FORMATION OF FURO[3,2-c]QUINOLINE DERIVATIVES THROUGH THE FRIES-TYPE ACID-CATALYZED REARRANGEMENT OF 1-ARYLAZETIDIN-2-ONES†

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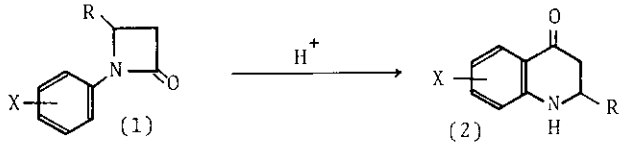
Abstract 1-Aryl-3-(2-hydroxyalkylidene)azetidin-2-ones were heated with trifluoroacetic acid under reflux for 1.5 hr to give furo[3,2-c]quinoline derivatives in one-step through 2,3-dihydro-3-β-ketoalkyl-4(1H)-quinolone intermediates. By this method, 7,8,9,10-tetrahydro-2-methoxybenzofuro[3,2-c]quinoline (11), 2-methyl-3-phenylfuro[3,2-c]quinoline (15), 2-methylfuro[3,2-c]-quinoline (20a), 2-ethylfuro[3,2-c]quinoline (20b) and 2-methyl-8-methoxyfuro[3,2-c]quinoline (20c) were obtained from the corresponding 1-aryl-3-(2-hydroxyalkylidene)azetidin-2-ones.

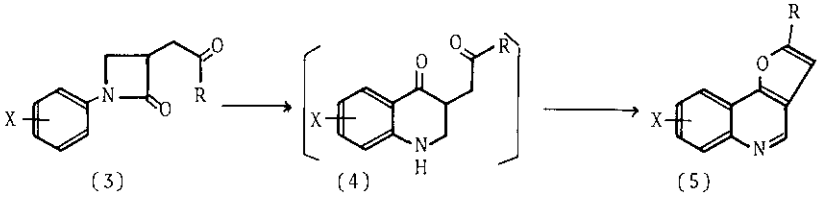
In the previous papers[1,2], we reported that monocyclic 1-arylazetidin-2-ones (1) were easily converted to 2,3-dihydro-4(1H)-quinolones (2) by an action of acids. (Scheme 1). This acid-catalyzed acyl migration reaction might be applicable to a synthesis of furo[3,2-c]quinoline derivatives (5) upon treatment of 1-aryl-3-(β-ketoalkyl)azetidin-2-ones (3) with acids through 2,3-dihydro-4(1H)-quinolones (4) as intermediates. (Scheme 2). Based upon this assumption, we have further investigated the acid-catalyzed rearrangement of 1-aryl-3-(2-hydroxyalkylidene)azetidin-2-ones, in the expectation that they might behave as 3-(β-ketoalkyl)azetidin-2-ones and give furo[3,2-c]quinolines, as an extention of the previous works. We wish to report the results of our studies in this paper.

