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Novel [3 + 2] and [3 + 3] 4-Quinolone Annulations by Tandem Claisen–Cope-Amidoalkylation Reaction

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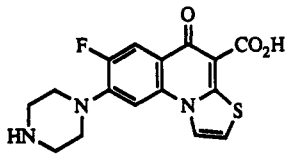
Received August 4, 1992

The thermal rearrangement of 4-(allyloxy)-2,3-dimethylquinoline (1) to produce 2-(3-butenyl)-1,4-dihydro-3-methyl-4-oxoquinolone (4) was first described by Makisumi over 25 years ago and was thought to proceed by a mechanism involving an initial Claisen rearrangement to give dienone 2 and a subsequent Cope rearrangement via the tautomeric enamine 3 (Scheme I).[1] As an interesting and potentially useful reaction for the introduction of functionalized side chains into the C-2 position of the 4-quinolone nucleus, we sought to apply it to the synthesis of novel tricyclic quinolone antibacterial agents[2] containing carbocyclic rings fused between N-1 and C-2 and patterned after the potent thiazolo-fused quinolone 5.[3] We now wish to report a convenient one-pot annulation method leading to the formation of 5- and 6-membered ring-fused 4-quinolones 6 and 7 in which migrating allyl/propargyl groups in the tandem Claisen–Cope rearrangement undergo further reaction at the quinolone nitrogen.



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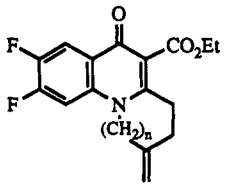


6: n = 0; 7: n = 1

4-(Allyloxy)quinolines 11 and 13 and 4-(propargyloxy)quinoline 12 were prepared as substrates for the tandem Claisen–Cope rearrangement as shown in Scheme II. The chloroimidate derived from treatment of 3,4-difluoroacetanilide (8) with PCl_5 was condensed with diethyl sodiomalonate to give an intermediate enamino diester, which was cyclized thermally in Dowtherm to afford a regioisomeric mixture of difluoroquinolones 9 and 10, with the desired 6,7-difluoro isomer 9 predominating by ≈3.3:1. Alkylation of the mixture of 9 and 10 under standard conditions with allyl bromide, propargyl bromide, and (β-chloromethyl)allyl chloride, respectively, provided quinolines 11–13. In each case the undesired 5,6-difluoroquinoline derived from 10 could be cleanly separated by flash chromatography. Although pure 9 could be obtained by two recrystallizations from EtOH, it was just as convenient to alkylate the mixture of 9 and 10. It is interesting to note that the 2-methyl group of 9 and 10 steers the alkylation onto the quinolone carbonyl; alkylation of the corresponding *des*-2-methyl derivatives is known to occur on nitrogen.[4]

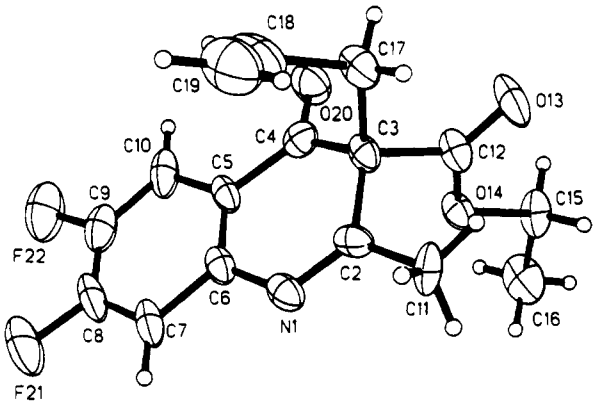


Figure 1. ORTEP drawing of the X-ray structure of dienone 14. Two crystalline forms were found; only one is shown for clarity.

To see if the tandem Claisen–Cope rearrangement was compatible with the 3-carbethoxy and 6,7-difluoro substitution in the quinoline ring, which is required for elaboration to quinolone antibacterials, (allyloxy)quinoline 11 was subjected to thermolysis in refluxing chlorobenzene (bp 132 °C), smoothly affording the expected 2-(3-butenyl)-4-quinolone 16 in 85% yield (Scheme III). Interestingly, when the reaction was performed in refluxing xylenes (bp 139–141 °C), the putative dienone intermediate 14 could be detected by TLC and was isolated by careful flash chromatography.[5] As one of the rare examples of a nonaromatic Claisen product to be isolated in the aromatic Claisen rearrangement,[6] an X-ray structure[7] of 14 was obtained (Figure 1) and, to our knowledge, is the first of such a species. The isolation of 14 and its smooth conversion to 16 upon resubjection to the reaction conditions now provides the first direct evidence of Makisumi's mechanism. It also should be noted that 14 exists as the imine tautomer, as shown, and hence conversion to the enamine tautomer 15 requires thermal equilibration.

The synthesis of pyrrolo[1,2-*a*]quinolone 6 was carried out initially by treatment of 16 with NBS to give tricycle 17 and subsequent dehydrobromination with ethanolic KOH (Scheme III). Alternatively, 6 could be obtained in a more direct fashion and in 54% overall yield by simple thermolysis of 4-(propargyloxy)quinoline 12 in refluxing *o*-dichlorobenzene (bp 179–180 °C). Presumably, 2-(3-butynyl)quinolone 19 is the penultimate intermediate, generated via allene 18, which cyclizes to 6 by intramo-

† To whom correspondence should be sent concerning the X-ray determination of dienone 14.

