One-Pot Synthesis of Substituted Δ^1-Pyrrolines through the Michael Addition of Nitroalkanes to Chalcones and Subsequent Reductive Cyclization in Aqueous Media

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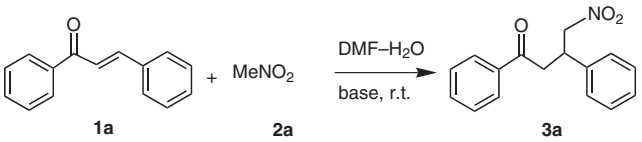
Abstract: A facile and efficient one-pot synthesis of substituted Δ^1-pyrrolines in aqueous media has been developed. Upon treatment with aqueous sodium hydroxide in *N*,*N*-dimethylformamide, a range of chalcones underwent room temperature Michael addition reactions with nitroalkanes. The resulting adducts were directly reduced in situ with Zn/HCl (aq) and subsequently underwent an intramolecular cyclization, affording the corresponding substituted Δ^1-pyrrolines in high yields.

Key words: chalcones, cyclizations, Michael additions, hydrogenations, pyrrolines

Over the past few decades, the use of nitroalkanes as key building blocks in organic synthesis has been steadily growing. They are easily available, versatile, and stabilized carbon nucleophiles that can react with common electrophiles such as haloalkanes, aldehydes, and Michael acceptors, leading to carbon–carbon bond formation.[1,2] With regard to the Michael addition reactions of nitroalkanes, the adducts obtained still retain the nitro function and, therefore, are capable of undergoing subsequent transformation of the nitro group after the main addition process. The nitro group can be removed from the molecule by two distinct strategies: 1) replacement of the nitro group with hydrogen through a nucleophilic addition-denitration process[3–5] and 2) conversion of the nitro group into a carbonyl group by the Nef reaction.[6–8] Alternatively, reduction of the nitro group to a primary amine can be easily realized, thus modifying of the oxidation state of the nitrogen atom.[9–11] This latter process is often accompanied by a subsequent nucleophilic ring closure, when a carbonyl or an ester function is present in the structure, to directly afford pyrrolidines or pyrrolidinones.[12–14] Most of these reductions involve the use of catalytic hydrogenation in the presence of Raney nickel or Pd/C, while in some cases, complex hydrides and metals such as zinc or iron are used. It has been demonstrated that the reducing system employed plays an important role in the transformations. The reductive cyclization of γ-nitroketones with Zn/HCO_2H–EtOH has been reported to consistently produce a mixture of pyrroline *N*-oxides and pyrrolines.[15] When γ-nitro diketone is treated with complex hydrides in methanol, a different diastereomeric composition to that obtained by catalytic hydrogenation with Pd/C is observed.[16] It is assumed that, in the course of the reduction, the nitro group in the adduct may first be transformed by a Nef conversion into a carbonyl group, and the nitrogen present in the final product could be provided by ammonium acetate.

It should be mentioned that the above transformations were carried out by a sequence of separate reaction steps, each of which required its own conditions, reagents, solvent, and catalyst. After each reaction was complete, the solvent and the waste were removed and discarded, and the intermediate product was separated and purified. However, increasing environmental and economic pressures are forcing the chemical community to search for more efficient synthetic methods that use small, simple components and environmentally benign solvents to generate complex structures in one pot, much the same as nature does.[17] These considerations, together with our continuing interest in the synthetic utility of nitroalkanes,[18] drove us to develop new methodologies for the synthesis of important targets. We wish to report here the one-pot synthesis of substituted Δ^1-pyrrolines in aqueous media.

The Michael addition reactions of nitroalkanes to electron-deficient alkenes have been extensively reported.[1a,b,19] It has been revealed that highly polar solvents such as dimethyl sulfoxide, methanol, and water are able to facilitate the addition of nitroalkanes even to less reactive alkenes such as methylvinyl ketone under neutral conditions.[20] Of these solvents, water minimizes the formation of undesired multiple adducts.



Scheme 1 Michael addition of nitromethane **2a** to chalcone **1a**.

