A CONVENIENT SYNTHESIS OF 1,4-DIHYDRO-4-OXONICOTINIC ACID DERIVATIVES

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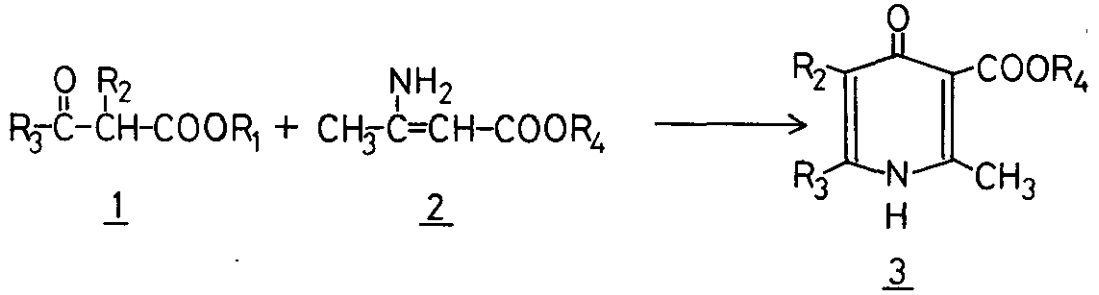
Abstract-------- The cyclization of β-ketoesters with β-amino-crotonates in the presence of molecular sieves gave 6-substituted or 5,6-disubstituted-1,4-dihydro-4-oxonicotinic acid esters by one step reaction.

1,4-Dihydro-4-oxonicotinic acid is the essential component of antibacterial agents, e.g., nalidixic acid,[1] oxolinic acid,[2] pyromidic acid,[3] and pipemidic acid.[4]

The most common synthetic methods of 1,4-dihydro-4-oxonicotinic acid derivatives are 1) Gould-Jacobs reaction,[5,6] 2) reactions of acylketene[7] or diketene[8,9] with enamines. The former method is consisted of two steps and the yield is generally low with difficulty for preparing enaminomethylene malonate intermediate. The latter has limitation of substituents.

We wish to report a new synthesis of 6-substituted or 5,6-disubstituted-1,4-dihydro-4-oxonicotinic acid esters. Thermal cyclization of β-ketoesters (1) with β-aminocrotonates (2) in the presence of molecular sieves afforded smoothly compounds (3).

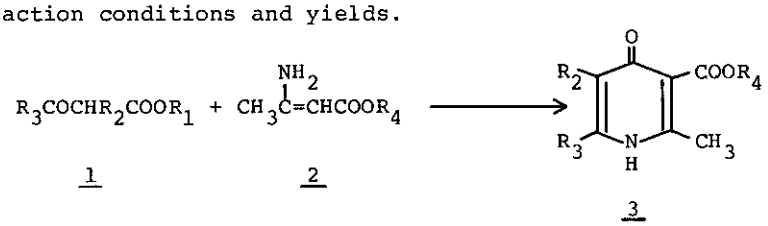
Chart 1



1 2 3

The cyclization of ethyl or methyl acetoacetate with methyl or ethyl 3-aminocrotonate[10] was examined with various reaction conditions. (Table 1)

Table 1. Reaction conditions and yields.