(1) Makisumi, Y. *J. Org. Chem.* **1965**, *30*, 1989.

(2) For a recent review on quinolone antibacterials, see: Rosen, T. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier Science: Amsterdam, New York, Oxford, 1990; Vol. 27, p 235.

(3) Matsumura, S.; Kise, M.; Ozaki, M.; Tada, S.; Kazuno, K. Watanabe, H.; Kunimoto, K., Tsuda, M. U.S. Patent 4,426,381; *Chem. Abstr.* **1983**, *98*, 53877w.

(4) For a general review of quinolone chemistry, including the synthesis of N-substituted quinolones, see: Albrecht, R. *Prog. Drug. Res.* **1977**, *21*, 9.

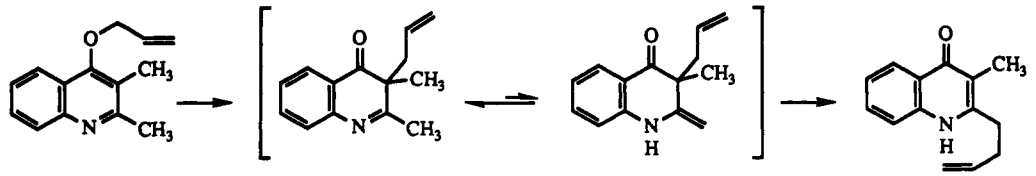
(5) The detection of 14 in refluxing xylenes and not in chlorobenzene could be due to the difference in dielectric constant between the two solvents, which could change the free energy profile of the reaction and therefore alter the stability of 14 relative to 15 and 16. The dielectric constants of xylenes and chlorobenzene are 2.3–2.6 and 5.7, respectively, at 20 °C.

(6) For examples of other dienones which have been isolated from the aromatic Claisen rearrangement, see: Bender, D. R.; Kanne, D.; Frazier, J. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2709 and references cited therein (footnote 29).

(7) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

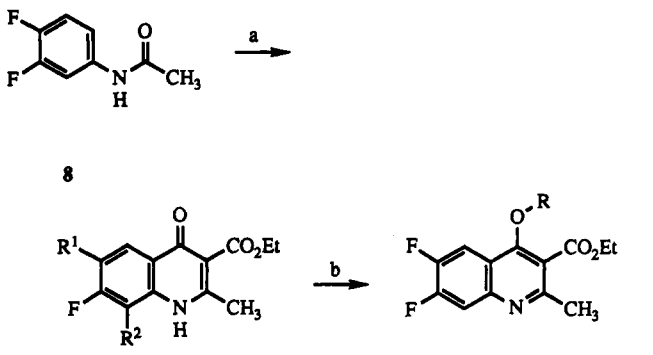
0022-3263/92/1957-6991$03.00/0

Scheme I



1 2 3 4

Scheme II[a]



8

9 (R^1=F, R^2=H)
10 (R^1=H, R^2=F)

R
11 H_2C=CH−CH_2
12 HC≡C−CH_2
13 H_2C=C(CH_2Cl)−CH_2

[a] Key: (a) (i) PCl_5, $PhCH_3$; (ii) $CH_2(CO_2Et)_2$, NaH, $PhCH_3$ (89%); (iii) Dowtherm A, 220 °C (78%); (b) allyl bromide (52%), propargyl bromide (58%), or 3-chloro-2-(chloromethyl)-1-propene (33%), K_2CO_3, DMF, 70 °C.

lecular amidoalkylation.[8] The ring closure appears to be rapid, as we were unable to detect **19** by TLC.

The tandem Claisen–Cope-amidoalkylation reaction next was applied to the rearrangement of [[β-(chloromethyl)allyl]oxy]quinoline **13**, which, in refluxing *o*-dichlorobenzene, afforded 1*H*-benzo[*c*]quinolizine **7** in 48% yield (Scheme IV). In this case, the Claisen–Cope product, 2-[3-(chloromethyl)-3-butenyl]-4-quinolone **20**, cyclizes to **7** by an S_N2- or an S_N2'-like displacement of the allylic chloride. As in the formation of **6** above, the penultimate intermediate, **20**, could not be detected by TLC. The reaction also was accompanied by the formation of the parent 2-methyl-4-quinolone **9** (27%). This likely occurred by decomposition of the HCl salt of 4-(allyloxy)quinoline **13**, which was generated by the equivalent of HCl expelled in the cyclization step. The cleavage of the allyl group of **13**·HCl is not surprising in view of the high temperature of the reaction and the excellent leaving group ability of the allyl side chain.

To avoid formation of **9** and, at the same time, further shorten the synthesis of **7**, a one-pot synthesis starting from **9** was attempted under conditions compatible with exhaustive alkylation of **9** and with the ensuing Claisen–Cope-amidoalkylation process. Thus, treatment of **9**[9] with 3 equiv of (β-chloromethyl)allyl chloride and excess K_2CO_3 in refluxing *o*-dichlorobenzene (5 h) furnished **7** in 51% overall yield (Scheme V).[10] The overall process can be viewed as a fascinating tandem alkylation–Claisen–Cope-amidoalkylation reaction.

(8) We postulate that the amidoalkylation reaction occurs via the hydroxypyridine tautomer of **19** rather than the quinolone tautomer, as shown, because in the former the nitrogen is more nucleophilic.

