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Article

Reaction of Diphenylcyclopropenone with *N*-Acylamidine Derivatives. Synthetic and Mechanistic Implications

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A reatividade de ciclopropenonas frente a derivados de *N*-acilamidinas foi investigada. Difenilciclopropenona reagiu com *N*-benzoilacetamidina e com *N*-(metoxicarbonil)benzamidina formando 1,2-diidro-3*H*-pirrol-3-onas em rendimentos moderados, porém alquilfenilciclopropenonas não reagiram com os mesmos nucleófilos investigados. A teoria dos orbitais moleculares de fronteira foi empregada para racionalizar a formação dos produtos.

In this work, the reactivity of cyclopropenones toward *N*-acylamidine derivatives was investigated. Diphenylcyclopropenone reacted with *N*-benzoylacetamidine and *N*-(methoxycarbonyl)benzamidine affording 1,2-dihydro-3*H*-pyrrol-3-ones in moderate yields. However, alkylphenylcyclopropenone did not react. The formation of the compounds is examined mechanistically within frontier molecular orbital considerations.

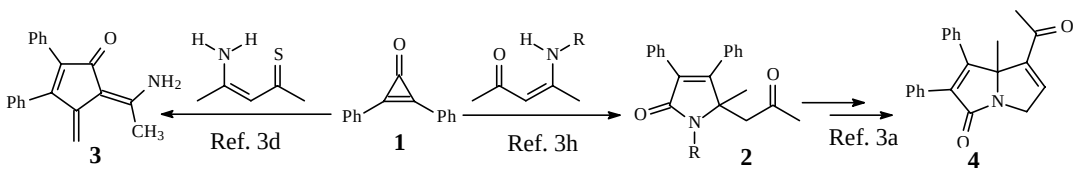
Keywords: diphenylcyclopropenone, *N*-acylamidines, 1,2-dihydro-3*H*-pyrrol-3-ones

Introduction

Over the past four decades, the fascinating chemistry of cyclopropenones has attracted considerable attention both in utilization as a synthetic building block[1] and as rare naturally occurring compounds[2]. Our systematic interest in the use of cyclopropenone chemistry in the construction of a wide variety of heterocycles[3] prompted us to study the behavior of cyclopropenones towards *N*-acylamidine derivatives. Additionally, *N*-acylamidines can be envisioned as enaminone aza analogs (an "aza-enaminone"). Enaminones are versatile nucleophiles toward diphenylcyclopropenone (**1**) in the synthesis of nitrogen-containing compounds, Scheme 1[3a,d,h]. Because of the ambiphilic and ambident proprieties of cyclopropenones, the reactions of this class of compound with nucleophiles is a complex matter[1b-c]. Herein we present our results of the reactions of cyclopropenones with *N*-acylamidine derivatives with emphasis on synthetic and mechanistic implications.

Results and Discussion

Diphenylcyclopropenone (**1**) reacted smoothly with *N*-benzoylacetamidine (**5**) in benzene under reflux. An insoluble, crystalline solid was isolated, and this material was a 1:1 adduct as indicated by mass spectrum and NMR integration. The NMR spectrum contained two low field N-H protons (D_2O exchangeable) as sharp signals which suggests their participation in intramolecular hydrogen bonding. Moreover, the IR spectrum which showed an intense carbonyl absorption at 1640 cm^{-1}, ruled out the formation of a 1,5-dihydro-2*H*-pyrrol-2-one nucleus analogous to **2**[3h], for which this absorption appears at 1695-1700 cm^{-1}. To accommodate these spectral features



Scheme 1.

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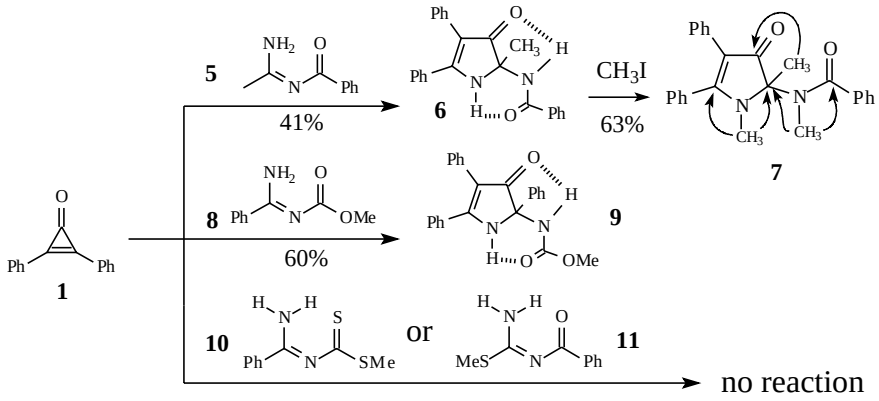
structure **6** (Scheme 2) was proposed in agreement with the carbonyl absorption (1638-1650 cm^{-1}) of some model 1,2-dihydro-3*H*-pyrrol-3-ones[4].