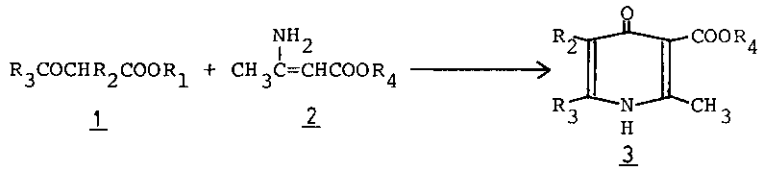


1 2 3

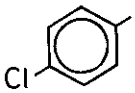
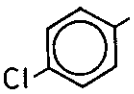
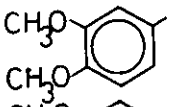
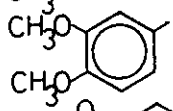
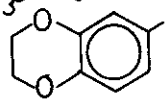
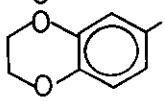
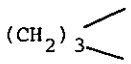
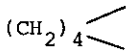
Entry No.	R_1	R_2	R_3	R_4	Solvent Temp.	Molecular Sieves	Time	Compd. No.	Yield
I	C_2H_5	H	CH_3	CH_3	xylene reflux	3A	24 h	4	10 %
II	C_2H_5	H	CH_3	CH_3	xylene reflux	4A	24 h	4	32 %
III	C_2H_5	H	CH_3	CH_3	neat 140°C	4A	24 h	4	27 %
IV	C_2H_5	H	CH_3	CH_3	xylene reflux	5A	24 h	4	42 %
V	C_2H_5	H	CH_3	CH_3	DMF reflux	5A	24 h	4	33 %
VI	CH_3	H	CH_3	C_2H_5	xylene reflux	4A	24 h	5	64 %
VII	CH_3	H	CH_3	C_2H_5	xylene reflux	5A	24 h	5	65 %

This reaction occurred neither with absence of molecular sieves nor under low temperature, for example, with refluxing benzene. The thermal cyclization in diphenyl ether (250-260°C) formed many by-products and the use of molecular sieves 13X gave the products, but in low yield. From above results, it appeares that xylene reflux condition in the presence of molecular sieves 5A is suitable for preparation of compound 4 and 5. (Entry No. IV and VII). Then this reaction was attempted to the cyclization of other β-ketoesters with appropriate β-aminocrotonates. (Table 2)

Table 2. The cyclization of β-ketoesters with β-aminocrotonates in refluxing xylene in the presence of molecular sieves 5A for 24 h.



1 2 3

Entry No.	R_1	R_2	R_3	R_4	Compound No.	Yield
VIII	C_2H_5	H		CH_3	6	25 %
IX	CH_3	H		C_2H_5	7	46 %
X	C_2H_5	H		CH_3	8	18 %
XI	CH_3	H		C_2H_5	9	37 %
XII	C_2H_5	H		CH_3	10	16 %
XIII	CH_3	H		C_2H_5	11	38 %
XIV	C_2H_5	H		CH_3	12	13 %
XV	CH_3	H		C_2H_5	13	48 %
XVI	C_2H_5			CH_3	14	24 %
XVII	C_2H_5			CH_3	15	18 %

The structure of above compounds was determined by chemical and physicochemical means. Namely, the compound 5 (mp 171-172°C) was identified with the authentic sample (lit. mp 168°C).[8] Compound 6 or 15 afforded the known compounds 2-methyl-6-phenyl-1,4-dihydro-4-oxopyridine (mp 184-185°C, lit. 175-177°C)[11] or 1,4,5,6,7,8-hexahydro-2-methyl-4-oxoquinoline (mp 240°C, lit. 240-242°C)[12] by hydrolysis of corresponding esters followed by decarboxylative sublimation under pyrolysis (bath temp. 240-260°C) with diminished pressure (18 mm Hg).

Table 3. 2-Methyl-6-substituted or -5,6-disubstituted-1,4-dihydro-4-oxonicotinic acid esters.