(9) Pure recrystallized **9** was used.

(10) The reaction was monitored by TLC for the formation and disappearance of [[β-(chloromethyl)allyl]oxy]quinoline **13**.

In summary, extension of the thermal rearrangement reaction of 4-(allyloxy)-2-methylquinolines using migrating allyl groups capable of further reaction at the quinolone nitrogen has led to novel [3 + 2] and [3 + 3] 4-quinolone annulation reactions within the quinolone antibacterial series. The annulation products, pyrrolo[1,2-*a*]quinolone **6** and 1*H*-benzo[*c*]quinolizine **7**, are functionalized with an exo methylene group in the fused ring, making elaboration to other novel heterocycles containing a 4-quinolone nucleus possible. Also, the isolation of dienone **14** in the thermolysis of 4-(allyloxy)quinoline **11** confirms that the overall rearrangement reaction proceeds via a Claisen–Cope pathway, as first proposed by Makisumi.

Experimental Section

^{1}H NMR spectra were determined with a Bruker AM-300 spectrometer. Chemical shifts are expressed in ppm relative to deuteriochloroform or deuterio dimethyl sulfoxide. Significant ^{1}H NMR are tabulated in order (number of protons, multiplicity, coupling constant (Hz)). Mass spectra (MS) were determined with a Finnigan 4510 GSMS mass spectrometer; exact masses were determined on an A.E.I.-MS30 or Kratos Concept 1S high-resolution mass spectrometer. Infrared (IR) spectra were determined with a Nicolet Model 510 FTIR spectrometer. Ultraviolet spectra were determined on a Hewlett-Packard 8450A diode array spectrophotometer. Elemental analyses were performed by the Pfizer Analytical Chemistry Department. Melting points are uncorrected and were obtained in open capillaries on an Electrothermal digital melting point apparatus.

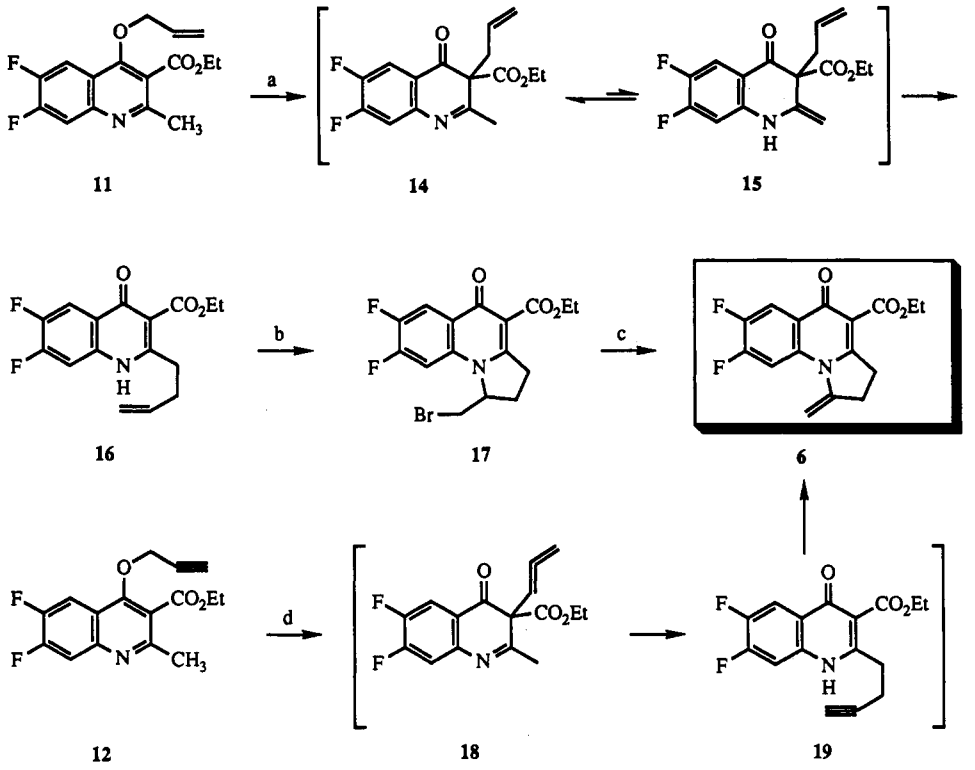
1,2-Dichlorobenzene was distilled prior to use. Other solvents and reagents were commercially available and were used directly unless otherwise noted.

Flash chromatography was performed using Silica Woelem 32–63 μm. Analytical thin-layer chromatography (TLC) was performed on 255 μm, 5- × 10-cm silica gel plates (Kieselgel 60 F_{254}) using ultraviolet light for visualization.