In the present work, the reaction of chalcone **1a** and nitromethane **2a** was investigated in the presence of various bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K_2CO_3, Et_3N and NaOH in the aqueous medium. Much to our delight, all the reactions proceeded smoothly in a mixture of *N*,*N*-dimethylformamide (DMF) and water at room temperature, affording the Michael adduct 4-ni-

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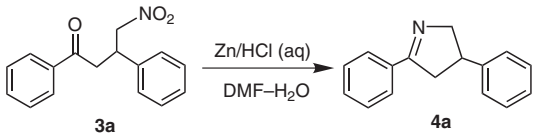
tro-1,3-diphenylbutan-1-one (**3a**), in good to high yields (Scheme 1). When the reaction was performed in the presence of aqueous NaOH in DMF at room temperature, for example, TLC indicated that the substrates were converted into one main product within ten minutes. After workup and purification by column chromatography of the resulting reaction mixture, the sole product **3a** was obtained in 92% yield. However, it was observed that the same reaction proceeded sluggishly in ethanol–water and no reaction occurred in tetrahydrofuran–water mixtures under the same conditions. A combination of DMF and aqueous NaOH proved to be the most suitable and effective solvent/base pair among those examined, giving **3a** in good yield within a short reaction time. It is worth mentioning that similar reactions reported recently took several hours for complete conversion at room temperature or under reflux conditions.[21]



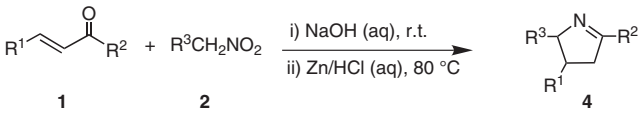
Scheme 2 The reduction of the Michael adduct **3a**.

We then turned our attention to the reduction of the Michael adduct. Thus, when **3a** was reduced with Zn/HCl (aq.) in DMF–H_2O (1:1 by v/v) at 80 °C for about 90 minutes, workup and column chromatography of the resulting reaction mixture gave only a single product in 85% yield. Spectral and analytical data characterized this compound as a mixture of racemic enantiomers of the Δ^1-pyrroline 3,5-diphenyl-3,4-dihydro-2*H*-pyrrole (**4a**) (Scheme 2). Unfortunately, these enantiomers could not separated using conventional chromatographic techniques. Apparently, the reduction of the nitro group in adduct **3a** was followed by an intramolecular cyclization, generating the substituted Δ^1-pyrroline **4a** in high yield, without isomerization to the Δ^2-pyrroline[22] or further hydrogenation to the corresponding pyrrolidine.[23] It is worth noting that, unlike other reported reducing conditions,[15,24] the pyrroline *N*-oxide could not be detected in the present reaction system. The results indicate that the reaction media greatly effects the reductive cyclization of the Michael adducts of nitroalkanes.

The success of the Michael addition reaction and the reductive cyclization, promoted us to explore a possible one-pot transformation of nitroalkanes directly into substituted Δ^1-pyrrolines in aqueous media. Thus, the reaction of **1a** with **2a** was performed in DMF/NaOH at room temperature and, after stirring for about ten minutes, the mixture was then subjected to the above reductive cyclization conditions directly with Zn/HCl. The mixture was kept at 80 °C under the reducing conditions for about 90 minutes, during which TLC monitoring indicated that **3a** had been completely consumed. Workup and column chromatography of the resulting reaction mixture furnished a white product characterized as **4a** in 82% yield (Table 1, entry 1).

To test the scope of the protocol, a series of chalcones **1b–f** and nitroalkanes **2a** and **2b** were also subjected to the conditions described above. The reactions of **1b–f** with **2a** proceeded smoothly, affording the corresponding substituted Δ^1-pyrroline **4b–f** in high yields (Table 1, entries 2–8). In the same fashion, the reaction of chalcone **1a** with nitroethane **2b** led to the corresponding substituted Δ^1-pyrroline **4g** under the mild conditions, within 150 minutes, in good yield (Table 1, entry 7). It should be mentioned that the diastereomers of **4g** were successfully separated by column chromatography on silica gel (elu-

Table 1 One-Pot Synthesis of Substituted Δ^1-Pyrrolines **4** in Aqueous Media from Nitroalkanes **1**