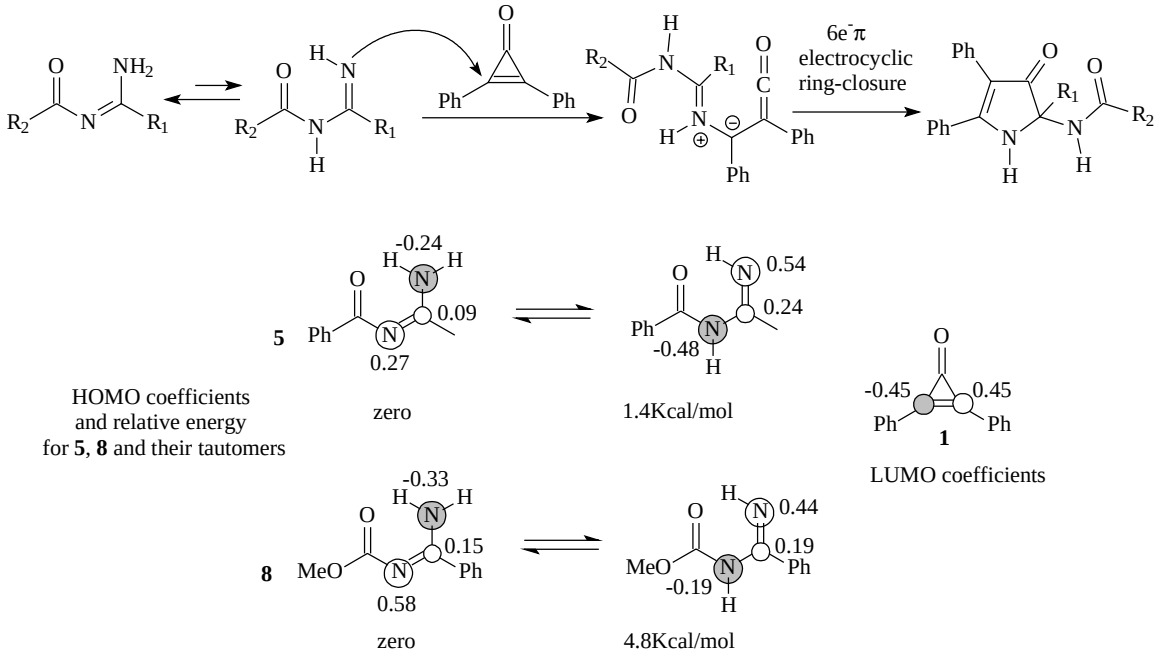
The structure **6** was corroborated by analysis of a long-range heterocorrelation (COLOC) spectrum of derivative **7**. This showed a correlation (^3J) of the carbonyl C-4 with the methyl group at C-5 as well as the other correlations indicated in structure **7** (Scheme 2) in agreement with the regiochemistry assigned to **6**. No such correlations would be observed if a 1,5-dihydro-2*H*-pyrrol-2-one analogous to **2** had formed.

This reaction proved to be very sensitive to substitution both in the cyclopropenone and in the "aza-enaminone". While diphenylcyclopropenone reacted with *N*-(methoxycarbonyl)benzamidine (**8**) to afford **9** in good yield, it failed to react with derivatives **10** and **11** under the conditions employed (Scheme 2). In addition, compounds **5** and **8** did not react with methylphenyl-cyclopropenone and isopropylphenylcyclopropenone, showing that formation of the 1,2-dihydro-3*H*-pyrrol-3-one nucleus is effective only with **1** (**1** is more reactive towards nucleophiles than are alkylphenylcyclo-propenones because it has the lower-lying LUMO[5]).

Recently, we demonstrated that reactivity of cyclopropenones can be rationalized by a frontier orbital approach in combination with the hardness-softness concept[5]. The results of AM1[6] calculations, as implemented in the SPARTAN 4.0 package[7], are show in Scheme 3. Thus, it would appear that reaction of **1** is kinetically favored for the tautomeric forms of **5** and **8**,



Scheme 2.



Scheme 3.

wherein the terminal imine nitrogen has the largest HOMO coefficient. A slow and irreversible attack at the phenyl-C of **1** followed by an electrocyclic five-membered ring formation results in the regiochemistry observed for compounds **6** and **9**.

The present study complements the reported[3h] formation of the dihydropyrrolone nucleus from diphenylcyclopropenone and enaminones, furnishing a convenient route to 1,2-dihydro-3*H*-pyrrol-3-one derivatives and expands the frontier of utilization of cyclopropenones as synthetic building blocks for densely substituted heterocyclic compounds.

