Michael Addition and Derivatives of 2-Carboxamido-3-phenylindenone[1]

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Introduction

Recently we have submitted several reports (6,7,8) dealing with the synthesis and reactions of 3-substituted 2-carboxamidoindenones. Among the reactions which these compounds undergo is a fascile Michael addition, and we wish to report here the addition of a variety of nucleophiles to 2-carboxamido-3-phenylindenone (1) and some of the products derived from these compounds.

The Michael reaction, now one hundred years old, is a useful synthetic tool that has led to a vast amount of research on its scope and limitations. It is the subject of an extensive review (1). The reaction generally refers to the addition of a nucleophile to a conjugated double bond which involves a series of reversible equilibrium reactions. Thus the reverse of Michael addition may occur, and products may be unstable on isolation.

The synthesis of indenones *via* the cyclization of ylidenemalononitriles has been extensively studied in our laboratories (5). The first reported Michael addition to an indenone was rather recent. In 1960, Koelsch (9) found that 2-carbethoxy-3-phenyl-1-indenone reacts readily with a variety of carbanions and other nucleophiles to give Michael adducts, but he was unable to alkylate the intermediate ions formed by these reactions. Addition of hydroxide, alkoxide, or amines led to the isolation of unstable crude adducts, which reverted to the starting indenones on standing or in solution (10).

Discussion

The preparation of 3-cyano-3-phenyl-2-carboxamidoindanone (2a, Scheme 1) by the addition of cyanide to 1 has been previously reported (6). Contrary to observations of Koelsch (9), we were able to alkylate 2a readily by reaction with sodium hydride to form the anion, followed by addition of methyl iodide to produce 2-carboxamido-2-methyl-3-cyano-3-phenylindanone (3a) in good yield. Similarly, the 2-ethyl and 2-carbethoxymethyl derivatives 3b and 3c were formed by treating the anion of 2a with ethyl bromide or ethyl bromoacetate. In these cases, yields were improved by generating 3b or 3c from 1 in one step, by adding cyanide to 1 in dimethylsulfoxide, followed by reaction of the intermediate anion with alkylating agent.

The anion of malononitrile adds readily to 1 as shown by the isolation of the methylated derivative 3d in 88% yield, after treatment of 1 with the sodium salt of malononitrile, followed by methyl iodide.

Sodium hydride reacts with acetone to generate a carbanion, which can behave as a Michael nucleophile. When a solution of 1 in acetone was treated with sodium hydride, a clear amber solution was obtained. When this solution was diluted with water and acidified, a new compound, 3-methyl-4a-phenyl-1,2,4a,9a-tetrahydro-2-azafluoren-1,9-dione (4), was obtained. This product must be the result of addition of acetonyl

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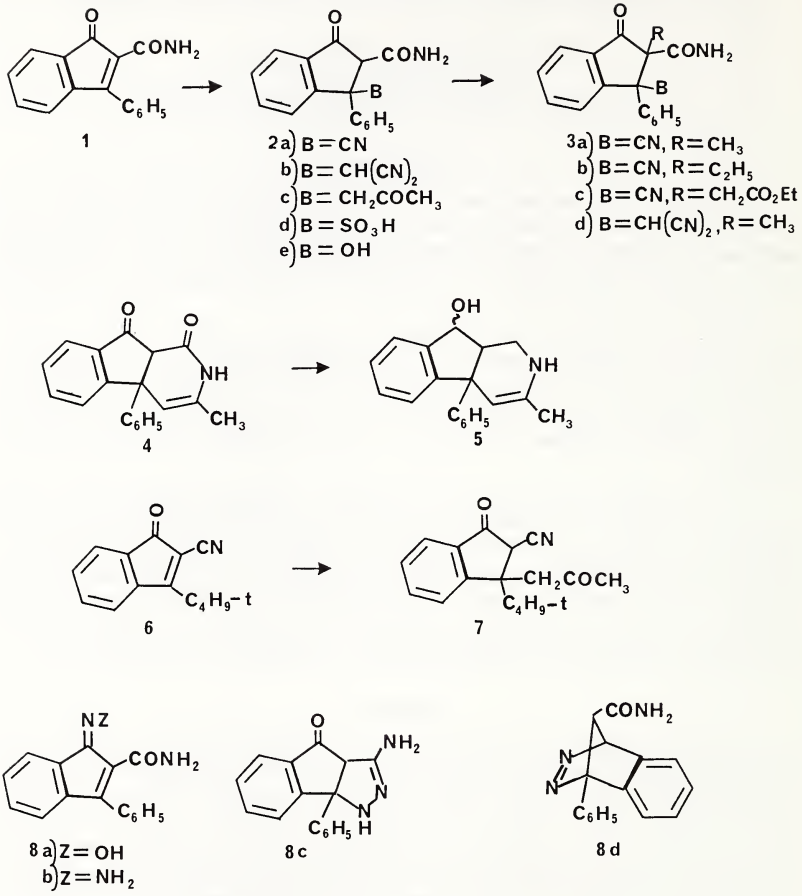
SCHEME 1.