Scheme 1



X=H, OH, OCH_3, Cl, Br, $N(CH_3)_2$; R=H, alkyl, COOEt

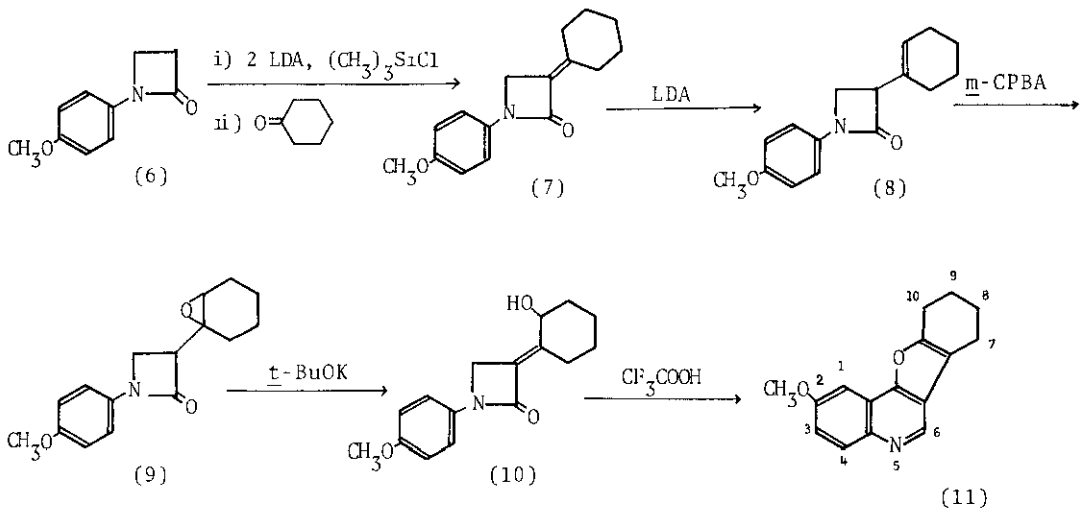
Scheme 2



(3) (4) (5)

First, we examined the acid-catalyzed rearrangement of 1-(4-methoxyphenyl)-3-(2-hydroxycyclohexylidene)azetidin-2-one (10), easily prepared as follows. Condensation of 1-(4-methoxyphenyl)azetidin-2-one (6)[3] with cyclohexanone by the method as we reported[4,5] afforded the cyclohexylideneazetidin-2-one (7[6,7], 90 %), mp 132-133 °C. Treatment of (7) with lithium diisopropylamide (LDA) in THF at -78 °C gave the 3-cyclohexenyl derivative (8)[5,8] in nearly quantitative yield, mp 75-77 °C. Oxidation of (8) with m-chloroperbenzoic acid in methylene chloride at room temperature for 14 hr yielded the 3-(1,2-epoxycyclohexyl)azetidin-2-one (9, 90 %) as a diastereoisomeric mixture, mp 99-101 °C. Treatment of (9) with one equivalent of t-BuOK in EtOH under reflux for 0.5 hr gave the 3-(2-hydroxycyclohexylidene)azetidin-2-one (10[9], 88 %), mp 159-161 °C. The azetidin-2-one (10), thus obtained, was heated with trifluoroacetic acid under reflux for 1.5 hr to give the expected 7,8,9,10-tetrahydro-2-methoxybenzofuro[3,2-c]quinoline (11).

Scheme 3



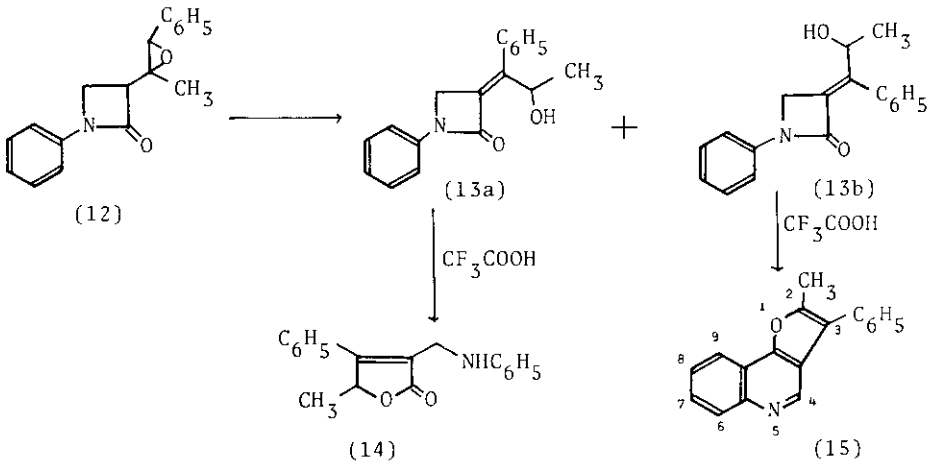
(6) (7) (8) (9) (10) (11)

Since the 1-aryl-3-(2-hydroxycyclohexylidene)azetidin-2-one was found to be an excellent precursor for the synthesis of furo[3,2-c]quinoline system, successively,

we examined the acid-catalyzed rearrangement of some 1-aryl-3-(2-hydroxyalkylidene)azetidin-2-ones.

The azetidin-2-one (12)[5] was treated with t-BuOK as above to give two products (13a[10], 30 %), mp 111-113 °C, and (13b[11], 35 %), mp 164-166 °C. These were separated by column chromatography on silica gel by using chloroform as an eluent. The structure of the first product was deduced as (13a) by the fact that the butenolide (14)[5] was obtained upon heating with trifluoroacetic acid. On the other hand, on heating the second product, the desired 2-methyl-3-phenylfuro[3,2-c]quinoline (15) was obtained.