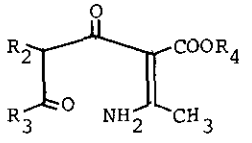
Compd. No.	Mp °C (Recryst. solv.)	Nmr[a] δ	Ir cm^{-1} (nujol)	Mass m/e
4	205.5-206.5 CH_2Cl_2-MeOH	2.07 (6H, s), 3.50 (3H, s), 5.67 (1H, s)	1720 1640 1612	181 (M^+), 149, 121, 93, 67
5	171-172 CH_2Cl_2-MeOH	1.27 (3H, t), 2.27, 2.37 (3H, s), 4.17 (2H, q), 6.15 (1H, s), 12.15 (1H, br s)	1720 1637 1612	195 (M^+), 149, 121, 93, 67
6	207-207.5 CH_2Cl_2-MeOH	2.43 (3H, s), 3.83 (3H, s), 6.63 (1H, s), 7.52 (5H, m)	1720 1632 1610 1578	243 (M^+), 211, 183, 149, 129, 116
7	144-145 IPE-AcOEt	1.33 (3H, t), 2.66 (3H, s), 4.30 (2H, q), 6.80 (1H, s), 7.00 (3H, m), 7.60 (2H, m), 11.10 (1H, s)	1725 1655 1600	257 (M^+), 211, 183, 149, 129, 116
8	205-206 CH_2Cl_2-MeOH	2.26 (3H, s), 3.60 (3H, s), 6.43 (1H, s), 7.30 (4H, q)	1730 1625 1570	279 (M+2), 277 (M^+), 245, 217, 163, 150
9	158-159.5 IPE-AcOEt	1.37 (3H, t), 2.66 (3H, s), 4.25 (2H, q), 6.78 (1H, s), 7.27 (4H, q), 11.35 (1H, s)	1720 1635 1610 1567	293 (M+2), 291 (M^+), 245, 217, 163, 150
10	218-219 CH_2Cl_2-MeOH	2.23 (3H, s), 3.60 (3H, s), 3.65, 3.70 (3H, s), 6.70 (1H, s), 7.00 (3H, m)	1730 1625 1580	303 (M^+), 271, 256, 228, 225, 200, 149
11	200-201 $CHCl_3$	1.37 (3H, t), 2.66 (3H, s), 3.70, 3.76 (3H, s), 4.23 (2H, q), 6.50, 7.20 (1H, d), 6.73 (1H, s), 7.30 (1H, s), 11.3 (1H, s)	1710 1625 1605 1582	317 (M^+), 271, 256, 228, 225, 200, 149
12	230-231 CH_2Cl_2-MeOH	2.20 (3H, s), 3.67 (3H, s), 4.07 (4H, s), 6.27 (1H, br s), 6.86 (1H, d), 6.95 (2H, m)	1707 1630 1580	301 (M^+), 268, 241, 213, 185, 174, 149
13	208.5-210 CH_2Cl_2-MeOH	1.36 (3H, t), 2.63 (3H, s), 4.03 (4H, s), 4.23 (2H, q), 6.56, 7.13 (1H, d), 6.70 (1H, s), 7.20 (1H, s), 11.1 (1H, br s)	1720 1625 1615 1580	315 (M^+), 268, 241, 213, 185, 174, 149
14	235 (dec.) CH_2Cl_2-MeOH	2.15 (2H, m), 2.35 (3H, s), 2.85 (4H, m), 3.85 (3H, s)	1725 1625 1607	207 (M^+), 175, 147, 119, 107
15	253-254.5 CH_2Cl_2-MeOH	1.73 (4H, m), 2.17 (3H, s), 2.20 (4H, m), 3.70 (3H, s)	1725 1623 1610	221 (M^+), 189, 161, 133, 121

a) $(CD_3)_2SO$ was used for compd. 1, 3, 5, 7, 9, 11, and 12 as solvent.

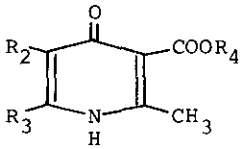
$CDCl_3$ was used for compd. 2, 4, 6, 8, and 10 as solvent.

Mass spectral data were particularly useful for structural assignment of 1,4-dihydro-4-oxonicotinic acid esters. The fragmentation pathways (Table 3) indicated the further evidence for the structures.[13] Nmr spectra, ir spectra and elemental analysis also supported their structures. (Table 3).

It was clear, shown in the Table 1 and 2, that in any trial the ester of β-aminocrotonate was incorporated in ester moiety of nicotinic acid and the alkoxy group of β-ketoester was eliminated. This observation suggests that compound type (A) might be the intermediate to afford the product (3).



