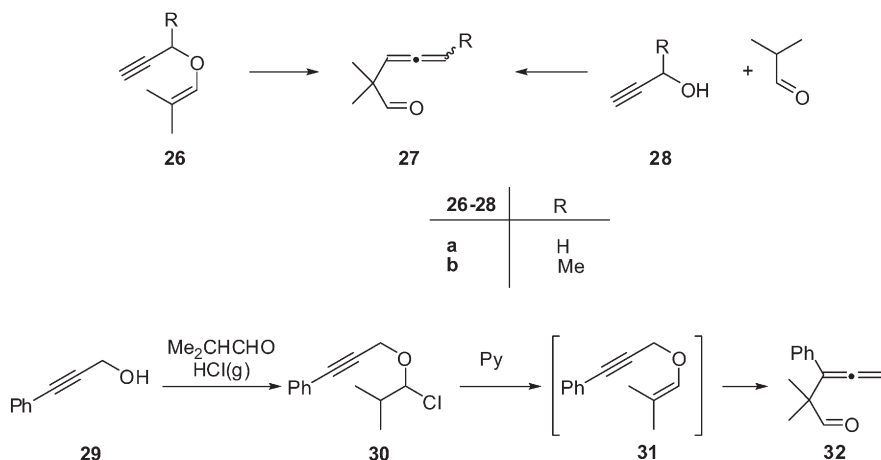
We have not extensively studied the cyclization using gold catalysts for their higher price which could prevent their industrial application. AuCl₃, the only gold catalyst tested, provided virtually identical results as AgBF₄. Our attempts to use other catalysts were successful only with PdCl₂, but the reaction was rather slow (70% conversion after 24 h). Due to the longer reaction time also some impurities were formed. The other catalysts tested, e.g. Pd/C, SmI₂, Ni(II) acetylacetonate or NaF, failed to give any cyclization products. During these studies we found, that under some conditions, e.g. Pd/C, using a 4:1 mixture of **22** and **23**, allenic compound **23** cyclized while the acetylenic compound **22** did not change. However, we found later that similar results can be achieved without any catalyst, e.g. in refluxing chloroform (Scheme 5).

Compound **21a** can be obtained also by isomerization of Schiff base **24**, which is formed from the corresponding aldehyde **25** (Scheme 6).

Black and Landor¹⁷ prepared only low yields (10–30%) of 2,2-dimethylpenta-3,4-dienal (**27a**) and 2,2-dimethylhexa-3,4-dienal (**27b**) by thermally induced Claisen rearrangement of 2-methyl-1-(prop-2-yn-1-yloxy)prop-1-ene (**26a**) and 3-(2-methylprop-1-en-1-yloxy)but-1-yne (**26b**), respec-


 SCHEME 5
 Synthesis of **1**

 SCHEME 6
 Retrosynthesis of **21a**

tively. There are several papers^{18–21} describing condensation of propargylic alcohols **28** and isobutyraldehyde catalyzed with *p*-toluenesulfonic acid affording low to moderate yields of 3-(un)substituted 2,2-dimethylpenta-3,4-dienal derivatives **27**. However, no reaction occurred with 1-phenylprop-2-yn-1-ol **28** (R = Ph). A good yield of **32** was obtained by the Claisen rearrangement of the corresponding 2-methylprop-1-en-1-yl 3-phenylprop-2-yn-1-yl ether (**31**) formed in situ from 1-chloro-2-methylpropyl 3-phenylprop-2-yn-1-yl ether **30** (ref.²²) (Scheme 7). We have tried to apply this methodology to the synthesis of aldehyde **25**, but only a complex mixture was obtained.