6,7-Difluoro-1,4-dihydro-2-methyl-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (9). To a solution of 35.0 g (0.205 mol) of 3′,4′-difluoroacetanilide[11] in 500 mL of dry toluene at 0 °C was added in small portions 42.6 g (0.205 mol) of solid phosphorus pentachloride. When the addition was complete, the mixture was allowed to warm slowly to room temperature. Meanwhile, in a flame-dried 3-L three-necked, round-bottom flask equipped with a mechanical stirring apparatus, pressure-equalizing funnel, and reflux condenser was placed 29.5 g (0.614 mol) of 50% sodium hydride dispersion in mineral oil. The sodium hydride dispersion was washed three times with dry pentane, suspended in 1 L of dry toluene, and stirred while a solution of 32.8 g (0.205 mol) of diethyl malonate in 100 mL of dry toluene was added dropwise. When the addition was complete, the mixture was heated to 65 °C for 1 h and then cooled to 15 °C. At this time the reaction mixture containing the imidoyl chloride was concentrated to an oil, dried under high vacuum, diluted with 150 mL of dry toluene, and added dropwise at 15 °C to the suspension of diethyl sodiomalonate. After stirring 0.5 h at 15 °C and 1 h at room temperature, the reaction mixture was *carefully* poured in small portions onto 600 mL of water with vigorous stirring. The toluene layer was separated, and the aqueous layer was extracted with EtOAc (4 × 200 mL). The EtOAc extracts were combined with the original toluene layer and were washed with brine, dried

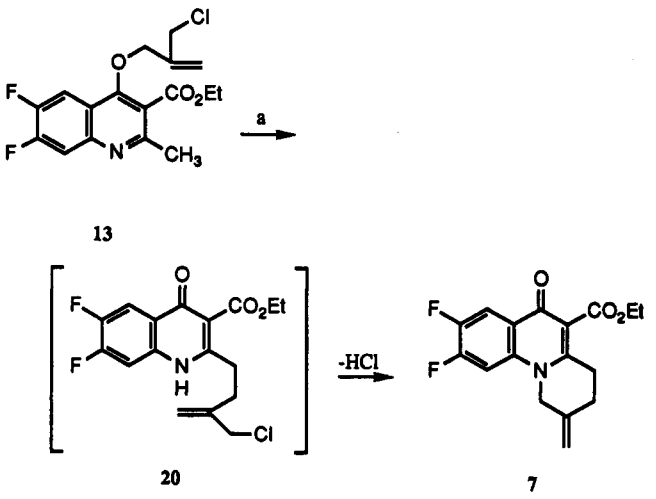
(11) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034.

Scheme III[a]

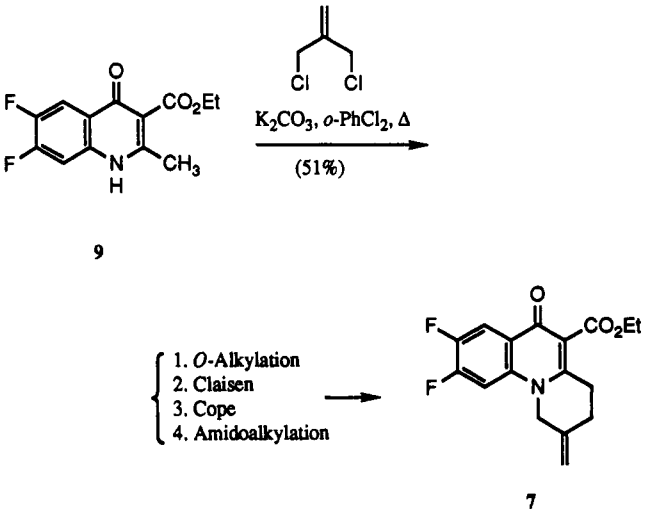


[a] Key: (a) PhCl, reflux, 16 h (85%); (b) NBS, CCl_4, (58%); (c) KOH, EtOH, THF (47%); (d) o-$PhCl_2$, reflux, 2 h (54%).

Scheme IV[a]



Scheme V



[a] Key: (a) o-$PhCl_2$, reflux, 1.25 h (48%).

(K_2CO_3), and evaporated to give 57.0 g (89%) of 3-(3,4-difluoroanilino)-2-butenedioic acid diethyl ester as an oil: R_f 0.39, 1:3 EtOAc–hexanes; ^{1}H-NMR ($CDCl_3$) δ 1.21–1.32 (6 H, m), 2.05 (3 H, s), 4.13–4.28 (4 H, m), 6.78–7.23 (3 H, m).

A mixture of the above diester and in 80 mL of Dowtherm A (Fluka) was heated at 220 °C for 4.5 h. After being cooled to room temperature, the mixture was poured onto 100 mL of hexanes and the precipitate was filtered and washed with ether to give 37.7 g (78%) of a mixture of **9** and the corresponding 5,6-difluoro isomer **10** as a light brown solid, mp > 280 °C dec: ^{1}H-NMR (DMSO-d_6) δ 1.27 (3 H, t, J = 7), 2.39 (3 H, s), 4.24 (2 H, q, J = 7), 7.33–7.41 (m) and 7.49 (dd, J = 7 and 11), two 1 H signals, intensity ratio 1:3.3, 7.76 (q, J = 9) and 7.92 (dd, J = 8 and 10).

Two recrystallizations of 20 g of the above from absolute EtOH (1.5 and 1 L, respectively) yielded 10 g of **9** as a white solid, mp 301–303 °C dec: ^{1}H NMR (DMSO-d_6) δ 1.27 (3 H, t, J = 7), 2.39 (3 H, s), 4.24 (2 H, q, J = 7), 7.49 (1 H, dd, J = 7 and 11), 7.92 (1 H, dd, J = 9 and 11); IR (KBr) 3300–2800 (bd), 1730, 1600, 1525, 1500, and 1295 cm^{-1}; UV (EtOH) λ_{max} = 210 (ε 28 300), 235 (ε 15 100), 246 (ε 16 200), 315 (ε 9100), and 327 nm (ε 8700); MS m/e 267 (parent), 221 (base), 165, 153, 138, 125, 112. Anal. Calcd for $C_{13}H_{11}NO_3F_2$: C, 58.42; H, 4.16; N, 5.24. Found: C, 58.27; H, 4.05; N, 5.23.