(A)



(3)

Acylation of enamine α-carbon was generally carried out by the use of ketene or diketene. On the contrary, in the reaction reported here, molecular sieves caused direct dealcoholyration of β-ketoesters with β-aminocrotonates following dehydration to afford compound type (3).[14] Exclusively methyl ester of β-keto acids gave higher yield than corresponding ethyl esters, probably depending on easy removal of methanol than of ethanol.

Experimental

All melting points are uncorrected. The ir spectra were measured with a JASCO IR-G recording spectrometer, nmr spectra with a Varian T-60A spectrometer using tetramethylsilane as an internal standard, and mass spectra with JMS-01SG spectrometer.

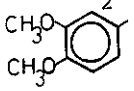
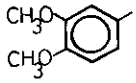
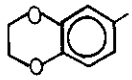
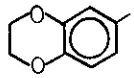
Methyl acetoacetate, ethyl acetoacetate, ethyl benzoylacetate, ethyl 2-cyclopentanonecarboxylate, and ethyl 2-cyclohexanonecarboxylate were commercially available. Methyl benzoylacetate,[15] methyl p-chlorobenzoylacetate,[16] and ethyl p-chlorobenzoylacetate[17] were prepared as follows.

General Procedure for Preparation of Substituted Benzoylacetates.

A solution of substituted-benzoylacetophenone (0.2 mol) in dry benzene (100 ml) was added dropwise into a refluxing suspension of sodium hydride (0.5 mol)

prewashed with benzene (100 ml X 4) and dimethyl or diethyl carbonate (0.4 mol) in dry benzene (400 ml). After the reaction mixture was refluxed for 3 h, acetic acid (50 ml) was added to the residual brown suspension under cooling with ice, and the mixture was diluted with water (300 ml). The organic layer was separated and washed with water, saturated aqueous sodium bicarbonate, water, and dried over magnesium sulfate. Evaporation of the filtrate gave substituted-benzoylacetates whose spectral data are shown in Table 4.

Table 4. $R_2COCH_2COOR_1$

Compound	R_1	R_2	Nmr ($CDCl_3$) δ	Ir cm^{-1} (neat)
a	C_2H_5		1.23 (3H, t), 3.86 (8H, s), 4.16 (2H, q), 6.80 (1H, d), 7.40 (1H, d), 7.46 (1H, d)	1730, 1670
b	CH_3		3.53 (2H, s), 3.73 (9H, s), 6.46 (1H, d), 7.00 (1H, d), 7.06 (1H, s)	1740, 1670
c	C_2H_5		1.23 (3H, t), 3.90 (2H, s), 4.20 (2H, q), 4.26 (4H, s), 6.95 (1H, d), 7.46 (2H, m)	1730, 1675
d	CH_3		3.53 (3H, s), 3.70 (2H, s), 4.06 (4H, s), 6.53 (1H, d), 7.16 (2H, m)	1737, 1670

General Procedure for Condensation of β-Keto Acid Ethyl Esters with Methyl 3-Aminocrotonate.

A solution of β-keto acid ethyl ester (10 mmol) and methyl 3-aminocrotonate (11 mmol) in xylene (10 ml) was refluxed in the presence of molecular sieves (4 g, 3A or 4A or 5A) for 24 h. The suspension was filtered, and the precipitate and molecular sieves were washed with chloroform-methanol (1:1, 100 ml). The washed solvents were evaporated. The resulting syrup was recrystallized from appropriate solvent to give methyl 2-methyl-6-substituted or -5,6-disubstituted-1,4-dihydro-4-oxonicotinate. Yields and physical data were shown in Table 1, 2 and 3.

General Procedure for Condensation of β-Keto Acid Methyl Esters with Ethyl 3-Aminocrotonate.