Experimental

Melting points were determined on a Hoover-Unimelt apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a Perkin Elmer FT-IR 1600 instrument. NMR spectra were obtained for ^{1}H at 300 MHz and for ^{13}C at 75 MHz using a Varian Gemini 300 or a Bruker AC300P spectrometer. Chemical shifts are reported in δ (ppm) units downfield from reference. HRMS were obtained on a Fisions VG Autospec. *N*-benzoylacetamidine[8], *N*-(methoxycarbonyl)benzamidine[9] and diphenylcyclopropenone[10] were prepared according to known procedures.

Reaction of *N*-benzoylacetamidine (5) with 1: a solution of 206,5mg (1mmol) of diphenylcyclopropenone (**1**) and 173,8mg (1mmol) of *N*-benzoylacetamidine (**5**) in 10cm^3 of benzene was heated at reflux with stirring for 1 day (the solution turned yellow and a precipitate began to form after 30 min.), after which time the reaction mixture was cooled at room temperature, petroleum ether was added and allowed to cool in the freezer (-25ºC). The solution was decanted from **6** (lemon yellow crystals, 115.1mg, 41% yield), mp 240-242ºC. IR (KBr): ν_{max}/cm^{-1} 3283, 1670, 1640, 1602. ^{1}H NMR (DMSO-D_6): 1.54 (s, 3H), 7.15-7.20 (m, 5H), 7.42-7.55 (m, 8H); 7.88-7.91 (d, ^3J 1.5Hz, 2H); 8.31 (s, 1H); 8.90 (s, 1H). ^{13}C NMR (DMSO-D_6): 23.7 (CH_3), 72.1 (C), 107.6 (C), 125.1 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 130.8 (CH), 131.6 (CH), 132.0 (C), 133.3 (C), 133.6 (C), 165.0 (C), 168.5 (C), 198.1 (C). EM, m/z (%): 369 (M^+ +1; 1.3%), 368 (M^+, 13%), 235 (44%), 178 (100%), 105 (74%), 77 (81%).

Methylation of 6: To a solution of **6** (55.7mg, 0.15mmol) in 1cm^3 of dimethyl sulfoxide was added approximately 170mg (3.04mmol) of powdered potassium hydroxide. The yellow solution turned dark orange, and 0.3cm^3 (2.2mmol) of methyl iodide was added. The reaction mixture was left stirring for 1h, after which time water (20cm^3) was added and the solution was extracted with methylene chloride (5 X 10cm^3). The organic layer was washed with water (6 X 10cm^3), dried over anhydrous potassium carbonate, filtered, and the solvent was evaporated. The residue was purified by column chromatography (Florisil®, hexane/ethyl acetate 50% as eluant) to afford **7** (38mg, 63% yield) as a colorless solid, mp 128-130ºC (with decomposition). IR (KBr): ν_{max}/cm^{-1} 1700, 1649. ^{1}H NMR ($CDCl_3$): 1.78 (s, 3H), 2.92 (s, 3H), 3.14 (s, 3H), 6.97-7.16 (m, 5H), 7.16-7.54 (m, 10H). ^{13}C NMR ($CDCl_3$): 20.7 (CH_3), 29.1 (CH_3), 35.6 (CH_3), 79.5 (C), 109.6 (C), 125.0 (CH), 127.5 (CH), 127.7 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 129.9 (CH), 130.2 (CH), 131.0 (C), 132.3 (C), 136.4 (C), 170.9 (C), 172.6 (C), 198.0 (C). HRMS m/z 396.1838 (396.1838 calculated for $C_{26}H_{24}N_2O_2$).

Reaction of *N*-(methoxycarbonyl)bezamidine (8) with 1: A solution of 103,5mg (0,5mmol) of diphenylcyclopropenone (**1**) and 91,1mg (0,5mmol) of *N*-(methoxycarbonyl)benzamidina (**8**) in 10cm^3 of acetonitrile was heated at reflux for 2 days. After this time, the reaction mixture was concentrated to half volume under reduced pressure, and the solution allowed to cool in the freezer (-25ºC). The solid that formed was separated from the solvent and was recrystallized from CH_2Cl_2/hexane affording 114.6mg (60% yield) of **9** as a lemon yellow solid, mp 227-229ºC (with decomposition). IR (KBr): ν_{max}/cm^{-1} 3322, 3259, 1707, 1661. ^{1}H NMR (DMSO-D_6): 3.37 (s, 3H), 7.03-7.14 (m, 5H), 7.31-7.61 (m, 10H), 8.33 (sl, 1H), 9.06 (s, 1H). ^{13}C NMR (DMSO-D_6): 51.6 (CH_3), 76.0 (C), 105.7 (C), 125.3 (CH), 126.1 (CH), 127.9 (CH), 128.3 (C), 128.5 (CH), 128.6 (CH), 128.8 (CH), 131.2 (CH), 131.4 (C), 132.9 (C), 137.4 (C), 155.4 (C), 171.7 (C), 195.9 (C). HRMS m/z 384.1473 (384.1474 calculated for $C_{24}H_{20}N_2O_3$).

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