carbanion to 1, followed by a cyclodehydration reaction between the acetonyl ketone and the carboxamido group. That the cyclodehydration formed a carbon-carbon double bond rather than a carbon-nitrogen double bond was confirmed by the pmr spectrum which showed a vinyl proton multiplet and a methyl doublet. Reduction of 4 with lithium aluminum hydride produced the unsaturated amino-alcohol 5. Retention of the double bond in 5 confirms the structure of 4, since a carbon-nitrogen double bond should be reduced by lithium aluminum hydride.

In order to confirm the direct addition of acetone to an indenone, the reaction was attempted on 2-cyano-3-t-butyl-indenone (6). This compound, previously reported (4), could not be hydrated to 2-carboxamido-3-t-butyl-indenone, and hence should not undergo the secondary cyclodehydration step. Indeed, addition of sodium hydride to an acetone solution of 6 gave a high yield of the adduct 7.

Addition of non-carbon nucleophiles to indenone 1 met with varying degrees of success. Addition of the neutral nucleophile sodium bisulfite, followed by treatment with S-benzylisothiuronium chloride produced the S-benzylisothiuronium salt of the corresponding sulfonic acid 2d. The corresponding sodium salt of 2d was prepared by evaporating

an alcohol solution of 1 which had been decolorized by addition of sodium bisulfite, but it could not be recrystallized, and acidification in solution led to the isolation of 1, formed by a reverse Michael addition of the acid 2d.

When orange indenone 1 was added to an ethanolic sodium hydroxide solution, after initial solution a white precipitate of the sodium salts of 2e formed, which dissolved on addition of water. Acidification gave a white solid which decomposed on the funnel to form indenone 1. This unstable white solid is undoubtedly the hydroxide adduct 2e. Attempts to trap the intermediate salt with methyl iodide failed and led to the isolation of 1 in 86% recovery.

Indenone 1 reacts with hydroxylamine or hydrazine to form simple 1:1 adducts which have lost a molecule of water, and are probably the simple oximes or hydrazones 8a and 8b. Since α, β-unsaturated ketones are known to react with hydroxylamine and hydrazine to form isoxazolines and pyrazolines *via* Michael additions, the possibility of such reactions occurring with indenone 1 had to be eliminated. Elementary analysis would not differentiate between the two possibilities. Infrared spectra are inconclusive, since unequivocal assignments cannot be made. However, the structure 8a for the hydroxylamine adduct is supported by the fact that the derivative is highly colored, indicating that the extended conjugated system is intact. Indeed, the ultraviolet spectrum of 1 and 8a are nearly identical. Finally any isoxazoline derived from 1 must have a bridgehead double bond, which is a violation of Bredt's rule (2).