A solution of β-keto acid methyl ester (10 mmol) and ethyl 3-aminocrotonate

(11 mmol) in xylene (10 ml) was refluxed in the presence of molecular sieves (4 g, 4A or 5A) for 24 h. The reaction mixture was filtered and washed with chloroform-methanol (1:1, 30 ml). The filtrates were combined and evaporated to dryness. The residue was dissolved in benzene (5 ml) and chromatographed on a silica gel column (100-150 g, packed with benzene). The column was eluted successively with benzene (600 ml), benzene-ethyl acetate (10:1, 600 ml), and benzene-ethyl acetate (1:1, 400 ml). The last solvent system afforded ethyl 2-methyl-6-substituted or -5,6-disubstituted-1,4-dihydro-4-oxonicotinate. Yields and physical data were shown in Table 1, 2 and 3.

References

1) G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey, and R. P. Brundage, J. Med. Pharm. Chem., 5, 1063 (1962)

2) D. Kaminsky and R. I. Meltzer, J. Med. Chem., 11, 160 (1968)

3) S. Minami, T. Shono, and J. Matsumoto, Chem. Pharm. Bull., 19, 1426 (1971)

4) J. Matsumoto and S. Minami, J. Med. Chem., 18, 74 (1975)

5) H. Agui, H. Tobiki, and T. Nakagome, J. Heterocyclic Chem., 12, 1245 (1975)

6) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusama, H. Sugi and K. Kawasaki, J. Heterocyclic Chem., 14, 477 (1977)

7) E. Ziegler, I. Herbst, and Th. Kappe, Monatsh. Chem., 100, 132 (1969)

8) T. Kato, H. Yamanaka, and T. Hozumi, Yakugaku Zasshi, 91, 740 (1971)

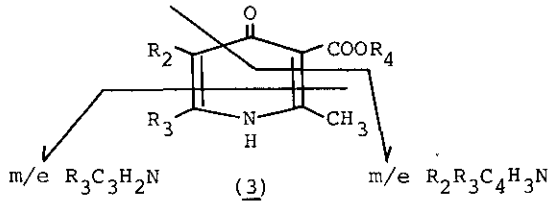
9) L. Capuano, T. Tammer, and R. Zander, Chem. Ber., 109, 3497 (1976)

10) H. Precht, Ber., 11, 1193 (1878)

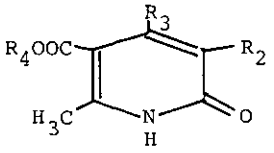
11) R. J. Light and C. R. Hauser, J. Org. Chem., 25, 538 (1960)

12) S. Hünig, E. Benzing, and K. Kübner, Chem. Ber., 94, 486 (1961)

13) Compounds 4, 5, 6, 7, 8 and 9 showed the fragments m/e 67, 67, 129, 129, 163 and 163, respectively. Possible mechanism to give these fragments ($R_3C_3H_2N$) seeme to proceed by dealcoholyration followed by loss of 2 molar ketene. Compounds 14 [R_2=R_3= $-(CH_2)_3-$] and 15 [R_2=R_3= $-(CH_2)_4-$] showed m/e 107 and 121, respectively. These frsgments indicated that compound 3 was dealcoholyrated, then the resultant fragment lost 1 molar ketene and 1 molar CO to give the fragments $R_2R_3C_4H_3N$. The pathway leading to these fragments can be visualized as shown below.



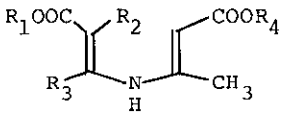
(3)



(B)

Another possible product of this reaction is 1,2-dihydro-2-oxopyridine (B) as it is undesirable. But the fragments $R_3C_3H_2N$ and $R_2R_3C_4H_3N$ discussed above could not be derived from (B).

14) The other possible mechanism is a formation of enaminomethylene malonate intermediate (C) as shown below.



(C)

But in this case, the selective introduction of ester moiety (R_1, R_4) to the product (3) might be lost.

15) K. H. Meyer and V. Schoeller, Ber., 53, 1415 (1920)

16) W. Theilheimer, Synthetic Methods of Organic Chemistry, 13, (1959), pp. 798

17) V. H. Wallingford, A. H. Homeyer, and D. M. Jones, J. Amer. Chem. Soc., 63, 2252 (1941)

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