General Procedure for the Preparation of 4-(Allyloxy)- and 4-(Propargyloxy)-3-quinolinecarboxylic Acid Ethyl Esters 11–13 by Alkylation of the Mixture of 9 and 10. Into a 100-mL three-necked, round-bottom flask equipped with a magnetic stirring bar, N_2 inlet tube, and rubber septum was placed 5.60 mmol of a mixture of **9** and **10**, 22.4 mmol of K_2CO_3, and 20 mL of DMF. The mixture was preheated to 70 °C, and the corresponding allyl or propargyl halide was added via syringe. The progress of the reaction was monitored by TLC. When the reaction was complete, the flask was fitted with a short-path distillation apparatus and the solvent and excess alkylating agent were removed by vacuum distillation. The residue was partitioned between 150 mL of EtOAc and 150 mL of water, and the organic

layer was separated, washed with water (2 × 150 mL), dried (K_2CO_3), and evaporated. The residue was purified by flash chromatography, eluting with the appropriate combination of EtOAc and hexanes. The minor 5,6-difluoroquinoline isomer eluted slower than the 6,7-difluoroquinoline isomer and normally was not collected. Yields are based on chromatographically pure products. Analytical samples were obtained on chromatographed products or were prepared as described. Melting points are reported for analytical samples.

6,7-Difluoro-2-methyl-4-(2-propenyloxy)-3-quinolinecarboxylic Acid Ethyl Ester (11). Alkylating agent, allyl bromide: yield 52%; mp 51–53 °C; R_f = 0.6, 1:1 EtOAc–hexanes; ^{1}H NMR ($CDCl_3$) δ 1.42 (3 H, t, J = 7), 2.66 (3 H, s), 4.46 (2 H, q, J = 7), 4.68 (2 H, dt, J = 1 and 6), 5.34 (1 H, dq, J = 10 and 1), 5.45 (1 H, dq, J = 18 and 1), 6.01–6.14 (1 H, m), 7.71 (1 H, dd, J = 7 and 11), 7.81 (1 H, dd, J = 9 and 11); IR (KBr) 3100, 3040, 2990, 2940, 1720, 1640, 1600, 1510, and 1240 cm^{-1}; UV (EtOH) λ_{max} = 221 (ϵ 52 100), 273 (ϵ 6300), 302 (ϵ 3000), and 315 nm (ϵ 3000); MS m/e 307 (parent), 262, 234, 221 (base), 194, 182, 166, 138, 112, 86. Anal. Calcd for $C_{16}H_{15}NO_3F_2$: C, 62.53; H, 4.92; N, 4.55. Found: C, 62.37; H, 4.74; N, 4.48.

6,7-Difluoro-2-methyl-4-(2-propynyloxy)-3-quinolinecarboxylic Acid Ethyl Ester (12). Alkylating agent, propargyl bromide: yield 58%; mp 110–111 °C; R_f = 0.6, 1:1 EtOAc–hexanes; ^{1}H NMR ($CDCl_3$) δ 1.44 (3 H, t, J = 7), 2.61 (1 H, t, J = 2), 2.68 (3 H, s), 4.48 (2 H, q, J = 7) 4.85 (2 H, d, J = 2), 7.73 (1 H, dd, J = 7 and 11), 7.93 (1 H, dd, J = 9 and 11); IR (KBr) 3200, 2990, 2120, 1705, 1640, 1600, 1520, and 1245 cm^{-1}; UV (EtOH) λ_{max} = 223 (ϵ 46 300), 273 (ϵ 5600), 303 (ϵ 2800), and 316 nm (ϵ 3000); MS m/e 305 (parent), 276, 260, 232 (base), 221, 204, 182, 166. The analytical sample was prepared by trituration of the chromatographed solid with ether–hexanes. Anal. Calcd for $C_{16}H_{13}NO_3F_2$: C, 62.95; H, 4.29; N, 4.59. Found: C, 62.79; H, 4.18; N, 4.57.

4-[[2-(Chloromethyl)-2-propenyl]oxy]-6,7-difluoro-2-methyl-3-quinolinecarboxylic Acid Ethyl Ester (13). Alkylating agent, 3-chloro-2-(chloromethyl)-1-propene: yield 33%; mp 37–38 °C; R_f = 0.6, 1:1 EtOAc–hexanes; ^{1}H NMR ($CDCl_3$) δ 1.42 (3 H, t, J = 7), 2.67 (3 H, s), 4.25 (2 H, s), 4.46 (2 H, q, J = 7), 4.77 (2 H, s), 5.45 (1 H, s), 5.47 (1 H, s), 7.74 (1 H, dd, J = 7 and 11), 7.81 (1 H, dd, J = 8 and 11); IR (KBr) 3030, 2980, 1725, 1640, 1600, 1510 and 1255 cm^{-1}; UV (EtOH) λ_{max} = 221 (ϵ 47 200), 273 (ϵ 5800), 302 (ϵ 2700), and 316 nm (ϵ 2900); MS m/e 357 and 355 (parent), 320, 276, 248, 221, 99, 89, 53 (base). The analytical sample was prepared by trituration of the chromatographed solid with hexanes at 0 °C. Anal. Calcd for $C_{17}H_{16}NO_3F_2Cl$: C, 57.39; H, 4.53; N, 3.94. Found: C, 57.08; H, 4.41; N, 3.99.