The possibility of Michael addition of hydrazine followed by cyclization, with loss of water, to either the carboxamide group, to give the aminopyrazoline 8c or to the ketone with a hydride shift, to give pyrazoline 8d,are not so easily ruled out. Evidence for structures 8c or 8d are as follows: the compound is colorless, whereas compounds 1 and 8a, having the conjugated system, are yellow or orange. Compounds 1 and 8a have a strong ultraviolet absorption peak at 248 mμ, whereas the hydrazine adduct has a peak at 223 mμ, and none at 248 mμ. The compound decomposes with the evolution of gas at its melting point, a common property of pyrazoline derivatives like 8c or 8d. However, the pmr spectrum of the compound is consistent with the hydrazone structure 8b, showing only two peaks, roughly in a ratio of 11:2, a high field complex multiplet of aromatic and amide protons and a broad singlet at δ 4.17, indicating an NH_2 group. It is unlikely that the protons at N-1 and C-3a of 3-amino-4-oxo- 8b-phenyl-1,3a,4,8b-tetrahydro[1,2-c]pyrazole (8c), or those at C-1 and C-7 of 5,6-benzo-4-phenyl-7-carboximido-2,3-diazabicyclo[2.2.1]-2,5-heptadiene (8d), would have exactly the same chemical shift, or fall within the aromatic range. In addition, the lack of ketone absorption at about 5.85 μ in the infrared eliminates compound 8c. Therefore, we believe the hydrazone structure 8b is the most reasonable for this product.

Experimental

All melting points were determined in open capillary tubes with a Mel-Temp heating block apparatus and are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, IN, and Huffman Laboratories, Inc., Wheatridge, CO. Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 137 Infracord and were calibrated with polystyrene. Ultraviolet spectra were determined in 95% ethanol with a Bausch and Lomb Spectronic 505 Recording Spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer in the indicated solvents using tetramethylsilane as an internal standard.

2-Carboxamido-2-methyl-3-cyano-3-phenyl-1-indanone (3a).

Sodium hydride (0.26 g of 50% NaH in mineral oil, 5.5 mmoles) was added to a suspension of 2a , prepared as previously described (6), in tetrahydrofuran (20 mL); following the evolution of hydrogen methyl iodide (3 mL) was added. The reaction mix-

ture was stirred at room temperature for 24 hr, diluted with 150 mL of water, and excess methyl iodide removed on a steam bath. The solution was cooled and the resulting precipitate collected by filtration to give 3a (0.95 g, 65%). Compound 3a was purified for analysis by recrystallization from 95% ethanol to give white crystals: mp 206-208°; ir 2.95 and 3.15 (NH_2), 4.44 (CN), 5.85 (CO), 5.98 ($CONH_2$), and 6.30 μ (aromatic); uv (λ max) 211 (ϵ 28,300), 250 (ϵ 13,700), and 295 mμ (ϵ 2,120); pmr (DMSO-d_6) δ 7.83 (4H multiplet, aromatic), 7.30 (7H, multiplet, aromatic and amide), and 1.80 (3H, singlet, methyl).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.82; N, 9.65. Found: C, 74.27; H, 4.95; N, 9.65.

2-Carboxamido-2-ethyl-3-cyano-3-phenyl-1-indanone (3b).

A mixture of indenone 1 (3) (5 g, 20 mmoles) and 1.5 g of sodium cyanide (30.8 mmoles) in 35 mL of dimethylsulfoxide was warmed on a steam bath to give a red solution. The solution was cooled and excess (5 mL) of ethyl bromide added. After 48 hr the reaction mixture was diluted with water and excess ethyl bromide removed on a steam bath. The solution was cooled and a white precipitate was collected and recrystallized from ethanol to give 5.7 g (94%) of white crystals of 3b melting at 208-210°; ir 2.84, 2.94 (NH_2), 4.43 (CN), 5.97 (CO) and 6.05μ ($CONH_2$).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 75.00; H, 5.26; N, 9.21. Found: C, 75.08; H, 5.51; N, 9.26.

2-Carboxamido-2-carbethoxymethyl-3-cyano-3-phenyl-1-indanone (3c).