SCHEME 7

Preparation of allenic aldehydes **27** and **32**

EXPERIMENTAL

Melting points were measured on a Kofler block and are uncorrected. The IR spectra were measured on a Perkin–Elmer Spectrum BX FT-IR instrument by the diffuse reflectance method (KBr), and FT-Raman spectra on a Bruker RFS 100/S instrument; wavenumbers are given in cm^{-1} . UV spectra were recorded on a Hewlett–Packard 8452A spectrophotometer (ethanol) in the range 190–400 nm. NMR experiments (δ , ppm; J , Hz) were carried out on a Bruker Avance 500 instrument at 500.13 MHz (^1H), 125.77 MHz (^{13}C) using residual deuterated solvent signals as internal standards (for ^1H δ 7.26 ppm, for ^{13}C δ 77.0 ppm, both in CDCl_3). All experiments were performed in CDCl_3 at 298 K, unless otherwise stated. Mass spectra (MS/MS; ionization mode APCI(+)) were measured on an API 3000 PE spectrometer (Sciex Instruments, Applied Biosystems). GC was performed on a Finnigan Focus GC instrument using Restek RTX-5 amine column. The purity of the prepared substances was evaluated by TLC on silica gel (FP KG F 254, Merck). 2,2-Dimethyl-5-phenylpent-4-ynal (**14**) was prepared according to the literature procedure^{7,8}; Potassium 3,7-dimethyl-3-octan-3-olate (KDMO) was obtained from BASF. Other chemicals used in the synthesis were purchased from Sigma–Aldrich and were used without purification.

Preparation of (*E*)-*N*-(2,2-dimethyl-5-phenylpent-4-yn-1-ylidene)benzylamines (**19**).

General Procedure

2,2-Dimethyl-5-phenylpent-4-ynal (**14**; 21.3 g, 114 mmol) and appropriate benzylamine (114 mmol) was added to a stirred suspension of anhydrous MgSO_4 (20 g, 167 mmol) in tetrahydrofuran (150 ml) and the mixture was stirred at room temperature for 6 h. The insoluble portion was filtered off and the filtrate was evaporated under reduced pressure to give the desired product, which was used without purification in the next step.

(*E*)-*N*-(2,2-Dimethyl-5-phenylpent-4-yn-1-ylidene)benzylamine (**19a**). Colorless oil. ^1H NMR (CDCl_3): 1.26 (s, 6 H, $2 \times \text{CH}_3$), 2.57 (s, 2 H, CH_2), 4.62 (s, 2 H, CH_2), 7.19–7.38 (m, 10 H, Ar), 7.75–7.79 (m, 1 H, Ar). ^{13}C NMR (CDCl_3): 21.5, 24.9, 30.9, 39.8, 64.7, 82.8, 87.5, 124.0, 126.9, 127.7, 127.8, 128.3, 128.5, 131.7, 139.6, 171.5. ATR-IR: $\nu(\text{CH})$ 3029, $\nu(\text{CH})$ 2964, $\nu(\text{CH})$ 2826, $\nu(\text{C}\equiv\text{C})$ 2225, $\nu(\text{C}=\text{N})$ 1666, $\nu(\text{C}=\text{C})$ 1490, $\delta(\text{CH})_{\text{Ar}}$ 755. FT-Raman: $\nu(\text{CH})$ 3061, $\nu(\text{CH})$ 2904, $\nu(\text{C}\equiv\text{C})$ 2221, $\nu(\text{C}=\text{N})$ 1667, $\nu(\text{C}=\text{C})$ 1598, $\delta(\text{CH})$ 1258, $\delta(\text{CH})_{\text{Ar}}$ 1002. UV (EtOH), λ_{max} (log ϵ): 204 (4.60), 240 (4.35), 250 (4.30). HRMS, m/z : calculated for $\text{C}_{20}\text{H}_{22}\text{N}$ ($\text{M} + \text{H}$) 276.1752, found 276.1746. EI MS (m/z , %): 276.1 (M^+ , 95), 234.2 (25), 161.4 (20), 91.2 (100).

