Reaction of N^1,N^2-Diarylamidines with 2,3-Diphenylcyclopropenone

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Reaction of N^1,N^2-diarylacetamidines **1a – c** with 2,3-diphenylcyclopropenone **2** led to formation of addition products 2-methyl-1-aryl-2-arylamino-4,5-diphenyl-1,2-dihydro-3*H*-pyrrol-3-ones **3a – c**. While N^1,N^2-diarylformamidines **1d – f** reacted with 2,3-diphenylcyclopropenone **2** to afford 3-aryl-(*N*-4-arylformamidoyl)amino-2,3-diphenyl propionic acids **7a – c**.

Key words: Amidine, Pyrrole, Diphenylcyclopropenone, 3-Formamidoylpropionic Acid

Introduction

The fascinating chemistry of cyclopropenones has attracted the attention of numerous researchers over the past three decades [1, 2] with special emphasis on the behaviour of diphenylcyclopropenone **2** [3]. Diphenylcyclopropenone has been found to react with a wide range of imines, 1,1-tetraalkylguanidines and other compounds containing the C=N moiety to form almost aza-cyclo-pentenones (pyrrolinones) *via* a formal [2 + 3] cycloaddition reaction [4 – 9]. In some cases, reaction of **2** with guanidine, 1-alkyl- and 1-phenylsubstituted guanidines, 1,2-diphenyl- and 1,2,3-triphenylguanidine gave the corresponding 5,6-dihydro-4(1*H*)pyrimidinone *via* a formal [3 + 3] cycloaddition reaction [8].

Recently we have synthesized some 2-(arylamino-pyridinylidene)propanedinitriles from the reaction of N^1,N^2-diarylacet- and propionamidines with (2,3-diphenylcyclopropen-2-ylidene)propanedinitrile [10]. Also we have synthesized some of 2-cyclohexyl- and 2-arylaminomethylene-Δ^4-pyrrolin-3-ones from the reaction of N,N'-dicyclohexyl- and diarylethane-1,2-diylidenediamines with **2** [11].

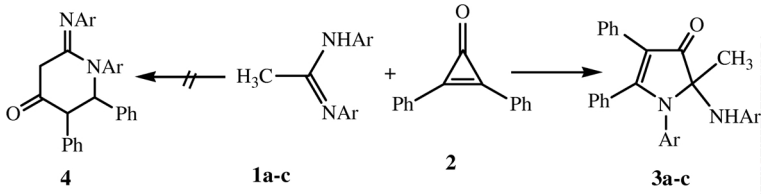
As part of our programme to develop efficient procedures for the synthesis of heterocycles *via* the nucleophilic reactions of an amidine group (–HN–CR=N–) with π-deficient compounds we have synthesized several heterocyclic compounds like diazepines [12], azepines [13], 1,2-Dihydropyridines [14], indoles [15], benzoindoles [15], spiroindoles [13, 16, 17] and benzoisoquinolines [18].

In the literature survey we have found that the reaction of N^1,N^2-Diarylacetamidines and formamidines and 2,3-diphenylcyclopropenone **2** was not reported. So, this prompted us to investigate the behaviour of N^1,N^2-Diarylacetamidines and formamidines **1a – f** towards 2,3-diphenylcyclopropenone **2**.

Results and Discussion

First we investigated the reaction of N^1,N^2-Diarylacetamidines **1a – c** and 2,3-diphenylcyclopropenone **2** in diethyl ether which led to formation of Δ^4-pyrrolin-3-ones **3a – c** (Scheme 1). The structure of compounds **3a – c** was deduced from their elemental analyses and their IR and ^{1}H NMR spectra. For example, the ^{1}H NMR spectrum of **3a** exhibited three singlets identified as methyl groups ($\delta = 1.56$, 2.26 and 2.34), and the amino proton as a singlet ($\delta = 10.15$) along with multiplets ($\delta = 7.11 - 7.52$) for the aromatic protons. Also ^{13}C-135/90-DEPT spectra of **3a** showed the presence of the quaternary carbon atom C-2 ($\delta = 53.42$). Its IR spectrum showed two absorptions at $\nu = 3295$ cm^{-1} for the amino group (NH) and at $\nu = 1676$ cm^{-1} for the carbonyl group (C=O). Thus the presence of the acetamidinic methyl group and the difference observed in the number of signals excludes structure **4** and supports structure **3**. For more details see the Experimental Section.