Following the procedure described above for 3b, 5 g (20 mmoles) of 1 was treated with an excess (5 g) of ethyl bromoacetate. The product, which melted at 168-169° after two recrystallizations from isopropanol, weighed 7.0 g (93%); ir 2.90 (NH), 4.45 (CN), 5.72 (COOR), 5.92 (CO) and 6.02 μ ($CONH_2$).

Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.61; H, 4.97; N, 7.73. Found: C, 69.35; H, 5.01; N, 7.77.

2-Carboxamido-2-methyl-3-dicyanomethyl-3-phenyl-1-indanone (3d).

The sodium salt of malononitrile was prepared by the addition of sodium hydride (0.75 g of 50% NaH in mineral oil, 15.6 mmoles) to a solution of malononitrile (1.3 g, 20 mmoles) in dimethyl sulfoxide (25 mL). The solution was stirred at room temperature for 15 min and then 2-carboxamido-3-phenyl-1-indenone (1) (2.49 g, 10 mmoles) was added to the reaction mixture. The solution was stirred at room temperature for 1.5 hr, methyl iodide (5 mL) was added and the solution stirred for an additional 48 hr. The reaction was quenched with 300 mL of water and the excess methyl iodide was removed on a steam bath. The resulting solid was collected by filtration to give 2.9 g (88%) of 3d, mp 218-222°. Recrystallization from 95% ethanol (Norit) gave an analytical sample of white plates, mp 239-240° (dec) with partial melting at 200°; a sample of this compound maintained at 200° completely melted after 1.5 hr; ir 2.90 and 3.00 (NH_2), 3.37 and 3.40 (CH), 4.43 (CN), 5.82 (CO), 6.00 ($CONH_2$) and 6.31μ (phenyl); pmr (DMSO-d_6) δ 7.9-7.3 (11H, complex multiplet, aromatic and amide), 6.80 (1H, singlet, methine), and 0.90 (3H, singlet, methyl).

Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.95; H, 4.56; N, 12.76. Found: C, 73.09; H, 4.77; N, 12.78.

3-Methyl-4a-phenyl-1,2,4a,9a-tetrahydro-2-azafluoren-1,9-dione (4).

To a solution of compound 1 (3.0 g, 12.1 mmoles) in acetone (100 mL) was added sodium hydride (0.7 g of 53.7% NaH in mineral oil, 15.7 mmoles). The solution was stirred at room temperature for 30 min, diluted with water (300 mL) and acidified with 20% sulfuric acid. The excess acetone was removed under a stream of air and the resulting precipitate was collected by filtration to give 3.15 g (90%) of 4, mp 214-216°.

Recrystallization from 95% ethanol gave white crystals: mp 230-231°; ir 3.15 (NH), 5.77 (CO) and 6.00 μ (CONH); pmr (DMSO-d_6) δ 7.85-7.20 (9H, multiplet, aromatic), 6.30 (1H, multiplet, vinyl), 4.90 (1H, doublet, J = 1 cps, due to long range coupling, methine), 1.77 (3H, doublet, J = 2 cps, methyl).

Anal. Calcd. for $C_{19}H_{15}NO_2$: C, 79.04; H, 5.19; N, 4.84. Found: C, 79.21; H, 5.22; N, 4.83.

3-Methyl-4a-phenyl-1,2,4a,9a-tetrahydro-2-azafluoren-9-ol (5).

A solution of compound 4 (12 g, 41.5 mmoles) in tetrahydrofuran (500 mL) was added dropwise to a refluxing mixture of lithium aluminum hydride (18 g, 95%, 0.5 mol) in tetrahydrofuran (125 mL), and the mixture was refluxed for 5 hr with stirring. The reaction mixture was cooled and the excess hydride was cautiously hydrolyzed with saturated sodium sulfate solution. The resulting solid was removed by filtration and rinsed with chloroform. The chloroform-tetrahydrofuran solution was dried (magnesium sulfate), decolorized (activated charcoal) and concentrated to dryness at reduced pressure. The resulting oil was triturated with petroleum ether to produce 8 g (69%) of 5. Three recrystallizations from acetonitrile gave light beige plates: mp 179-181°; ir 3.0-3.15 (OH-NH hydrogen bonded), 6.00 (C=C), and 6.24μ (aromatic).