(*E*)-*N*-(2,2-Dimethyl-5-phenylpent-4-ynylidene)-4-chlorobenzylamine (**19b**). Yellowish oil. ^1H NMR (CDCl_3): 1.28 (s, 6 H, $2 \times \text{CH}_3$), 2.57 (s, 2 H, CH_2), 4.58 (s, 2 H, CH_2), 7.21 (s, 4 H, Ar), 7.26–7.39 (m, 5 H, Ar), 7.75–7.78 (m, 1 H, Ar). ^{13}C NMR (CDCl_3): 24.9, 30.8, 39.8, 63.9, 82.9, 87.39, 123.9, 127.8, 128.3, 128.6, 129.1, 131.7, 132.6, 138.1, 171.8. ATR-IR: $\nu(\text{CH})$ 2961, $\nu(\text{CH})$ 2826, $\nu(\text{C}\equiv\text{C})$ 2223, $\nu(\text{C}=\text{N})$ 1665, $\nu(\text{C}=\text{C})$ 1189, $\nu(\text{CCl})$ 1088, $\nu(\text{CCl})$ 1014, $\delta(\text{CC})_{\text{Ar}}$ 755. FT-Raman: $\nu(\text{CH})$ 3060, 2907, $\nu(\text{C}\equiv\text{C})$ 2221, $\nu(\text{C}=\text{N})$ 1666, $\nu(\text{C}=\text{C})$ 1596, $\delta(\text{CH})$ 1061, $\nu(\text{CCl})$ 1089, $\delta(\text{CH})_{\text{Ar}}$ 1001. UV (EtOH), λ_{max} (log ϵ): 204 (4.48), 224 (4.24), 240 (4.27). HRMS, m/z : calculated for $\text{C}_{20}\text{H}_{21}\text{ClN}$ ($\text{M} + \text{H}$) 310.1363, found 310.1356. EI MS (m/z , %): 310.4 ($\text{M} + \text{H}^+$, 65), 268.3 (15), 184.1 (10), 124.9 (100).

(*E*)-*N*-(2,2-Dimethyl-5-phenylpent-4-ynylidene)-4-methoxybenzylamine (**19c**). Yellowish oil. ^1H NMR (CDCl_3): 1.24 (s, 6 H, $2 \times \text{CH}_3$), 2.56 (s, 2 H, CH_2), 3.74 (s, 3 H, CH_3), 4.55 (s, 2 H, CH_2), 6.75–6.78 (m, 2 H, Ar), 7.14–7.17 (m, 2 H, Ar), 7.24–7.38 (m, 5 H, Ar), 7.73–7.75 (m, 1 H, Ar). ^{13}C NMR (CDCl_3): 24.9, 30.9, 39.7, 55.4, 64.2, 82.8, 87.6, 113.9, 124.0, 127.7, 128.0, 128.9, 131.7, 131.8, 158.6, 171.1. ATR-IR: $\nu(\text{CH})$ 3009, 2985, 2820, $\nu(\text{C}\equiv\text{N})$ 2231, $\nu(\text{C}=\text{N})$ 1662, $\nu(\text{C}=\text{C})$ 1511, $\nu(\text{CO})$ 1241, $\nu(\text{CC})_{\text{Ar}}$ 757. FT-Raman: $\nu(\text{CH})$ 3066, 2918, 2895, $\nu(\text{C}\equiv\text{C})$ 2236, 2220, $\nu(\text{C}=\text{N})$ 1662, $\nu(\text{C}=\text{C})$ 1597, $\nu(\text{CO})$ 1257, $\delta(\text{CH})_{\text{Ar}}$ 1001. UV (EtOH), λ_{max} (log ϵ): 204 (4.55), 230 (4.36), 240 (4.35). HRMS, m/z : calculated for $\text{C}_{21}\text{H}_{24}\text{NO}$ ($\text{M} + \text{H}$) 306.1858, found 306.1852. EI MS (m/z , %): 306.4 ($\text{M} + \text{H}^+$, 100), 121.1 (85).

2,2-Dimethyl-5-phenylpent-4-yn-1-amine Oxalate (**22**)