Entry	Substrates					Reaction Time (min)		Product	Yield (%)[a]
	1	R^1	R^2	**2**	R^3	i	ii		
1	**1a**	Ph	Ph	**2a**	H	10	90	**4a**	82
2	**1b**	Ph	4-ClPh	**2a**	H	10	90	**4b**	79
3	**1c**	4-ClPh	Ph	**2a**	H	10	90	**4c**	78
4	**1d**	4-MePh	4-ClPh	**2a**	H	10	90	**4d**	80
5	**1e**	4-MeOPh	Ph	**2a**	H	10	90	**4e**	77
6	**1f**	4-MeOPh	4-ClPh	**2a**	H	10	90	**4f**	76
7[b]	**1a**	Ph	Ph	**2b**	CH_3	15	150	**4g-1** **4g-2**	38 35

[a] Isolated yields after silica gel chromatography of racemic enantiomers for **4a–g**.
[b] **4g-1** and **4g-2** are diastereomers.

ent: petroleum ether–ethyl acetate, 50:1). The present protocol thus provides a facile and convenient route to five-membered aza-heterocycles, Δ^1-pyrrolines **4**, which are found in numerous natural products that possess important bio- and pharmacological activities such as pheromones, alkaloids, steroids, hemes, and chlorophylls.[25] This Δ^1-pyrroline unit is also an important synthetic building block for a large variety of functionalized aza-heterocycles, especially as the pro-chiral center, as part of a cyclic imine, is amendable to further transformations.[26]

In summary, a facile and efficient one-pot synthesis of substituted Δ^1-pyrrolines has been developed. The strategy centers around Michael addition of nitroalkanes to chalcones with subsequent reductive cyclization in aqueous media. The simplicity of execution, the mild conditions, good yields, ready availability of substrates and a broad range of synthetic utility of the products, especially in relation to recent environmental concerns, makes the protocol very attractive for academic research and practical applications. The scope and an asymmetric version of the protocol are under investigation in our laboratory.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard at 25 °C on a Varian Inova-500 spectrometer. IR spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer in the range of 400–4000 cm^{-1}. Petroleum ether (PE) used was the fraction boiling in the range 30–60 °C.

Synthesis of Substituted Δ^1-Pyrrolines 4; Typical Procedure

NaOH (1.0 M, 10 mL) was added to a stirred solution of **1a** (2.08 g, 10 mmol) and **2a** (0.61 g, 10 mmol) at r.t. in DMF (10 mL) and the resulting mixture was stirred until the reaction was complete (~10 min as indicated by TLC) then granular Zn (3.27 g, 50 mmol) was added. The mixture was stirred at 80 °C and conc HCl (20 mL) was added very slowly. The mixture was stirred at 80 °C under the reducing conditions for about 90 min, then allowed to come to r.t., neutralized with sat. aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (PE–EtOAc, 50:1) to give the substituted Δ^1-pyrroline **4a**.

3,5-Diphenyl-3,4-dihydro-2*H*-pyrrole (4a)

White solid; mp 56–57 °C.

IR (KBr): 696, 760, 1449, 1495, 1548, 1615, 1689, 2931 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.12 (m, 1 H), 3.48 (m, 1 H), 3.66 (m, 1 H), 4.13 (m, 1 H), 4.54 (m, 1 H), 7.24 (m, 3 H), 7.32 (m, 2 H), 7.45 (m, 3 H), 7.89 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 43.2, 44.3, 69.9, 126.7, 127.1, 127.9, 128.8, 129.0, 130.8, 134.5, 145.3, 172.7.

Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.70; H, 6.90; N, 6.40.

5-(4-Chlorophenyl)-3-phenyl-3,4-dihydro-2*H*-pyrrole (4b)

White solid; mp 65.5–67.5 °C.

IR (KBr): 761, 828, 1400, 1456, 1558, 1593, 1620, 2923 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.06 (m, 1 H), 3.45 (m, 1 H), 3.68 (m, 1 H), 4.11 (m, 1 H), 4.52 (m, 1 H), 7.22 (m, 3 H), 7.31 (m, 2 H), 7.40 (d, *J* = 7.0 Hz, 2 H), 7.80 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 43.2, 44.2, 69.9, 126.8, 127.0, 129.02, 129.03, 129.2, 133.0, 136.9, 145.0, 171.6.

Anal. Calcd for $C_{16}H_{14}ClN$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.41; H, 5.40; N, 5.27.

3-(4-Chlorophenyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole (4c)

White solid; mp 68–69 °C.

