FACILE α,β'-ANNELATION OF 1,6-DIHYDRO-3(2*H*)-PYRIDINONES WITH 1,3-DICARBONYL COMPOUNDS. A NEW SYNTHETIC METHOD FOR 2-AZA-BICYCLO[2.2.2]OCTAN-6-ONES

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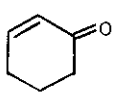
Abstract —— On treatment of N-substituted 1,6-dihydro-3(2*H*)-pyridinones with 1,3-dicarbonyl compounds proceeded a facile α,β'-annelation to give the 2-azabicyclo[2.2.2]octan-6-ones under a basic condition, while the reaction with dimethyl acetonedicarboxylate afforded a 3-azabicyclo[3.3.1]nonanone.

2-Cyclohexenone (1) is well known to afford the bicyclo[3.3.1]nonan-3-ones (2) by the base-catalyzed reaction with ethyl acetoacetate.[1] As an application of this method to azacyclic enones, we have investigated the reaction of N-substituted 1,6-dihydro-3(2*H*)-pyridinones with several 1,3-dicarbonyl compounds and now wish to report the exclusive abnormal cyclization to the 2-azabicyclo[2.2.2]octan-6-one system (3) through an α,β'-annelation reaction.[2]



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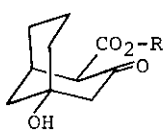
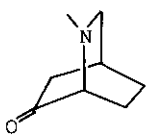


R=Et, H

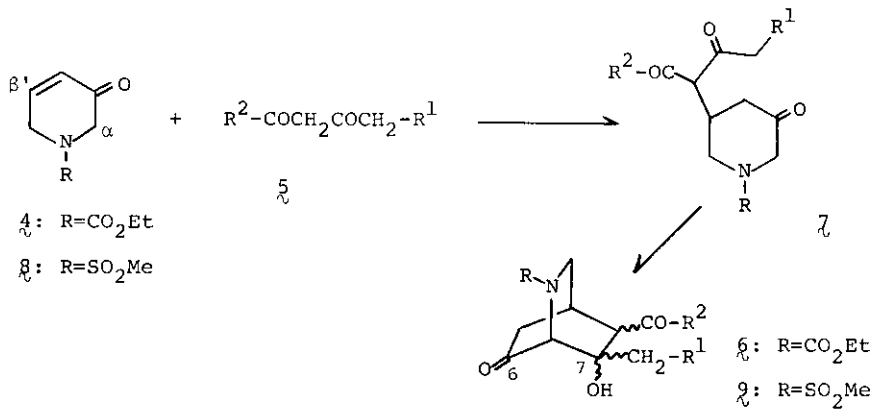
2



3

Treatment of ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate[3] (4) with one equivalent of ethyl acetoacetate (5a) in ethanol containing 0.2 equivalent of sodium ethoxide at room temperature afforded diethyl 7-hydroxy-7-methyl-2-azabicyclo-

[2.2.2]octan-6-one-2,8-dicarboxylate (6a) in 70% yield as a sole product *via* the Michael adduct (7a), which could be obtained by the reaction in the presence of a catalytic amount of the base. The adduct (7a) [δ 2.24(3H, s), positive $FeCl_3$ test] cyclized easily to afford 6a in good yield by passing through alumina or on further treatment with sodium ethoxide in ethanol. The planar structure of 6a was established from the spectral evidences. The IR spectrum showed a carbonyl band at 1735 cm^{-1} characteristic of this ring system[4] and the PMR spectrum exhibited the C_7-methyl singlet at 1.56 ppm.[5] N-Methanesulfonyl-1,6-dihydro-3(2*H*)-pyridinone[6] (8) also gave the corresponding isoquinuclidinone (9a) [ν 3475(OH), 1735(CO), 1340, 1160(SO_2), δ 1.30(3H, t, *J*=7), 1.67(3H, s), 2.71(3H, s), 4.20(2H, q, *J*= 7)] by the reaction with ethyl acetoacetate under the same condition in 78% yield. The results of the reaction using other 1,3-dicarbonyl compounds (5b-5e) are summarized in Table I.



4: R=CO_2Et

8: R=SO_2Me

6: R=CO_2Et

9: R=SO_2Me

Table I. Reaction of Dihydropyridinones (4 and 8) with 1,3-Dicarbonyl Compounds (5)[a]

Substrate	1,3-Dicarbonyl Compd.	Yield(%) of Product	Chemical Shift of C_7-Substituent(δ)
4	5a: R^1=H, R^2=OEt	6a: 70	1.56(s)
8	5a	9a: 78	1.67(s)
4	5b: R^1=Me, R^2=OEt	6b: 60	1.00(t), 1.76(q)
8	5b	9b: 52	1.00(t), 2.01(q)
4	5c: R^1=H, R^2=OMe	6c: 73	1.55(s)
4	5d: R^1=H, R^2=Me	6d: 62	1.68(s)
4	5e: R^1=H, R^2=NHC_6H_5	6e: 52	1.42(s)

a Reaction with 5 (1 equiv.) in the presence of NaOEt (0.2 equiv.) in EtOH at room temperature for 4 hr.