A solution of potassium 3,7-dimethyloctan-3-olate (50 wt.% solution in heptane; 3.6 ml, 7.3 mmol) was added dropwise to a stirred solution of the Schiff base (**19a**; 1 g, 3.6 mmol) in tetrahydrofuran (40 ml) at -50°C and the solution was stirred at this temperature for 20 h. Water (10 ml) was added and the stirred solution was allowed to warm up to room temperature and then extracted with diethyl ether (3×20 ml). The combined extracts were dried with anhydrous MgSO_4 and evaporated under reduced pressure. The residue was dissolved in toluene and added to a stirred solution of oxalic acid dihydrate (0.45 g, 3.6 mmol) in water (25 ml). This solution was refluxed for 1 h and the hot aqueous layer was separated and cooled (10°C). The formed crystals were isolated by filtration and dried at 40°C to give 0.6 g (70%) of white crystals of oxalate **22**; m.p. $168\text{--}170^\circ\text{C}$. For $\text{C}_{15}\text{H}_{19}\text{NO}_4$ (277.32) calculated: 64.97% C, 6.91% H, 5.05% N; found: 65.35% C, 7.09% H, 5.23% N. ^1H NMR ($\text{DMSO}-d_6$): 1.09 (s, 6 H, $2 \times \text{CH}_3$), 2.49 (s, 2 H, CH_2), 2.83 (s, 2 H, CH_2), 6.99–7.61 (m, 8 H, Ar + NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): 24.2, 29.7, 33.4, 47.7, 82.8, 87.2, 122.9, 128.1, 128.6, 131.3, 164.2. ATR-IR: $\nu(\text{NH})$ 3361, $\nu(\text{CH})$ 3054, $\nu(\text{CH})$ 2966, $\nu(\text{C}=\text{O})$ 1721, $\nu(\text{C}=\text{O})$ 1699, $\nu(\text{CC})_{\text{Ar}}$ + $\delta(\text{NH}^+)$ 1602, $\nu(\text{CH})$ + $\delta(\text{NH}^+)$ 1211. FT-Raman: $\nu(\text{CH})$ 3061, 2969, $\nu(\text{C}\equiv\text{C})$ 2251, 2222, $\nu(\text{C}=\text{O})$ 1718, $\nu(\text{C}=\text{C})$ 1598, $\delta(\text{CH})$ 1429, $\delta(\text{CH})$ 1029, 1001. UV (EtOH), λ_{max} (log ϵ): 204 (4.57), 240 (4.34), 250 (4.32). HRMS, m/z : calculated for $\text{C}_{13}\text{H}_{18}\text{N}$ ($\text{M} + \text{H}$) 188.1439,

found 188.1434. EI MS (m/z , %): 188.2 (M^+ , 5), 186.3 (M^- , 10), 172.2 (75), 170.1 (35), 155.2 (100), 141.3 (35), 128.2 (30), 115.2 (50), 91.2 (30).

Preparation of 2,2-Dimethyl-5-phenylpent-4-yn-1-amine Oxalate (**22**) and 2,2-Dimethyl-5-phenylpenta-3,4-dien-1-amine Oxalate (**23**)

Method A. To a stirred solution of Schiff base (**19**; 114 mmol) in toluene (150 ml) was added *t*-BuOK (12.8 g, 114 mmol) and the solution was refluxed for 1 h. The solution was cooled to room temperature and diluted with water (200 ml). The toluene layer was separated and washed with water (100 ml). A solution of oxalic acid dihydrate (14.5 g, 114 mmol) in water (500 ml) was added to the stirred toluene layer and the mixture was refluxed for 30 min. The hot layers were separated and the aqueous layer was washed with hot toluene (100 ml) and cooled (10 °C). The formed crystals were filtered off and dried at 40 °C to give the desired mixture of oxalates **22** and **23** (**22/23** 5:1). The ratio was determined by ^1H NMR (DMSO) and the results are summarized in Table I. For $\text{C}_{15}\text{H}_{19}\text{NO}_4$ (277.32) calculated: 64.97% C, 6.91% H, 5.05% N; found: 65.27% C, 7.14% H, 5.30% N.

Method B. To a stirred solution of Schiff base (**19**; 114 mmol) in THF (150 ml) was added *t*-BuOK (12.8 g, 114 mmol) and the solution was refluxed for 1 h. The solution was cooled to room temperature, diluted with water (200 ml) and then extracted with diethyl ether (3 × 150 ml). The combined extracts were washed with brine (100 ml) and dried with anhydrous MgSO_4 . The residue after evaporation was dissolved in toluene (100 ml), a solution of oxalic acid dihydrate (14.5 g, 114 mmol) in water (500 ml) was added and the mixture was refluxed for 30 min. The hot layers were separated, the aqueous layer was washed with hot toluene (50 ml) and cooled (10 °C). The formed crystals were filtered off and dried at 40 °C to give 24 g (76%) of the desired mixture of oxalates **22** and **23** (**22/23** 4:1). Comparison of the NMR and FT-Raman spectra with the corresponding spectra of **22** led to the following spectral characteristics of 2,2-dimethyl-5-phenylpenta-3,4-dien-1-amine oxalate (**23**): ^1H NMR ($\text{DMSO}-d_6$): 1.10 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 2.84 (s, 2 H, CH_2), 5.75 (d, 1 H, $J = 6.55$, $\text{CH}=\text{C}$), 6.42 (d, 1 H, $J = 6.55$, $\text{CH}=\text{C}$), 6.20–7.48 (m, 8 H, Ar + NH_3). ^{13}C NMR ($\text{DMSO}-d_6$): 24.1, 25.5, 35.0, 48.8, 96.9, 102.1, 126.5, 127.1, 128.7, 133.9, 163.3, 203.1. FT-Raman: $\nu(\text{CH})$ 3068, $\nu(\text{C}=\text{C})$ 1952, 1600, $\delta(\text{CH})$ 1495, $\delta(\text{CH})$ 1003. HRMS, m/z : calculated for $\text{C}_{13}\text{H}_{18}\text{N}$ ($M + \text{H}$) 188.1439, found 188.1433. EI MS (m/z , %): 187.2 (M , 100), 172.2 (40), 143.2 (80), 128.2 (45), 115.2 (30), 91.2 (25).