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.31; H, 6.86; N, 5.05. Found: C, 82.31; H, 6.79; N, 5.06.

2-Cyano-3-acetonyl-3-t-gutyl-1-indanone (7).

Sodium hydride (1.45 g of 53.7% NaH in mineral oil, 32.6 mmoles) was cautiously added to a solution of compound 6 (3) (6.0 g, 28.4 mmoles) in acetone (180 mL). The mixture was stirred at room temperature for 40 min. The resulting clear amber solution was diluted with water (300 mL) and acidified to pH 4 with 20% sulfuric acid. The excess acetone was removed under a stream of air. The solid was collected by filtration, yielding 7.4 g (97%) of 7, melting at 172-172.5°. Several recrystallizations from isopropanol yielded white crystals: mp 176-178°; ir 4.48 (CN), 5.8.5.9μ (CO); pmr ($CDCl_3$) δ 7.92-7.32 (4H, multiplet, aromatic), 3.80 (1H, singlet, methine), 3.32 (2H, singlet, methylene), 2.03 (3H, singlet, methyl), and 1.08 (9H, singlet, t-butyl).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.98; H, 7.07. Found: C, 76.14; H, 7.26.

Salts of 2-Carboxamido-3-phenyl-1-indanone-3-sulfonic Acid (2d).

A mixture of indenone 1 (2.49 g, 10 mmoles), sodium bisulfite (1.1 g, 10.5 mmoles) and 50% ethanol (50 ml) was heated on a steam bath until a clear amber solution was obtained (10 min). The solution was then evaporated to dryness at reduced pressure to give 3.5 g (99%) of the sodium salt of 2d. The S-benzyl-isothiouronium salt was prepared by dissolving this salt (1 g, 2.84 mmoles) in 10 mL of water and adding S-benzylisothiouronium chloride (1.01) g, 5 mmoles) in 5 mL of water. The precipitate was collected by filtration, yielding 1.35 g (96%) of S-benzylisothiouronium 2-carbamyl-3-phenyl-1-indanone-3-sulfonate. An analytical sample was prepared by recrystallization from 50% ethanol (care must be taken in recrystallization, because a retro-Michael reaction occurs on prolonged heating as evidenced by the formation of an orange color.): mp 148-151° (dec), ir 2.9-3.3 (H-bonding), 5.80 (CO, weak), 6.0-6.15 and 6.20-6.40 ($CONH_2$ and enol and aromatic carbon-carbon double bonds), and 6.98 and 8.3-8.6μ (SO_3).

Anal. Calcd. for $C_{24}H_{23}N_3O_5S_2$: C, 57.94; H, 4.66; N, 8.45. Found: C, 58.06; H, 4.83; N, 8.54.

Attempted Addion of Hydroxide to Indenone 1.

A mixture of orange indenone 1 (1.2 g, 4.7 mmoles), 10% sodium hydroxide (10 mL) and 95% ethanol was stirred at room temperature; after 3 hr a voluminous white precipitate

formed. The precipitate dissolved upon addition of 200 mL of water, acidification produced a white precipitate, which turned orange on standing to give 1.15 g (96%) of starting indenone 1 as evidenced by congruent infrared spectrum and melting point.

A mixture of indenone 1, 10% sodium hydroxide (15 mL), and 95% ethanol (25 mL) was stirred at room temperature; after 3 hr the orange color disappeared and a voluminous white precipitate formed. The mixture was treated with methyl iodide (6 mL), stirred at room temperature for 24 hr, then quenched with 250 mL of water and the excess methyl iodide removed on a steam bath. The cooled solution afforded 1.85 g (74%) of starting material and acidification of the solution yielded an additional 0.3 g (12%) of indenone 1 as shown by infrared spectrum, color, and melting point.