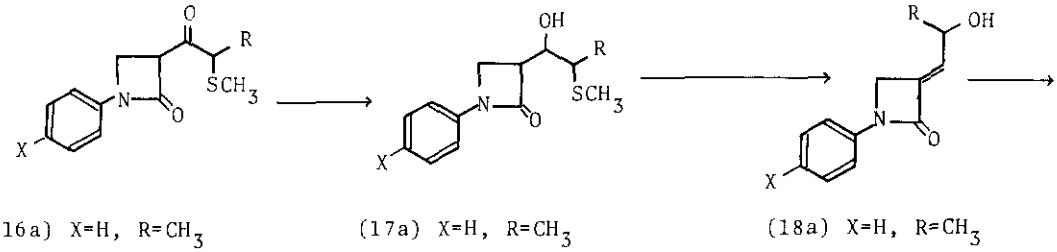
Scheme 4



Furthermore, we investigated the alternative method for yielding 1-aryl-3-(2-hydroxyalkylidene)azetidin-2-ones. Methylation of the azetidin-2-one (17a)[12] with methyl iodide in MeOH under reflux for 2 hr, followed by treatment of the resulting sulfonium iodide, without purification, with two equivalent of t-BuOK in EtOH afforded 3-(2-hydroxypropylidene)-1-phenylazetidin-2-one (18a[13], 73 %), mp 127-129 °C. In a similar fashion, 3-(2-hydroxybutylidene)-1-phenylazetidin-2-one (18b[14], 70 %), mp 96-98 °C, was also obtained from the azetidin-2-one (17b)[12]. Condensation of the lithio salt[15] of (6) with ethyl α-methylthiopropionate gave the 3-acyl derivative (16c), mp 112-114 °C, reduction of which with $NaBH_4$ in MeOH at -78 °C afforded the alcohol (17c) as a mixture of stereoisomers, mp 100-103 °C. The compound (17c) was converted to 3-(2-hydroxypropylidene)-1-(4-methoxyphenyl)-azetidin-2-one (18c)[16], mp 114-117 °C, by the same method as above. These azetidin-2-ones (18a)-(18c) were heated with trifluoroacetic acid under reflux for 1.5 hr to give the corresponding furo[3,2-c]quinolines (20a)-(20c) contaminated with

the 4,5-dihydro intermediates (19a)-(19c)[17]. Hence, the crude products were refluxed in toluene in the presence of 5 % Pd-C for 2 hr for dehydrogenation of (19a)-(19c). By this way, the yields of (20a)-(20c) were enhanced. Physical data of furo-[3,2-c]quinolines (11), (15), (20a)-(20c) were listed in the Table 1.

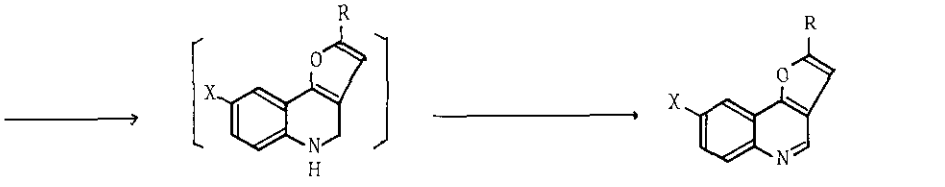
Scheme 5



(16a) X=H, R=CH_3 (17a) X=H, R=CH_3 (18a) X=H, R=CH_3

(16b) X=H, R=C_2H_5 (17b) X=H, R=C_2H_5 (18b) X=H, R=C_2H_5

(16c) X=OCH_3, R=CH_3 (17c) X=OCH_3, R=CH_3 (18c) X=OCH_3, R=CH_3



(19a) X=H, R=CH_3 (20a) X=H, R=CH_3

(19b) X=H, R=C_2H_5 (20b) X=H, R=C_2H_5

(19c) X=OCH_3, R=CH_3 (20c) X=OCH_3, R=CH_3

Table 1. Physical Data of Furo[3,2-c]quinolines (11), (15), (20a), (20b) and (20c)