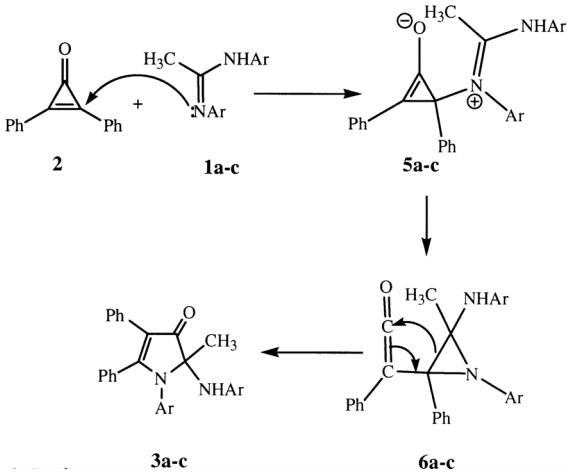
Formation of **3a – c** may be rationalized as a formal [2 + 3] cycloaddition reaction similar to the rationalization given by Eicher [6] for the reaction of **2** with imines as depicted in Scheme 2 through an initial at-



4 **1a-c** **2** **3a-c**

a: Ar = 4-MeC_6H_4; **b**: Ar = 4-$MeOC_6H_4$; **c**: Ar = C_6H_5

Scheme 1.

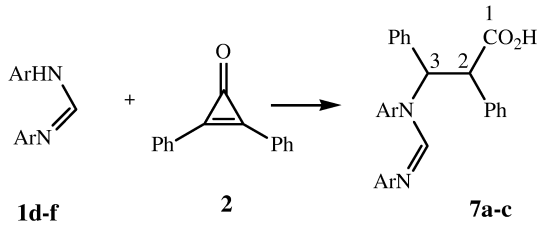


2 **1a-c** **5a-c** **3a-c** **6a-c**

Scheme 2.

tack of the imino nitrogen atom C=N of the amidine on carbon atoms C-2 or C-3 of the cyclopropenone **2** giving immonim betaines **5a – c** which rearrange to the aziridineketenes **6a – c** to give ultimately **3a – c**.

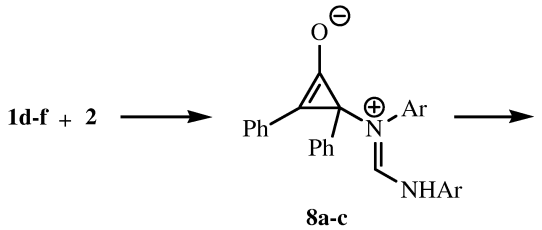
Next, the reaction of N^1,N^2-diarylformamidines **1d – f** with 2,3-diphenylcyclopropenone **2** gave unexpectedly 3-formamidoyl propionic acid derivatives **7a – c** in 67 – 80% yield. Elucidation of structure **7a – c** was assigned on the basis of analytical and spectroscopic data. The IR spectra of **7a – c** showed absorptions at 3280 – 3295 cm^{-1} and 1678 – 1680 cm^{-1} indicating the presence of a COOH group. The ^1H NMR spectra showed the presence of two AB-systems at $\delta_A = 4.55 - 6.26$ and $\delta_B = 6.04 - 6.42$ ppm with coupling constants $^3J = 10.8 - 12.0$ Hz which indicate the presence of a vicinal coupling between 2-H and 3-H protons and singlet at 7.92 – 8.05 ppm was assigned to the formyl proton (CH=N) of the formamidoyl group, and a singlet at 10.13 – 10.48 ppm to the carboxylic proton. Moreover ^{13}C-135/90-DEPT spectra of **7a** for example showed two characteristic signals with a positive amplitude at higher field at $\delta = 52.73$ and 62.82 ppm, which were assigned to C-2 and C-3, respectively; another signal with a positive amplitude