General Procedure for the Thermolysis of 11–13 To Produce 16, 6, and 7, Respectively. A 0.125–0.175 M chlorobenzene or *o*-dichlorobenzene solution of the 4-(allyloxy)- or 4-(propargyloxy)-3-quinolinecarboxylic acid ethyl ester was heated to reflux under nitrogen (example 11) or argon (examples 12 and 13), and the progress of the reaction was monitored by TLC. When the reaction was complete, the mixture was allowed to cool to room temperature. In the reaction of 11, the product 16 precipitated out of solution and was filtered and washed with ether. In the reaction of 13, the byproduct 9 was isolated as a precipitate. All other products were isolated by removal of the solvent under high vacuum and purification of the residue by flash chromatography, eluting with the appropriate combination of EtOAc and hexanes. Yields reported are of chromatographically pure products. Analytical samples were obtained on chromatographed products or were prepared as described. Melting points are those of analytical samples.

2-(3-Butenyl)-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (16). Reaction solvent, chlorobenzene: time 16 h; yield 85%; mp 238–239 °C; R_f = 0.30, 1:1 EtOAc–hexanes; ^{1}H NMR (DMSO-d_6) δ 1.26 (3 H, t, J = 7), 2.38–2.48 (2 H, m), 2.74 (2 H, t, J = 7), 4.25 (2 H, q, J = 7), 5.02 (1 H, d, J = 10), 5.07 (1 H, d, J = 19), 5.80–5.90 (1 H, m), 7.53 (1 H, dd, J = 7 and 11), 7.92 (1 H, dd, J = 9 and 11); IR (KBr) 3300–2800 (bd), 1720, 1600, 1530, 1495, 1290 and 1195 cm^{-1}; UV (EtOH) λ_{max} = 211 (ϵ 27 800), 246 (ϵ 18 700), 316 (ϵ 9800) and 328 nm (ϵ 9700); MS m/e 307 (parent), 261, 232 (base), 166, 151, 138, 112. The analytical sample was prepared by recrystallization from EtOAc. Anal. Calcd for $C_{16}H_{15}NO_3F_2$: C, 62.53; H, 4.93; N, 4.56. Found: C, 62.24; H, 4.66; N, 4.48.

7,8-Difluoro-1-methylene-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic Acid Ethyl Ester (6). Reaction solvent, *o*-dichlorobenzene: time, 2 h; yield 54%; mp 164–165 °C; R_f = 0.40, 1:1 EtOAc–hexanes; ^{1}H NMR ($CDCl_3$) δ 1.39 (3 H, t, J = 7), 2.84 (2 H, t, J = 8), 3.41 (2 H, t, J = 7), 4.38 (2 H, q, J = 7), 5.10 (1 H, s), 5.38 (1 H, s), 7.89 (1 H, dd, J = 6 and 12), 8.22 (1 H, dd, J = 9 and 10); IR (KBr) 3060, 3010, 2970, 2895, 1720, 1620, 1200, and 1100 cm^{-1}; UV (EtOH) λ_{max} = 215 (ϵ 18 500), 256 (ϵ 21 200), and 329 nm (ϵ 11 700); MS m/e 305 (parent), 266, 233 (base), 203, 165. The analytical sample was prepared by trituration of the chromatographed solid with ether–hexanes. Anal. Calcd for $C_{16}H_{13}NO_3F_2$: C, 62.94; H, 4.30; N, 4.59. Found: C, 62.69; H, 4.10; N, 4.60.

8,9-Difluoro-2-methylene-6-oxo-2,3,4,6-tetrahydro-1*H*-benzo[*c*]quinolizine-5-carboxylic Acid Ethyl Ester (7). Reaction solvent, *o*-dichlorobenzene: time 1.25 h; yield 48%; mp 149–150 °C; R_f = 0.20, 1:1 EtOAc–hexanes; ^{1}H NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7), 2.59 (2 H, t, J = 7), 3.07 (2 H, t, J = 7), 4.39 (2 H, q, J = 7), 4.62 (2 H, s), 5.14 (1 H, s), 5.20 (1 H, s), 7.35 (1 H, dd, J = 6 and 12), 8.22 (1 H, dd, J = 9 and 10); IR (KBr) 3075, 3055, 2990, 2960, 2870, 1730, 1605, 1585, 1540, 1490, 1200, and 1100 cm^{-1}; UV (EtOH) λ_{max} = 211 (ϵ 20 200), 250 (ϵ 11 200), 322 (ϵ 7500), and 334 nm (ϵ 8000); MS m/e 319 (parent), 274, 247 (base), 203. The analytical sample was prepared by trituration of the chromatographed solid with ether–hexanes. Anal. Calcd for $C_{17}H_{15}NO_3F_2$: C, 63.95; H, 4.73; N, 4.39. Found: C, 63.79; H, 4.47; N, 4.34.