Method B was also used for preparation of **22** and **23** from (*E*)-*N*-(2,2-dimethyl-5-phenylpent-4-ynylidene)-4-chlorobenzylamine (**19b**) and (*E*)-*N*-(2,2-dimethyl-5-phenylpent-4-yn-1-ylidene)-4-methoxybenzylamine (**19c**) providing compounds **22** and **23** in ratios of 3.5:1 and 3:1, respectively.

5-Benzyl-3,3-dimethyl-3,4-dihydro-2*H*-pyrrole (**1**)

Method A. Catalyst screening. To a stirred solution of the mixture of amines **22** and **23** (200 mg, 0.72 mmol) in dichloromethane (5 ml) was added the relevant catalyst (3 mole %) and the solution was refluxed for appropriate time. The solution was cooled to room temperature and diluted with brine (2 ml). The black precipitate was removed by filtration, the dichloromethane layer was separated and dried with anhydrous MgSO_4 . The solution after removal of MgSO_4 was evaporated under reduced pressure to give the desired product as unstable yellow oil, which was analyzed by GC (RTX-5 amine column). The results are given in Table II.

Method B. To a stirred solution of amine **22** (2 g, 11 mmol) in dichloromethane (15 ml) was added AgBF_4 (40 mg, 0.2 mmol) and the solution was refluxed for 6 h. The solution was cooled to room temperature and diluted with brine (5 ml). The black precipitate was removed, the dichloromethane layer was separated and dried with anhydrous MgSO_4 . The solution after removal of MgSO_4 was evaporated under reduced pressure to give 2 g (quantitative yield) of the desired product as unstable yellow oil which was immediately used in the next step.

Method C. To a stirred suspension of oxalates **22** and **23** (4:1; 23 g, 83 mmol) in dichloromethane (150 ml) was added a solution of NaHCO_3 (200 ml, 10%). The aqueous layer was extracted with dichloromethane (100 ml), the combined extracts were washed with brine (100 ml) and dried with anhydrous MgSO_4 . After its removal, AgBF_4 (325 mg, 1.7 mmol) was added and the solution was refluxed for 6 h. The reaction mixture was then cooled to room temperature, diluted with brine (50 ml) and the formed black precipitate was removed by filtration through a Celite pad. The dichloromethane layer was separated and dried with anhydrous MgSO_4 . The yellow oily residue (15.5 g, quantitative yield) obtained after evaporation under reduced pressure was immediately used in the next step.

6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (**3**)

Sodium hydrogen carbonate (14.5 g, 1.7 mol) was added to a stirred solution of 5-benzyl-3,3-dimethyl-3,4-dihydro-2H-pyrrole (**1**; 15.3 g, 82 mmol) in methanol (210 ml) and, after short stirring, solid 2-bromo-1-(4-chlorophenyl)ethan-1-one (**2**; 23.9 g, 102 mmol) was added. The mixture was stirred for 20 h, the solid portion was filtered off, washed with small amount of methanol, introduced into vigorously stirred water (150 ml) and stirred at 40 °C for 1 h. The product was filtered off, washed with water and dried at 40 °C to give 22.2 g (84%) of yellow crystals of **3**; m.p. 104–106 °C. ^1H NMR (CDCl_3): 1.28 (s, 6 H, CH_3), 2.78 (s, 2 H, CH_2), 3.71 (s, 2 H, CH_2N), 6.69 (s, 1 H, pyrrole CH), 6.97–7.51 (m, 9 H, Ar).

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