The difference between 2-cyclohexenone (1) and the azacyclic enone (4 or 8) in behavior toward ethyl acetoacetate would be attributed to the high acidity of α-H in 4 or 8 in comparison with that of 1. The higher acidity is due to an inductive effect of the electron-withdrawing substituent attached at the nitrogen atom. Although there are lots of reports[7] concerning syntheses of 2-azabicyclo[2.2.2]-octanones, the present method seems to be noteworthy from the viewpoint of facility in operation and functionality in products, and would serve as a novel synthetic method for 2-azabicyclo[2.2.2]octan-6-one moiety.

On the contrary, the normal cyclization to 3-azabicyclo[3.3.1]nonanone was achieved by the condensation with the 1,3,5-tricarbonyl compound. Reaction of 4 with dimethyl acetonedicarboxylate in the presence of a catalytic amount of sodium ethoxide yielded the 3-azabicyclo[3.3.1]nonan-7-one (10)[64%, positive $FeCl_3$ test, δ 12.00(1H, enol H)] without any amount of 2-azabicyclooctanones. The same ring

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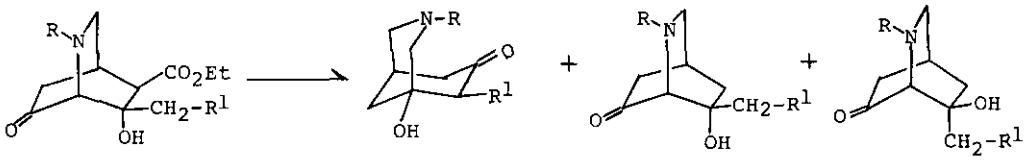
system is also accessible from the 2-azabicyclo[2.2.2]octanonecarboxylate (6a,b and 9a,b) *via* ring isomerization. Hydrolysis of 6a with 10% hydrochloric acid in acetic acid was accompanied by decarboxylation to give the 3-azabicyclo[3.3.1]-nonanone (11a)[20%, ν 3350(OH), 1680(CO, NCO), δ 2.20(2H, broad s, C_9-H)] along with the 2-azabicyclo[2.2.2]octanones,[8] 12a[24%, ν 3400(OH), 1735(CO), 1675(NCO), δ 1.35(3H, s)] and 13a[3%, ν 3400(OH), 1738(CO), 1675(NCO), δ 1.25(3H, s)]. The longer treatment of 6a under the same condition effected complete ring isomerization to give 11a as a sole product. Other results are summarized in Table II. Such ring isomerization would proceed through the retro-aldol and subsequent aldol reaction.



6: R=CO_2Et 11: R=CO_2Et 12: R=CO_2Et 13: R=CO_2Et

9: R=SO_2Me 14: R=SO_2Me 15: R=SO_2Me 16: R=SO_2Me

a: R^1=H, b: R^1=Me

Table II. Acid Hydrolysis of 2-Azabicyclo[2.2.2]octanone-carboxylates (6a,b and 9a,b)[a]

Substrate	Reaction Time(hr)	Products(%)		
6a	3	11a(20)	12a(24)	13a(3)
6b	3	11b(80)	-	-
9a	3	-	15a+16a(35)[b]	
9b	1	14b(56)	-	-

a On treatment of the esters (1 mmole) with 10%HCl (4 ml) in AcOH (4 ml) under reflux. b Obtained as a diastereoisomeric mixture of 15a and 16a (*ca.* 2:1).

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2. So named based on the term α,α'-annelation, which has been used in earlier literatures. For example, see T.R. Bok and W.N. Speckamp, Tetrahedron, 1977, 33, 787.
3. T. Imanishi, I. Imanishi, and T. Momose, Syn. Commun., 1978, 8, 99.
4. Z. Horii, T. Imanishi, M. Hanaoka, and C. Iwata, Chem. Pharm. Bull., 1972, 20, 1774. See also ref. 7.
5. Stereochemistry of 6 and 9 remains unsolved.
6. Prepared from 1,2,3,6-tetrahydropyridine according to the method of ref. 3.
7. M.P. Cava, C.K. Wilkins, Jr., D.R. Dalton, and K. Bessho, J. Org. Chem., 1965, 30, 3772; G. Büchi, P. Kalsa, and R.L. Rosati, J. Amer. Chem. Soc., 1968, 90, 2448; H. Tomisawa and H. Hongo, Tetrahedron Lett., 1969, 2465; R. Furstoss, P. Teissier, and B. Waegell, ibid., 1970, 1263; M. Narisada, R. Watanabe, and W. Nagata, ibid., 1971, 3681; G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Pannella, G. DeVicaris, and M. Grippi, J. Amer. Chem. Soc., 1973, 95, 5273; A.J.G. Baxter and A.B. Holmes, J. Chem. Soc. Perkin I, 1977, 2343; K. Somekawa, T. Watanabe, and S. Kumamoto, Nippon Kagaku Kaishi, 1978, 412.
8. Stereochemistry of 12a and 13a was determined from the chemical shift of C_7-Me in the PMR spectra. The chemical shift (δ 1.25) of the latter is higher than that (δ 1.35) of the former owing to a diamagnetic effect of the C_6-carbonyl function. A similar argument has appeared in T. Ibuka, Y. Mori, T. Aoyama, and Y. Inubushi, Chem. Pharm. Bull., 1978, 26, 456.

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