Isolation of 6,7-Difluoro-3,4-dihydro-2-methyl-4-oxo-3-(2-propenyl)-3-quinolinecarboxylic Acid Ethyl Ester (14). A solution of 200 mg (0.650 mmol) of 11 in xylene was refluxed for 5 h; the progress of the reaction was carefully monitored by TLC in order to maximize the amount of 14 relative to 11 and 16. The mixture was cooled, and the precipitate (16) was removed by filtration. The filtrate was concentrated to a yellow oil which was purified by flash chromatography, eluting with 20:80 EtOAc–hexanes, to give 100 mg (50%) of 14 as a light yellow solid, mp 92–93 °C: R_f = 0.4, 20:80 EtOAc–hexanes (fluorescent under UV); ^{1}H NMR ($CDCl_3$) δ 1.17 (3 H, t, J = 7), 2.26 (3 H, s), ABX pattern; ν_A = 2.93, ν_B = 3.12 (2 H, J_{AB} = 14, J_{AX} = 8, J_{BX} = 7), 4.10–4.26 (2 H, m), 4.92 (1 H, d, J = 10), 5.04 (1 H, d, J = 17), 5.24–5.38 (1 H, m), 7.36 (1 H, dd, J = 7 and 11), 7.76 (1 H, dd, J = 9 and 10); IR (KBr), 3175, 3155, 2990, 1740, 1680, 1615, 1495, and 1240 cm^{-1}; UV (EtOH) λ_{max} = 208 (ϵ 26 800), 223 (ϵ 38 300), 268 (ϵ 5600) and 324 nm (ϵ 3200); MS (m/e) 307 (parent), 292, 277, 261, 248 and 234. The analytical sample was prepared by recrystallization from hexane at −78 °C, mp 97–99 °C. Anal. Calcd for $C_{16}H_{15}F_2NO_3$: C, 62.53; H, 4.93; N, 4.56. Found: C, 62.37; H, 4.82; N, 4.45.

One-Pot Synthesis of 7 from 9. Into a 250-mL flask was placed 5.00 g (18.7 mmol) of 9 (pure recrystallized material), 10.3 g (7.48 mmol) of K_2CO_3, and 100 mL of *o*-dichlorobenzene. The suspension was degassed with argon, and 7.01 g (56.1 mmol) of 3-chloro-2-(chloromethyl)-1-propene was added. The mixture was heated to reflux under argon, and the progress of the reaction, including formation and disappearance of 13, was monitored by TLC. After 5 h of reflux, the reaction mixture was allowed to cool to room temperature and the solvent and other volatiles were removed under high vacuum. The residue was partitioned between 150 mL of water and 200 mL of EtOAc. The organic layer was separated, and the aqueous layer was backwashed with EtOAc (1 × 150 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated to 7 g of a brown oil which was purified by flash chromatography, eluting with 3:7–1:1 EtOAc–hexanes to afford 4.2 g of a yellow solid, mp 140–143 °C. Trituration with hexanes yielded 3.03 g (51%) of 7 as a pale yellow solid, mp 143–145 °C, which was identical by 300-MHz NMR to that obtained directly from 13.

1-(Bromomethyl)-7,8-difluoro-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic Acid Ethyl Ester (17). A suspension of 1.00 g (3.25 mmol) of 16, 694 mg (3.90 mmol) of *N*-bromosuccinimide, and 75 mL of CCl_4 was heated to reflux for 16 h. The cooled, pale yellow mixture was evaporated, and the residue was partitioned between 150 mL of $CHCl_3$ and water (150 mL). The organic layer was separated, washed with saturated aqueous $NaHSO_3$ solution (150 mL), dried (Na_2SO_4), and evap-

orated. The residue was triturated in nm (ε 9100); 731 mg (58%) of 17 as a light green solid, mp 219–221 °C: R_f 0.2, 1:1 EtOAc–hexanes; ^{1}H NMR ($CDCl_3$) δ 1.39 (3 H, t, J = 7), 2.42–2.58 (2 H, m), 3.49–3.67 (4 H, m), 4.37 (2 H, q, J = 7), 4.97 (1 H, bd t), 7.11 (1 H, dd, J = 6 and 11), 8.23 (1 H, dd, J = 9 and 10); IR (KBr) 3040, 2980, 2900, 1710, 1610, 1495, 1300, and 1090 cm^{-1}; UV (EtOAc) λ_{max} = 213 (ε 28 300), 248 (ε 15 800), 257 (ε 17 500), 318 (ε 9800), and 330 nm (ε 9100); MS (m/e) 388, 387, 386, 385, 315 (base), 313. The analytical sample was prepared by recrystallization from MeOH, mp 231–233 °C. Anal. Calcd for $C_{16}H_{14}NO_3F_2Br$: C, 49.76; H, 3.65; N, 3.63. Found: C, 49.64; H, 3.48; N, 3.56.

6 by Dehydrobromination of 17. To a mixture of 2.0 g (5.2 mmol) of 11 and 200 mL of THF containing 1% ethanol was added 0.30 g (5.3 mmol) of KOH (pellets). The suspension was stirred for 3 h at room temperature and then was treated with an additional 0.070 g (1.3 mmol) of KOH. Following additional stirring for 0.5 h, the dark mixture was diluted with 50 mL of 1 N aqueous HCl solution and the THF was removed by rotary evaporation. The aqueous residue was extracted with $CHCl_3$ (200 mL), and the organic layer was backwashed with water (2 × 100 mL), dried ($MgSO_4$), and evaporated to give a tan solid. Recrystallization from EtOAc–hexanes gave 0.75 g (47%) of 6, mp 165–166 °C, which was identical by 300-MHz NMR and TLC to that obtained by thermolysis of 12.