Compd	Yield (%)	mp °C	m/e (M^+)	^{1}HNMR ($CDCl_3$) δ
11	63	105-107	253	1.75-2.15 (m, 4H), 2.57-2.98 (m, 4H), 3.98 (s, 3H), 7.27-7.48 (m, 2H), 8.01 (d, J=8.5 Hz, 1H), 8.85 (s, 1H)
15	58	91-93	259	2.66 (s, 3H), 7.20-7.82 (m, 7H), 8.05-8.41 (m, 2H), 9.12 (s, 1H)
20a	55	oil	183	2.57 (bs, 3H), 6.54 (bs, 1H), 7.50-7.78 (m, 2H), 8.03-8.35 (m, 2H), 9.05 (s, 1H)
20b	60	oil	197	1.39 (t, J=7 Hz, 3H), 2.91 (q, J=7 Hz, 2H), 6.53 (bs, 1H), 7.48-7.79 (m, 2H), 7.98-8.37 (m, 2H), 9.05 (s, 1H)
20c	55	oil	213	2.56 (s, 3H), 3.96 (s, 3H), 6.51 (bs, 1H), 7.07-7.50 (m, 2H), 8.05 (d, J=9 Hz, 1H), 8.88 (s, 1H)

References and Footnotes

† Dedicated to Professor Tetsuji Kametani on the occasion of the retirement from the chair of Organic Chemistry of Pharmaceutical Institute of Tohoku University.

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6. ^{1}HNMR ($CDCl_3$) δ : 1.37-1.92 (m, 6H), 1.95-2.30 (m, 2H), 2.52-2.83 (m, 2H), 3.78 (s, 3H), 3.98 (s, 2H), 6.83 (d, J=9 Hz, 2H), 7.29 (d, J=9 Hz, 2H).
7. All new compounds gave satisfactory microanalysis or high resolution mass spectral data.
8. ^{1}HNMR ($CDCl_3$) δ: 1.42-1.82 (m, 4H), 1.82-2.34 (m, 4H), 3.78 (s, 3H), 3.33-3.98 (m, 3H), 6.83 (d, J=9 Hz, 2H), 7.30 (d, J=9 Hz, 2H).
9. The geometry of (10) could not be determined. Most possibly, (10) would be an isomeric mixture.
10. ^{1}HNMR ($CDCl_3$) δ: 1.45 (d, J=6 Hz, 3H), 3.98 (d, J=8 Hz, 1H), 4.25 (d, J=8 Hz, 1H), 4.94 (q, J=6 Hz, 1H), 6.85-7.55 (m, 10H). m/e 279 (M^+).
11. ^{1}HNMR ($CDCl_3$) δ: 1.29 (d, J=6 Hz, 3H), 4.32 (s, 2H), 4.57-4.98 (m, 1H), 6.82-7.55 (m, 10H). m/e 279 (M^+).
12. S. Kano, T. Ebata, Y. Yuasa, and S. Shibuya, Heterocycles, 14, 589 (1980).
13. ^{1}HNMR ($CDCl_3$) δ: 1.35 (d, J=7 Hz, 3H), 4.28 (bs, 2H), 4.53 (m, 1H), 6.31 (m, 1H), 6.87-7.52 (m, 5H).
14. ^{1}HNMR ($CDCl_3$) δ: 1.01 (t, J=7 Hz, 3H), 1.53-1.82 (m, 2H), 4.24 (s, 2H), 4.21 (m, 1H), 6.24 (m, 1H), 6.92-7.43 (m, 5H). m/e 217 (M^+).
15. S. Kano, T. Ebata, and S. Shibuya, Chem. Pharm. Bull., 27, 2450 (1979).
16. ^{1}HNMR ($CDCl_3$) δ: 1.36 (d, J=7 Hz, 3H), 3.76 (s, 3H), 4.17 (bs, 2H), 4.57 (m, 1H), 6.22 (m, 1H), 6.79 (d, J=9 Hz, 2H), 7.23 (d, J=9 Hz, 2H).
17. In some cases, formation of considerable amounts of 4,5-dihydro derivatives (19) was observed by their ^{1}HNMR ($CDCl_3$) spectra.

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