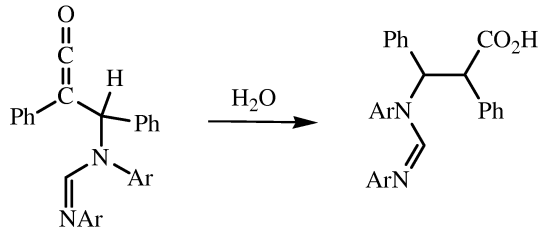
1d-f **2** **7a-c**

1d, 7a : Ar = 4-MeC_6H_4; **1e, 7b**: Ar = 4-$MeOC_6H_4$;
1f, 7c : Ar = 4-ClC_6H_4

Scheme 3.



8a-c



9a-c **7a-c**

Scheme 4.

at $\delta = 163.02$ ppm was assigned to the formamidinyl carbon atom. Compounds **7a – c** were isolated as a mixture of diastereomers, for more details see the Experimental Section.

Formation of **7a – c** may be rationalized as an initial attack of the nitrogen atom of CH=N of the amidine on the carbon atom C-2 or C-3 of the cyclopropenone **2** giving imminim betaines **8a – c** which rearrange (similarly as in Scheme 2) to the aziridineketenes **9a – c**. The latter undergo hydration to give the formamidoyl-

propionic acid derivatives **7a – c** (Scheme 4). Similar results were reported by Kascheres *et. al.* [19] for the reaction of pyrazoles with diphenylcyclopropenone. The source of water may be coming from the atmosphere or from the solvent.

Conclusion

This study showed that N^1,N^2-Diarylacetamidines behave like imines and benzamidines with **2** through formal [2 + 3] cycloaddition reaction giving the corresponding Δ^4-pyrrolin-3-ones. In contrast N^1,N^2-diarylformamidines led to formation of formamidoyl propionic acid derivatives when reacted with **2**.

Experimental Section

General

The uncorrected melting points were determined on a Griffin & George apparatus. Elemental analyses were carried out by Microanalytical Centre at Cairo University. The IR spectra (KBr) were recorded on a Shimadzu 470 spectrophotometer. The 400 MHz ^{1}H NMR, spectra were observed on a Bruker AM 400 spectrometer. The MS (70 eV, electron impact mode) were recorded on a Jeol JMS600 instrument. Preparative layer chromatography (plc) used air dried 1.0 mm thick layers of slurry applied silica gel Merck PF_{254} on 48 cm wide and 20 cm high glass plates and toluene-ethyl acetate (2:1) as developing solvent. Zones were detected by the colour or by quenching of indicator fluorescence upon exposure to 254 nm light and eluted with acetone. Reactions were monitored by TLC.

Starting materials

N^1,N^2-Diarylacetamidines **1a – c** [20] and N^1,N^2-diarylformamidines **1d – f** [21] were prepared as reported.

General procedure for preparation of Δ^4-pyrrolin-3-ones **3a – c**

A solution of **2** (206 mg, 1.0 mmol) in diethyl ether (10 ml) was added to solutions of **1a – c** (1.0 mmol) in diethyl ether (20 ml). The mixtures were left at room temperature for 2 – 3 h. The mixtures were concentrated and the residues were subjected to PLC using toluene/ethyl acetate (2:1) as the developing solvent to give one or two main zones. The faster moving one contained **3a, 3b** or **3c** respectively, while the more slowly moving one contained the unreacted cyclopropenone **2**. The zones were extracted, and recrystallized from ethanol and identified as follows:

*2-Methyl-1-(4-methylphenyl)-2-[(4-methylphenyl)amino]-4,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (***3a***)*