Acknowledgment. We would like to thank Vinod D. Parikh for technical assistance.

Synthesis of 7-Azaindole and 7-Azaoxindole Derivatives through a Palladium-Catalyzed Cross-Coupling Reaction

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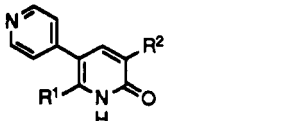
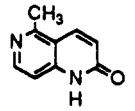
Received July 28, 1992

Cardiac glycosides (such as digitalis) have, historically, been used as positive inotropic agents for the treatment of congestive heart failure, a chronic and debilitating disease.[1-3] The search for an orally active non-glycoside inotropic agent displaying a greater safety profile and improved efficacy compared to digitalis resulted in the discovery of a new class of agents, the cAMP phosphodiesterase III inhibitors. These agents comprise a chemically diverse group of compounds including amrinone (1),[4] milrinone (2),[5] medorinone,[6] indolidan, and imazodan.[3,7]

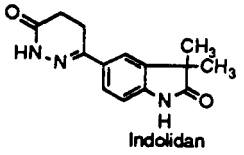


1, R^1 = H, R^2 = NH_2, Amrinone

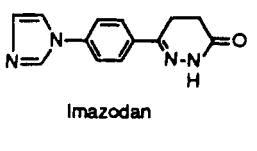
2, R^1 = CH_3, R^2 = CN, Milrinone



Medorinone

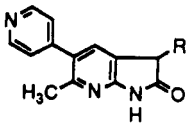


Indolidan



Imazodan

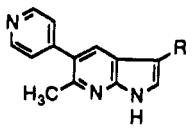
In an effort to improve upon the potency and duration of action of milrinone (2), we have synthesized 7-azaoxindole derivatives (3) (1,3-dihydro-6-methyl-2H-pyrrolo[2,3-b]-pyridin-2-one). These compounds have the essential features that appear to be important for the inotropic activity: a cyclic unsubstituted amide function and an appropriately positioned hydrogen acceptor ring. These structural features were derived from a pharmacophoric analysis of several well-known cardiotonic cAMP phosphodiesterase III inhibitors, primarily milrinone, medorinone, and indolidan. After a similar analysis of several cadiotonic agents, a five-point model for positive inotropic activity has been proposed by Bristol and co-workers.[8]



3

a, R = H

b, R = CH_3



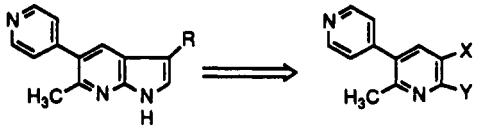
4

a, R = H

b, R = CH_3

Limited general synthetic pathways exist in the literature for the preparation of 7-azaindoles.[9] Taylor[10] and Seitz[11] have recently utilized an intramolecular inverse electron demand Diels–Alder reactions of appropriately substituted 1,2,4-triazines to prepare 7-azaindoles. However, application of this procedure to synthesize more elaborate 7-azaindoles is limited because of the higher temperatures required to effect the Diels–Alder reaction which was often accompanied by the significant decomposition of the starting materials resulting in low yields of the desired products. In addition, substitution of the 1,2,4-triazines further reduces the product yield. We anticipated a similar fate utilizing this Diels–Alder strategy to prepare the above target compounds. Thus we needed a procedure that would provide these fused heterocyclic compounds in good overall yields. We describe, herein, the synthesis of 7-azaoxindole derivatives (3) through the key intermediate, 7-azaindole derivatives 4 (5-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridines) which in turn were prepared by a palladium-catalyzed cross-coupling reaction of appropriately substituted pyridines.

Retrosynthetic Strategy:



4 8

The general application of palladium-catalyzed cross-coupling reactions has provided new avenues to obtain key synthetic intermediates for the preparation of condensed heteroaromatic compounds that were inaccessible through

† Deceased.

(1) Robertson, D. W.; Hayes, J. S. *ISI Atlas Sci. Pharmacol.* **1988**, *2*, 129.
(2) Grolin, R. *Circulation* **1987**, *75*, IV-108.
(3) Taylor, M. P.; Sircar, I.; Steffen, R. P. *Annu. Rep. Med. Chem.* **1987**, *22*, 85.
(4) Farah, A. E.; Alousi, A. A. *Life Sci.* **1978**, *22*, 1139.
(5) Alousi, A. A.; Canter, J. M.; Montenaro, M. J.; Fort, D. J.; Ferrari, R. A. *Cardiovasc. Pharmacol.* **1983**, *5*, 792.
(6) Singh, B.; Lesher, G. Y. *J. Heterocycl. Chem.* **1990**, *27*, 2085.
(7) Coates, W. J.; Prain, H. D.; Reeves, M. L.; Warrington, B. H. *J. Med. Chem.* **1990**, *33*, 1735 and references cited therein.
(8) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1099.
(9) Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428 and references cited therein.
(10) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145.
(11) John, R.; Seitz, G. *Arch. Pharm. (Weinheim)* **1989**, *322*, 561.

0022-3263/92/1957-6995$03.00/0