2-Carboxamido-3-phenylinden-1-oxime (8a).

A solution of indenone 1 (2.49 g, 10 mmoles), hydroxylamine hydrochloride (0.69 g, 10 mmoles) and pyridine (0.79 g, 10 mmoles) in 100 mL of 95% ethanol was refluxed with stirring for 3 hr. The reaction was poured into 200 mL of water and the resulting solid (2.35 g, 89%) collected by filtration. Recrystallization from 95% ethanol afforded an analytical sample of golden prisms: mp 238.5-240° (dec); ir 3.00-3.40 (broad H-bonding), 6.00 ($CONH_2$), and 6.30 and 6.44μ (C=C and C=N); uv (λ max) 248 (ϵ 38,000), 270 (broad shoulder, ϵ 21,000), and 305-325mμ (ϵ 10,500).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.54; N, 10.61. Found: C, 72.74; H, 4.79; N, 10.53.

2-Carboxamido-3-phenylinden-1-hydrazone (8b).

Indenone 1 (5.0 g, 20 mmoles) was dissolved in 400mL of 95% ethanol by warming on a steam bath, and hydrazine hydrate (85%, 1.16 g, 20 mmoles) was added to the solution. The reaction was kept at room temperature for 3 hr and the clear solution concentrated to a volume of 100 mL on a hot plate, cooled in an ice bath and the resulting white solid collected to give 4.35 g (82%) of 8b, mp 216-218°. Recrystallization from 95% ethanol afforded an analytical sample of white crystals: mp 218.5-220° with decomposition and gas evolution; ir 2.98 and 3.15 (NH), 6.00 ($CONH_2$), and 6.18 and 6.40μ (C=C and C=N); uv (λ max) 223 (ϵ 36,200) and 280 mμ (ϵ 9,800); pmr (DMSO-d_6) the spectrum showed only two peaks in a ratio of 11 H to 1.8 H which were at δ 8.3-7.17 (complex aromatic and amide multiplet) and 4.17 (singlet NH_2), respectively.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 73.00; H, 4.94; N, 15.96. Found: C, 72.97; H, 5.14; N, 15.94.

Literature Cited

1. Bergmann, E.D., D. Ginsberg and R. Pappo, 1959. The Michael Reaction. Org. Reactions *10*: 179-555.
2. Bredt, J., 1924. Uber sterische Hinderung in Brückenringen (Bredtsche Regel) und über die meso-trans Stellung in Kondensierten Ringsystem des Hexamethylens. Lieb. Ann. *437*: 1-13.
3. Campaigne, E., G.F. Bulbenko, W.E. Krieghbaum, and D.R. Maulding, 1962. Ring Closure of Ylidenemalononitriles. J. Org. Chem. *27*: 4428-4432.
4. Campaigne, E. and D.R. Maulding, 1963. Rearrangement of 2-Cyano-3-t-butyl-1-indenone. J. Org. Chem. *28*: 1391-1393.
5. Campaigne, E. and S.W. Schneller, 1976. Cyclization of Ylidenemalonodinitriles. Synthesis, No. *11*: 705-716.
6. Campaigne, E. and R.F. Weddleton, 1986. Succinimido[3,4-b]indan-8-one Derivatives. Proc. Ind. Acad. Sci. *95*: 167-170.
7. Campaigne, E. and R.F. Weddleton, 1986. Substituted Derivatives of 3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one. Proc. Ind. Acad. Sci. *95*: 159-165.

8. Campaigne, E. and E.M. Yokley, 1980. Tetrahydropyrrolidoacenaphthene and Benzazapropellane Derivatives as Potential Analgetics and Narcotic Antagonists. Proc. Ind. Acad. Sci. *89*: 136-141.
9. Koelsch, C.F., 1960. Electrophilic Properties of Ethyl 3-Phenylindone-2-carboxylate. J. Org. Chem. *25*: 2088-2094.
10. Koelsch, C.F., 1961. An Indone to Naphthol Ring Expansion. J. Org. Chem. *26*: 1003-1005.