Yield 0.2 g (90%). – M.p. 226 – 227 °C. – IR (KBr): ν = 3295 (NH), 1676 (C=O) cm^{-1} . –^{1}H NMR (400 MHz, d_6– DMSO): δ = 1.53 (s, 3H, Me), 2.26 (s, 3H, Me), 2.34 (s, 3H, Me), 7.11 – 7.52 (m, 18H, Ar-H), 10.15 (s, 1H, NH). – ^{13}C{^{1}H} NMR (100 MHz, d_6– DMSO) δ = 19.23, 20.31, 20.53 (3 × Me), 53.42 (C-2), 114.36, 116.40, 126.35, 127.12, 127.75, 128.882, 129.33, 129.94, 130, 13, 131.44 (all Ar-*C*H), 110.65, 128.45, 131.10, 134.74, 137.13, 137.54, 143.40, 187.67. – MS (EI, 70 eV): m/z (%) = 444 (22) [M$^+$], 367 (11), 313 (49), 238 (28), 207 (48), 196 (91), 179 (100), 107 (28), 91 (28). – $C_{31}H_{28}N_2O$ (444.57): calcd. C 83.75, H 6.35, N 6.30; found C 83.63; H 6.30, N 6.22.

*2-Methyl-1-(4-methoxyphenyl)-2-[(4-methoxyphenyl)amino]4,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (***3b***)*

Yield 0.26 g (85%). – M.p. 203 – 206 °C. – IR (KBr): ν = 3300 (NH), 1685 (C=O) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 3H, Me), 3.78 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.82 – 7.54 (m, 18H, Ar-H), 8.50 (s, 1H, NH). – MS (EI, 70 eV): m/z (%) = 476 (100) [M$^+$], 445 (45) [M$^+$ -OMe], 399 (15), 345 (56), 270 (17), 207 (34), 123 (44), 91 (31). – $C_{31}H_{28}N_2O_3$ (476.57): calcd. C 78.13, H 5.92, N 5.88; found C 78.20, H 5.96, N 5.62.

*2-Anilino-2-methyl-1,4,5-triphenyl-1,2-dihydro-3H-pyrrol-3-one (***3c***)*

Yield 0.18 g (88%). – M.p. 220 – 222 °C. – IR (KBr): ν = 3290 (NH), 1680 (C=O) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (s, 3H, Me), 7.05 – 7.63 (m, 20H, Ar-H), 8.55 (s, 1H, NH). – MS (EI, 70 eV): m/z (%) = 416 (11) [M$^+$], 342 (9), 299 (10), 272 (14), 224 (38), 210 (3), 182 (100), 179 (69), 165 (50), 91 (79), 78 (18). – $C_{29}H_{24}N_2O$ (416.51): calcd. C 83.63, H 5.81, N 6.73; found C 83.55, H 5.72, N 6.70.

General procedure for preparation of 3-formamidoyl propionic acid **7a – c**

A solution of **2** (206 mg, 1.0 mmol) in diethyl ether (10 ml) was added to solutions of **1d – f** (1.0 mmol) in diethyl ether (20 ml). The mixtures were left at room temperature for 2 – 4 h. The mixtures were concentrated and the residues were subjected to PLC using toluene/ethyl acetate (2:1) as the developing solvent to give one or two main zones. The faster moving one contained **7a, 7b** or **7c** respectively. The zones were extracted, and recrystallized from the proper solvent and identified as follows:

*3-{(4-Methylphenyl)-[N-4-(methylphenyl)-formamidoyl]-amino}-2,3-diphenylpropionic acid (***7a***) as a mixture (3:1) diastereomers (A = major, B = minor)*

Yield 0.33 g (74%). – M.p. 220 – 222 °C. – IR(KBr): ν = 3295 (CO*OH*) 1676 (C=O) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H, Me, B), 2.15 (s, 3H, Me, A), 2.20