IR (KBr): 690, 820, 1462, 1498, 1548, 1647, 1694, 2926 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.05 (m, 1 H), 3.48 (m, 1 H), 3.64 (m, 1 H), 4.07 (m, 1 H), 4.52 (m, 1 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 7.44 (m, 3 H), 7.86 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 42.5, 44.3, 69.8, 127.9, 128.4, 128.8, 129.1, 130.9, 132.4, 134.3, 143.8, 172.5.

Anal. Calcd for $C_{16}H_{14}ClN$: C, 75.14; H, 5.52; N, 5.48. Found: C, 75.52; H, 5.38; N, 5.30.

5-(4-Chlorophenyl)-3-*p*-tolyl-3,4-dihydro-2*H*-pyrrole (4d)

White solid; mp 66–67 °C.

IR (KBr): 819, 1392, 1457, 1483, 1551, 1600, 1646, 2922 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.33 (s, 3 H), 3.03 (m, 1 H), 3.43 (m, 1 H), 3.64 (m, 1 H), 4.08 (m, 1 H), 4.50 (m, 1 H), 7.11 (m, 4 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.2, 42.9, 44.2, 69.9, 126.9, 129.0, 129.2, 129.7, 133.1, 136.3, 136.8, 142.0, 171.6.

Anal. Calcd for $C_{17}H_{16}ClN$: C, 75.69; H, 5.98; N, 5.19. Found: C, 75.38; H, 6.10; N, 5.26. MS: *m*/*z* = 252.1 $[M + H]^+$.

3-(4-Methoxyphenyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole (4e)

White solid; mp 55–56 °C.

IR (KBr): 762, 827, 1452, 1513, 1614, 1646, 2928 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.04 (m, 1 H), 3.45 (m, 1 H), 3.62 (m, 1 H), 3.78 (s, 3 H), 4.10 (m, 1 H), 4.51 (m, 1 H) 6.86 (d, *J* = 7.0 Hz, 2 H), 7.15 (d, *J* = 7.0 Hz, 2 H), 7.44 (d, *J* = 7.0 Hz, 3 H), 7.89 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 42.4, 44.3, 55.5, 70.0, 114.3, 127.9, 128.1, 128.4, 128.8, 128.9, 130.8, 134.6, 137.3, 158.4, 172.7.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.02; H, 6.70; N, 5.80.

5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyrrole (4f)

White solid; mp 65–67 °C.

IR (KBr): 676, 821, 1448, 1483, 1545, 1652, 1690 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.01 (m, 1 H), 3.42 (m, 1 H), 3.63 (m, 1 H), 3.78 (s, 3 H), 4.06 (m, 1 H), 4.49 (m, 1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.79 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 42.5, 44.3, 55.5, 69.9, 114.4, 129.0, 129.2, 129.4, 133.1, 136.8, 137.0, 158.4, 171.7.

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.27; H, 5.45; N, 4.71.

2-Methyl-3,5-diphenyl-3,4-dihydro-2*H*-pyrrole (4g-1)

White solid; mp 79–80 °C.

IR (KBr): 698, 768, 1449, 1496, 1550, 1603, 1694, 2910 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.44 (d, *J* = 6.5 Hz, 3 H), 3.12 (m, 2 H), 3.56 (m, 1 H), 4.27 (m, 1 H), 7.23 (m, 3 H), 7.32 (m, 2 H), 7.42 (m, 3 H), 7.87 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.5, 44.8, 52.1, 76.9, 126.8, 127.5, 127.9, 128.7, 129.0, 130.8, 134.6, 144.1, 170.8.

Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.45; H, 7.18; N, 5.84.

2-Methyl-3,5-diphenyl-3,4-dihydro-2*H*-pyrrole (4g-2)
White solid; mp 81–82 °C.

IR (KBr): 695, 761, 1216, 1451, 1548, 1647, 1694 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.96 (d, *J* = 7.0 Hz, 3 H), 3.34 (m, 2 H), 3.74 (m, 1 H), 4.58 (m, 1 H), 7.15 (m, 2 H), 7.23 (m, 1 H), 7.29 (m, 2 H), 7.45 (m, 3 H), 7.91 (m, 2 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 17.4, 41.3, 47.3, 71.4, 126.7, 127.9, 128.3, 128.5, 128.8, 130.8, 134.7, 141.5, 172.2.

Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.46; H, 7.34; N, 5.80.

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