(s, 3H, Me, B), 2.25 (s, 3H, Me, A), 4.56 (d, $^3J = 12.0$ Hz, 1H, 2-H, B), 6.04 (d, $^3J = 12.0$ Hz, 1H, 3-H, B), 6.13 (d, $^3J = 11.0$ Hz, 1H, 2-H, A), 6.26 (d, $^3J = 11.0$ Hz, 1H, 3-H, A), 6.95 – 7.73 (m, 18H, Ar-H, A and B), 7.95 (s, 1H, formamidoyl-H, A and B), 10.16 (s, 1H, CO_2H, B), 10.20 (s, 1H, CO_2H, A). – $^{13}C\{^1H\}$ NMR (100 MHz, d_6–DMSO) $\delta = 20.45$ and 20.55 (2×Me, A), 20.46 and 20.65 (2×Me, B), 52.73 (C-2, A), 53.25 (C-2, B), 62.82 (C-3, A, B), 119.02, 127.67, 127.82, 128.05, 128.31, 128.38, 128.42, 128.53, 128.71, 128.80, 129.05, 129.13, 129.55 (all aryl *C*H), 163.02 (formamidinyl *C*H, A), 163.75 (formamidinyl CH, B), 127.27, 128.22, 129.07, 132.44, 132.48, 133.95, 136.33, 136.46, 137.13, 137.29, 138.47, 139.23, 168.87 (*C*O_2H, B), 169.04 (*C*O_2H, A) (all quart. *C*). – MS (EI, 70 eV): m/z (%) = 448 (4) [M^+], 342 (4), 313 (17), 224 (100), 196 (70), 179 (31), 107 (15), 91 (31), 44 (5). – $C_{30}H_{28}N_2O_2$ (448.56): calcd. C 80.33, H 6.29, N 6.25; found C 80.15, H 6.18, N 6.20.

*3-{(4-Methoxyphenyl)-[N-4-methoxyphenyl)-formamidoyl]-amino}-2,3-diphenyl propionic acid (***7b***) as a mixture (2:1) diastereomers (A = major, B = minor)*

Yield 0.37 g (80%). – M.p. 280 – 283 °C. – IR KBr): $\nu =$ 3290 (CO*OH*), 1680 (C=O); cm^{-1}. – ^1H NMR (400 MHz, d_6–DMSO): $\delta = 3.65$ (s, 3H, OMe, A and B), 3.72 (s, 3H, OMe, A and B), 4.56 (d, $^3J = 11.0$ Hz, 1H, 2-H, B), 6.05 (d, $^3J = 11.0$ Hz, 1H, 3-H, B), 6.18 (d, $^3J = 11.0$ Hz, 1H, 2-H, A), 6.28 (d, $^3J = 10.8$ Hz, 1H, 3-H, A), 6.74 – 7.58 (m, 18H, Ar-H, A and B), 7.92 (s, 1H, formamidoyl-H, A and B), 10.13 (s, 1H, CO_2H, B) 10.18 (s, 1H, CO_2H, A). – MS (EI, 70 eV): m/z (%) = 480 (14) [M^+], 462 (1) [M^+-H_2O], 246 (37), 244 (100), 179 (33), 123 (6), 91 (10), 55 (28). – $C_{30}H_{28}N_2O_4$ (480.55): calcd. C 74.98, H 5.78, N 5.83; found C 74.91, H 5.75, N 5.77.

*3-{(4-Chlorophenyl)-[N-4-chlorophenyl)-formamidoyl]amino}-2,3-diphenyl propionic acid (***7c***) as a mixture (2:1) diastereomers (A = major, B = minor)*

Yield 0.32 g (67%). – M.p. 235 – 237 °C. – IR (KBr): $\nu =$ 3280 (CO*OH*), 1679 (C=O) cm^{-1}. – ^1H NMR (400 MHz, d_6–DMSO): $\delta = 4.55$ (d, $^3J = 11.3$ Hz, 1H, 2-H, B), 6.15 (d, $^3J = 11.3$ Hz, 1H, 3-H, B), 6.26 (d, $^3J = 11.2$ Hz, 1H, 2-H, A), 6.42 (d, $^3J = 11.2$ Hz, 1H, 3-H, A), 7.24 – 7.73 (m, 18H, Ar-H, A and B), 8.05 (s, 1H, formamidoyl-H, A and B), 10.41 (s, 1H, CO_2H, B), 10.48 (s, 1H, CO_2H, A). – MS (EI, 70 eV): m/z (%) = 488 (2) [M^+], 368 (2), 334 (4), 244 (100), 216 (80), 179 (44), 137 (57), 127 (15), 111 (35), 91 (11), 77 (15). – $C_{28}H_{22}Cl_2N_2O_2$ (489.39): calcd. C 68.72, H 4.53, N 5.72; found C 68.58, H 4.43, N 5.66.

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